Endocrine, Original Article

The Impact of Thyroid Stunning on Radioactive Iodine Ablation Compared to Other Risk Factors

Abd El-Kareem, M[*], El-Refaie, SH[*], Zaher, A[**], Abo-Gaba, MI[*] and Abdo, S[*]

Nuclear medicine units, NEMROCK [*] & NCI [**], Cairo University

ABSTRACT:

Purpose: To evaluate the impact of post-operative diagnostic I131 whole body scan (WBS) on thyroid ablation compared to other risk factors. **Patient and Methods:** A prospective study of 336 patients with differentiated thyroid carcinoma was included after near-total thyroidectomy. They were classified into 2 major groups: Group 1 (183 patients) received ablative dose after performing diagnostic I131 WBS and group 2 (153 patients) received ablative dose without prior I131 WBS. In patients who received diagnostic I131 WBS, ablative dose was planned and given within 1-6 weeks after performing the diagnostic study. Follow up WBS and stimulated serum Tg for all patients were done 6 months after initial ablative dose, image interpretation was made qualitatively and our criteria for successful remnant ablation defined as absence of any significant RAI uptake at the thyroid bed and stimulated serum Tg level less than 2 ng/mL. Accordingly two categories were identified either complete or incomplete ablation. **Results:** Successful complete ablation was reported in 237 patients representing 70.5% of the whole patient population, while incomplete ablation was found in the remaining 99 patients (29.5%).

A statistically significant difference in ablation outcome was found between patients who had performed I131 WBS and those who received ablation directly without prior diagnostic imaging in favor of the latter group. Successful complete ablation was reported in 54.1% and in 90.2% of patients in group 1,4 and failure of complete ablation was encountered in 45.9% and 9.8% in patients who performed DxWBS and those who received I131 ablation without prior imaging respectively (p value < 0.001). Comparing this factor (post operative I131 WBS before I131 ablation), which may lead to stunning with affect ablation outcome. We found that this was the major independent variable that significantly affected response rate with OR of 4.6 (95% CI 2.2-9.7), whereas there is no statistically significant difference in success of thyroid remnant ablation regarding the age (less than or more than 45 years old), gender (male or female), tumor histology (papillary, minimally invasive follicular and widely invasive follicular cancer thyroid), associated pathology (Colloid/ multinodular goitre and Hashimoto's thyroiditis), tumor multifocality, presence or absence of minimal extrathyroidal extension and vascular invasion.

Conclusion: Post-operative diagnostic I131 WBS will significantly affect the success of I131 ablation if the ablative dose is planned within 1-6 weeks after the diagnostic study.

Keywords: Differentiated thyroid cancer – Radioactive iodine ablation – Thyroid stunning – risk factors.

E-mail: maha_abdelkareem@yahoo.com

INTRODUCTION:

Differentiated thyroid carcinoma (DTC) (Papillary and follicular) represents approximately 80%-85% of thyroid cancer. Both have an excellent prognosis, with a 20- year survival of 90% and 75%, respectively [1].

The standard surgical treatment is total (or near-total) thyroidectomy. This procedure decreases the risk of local recurrence and facilitates postsurgical radioiodine ablation and adequate follow up compared to more limited thyroidectomy that should not be performed [2].

The goals of radioactive iodine ablation are to destroy any microscopic tumor foci and to destroy any remaining normal thyroid tissue. This would then make serum Tg more specific tumor marker. If microscopic deposits of differentiated thyroid cancer are destroyed, one should expect lower recurrence rates and possibly improved overall survival [3].

A diagnostic scan of 2-5 mCi iodine ^{131}I is usually obtained within 4-6 weeks after surgery to demonstrate residual functioning thyroid remnant and/or metastases.

Radioactive iodine ablation is performed on the basis of tumor size, histologic classification, and stage of disease[4].

Numerous reports suggest that diagnostic scanning with low amount of ^{131}I may diminish the subsequent uptake of a therapeutic dose (termed "stunning") [5].

