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Low-dose versus high-dose radioactive iodine ablation of differentiated thyroid carcinoma: a prospective randomized study

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Original Article

Abstract

Purpose: Following total thyroidectomy of differentiated thyroid carcinoma (DTC), some patients are ablated with radioactive iodine I-131 (RAI). We compare the success of ablation with 30 millicurie (mCi) versus 80 mCi. **Methods:** We randomized the patients to 30 mCi or 80 mCi RAI after surgery. T1-T3, N0-N1, M0 tumors were included (based on the AJCC 7th edition). Pre-ablation baseline serum thyroglobulin (sTg), and thyroglobulin antibody (Tg Ab) were performed. Six months post-ablation successful thyroid ablation was defined as a negative whole body scan (WBS) and undetectable sTg. **Results:** Out of 50 patients with DTC, 45 patients fulfilled the eligibility criteria. Total thyroidectomy was performed in 27/45 (60%). 26/45 (57.8%) of patients received 30 mCi while 19/45 (42.2%) patients received 80 mCi. The median age was 37 and 36.5 years in the arms 80 and 30 mCi respectively. Papillary carcinoma predominated in 42/45 (93.3%) of patients. T2 tumors predominated in 10/19 (52.6%), and 15/26 (57.7%) of the 80 and 30 mCi arms respectively. According to the American Thyroid Association (ATA) risk classification, all of the patients had low risk disease. Success of ablation was achieved in 15/19 (78.9%), and in 15/26 (57.7%) of the arms 80 and 30 mCi respectively. No patients developed distant metastases in both arms. The patients who received 80 mCi had longer hospital isolation than the 30 mCi arm (p 0.008). 6/26 (23.1%) patients in the 30 mCi arm were isolated for 2-4 days, whereas all the 80 mCi arm patients were isolated for 3-5 days. **Conclusion:** Both 80 mCi and 30 mCi RAI have similar success rate in the ablation of thyroid remnant of low risk DTC patients. The low dose is associated with fewer side effects, shorter hospital admission duration, and is less expensive in low risk DTC patients.

Keywords: Differentiated thyroid carcinoma, Radioactive iodine remnant ablation, I-131 optimal dose, Randomized study.

1. Introduction

Thyroid cancer represents 3.8% of all new cases of cancer in the United States[1]. In Egypt, according to the National Cancer Institute (NCI) Registry from 2002-2004 thyroid cancer represented 2.2% of female malignancies. The National Cancer Registry Program (NCRP) of Egypt 2008-2011 showed that thyroid cancer is one of the most frequent malignancies in females representing 3.28% while it was not one of the most frequent cancers in males[2]. The incidence is increasing all over the world[3]. This increased incidence over the past three decades maybe attributed to the more use of ultrasound guided aspirations, imaging studies such as computed tomography, magnetic resonance imaging, and positron emission tomography scans, leading to detection of small non-palpable tumors in asymptomatic patients[4]. The documented increased incidence is of both small non-palpable tumors[5-6] and large tumors (> 2cm)[6]. Moreover, the thyroid cancer incidence is sharply increasing in children, adolescents and young adults[7]. The current treatment modalities kept the mortality rate for differentiated thyroid carcinoma (DTC) low despite the recent increase in its incidence[8].

DTC represents the vast majority of cases and is associated with a high 10-year survival rate (90-95%)[9]. Total or near-total thyroidectomy is the gold standard therapy for DTC. Surgery is usually followed by radioactive iodine therapy (RAI) for remnant ablation or as adjuvant therapy to treat potential metastatic disease. Total thyroidectomy increases survival rates and

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decreases recurrence rates in patients with thyroid cancer. Molecular-targeted therapies, such as tyrosine kinase inhibitors (TKIs), have been approved in the past few years for the treatment of patients with advanced thyroid cancer[8].

