European Review for Medical and Pharmacological Sciences 2011; 15: 1215-1221

Evaluation of radioiodine therapy in differentiated thyroid cancer subjects with elevated serum thyroglobulin and negative whole body scan using ^{131}I with emphasize on the thallium scintigraphy in these subgroups

A. ZAKANI[1], M. SAGHARI[2], M. EFTEKHARI[1,2], A. FARD-ESFAHANI[2], B. FALLAHI[2], J. ESMAILI[1], M. ASSADI[3]

[1]Nuclear Medicine Department, Vali Asr Hospital, Faculty of Medicine, Tehran University of Medical Sciences, Tehran (Iran)
[2]Research Institute for Nuclear Medicine, Shariati Hospital, Tehran University of Medical Sciences, Tehran (Iran)
[3]The Persian Gulf Nuclear Medicine Research Center, Bushehr University of Medical Sciences, Bushehr (Iran)

Abstract. – ***Objective:*** **Negative diagnostic ^{131}I whole body scans with elevated serum thyroglobulin (Tg) levels are found in 20% of patients with differentiated thyroid cancer (DTC). Empirical radioiodine treatment has been advocated by some researchers, but has had with controversial outcomes. This anterospective study was performed to examine this dilemma and also to determine the capability of thallium (^{201}Tl) scintigraphy in these patients.**

Materials and Methods: **A total of 21 patients who had a history of DTC and elevated serum Tg levels, together with a negative diagnostic ^{131}I whole body scans (WBS), were included in the study. All patients underwent posttreatment ^{131}I WBS. Patients with negative posttreatment ^{131}I WBS then underwent ^{201}Tl scintigraphy.**

Results: **The 21 included patients (9 women and 12 men) had a mean age of 53 ± 14.17 years. The mean pretreatment and posttreatment Tg levels were 227.23 ± 208.50 ng/ml and 163.43 ± 282.57 ng/ml, respectively (p value <0.05). Eleven cases showed at least a 50 % decrease in Tg value (remission group), 6 patients revealed less than a 50 % decrease in Tg value (stable group), while 4 subjects demonstrated an increment in posttreatment Tg relative to pretreatment Tg value (progression group). The cumulative and last ^{131}I doses in the remission, stable, and progression groups were not significantly different (p value >0.05). In the posttreatment ^{131}I WBS, 10 patients showed abnormal findings in their images. In a follow-up scan after ^{201}Tl treatment, 7 out of 11 patients had positive scans.**

Conclusion: **The study indicates a positive effect of RAI therapy in DTC patients with elevated Tg and negative ^{131}I WBS. In addition, ^{201}Tl scintigraphy can be useful as an alternative modality to improve tumoral detection in this situation and when access to a PET system is limited.**

Key Words:

Differentiated thyroid cancer (DTC), ^{131}I whole body scan, Thyroglobulin (Tg), ^{201}Tl.

Introduction

Differentiated thyroid carcinoma (DTC) generally is characterized by an indolent course with low morbidity and mortality[1-4]. In most cases, initial treatment for DTC is total or near-total thyroidectomy together with radioiodine ablation[3,4]. The follow-up of previously thyroidectomized patients consists of diagnostic whole body ^{131}I scans (WBS) with the aim of detecting either local recurrence or distant metastases[3].

An excellent association is noted between the persistence of disease and thyroglobulin (Tg) levels (in the absence of thyroglobulin autoantibody)[3]. Conversely, discordant results between ^{131}I WBS and serum thyroglobulin have been found in 15-20% of patients, who show high serum Tg but negative ^{131}I WBS[5,6]. These phenomena may be related to the low dose of iodine

Corresponding Author: Majid Assadi, MD; e-mail: assadipoya@yahoo.com, asadi@bpums.ac.ir

administered (diagnostic dose), the presence of tumor deposits too small to be detected by a scintillation camera, or the loss of iodine concentration as a result of tumor dedifferentiation.

Several recent reviews have discussed this clinical predicament, and some experts advise treatment with high doses of ^{131}I to localize and eradicate the metastatic lesions[7]. In contrast, a number of recently published studies have shown a lack of effect of radioiodine therapy in these subjects[8-10]. Thus, radioiodine therapy has been proposed as a therapeutic management, but with controversial outcomes[11].

