Original Article

Rate of thyroglossal duct remnant visualization after total thyroidectomy for differentiated thyroid carcinoma and its impact on clinical outcome of radioactive iodine (I-131) ablation

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ABSTRACT

Objectives: The rate and impact of thyroglossal duct remnant (TGDR) visualization in patients with hypothyroidism after total thyroidectomy for differentiated thyroid carcinoma (DTC) have not yet been fully determined. The aim of this study was to assess the rate of TGDR visualization in post total thyroidectomy whole body scan (WBS) for DTC and to evaluate its impact on the outcome of I-131 ablation. **Methods:** A total of 60 consecutive DTC patients (51 papillary thyroid Ca., and 9 Follicular thyroid Ca.), underwent total thyroidectomy, followed by WBS (using I-131 in 28 patients and I-123 in 32 patients), neck ultrasound (US), thyroglobulin (Tg) and Tg anti-bodies (TgAb) assay after 40 days and subsequent I-131 ablation. At 6 months later follow-up I-131 WBS, neck U/S, Tg and TgAb were performed following suspension of L-thyroxine for 1-month (thyroid stimulating hormone [TSH] >30 μIU/ml) in 53 patients and following recombinant human TSH stimulation in seven patients. **Results:** Of the studied 60 patients, 19/60 (31.7%) had a linear or focal radioactivity at the superior midline of the neck, suggesting TGDR (Group 1), and 41/60 (68.3%) had no uptake to suggest TGDR (Group 2). No significant difference regarding age, gender and histopathology between both groups. Neck US showed no evidence of thyroid tissue in the superior midline of the neck in both groups, and only a small or no residual thyroid tissue in patients of Group 1. There was a significant successful I-131 ablation rate among patients of group 1 compared to group 2 (79% in Group 1 vs. 41.5% in Group 2) ($P = 0.007$). **Conclusions:** Thyroglossal duct remnant visualization on WBS of hypothyroid subjects after total thyroidectomy suggests presence of only a small or no residual functioning thyroid tissue at the thyroid bed and can predict a good response to I-131 ablation.

Keywords: Ablation, differentiated thyroid carcinoma, thyroglossal duct remnant

INTRODUCTION

Ectopic thyroid tissue (ETT) is a rare developmental abnormality involving aberrant embryogenesis of the thyroid gland during its passage from the floor of the primitive foregut to its final pretracheal position.[1-3] Its true prevalence in the general population is hard to determine because most patients with an ETT are asymptomatic.[4] In 70–90% of cases, it is the only thyroid tissue present.[1]

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The clinician must distinguish between ETT and metastatic deposits emerging from an orthotopic gland, as well as other benign or malignant masses.[1] Scintigraphy, using Tc-99 m, I-131, or I-123, is the most important diagnostic tool to detect ETT and shows the absence or presence of thyroid in its normal location. Thyroid scan can also unmask additional sites of thyroid tissue. It is both sensitive and specific for differentiation of an ETT from other causes of midline neck masses,[1,5-7] obviating the need for a biopsy.[8,9]

Despite several previous case reports of unexpected ETT in I-131 scans of patients with a history of differentiated thyroid carcinoma (DTC),[10,11] only two studies published on its prevalence in patients with DTC with a large discrepancy in the results.[4,12] The current study was undertaken to assess the rate of thyroglossal duct remnant (TGDR) visualization in

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whole body scan (WBS) for hypothyroid DTC patients after total thyroidectomy and to evaluate its impact on the outcome of I-131 ablation.

MATERIALS AND METHODS

Patients

Following approval by the institutional ethics committee, 60 consecutive patients (age 36.8 ± 8.5 years, female:male = 40:20) with DTC, who underwent postthyroidectomy WBS, subsequent I-131 ablation, and follow-up WBS from January 2010 to December 2012, were retrospectively enrolled in this study. Fifty-one patients were diagnosed with papillary thyroid cancer, and nine with follicular thyroid cancer.

Initial treatment was total or near total thyroidectomy. Postoperatively, all patients underwent WBS, neck ultrasound (US), serum thyroglobulin (Tg) and Tg anti-bodies (TgAb) assay after 40 days without thyroid hormone replacement to induce a hypothyroid state. Physical examinations revealed no palpable midline neck mass in any of the subjects. The patients followed a low-iodine diet for 10–15 days before the WBS. Subsequently, I-131 ablation dose was administered to all patients to ablate normal thyroid and residual disease and to treat metastatic lesions, followed by a postablation WBS.