Thyroid stunning is usually defined as decreased uptake or trapping of radioiodine ^{131}I by normal thyroid tissue or DTC after diagnostic administration of ^{131}I[6].

Lassmann et al. have found that administration of as little as 74 MBq (2 mCi) of ^{131}I could reduce subsequent thyroid remnant uptake by more than 50% [5]. However, the question of whether pre-exposure to diagnostic amounts of ^{131}I might influence the outcome of ^{131}I radiation therapy is still being debated [7].

Thyroid stunning is a radiobiological suppressive phenomenon defined as a temporary suppression of iodine trapping function of the thyrocytes and thyroid cancer cells as a result of the radiation given off by the scanning dose of ^{131}I [8].

On measurements of uptake made within 1–3 days of the ablation activity, there is no evidence of a large rapid loss of the given 131I. This would suggest that stunning results from decreased ability of thyroid tissue to trap rather than decreased ability to retain radioiodine [9].

The frequency of stunning is reported to be 40%, 67%, and 89% after 3, 5, and 10 mCi (111, 185, and 370 MBq) doses of ^{131}I, respectively [10].

Aim of the work

The aim of the work is to evaluate the effect of diagnostic I131 whole body scan as a factor for stunning on thyroid ablation compared to other risk factors.

PATIENTS AND METHODS:

This prospective study included 341 patients who had undergone near total thyroidectomy for WDTC (papillary and follicular cancer thyroid) and were referred to the Nuclear medicine unit for ^{131}I ablation of the residual functioning thyroid tissue. The patients were collected from nuclear medicine units at Kasr Al aini Hospital (NEMROK) and National Cancer Institute, Cairo University, from August 2008 till July 2012.

We excluded 5 out of 341 patients because they had distant functioning metastases on diagnostic or post therapy whole body scans. 336 patients were illegible for the study with 78.3% females & 21.7% males. The median age was 48 years (range 20–62 years). Most patients were treated for papillary carcinoma 91.7% versus 8.3% follicular cancer thyroid. They were classified into 2 major groups:

Group 1: patients who received ablative dose after performing diagnostic whole body scan (183 patients).

Group 2: patients who received directly ablative dose without diagnostic whole body scan (153 patients).

Patients in group 1 performed the diagnostic imaging study 4-6 weeks following surgery. Images were interpreted qualitatively by visual assessment of the size & tracer uptake intensity of the residual uptake. Patients in group 2 were evaluated by the same manner as group 1 but with no initial DxWBS. Therapy dose (100 mCi) were given 4-6 weeks following surgery.

DxWBS for all patients were done 6 months after initial therapy, all patients were prepared in the same way for the administration of radioiodine by withdrawal of LT4 medication 4 weeks before administration of 2-5 mCi of 131 (TSH level should be > 30 uIU/mL) and were asked to follow a low iodine diet 1 week before dose. Blood samples were taken to measure Tg levels and TSH few days before administration of diagnostic dose. On the third day after administration of 131I, DxWBS was performed. Image interpretation was made qualitatively and our criteria for successful remnant ablation defined as: Absence of any significant RAI uptake at the thyroid bed and stimulated serum Tg level should be less than 2 ng/mL.

Accordingly two categories were identified: either complete or incomplete ablation. The latter means the presence of significant residual functioning thyroid tissue at the thyroid bed with or without elevated elevated serum Tg more than 2 ng/mL.

Statistical methods

Data was analyzed using SPSSwin statistical package version 17 (SPSS Inc., Chicago, IL). Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. Multivariate analysis was done using forward stepwise logistic regression method for the significant factors affecting response on univariate

analysis. Odds ratio (OR) with 95% confidence interval (CI) were used for risk estimation. A p-value < 0.05 was considered significant.