Over the past several years, given the increasing incidence of low-risk DTC, there has been a growing interest in tailoring the intensity of therapy and of monitoring the disease risk[10-12]. Lower doses of RAI are investigated to achieve an attractive risk-benefit ratio, namely low toxicity and no impact on quality of life. The advantages of lower RAI doses include lower toxicity which will improve quality of life, shorter hospital isolation, and lower radiation dose to the extra-thyroid compartments. High dose RAI ablation is associated with a higher rate of successful ablation of around 80 to 87%[13]. However, this high dose of RAI has certain disadvantages, including patient isolation, high cost, more incidences of adverse effects, and increased risk of second malignancies[14-17]. A retrospective study by Mazzaferri and Jhiang[18] demonstrated that low-dose RAI ablation (29 - 50 mCi) is as effective as high-dose RAI ablation (51-200 mCi) in controlling tumor recurrence and improving overall survival. The authors also found no difference in the long term tumor recurrence rate (7% vs. 9%). In 1996, Bal *et al.*[19] carried out the first prospective randomized clinical study to evaluate the optimal dose of radioactive I-131. They studied 149 DTC patients with thyroid remnant after near total thyroidectomy. The patients were randomly divided into 4 treatment groups, 25-34 mCi of I-131 (27 patients), 35-64 mCi (54 patients), 65-119 mCi (38 patients) and 120-200 mCi (30 patients). Six months to one year after RAI ablation the authors observed complete remnant ablation in the 30 mCi group (63%), 77.8% in the 50 mCi group, 73.7% in the 90 mCi group and 76.7% in the 155mCi group. The calculated radiation-absorbed dose was approximately 20,000 cGy delivered by 30 mCi dose, about 30,000 cGy delivered by 50 mCi dose, about 50,000 cGy delivered by 90 mCi, and approximately 130,000 cGy by 155 mCi dose. The authors concluded that doses above 50 mCi resulted in plateauing of the dose response curve. So, based on the dosimetry studies they recommended RAI doses of about 50 mCi for thyroid remnant ablation because higher doses do not appear to achieve a higher ablation rate. Several randomized trials and meta-analyses including both observational and randomized trials investigated the role of lower dose RAI for remnant ablation. Most of these studies showed comparable effectiveness of both low and high doses of postoperative ablative RAI. However, there is no recommendation for a definite dose of I-131 for remnant ablation[20-25]. Mäenpää *et al.* [25] in a randomized study showed no difference between RAI doses of 100 mCi and 30 mCi as regards the effectiveness of thyroid remnant ablation and long term results.

The objective of this prospective randomized study was to compare the success of thyroid remnant ablation with low and high dose I-131 iodine therapy after total or near total thyroidectomy of differentiated thyroid carcinoma with no distant or local metastases. We also compared the short term adverse effects, and hospital isolation duration.

2. Methods and Materials

We prospectively studied patients with the following inclusion criteria: (1) Age 18 years or older. (2) DTC (papillary, follicular, excluding aggressive histologic subtypes). (3) TNM stages of T1- T3 N0 N1 M0 [AJCC 7th edition]. (4) All the patients had total or near total thyroidectomy. (5) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Forty –five out of 50 patients referred to the Clinical Oncology Department of Ain-Shams University matched the inclusion criteria. The study was conducted from June 2013 to October 2015. The protocol was approved by the institutional review board of Faculty of Medicine, Ain-Shams University.

2.1. Preparation to Iodine remnant ablation

In preparation to ablation all the patients had the following laboratory work done; serum T3, T4, TSH, baseline serum thyroglobulin, and thyroglobulin antibodies. In addition to complete blood picture, liver and kidney functions tests, serum calcium, pregnancy test for female patients in the child bearing period (CBP) and postoperative neck ultrasound. Chest x-ray was also done. All female patients in the CBP were referred to the Gynecologic Department Ain- Shams University to use reliable contraception methods. All patients were instructed to have a low iodine diet for at least 2 weeks prior to iodine ablation.

2.2. Iodine- 131 remnant ablation administration

The patients were randomized to receive either 80 mCi or 30 mCi RAI. RAI remnant ablation was performed after thyroid hormone withdrawal for 4-6 weeks until serum TSH reached a level of 25- 30 mU/L. The patients in the 80 mCi arm were kept in isolation till the dose rate was < 5 mR/hr at 1 meter distance. Most of the patients of the arm 30 mCi were not isolated.