Radioiodine whole body scan and remnant ablation

A WBS, and static views of the head and neck were performed before radioiodine ablation in all subjects to detect any remnant thyroid tissue or metastatic lesions. In 28 patients, scans were acquired using a high energy parallel hole collimator fitted to the Forte dual head gamma camera (Phillips Medical Systems) set at 364 keV with a 20% energy window, 48 h after an oral administration of 74–185 MBq (2–5 mCi) of I-131. In 32 patients, scans were acquired using a low energy parallel hole collimator fitted to the Forte dual head gamma camera set at 159 keV with a 20% energy window, 24 h after an oral administration of 37–111 MBq (1–3 mCi) of I-123.

Patients received an ablation radioiodine doses in the range of 1.11–6.4 GBq (30–173 mCi) depending on the results of postthyroidectomy WBS, Neck US and histologic findings, followed by thyroid stimulating hormone (TSH)-suppressive doses of L-thyroxine. Postablation WBS and static views of the anterior neck were acquired within 5 days after the radioiodine ablation.

A focal or linear uptake at the anterior midline of the neck above the thyroid bed in a postthyroidectomy WBS was considered scintigraphic evidence of functioning thyroid tissue in TGDR, especially when the location, and shape remained unchanged in postablation WBS. Patients exhibiting the presence of TGDR were classified according to the location (lingual or sublingual vs. prelaryngeal) and shape (focal vs. linear activity) of the abnormal midline neck uptake. The location in the scintigraphy was defined as follows: Lingual or sublinguall – increased uptake from the oral cavity to the submandibular gland; prelaryngeal – increased uptake from below the submandibular gland to the thyroid bed.

Thyroid stimulating hormone, thyroglobulin, and thyroglobulinanti-bodies measurement

The TSH, Tg, and TgAb were measured before oral intake of the radioiodine and compared between the patients with positive and negative findings of TGDR. The Tg level was considered as not accurately measured in the presence of TgAb.

Neck ultrasonography

Ultrasound evaluation of the thyroid bed and both central and lateral neck compartments was performed on the day of administration of the diagnostic dose of radioiodine using a 7.5 MHz linear-array transducer (Accuvix A30 US System; Samsung Medison Healthcare). Lymph node sizes were measured along the longest diameter on transverse scans. Suspicion of malignant lymph node was based on the following criteria: Hyperechoic punctuations, cystic appearance, hypervascularization, round shape node without hyperechoic hilum, and a short axis >7 mm.[13]

Follow-up and evaluation of successful ablation

Six months after radioiodine ablation, follow-up including clinical assessment, I-131 WBS, neck U/S, Tg and TgAb assay were performed following suspension of L-thyroxine for 1-month (TSH >30 μIU/ml) in 53 patients and following recombinant human TSH stimulation in seven patients. Stimulated Tg <1 ng/mL, negative WBS, and normal US were considered as the criteria for successful ablation.

Statistical analysis

Quantitative data were expressed as mean ± standard deviation, and qualitative data were expressed in percentage. Statistical analysis of the categorical variables was conducted using a Chi-square test or Fisher's exact test. Comparisons between continuous variables were performed with an independent *t*-test. A $P < 0.05$ was considered as statistically significant. All the analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Among the 60 patients with DTC, 19 (31.7%) showed a focal or linear area of abnormal radiotracer activity at the anterior midline of the neck, suggesting the presence of functioning thyroid tissue in TGDR. The postthyroidectomy and postablation WBS were concordant in all cases of abnormal uptake at the anterior midline of the neck, although the delineation of TGDR activity in postablation WBS can be difficult due to prominent photon scattering in most cases [Figures 1 and 2]. Clinical, histological, scintigraphic characteristics and factors of prognostic relevance are summarized in Table 1. There was no significant difference regarding age, gender and histopathology between DTC patients with and without ETT in TGDR.