RESULTS:

The current prospective study included 336 patients, 263 females (78.3%) and 73 males (21.7%) referred for ^{131}I ablation after near total thyroidectomy. Their age ranged from 20 to 62 years with a mean value of 48. Two hundred and thirty patients were less than 45 years, while the remaining 106 patients were in the older age group (>45years). The commonest histopathology was PTC, encountered in 308 patients (91.7%). Twenty eight patients (8.3%) have FTC (22 minimally invasive and 6 widely invasive). Histopathological data analysis showed the presence of multifocal malignant lesions, minimal capsular invasion and vascular invasion in 85 (25.1%), 30 (8.9%) and 14 (4.2%) patients respectively (table 1).

Lymph node sampling or dissection was performed in 172 patients; out of them 105 were negative for LN metastases and 67 showed positive LN involvement. Histopathology of associated non neoplastic thyroid tissue included Hashimoto`s thyroiditis in 37 patients (11%), colloid/multinodular goiter in 69 patients (20.5%) and normal thyroid tissue in the remaining 230 patients (68.5%).

The patients were classified into 2 major groups matched for homogeneity regarding age (less than or more than 45 years old), gender (male or female), tumor histology (papillary, minimally invasive follicular and widely invasive follicular cancer thyroid), associated pathology (Hashimoto`s thyroiditis and colloid nodular goiter), mutifocality, the presence or absence of minimal thyroid capsule infiltration, the presence or absence of LN metastases and vascular invasion.

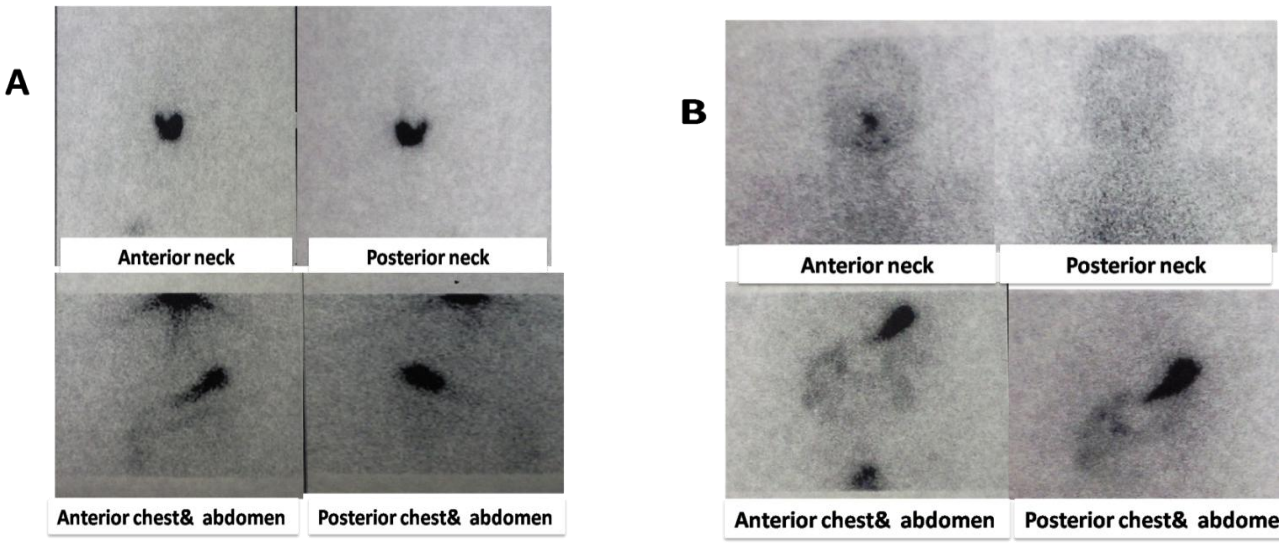

Fig 1: (A) a 30 years old female patient with papillary thyroid with Post therapy scan (100 mCi) RAI 131 without proceeding diagnostic dose for, showed proper tracer localization in residual thyroid tissues in the neck. (B) Follow up diagnostic scan 6 months later revealed complete successful ablation of the residual functioning thyroid tissues.

