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Relationship Between Actual I-131 Retention and the Success Rate of I-131 Ablation in Differentiated Thyroid Carcinoma

Sayed, M.H.[1, 2], Aljuneidi, B.M.[3], Yasir, M.A.[4]

[1]Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Assiut University, Assiut, Egypt; [2]Department of Nuclear Medicine, Almana General Hospital, Dammam. [3]Department of Radiology and Medical Imaging, Almana General Hospital, Khobar, [4]Department of Endocrinology, Almana General Hospital, Khobar, Saudi Arabia.

ABSTRACT:

Objectives: I-123 is considered an ideal isotope for diagnostic studies. A significant advantage of I-123 over I-131 is that, the radiation dose delivered is about 100-fold less. Consequently, potential ‘‘stunning’’ because of the dosimetry procedure prior to treatment would be less concerning. However, its relatively short half-life makes it impractical for a prolonged bio kinetic study. The aim of the current study was to assess the relationship between actual I-131 retention and the success rate of I-131 ablation in patients with differentiated thyroid carcinoma (DTC) following I-123 whole body scan (WBS).

Patients and methods: 23 consecutive patients with newly diagnosed DTC (21 papillary, and 2 Follicular), underwent total or near total thyroidectomy, followed by I-123 WBS, and subsequent I-131 ablation were enrolled in current study. The whole body external exposure rate from the patient at 1 meter was measured immediately after ingestion of I-131, after 24 and 48 hours, using a calibrated Victoreen 451P ionization chamber survey meter (Fluke Biomedical, USA). The retained activity at 48h and the whole body effective half-life for each patient were then calculated. Patients were classified according to their follow up data after 6 months into two groups; those who have successful ablation (Negative WBS and an undetectable serum thyroglobulin level in

the absence of antithyroglobulin antibodies), and those who need reablation (Positive WBS and/ or elevated serum Thyroglobulin). **Results:** Of the 23 patients studied, 15 were considered to have successful ablation and 8 still need re-ablation. No significant difference regarding age, gender, histopathology, and activity of I-131 ablation dose between both groups. The retained I-131 activity at 48 hours was 13.50±3.87% of the administered dose, and the effective half-life was 16.37±2.43 hours for patients who have successful ablation compared to 7.79±3.28% (p =0.002), and 12.64±2.27 hours (p = 0.002) respectively for patients who need re-ablation.

Conclusions: We found a significantly higher retained I-131 activity at 48 hours and longer effective half-life among patients successfully ablated compared to those who need re-ablation, and recommend dosimetry adjusted I-131 ablation dose whenever feasible accordingly

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Keywords: Differentiated thyroid cancer; ^{131}I; Total/near-total thyroidectomy; Retained activity; Effective half-life.

Corresponding Authors: Sayed M.H. **E-mail:** mkeshk2010@gmail.com.

INTRODUCTION:

The role of radioactive Iodine-131 (I-131) as an adjuvant therapy following surgery in the management of patients with differentiated thyroid cancer (DTC) is well established [(1-7)]. Radioactive Iodine ablation has five proposed objectives. First, to increase the sensitivity of detecting metastatic disease on subsequent follow-up I-131 diagnostic whole-body scans (WBS). Second, to facilitate the interpretation of follow-up serum thyroglobulin (TG) levels. Third, to obtain post-ablation WBSs, which have higher sensitivity than diagnostic scans? Fourth, to decrease the recurrence rate; and finally, to increase survival [(8-11)]. Several approaches have been proposed for the selection of the prescribed ablative I-131 activity and are currently being used [(8)].Usually, patients are treated with standard activities selected empirically, relying on practical experience rather than with an optimized treatment activity based on prior measurement of the patient's

Individual bio kinetics. Such an empirical activity poses a risk of either under-dosing the patient or of exceeding common safety limits [12-13].