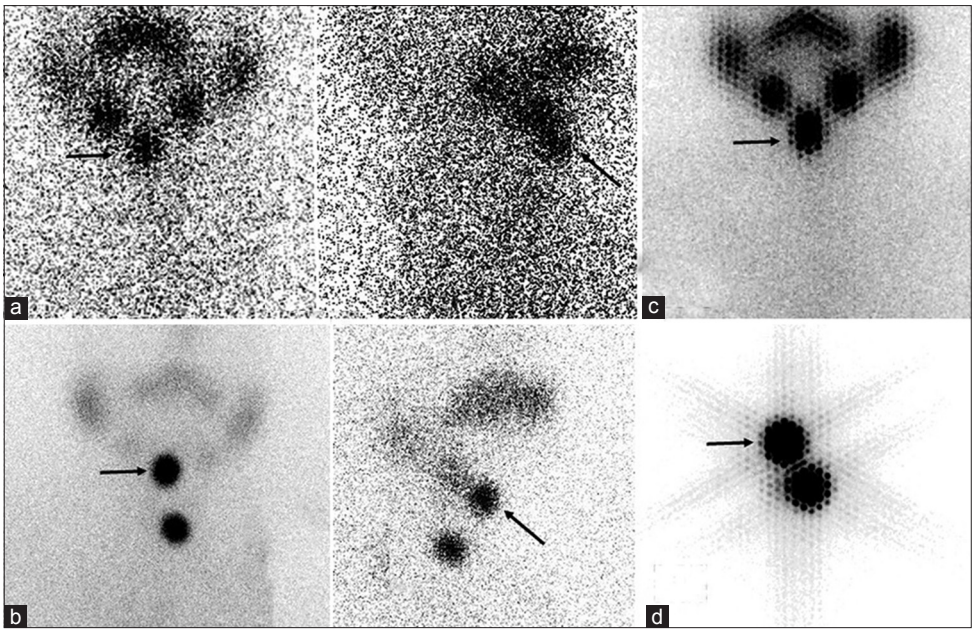

Figure 1: Anterior and right lateral neck images of (a) I-131 whole body scan (WBS) and (b) I-123 WBS showed abnormal radiotracer uptake (arrow) at the anterior midline of the neck, suggesting the presence of functioning thyroid tissue in thyroglossal duct remnant (TGDR) as well as another remnant uptake in the thyroid bed in the second patient.(c and d) Anterior neck images of I-131 WBS after ablation therapy showed tracer uptake in the corresponding areas in both patients, confirming the presence of TGDR

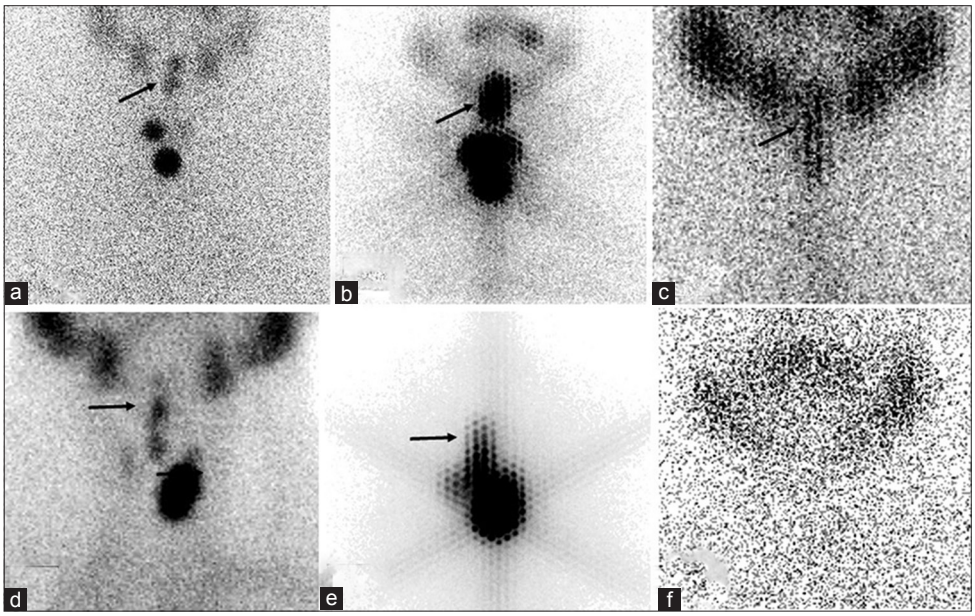

Figure 2: (a and d) Anterior neck images of I-123 whole body scan (WBS) showed abnormal radiotracer uptake (arrow) at the anterior midline of the neck, suggesting the presence of functioning thyroid tissue in thyroglossal duct remnant (TGDR) as well as another remnant uptake in the thyroid bed.(b and e) Anterior neck images of I-131 WBS after ablation therapy showed tracer uptake in the corresponding areas in both patients, confirming the presence of TGDR. 6 months later (c) anterior neck images of I-131 diagnostic whole body scan showed residual uptake at the area of TGDR in the first patient, and (f) no evidence of functioning thyroid tissue in the neck of the second patient indicating successful ablation

