Ablation outcomes of low versus high doses of radioiodine (^{131}I) in patients with differentiated thyroid carcinoma following thyroidectomy

Walaa O. Thabet[a], Nadia M. Mostafa[a], Yasser G. Ali[c], Mohamed A.E.-H. Mekkawy[b]

Departments of [a]Nuclear Medicine, [b]Clinical Oncology, Faculty of Medicine,[c]Department of Nuclear Medicine, South Egypt Cancer Institute, Assiut University, Assiut, Egypt

Correspondence to Walaa O. Thabet, MSc, Department of Oncology Nuclear Medicine, Faculty of Medicine, Assiut University Hospital. Assiut University, Assiut, Egypt.
Post Code 41111.
Tel: +20 102 014 0716;
e-mail: dr.walaaotify@yahoo.com

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Objective
The aim was to compare the ablative efficacy of low vs high doses of radioactive iodine-131 (^{131}I) in patients with differentiated thyroid carcinoma (DTC) after total or near total thyroidectomy.

Materials and methods
A randomized, double-armed clinical study compared the ablation outcomes of patients with low and intermediate risk DTC after administration of low (30 mCi) vs high doses (80–120 mCi) of ^{131}I for 20 and 25 patients, respectively. All the included patients were re-examined under thyroid-stimulating hormone stimulation 6–8 months after ^{131}I administration. Successful ablation is defined as follows: Absence of any significant ^{131}I uptake at the thyroid bed or abnormal uptake elsewhere in the body in the diagnostic whole-body scan, stimulated serum thyroglobulin less than 2 ng/ml with negative antithyroglobulin antibodies, and free neck ultrasonography (no thyroid residue or pathological cervical lymph nodes).

Results
Overall successful ablation after a single dose of ^{131}I was reported in 34/45 patients representing 75.6% of the whole patient population, while unsuccessful ablation was reported in the remaining 11 (24.4%) patients. Successful ablation was reported in 15 out of 20 patients (75%) in the low-dose group and in 19 out of 25 cases in the high-dose group (76%) (P=1.000).

Conclusion
Ablation with low-dose radioactive iodine (30 mCi) in patients with DTC who did not have gross residual disease or cervical lymphadenopathy after surgical treatment is as effective as the high one (80–120 mCi).

Keywords:
differentiated thyroid carcinoma, radioactive iodine-131, randomized study, thyroid remnant ablation

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Introduction

Thyroid cancer represents the most frequently occurring endocrine cancer, and its incidence has been increasing worldwide during recent decades [1]. Papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) histologic subtypes, known as differentiated thyroid carcinoma (DTC), account for more than 90% of all thyroid cancers and are associated with a 10-year cancer-specific mortality rate of less than 10% [2]. The principal standard treatment for these patients includes total or near-total thyroidectomy, followed by radioactive iodine therapy (RAIT) and lifelong thyroid hormone suppressive therapy [3]. Remnant radioiodine ablation (RRA) aims at the elimination of postsurgical residual thyroid tissue and seeking for any microscopic tumor deposits; therefore, it facilitates serologic surveillance via Tg and reduces the probability of cancer recurrence, respectively [4].

Results from two large multicenter randomized trials have shown that 30 mCi of ^{131}I was as effective as 100 mCi in ablating thyroid remnant, with fewer adverse events in the 30 mCi group; in these studies, all patients had undergone total thyroidectomy. Most patients were staged pT1 N0 and pT2 N0 [5]. One of the trials included patients with pT3 tumors and patients with N1 disease were ablated successfully with 30 mCi [6].

Materials and methods

Study design

A randomized study compared the ablation outcomes of patients with low-risk and intermediate-risk DTC

after administration of low dose (30 mCi) vs high dose (80–120 mCi) of ^{131}I for 20 and 25 patients, respectively, with the following inclusion criteria: Age at diagnosis greater than or equal to 18 years, total or near-total thyroidectomy with or without regional lymph node dissection, histopathological evidence of DTC (T1–T3 tumor staging, N0–N1 nodal staging, M0) according to the seventh edition of the American Joint Committee on Cancer Staging (TNM), and low/intermediate risk DTC according to the American Thyroid Association (ATA) criteria.

Forty-five patients (eight men and 37 women; age range from 20 to 66 years with DTC (42 PTC and 3 FTC) matched the inclusion criteria were referred to the Nuclear medicine Unit of Assiut University Hospital to receive an ablative dose of ^{131}I. The study was conducted from July 2016 to September 2017. The study protocol was approved by the Medical Ethics Committee of Faculty of Medicine, Assiut University on 10/7/2016. Exclusion criteria were poorly differentiated, insular, anaplastic or medullary thyroid carcinoma, pathological cervical lymphadenopathy or suspicious *in situ* residual thyroid lesion in postoperative neck ultrasonography (NU), incomplete tumor resection, distant metastasis, pre-ablation ^{131}I diagnostic whole-body scan (Dx-WBS), and positive antithyroglobulin (TG) antibodies.