According to the current Society of Nuclear Medicine (SNM) and European Association of Nuclear Medicine (EANM) guidelines, there is a broad range of fixed activities of I-131 recommended to be administered [14-15]. Although many facilities use a fixed-standard empiric prescribed activity for all patients, other facilities alter the empiric prescribed activity based on the patient's level of risk, uptake in the thyroid bed, number of foci of uptake in the thyroid bed, patient weight, body surface area, the patient's fear regarding radiation, and regulations in terms of hospitalization. However, there are no standardized rules by which these adjustments in the empiric prescribed activity can be made quantitatively and objectively [8]. Fractionated empiric activities have also been prescribed [16-18]. However, multiple smaller doses may have lower therapeutic benefit than the same total dose given at one time [19] and small non-lethal doses may reduce the effectiveness of subsequent doses [20].

The prescribed activity of radioiodine ablation may also be determined for each individual patient based on lesional dosimetry [21], whole-body dosimetry [22], or both. There are many factors that impact the results of I-131ablation including extent of surgery, percent uptake of radioiodine in residual thyroid tissue, volume of residual thyroid tissue, effective half-life of I-131 in the residual thyroid tissue, geometrical shape of residual thyroid tissue, patient compliance with low-iodine diet, level of TSH, previous diagnostic activity of I-131 "Stunning" [8]. It has been reported that the success rate of I-131 ablation is severely reduced after a dosimetry study with diagnostic activity of 40 MBq I-131 [23]. Diagnostic activity of I-123 has been used as an alternative to I-131, and no known stunning has been reported (24). However, its relatively short half-life makes it impractical for a prolonged bio kinetic study [25].

The aim of the current study was to assess the relationship between actual I-131 retention and the success rate of I-131 ablation in differentiated thyroid carcinoma (DTC) following post-thyroidectomy I-123 WBS.

MATERIAL and METHODS:

Patients: We retrospectively reviewed 42 DTC patients who underwent post-thyroidectomy I-123 diagnostic WBS followed by an ablative dose of I-131

And had their follow up after 6 months at our institution from January 2011 through December 2013. Patients were included if the measurements of whole body external exposure rate from the patients and follow-up data were documented in their medical records. An informed consent was waived for this retrospective analysis by our institutional ethics committee.

Methods: The whole body external exposure rate from the patient at one meter was measured immediately after ingestion of I-131, after 24 and 48 hours, using a calibrated Victoreen 451P ionization chamber survey meter (Fluke Biomedical, USA). The retained activity at 48 hours and the whole body effective half-life were then calculated.

Calculation of retained activity: The retained activity at 48 h was calculated based on the external exposure rate measurement using the following formula: A48 = A0 EWB48 / EWB0 (1)

Where A48 is the retained activity at 48 h; A0 is the administered activity; EWB48, EWB0 are the whole body external exposure rates at one meter from the patient 48 h and immediately after ingestion of the 131I activity respectively.

Calculation of the whole body effective half-life of I-131The whole body effective half-life was then calculated using the following formula: (2). Where A (t) is the whole body retained activity at t days after administration as measured in equation 1 (in MBq); A0 is the administered activity (in MBq), t is the post administration time (in days); Teff is the whole body effective half-life (in days). Then we convert the result into hours by multiplying it by 24.

After surgical treatment, each patient was stratified using the American Joint Cancer Committee/Union International Centre le Cancer (AJCC/UICC) staging system and the American Thyroid Association (ATA) system.

All data obtained after post-thyroidectomy I-123 diagnostic WBS and stimulated TG was used for risk stratification of patients.

The patients were classified according to their follow up data after 6 months into two groups; those who have successful ablation (Negative WBS and an undetectable TSH-stimulated serum TG level in the absence of anti-TG antibodies), and those who need reablation (Positive WBS and/ or elevated serum TG).

Statistics: All data were analyzed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). 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.