Twenty percent (4/20) of the male patients and 37.5% (15/40) of the female patients were found to have abnormal distinct uptake at the anterior midline of the neck suggesting functioning ETT in TGDR in postthyroidectomy WBS. There were 18 cases (18/51, 35.3%) of papillary thyroid cancer, and one case (1/9, 11%) of follicular thyroid cancer. 40.6% (13/32) of the patients studied with I-123 WBS were found to have positive findings suggesting functioning ETT in TGDR, compared to 21.4% (6/28) of the patients studied with I-131 WBS ($P = 0.09$).

All subjects were in a hypothyroid state with serum levels of TSH over 30 μIU/mL (97.54 ± 60.84 μIU/mL) during the scintigraphic evaluation. The TSH levels were 97.88 ± 55.23 μIU/mL in the patients with a positive finding of TGDR and 97.30 ± 65.67

Table 1: Comparison of clinical, histopathological and scintigraphic characteristics among TGDR positive and TGDR negative DTC patients

	DTC (%)	
	TGDR positive	TGDR negative
Number	19 (31.67)	41 (68.33)
Age	35.58±10.01	37.34±7.74
Sex		
Male	4 (20)	16 (80)
Female	15 (37.5)	25 (62.5)
Histology		
Papillary	18 (35.3)	33 (64.7)
Follicular	1 (11)	8 (89)
Maximum tumor size, cm	2.06±1.57	2.53±1.55
Thyroiditis on pathology	7/19 (37)	12/41 (29)
Multiplicity	4/19 (21)	19/41 (46)
Bilaterality	3/19 (16)	11/41 (27)
Extrathyroidal extension	2/19 (11)	7/41 (17)
Lymphatic invasion	2/19 (11)	2/41 (5)
Lymph node metastasis	3/19 (16)	11/41 (27)
Shape and location of TGDR		
Focal lingual or sublingual	18 (95)	
Linear prelaryngeal	1 (5)	

DTC: Differentiated thyroid carcinoma, TGDR: Thyroglossal duct remnant

μIU/mL in the patients with a negative finding (P = 0.98), and the Tg levels were 5.42 ± 8.5 ng/mL and 9.34 ± 12.2 ng/mL (P = 0.24), respectively.

As regards the shape and the location of abnormal midline neck uptake, 18 patients (18/19, 95%) exhibited a focal lingual or sublingual uptake, and one patient (1/19, 5%) exhibited a linear, prelaryngeal uptake.

Neck US showed no evidence of thyroid tissue or enlarged Lymph nodes in the superior midline of the neck in both groups. In addition, US revealed no evidence of residual thyroid tissue at the thyroid bed in (6/19, 32%) and only a small residual thyroid tissue (0.64 cm ± 0.61 cm) in (13/19, 68%) DTC patients with ETT in TGDR, compared to no residual thyroid tissue in (6/41, 15%) and a larger residual thyroid tissue at the thyroid bed (1.2 cm ± 1.9 cm) in (35/41, 85%) DTC patients without ETT in TGDR (P = 0.30).

The average ablation dose of radioiodine was 4.53 ± 1.18 GBq (122.48 ± 31.82 mCi) in the patients with ETT in TGDR and 3.85 ± 1.15 GBq (104.06 ± 31.02 mCi) in the patients without ETT in TGDR (P = 0.039). The success rate of remnant radioiodine ablation was significantly higher among patients with ETT in TGDR (15/19, 79%) compared to patients without ETT in TGDR (17/41, 41.5%) (P = 0.007). The stimulated serum Tg levels measured 6 months after ablation were also significantly different between the two groups (1.45 ± 2.63 ng/mL vs. 6.24 ± 13.27 ng/mL, P = 0.007). The percentage of negative I-131 DWBS 6 months after ablation was 79.0% (15/19) for the patients with ETT in TGDR and 61% (25/41) for the patients without ETT in TGDR (P = 0.24).