The present study was performed with the aim of providing an answer to this dilemma and also to determine the potential benefit of ^{201}Tl scintigraphy in patients with elevated serum thyroglobulin (Tg) levels and negative WBS.

Materials and Methods

Participants and Study Design

This anterospective study recruited 21 patients over a period of two years, from August 2004 to May 2006. All studied patients had a history of DTC and elevated serum Tg levels, with a negative ^{131}I diagnostic WBS. All patients had also been treated at least once with radioiodine (RAI). Serial monitoring was carried out using serum Tg measurements and WBS. Patients were followed for surgical and pathologic findings, status of the DTC at the time of the initial surgery, extent of metastasis at the time of radioisotope scanning, subsequent operations, clinical findings, and serum Tg and TSH levels. The interval between the previous ablative or therapeutic RAI and the WBS was more than 6 months in all patients. Patients were carefully questioned about any exposure to exogenous iodine before scanning and all patients were advised to avoid medication containing iodine during the preparation time for diagnostic scan. The clothing of the participants prior scanning was changed to prevent contamination. Both the WBS and Tg level were performed after stopping levothyroxine for one month and liothyronine for 2 weeks.

At the time of the diagnostic WBS, all patients had a serum TSH levels above 30 mIU/l. The post therapy scans were prepared just before the patient was released following ^{131}I therapy. The 11 patients who had a negative posttreatment ^{131}I WBS also underwent ^{201}Tl scintigraphy.

This study was approved by the institutional Ethics Committee of Tehran University of Medical Science and all patients gave written informed consent.

Acquisition Protocols

For ^{131}I scintigraphy, the patients were orally administered 185 MBq ^{131}I, and scintigraphy was performed 48 h later. Planar images were obtained by means of a gamma camera (Scintronix, Livingston, UK) with a high energy parallel hole collimator, where the energy setting was at 364keV± 10%.

The ^{201}Tl scintigraphy was performed using a double head gamma camera (ADAC Genesys Malpitas, CA, USA) fitted with a low-energy parallel hole collimator. Planar images were obtained 5 min after intravenous administration of 74 MBq of $^{201}T1$. Single photon emission computed tomography (SPECT) images were then obtained 20 min later. Data were obtained from 60 projections of 30 s each in the 70 KeV photopeak, over an 360° arc in a 64×64 matrix. The data were reconstructed utilizing a Butterworth prefilter and filtered backprojection with a Ramp filter. Images were observed and interpreted by two experienced nuclear medicine physicians.

Measurement of Serum Thyroglobulin

Serum thyroglobulin (Tg) and anti-Tg antibody levels were determined by radioimmunoassay using commercial kits (Dynotest Tg-plus and Dynotest anti-Tgn; Brahms Diagnostica, Berlin, Germany respectively). In addition, serum TSH was measured with a third-generation double antibody assay. Because TSH was elevated in all patients, Tg levels more than 10 μg/L were considerated abnormal[12].

Since circulating AbTg interferes with Tg assays, producing false results, we routinely screened all patients for serum anti-Tg antibody by passive hemagglutination. Patients with positive anti-Tg antibody and negative Tg were excluded from this analysis.

Statistical Methods

Serum thyroglobulin levels before and after ^{131}I therapy were compared using a Wilcoxon signed-rank test. When more than one post therapy Tg was available, the lowest value was used. In addition, a Chi-square test was used to compare differences between categorical variables. A p value of 0.05 or less was considered significant. Statistical analysis was performed utilizing SPSS version 15 (SPSS Inc., Chicago, IL, USA).

Results

A total of 21 patients (9 females and 12 males) with a mean age of 53 ± 14.17 years were took part in the study. Twenty patients had the papillary type of differentiated thyroid cancer (PCDTC) and 1 case had the follicular type of differentiated thyroid cancer (FCDTC). At the initial operation, 7 patients underwent total thyroidectomy and the remaining 14 patients had near-total thyroidectomies.

