ORIGINAL ARTICLE

EFFICIENCY OF LOW DOSE 30MCI OF I-131 FOR LOW TO INTERMEDIATE RISK THYROID CANCERS USING TRIPLE NEGATIVE CRITERIA

Asifa Jamali, Nanik Ram✉, Farah Khalid, Mabrooka Kazi, Najmul Islam
Department of Medicine, Aga Khan University Hospital, Karachi-Pakistan

Background: Radioiodine-131 ablation (RAI) of residual functioning thyroid tissue is a staple in the treatment of many Thyroid Cancer patients after surgery. However, it is debated and re-examined to avoid overtreatment of low-risk carcinomas and improve the detection of tumours that are more aggressive. We determined the difference in treatment response during one year after ablation. Moreover, we investigated differences between patients who did not undergo RAI Treatments and compared them to patients receiving a low dose of iodine (30 mCi). **Methods**: This was a retrospective study conducted at Aga Khan University Hospital (AKUH) in Karachi, Pakistan. The study population was patients with low to intermediate risk of well Differentiated thyroid cancers (DTC). A descriptive analysis was done. Categorical variables were represented as frequencies and percentages. The comparison was done by Chi-square. **Results:** Out of 102 participants, mean age was 41.88 years and the majority were females (73.5%). The common diagnosis was papillary thyroid carcinoma (84.3%). A low recurrence risk was reported in 89.2%. 98% of patients were given a 30-mci dose of RAI. The majority 83.3% of participants reported a Post-ablative Whole-body iodine scan (WBIS) showing no distant metastasis 1 year after RAI ablation. 55.8% of participants reported an excellent response to treatment, followed by 17.65% of participants having incomplete biochemical responses. **Conclusion:** This study concludes that a low dose of RAI provided an excellent response to treatment in contrast to patients who had no RAI dose. After 1 year of follow-up, ultrasound imaging showed negative structural recurrence in the majority of patients which proves that a low dose of RAI can help for a disease-free follow-up.

Keywords: Differentiated thyroid cancers (DTC); Radioiodine ablation (RAI)

Citation: Jamali A, Ram N, Khalid F, Kazi M, Islam N. Efficiency of low dose 30 mCi of I-131 for low to intermediate risk thyroid cancers using triple negative criteria. J Ayub Med Coll Abbottabad 2025;37(1):3–8.

DOI: 10.55519/JAMC-01-12782

INTRODUCTION

The vast majority of thyroid malignancies arise from follicular epithelial cells, with the major histological subtypes being papillary thyroid cancer (80%) and follicular cancer (10%). These subtypes are referred collectively as well-differentiated thyroid cancers (DTC) and are associated with a high 10-year survival rate (90–95%) and low recurrence rates.[1]

While thyroid cancer remains a common phenomenon in high-income countries, its incidence has been increasing in low- and middle-income countries.[2] Adequate surgery is the most critical therapeutic variable impacting prognosis, and adjuvant radioiodine-131 ablation (RAI) of residual functioning thyroid tissue is regarded as a staple in the treatment of many tumours.[3]

In recent years, this convention has been actively debated and re-examined to avoid the overtreatment of low-risk carcinomas, along with improvement in the detection of more aggressive tumours.[3] There is a need for risk stratification and disease staging to ascertain the optimal RAI dosage required for successful ablation, particularly in individuals with low-risk disease.[4] The American Thyroid Association has endorsed RAI ablation to be considered in cases of low-risk tumours with aggressive histology, and a low dose is an acceptable strategy to eradicate residual thyroid tissue and facilitate ongoing surveillance.[3] RAI treatment has an adjuvant role of preventing recurrences in patients with intermediate-risk tumours, with customized dosages required to achieve this goal (30–50 mCi). Finally, RAI ablation has a therapeutic goal of completely eradicating illness in high-risk tumours, and greater doses are preferable for this purpose.[5] Despite the results suggesting that low-dose RAI ablation is ineffective in patients with low- and intermediate-risk thyroid cancer[6] there is still no international consensus on the dosage of RAI. The aim of this study was to determine the difference in treatment response in patients one year following RAI ablation. The current study also investigated the differences between the patients

who did not undergo RAI treatments and those receiving low dose iodine (30 mCi).

