RESEARCH ARTICLE

Comparable Ablation Efficiency of 30 and 100 mCi of I-131 for Low to Intermediate Risk Thyroid Cancers Using Triple Negative Criteria

Nosheen Fatima, Maseeh uz Zaman*, Areeba Zaman, Unaiza Zaman, Rabia Tahseen

Abstract

Background: There is controversy about ablation efficacy of low or high doses of radioiodine-131 (RAI) in patients with differentiated thyroid cancers (DTC). The purpose of this prospective study was to determine efficacy of 30 mCi and 100 mCi of RAI to achieve successful ablation in patients with low to intermediate risk DTC. Materials and Methods: This prospective cross sectional study was conducted from April 2013 to November 2015. Inclusion criteria were patients of either gender, 18 years or older, having low to intermediate risk papillary and follicular thyroid cancers with T1-3, N0/N1/Nx but no evidence of distant metastasis.Thirty-nine patients were administered 30 mCi of RAI while 61 patients were given 100 mCi. Informed consent was acquired from all patients and counseling was done by nuclear physicians regarding benefits and possible side effects of RAI. After an average of 6 months (range 6-16 months; 2-3 weeks after thyroxin withdrawal), these patients were followed up for stimulated TSH, thyroglobulin (sTg) and thyroglobulin antibodies, ultrasound neck (U/S) and a diagnostic whole body iodine scan (WBIS) for ablation outcome. Successful ablation was concluded with stimulated Tg< 2ng/ml with negative antibodies, negative U/S and a negative diagnostic WBIS (triple negative criteria). ROC curve analysis was used to find diagnostic strength of baseline sTg to predict successful ablation. Results: Successful ablation based upon triple negative criteria was 56% in the low dose and 57% in the high dose group (non-significant difference). Based on a single criterion (follow-up sTg<2 ng/ml), values were 82% and 77% (again non-significant). The ROC curve revealed that a baseline sTg level ≤ 7.4 ng/ml had the highest diagnostic strength to predict successful ablation in all patients. Conclusions: We conclude that 30 mCi of RAI has similar ablation success to 100 mCi dose in patients with low to intermediate risk DTC. A baseline sTg ≤ 7.4 ng/ml is a strong predictor of successful ablation in all patients. Low dose RAI is safer, more cost effective and more convenient for patients and healthcare providers.

Keywords: Radioiodine ablation - differentiated thyroid cancer - successful ablation - low dose - high dose

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Introduction

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy comprised of papillary (80%) and follicular (10%) types and is associated with high 10-year survival rate (90 to 95%) (Sawka et al., 2004; Zaman et al., 2013). Adjuvant ablation of residual functioning thyroid tissue using radioiodine-131 (RAI) is considered a mainstay of managing these cancers (Cooper et al., 2006) due to advantages of eradication of occult cancer and improved sensitivity of sTg and post-operative whole body iodine scan (WBIS) as a marker for disease recurrence (Sherman 2003).

Successful ablation is defined as undetectable sTg and a negative WBIS (Pacini et al., 2006). However, the effective dose of RAI required to achieve successful ablation is not known and a systemic review was inconclusive about the efficacy of 30 mCi or 100 mCi of RAI (Hackshaw et al., 2007). In Pakistan as per local nuclear regulatory authority, a patient receiving ≥ 30 mCi of RAI needs to be admitted in isolation till radiation exposure falls down to <50microSievert/hour at 1 meter distance (Fatima et al., 2016).This certainly has a financial, social and psychological impact upon patients receiving higher dose of RAI.

The purpose of this prospective study was to find out the efficacy of low dose (30 mCi) and high dose (100 mCi) of radioiodine-131 to achieve successful ablation in thyroidectomized patients with low to intermediate risk DTC.

*[1]Department of Nuclear Medicine, Dr Ziauddin Hospital, [2]Department of Radiology, Aga Khan University Hospital, [3]Students MBBS, Dow University Health Sciences, Karachi, Pakistan *For correspondence: maseeh.uzzaman@aku.edu*

Materials and Methods

This was a prospective cross sectional study which was conducted at Nuclear Medicine Departments of Dr Ziauddin Hospital and Aga Khan University Hospital Karachi from April 2013 till November 2015. The study was duly approved by ethical review committee of primary institute. The inclusion criteria of the study were patients of either gender, 18 years or older, having low to intermediate risk papillary and follicular thyroid cancers with T1-3, N0/N1/Nx but no evidence of distant metastasis (01 female patient was excluded due to positive post-ablative WBIS for distant bony metastases confirmed on subsequent MRI study as well). Six patients with positive thyroglobulin antibodies were also excluded from the study.

