

# Comparison of radioiodine ablation rates between low versus high dose, and according to the surgeon's expertise in the low-risk group of differentiated thyroid cancer

## ABSTRACT

Radioiodine ablation following surgery is the accepted treatment for patients with differentiated thyroid cancer (DTC). Since that surgical volume and radioiodine dose can have impact on treatment outcome, we aimed to evaluate them on the treatment outcome of low-risk DTC patients. Low-risk DTC patients were classified into four groups, including (1) thyroidectomy was performed by thyroid surgeon and low-dose (1850 MBq [30 mCi]) radioiodine was administered ( $n = 17$ ), (2) thyroidectomy was performed by thyroid surgeon and high-dose (3700 MBq [100 mCi]) radioiodine was administered ( $n = 10$ ), (3) thyroidectomy was performed by general surgeon and low-dose radioiodine was administered ( $n = 22$ ), and (4) thyroidectomy was performed by general surgeon and high-dose radioiodine was administered ( $n = 29$ ). All patients were followed at least for 6 months and also for evaluation of treatment success, neck sonography, thyroid-stimulating hormone-off, thyroglobulin (Tg)-off, and anti-Tg-off tests were performed. Furthermore, two common radioiodine treatment-associated side effects, including dry mouth, and nausea/vomiting were assessed for all patients. Seventy-eight low-risk DTC patients (female: 70 [89.7%]; male: 8 [10.3%]) aged from 18 to 78 years old with mean of  $41.96 \pm 13.42$  years were enrolled in this study. In total, the treatment was successful in 96.2% of patients. There was no significant difference in treatment success among groups ( $P > 0.05$ ), while there was a significant association among administered activity and side effects. In low dose patients, only one patient complained from dry mouth; however, 11/39 patients who received high dose of iodine complained from dry mouth ( $P = 0.002$ ). In addition, 9/39 high dose patients suffered from vomiting/nausea, while none of low-dose patients suffered from vomiting/nausea ( $P = 0.001$ ). In low-risk DTC patients, surgical volume and amounts of radioiodine had no significant impact on treatment results; therefore, low dose radioiodine following thyroidectomy may be preferable to low-risk DTC patients to avoid side effects.

**Keywords:** Radioiodine ablation, surgical volume, thyroid cancer, thyroidectomy

## INTRODUCTION

Thyroid cancer is one of the most common endocrine malignancies, with an increasing incidence during the last decades. Differentiated thyroid cancer (DTC) comprising >95% of all of the thyroid cancer and is generally associated with an excellent prognosis.<sup>[1-3]</sup>

Ablation with radioiodine (I-131) following thyroidectomy is the widely accepted therapeutic procedure for DTC with the aims of removal remained thyroid tissues after thyroidectomy, prolong disease-free survival, and also treating high-risk patients with persistent tumor.<sup>[4]</sup>

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According to the literature, surgical volume and precise dose of radioiodine have a great impact on the results of the treatment procedure. Several studies revealed better treatment outcomes for high-volume surgeons for thyroid surgery. It has been shown that thyroid surgery with the high-volume surgeon has less surgical complications, lower readmission rate, and also shorter hospitalization.<sup>[5-7]</sup>

Besides its advantages in the removal of residual thyroid tissue, radioiodine presents potential risks on normal tissues.<sup>[4]</sup> According to the 2015 American Thyroid Association (ATA), the DTC patients for the evaluation of the risk of postsurgery recurrence were classified into low-, intermediate-, and high-risk groups.<sup>[8]</sup> Nowadays, radioiodine therapy (RIT) after thyroidectomy is well accepted for high-risk DTC patients. It is controversial for low- and intermediate-risk patients. RIT in low and intermediate patients is performed mainly for residual thyroid tissue ablation. Previously, a fixed dose of radioiodine “commonly 3.7 GBq (100 mCi)” was used in these DTC patients. However, recent publications have reported almost similar results of ablation with 1.1 GBq (low dose) compared to 3.7 GBq (high dose) of radioiodine in low- and intermediate-risk patients after total thyroidectomy (TT) or near total thyroidectomy (NTT).<sup>[4,9,10]</sup>

The aim of this study was to evaluate the impact of surgical volume and radioiodine doses (low vs. high doses) on the treatment outcome of low-risk DTC patients.