MATERIAL AND METHODS

A retrospective study was conducted at session of endocrinology, department of medicine from January 2014 to 31st December 2020 at aga khan university hospital (AKUH) Karachi, Pakistan.

The study population were patient with age more than 18 years, can be of either sex, have a low intermediate risk of DTC. The exclusion criteria include a patient with less than one year of follow up after RAI ablation and those with recurrence of thyroid carcinoma.

After getting permission from ethical review committee of agha khan university hospital ERC the data was collected with the help of information from the department of HIMS. The data was collected in the google form by health care professionals. The data was collected through unique identification number. The patient's identities were protected.

During the course of study, all information gathered was stored in an isolated data base devoid of any personal identification. It should be noted that record that contained sensitive personal data were not physically transferred from research facility are electronically saved in non-secure location. It is important to mention that assumption from the ethical review committee (ERC) of Agha Khan University hospital had been obtained.

The analyses was conducted by using the Statistical package for social science SPSS (Release 19.0, standard version, copyright © SPSS; 1989-02). A descriptive analysis was done. Categorical variables were represented as frequencies and percentages. Comparison was done by Chi square. A *p*-value of less than 0.05 was considered significant with a confidence level of 95%.

RESULTS

A total of 102 participant were enrolled in this study. The mean age of the participants was 41.88 and majority were females (75, 73.5%). The most common diagnosis found through histology was papillary thyroid carcinoma (86, 84.3%). Almost half of the patients had T1 tumour size (53, 52%) and a lymph node affection of N0 (95, 93.1%). A slow recurrence risk was reported in the result (91, 89.2%). 100 (98%) patients were given 30 mci dose of RAI. 75 (73.5%) of the participants had Negative for Structural recurrence. Majority (85, 83.3%) of the participants reported no post-ablative Whole-body iodine scan (WBIS) showing distant metastasis 1 year after RAI ablation. 57 (55.8%) of the participants reported an excellent response of treatment, followed by 18 (17.65%) of the participants having incomplete biochemical response. Further details are reported in table 1.

A significant association (*p*-value 0.004) was reported amongst association of gender and treatment response where majority of the female participants (47, 62.7%) reported an excellent response to treatment while only 10 men (37%) out of 27 had an excellent response. It was also reported that 50 (61%) of the participants had no presence of multifocality due to excellent response of treatment, followed by 15 (18.3%) having incomplete biochemical response. It is also worth noticing that seven (35%) participants out of 20, had presences of multifocality even after excellent response to treatment (*p*-value 0.001). There was a significant association (*p*-value 0.017) found between participants who received RAI dose, 57 (57%) out of 100 participants reported an excellent response to treatment, followed by 17 (17%) had incomplete biochemical response. Only two participants who did not receive the dose had incomplete biochemical response and incomplete structural response respectively. Amongst the significant association (*p*-value <0.001) of lymph node affection and response to treatment, 56 (58.9%) of the patients who had N0 lymph node affection had an excellent response to treatment while 17 (17.9%) had incomplete biochemical response.

This study reports a major participation of females. Similarly, 75 (73.5%) of them received 30 mCi were as only 25 (24.5%) males were given 30 mCi. 84 (82.4%) of the participants having Papillary Thyroid Carcinoma were given 30 mCi were as only 16 (15.75) patients with Follicular Thyroid Carcinoma were given 30 mCi. 56 (54.9%) participants with free margins were given 30 mCi whereas only one participant with free margin and near margin were given no RAI. There was a significant association found between Lymph node affection and RAI dose. 95 (93.1%) of participants with N0 lymph node affection were given 30 mCi dose. A significant association was also found between the results of Ultrasound Imaging at 1 year and Dose of RAI. 75 (86.2%) of the participants had negative for structural recurrence who were given 30 mCi dose while there were only 10 (11.5%) participants with positive for structural recurrence who were given 30 mCi.