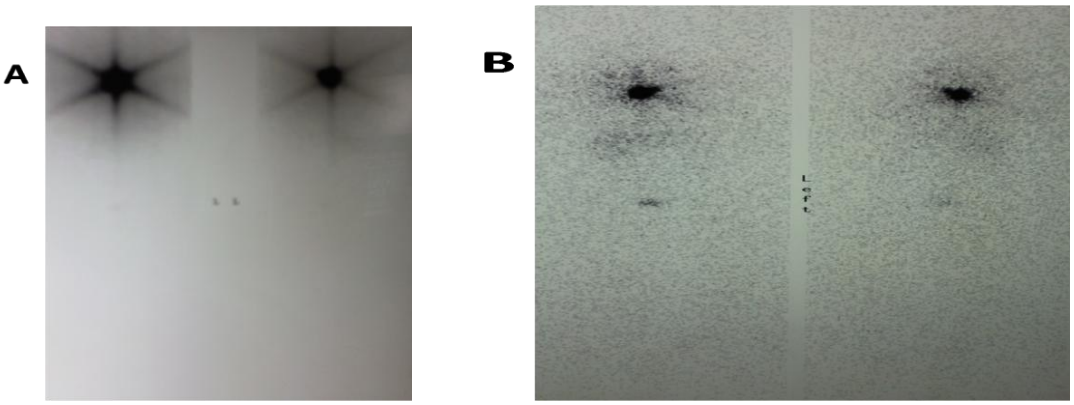

Fig 2: (A) a 47 years old female patient with papillary thyroid carcinoma with whole body diagnostic scan after surgery revealed residual functioning thyroid tissues at the thyroid bed. She received ablative dose (100 mCi) RAI 131. (B) Follow up 6 months later was done and revealed incomplete ablation of the residual functioning thyroid tissues.

(**Table 1**): **Patient characteristics of 336 patients with cancer thyroid.**

	Group I	**Group II**
Number of cases	**183**	**153**
PATHOLOY OF DIFFERENTIATED CANCER THYROID		
Papillary	**167**	**141**
Minimally invasive follicular	**14**	**8**
Widely invasive follicular	**2**	**4**
ASSOCIATED PATHOLOGY		
Hashimoto`s thyroiditis	**21**	**16**
MNG/Colloid	**45**	**24**
MULTIFOCALITY		
Number of multifocal cases	**46**	**39**
TNM VARIANTS		
Thyroid capsule invasion	**13**	**17**
LN involvement	**37**	**30**
Vascular invasion	**8**	**6**

All factors that may have an effect on response rate of successful thyroid remnant ablation were studied individually. Successful complete ablation after single dose of ^{131}I was reported in 237 patients representing 70.5% of the whole patient population, while incomplete ablation was found in the remaining 99 patients (29.5%) (Fig 1,2).

A statistically significant difference in ablation outcome was found between patients who had performed ^{131}I WBS and those who received ablation therapy without prior diagnostic imaging in favor of the latter group. Successful complete ablation was reported in 54.1% and in 90.2% of patients and failure of complete ablation was encountered in 45.9% and 9.8% in patients who performed DxWBS and those who received ^{131}I therapy without prior imaging respectively (p value < 0.001).

There was no significant difference in thyroid remnant ablation between the 2 major groups regarding the age of the patient, P value 0.442. Similarly, no significant effect on response was detected regarding gender (P value 0.316), tumor histology, associated pathology (P value 0.312), tumor multifocality (P value 0.891), presence or absence of vascular invasion (P value 0.765) , Presence or absence of minimal extra-thyroidal extension (P value 0.403).

Regarding the Presence or absence of lymph node involvement there was relative mild significant difference between patients with negative lymph node metastases and those with positive lymph node involvement with more successful ablation outcome in the second group, P value 0.011. Using multivariate analysis; administration of diagnostic dose of RAI before ablative dose and to a lesser extends involvement of LN were the independent variables that affect response with OR of 4.6 (95% CI 2.2-9.7) as compared to 2.2 (95%CI: 1.1-4.5) respectively.