## MATERIALS AND METHODS

### Patients

This quasi-experiment study included 78 DTC patients aged from 18 to 78 years old who were referred from the Research Institute for Endocrine Sciences to the Department of Nuclear Medicine in a tertiary university-affiliated hospital from October 2016 to January 2019. Inclusion criteria included age  $\geq 18$  and low-risk DTC (tumor stage T1–T3 with or without lymph node involvement but no distant metastasis). Exclusion criteria included patients with distant metastasis, patient without surgery of TT, cases with intermediate to high-risk stratification according to the ATA 2015, patients with a history of RIT, and patients with insufficient data. An informed consent form was signed by each patient for entering the study. The study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (Registration No: IR.SBMU.MSP.REC.1397.132).

### Study procedures

The patients were classified into four groups: (1) Thyroidectomy was performed by thyroid surgeon and low-dose (1850 MBq [30 mCi]) radioiodine was administered

( $n = 17$ ), (2) Thyroidectomy was performed by thyroid surgeon and high-dose (3700 MBq [100 mCi]) radioiodine was administered ( $n = 10$ ), (3) Thyroidectomy was performed by general surgeon, and low-dose radioiodine was administered ( $n = 22$ ) and (4) Thyroidectomy was performed by a general surgeon and high-dose radioiodine was administered ( $n = 29$ ) [Figure 1].

All patients underwent TT. Lymph node dissection was performed for patients showing lymph-node involvement. The patients were asked to discontinue levothyroxine and have a low iodine diet for 1 month before ablation. For each patient, preablation tests were performed, including clinical history, physical examination, thyroid-stimulating hormone (TSH), serum thyroglobulin (Tg), serum anti-Tg, neck ultrasonography, and chest X-ray.

We defined the thyroid surgeon when a surgeon performs at least 100 thyroid operations annually. Those who perform  $< 100$  thyroid surgery we define them as general surgeons.

After the administration of radioiodine, all patients were hospitalized in isolation rooms until the dose rate decreased to 30 mSv/h at a distance of one meter measured by a Geiger counter and clinical conditions allowed discharge. I-131 whole-body scan (WBS) was performed 5–7 days after ablation with a dual-head gamma camera (Philips (ADAC) Vertex Plus) equipped with high energy parallel-hole collimators.

### Follow up

The patients were followed for at least 6 months after ablation. Follow up neck ultrasonography, TSH-off levothyroxine, Tg-off levothyroxine and anti-Tg-off levothyroxine tests were performed for evaluation of ablation success. The ablation was considered complete response when: (i) serum Tg-off  $\leq 2$  ng/mL, (ii) no abnormal activity throughout the body on follow-up diagnostic imaging including neck ultrasonography and I-131 WBS.

In addition, two common side effects associated with radioiodine ablation, including dry mouth, nausea, vomiting, were evaluated in all patients.

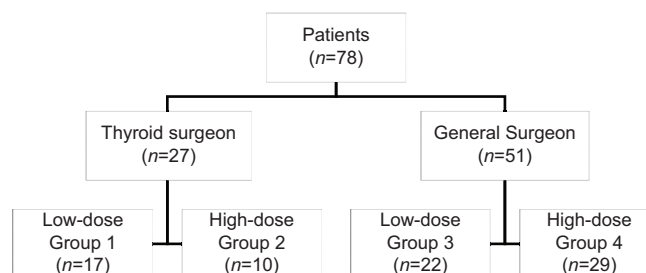


Figure 1: Flow-chart of research design

## Statistical analysis

The sampling method was based on nonprobability sampling. The study was done as a control group pretest-posttest design. All quantitative data were presented as the mean  $\pm$  standard deviation., with ranges given when proper. The qualitative data were expressed as a percentage. A Chi-square test was used for the analysis of qualitative variables, and *t*-test was applied for quantitative values. The Mann–Whitney U-test also was used when the data did not approximate a normal distribution. SPSS v 20 (SPSS, Inc., IBM Corporation, Somers, NY, USA) was used for statistical analysis.  $P < 0.05$  was considered statistically significant difference.