Table-1: Frequency table

Variable Name	
Age	41.88±13.16
Gender	
Male	27 (26.5%)
Female	75 (73.5%)
Histology	
Papillary Thyroid carcinoma	86 (84.3%)
Follicular thyroid carcinoma	16 (15.7%)
Multifocality	
No	82 (80.4%)
Yes	20 (19.6%)
Margins	
Free	57 (55.9%)
Near contact capsule	17 (16.7%)
Contact with Capsule	16 (15.7%)
Capsule Invasion	12 (11.8%)
Tumour Size	
T1	53 (52%)
T2	31 (30.4%)
T3	18 (17.6%)
Lymph node affection:	
N0	95 (93.1%)
N1a	5 (4.9%)
N1b	2 (2%)
Initial recurrence risk:	
Low	91 (89.2%)
Intermediate	11 (10.8%)
Radioactive Iodine dose:	
NO RAI	2 (2%)
30 mci	100 (98%)
Post-ablative Whole-body iodine scan showing distant metastasis	
No	99 (97.1%)
Yes	3 (2.9%)
Ultrasound imaging at 1 year	
Negative for Structural recurrence	75 (73.5%)
Positive for Structural recurrence	12 (11.8%)
Post-ablative Whole-body iodine scan showing distant metastasis 1 year after RAI ablation:	
No	85 (83.3%)
Yes	3 (2.9%)
Response to treatment:	
Excellent	57 (55.9%)
Incomplete Biochemical response	18 (17.6%)
Incomplete structural response	4 (3.9%)
Incomplete Biochemical response and Incomplete structural response	5 (4.9%)
Indeterminate response	4 (3.9%)
Lost to follow up	14 (13.7%)

Table-2: Association of treatment Response to demographic and clinical characteristics

	Excellent	**Incomplete Biochemical response**	**Incomplete structural response**	**Incomplete Biochemical response and Incomplete structural response**	**Indeterminate response**	**Lost to follow up**	***p*-Value**
Gender							
Male	10 (17.5%)	7 (38.9%)	4 (100%)	2 (40%)	2 (50%)	2 (14.3%)	
Female	47 (82.5%)	11 (61.1%)	0 (0%)	3 (60%)	2 (50%)	12 (85.7%)	0.004
Histology							
Papillary Thyroid carcinoma	48 (84.2%)	14 (77.8%)	4 (100%)	3 (60%)	3 (75%)	14 (100%)	0.267
Follicular thyroid carcinoma	9 (15.8%)	4 (22.2%)	0 (0%)	2 (40%)	1 (25%)	0 (0%)	
Multifocality:							
No	50 (87.7%)	15 (83.3%)	4 (100%)	1 (20%)	4 (100%)	8 (57.1%)	0.001
Yes	7 (12.3%)	3 (16.7%)	0 (0%)	4 (80%)	0 (0%)	6 (42.9%)	
Tumour size							
T1	30 (52.6%)	9 (50%)	2 (50%)	1 (20%)	2 (50%)	9 (64.3%)	0.428
T2	18 (31.6%)	4 (22.2%)	2 (50%)	3 (60%)	0 (0%)	4 (28.8%)	
T3	9 (15.8%)	5 (27.8%)	0 (0%)	1 (20%)	2 (50%)	1 (7.17%)	

	Excellent	Incomplete Biochemical response	Incomplete structural response	Incomplete Biochemical response and Incomplete structural response	Indeterminate response	Lost to follow up	*p*-Value
Radioactive Iodine Dose							
NO RAI	0 (0%)	1 (5.6%)	1 (25%)	0 (100%)	0 (0%)	0 (0%)	0.017
30 mci	57 (100%)	17 (94.4%)	3 (75%)	5 (100%)	4 (100%)	14 (100%)	
Margins							
Free	31 (54.4%)	13 (72.2%)	0 (0%)	2 (40%)	3 (75%)	8 (57.1%)	0.246
Near	8 (14%)	3 (16.7%)	2 (50%)	1 (20%)	1 (25%)	2 (14.3%)	
Contact Capsule	10 (17.5%)	2 (11.1%)	2 (50%)	0 (0%)	0 (0%)	2 (14.3%)	
Capsule Invasion	8 (14%)	0 (0%)	0 (0%)	2 (40%)	0 (0%)	2 (14.3%)	
Lymph node Affection							
N0	56 (98.2%)	17 (94.4%)	1 (25%)	4 (80%)	4 (100%)	13 (92.9%)	<0.001
N1a	1 (1.8%)	1 (5.6%)	2 (50%)	0 (0%)	0 (0%)	1 (7.1%)	
N1b	0 (0%)	0 (0%)	1 (25%)	1 (20%)	0 (0%)	0 (0%)	
Initial Recurrence risk							
Low	53 (93%)	15 (83.3%)	3 (75%)	5 (100%)	3 (75%)	12 (85.7%)	0.556
Intermediate	4 (7%)	3 (16.7%)	1 (25%)	0 (0%)	1 (25%)	2 (14.3%)	
Ultrasound Imaging at 1 Year							
Negative for Structural recurrence	56 (98.2%)	17 (94.4%)	0 (0%)	0 (0%)	0 (0%)		<0.001
Positive for Structural recurrence	0	1	4 (100%)	4 (100%)	5 (100%)		