DISCUSSION:

Diagnostic dose of ^{131}I given before ablative dose is significantly reduce the uptake of the subsequently given ablative dose even if low diagnostic doses leading to stunning[11]. The importance of the stunning phenomenon is that it may influence the rate of successful ablation. However, data about thyroid stunning is controversial, whether it actually exists,

whether there is a dose threshold, and whether it actually affects therapeutic outcome [12]. It was shown by Verburg et al., [13] that a successful ablation itself seems to be a highly important prognostic factor for long-term outcome. They found that of the patients with a successful ablation, 87% were still free of disease after 10 years, whereas of the patients with an unsuccessful ablation, only 50% were free of disease, while thyroid cancer-related survival was (93% versus 78%) (P < 0.001).Also, Mazzaferri and Kloos [14] also found remnant ablation to be an independent variable that reduced loco-regional recurrence, distant metastases, and cancer death after four decades of follow-up of 1510 patients without distant metastases at the time of initial therapy.

In the current study, successful ablation was achieved in 54.1% from a total of 183 included in group I with diagnostic followed by therapy dose as compared to group II with immediate therapeutic dose with ablation rate of 90.2% (P value < 0.001). The significant difference in ablation rate between the two main groups was mainly attributed to the effect of stunning caused by giving the diagnostic dose before the ablative dose with 4.6 times risk not to enter in complete remnant ablation on multivariate analysis.

Gerard et al. analyzed 11 published studies on thyroid stunning and found a total of 1412 patients with thyroid cancers reported to have thyroid tissues stunned by diagnostic doses of ^{131}I ranging from 0.5 to 10 mCi (18.5–370 MBq) [8], also Koch et al. & Huic et al., also reported similar findings[15] , [16].

Kao et al. reported , through reviewing a significant reduction of therapeutic uptake ranging from 40% up to 89% with increasing diagnostic dose [17] , other studies that did not support the stunning phenomenon as that done by Morris et al., who suggested that stunning phenomenon has been overemphasized. They compared the outcome in two well matched patient groups. One group had a prior diagnostic scan using doses of 3–5 mCi (111–185 MBq) of ^{131}I, and the other did not. They found that no difference in outcome where 65% of the former group were ablated versus 67% of the latter group [18]**.** The stunning effect was also denied by Bajen etal, after WBS with 5 mCi of I131. Karma et al found that there is no effect on ablation outcome on using higher diagnostic doses of I131.in DxWBS prior to ablation therapy[19, 20].

The second factor seems to affect successful remnant ablation in our study is the presence of LN metastases, a significant difference in thyroid remnant ablation rate was found between patients with negative LN metastases (78.1%) and those with LN involvement (59.7 %) (P= 0.01). On multivariate analysis those who had LN metastases have 2.2 times risk not to enter into successful ablation following the first administered ablative dose. The lesser risk for affecting the response rate (OR 2.2 versus 4.6) compared to the administration of diagnostic dose may suggest that this factor has less pronounced effect on remnant ablation compared to the stunning effect of the diagnostic dose. The significant negative effect of lymph nodal involvement on ablation outcome was previously reported by Verkoijen et al [21]. Tamili et al,[22]. Verburg et al [13]., and Rosaria et al[23].

Babak et al., stated that the pathologic type of tumor, age, extent of post-surgical functioning remnant and type of thyroidectomy (total thyroidectomy vs. near total thyroidectomy) were not significant predictors of successful ablation[24]. Similarly we also found no association between age, gender, tumor histology of DTC and successful ablation.

In the current study, for those with malignancy in a background of Hashimoto thyroiditis, they have slightly higher rate of failure of complete ablation (37.8%) compared to those with non neoplastic thyroid tissue of colloid / multinodular goitre and normal thyroid tissue with failure of ablation in 33.3% and 27% respectively, yet the difference was statistically insignificant. (*P*=0.312). This is in contradiction to the only report published by Wagieh et al, 2011, who stated a significant difference between ablation outcome in those with non neoplastic thyroid tissue of autoimmune disorders compared to those with a background of colloid goiter or normal thyroid tissue, with significantly more failure of ablation in the former group. This can be explained by different patient population and possibly interference of other factors affecting ablation outcome[25].