2.3. Post-RAI success of ablation and follow-up

A post-ablation WBS was done within 5-7 days after the administration of I-131. Thyroxine suppression therapy was started 24-48 hours after the I-131 ablation. If any distant uptake was detected the patient was excluded from the study. At 3 months post-ablation clinical evaluation, a thyroid ultrasound (U/S), serum T3, T4 and TSH were performed. If any suspicious findings at the thyroid bed or cervical lymph nodes were detected WBS was performed. A successful ablation was defined as negative diagnostic WBS (5 mCi of I-131), and undetectable sTg 2 ng/mL at 6 months post ablation. If

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more than minimal activity was detected in the thyroid bed or cervical lymph nodes the I-131 would be repeated until successful ablation was achieved.

2.4. Statistical analysis

Analysis of data was done by IBM computer using SPSS (statistical program for social science version 20). The Chi-square test was used to compare qualitative variables between groups (sex, histologic type, successful ablation, incidence and types of and side effects of iodine ablation). The quantitative variables (age, duration of hospital isolation) were expressed as mean ± standard deviation and range by using the unpaired *t*-test. The qualitative variables were expressed as number and percentage. A P-value > 0.05 was considered insignificant, P < 0.05 significant, and P < 0.001 highly significant.

Table 1: Clinical characteristics of patients

Variable	80 mci arm n=19	30 mci arm n=26	*P* value
Age			
Median	37	36.5	0.59 NS
Range	41	44	
Sex			
Male	5	5	0.45 NS
Female	14	21	
Histology			
Papillary	15	21	
Papillary follicular variant	2	2	
Papillary columnar cell variant	0	2	0.66 NS
Micropapillary	0	1	
Follicular	2	0	
Grade			
One	11	14	
Two	6	11	0.30 NS
Three	2	1	
Tumor size			
T1	5	10	
T2	10	15	
T3	4	1	0.17 NS
Nodal involvement			
N0	18	25	
N1	1	1	0.36 NS
Stage			
I	16	24	
II	1	2	0.20 NS
III	2	0	
ATA risk			
Low risk	19	26	0.22 NS
Thyroglobulin (Tg) median			
Baseline (after surgery)	1.1	1.3	0.34 NS
Six months	0.2	0.8	
Surgery (Thyroidectomy)			
Subtotal	1	1	
Total	12	15	0.60 NS
Completion	6	10	
Time from surgery to ablation (days)			
Median			
Range	58	61	0.40 NS
	141	304	
Success of ablation at 6 months			
Successful	15 (79.5%)	15 (57.7%)	0.13 NS
failure	2 (10.5%)	6 (23.1%)	

3. Results

The baseline characteristics of the study subjects are summarized in Table 1. Five patients were not enrolled in the study: 1 patient had a postoperative bulky residuum by ultrasound and needed higher radioactive iodine dose, 1 patient was excluded due to presence of metastasis diagnosed at the post-ablation WBS, 1 patient had micropapillary carcinoma and radioactive iodine ablation was not indicated, and 2 patients were ineligible after randomization. Although we used simple randomization the patients' numbers were unequal in each group. This was because some patients were excluded after randomization.

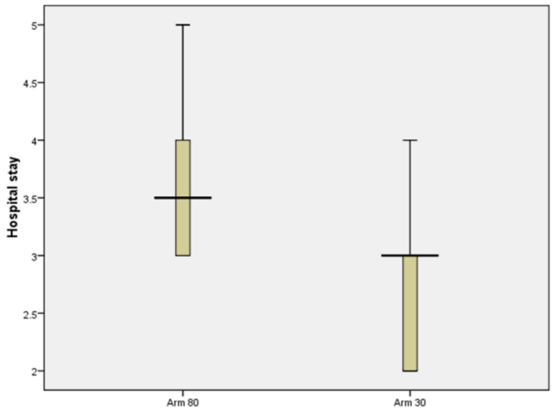

Figure 1: Number of Days in Hospital Isolation (P = 00.8)

3.1. Patients

The median age was 37 years old in both arms. Females represented 35/45 (77.8%) of the patients. The majority of patients had papillary thyroid carcinoma and its variants, only two patients had follicular carcinoma in the 80 mCi arm. Stage I predominant in 16/19 patients of arm 80 mCi and 24/26 patients of arm 30 mCi. Two patients of the arm 80 mCi had stage III disease. T1 and T2 tumors were more frequent in the 30 mCi arm. None of the patients had neck dissection. All the patients had normal work up and none had serious comorbidities.