RESULTS:

A total of 23 consecutive patients, including 15 female and 8 male with newly diagnosed DTC were included in current study. The mean age of patients was 39.1 ± 8.8 years (range, 19 to 54 years). Twenty-one patients were diagnosed with papillary thyroid cancer, and two with follicular thyroid cancer. Initial treatment was total or near total thyroidectomy. All patients followed a low iodine diet for 10-15 days prior to WBS. The mean TSH level prior to post-thyroidectomy I-123 WBS was 82.6 ± 46.7 μIU/mL, and the mean diagnostic activity of I-123 administered was 1.75 ± 0.73 mCi. Serum TG level assayed on the day of I-123 administration was 5.96 ± 7.16 ng/ mL. In the present study, the mean amount of I-131 administered was 128.6 ± 27.9 mCi. Among the 23 studied patients with DTC, 15 (65.2%) showed successful ablation based on their follow-up after 6 months (Negative WBS and an undetectable serum TG level in the absence of anti-TG antibodies) Demographic, histopathology and laboratory findings of the patients are summarized in ***table (1).*** No significant differences in terms of age, gender, histopathology, laboratory findings, and activity of I-131 ablation dose were detected between subjects with successful ablation and those with incomplete ablation. Risk stratification using AJCC/UICC staging system and the ATA system, and post-thyroidectomy I-123 WBS findings are summarized in ***table (2).***

Table (1): Comparison of demographic, histopathology and laboratory findings among DTC patients who had successful ablation and those who had incomplete ablation.

	Successful ablation Group	Incomplete ablation Group
Number	15 (65.2%)	8 (34.8%)
Age (years)	38 ± 9.7	41.3 ± 7.0
Gender		
Female	12(80%)	3 (37.5%)
Male	3 (20%)	5 (62.5%)
Histology		
Papillary	14 (93.3%)	7 (87.5%)
Follicular	1 (6.7%)	1 (12.5%)
Maximum tumor size, (cm)	1.7 ± 0.7	2.2 ±1.7
Thyroiditis on pathology	6/15 (40%)	2/8 (25%)
Multiplicity	6/15 (40%)	4/8 (50%)
Bilaterally	6/15 (40%)	4/8 (50%)
Extra thyroidal extension	3/15 (20%)	1/8 (12.5%)
Lymphatic invasion	1/15 (6.7%)	1/8 (12.5%)
Lymph node metastasis	4/15 (26.7%)	3/8 (37.5%)
TSH (µIU/mL)	78.2 ± 48.7	90.2 ± 45.7
Pre-ablative serum TG (ng/ mL)	4.7 ± 4.7	7.9 ± 10.0
I-131 therapeutic activity (mCi)	130.9 ± 30.4	124.4 ± 23.9
Follow-up TSH (µIU/mL)	101.2 ± 47.9	162.2 ± 67.4
Follow-up serum TG (ng/ mL)	0.8 ± 0.1	15.4 ± 25.3 (p = 0.033)

Table (2): Comparison of risk stratification and I-123 whole body scan (WBS) findings among DTC patients who had successful ablation and those who had incomplete ablation.

	Successful ablation Group (n = 15)	**Incomplete ablation Group (n = 8)**	**P value**
American Thyroid Risk Stratification Association (ATA)			
Low	9	4	0.372
Intermediate	6	3	
High	0	1	
Post-thyroidectomy I-123 WBS findings			
Small residual at the thyroid bed	12	6	0.297
Large residual at the thyroid bed	1	2	
Small residual at the thyroid bed and extra-thyroidal neck uptake	2	0	

DTC, differentiated thyroid carcinoma; ATA, American Thyroid Association

No significant. Differences in terms of risk stratification and I-123 WBS findings were detected between subjects with successful ablation and those with incomplete ablation. DTC, differentiated thyroid carcinoma; TG, thyroglobulin; TSH, thyroid stimulating hormone.

The retained I-131 activity at 48 hours was 13.50±3.87% of the administered dose, and the effective half-life was 16.37±2.43 hours for patients who have successful ablation compared to 7.79±3.28% (p = 002), and 12.64±2.27 hours (p = 002) respectively for patients who need re-ablation ***(Figures 1 and 2)***.

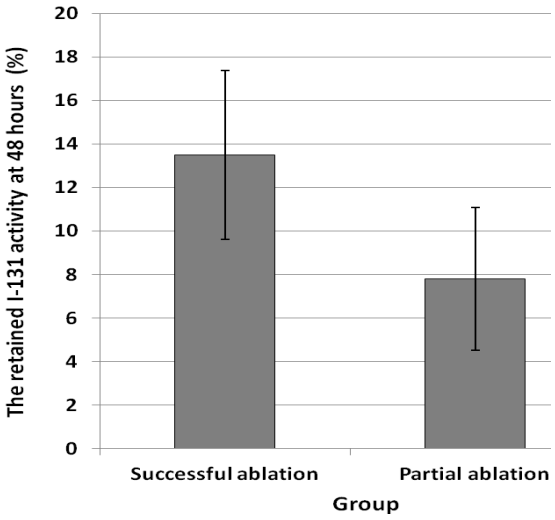

Figure 1: Comparison of the retained I-131 activity at 48 hours (mean ± standard deviation) between patients who have successful ablation and patients who need re-ablation.