Patients preparation

The indication and the procedure were explained to all patients, including keeping on a low-iodine diet and avoidance of iodide-containing medications for 7–14 days before ^{131}I administration. Exclusion of performing water-soluble iodinated contrast investigations within the previous 2 months had been confirmed. All the included patients had done the following laboratory investigations: thyroid-stimulating hormone (TSH), baseline serum Tg, anti-Tg antibodies, complete blood picture, kidney functions tests, and serum calcium. In addition, postoperative NU was also done. Pregnancy and breastfeeding were excluded, and contraception was confirmed for all female patients in the childbearing period.

RAI administration

The patients were randomized to receive either 30 or 80–120 mCi of RAI. RRA was performed after thyroid hormone withdrawal for up to 4 weeks in patients on thyroid hormonal therapy or waiting for 4–6 weeks after thyroidectomy until serum TSH level was greater than or equal to 30 mU/l. They had fasted for 4 h before and 2 h after ^{131}I administration. Patients in the 80–120 mCi arm were hospital admitted, while those in the 30 mCi arm were discharged on the same day of ^{131}I administration.

Short-term follow-up and assessment

After 6–8 months, all the patients underwent assessment, which is based on physical examination, NU, Dx-WBS, and measurement of the serum levels of TSH, stimulated serum TG, and anti-TG antibodies to evaluate the status of ablation.

Imaging procedure

Immediately before scanning, the patients were asked to void and then lie supine with the arms down; they scanned 5–7 or 2–3 days after oral administration of ablative dose (30, 80–120 mCi) or diagnostic dose (3–5 mCi) of ^{131}I, respectively.

^{131}I Whole-body scanning

^{131}I WBSs were obtained in the anterior and posterior projections using dual-head γ-camera (sympia T. Siemens, Erlangen, Geramany) equipped with parallel-hole high-energy collimators, using a 20% energy window set at 364 kev. The table speed was 8 cm/min; matrix size was 256 × 1024. After that, anterior and posterior static views of the neck and the thorax (10 min/view) were routinely obtained for all patients.

Study endpoints

Successful ablation is defined as follows: absence of any significant ^{131}I at the thyroid bed or abnormal uptake elsewhere in the body at Dx-WBS, stimulated serum TG after thyroid hormone withdrawal less than 2 ng/ml with negative anti-TG antibodies, and free NU (neither detectable thyroid tissue nor pathological cervical lymph nodes).

Statistical analysis

Data were analyzed using SPSS win the Statistical Package Version 17 (SPSS Inc., Chicago, Illinois, USA). Qualitative data were expressed as frequency and percentage. χ^2-test and Fisher's exact test were used to examine the relationship between qualitative variables. Mann–Whitney test was done to compare quantitative variables in the case of nonparametric data. A P value less than 0.05 was considered significant. The differences between the two success rates are provided for each group: low-dose vs high-dose of ^{131}I.

Results

We studied 45 patients, most of them were women 37 (82.2%) vs 8 (17.8%) men (range: 20–77 years). They

were classified into two groups: group 1 included patients who received a low ablative dose of ^{131}I (20 patients) and group 2 included patients who received a high ablative dose of ^{131}I (25 patients). Forty-two patients had PTC, and three patients had FTC. Twenty-eight were of low risk, from them 14 patients received low dose and 14 patients received high dose. Seventeen patients were of intermediate risk, from them six patients received low dose, and 11 patients received high dose. The patient characteristics were well balanced between the two groups at baseline with no significant difference, regarding the patient characteristics or the specific risk factors except for multifocality which is higher in high-dose ablation (Table 1).

Overall successful ablation after a single dose of ^{131}I was reported in 34/45 patients, representing 75.6% of the whole patient population, while unsuccessful ablation in the remaining 11 patients (24.4%). Successful ablation was reported in 15 out of 20 patients (75%) in the low-dose group and in 19 out of 25 cases in the high-dose group (76%) (P = 1.000) (Fig. 1).

In the low-dose group, five (25%) cases had unsuccessful ablation on their follow-up, three of them (3/5) had thyroid residue which was detected in ^{131}I Dx-WBS with stimulated TG greater than 2 and free NU. The remaining two (2/5) cases had negative ^{131}I Dx-WBS and free NU but TG greater than 2 ng/ml (biochemical disease) (Fig. 2).

In the high-dose group, six (24%) cases showed unsuccessful ablation in response to the given dose on their follow-up, one of them (1/6) had thyroid residue that was detected in ^{131}I Dx-WBS with TG greater than 2 ng/ml and free NU. The remaining five (5/6) cases had negative ^{131}I Dx-WBS and free NU but TG greater than 2 ng/ml (biochemical disease) (Fig. 3).

