Original article, Endocrine

Thyroid Remnant Ablation of Differentiated Thyroid Carcinoma: a comparison of Ablation success with High and Low Doses of Radioiodine

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ABSTRACT:

Objectives: To assess efficiency of low dose ^{131}Iin thyroid remnant ablation of patients with differentiated thyroid cancer after surgical treatment. **Material and Methods**: 88 patients with differentiated thyroid cancer, (age 20-75 years) tumor stage T1 to T3, with disease confined to the thyroid or cervical lymph nodes. All patients were treated with ^{131}I after total thyroidectomy and pathologic lymph node resection, if present. A randomized double-armed prospective trial comparing low-dose [1110MBq (30mCi)] and high-dose [3700 MBq (100mCi)] radioiodine ablation.39 patients received low dose and 49 patients received high dose. Six months after the administration of radioiodine, measurements of TG, anti-TG antibodies together with neck ultrasound exam and ^{131}Iwhole-body scan were performed. The success rate of ablation is determined by negative whole body ^{131}I scan, negative neck ultrasonography and serum thyroglobulin level less than 2 ng/mL. **Results:** Successful ablation reported in 23 out of 39 cases (58.9 %) in the group receiving low-dose radioiodine [1110MBq] versus 37 out of 49 cases (75.5 %) in the group receiving the high dose [2960-3700 MBq] (P value= 0.098). A second follow up was performed one year after the ablative dose for the cases who had successive ablation from both groups. In the low dose group, only 12 out of 23 patients (52%) were available, all of them didn't show any disease recurrence, versus 17 cases out of 37 in the high dose group, 16/17 patients didn't had recurrence, while in one case there was a recurrent disease at the thyroid bed. **Conclusion:** From this ongoing data, non-significant higher success thyroid remnant ablation was recorded for high compared to low radioiodine doses.

Key words: Differentiated thyroid cancer, radioactive iodine-131, remnant ablation.

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INTRODUCTION:

Thyroid cancer is the most frequently occurring endocrine cancer, with more than 2100 new cases each year in the United Kingdom and more than 48,000 in the United States.(1) Most cases are differentiated thyroid cancer, which is associated with a high 10-year survival rate (90 to 95%).3 Many patients with differentiated thyroid cancer undergo radioiodine ablation to remove residual normal thyroid tissue after surgery. Some non-randomized studies have suggested that radioiodine ablation reduces rates of death and recurrence (2-5). However, there is uncertainty over the dose (administered activity) of radioiodine required for effective ablation. There are few of randomized and observational studies were inconclusive results regarding whether low-dose radioiodine (1.1 GBq [30 mCi]) was associated with good rate of ablation success as compared to high-dose radioiodine (3.7 GBq [100 mCi]).The European consensus report (2006) and American Thyroid Association (2009) reported that clinicians can choose between the low dose and the high dose without any reliable evidence from large randomized studies (6-8).The use of a smaller dose of radioiodine has important advantages. Many patients are women with children can spend less time in hospital isolation, and fewer side effects, especially a reduced risk of a second primary cancer(9, 10).Also lower-dose radiation reduces financial costs incurred by the health service provider and reduces exposure to radioactive iodine in the environment.

MATERIAL AND METHOD:

Study Design: A randomized, study, aimed to determine whether low-dose radioiodine could be used instead of high-dose radioiodine for post-operative thyroid remnant ablation in the period from January 2013 to January 2015, we conducted in Nuclear Medicine Unit, Faculty of Medicine, Cairo University, Egypt. Approval was obtained from the national research ethics panel. All patients provided written informed consent to participate in the study. Eligibility criteria were an age of 16 to 80 years., histological confirmation of differentiated thyroid cancer, tumor stage T1 to T3 with or without regional lymph-node involvement in surgical specimen but with no distant metastasis, total or Near total thyroidectomy with or without resection of cervical lymph nodes with no evidence of residual malignancy. Exclusion criteria were pathological cervical lymphadenopathy found in postoperative ultrasonography, distal metastasis, incomplete surgical resection of the tumor, anaplastic or medullary thyroid carcinoma, pregnancy, severe coexisting conditions, previous cancer with limited life expectancy, previous iodine-131 pre-ablation scanning and previous treatment for thyroid