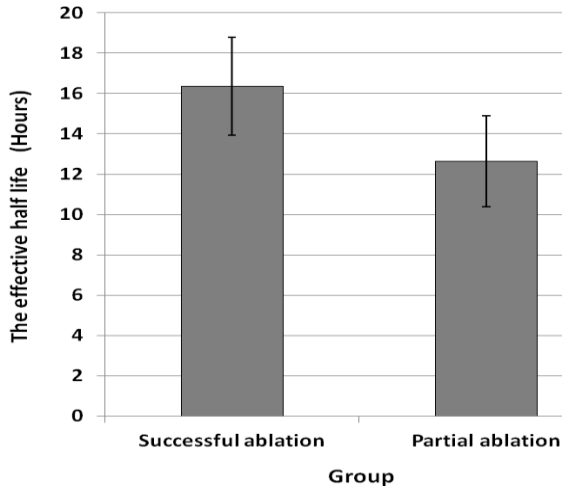

Figure 2: Comparison of the effective half-life (mean ± standard deviation) between patients who have successful ablation and patients who need re-ablation.

The effect of gender on the whole body retained I-131 activity at 48 hours is shown in ***Table 3*** and the effect of gender on the I-131 effective half-life is shown in ***Table 4***.

There was no significant difference in either the whole body retained I-131 activity at 48 hours or the I-131 effective half-life between male and female patients with DTC.

Table (3): The effect of gender on the whole body retained I-131 activity at 48 hours.

	Whole body retained activity at 48 hrs (mean ± SD)		P value
Gender	**Female**	**Male**	
Successful ablation Group	13.94 ±3.97	11.53 ±3.39	0.35
Incomplete ablation group	5.5 ± 1.87	9.12 ± 3.34	0.142

SD, standard deviation

Table (4): The effect of gender on the I-131 effective half life

	Effective half-life (mean ± SD)		P value
Gender	**Female**	**Male**	
Successful ablation Group	16.70 ±2.43	15.06 ±2.36	0.313
Incomplete ablation group	11.04 ± 1.41	13.61 ± 2.21	0.126

SD, standard deviation

DISCUSSION:

Radioactive iodine (I-131) therapy is a well-known and effective procedure in the treatment of patients with DTC [(1 – 7)]. Successful I-131 therapy depends on the therapeutic activity administered and retention of radioiodine in the target tissue. Until now there is no consensus on the activity of I-131 to be administered. Also iodine retention in the target tissue depends primarily on the degree of cell differentiation and normal physiologic functions of the tissue and is widely influenced by the TSH level and possibly by other parameters such as the individual iodine supply [(26)].

Individualized patient-specific therapy is ideally based on a pre-therapeutic dosimetry which provides information on the activity necessary to treat all lesions in a way that an effective tumor dose can be reached without exceeding the tolerable dose to the bone marrow [(22)]. However, it has been reported that the success rate of I-131 ablation is severely reduced after a dosimetry study with very small activities of I-131 [(23)].

At our institution we adopted I-123 WBS for evaluation of patients with DTC after thyroidectomy in order to avoid stunning and to improve the success rate of I-131 ablation. Although a higher I-131 successful ablation rate has been reported in patients with DTC who underwent post-thyroidectomy I-123 WBS prior to I-131 ablation therapy compared to those who underwent post-thyroidectomy I-131 WBS [(27)], still there is a significant proportion of patients with DTC had incomplete ablation following diagnostic studies using I-123. Which may be related to the relationship between actual I-131 retention and the success rate of I-131 ablation in patients with DTC following post-thyroidectomy I-123 WBS as demonstrated in this study with the whole body retained I-131 activity at 48 hours was significantly higher in patients who have successful ablation compared to those with incomplete ablation [13.50±3.87%, and 7.79±3.28% of the administered dose respectively (p = 002)].