## RESULTS

### Patients

In total, 78 low-risk DTC patients (female: 70 [89.7%]; male: 8 [10.3%]) aged from 18 to 78 years old with a mean of  $41.96 \pm 13.42$  years old were enrolled in this study. The clinical characteristics of patients are shown in Table 1.

In the initial assessment, the mean values of TSH, Tg, and anti-Tg were  $76.64 \pm 55.54$   $\mu$ IU/L,  $3.68 \pm 6.80$  ng/mL and  $101.58 \pm 215.89$  IU/mL, respectively, in all included patients. When we divide patients into two subgroups based administered doses, there was a significant

difference in terms of tumor size ( $7.95 \pm 4.75$  vs.  $17.38 \pm 11.74$  mm), T stage and local lymph node involvement (14 [35.9%] vs. 5 [12.8%]) ( $P < 0.05$ ) [Table 1]. When we divide included patients into four subgroups based upon administered doses and the surgeon's expertise, there was no significant difference among them in terms of sex, age, initial TSH, Tg, anti-Tg, and histopathology of the tumor ( $P > 0.05$ ).

When we divide patients into two subgroups based on the surgeon's experience, there was a significant difference of preablation serum Tg level between thyroid and general surgeons (2 (0) ng/mL vs. 4 (1) ng/mL respectively,  $P < 0.05$ ). In addition, number of dissected cervical lymph nodes was significantly higher in patients whom operated by thyroid surgeons relative to general surgeons (11 (3) vs. 3 (0), respectively,  $P < 0.05$ ). However, the number of resected cervical lymph nodes and preablation serum Tg levels were not associated with the final outcome ( $P > 0.05$ ).

Patients with chronic thyroiditis observed on the cytopathology had the lower Tg serum level but higher anti-Tg serum level relative to patients without that issue (Tg, 2 (0) ng/mL vs. 5 (1) ng/mL, value  $< 0.05$  and anti-Tg, 179 (48) IU/mL vs. 31 (5) IU/mL,  $P$  value  $0 < 0.05$ , respectively). Figures 2 and 3 show post-ablation whole-body I-131 scan in DTC patients in whom

**Table 1: Patients baseline characteristics**

Characteristic	All patients	Low-dose (n=39)	High-dose (n=39)	P
Age, years	41.96 $\pm$ 13.42	44.67 $\pm$ 14.84	39.26 $\pm$ 11.39	0.07
Female sex, n (%)	70 (89.7)	35 (89.7)	35 (89.7)	1.00
Surgeon, n (%)				
Thyroid surgeon	27 (34.6)	17 (43.6)	10 (25.6)	0.07
General surgeon	51 (65.4)	22 (56.4)	29 (74.4)	
Histology, n (%)				
Papillary	74 (94.9)	38 (97.4)	36 (92.3)	0.77
Follicular	4 (5.1)	1 (2.6)	3 (7.7)	
Tumor size, mm	12.67 $\pm$ 10.09	7.95 $\pm$ 4.75	17.38 $\pm$ 11.74	0.001
T stage, n (%)				
T1	69 (88.5)	37 (94.9)	32 (82.1)	0.0001
T2	4 (5.1)	2 (5.1)	2 (5.1)	
T3	5 (6.4)	0	5 (12.8)	
Lymph node metastasis, n (%)				
N0	63 (80.8)	35 (89.7)	28 (71.8)	0.001
N1a	13 (16.6)	4 (10.3)	9 (23.1)	
N1b	2 (2.6)	0	2 (5.1)	
Serum Tg-off (ng/mL)	3.68 $\pm$ 6.80	3.80 $\pm$ 8.00	3.55 $\pm$ 5.43	0.87
TSH ( $\mu$ IU/mL)	76.64 $\pm$ 55.54	58.87 $\pm$ 34.68	94.42 $\pm$ 66.33	0.04
Anti-Tg (IU/mL)	101.58 $\pm$ 215.89	125.27 $\pm$ 275.35	77.89 $\pm$ 132.18	0.33
Postablation WBS, n (%)				
No significant uptake	6 (7.7)	0	6 (15.4)	0.0001
Remnant	53 (67.9)	34 (87.2)	19 (48.7)	
Lymph node involvement	19 (24.3)	5 (12.8)	14 (35.9)	