We recruited 39 (32 females and 07 males) biopsy proven patients with DTC who were stratified by their referring physicians as low to intermediate risk and were prescribed 30 mCi dose of RAI which was administered at one of two primary institutes. During this study period we have also selected a propensity matched group of patients who were also stratified by their physicians as low to intermediate risk group and suggested 100 mCi of RAI which was administered at Dr Ziauddin Hospital only. As per study protocol all patients had a serum thyroid stimulating hormone (TSH) [>30 ulU/ml], stimulated thyroglobulin level (ng/ml) with negative thyroglobulin antibodies (IU/ml) before RAI administration. They were also advised to be on low iodine diet 2 weeks prior and one week after RAI to deplete iodine pool of their bodies. Informed consents were acquired from all patients and counseling was done by nuclear physicians regarding benefits and possible side effects of RAI. RAI was administered in liquid form and patients who received 30 mCi of RAI were released 45 minutes after administration (noadmission) while patients who had 100 mCi were admitted in isolation room for 1-2 days till their exposure rate declined to required statutory limits. A post-ablative WBIS was performed 3-8 days after RAI administration. Uptake over thyroid bed, cervical region and extra-cervical region were labeled as residual functioning thyroid tissue, functioning nodal and distant metastasis respectively. After 06 months (range 6-16 months; after 2-3 weeks thyroxin withdrawal), these patients were followed up with stimulated TSH, sTg and thyroglobulin antibodies, ultrasound neck and a diagnostic WBIS with 2-4 mCi of RAI for ablation outcome. Successful ablation was considered if stimulated Tg< 2ng/ml with negative antibodies, negative neck ultrasound and a negative diagnostic WBIS (triple negative criteria).

Statistical Analysis: Data were analyzed using commercially available packages such as the Medcalc statistical software (MedCalc Software, Ostend, Belgium), version 11.3.10 and the statistical package for social sciences (SPSS version 17; SPSS Inc., Chicago, Illinois, USA). Comparisons between patient groups were made using the Student t-test for continuous variables and the $\chi 2$-test for categorical variables. Continuous variables were described by mean±SD. Receiver-operating characteristic curves (ROCs) were plotted for predictive strength of baseline sTg for successful ablation. P-values less than 0.05 were considered significant.

Results

We included 100 patients during the study period and out of which 39 patients did receive 30 mCi of RAI on out-patient basis (Low Dose Group) and 61 were administered 100 mCi on an in-patient basis and admitted in anisolation room (High Dose Group). The mean age of participants in low and high dose groups were 38±13 years and 39±15 years respectively (p value non-significant). There was a gross female preponderance in both groups which was significantly higher in high dose group. More than 2/3rd patients in both groups had papillary cancerswithout any statistical significance. Tumor staging in low and high dose

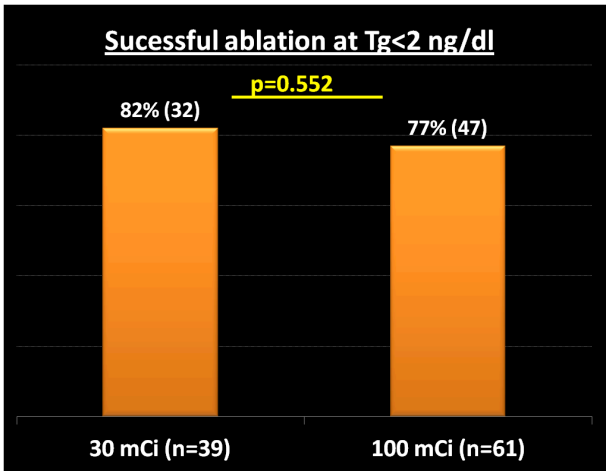

Figure 1. Compartive analysis of sucessful I-131 ablation in both groups at single cut off serum thyroglobulin <2 ng/dl