3.2. Pre-ablation

Serum TSH values had a median value of 53 and a range from 27.3 - 420 μIU/ml. The baseline sTg value was found to range from 0.1-248 ng/ml and had a median of 1.3 depending on the mass of the residual tissue. Pre-iodine ablation serum Tg Abs was negative in 27/45, positive in 4/45, and not done in 14/45. Pre-ablation ultrasound was performed in most of the patients where it showed no residual thyroid tissue in 12/45, small residual in 27/45, reactionary lymph nodes in 2/45 and was not done in 4/45 patients. The median time from surgery to ablation was 119 days.

3.3. Iodine remnant ablation

A total of 19/45 patients were ablated with 80 mCi and 26/45 patients were ablated with 30 mCi. Both arms had no statistically significant differences in age, sex, type of surgery, tumor size, and pathological subtypes.

3.4. Hospital isolation

The patients of the arm 80 mCi had a longer time spent in hospital isolation that was statistically significant (P = 0.008) (Table 2). All the patients who received 80 mCi were isolated for a range of 3-5 days. The patients in the arm 30 mCi were not intended to be hospital isolated. However, only 6/26 (23%) were isolated mainly because of transportation issues and they spent a range of 2-4 days.

Table 2: Comparison between both arms as regards hospital isolation.

Variables	Arm 80 mCi (n=19)	Arm 30 mCi (n=26)	*t*	P
Mean±SD	3.7 ± 1.1	2.7 ± 1.3	2.8	0.008
Range	3-5	2-4		

Table 3: Comparison between both arms as regards I-131 side effects.

Variables	Arm 80 mCi (n=19)	Arm 30 mCi (n=26)	*t*	P
Yes	15 (78.9%)	6 (23.1%)	12.8	0.000
No	4 (21.1%)	20 (76.9%)		

Table 4: Comparison between both arms as regards type of side effects.

Variable	Arm 80 mCi (n=19)	Arm 30 mCi (n=26)	X2	P
Neck pain	7 (36.8%)	3 (11.5%)		
Headache	7 (36.8%)	2 (7.7%)		
Sialadenitis	9 (47.2%)	1 (3.8%)	23	0.000
Muscle cramps	1(5.3%)	0 (0%)		
No side effects	3 (15.8%)	19 (73.1%)		

Table 5: Ablation results at six months after 30 mCi and 80 mCi radioactive I-131 remnant ablation.

Variable	Arm 80 mCi (n=19)	Arm 30 mCi (n=26)
Lost follow-up	2 (10.5%)	1 (3.84%)
Out of trial (after ablation)	0	1 (3.84%)
Serum Tg		
Undetectable (median value)	0.2	0.8
Increased (due to failure of ablation)	NA sTg (1/19, 5.36 %)	106.96 (3/26, 11.5 %)
Unavailable (due to lost follow-up or out of trial after ablation)	NA sTg (2/19, 10.5 %)	NA sTg (2/26, 7.7 %)
Neck US done	17	17
Normal	17	10
Suspicious	0	7
Diagnostic WBS		
No uptake	15	15
Thyroid bed uptake	1	2
Lymph node uptake	1	4
Not done (due to lost follow up and/or out of trial)	2	5
Successful ablation	15	15
Second ablative I-131 dose	2	6
Neck dissection followed by I-131 dose	1	1

NA: Not Available

3.5. Adverse events

The proportion of patients who had adverse events was higher in the high dose arm (78.9%) versus (23.1%) in the low dose arm that was highly statistically significant (P = 0.00) (Table 3). (Table 4) shows a comparison between both arms as regards the type of side effects, where most of the patients receiving 80 mCi had sialadenitis (9/19, 47.2%) whereas neck pain was the most frequent side effect in the 30 mCi (3/26, 11.5%).

3.6. Successful ablation

At 6 months was achieved in 15/19 patients (79.5%) who received the high-dose ablation versus 15/26 (57.7%) patients ablated with low-dose. Although there was no statistical difference (P = 0.13), these results indicate equal efficacy of both dose regimens.