TSH: Thyroid-stimulating hormone, WBS: Whole-body scan, Tg: Thyroglobulin

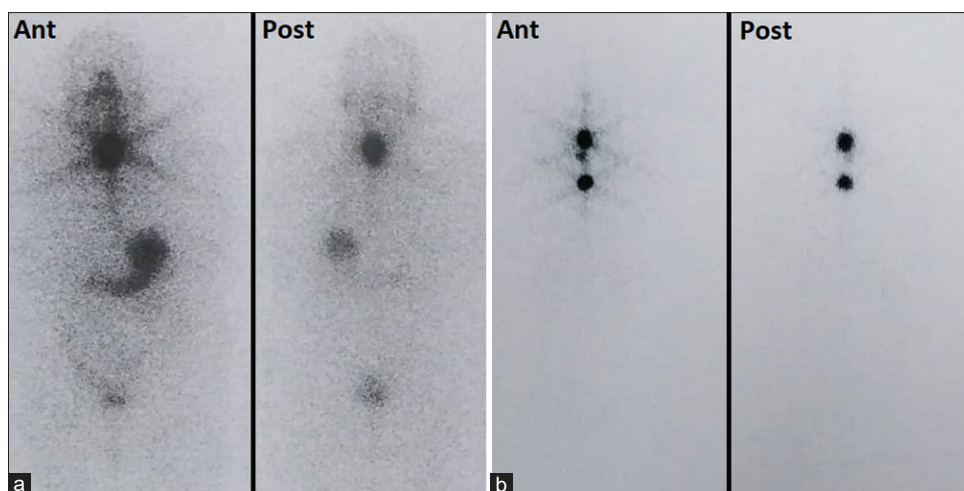


Figure 2: Postablation whole body I-131 scan in differentiated thyroid cancer patients (2 cases) in whom thyroidectomy was carried out by general surgeon

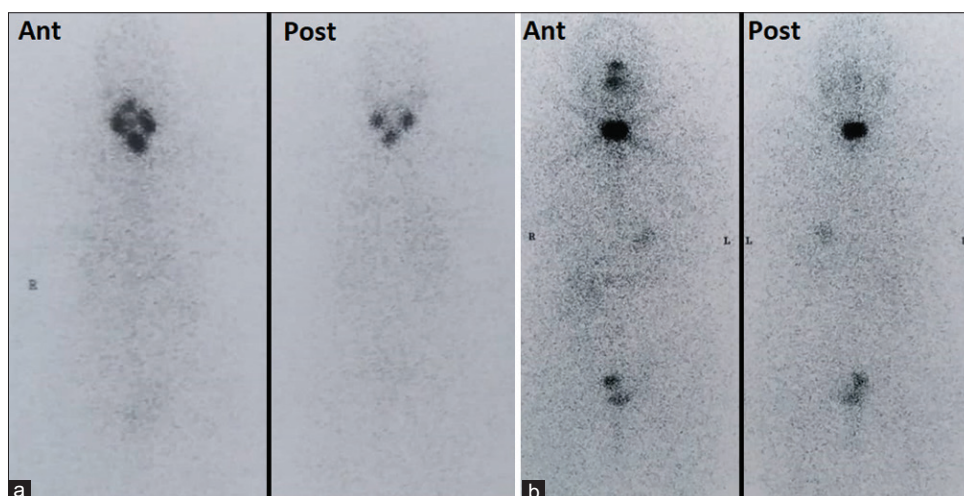


Figure 3: Postablation whole body I-131 scan in differentiated thyroid cancer patients (2 cases) in whom thyroidectomy was carried out by thyroid surgeon

thyroidectomy was carried out by the general surgeon and thyroid surgeon, respectively.