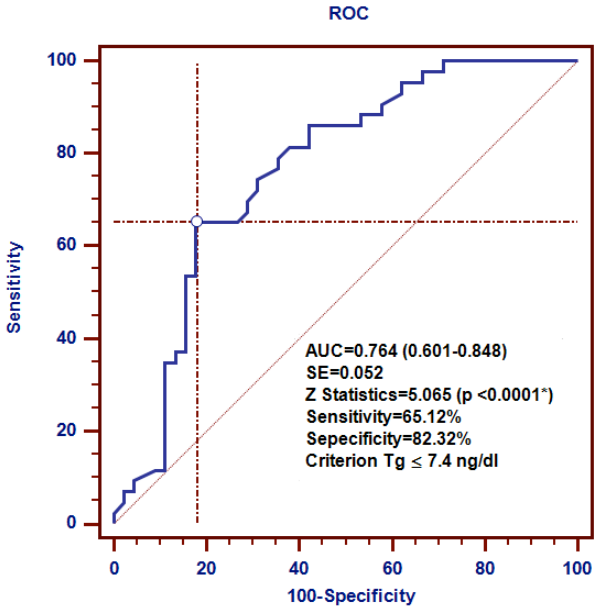

Figure 2. Receiver Operating Characteristics curve of baseline serum thyroglobulin as predictor of successful I-131 ablation for both groups

Table 1. Patients' Demographic Data

Variables	30 mCi (n=39)	100 mCi (n=61)	X2/t-test	P values
Age (mean ±SD) years	38 ± 13	39 ± 15	0.342	0.733
Gender (Male: Female)	07:32 (18:82%)	22:39 (39:64%)	4.872	0.027*
T1	14 (36%)	27 (44%)	0.624	0.429
T2	20 (51%)	25 (41%)	0.952	0.329
T3	05 (13%)	06 (10%)	0.214	0.644
T4	00 (00%)	03 (05%)	1.991	0.158
Tx	00 (00%)	00 (00%)	---	---
Baseline Nodal status				
N1	04 (10%)	23 (38%)	9.351	0.002*
N0	17 (44%)	28(46%)	0.038	0.845
Nx	18 (46%)	10 (16%)	10.584	0.001*
Type of WDTC				
PC	30 (77%)	50 (82%)	0.369	0.544
FC	09 (23%)	11 (18%)	0.369	0.544
Baseline TSH status (Pre ablation)	89	62	-2.843	0.005*
median (range)	(4.32-150)	(0.3->100)		
Baseline STg	5.56 (<0.2-88)	17.7 (<0.2-415)	7.788	<0.0001*
(Negative Tg Antibodies)				
Follow up months	10 ± 04	11 ± 05	1.052	0.296
Successful ablation (STg <2 ng/ml negative I-131 and US)	22 (56%)	35 (57%)	0.01	0.922

*p<0.05; PTS=Primary Tumor size; PC=Papillary Carcinoma; FC=Follicular Carcinoma; TSH=Thyroid Stimulated Hormone; STg=Stimulated Thyroglobulin; FU=Follow up

groups for T1 (36% *vs* 44%), T2 (51% *vs* 41%) and T3 (13% *vs* 10%) was statistically not different. Nodal staging in low and high dose group was significantly different for N1 (10% *vs* 38%) and Nx (46% *vs* 16%) while it was not significant for N0 (44% *vs* 46%). Baseline sTg level was significantly lower in low dose group (5.56 ng/ml; range: <0.2-88) than high dose group (17.7ng/ml; range: <0.2- 415). Successful ablation based upon triple negative criteria was 56% in low dose and 57% in high dose (non-significant p value) [Table 1]. Successful ablation based on single criterion (follow-up sTg<2 ng/ml) was 82% in low dose group than 77% in high dose group which was again statistically non-significant (Figure 1). We used ROC curve analysis to find out diagnostic strength of baseline sTg levels to predict successful ablation. The ROC analysis measured that baseline sTg level ≤ 7.4 ng/ml has the highest diagnostic strength to predict successful ablation in all patients who received RAI (both low and high dose groups) (Figure 2).