The mean dose of the last radioiodine therapy was 5.46 ± 0.87 GBq (3.7-7.4 GBq). The cumulative doses of ^{131}I dose were 12.23 ± 5.94 GBq, ranged from 4.81 to 27.75 GBq. All patients had a serum TSH levels above 30 mIU/l. After withdrawal of T4 therapy, the mean pretreatment Tg was 227.23 ± 208.50 ng/ml (range, 17-600 ng/ml), the mean posttreatment Tg was 163.43 ± 282.57 ng/ml (range, 0.10-910 ng/ml), and the difference was statistically significant (*p* value <0.05). According to the serum Tg assessment, 11 patients showed at least a 50% decrease in Tg value (remission group), while 6 patients revealed less than a 50% decrease in Tg value (stable group). Four subjects demonstrated an increment in posttreatment Tg relative to pretreatment Tg values (progression group).

In the posttreatment WBS, 4 patients showed increased activity in the cervical lymph node, 3 thyroid beds, and 3 lungs. The remaining 11 cases were also negative in WBS in the posttreatment survey.

The patients were also categorized according to their surgical stage (TNM classification). Four cases were in stage 1, 1 in stage 2, 15 in stage 3, and 1 in stage 4. The highest frequency of tumor recurrence occurred in stage 3 patients.

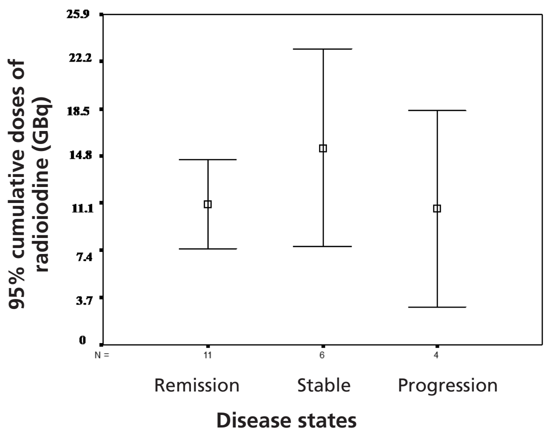

Figure 1. The cumulative doses of the radioiodine according to disease states.

In the posttreatment follow-up, 5 out of 12 cases with cervical lymph node involvement in pretreatment examination showed evidence of recurrence. In contrast, 7 cases showed no evidence for involvement of any part and 2 cases of lung involvement revealed no recurrence in the follow-up survey. In total, 5 of the 11 remission patients, 3 of the 6 stable cases, and all 4 of the progression cases were male. We compared the cumulative and also the last ^{131}I doses in the remission, stable, and progression groups and found no significant differences among the groups (*p* value >0.05) (Figure 1).

In pretreatment chest X-rays, 3 out of 12 remission cases, 2 out of 6 stable cases, and 1 out of 3 progression patients revealed abnormal findings. Posttreatment WBS showed abnormal findings in 10 of 21 studied cases, while the remaining 11 patients showed no abnormal lesions throughout their bodies in the WBS. Details of the posttreatment WBS for each group are shown in Table I.

In follow-up scans with ^{201}Tl, the number of metastatic regions totaled 7 out of 11 cases and included 4 regions in the neck, 2 regions in the

Table I. The detailed data of posttreatment whole body scan using ^{131}I in three studied groups.

	Negative	Cervical lymph node	Thyroid bed	Lung	Total
Remission	7	3	1	1	12
Stable	3	1	1	1	6
Progression	1	0	1	1	3
Total	**11**	**4**	**3**	**3**	**21**

lung, and 1 region in the iliac bone. The 4 remaining subjects showed no abnormal activity throughout their bodies in the ^{201}Tl scan.

Discussion

The standard therapy for differentiated thyroid cancer (DTC) is surgical resection followed by radioiodine (^{131}I) ablation[8]. However, even with this treatment, the overall recurrence rate of thyroid cancer is 20%[13]. For follow-up, ^{131}I WBS is one of the most important tests for use in DTC patients. However, a negative diagnostic ^{131}I WBS in the presence of known residual or metastatic FCDTC is not uncommon[14]. A false negative ^{131}I WBS can be due to technical factors, such as an excessive iodine pool, poor instrumentation, and inadequate serum TSH elevation[14]. Because the patients in our study had well-characterized cancers, our patients did not represent false-negative ^{131}I WBSs. There was adequate TSH elevation, and all patients had undergone at least one previous negative diagnostic ^{131}I WBS despite elevated Tg.