#### Follow-up

The patients were followed for 6–12 months after ablation (mean:  $9.10 \pm 2.62$  months). The treatment was successful in 75/78 (96.2%) of patients. The rate of treatment success in groups is shown in Figure 1. There was no significant difference in treatment success among groups ( $P > 0.05$ ). Neither surgical volume nor administered activity had a significant influence on treatment results ( $P > 0.05$ ).

In the multivariable analysis, none of the sex, age, administered activity, type of surgeon, histopathology of the tumor, metastasis, TT and NTT, baseline serum Tg, anti-Tg and TSH, initial neck ultrasonography parameters, had no sole factor which independently had a significant impact of ablation result.

#### Side effects

Dry mouth and vomiting/nausea were reported in 12 (15.4%) and 9 (11.5%) of all patients. There was a significant association between administered activity and side effects. In low dose patients, only one patient complained from dry mouth; however, 11/39 patients who received the high dose of radioiodine complained from dry mouth ( $P = 0.002$ ). In addition, 9/39 high dose patients suffered from vomiting/nausea; however, none of the low dose patients suffered from vomiting/nausea ( $P = 0.001$ ).

#### DISCUSSION

In this study, we evaluated the effect of radioiodine dose and also surgical volume, including thyroid surgeon as high volume and general surgeon as low volume on treatment outcome in low-risk DTC patients. There was no statistical difference between treatment outcome and the surgical volume because a large percentage of studied patients (96.2%)

showed a complete response. The success rate of the patients in this paper was very good (96.2%). It is hard to find differences in the subjects showing homogeneously good results. It has shown that the significant impact of surgical volume on treatment outcome of thyroid cancer was revealed in several studies.<sup>[5,6]</sup> In a study, Al-Qurayshi *et al.* evaluated the association of surgical volume with clinical outcomes and costs of thyroidectomy. They observed that the higher volume of the surgeon is related to favorable clinical and financial outcomes.<sup>[11]</sup> Furthermore, Meltzer *et al.* assessed the impact of surgical volume on clinical outcome and surgical efficacy in thyroid surgery. They reported that high volume surgeons provide patients with favorable clinical outcomes and contribute to organizational efficiency.<sup>[6]</sup>

In this study, there was no statistically significant association between RIT outcomes in low-risk DTC patients after surgery with low dose and high dose of radioiodine. In correlation with our study, there were several studies that revealed no significant difference in treatment outcomes of ablation with low and high doses of radioiodine.<sup>[4,10,12]</sup> However, in contrast to our results, Fallahi *et al.* performed a double-blinded randomized controlled trials and reported better treatment outcomes in high dose (3.7 GBq) in comparison with low dose (1.1 GBq).<sup>[9]</sup>

In addition to treatment outcome, we evaluated the common RIT-related adverse effects, including dry mouth and vomiting/nausea following radioiodine ablation. We observed a significant relationship between high administered dose and adverse effects, which was in correlation with a study performed by Qu *et al.*<sup>[4]</sup>

On the other hand, one point that precludes a strong conclusion in the current study is that a significant difference in tumor size, T stage, and lymph node involvement between low and high-risk patients. There are some reports that showed the T stage has a significant impact on treatment response, which higher T stage is related to the lower possibility of complete response in low dose DTC patients.<sup>[13]</sup> Therefore, our study may indicate low dose radioiodine ablation is preferred in low-risk DTC patients with T stage <2 and without any lymph node involvement with consideration of lower side effects, lower cost and also no need to hospitalization in compared to high dose.

Our study has several drawbacks. The major limitation was low sample size and short follow-up period of the study that could have a large impact on our final appraisal. Another limitation was the impossibility of randomization, particularly on the surgeon selection. However, further well-designed

studies, especially considering the large number of patients and long follow up to ascertain the progression-free survival and overall survival are needed.

## CONCLUSION

The study may show that the volume of the surgeon and administered radioiodine dose had no significant impact on treatment outcomes in patients with low-risk DTC. In addition, it may demonstrate that low dose radioiodine ablation is preferred for low-risk DTC patients, especially in patients with T stage <2 without any lymph node involvement.

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## Conflicts of interest

There are no conflicts of interest.

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