DISCUSSION

Ectopic thyroid tissue has been reported as a rare developmental abnormality.[1] This anomaly is due to abnormal embryologic development and/or migration of the gland. A somatic mutation of the transcription factor responsible for thyroid migration could explain these findings. Thus, ETT may be found anywhere along the line of the obliterated thyroglossal duct, usually from the tongue to the diaphragm.[14,15] The prevalence of ETT would appear to differ considerably between histologic and clinical reports, which may result from the facts that most cases are partial ectopies and asymptomatic,[16] thereby leading to under-estimation of its prevalence in clinical reports.[14] Its prevalence is about 1/100 000–300 000 people, rising to 1/4000–8000 patients with thyroid disease.[1-3] However, in autopsy studies, the prevalence ranges from 10 to 41.3%.[17,18] ETT is most common in females, especially in populations of Asian origin.[19,20] The thyroid gland during its development and descent, lies in anatomical juxtaposition with the heart. The mechanical pull of the descending heart on the thyroid gland may lead to its positional anomalies.[14,21] TGDR may persist as isolated nests of functioning thyroid tissue. The majority of ETTs are in the cervical midline area extending from lingual, sublingual, subhyoid, laryngeal, to the submandibular regions. Lingual ectopic thyroid is the most frequent ETT (90%).[14,22] Extralingual ETT is commonly located in the anterior cervical area along the path of the thyroglossal duct.[14]

The rate of visualization of ETT at TGDR in patients with hypothyroidism after total thyroidectomy for DTC, have not yet been fully determined. In the present study, a focal or linear area of abnormal radiotracer activity at the anterior midline of the neck, suggesting the presence of functioning thyroid tissue in TGDR was found in (31.7%) of WBS of patients with hypothyroidism following a thyroidectomy for DTC. Our results are consistent with those reported by Lee *et al*.[4] who found a remarkably high prevalence (up to 33.6%) of functioning ETT, presumably in TGDR, in scintigraphy of patients with hypothyroidism following a thyroidectomy for DTC. None of the subjects had any clinical symptoms of a midline neck mass, such as dysphagia, dyspnea, or a feeling of a foreign body in the throat. Therefore, the high prevalence of functioning ETT in TGDR is more of a reflection of the asymptomatic general population, making it similar to a histologic report.[18] In contrast with our findings, Zanotti-Fregonara *et al*.[12] studied 548 consecutive patients who underwent a diagnostic WBS, as part of the follow-up for a DTC. Every patient had been previously treated with a total thyroidectomy and had received 3.7 GBq (100 mCi) of I-131 for remnant ablation. A focus of uptake located between the 2 submandibular salivary glands, suggestive of ETT in the tongue or in the upper part of the thyroglossal duct, was found in 5 of the 548 patients (0.9%) and in only one of these patients was the uptake visible at the time of postsurgery thyroid remnant ablation scan. The difference between this study and our study results may be explained based

on that, since ectopic tissue is usually hypofunctional, it would remain scintigraphically quiescent while the normal thyroid or large volume of residual functioning thyroid tissues is *in situ*, and the exposure of hypofunctioning tissues to elevated TSH levels facilitates their accumulation of I-131.[11] This explanation is further supported by the results of last study that showed the uptake suggestive of ETT, is visible at the time of postsurgery thyroid remnant ablation scan in only one of five patients who had uptake suggestive of ETT in follow up diagnostic WBS.

In the present study, ETT in TGDR were found in lingual and sublingual position in 95% (18/19) of patients with positive TGDR after a thyroidectomy. These small ETTs in TGDR seldom create a clinical symptom and are rarely detected by physical examination and conventional anatomic imaging modalities and thyroid scintigraphy in the presence of a normal functioning thyroid gland.[4] Sud and Gross[11] reported two cases of scintigraphically demonstrated ETT following a thyroidectomy for DTC. Another recent study reported incidental focal uptake in oropharynx due to lingual thyroid on diagnostic I-131 WBS after total thyroidectomy.[23]