Discussion

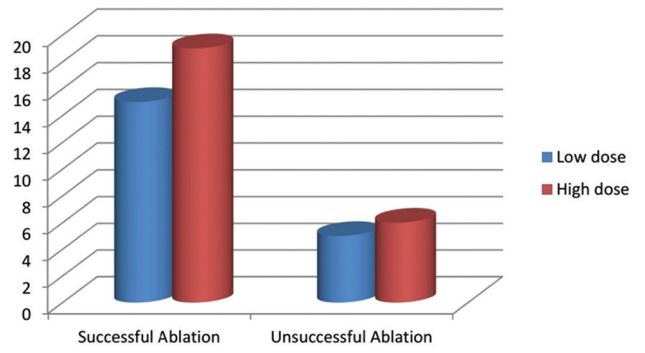
DTC is usually curable when discovered at an early stage. The comprehensive management of DTC patients consists of surgery, RAIT, and thyroxin-suppressive therapy. There have been controversies in the management aspect of patients with DTC. The most important controversial issues are the extent of thyroidectomy, the indication, and dose of RAI [7].

Table 1 Patient characteristics and demographic data

	Low dose (n=20) [n (%)]	High dose (n=25) [n (%)]	P
Age (years)			0.230
Mean±SD	41.25±11.79	37.64±12.60	
Range	20.0-66.0	22.0-60.0	
Sex			0.269
Male	2 (10.0)	6 (24.0)	
Female	18 (90.0)	19 (76.0)	
Surgery			0.716
Total thyroidectomy	17 (85.0)	20 (80.0)	
Total thyroidectomy and LN dissection	3 (15.0)	5 (20.0)	
Pathology			0.242
Papillary	20 (100.0)	22 (88.0)	
Follicular	0	3 (12.0)	
Tumor staging			
Tx	2 (10.0)	1 (4.0)	0.577
T1a	8 (40.0)	11 (44.0)	0.787
T1b	5 (25.0)	3 (12.0)	0.435
T2	4 (20.0)	6 (24.0)	0.748
T3	1 (5.0)	4 (16.0)	0.362
Lymph node staging			
N x	11 (55.0)	16 (64.0)	0.540
N0	8 (40.0)	8 (32.0)	0.577
N1	1 (5.0)	1 (4.0)	1.000
Focality			0.066
Unifocal	15 (75.0)	12 (48.0)	
Multifocal	5 (25.0)	13 (52.0)	
ATA risk stratification			0.336
Low	14 (70.0)	14 (56.0)	
Intermediate	6 (30.0)	11 (44.0)	
Baseline TG			0.790
Mean±SD	7.22±8.13	8.34±9.97	
Median (range)	3.63 (0.5-31.5)	4.9 (0.01-34.7)	

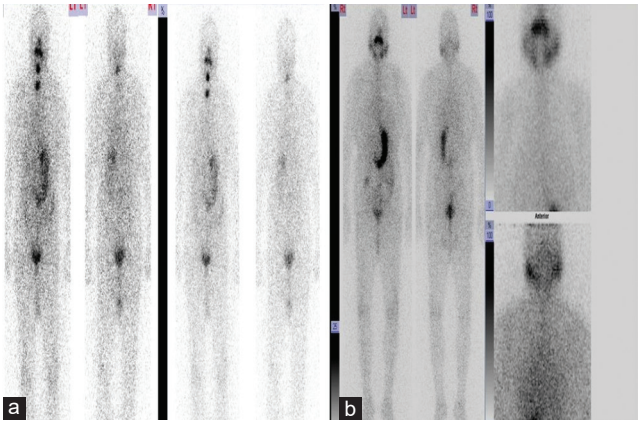
ATA, American Thyroid Association; TG, thyroglobulin.

Figure 1



Bar chart of the overall response rate in the two studied groups

Figure 2



A 55-year-old female patient with PTC, the nodule measured 2 × 2 cm, underwent total thyroidectomy, baseline TG was 6 ng/ml. Postoperative NU confirmed absence of sizable thyroid residue or cervical lymph nodes (LNs). She received 30 mCi of ^{131}I: (a) Rx-WBS obtained at fifth day post-therapy showed tracer localization only in the thyroid bed. (b) Six months later, her follow up stimulated serum TG which was 1.8 ng/ml with negative anti-TG antibodies; NU was free; Dx-WBS acquired at 72 h was negative (successful ablation). NU, neck ultrasonography; PTC, Papillary thyroid carcinoma; TG, thyroglobulin.

Unlike most other cancers, thyroid cancer affects young adults. Potential implications for improvements in treatment by making therapies safer, more cost-effective, and more convenient. Out-patient ablation has been proposed for low-dose RAI [8].