From the diagnostic point of view, our results show the high sensitivity of post therapy ^{131}I WBS in Tg+/WBS- patients and indicate that this procedure allows the detection of neoplastic foci not seen with diagnostic doses of ^{131}I. Our findings suggested that the administration of a high ^{131}I dose to Tg+/WBS-patients is effective in these subgroups of DTC patients. Similar findings have been acquired in previous studies[15]. For example, Pineda et al[16] reported therapeutic effectiveness of ^{131}I treatment in 14 patients with elevated Tg and negative ^{131}I WBS, as assessed by a significant reduction in serum Tg, to 5 ng/ml or less, and by normalization of previously positive post therapy WBS. Fautorechi et al[15] concluded that treatment with high doses of ^{131}I in Tg+/WBS- patients allows the detection of abnormal uptake in post therapy WBS, particularly micrometastases. In their experience, aggressive macrometastases with negative diagnostic WBS did not show significant uptake after therapeutic doses of ^{131}I. In a study by Koh et al[17], 60 DTC patients with elevated serum Tg levels and negative ^{131}I WBSs were divided into two groups: those treated with RAI (28 patients) and untreated (32 patients). A meaningful reduction of Tg was obtained and these Authors concluded that RAI therapy has a therapeutic effect, at least for short-term follow-up[17].

In a meta-analysis of 10 observation studies and 3 nonrandomized controlled trial investigations, a reduction in Tg levels was observed in 63% of DTC patients with elevated Tg and negative WBSs, and the researchers concluded that ^{131}I therapy does have a therapeutic effect in this condition[14]. In a study of 56 patients with a 4.2 years of follow-up, 18 of the 28 patients with a positive posttreatment ^{131}I WBS went into complete remission, as compared with 10 of the 28 patients with a negative post-treatment WBS[18]. In total, 9 patients in the negative posttreatment ^{131}I WBS group died, but no patients died in the positive posttreatment group. The Authors concluded that RAI treatment can be used as a diagnostic tool and also as a therapeutic effect in individual cases[18].

Some previous studies[17,19,20] have extensively supported the empiric therapy. These Authors suggested that ^{131}I uptake may be too small to be visualized on diagnostic scans, either because the ability of the neoplastic tissue to concentrate iodine is low or the mass of the metastasis is too small. Therefore, a larger dose makes visualization of uptake possible[19]. No conclusive evidence exists that this approach changes patient outcome, although it suggested that some parameters of disease activity may get better. In one article, Mazzaferri et al[21] evaluated this issue in 10 diagnostic WBS-negative patients with serum Tg levels more than 15 ng/ml (TSH more than 30 mIU/liter). Eight of these patients had evidence of distant metastases on post therapy scans. Three patients had subsequent negative post therapy scans within 2-4 yr, with a reduction in serum Tg to 5 ng/ml[21]. The report by Pacini et al[7] compared the results of 28 untreated patients encountered before 1984 with those of 42 treated patients seen after that date. The Authors found positive post therapy WBS in 71%, which was similar to our present results. They noted a reduction in Tg and disappearance of lung uptake with repeated therapy and recommend treating all Tg-positive, WBS-negative cases once with 3.7 GBq of ^{131}I and continuing therapy until post therapy WBS becomes negative[7].

Recently, Kim et al compared empiric RAI therapy in 39 DTC patients with detectable serum thyroglobulin, but negative cervical sonography and 18F-FDG PET scans, and found no significant results[22]. In our previous study of 32 patients, we observed reduction or normalization of thyroglobulin in 9 of 10 partial and complete responders in the first post-treatment year and we concluded that at least one course of radioiodine therapy should be applied in the Tg-positive, WBS-negative subgroup patients[20]. In the most recent meta-analysis of 18 investigations, empirical therapy was administered in 16 of the studies that included DTC patients with elevated Tg and negative scan results[11]. They RAI treatment was suggested to have a therapeutic effect for this condition[11].

