Data on repeated ^{131}I-WB scans and the incidence of positive Tg and negative ^{131}I-WBS in DTC patients from a 24 month study

Kayode S. Adedapo[1] MBBS, FWACP, MSc,
Mboyo Di Tamba Vangu[2] MD, MMed, MSc, PhD

1. Department of Nuclear Medicine, University College Hospital, University of Ibadan, Ibadan, Nigeria
2. Department of Nuclear Medicine, University of the Witwatersrand, Johannesburg, South Africa

***

Key words: Thyroglobulin elevation
- Negative iodine scan
- Differentiated thyroid cancer
- Follow-up

Correspondence address:
Kayode S. Adedapo Department of Nuclear Medicine, University College Hospital, P.M.B. 5116 Dugbe Post Office, Ibadan South West Nigeria
E-mail: ksadedapo@yahoo.com;
E-mail: kayglow65@gmail.com

Received:
20 May 2011
Accepted revised:
10 June 2011

Abstract

We present data on repeated iodine-131 whole body scans (^{131}I-WBS) in differentiated thyroid cancer patients (DTC) after surgery and ^{131}I remnant ablation and on increased thyroglobulin (Tg) with negative ^{131}I-WBS, in a retrospective study at our hospital. A total of 106 patients (91 female and 15 male) treated with ^{131}I for DTC met the inclusion criteria. The mean age of the patients was 45 years, age range 16-81 years. A total of 101 patients had complete 24 months follow-up following ^{131}I remnant ablation treatment. The mean ^{131}I dose administered after the first 6 months of follow-up was 3GBq while mean total dose was 4.9GBq, range 1.1-7.4GBq. *Our results showed that* at the end of the first 6 months post treatment, 58/101 patients had a negative ^{131}I-WBS. By the end of the 4th ^{131}I treatment at 24th months, the remaining 43 patients became negative for ^{131}I-WBS. We found increased Tg and negative ^{131}I-WBS in 2 of the 101 patients at the 24th months examination the so called Tg elevated negative ^{131}I-WBS (TENIS syndrome). The possible explanation of this syndrome is discussed. *In conclusion*, our study in DTC operated patients does not support the use of repeated diagnostic ^{131}I-WBS after an undetectable Tg because we found no Tg rebound in patients with negative ^{131}I-WBS, after 24 months of follow-up with serial measurements of Tg on and off suppression with L thyroxine.

Hell J Nucl Med 2011; 14(2): *Published on line: 16 June 2011*

Introduction

The efficacy of radioactive iodine-131 (^{131}I) in the management of differentiated thyroid cancer (DTC) has been known for a long time [1, 2]. After successful treatment, patients with DTC are at lifelong risk of recurrence local, regional or less commonly distant metastases [3]. In clinical practice thyroglobulin (Tg) elevated normal ^{131}I whole body scans (WBS), TENIS is a situation of unknown origin [4, 5]. Active thyroid cancer tissue that escaped ablation or recurrence of malignant tissue or the type of surgery could influence serum Tg levels post ^{131}I treatment. Serum Tg is the best marker of residual or metastatic disease after treatment of DTC and its high values need to be considered in clinical practice.

The aim of this study was to determine and discuss the frequency and the importance of negative ^{131}I-WBS and also of elevated serum Tg in patients with DTC after consecutive ^{131}I treatments for remnant ablation after surgery and during a 2 years follow-up.

Subjects and methods

Among 287 patients treated with ^{131}I, following thyroidectomy for DTC at the University of Witwatersrand (Medical) from 1986-2006, 101 patients were included in the study. All patients [1-4] had remnant ablation ^{131}I treatments post thyroidectomy and were followed-up for at least two years after ^{131}I treatment. Five additional patients that defaulted on follow-up were excluded. This study was approved by the Human Research Ethics Committee of Witwatersrand University.

The age, gender, type of surgery, neck dissection, histological type and the total dose of ^{131}I used, as well as the number of treatments that each patient received were retrieved from the patients' notes. The patients comprised of 91 females and 15 males aged 16-81years, with a mean age of 45±15.1 years.