Discussion

Radioiodine-131 use as an adjuvant option is well established in high risk patients with differentiated thyroid cancer (with or without distant metastasis). Over last two decades there has been an increasing trend of its use even in patients with low risk disease with a debate about the optimal dose to achieve successful ablation (Haymart et al., 2011). There has been conflicting data showing the ablative outcome with different doses of RAI (Hackshaw et al., 2007; Barbaro 2010). Our study clearly shows equal ablation efficacy of 30 mCi RAI as compared to 100 mCi dose. This finding will have a significant impact upon the management of low to intermediate risk patients as low dose RAI can be given on an outpatient basis. This obviously would reduce not only the cost associated with lower dose of isotope and hospital stay but also alleviates the anxiety of patients and their families regarding the stay in an isolation room. Our findings are in concordance with published randomized clinical trial including 160 patients with DTC with ablation efficacy of 52% and 56% for 30 mCi and 100 mCi of RAI respectively (Maenpa et al., 2008). However, our ablation efficacy is significantly lower than what has been published in two recent randomized clinical trials (about 92% in low and high dose groups (Schlumberger et al., 2012); 85% and 87% in low and high dose group respectively (Mallick et al., 2012). The plausible explanation for these higher ablation success rates in these studies is use of lenient criteria (dual negative criteria: undetectable sTg with a negative ultrasound [Schlumberger et al., 2012]) or undetectable sTg with a negative iodine scan [Mallick et al., 2012]) while we have used a strict triple negative criteria. However, our successful ablation ratesalso reach to 82% and 77% for low and high dose groups respectively for lenient criteria. Another important aspect of our and other published studies favoring 30 mCi dose of RAI is reduced radiation exposure to patients with low risk DTC and most these are young and this obviously reduce the risk of second primary malignancy (Rubino et al., 2003; Iyer et al., 2011). Based on these published facts and results of published results of randomized clinical trials,

American Thyroid Association in its recent guidelines has also favored the use of low dose RAI for low to intermediate risk patients (Byran et al., 2016).

In thyroidectomized patients with adjuvant RAI, stimulated Tg level considered as a reliable marker for detecting residual and recurrent disease (Fatima et al., 2015). Similarly pre-ablation stimulated Tg is assumed to have an indirect correlation with adequacy of thyroidectomy in low risk patients (Zaman et al., 2013). Our study shows that a baseline stimulated Tg level ≤ 7.4 ng/ml has a significantly high predictive value for successful ablation. This aspect draws our attention toward a direct association between residual tissue over thyroid bed and ablation success and this in concordance with previously published studies (Maenpa et al., 2008; Schlumberger et al., 2012; Fatima et al., 2015). This finding also elucidates the role of surgeons performing total thyroidectomy to ensure successful ablation after adjuvant RAI. However, a recently published randomized clinical trial does not favor this notion (Mallick et al., 2012).

There are few strengths of our study. First, all TSH, Tg and thyroglobulin antibodies were performed at a single laboratory using chemiluminescent assays. This avoids the possible variation in assays' values if it would have been measured at different laboratories. All histopathology samples were also reported by pathologists of Aga Khan University. Second, this study included patients with tumor sizes from T1-3 and also patients with nodal metastases (N1). This indeed tells us about the efficacy of low dose RAI in achieving an ablation rate as good as high dose of RAI in patients with larger tumor and nodal metastases (intermediate risk group). This has also been observed by a recently published clinical trial as well (Mallick et al., 2012). Third, we have used triple negative criteria (sTg<2 ng/ml with negative antibodies, negative ultrasound and diagnostic WBIS) for ablation success as compared to recently published large randomized clinical trials which have used dual negative criteria (undetectable sTg and negative ultrasound [Schlumberger et al., 2012] or diagnostic WBIS [Mallick et al., 2012]). This study has some limitations which are worth mentioning as well. First, we did not study the side effects associated with high and low doses of RAI. Second, we did not measure urinary iodine to ascertain iodine pool of patients undergoing RAI; although we have ensured a low iodine diet 2 week prior and 1 week after RAI treatment. Third, we did not mention the follow-up findings of these patients regarding the recurrence; however, currently we are collecting the data in this regard.

We conclude that 30 mCi of RAI has similar ablation success to 100 mCi dose in patients with low to intermediate risk DTC. Baseline sTg ≤ 7.4 ng/ml is a strong predictor of successful ablation in all patients. Low dose RAI is safer, more cost effective and more convenient for patients and healthcare providers.

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