Despite the above reports, the use of RAI therapy in Tg+/WBS- patients has been questioned by some Authors, mostly because of the deficient numbers of control studies[9,10,23]. In a study by Kamel et al[24], normalization of Tg levels in only 6 out of 38 Tg-positive, scan-negative patients was acquired and the researchers concluded that the overall effect of RAI treatment on long-term survival is obscure[24]. In the investigation by Fatourechi et al, since only 4 out of 24 patients revealed any evidence of ^{131}I uptake on posttreatment RAI scan, the widespread administration of RAI therapy was not recommended. The main difference between that study and our findings is the number of 10 positive posttreatment ^{131}I WBS in the current investigation[8]. In a study by Gutiérrez Cardo et al in 130 patients showing elevated Tg levels and negative findings for WBS and other imaging modalities, empirical treatments were considered not to be the only factor that contributes to normalization without other therapy interventions[10]. This study included patients without positive results for any other imaging modalities[10], which is unlike the current study where 10 cases had positive posttreatment ^{131}I WBS and 7 of the 11 remaining cases had positive ^{201}Tl scans.

New methods for detecting and localizing less differentiated metastatic lesions are vitally important for planning therapeutic measures with more effectiveness at eradicating these potentially lethal thyroid cancer variants. For example, 18F-FDG PET/CT can improve diagnostic accuracy and can be used to conduct therapeutic management in patients who are Tg positive but show negative ^{131}I WBS[24]. A recent meta-analysis reported 88.5 % sensitivity and 84.7% specificity in these patients[25]. The most important aspect of non-iodine isotope imaging is that it eliminates the need to discontinue levothyroxine consumption for preparation. Indeed, some 18F-FDG PET/CT studies have demonstrated detection of more lesions during elevated TSH conditions as compared with the suppressed TSH state[26]. However, performing 18F-FDG PET/CT in patients with Tg positive but negative ^{131}I WBS under TSH suppression or TSH stimulation remains controversial and needs further study[27]. When used as a tracer for oncoscintigraphy, ^{201}Tl accumulates in lung cancer, malignant lymphoma, parathyroid tumors, and DTC. As in myocardial scintigraphy, the distribution of perfusion tracer depends on blood flow and NA-K ATPase activity[28].

In our study, the sensitivity of ^{201}Tl was within the ranges noted in previous studies, where sensitivity of ^{201}Tl was reported as 45-94%[29-31]. Therefore, ^{201}Tl scintigraphy can be used as an alternative modality in institutes that lack PET systems. We believe that the available information and our present report support the benefits of empiric RAI therapy for diagnostic RAI scan-negative, Tg positive DTC patients. For the management of DTC patients who do not have RAI accumulation and have elevated Tg, other imaging modalities such as ^{201}Tl scans are needed.

The reasons for this discrepancy lie in study population, imaging modality, post RAI follow up time, Tg measurements while on or off thyroxin hormone treatment, the use of recombinant TSH, the ^{131}I doses received, the sample size, and most important, the lack of well-designed studies. Lastly, these findings support the claim that RAI treatment could be useful in patients with Tg positive but negative ^{131}I WBS, although further evidence needs to be obtained.

Limitations of the Study

One of the most important limitations of this study is its small sample size. Another limitation is that we could not provide follow-up over a prolonged time course. Thus, extended monitoring is among the parameters that should be taken into account in future studies. In addition, PET was not available to acquire the sensitivity and specificity, so we could not conclusively comment about the utility of this examination.

Conclusion

One of the most important findings of this study was that at least 50% of the subjects demonstrated a reduction or normalization of serum Tg in the first post-treatment follow-up. Therefore, for DTC patients with elevated Tg and negative WBS, at least one course of RAI therapy could be recommended. In ^{131}I WBS, ^{201}Tl scintigraphy, especially at institutions without access to PET, may be useful.

Acknowledgements

This study was the postgraduate thesis of Dr Alireza Zakani and was achieved with the sponsorship of Tehran University of Medical Sciences (grant no. 753). We extend our thanks to colleagues at our institutes and also colleagues form Mashhad Nuclear Medicine Research Center, especially Dr Kamran Aryana, for their technical help and assistance with data acquisition.

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