The patients had total or near-total thyroidectomy or lobectomy prior to ^{131}I treatment. They were then taken through management protocol of our Institution consisting of a diagnostic scan with 74-185MBq of ^{131}I, 4-6 weeks after surgery, this was followed by ablative treatment ranging from 1.1 to 7.4GBq of ^{131}I. Serum TSH levels in all

patients were above 30 IU/L at the time of ablation. After therapeutic ablation treatment, L-thyroxine suppressive treatment was initiated in all patients. Routine follow-up examinations were performed 6 months after every ablation treatment. Serum Tg measurements and ^{131}I-WBS were performed in all patients in the hypothyroid state. A negative ^{131}I WBS in conjunction with an undetectable serum Tg level was considered successful ablation, and patients were followed subsequently for 24 months with physical examination and serum Tg measurement while they were on and off suppressive L-thyroxine treatment. An elevated serum Tg level or ^{131}I accumulation on diagnostic WBS or any other positive findings on technetium-99m methyl-diphosphonate (^{99m}Tc-MDP) bone scan were considered as evidence of disease and such patients received further therapeutic doses of ^{131}I. During the follow-up examinations, diagnostic ^{131}I-WBS was performed 72h after oral administration of 74-185MBq of ^{131}I. Serum Tg was measured using an immunoradiometric assay (IRMA). The Tg assay at the Johannesburg hospital before 1998 had the limit of detection of 10ng/mL, while after 1998 this limit was 2ng/mL. Serum Tg auto-antibody levels were also measured at the time of Tg measurement. Statistical analysis was done using SAS software version 9 to determine the association between gender, age, the type of cancer, scan findings and Tg levels.

Results

The type of cancer versus type of surgery are shown in Table 1. Table 2 shows the negative ^{131}I-WBS with corresponding Tg after 6-24 months of follow-up. Discordance between WBS and Tg persisted in 2 patients.

The relationship between type of surgery and negative iodine-131-WBS by 6-24 months is shown in Table 3. The

Table 1. *Type of cancer vs type of surgery*

Diagnosis n=106	Total thyroidectomy (%)	Near total thyroidectomy (%)	Lobectomy (%)
Papillary 58 (54.7%)	35 (60.3)	15 (25.9)	8 (13.8)
Follicular30 (28.3%)	14 (46.7)	13 (43.3)	3 (10)
Mixed 8 (7.54%)	3 (37.5)	5 (62.5)	0
Hurthle 10 (9.43%)	6 (60)	3 (30)	1(10)

Table 2. *Negative 131I-WBS with corresponding Tg after 6-24 months of follow-up*

Patient N=101	*6*	*12*	*24months*
Negative iodine scan (%)	58(57.4)	86(85.1)	101(100)
Negative Tg	48	71	99
No discordant	10	15	2
Tg mean (SD)	45(22.5)	17.4(70.6)	43(20.8)
TSH mean (SD)	77.3(39.7)	81.6(43.3)	82.3(44.4)

Table 3. *Relationship between type of surgery and negative iodine-131-WBS by 6-24 months*

Surgery type	^{131}I scan 6	^{131}I scan at 12	^{131}I scan at 24
T/ thyroidectomy (%)	35 (60.3)	51 (87.9)	54 (93.1)
Near total (%)	19 (52.8)	25 (69.4)	33 (91.7)
Lobectomy (%)	4 (33.3)	10 (83.3)	12 (100)
X^2 0.22	0.082	0.60	

Table 4. *Profile of iodine-131 treatments and outcome of WBS*

Patients	1st ^{131}I treatment	2nd treatment	3rd treatment	4th treatment
WBS +ve	43	24	2	1
WBS –ve	58	77	99	100
Mean iodine				
Dose (GBq)	3.26 (1.11-7.4)			
Mean total dose (GBq)	15.87 (8.14-42.9)			

Table 5. *Proportion % of patients with suppressed Tg over time (off suppression on L-thyroxine) with concordant iodine-131 WBS*

Tg	6 months	12 months	24 months
<10(%) n = 55	37(67.3)	48 (87.3)	55 (100)
<2(%) n = 51	11 (21.6)	23 (45.1)	34 (66.7)

mean administered dose of ^{131}I by the first 6 months of follow-up was 3GBq while mean total dose was 4.9GBq, range 1.1-7.4GBq. This contrasted with total dose of 15.9GBq in patients that received multiple treatments, range 8.1- 42.9GBq (Table 4).

The median Tg value was 88 and ranged from 26-1732ng/mL. None of the patients with undetectable Tg at 24 months had significantly elevated serum Tg antibody.