cancer except surgery. **Randomization and Study Treatment:** Patients were randomly assigned to low-dose or high-dose radioiodine. All patients were instructed to follow a low-iodine diet for 3 weeks before ablation. Radioiodine ablation was recommended 1-4 months after surgery. Patients underwent thyroid hormone withdrawal 4 weeks before ablation. Radioactive iodine-131 was administered at a dose of 1.1 GBq (30 mCi) or 3.7 GBq (100mCi), depending on the study group. Patients receiving higher doses and hospital isolation until an assessment of radiation risk and clinical conditions permitted discharge. Patients received low ablative dose will be discharged on the day of ^{131}I administration with the usual written instructions for radiation protection. Pre and post- ablative dose administration Instructions were given in a written form (11). Patients from both groups underwent post-RAI-131 whole body scan (5-8) day later using dual-head gamma camera fitted with high-energy collimators and a bed speed of 8cm/min for simultaneous anterior and posterior whole body images. The energy window was set at 15 % centered on 364 kev with a 256×1024 size matrix. Ten minutes spot views of the head and using the same collimator and the same energy window as for the whole-body images were also obtained in a 128×128 matrix size and images were interpreted qualitatively by visual assessment of the size & tracer uptake intensity of the residual uptake. LT4 suppressive therapy was resumed after completion of the imaging. **Assessments:** All the patients underwent clinical examination; neck U.S was performed to determine the size of the postoperative residue and to exclude the presence of pathologically enlarged LN's. For all patients was performed 6-8 months after initial therapy , all patients were prepared in the same way for the administration of radioiodine by withdrawal of LT4 medication 4 weeks before administration of 3 mCi of ^{131}I (TSH level > 30 uIU/mL) and were asked to follow a low iodine diet 2-3 week before dose. Blood samples were taken to measure TG levels, and anti TG antibodies on the same day (just before) administration of diagnostic dose using radioimmunoassay. The serum TSH level was also measured. On the third day after administration of ^{131}I, Dx WBS was performed using dual-head gamma camera fitted with high-energy collimators and a bed speed of 6 cm/min for simultaneous anterior and posterior whole-body images. The energy window was set at 15 % centered on 364 keV with a 256×1024 size matrix. Ten minutes spot views of the head and neck with radioactive markers on the suprasternal notch using the same collimator and the same energy window as for the whole body images were also obtained in a 128×128 matrix size with a 15% energy window.

Study End Points: The primary end point was the success rate for ablation was defined as absence of any significant RAI-131 uptake at the thyroid bed, or abnormal iodine uptake elsewhere in the body, stimulated serum TG level less than 2 ng/mL, and neck ultrasonography didn't show any LN's or cervical mass or thyroid residue.
Statistical Analysis: Data was analyzed using SPSS win statistical package version 17 (SPSS Inc., Chicago, IL). Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. Multivariate analysis was done using forward stepwise logistic regression method for the significant factors affecting response on uni-variate analysis. Odds ratio (OR) with it 95% confidence interval (CI) were used for risk estimation. A p-value < 0.05 was considered significant. The differences between the two success rates are provided for each group: low-dose versus high-dose radioiodine

RESULTS:

Results were available for 88 patients, and most of these patients were females (79.5%) versus 20.5% males. The mean age was 40 years (range 20–77 years). Most patients were treated for papillary carcinoma 85.2% versus 14.8% follicular cancer thyroid. They were classified into 2 groups: (Group 1) includes patients who received low ablative dose of RAI^{131} (39 patients = 44.3%). (Group 2) includes patients who high ablative dose of RAI^{131} (49 patients= 55.7%). The patients' characteristics were well balanced between the two groups at baseline with no significant difference regarding the patient characteristics or the specific risk factors (Table 1). Overall successful complete ablation after single dose of 131I was reported in 60/88 patients representing 68.2% of the whole patient population, while incomplete ablation in the remaining 28 patients (31.8%). Successful complete 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 value = 0.098) (Fig. 1).In the group received (30 mCi) RAI^{131} dose, 16 cases (41.1%) had unsuccessful ablation on their follow up, 11 of them had thyroid residue that was detected in neck US and in WBS with RAI^{131}, 9 of them had follow up TG > 2 ng/ml, In 5 cases there was thyroid uptake in WBS with no corresponding thyroid tissue remnant on ultrasonography, with TG>2ng/ml ***(figure2).***

Table 1: Characteristics for the 88 patients treated with low and high dose of ^{131}I.