In the present study, a higher proportion (40.6%) of the patients studied with I-123 WBS were found to have positive findings suggesting functioning ETT in TGDR, compared to 21.4% of the patients studied with I-131 WBS. Radionuclide imaging is considered the definitive diagnostic test method for detecting ETT. I-131 possesses certain properties which makes it a unique radiopharmaceutical for the management of patients with DTC. It emits B-particles, is readily available, and has a low cost and a long half-life (8.02 days). It is the main agent for the ablation of residual thyroid tissue and the treatment of recurrent or metastatic DTC.[24,25] However, planar I-131 imaging has traditionally suffered from low resolution, and a paucity of anatomic information along with a long list of physiologic variants makes image interpretation challenging.[26] Therefore, it is assumed that the reason why functioning ETT in TGDR has been underestimated in patients with DTC is mainly due to the poor image quality of an I-131 scan.[4] In contrast, I-123 is considered an optimal agent for diagnostic purposes before therapy with I-131. It is a pure gamma-emitter with no stunning effect on functioning thyroid cells and has a gamma-energy of 159 keV, which is optimal for conventional scintillation cameras. It also delivers a lower radiation dose to patients owing to its relatively short half-life (13.3 h) and lacks B-particle emission.[27-30] Numerous studies indicate that I-123 is comparable to high-dose I-131 posttreatment imaging in the detection of thyroid remnants after thyroidectomy,[27,28,31] and offers excellent image quality as a diagnostic agent.[32] Wong *et al*.[26] reported that I-131 single photon emission computed tomography/computed tomography (SPECT/CT) findings led to reclassification of 10 foci in 53 patients (19%) as TGDR from thyroid bed remnant. I-131 SPECT/CT has improved localization and characterization of foci of radioiodine activity outside the expected biodistribution. Thus, based on the current data, it is important that the tracer uptake by ETT in TGDR should not be confused with metastatic foci in a WBS of hypothyroid patients with a history of DTC, especially in patients with no palpable midline neck mass and negative anatomical imaging modalities.

Although well localized uptake of iodine indicates the presence of thyroid tissue, making a biopsy unnecessary,[8,9] the differentiation between ETT and other causes of tracer uptake, such as metastatic lymph nodes, salivary, esophageal activity, and unresected pyramidal lobe can be difficult in planner images.[4] The use of multiple maneuvers including swallowing water, separate-day imaging, oblique and lateral imaging, correlating with other imaging techniques, is essential for accurate diagnosis.[26] In the current study physical examinations revealed no palpable midline neck mass in any of the subjects, and postoperative US revealed no abnormally enlarged lymph nodes in the central compartment of the anterior neck. Esophageal activity can be shown as midline neck uptake in a scintigraphy. However, the midline neck uptake in the present cases did not change its location or shape over the course of time and both postthyroidectomy and postablation WBS showed a complete concordance in all cases. Furthermore, the midline neck uptake was located in the anterior aspect of the neck, which was evident in the lateral images, whereas the salivary and esophageal activity was posterior. Thus, in the present cases, there was little chance of mistaking ETT for esophageal activity. Unresected pyramidal lobe can also mimic ETT in TGDR. However, during a total or near-total thyroidectomy for DTC, all grossly visible thyroid gland including pyramidal lobe was recognized and removed, postoperative US showed no residual thyroid tissue or minimal residual thyroid tissues at the thyroid bed, and most of the present cases showed focal distinct uptake at the anterior, superior midline of the neck suggesting ETT at lingual and sublingual position.

Basaria *et al*.[10] explained why a lingual thyroid is so resistant to ablation, based on the phenomenon of a rapid iodine turnover with a shorter biological half-life in lingual thyroid compared to the normal thyroid tissue.[33] In the current study, however, there was a significant higher successful I-131 ablation rate among patients with abnormal midline neck uptake suggesting ETT in TGDR compared to patients without ETT in TGDR. Postoperative neck US showed no or minimal residual thyroid tissues at the thyroid bed in patients with ETT in TGDR. Thus, it can be speculated that the residual tissue volume could be another important factor affecting the ablation rate, as well as the iodide turnover.

The distinguishing feature of this study was the use of I-123 for diagnostic WBS in more than half of patients allowing comparison with I-131 WBS for the evaluation of presence of ETTs in TGDR during hypothyroidism after thyroidectomy.

Study limitations

In the current study, no biopsies were performed, and histological evidence of ETT lacks on all subjects, which could be a limitation. However, none of the present cases ever had clinical symptoms

of a midline neck mass. Physical examination and neck US did not reveal any definite midline neck mass requiring the performance of a biopsy.

None of the present cases had SPECT/CT study to improve localization and characterization of foci of radioiodine activity in planner I-131 study.

CONCLUSIONS

Visualization of ETT in TGDR on WBS of hypothyroid subjects after total thyroidectomy suggests presence of only a small or no residual functioning thyroid tissue at the thyroid bed and can predict a good response to I-131 ablation. Therefore, care should be taken not to confuse the tracer uptake by TGDR with metastatic foci in postthyroidectomy WBS of patients with hypothyroidism after a thyroidectomy for DTC.

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