3.7. Retreatment and recurrence

Six months post-ablation, 2 patients in the arm 80 mCi (2/19, 10.5%) had unsuccessful ablation and needed re-ablation while 2 other patients lost follow up after receiving the RAI dose. Both patients who required second radioiodine dose had cervical lymph nodes failure. One patient received 100 mCi and the other patient had neck dissection followed by 100 mCi. On the other hand, (6/26, 23.1%) patients ablated with 30 mCi required a second ablative dose. Two patients had failure at the thyroid bed, one of these patients received 100 mCi and the other one received 80 mCi. Four patients had failure in the cervical lymph nodes one of whom received 80 mCi, one patient was referred to a different center and one was re-ablated with 30 mCi. The Last patient who had cervical lymph nodes failure underwent neck dissection followed by 100 mCi RAI treatment.

4. Discussion

In our clinical practice we routinely use an empiric fixed dose of 80-100 mCi I-131 for thyroid remnant ablation. Because of the possibility to use lesser activities, we decided to conduct a prospective randomized trial with short- term outcome assessment. We acknowledge the low number of patients however; the strength of the present study is that it is a randomized single center study, incorporating patients with uniform inclusion, exclusion, and ablation criteria. In our study the majority of patients were diagnosed with early stage of the disease, so the results are related to low risk DTC patients treated by radical surgery.

The treatment of DTC consists of surgery, radioactive I-131 ablation, and thyroxine suppressive therapy. The role of the RAI after thyroidectomy is known to eliminate microscopic residual disease after surgery [30, 31, 32, 33] to eliminate possible metastases, and to treat known persistent disease[10, 11, 26]. The RAI remnant ablation is indicated in patients with intermediate to high risk disease. However, RAI for low-risk disease is in debate, where most of these patients can be ablated with surgery alone for unifocal or multifocal tumors <1 cm and without high-risk features. Low-dose iodine (30 mCi) may be enough for low-risk patients to achieve ablation[23, 24, 27-29] with low- medium and long-term relapse rates. The advantages of low-dose RAI include duration of hospital isolation, decreased environmental exposure to radioiodine, lower financial cost, and lower risk of secondary malignancies[34]. Around 15 randomized controlled trials have studied low-dose RAI in low risk DTC including 2 randomized trials from India confirmed the role of low dose RAI in low risk DTC[19, 22, 35]. Two large prospective randomized trials, one from

France (the ESTIMABL study) by Schlumberger *et al*[24] and the HiLo trial[23] from UK by Mallick *et al* compared two different RAI regimens for low- to intermediate risk DTC. Both studies concluded that a low activity of radioiodine (1.1 GBq) 30 mCi is as effective as a high activity of radioiodine (3.7 GBq) 100 mCi to ablate small thyroid remnants after total thyroidectomy independent of the pre-treatment preparation, i.e., discontinuation of T4 or recombinant TSH. A meta-analysis of nine prospective trials including the ESTIMABL and HiLo trials recommended using the low-dose RAI due to less possibility of side effects and concluded that 30 mCi I-131 is sufficient for remnant ablation[36]. Another meta-analysis included only controlled randomized trials in which patients with DTC were allocated to low activity versus a high activity RAI. The lower activity was defined as 1100 MBq (30 mCi) and high activity as above 1100 MBq. The authors concluded that low dose RAI is as effective as high dose in patients with DTC. When the authors performed a sensitivity analysis to include only high quality trials based on their strict criteria, they detected no difference in successful ablation rate between low and high activity[37].

In the present study all the patients had low-risk early stage DTC; they were randomized to receive 30 mCi or 80 mCi RAI. Total or subtotal thyroidectomy was the least accepted surgery to be included in the trial. In this trial we showed that low dose RAI (30mCi) was as effective as high dose RAI (80 mCi) for thyroid remnant ablation in early stage low risk DTC. Six months post-ablation WBS was negative in 15/19 (79.5%) of the high dose arm and 15/26 (57.7%) of the low dose arm patients. The median serum undetectable level of sTg post-ablation was 0.2 ng/ml in the 80 mCi arm (in 84.2% of patients) versus 0.8 ng/ml (80.8% of patients) in the 30 mCi arm (P = 0.22). The ablation rate in our cohort was similar to a randomized prospective study of 40 patients by Zaman *et al.*[38] at 6 months post-ablation a negative WBS was detected in 70% of patients treated with 100 mCi of I-131 (Group A) and 50% of patients treated with 50 mCi of I-131 (Group B). Ha *et al*[39] found that the first RAI of 29.73 mCi was enough to achieve remnant ablation in 68.8% of patients with low to intermediate risk thyroid cancer as assessed by serum Tg and post-ablation diagnostic WBS. The ablation success rate of the present study was lower than that of some randomized trials, ranging from 90-94% [23, 24] which could be due to the different criteria for complete ablation. Bal *et al.*[40] retrospectively studied patients with low risk thyroid carcinoma, divided the patients into two groups, group 1(Group-1) patients were surgically ablated and received no RAI, group 2 (Group-2) patients had significant remnant in thyroid bed and received 30 mCi I-131. Among the (Group-2) 126 (82.3%) patients achieved successful ablation at the initial 6–9 months follow-up, whereas 27 (17.7%) patients failed to achieve ablation of thyroid remnant.