Risk Factor	High Dose	Low Dose	Total	P-value
Number of cases	49 (55.7%)	39 (44.3%)	88 (100%)	
Males	9 (18.4%)	9 (23.1%)	18 (20.5%)	0.58
Females	40 (81.6%)	30 (76.9%)	70 (79.5%)	
Age >45	16 (32.7%)	12 (30.8%)	28 (31.8%)	0.85
Age <45	33 (67.3%)	27 (69.2%)	60 (68.2%)	
PATHOLOY OF DIFFERENTIATED CANCER THYROID				
Papillary	42 (85.7%)	33 (84.6%)	75 (85.2%)	0.88
Follicular	7 (14.3%)	6 (15.4%)	13 (14.8%)	
Multifocal	15 (30.6%)	15 (38.5%)	30 (34.1%)	0.44
Unifocal	34 (69.4%)	24 (61.5%)	58 (65.9%)	
Tumor capsule +ve	11 (22.4%)	9 (23.1%)	20 (22.7%)	0.94
Tumor capsule–ve	38(77.6%)	30 (76.9%)	68 (77.3%)	
Vascular invasion	2 (4.1%)	3 (7.7%)	5 (5.7%)	0.65
No vs. invasion	47 (95.9%)	36 (92.3%)	83 (94.3%)	
T-STAGING				
Tx	1 (2%)	0 (0%)	1 (1.1%)	0.60
T1a	7 (14.3%)	10 (25.6%)	17 (19.3%)	
T1b	18 (36.7%)	9 (23.1%)	27 (30.7%)	
T2	16 (32.7%)	14 (35.9%)	30 (34.1%)	
T3	6 (12.2%)	5 (12.8%)	11 (12.5%)	
N-STAGING				
Nx	38 (77.6%)	30 (76.9%)	68 (77.3%)	0.42
N0	3 (6.15%)	5 (12.8%)	8 (9.1%)	
N1	8 (16.3%)	4 (10.3%)	12 (13.6%)	
Postoperative TG				
TG ≤10 ng/ml	28 (57.6%)	22 (71%)	41 (64.1%)	0.62
TG >10 ng/ml	14 (42.4%)	9 (29%)	23 (35.9%)	

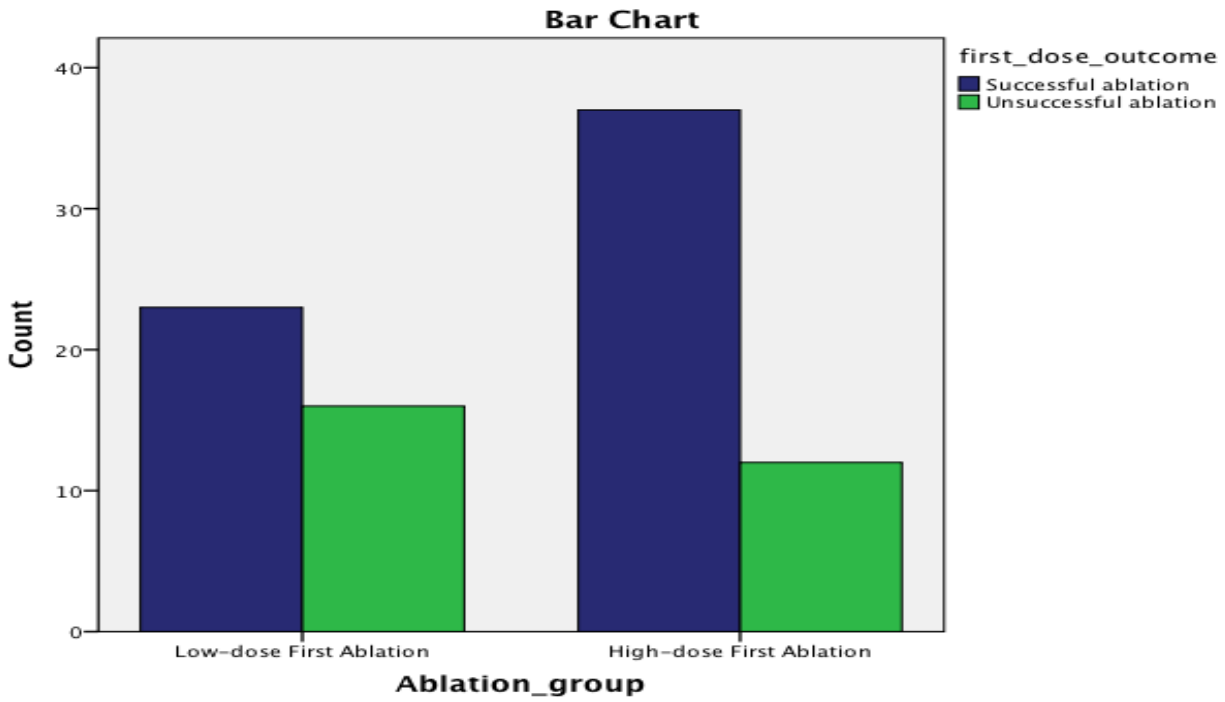

Figure 1. Bar chart of the overall response rate in the two studied groups.