Also there, and there was no significant difference in the whole body retained I-131 activity at 48 hours between male and female patients with DTC in either group.

Similar results was reported by Sisson **et al. 2003** [(28)] measured the fractional retention of diagnostic I-131 at 2 days. In 87 patients of 16.5 ± 8.7% with mean retention of I-131 at day 2 in females was almost identical to that in males (16.6%, and 16.4% respectively).

Another study, ***Van Nostrand et al***. [(29)] showed the utility of the radioiodine whole-body retention at 48 hours for modifying empiric activity of I-131 of 14.4 ± 8.9%, which is also in line with our results.

In current study, the effective half-life was significantly higher in patients who have successful ablation compared to patients with incomplete ablation [16.37±2.43 hours compared to 12.64±2.27 hours respectively (p = 002)]. There was no significant difference in the effective half-life of I-131 between male and female patients with DTC in either group. Similar Data was reported by ***Ravichandran et al.*** [(30)] in series 69 patients with thyroid cancer following administration of a therapeutic activity of I-131 in order to estimate the effective half-life of clearance of I-131 and reported an estimated effective half time of clearance of 14.4 h. ***Furthermore Ejeh et al.*** [(31)] studied a total of 82 patients with DTC. In order to compare the retention of I-131 following surgery in 37 had total thyroidectomy while 45 had non-total thyroidectomy.

They estimated the whole body retained activity at 24h and whole body effective half-life of I-131 for each patient based on the whole body external exposure rate measurement at 1m immediately after ingestion of the I-131 capsule and after 24 hours. The mean effective half-life was 12.24 ± 5.04 hrs (0.51 ± 0.21 days) for patients with total thyroidectomy, and was 14.88 ± 6.48 hrs (0.62 ± 0.27 days) for patients with non-total thyroidectomy.

Our findings of significantly higher whole body retained I-131 activity at 48 hours, and higher effective half-life in patients who have successful ablation compared to patients with incomplete ablation suggest that if those patients had a dosimetry study before I-131 ablation therapy, the group of patients that had incomplete ablation might be treated with a higher therapeutic dose, which could improve the I-131 ablation success rate. Thus, measurement of diagnostic retention can serve to modify the prescribed therapeutic activity to ensure safety and increase efficacy in as many as 32% of the patients treated with I-131 for DTC. Similarly, ***Van Nostrand et al.*** [(29)] found that the radioiodine whole-body retention at 48 hours is useful in identifying patients whose empiric therapeutic prescribed activity of I-131 should be modified.

Both I-123 and I-131 are not ideal for such a dosimetry. I-131 potentially induces stunning and the half-life of I-123 is too short and not suitable for a prolonged bio kinetic study [(25)]. Recently, I-124 positron emission tomography (PET)-based three dimensional dosimetry become available and seems to be more superior to currently used I-131 dosimetry procedures to individualize therapy and to increase the safety and efficacy of the treatment, but currently it is not widely available. Because most patients with DTC receive modest therapeutic activities of I-131 and appear to do well, it may be that the usual empiric therapeutic activities are sufficient [(28)].

Study limitations: In the current study, we used the whole body exposure at 1 meter to estimate the retained activity in the thyroid remnant. The whole body exposure may include additional considerable activity in the gastrointestinal tract (GIT), liver, urinary tract, salivary glands and soft tissue background. Some patients may have considerable amount of activity in the GIT due to hypo motility, which is not the case in our study, as we reviewed their post-therapy WBS and none of them has such considerable amount of activity in the GIT, urinary tract, or soft tissue background.

The study can be repeated by using a gamma probe counting only the thyroid activity at the thyroid bed up to 1 week after giving the therapy dose. This will be more accurate.

CONCLUSIONS: We found a significantly higher retained I-131 activity at 48 hours and longer effective half-life among patients successfully ablated compared to those who need reablation, and recommend dosimetry adjusted I-131 ablation dose whenever feasible accordingly.

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