In addition the added cost and patient inconvenience associated with performing a diagnostic scan where more visits to the nuclear medicine department are required as well as more delay in patient management.

In our study, the DxWBS did not significantly change the management of

patients as none of our 341 patients enrolled in this study were found to have negative post surgical WBS. Even after "total" thyroidectomy (according to the pathology report) remnants of thyroid tissue are almost always present, so the decision to change the management strategy through excluding the patients from RAI dose based on DxWBS has no practical impact in our study. In addition no patients from group 2 have negative post therapy whole body scan.

Our results agree with the results of Morris et al. (2001, 2003) who found that only 8 of 880 (0.1%) patients were eliminated from ^{131}I therapy for remnant ablation, yet, this was because of negative postsurgical DxWBS [18] [26].

There is also strong evidence that stunning does not only occur in the residual thyroid tissue affecting the ablative rate, but also occurs in the metastatic deposits thus greatly affect the response rate of metastases to the subsequently given therapy dose [27].

CONCLUSION:

We conclude that stunning is a real phenomenon that has the potential to impair the efficacy of ^{131}I ablation therapy. To a lesser extent this may also applicable to cervical lymph nodal involvement. On the other hand, other studied risk factors including age, gender, tumor histopathology and pathology of non neoplastic thyroid tissue have no impact on ablation outcome.

RECOMMENDATION:

We recommend to avoid thyroid stunning altogether, and to increase patient convenience, through administering ^{131}I ablation directly to the postoperative patients indicated for ablation guided by pathology report, operative data, neck U.S and non contrast CT chest without conducting a diagnostic scan. The diagnostic imaging should then be performed using the therapeutic dose.

REFERENCES:

1. Hoang, J.K., W.K. Lee, M. Lee et al. US Features of thyroid malignancy: pearls and pitfalls. Radiographics,; 27 (3): 847-60; discussion 61-5; 2007.

2. Pacini, F., M. Schlumberger, H. Dralle et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol,; 154 (6): 787-803; 2006.

3.Robbins, R.J. and M.J. Schlumberger. The evolving role of (131) I for the treatment of differentiated thyroid

carcinoma. J Nucl Med,; 46 Suppl 1: 28S-37S; 2005.

4. Pacini, F., M. Schlumberger, C. Harmer et al. Post-surgical use of radioiodine (131I) in patients with papillary and follicular thyroid cancer and the issue of remnant ablation: a consensus report. Eur J Endocrinol,; 153(5): 651-9; 2005.

5. Lassmann, M., M. Luster, H. Hanscheid et al. Impact of 131I diagnostic activities on the biokinetics of thyroid remnants. J Nucl Med,; 45(4): 619-25; 2004.

6. Lundh, C., M.M. Norden, M. Nilsson et al. Reduced iodide transport (stunning) and DNA synthesis in thyrocytes exposed to low absorbed doses from 131I in vitro. J Nucl Med,; 48 (3): 481-6; 2007.

7. Postgard, P., J. Himmelman, U. Lindencrona et al. Stunning of iodide transport by (131)I irradiation in cultured thyroid epithelial cells. J Nucl Med,; 43 (6): 828-34; 2002.

8. Park, H.-M. and S.K. Gerard, Stunning in Thyroid Cancer

A Comprehensive Guide to Clinical Management, L. Wartofsky and D. Nostrand, Editors., Humana Press Inc.: Totowa, NJ337-45; 2006.

9. Hilditch, T.E., M.F. Dempsey, A.A. Bolster et al. Self-stunning in thyroid ablation: evidence from comparative studies of diagnostic 131I and 123I. Eur J Nucl Med Mol Imaging,; 29(6): 783-82;002

10. Amdur, R. and E. Mazzaferri, Thyroid Stunning in Essentials of thyroid cancer management Cancer treatment and research, R.J. Amdur and E.L. Mazzaferri, Editors., Springer: New York55-9; 2005.