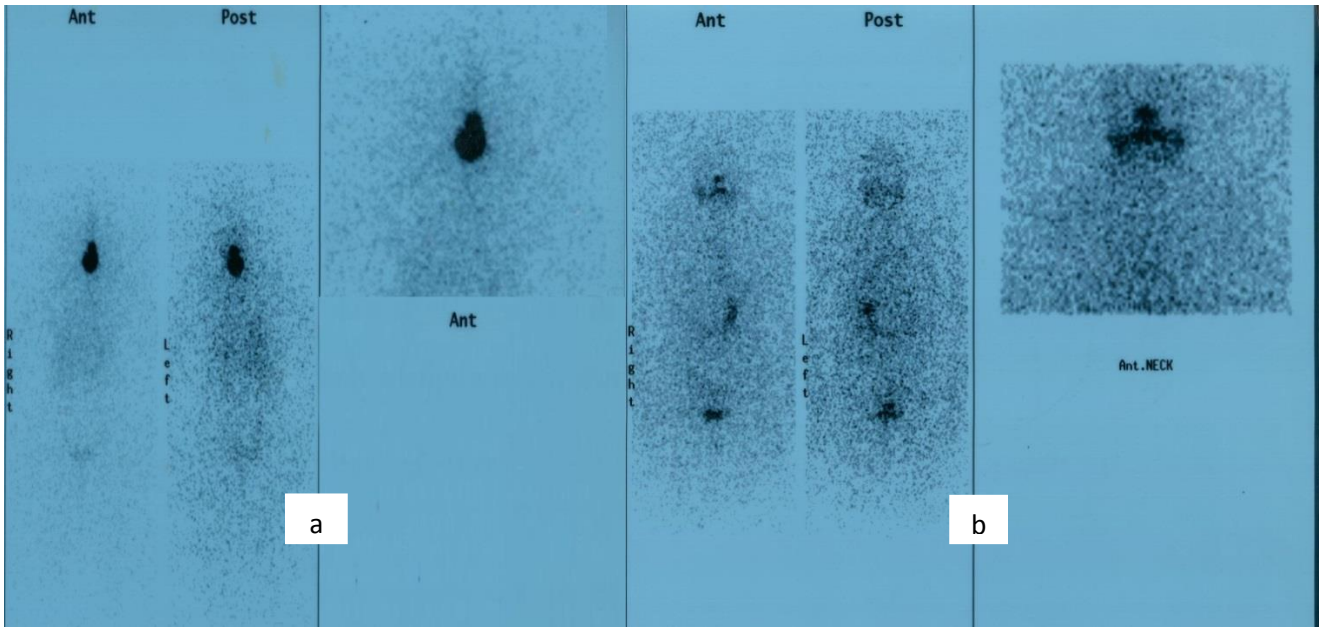

Figure 2. 48 years old female patient with papillary CA, the nodule measured 2×1.5 cm, with no invasion of thyroid capsule, followed by near total thyroidectomy, base line TG= 25ng/ml.US confirmed absence of sizable thyroid residue or cervical LNs **(a)** Low dose 131 of 30 mCi, followed by WBS at 5 days revealed tracer localization only in residual thyroid tissues. **(b)** 6 months later her follow up serum TG = <0.1 ng/ml, US showed no thyroid remnant, WBS following ablative acquired at 72 hours, it revealed complete ablation of residual functioning thyroid tissue in the neck.

In the group received RAI^{131} dose (100mCi), 12 cases (24.5%) showed unsuccessful ablation in response to the given dose on their first follow up. 8 of them had thyroid residue that was detected in neck US and in WBS with RAI^{131}, 6 of them showed TG >2 ng/ml, while the other 4 patients there was thyroid uptake that was not detected in ultrasonography, with Tg>2ng/ml ***(figure 3).*** Patients are further classified according to the ATA guidelines post-operative risk stratification criteria into low and intermediate risk (high risk patients are not eligible for the study) (7). Within the low ablation group, 15 out of 39 patients (38.5%) having low risk features, 7 of them had unsuccessful thyroid remnant ablation in response to the 1st dose of RAI-131, while 8 were successfully ablated. On the other hand, the 24 patients (61.5%) with intermediate risk only 9 patients were unsuccessfully ablated (37.5%) compared to 15 patients that were successfully ablated (62.5%) using the first doseNo statistical significant difference noted (P= 0.571).Within the high ablation group (n = 49), 16 patients (32.7%) out of them had low risk features, 6 had unsuccessful ablation while 10 were successfully ablated. On the other hand, the 33 patients (67.3%) with intermediate risk only 6 were unsuccessfully ablated compared to 27 that were successfully ablated using the first dose. No statistical significant difference noted (P = 0.14) ***table 2.***