This would reduce costs further, pose fewer radiation-protection issues, and the lower radiation exposure is likely to reduce the risk of late second cancers, satisfying the principle of exposure that is 'as low as reasonably achievable' (referred to as ALARA) [9].

The amount of RAI needed to achieve ablation of post-thyroidectomy functioning remnants is also a matter of debate, with estimates ranging from 30 mCi to 100–200 mCi [10].

In our clinical practice, we routinely use an empiric fixed dose of 80–120 mCi ^{131}I for RRA. We conducted this randomized trial with short-term outcome assessment at 6–8 months after ablation of both low- and intermediate-risk groups using a specific definition of ablation success on the basis of stimulated TG, Dx-WBS, and NU.

In our study, successful ablation was found in 15 out of 20 patients (75%) in the low-dose group and in 19 out of 25 cases in the high-dose group (76%) (P = 1.000). The two study groups are equal regarding their ablation outcome. Eleven patients had unsuccessful ablation, seven of them had biochemical disease.

Our results are similar to those of Elrasad *et al.* [11], who reported that nonsignificant higher successful RRA was recorded for high compared with low RAI doses. Successful ablation was reported in 23 out of 39 patients (58.9%) in the low-dose group and in 37 out of 49 cases in the high-dose group (75.5%) (P = 0.098).

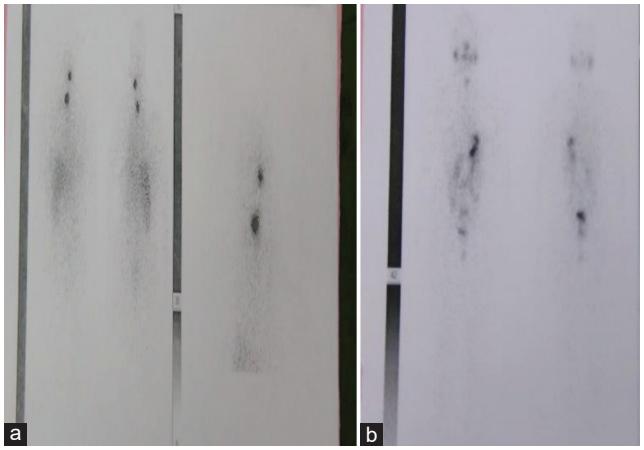
Du *et al.*[12] also found no conclusive evidence that 100 mCi activity is more effective for RRA than 30 mCi activity. Successful ablation was achieved in 42 (52%) of 81 participants, who received 30 mCi following administration of a single dose of ^{131}I and in 43 (56%) of the 77 subjects who received 100 mCi (P = 0.61).

However, conflicting results had also been reported by Zaman *et al.* [13], who studied 40 patients and stated that the high therapeutic dose (100 mCi) of ^{131}I is more effective than the low one (50 mCi) for RRA. In the high-dose group (20 patients), successful ablation was noted in 12 (60%) patients and failed ablation in the remaining eight (40%) patients, two of them (2/8) had biochemical disease, while in the low-dose group (20 patients), successful ablation was noted in eight (40%) patients and failed ablation in the remaining 12 (60%) patients, two of them (2/12) had biochemical disease. In this study, the higher value of sucessful ablation in the high-dose group compared with that of the low dose was explained by the higher number of patients with FTC involved in the study (17/40, 42.5%) which responds better to the high dose than the low one, while patients with PTC showed an equal response to both doses.

Limitations of the study

The study involved a small number of patients and was confined to short-term evaluation. Further long-term cinical trials to assess the incidence of recurrence and metastases after low vs high doses of RAI especially in

Figure 3



A 31-year-old female patient with PTC, underwent total thyroidectomy, baseline TG was 8.05 ng/ml. Postoperative NU showed normal left residual thyroid tissue 0.9 × 0.8 cm. She received high ablative doses of 131I (80 mCi): (a) Rx-WBS obtained seventh day postablation showed tracer localization only in the thyroid bed. (b) Six months later, her follow-up serum TG was 4.27 ng/ml with negative anti-TG antibodies; NU was free, Dx-WBS acquired at 72 h showed residual radiotracer uptake at the thyroid bed (unsuccessful ablation). NU, neck ultrasonography; PTC, Papillary thyroid carcinoma; TG, thyroglobulin.

the intermediate risk DTC are required. Our study is ongoing for this purpose.

Conclusion

Low ablative doses of ^{131}I (30 mCi) are sufficient for RRA in patients with DTC as compared with high doses (80–120 mCi) with similar quality of life, lower cost, and omit the need for hospital isolation. So, we kindly recommend using low ablative doses. However, further confirmation with more longer duration studies including a large number of patients is needed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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