Fifty five (55) 51.9% of the patients had their Tg assessed with a 10ng/mL cut-off while 51(48.1%) of the patients with a cut-off of 2ng/mL. Most patients (89/101) recorded undetectable Tg levels at 24 months, while 17/51 (33.3%) had significantly elevated Tg being among the Tg >2ng/mL group (Table 5).

Discussion

The management of patients with elevated serum Tg but negative ^{131}I-WBS scan has been a subject for discussion for some years [6]. Thyroglobulin is produced only by benign or malignant thyroid tissue; hence it should not be detectable in ablated patients. The management of such patients includes neck ultrasound (with or without fine needle aspiration cytology), or cervico-mediastinal magnetic resonance imaging (MRI) as the commonest site for recurrences are located at these sites [7]. If the outcome is negative, a CT scan of the chest should be done to exclude micronodular lung metastasis. A negative finding in the lungs turns the attention to the bones for bony secondaries which should be excluded either by ^{99m}Tc-MDP bone scintigraphy or another imaging agent like ^{99m}Tc-methoxyisobutylisonitrile (^{99m}Tc-MIBI). It has been estimated that 1gm of neoplastic tissue will increase serum Tg obtained during T_4 treatment by about 0.5-1ng/mL and that TSH stimulation will increase serum Tg values about 10 fold over baseline levels [8, 9]. As such, neck ultrasound can detect lymph node metastases as small as 2-3mm in diameter which cannot be reliably assessed by serum Tg and may remain undetectable even following TSH stimulation.

In the absence of any positive findings in all of the above, the patient should have a fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) scan or if this not available, a thallium-201 chloride or ^{99m}Tc-MIBI scintigraphic imaging to exclude potentially operative disease [7].

The incidence of Tg elevated and negative ^{131}I-WBS in this study was 2%, as 2 of 101 patients had elevated Tg at 24 months of follow-up. This was not keeping with the findings of others [10] who reported a 13% incidence in 135 patients. While all patients in that study had total thyroidectomy, the patients in our study were mixed and with total and partial thyroidectomy which suggests that the subject of thyroglobulin elevation could be secondary to the type of surgery performed. The type of surgery on the other hand seemed (**to affect**) the outcome of ^{131}I-WBS in our cohort. Sixty percent of the patients that had total thyroidectomy had negative ^{131}I-WBS by the 6th month of follow-up compared with 53% and 33% of patients that had near total thyroidectomy and lobectomy respectively.

Our patients with this condition routinely undergo a ^{18}F-FDG-PET/CT scan for identification of possible sites of micro or macro metastases after bone scan and chest X-rays have failed to reveal any positive findings. Others [3] indicated that surgery should be considered as primary treatment for any lesion in the neck or mediastinum or for any surgically accessible isolated lesion located anywhere in the body regardless of the ability of the lesion to accumulate ^{131}I. This should however be preceded by localization of the disease in order to determine the appropriate surgical treatment.

The empirical treatment of this category of patients is high therapeutic doses of ^{131}I which may show the site of Tg production [11, 12]. More than half (55%) of our patients

(58 of 101) became ^{131}I-WBS negative at the end of the first 6 months of treatment and they still remained negative at the end of the period of the study. This justified the finding of Berger et al. (2011) who concluded that a second routine ^{131}I-WBI 1 year after thyroablation was not indicated in low risk patients [13]. Although our patients were not classified according to risk factors, such as completeness of surgical dissection or Tg level before treatment, yet the finding of non rebound Tg in our patients probably places them in the low risk group. Furthermore, 42 of the 101 patients in our study had more than 2 ^{131}I treatments with 3.7GBq each, before becoming ^{131}I-WBS negative at the end of the 4th treatment and only 2 of them still remained positive with elevated Tg. Non optimal elevation of thyrotropin or TSH has been adduced as one reason why the diagnostic ^{131}I-WBS may be negative while Tg remained elevated [14]. In our study all patients with TENIS had TSH above 30mU/L as our protocol stipulated.

Tumors that do not or weakly trap ^{131}I or are too small to visualize may have a negative ^{131}I-WBS [15]. Treatment decision may have to be individualized for each patient and based on the institution's protocol [14, 16, 17].