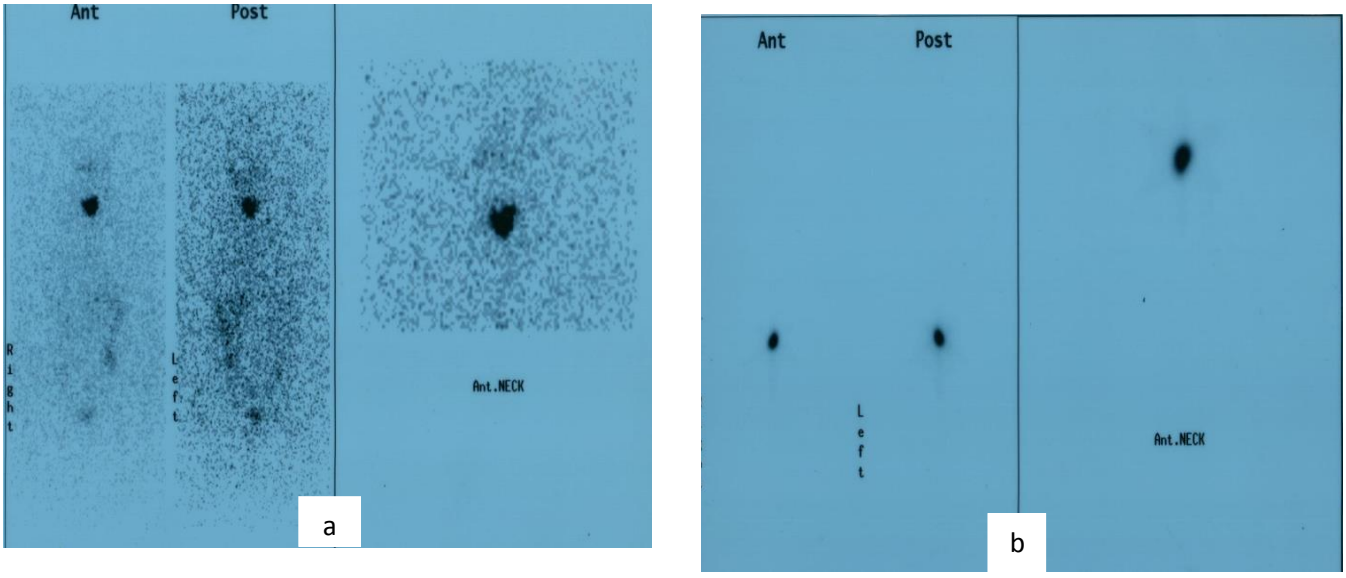

Figure 3: 32 years old male patient had uni-focal papillary Ca (3.6 X 3.2 cm), with no invasion of thyroid capsule. Following near total thyroidectomy, baseline TG= 14,8 ng/ml, TG-Ab's were -ve, US showed small thyroid residue (1.2X 0.8 cm) with no LNs ,**(a)** High dose 131 of 100 mCi, followed by WBS at 5 days, revealed only tracer uptake in residual thyroid tissues. **(b)** 7 months later her follow up serum TG = 8.6 ng/ml, US showed thyroid remnant (0.3 X 0.3 cm), follow up WBS revealed incomplete ablation of residual functioning thyroid tissue in the neck

Table 2: the relation between the ablation outcome to the risk group within the patients of high and low RAI groups

	Low Risk		**Intermediate Risk**	
	Ablated	**Non-ablated**	**Ablated**	**Non-ablated**
Low dose	7 (46.5%)	8 (53.5%)	15 (62.5%)	9 (37.5%)
High Dose	10 (62.5%)	6 (37.5%)	27 (81.8%)	6 (18.2%)

Recurrence: 12-18 months after the ablative dose, a second follow up was performed for the patients who had complete successive ablation from both groups. In the low dose group only 12 out of 23 patients (52%) was available with no evidence of disease recurrence, versus 17 out of 37 patients in the high dose group, 16 of them didn't had recurrence (43.2%), while one patient had a recurrent disease in the thyroid bed.