Short-term adverse events associated with high dose I-131 ablation of DTC are fairly common[41, 42]. Early complications include gastrointestinal symptoms, radiation thyroiditis, sialadenitis/xerostomia, bone marrow suppression, gonadal damage, dry eye, and nasolacrimal duct obstruction. Most of our patients in the 80 mCi group had side effects 84.2% whereas only 26.9% of patients receiving 30 mCi had adverse effects. In the randomized study by Mallick *et al.*[23]-the HiLo trial- the adverse event rate was 21% among patients receiving 30 mCi (220 patients) versus 33% among patients receiving 100 mCi (218 patients) (P = 00.7). Similarly in our cohort the incidence of short term side effects favored the high dose arm (P = 0.000). For example rates of neck pain in this present study was (11.5% versus 36.8% in the 30 and 80 mCi arms respectively, while in the HiLo trial neck pain occurred at rates of 7% and 17% in the 30 and 100 mCi groups respectively. Van Nostrand *et al*[15] reported that about 20% of patients presented with neck pain or swelling. Lu *et al.*[43] treated 117 patients with DTC after thyroidectomy with RAI 131 at doses ranging from 100-250 mCi for remnant ablation or treating distant metastases. Among 117 patients, 55 cases complained of neck pain, salivary gland pain or swelling occurred in 15 patients, headache in 10 patients, and fatigue or general malaise in 6 patients. In the present study among 45 patients 9 patients developed headache (7 cases in the 80 mCi arm, 2 cases in the 30 mCi arm), fatigue (4 patients received 80 mCi, 2 patients received 30 mCi), and sialadenitis (9 patients ablated with 80 mCi, and 1 patient ablated with 30 mCi). Administering 30 mCi reduces the adverse events to the patients and reduces the radiation exposure to household contacts of patients to well below the maximum annual limit of 5.0 mSv [44].

In the HiLo trial[23], a total of 21/220 patients (9.5%) who received low dose RAI needed a subsequent second dose, in comparison to 9/218 patients (4.15%) of the high dose group (P = 0.02). Among the 21 patients in the low-dose group, the second RAI doses were 29.7 mCi I-131 in 1 patient, 80 mCi-108 mCi in 8 patients, and more than 108 mCi in 21 patients. While all the 9 patients in the high dose group received more than 108 mCi. The RAI dose retreatment was given because of concerns about an initially positive scan or rise in the thyroglobulin levels at 6-9 months in patients receiving low dose radioiodine[45, 46]. In the present study, among the 30 mCi arm 6/26 patients (23.1%) required retreatment with RAI versus 2/19 (10.5%) patients in the 80mCi arm (P = 0.37). The second RAI doses in the arm 30 mCi were 100mCi in 1 patient with thyroid bed failure, 80 mCi in 2 patients (one thyroid bed failure, one cervical lymph node failure), 30 mCi in 2 patients (both with cervical lymph node failure) and neck dissection followed by 120 mCi in 1 patient. As for the 80 mCi arm the second doses were 80 mCi in 1 patient with cervical lymph node failure and 100 mCi in a patient with thyroid bed failure. Cho *et al.*[47] reported a successful

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confirmed remnant ablation in 51% of patients who received 29.7 mCi, which was achieved in only 24% of patients at the first RAI ablation. Kukulska *et al.*[48] conducted a two-stage prospective randomized study of 309 patients who underwent total or near total thyroidectomy. The first stage compared 30 mCi (86/309 patients) versus 60 mCi (128/309 patients) and the second stage compared 60 mCi versus 100 mCi (95/309 patients). In the group treated by 30 mCi 22% of patients needed second ablative dose of I-131. Thus the cumulative RAI activity administered was greater than 100 mCi in 22% of patients. Similarly 13.3% (128/309 patients) and 11.2% (95/309 patients) of patients treated with 60 and 100 mCi respectively required second ablative doses.