In conclusion, our study in DTC operated and treated with ^{131}I remnant ablation patients does not support the use of numerous diagnostic ^{131}I-WBS after the ^{131}I-WBS is negative and Tg undetectable because we found no Tg rebound in patients with negative ^{131}I-WBS after 24 months of follow-up after serial measurements of Tg on and off suppression with L thyroxine. Patients with negative ^{131}I-WBS and elevated Tg were only 2%.

The authors declare that they have no conflicts of interest

Bibliography

1. Seidlin SM, Marinelli LD, Oshry E. Radioactive iodine therapy: effect on functioning metastasis of adenocarcinoma of thyroid. *J Am Med Assoc* 1946; 132: 838-47.
2. Chao M. Management of Differentiated Thyroid Cancer with Rising Thyroglobulin and Negative Diagnostic Radioiodine whole body scan. *Clin Oncol* 2010; 22: 438-47.
3. Kabasakal L, Secuk NA, Shafipour H et al. Treatment of Iodine –negative thyroglobulin positive thyroid cancer: differences in outcome in patients with macrometastasis and patients with micrometastasis. *Eur J Nucl Med Mol Imaging* 2004; 31: 1500-4.
4. 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.
5. Mazzaferri, EL. An overview of the management of thyroid cancer: In Mazzaferri EL, Harmer C, Mallick UK, Kendall-Taylor P. Eds. *Practical Management of Thyroid Cancer: A Multidisciplinary Approach*. Springer Verlag London Limited 2006; 1-28.
6. Giovanella L, Suriano S, Ceriani L, Verburg F.A. Undetectable Thyroglobulin in patients with Differentiated Thyroid Carcinoma and Residual Radio-iodine uptake on a post ablation whole body scan. *Clin Nucl Med* 2011; 36: 109-12.
7. Choe KA, Maxon HR. The role of medical imaging in the diagnosis and follow-up of recurrent or metastatic thyroid cancer. In: Fagin JA, Ed. *Thyroid cancer.* Boston: Kluwer Academic Publishers. 1998: 207-32.
8. Bachelot A, Calieux AF, Klain M et al. Relationship between tumour burden and serum thyroglobulin leveling patients with papillary and follicular thyroid carcinoma. *Thyroid* 2002; 12: 707-11.
9. Demers LM, Spencer CA. Laboratory support for the diagnosis and monitoring of thyroid disease. Accessed on 12th Sept. 2008. Available at http:www.nacb.org/lmpg/ thyroid/LMPH.stm
10. Pacini F, Schlumberger M, Harmer C et al. Post surgical use of radioiodine in patients with papillary and follicular thyroid cancer and the issue of remnant ablation a consensus report. *European Journal of Endocrinology* 2005; 153: 651-9.
11. Kukulska A, Kwajeska J, Gawkowsk-Suwinska M et al. Radioiodine thyroid remnant ablation in patients with differentiated thyroid carcinoma: prospective comparism of long time outcomes of treatment with 30, 60 and 100mCi. *Thyroid Res* 2010; 3(1): 9.
12. Pacini F, Schlumberger M, Harmer C et al. Post surgical use of radioiodine in patients with papillary and follicular thyroid cancer and the issue of remnant ablation a consensus report. *European Journal of Endocrinology* 2005; 153: 651-9.
13. Berger F, Friedrich U, Knesewitsch P, Hahn K. Diagnostic ^{131}I whole body scintigrapghy 1 year after thyroablative therapy in patients with differentiated thyroid cancer:correlation of results to individual risk profile and long follow-up. *Eur J Nucl Med Mol Imaging* 2011; 38(3): 451-8.
14. Zanotti-Fregonara P, Keller I, Rubello D et al. Thyrotropin variation may explain some positive radioiodine therapy scans in patients with negative diagnostic scans. *J Endocrinol Invest* 2009; 32(3): 267-71.
15. Mazzaferri EL. Treating high thyroglobulin with radioiodine: A magic bullet or a shot in the dark? (editorial) *J Clin Endocrinol Metab* 1994; 80(5): 1485-7.
16. Alzahrani AS, Mohamed G, Al Shammary A et al. Long term course and predictive factors of elevated serum thyroglobulin and negative diagnostic radioiodine whole body scan in differentiated thyroid cancer. *J Endocrinol Invest* 2005; 28: 540-6.
17. Intenzo CM, JabbourS, Dam HQ, Capuzzi DM. Changing concepts in the management of differentiated thyroid cancer .*Semin Nucl Med* 2005; 35: 257-65.