DISCUSSION:

The incidence of thyroid cancer is increasing worldwide including an increase by a factor of 2.6 in the United States from 1973 through 2006(12, 13).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 radioiodine(14-16) 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).(14, 17, 18) As with other curable cancers, it is important to reduce the risk of a radiation induced second cancer, as cancer thyroid after ablation can life for long time. Our findings relate to ablation success at 6 to 9 months and do not address future recurrences. We included T3 and lymph-node–positive tumors, and pre-ablation cervical US was performed to confirm absence of any sizable thyroid residue (>1cm) or lymphadenopathy. Furthermore, we assessed the patients on the basis of a fixed timeline (6 to 9 months) after ablation, using a specific definition of ablation success on the basis of stimulated thyroglobulin testing and diagnostic RAI131 scanning and neck US. Several series, including two recent prospective, multicenter studies (19-31) have compared the effectiveness of RAI131 ablation when using low RAI131 or high RAI131 activities (>100mCi) and, their results indicate that low RAI131 activities are as effective as high RAI131 activities.

In our study ablation success rates showed higher ablation using high-dose radioiodine especially in subgroups of patients with T3 stage tumors and lymph-node involvement than to low ablative dose; however the difference between both subgroups was statistically insignificant. Such finding confirmed that patients receiving low-dose radioiodine don't need hospital isolation unlike those receiving the high dose(14, 17). Much debate still exists regarding the activities administered in intermediate risk (microscopic invasion of tumor into the peri-thyroidal soft tissues, aggressive tumor histology, and node positive). In this context, no evidences are provided regarding the optimal RAI^{131} activity to be administered and current recommendations, advocating the use of high RAI^{131} activities, are based mainly on the expert opinion rather than clinical evidence(7, 8).Castagn et al. evaluated, retrospectively, the impact of RAI^{131} activities on the outcome of 225 DTC patients classified as intermediate risk, their study design was similar to ours as their study involved 225 DTC patients classified as intermediate risk. They stratified DTC patients in two homogenous groups, according to the RAI activity given for remnant ablation: 85/225 patients (37.8%) were treated with low RAI activities (1110–1850 MBq) and 140/225 (62.2%) with high RAI activities (>3700 MBq). Patients treated with low and 84/140 (60%) patients treated with high RAI activities fulfilled the criteria for remission No difference in clinical status was found between patients treated with low or high RAI activities (P value= 0.56). Biochemical disease (detectable serum Tg with no evidence of disease) was found in 16/85 (18.8%) patients treated with low and in 20/140 (14.3%) patients treated with high RAI activities. Metastatic disease was found in 18/85 (21.2%) patients treated with low and in 36/140 (25.7%) patients treated with high RAI activities(32) **Mallick et al., 2012** also concluded that low-dose radioiodine plus thyrotropin alfa was as effective as high-dose radioiodine, with a lower rate of adverse events in their randomized study that was conducted at 29 centers in the United Kingdom involving 438 patients comparing low-dose and high-dose radioiodine, each in combination with either thyrotropin alfa or thyroid hormone withdrawal before ablation. Ablation success rates were 85.0% in the group receiving low-dose radioiodine versus 88.9% in the group receiving the high dose and 87.1% in the thyrotropin alfa group versus 86.7% in the group undergoing thyroid hormone withdrawal. All 95% confidence intervals for the differences were within ±10 percentage points, indicating no inferiority. Similar results were found for low-dose radioiodine plus thyrotropin alfa (84.3%) versus high-dose radioiodine plus thyroid hormone withdrawal (87.6%) or high-dose

radioiodine plus thyrotropin alfa (90.2%) (30).
Limitations of the Study: The small number of evaluated patients showed non-significant higher success for thyroid ruminant ablation using high compared to low Radio -iodine dose. Also, some of the patients lost follow up after treatment; however this study is still ongoing for larger number of patients.
To conclude: The use of low RAI-131 ablative dose (30mCi) in patients with differentiated thyroid cancer who doesn't have gross residual disease of extra thyroidal metastasis after surgical treatment, may be effective as the high dose (100 mCi) ablation. It's better to use low dose due to its lower cost, and to reduce the incidence and severity of RAI-131side effects & to skip the need for hospital admission foe isolation which has a high financial and psychological burden. However, more studies with longer duration involving more patients are needed to determine that concern, especially in patients with intermediate risk group.

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