11. Park, H.M. Stunned thyroid after high-dose I-131 imaging. Clin Nucl Med,; **17**(6): 501-2; 1992.

12. Bal, C.S., A. Kumar, and G.S. Pant. Radioiodine dose for remnant ablation in differentiated thyroid carcinoma: a randomized clinical trial in 509 patients. J Clin Endocrinol Metab,; **89**(4): 1666-73; 2004.

13. Verburg, F.A., B. de Keizer, C.J. Lips et al. Prognostic significance of successful ablation with radioiodine of differentiated thyroid cancer patients. Eur J Endocrinol,; 152(1): 33-7; 2005.

14. Mazzaferri, E.L. and R.T. Kloos. Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab,; 86(4): 1447-63; 2001.

15. Koch, W., P. Knesewitsch, K. Tatsch et al. Stunning effects in radioiodine therapy of thyroid carcinoma: existence, clinical effects and ways out]. Nuklearmedizin,; 42(1): 10-4; 2003.

16. Huic, D., M. Medvedec, D. Dodig et al. Radioiodine uptake in thyroid cancer patients after diagnostic application of low-dose 131I. Nucl Med Commun,; 17(10): 839-42; 1996.

17. Kao, C.H. and T.C. Yen. Stunning effects after a diagnostic dose of iodine-131. Nuklearmedizin,; 37(1): 30-2; 1998.

18. Morris, L.F., A.D. Waxman, and G.D. Braunstein. The nonimpact of thyroid stunning: remnant ablation rates in 131I-scanned and nonscanned individuals. J Clin Endocrinol Metab,; 86 (8): 3507-11; 2001.

19. Bajen, M.T., S. Mane, A. Munoz et al. Effect of a diagnostic dose of 185 MBq 131I on postsurgical thyroid remnants. J Nucl Med,; 41(12): 2038-42; 2000.

20. Karam, M., A. Gianoukakis, P.J. Feustel et al. Influence of diagnostic and therapeutic doses on thyroid remnant ablation rates. Nucl Med Commun,; 24(5): 489-95; 2003.

21. Verkooijen, R.B., F.A. Verburg, J.W. van Isselt et al. The success rate of I-131 ablation in differentiated thyroid cancer: comparison of uptake-related and fixed-dose strategies. Eur J Endocrinol,; 159(3): 301-7; 2008.

22. Tamilia, M., N. Al-Kahtani, L. Rochon et al. Serum thyroglobulin predicts thyroid remnant ablation failure with 30 mCi iodine-131 treatment in patients with papillary thyroid carcinoma. Nucl Med Commun,; 32(3): 212-20; 2011.

23. Rosario, P.W., J.S. Reis, A.L. Barroso et al. Efficacy of low and high 131I doses for thyroid remnant ablation in patients with differentiated thyroid carcinoma based on post-operative cervical uptake. Nucl Med Commun,; 25(11): 1077-81; 2004.

24. Fallahi, B., D. Beiki, M. Eftekhari et al. Predicting factors of successful post-surgical remnant ablation in radioiodinetreated patients with differentiated thyroid carcinoma. Iran J Nucl Med,; 18: 62; 2010.

25. Wagieh, S.M., S.M. El-Refaei, S.S. Salem et al. Impact of histopathology of non-neoplastic thyroid tissue on ablation outcome in patients with papillary thyroid cancer. Nucl Med Commun,; 32 (7): 597-604; 2011.

26. Morris, L.F., A.D. Waxman, and G.D. Braunstein. Thyroid stunning. Thyroid,; 13(4): 333-40; 2003.

27. Wu, H.S., H.H. Hseu, W.Y. Lin et al. Decreased uptake after fractionated ablative doses of iodine-131. Eur J Nucl Med Mol Imaging,; 32(2): 167-73; 2005.