The patients who receive high dose ablative RAI require hospital isolation. Some of these patients complain about the inconvenience of isolation and the anxiety from the solitude. In the HiLo trial[23] patients who received low dose RAI had shorter hospital isolation duration than those who received high dose RAI, where 39.6% versus 7.1% required only 1 day in hospital isolation and 13% versus 36.3% required 3 days or more ($P < 0.001$ for both comparisons). A meta-analysis by Cheng *et al.*[36] showed that patients receiving low dose I-131 spent less time in hospital isolation than patients receiving high dose I-131 ($P < .05$) without significant heterogeneity between studies ($P = 0.43$). These data accord with the results of our study where patients ablated with 80 mCi had a significantly longer hospital isolation (3-5 days) compared to the patients ablated with 30 mCi (2-4 days) ($P = 0.008$). Only 5/26 (19.2%) patients in the low dose arm were hospital isolated due to various non-medical reasons such as pregnant wife, or patients coming from distant governorates.

The number of studies evaluating differences in long term outcomes in patients treated with high or low I-131 is limited. Bal and Padhy[49] in their review of radioiodine remnant ablation could not confirm a significant, consistent, benefit of RAI in decreasing cause-specific mortality or recurrence in low-risk DTC. A randomized clinical trial is needed to study the long-term effect of RAI in low-risk thyroid carcinomas. Kukulska *et al.*[48] designed a two- stage randomized clinical trial where 309 patients with low-risk DTC after total or near total thyroidectomy were ablated with 30 mCi versus 60 mCi in the first stage then they compared 60 mCi versus 100 mCi in the second stage. The authors evaluated the 5 years efficacy of thyroid remnant ablation and found no significant difference using 30, 60, and 100 mCi. The local relapse was stated in 2 (2.4%), 4 (3%) and 3 (3%) patients treated with I-131 activities of 30 mCi, 60 mCi and 100 mCi respectively. The patients were evaluated with stimulated serum Tg and I-131 scan or by radiological examinations. Bal *et al.*[40] studied retrospectively the long term outcome (recurrence, persistence and progression of disease) of RAI thyroid remnant ablation in low risk DTC. The authors classified the patients into two groups Group-1: 169 patients who were surgically ablated and Group-2: 153 patients who were ablated with 30 mCi RAI due to presence of significant remnant in thyroid bed. Following a median follow-up duration of 10.3 years, one patient in Group-1 ($n = 169$) developed nodal recurrence at 14 months for which the patient received single dose 50 mCi RAI. As regards Group-2 126/153 of patients were ablated with single dose of RAI, one of these patients had recurrence. While the remaining 27/153 (29.7%) patients in Group-2 eight patients had persistent disease after multiple RAI doses. The event-free survival rates were 99.4% and 94.1% ($P = 0.006$) in Group-1 and Group-2, respectively. Mazzaferri and Kloos[30] found no difference in 30-yr recurrence rates (4 and 6%, respectively; $P = 0.1$) between low-activity (29–50 mCi) and high-activity (51–200 mCi) I-131 remnant ablation groups.

5. Conclusion

We demonstrated that both 80 mCi and 30 mCi of radioactive Iodine (I-131) have similar success rates in the ablation of thyroid remnant of low risk differentiated thyroid cancer patients. The 30 mCi I-131 dose has the advantage of fewer side effects, shorter hospital admission duration, and lower expenses in low risk DTC patients. This is in agreement with different meta-analyses of retrospective studies and the small number of randomized studies in the literature. However, these findings need to be confirmed with a long- term well designed trial to study the adverse effects, the incidence of relapse and metastases of high versus low dose radioactive iodine ablation in low risk DTC. RAI ablation omission may be considered in some low risk DTC patients who can be only surgically ablated. Two ongoing randomized clinical trials compare RAI (30 mCi) versus no RAI in low risk DTC patients.

Conflict of interest

The authors have no conflict to interest to declare. The authors alone are responsible for the content and writing of the paper.

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