Table-3: Association of Dose of RAI to demographic and clinical characteristics

	30 mCi	NO RAI	*p*-Value
Gender			
Male	25(24.5%)	2 (2.0%)	
Female	75 (73.5%)	0 (0%)	0.068
Histology			
Papillary Thyroid carcinoma	84 (82.4%)	2 (2%)	1.000
Follicular thyroid carcinoma	16 (15.7%)	0 (0%)	
Multifocality:			
No	80 (78.4%)	2 (2%)	1.000
Yes	20 (19.6%)	0 (0%)	
Tumour size			
T1	53 (52.0%)	0 (0%)	0.097
T2	29 (28.4%)	2 (2.0%)	
T3	18 (17.6%)	0 (0%)	
Margins			
Free	56 (54.9%)	1 (1%)	0.587
Near	16 (15.7%)	1 (1%)	
Contact Capsule	16 (15.7%)	0 (0%)	
Capsule Invasion	12 (11.8%)	0 (0%)	
Lymph node Affection			
N0	95 (93.1%)	0 (0%)	<0.001
N1a	4 (3.9%)	1 (1%)	
N1b	1 (1%)	1 (1%)	
Initial Recurrence risk			
Low	89 (87.3%)	2 (2%)	1.0000
Intermediate	11 (10.8%)	0 (0%)	
Ultrasound Imaging at 1 Year			
Negative for Structural recurrence	75 (86.2%)	0 (0%)	0.018
Positive for Structural recurrence	10 (11.5%)	2 (2.35%)	

DISCUSSION

The RAI ablation therapy for residual disease following surgical resection in DTC patients remains an important question with controversy regarding its necessity and required dosage in cases where it is employed. This has made the decision difficult since there are currently no randomized control trials comparing the efficacy of surgical resection alone vs. surgical resection followed by residual RAI ablation, however, there has been an attempt to evaluate this question through various single and multi-institutional series. These different studies have shown conflicting results about successful ablation at different doses.[7]

Our study compared the post-treatment response at 1 year-follow up of patients who did not undergo RAI treatments with those receiving low dose of iodine (30 mCi). The results of our study yielded a significant association with between treatment response and dose of RAI with 57 (55.8%) of the participants reported complete biochemical response to low dose of iodine. The success of low-dose iodine has been elucidated by previous papers studying ablative outcomes in low to intermediate risk patients including Zaman *et al*. in their study on low/intermediate risk patients receiving low (30 mCi) and high dose (100 mCi) RAI therapy resulting in equal ablation efficacy between the two groups.[1] Iconaru and colleagues in Brussels also demonstrated equal rate of complete response with low dose (30 mCi) RAI therapy. in accordance with the 2015 ATA guidelines, in their prospective cohort when compared to their historical control group treated with high dosages (100 mCi) between 2007 and 2014, irrespective of patient's risk stratification.[5] Li *et al*. conducted a study which also showed that the median 5 year follow up results of 139 patients in the low to intermediate risk group had similar recurrence rates when treated with low or intermediate dose RAI therapy vs. high dose therapy. The results published by Suss *et al*. from their study of low and intermediate risk non-metastatic DTC patients at two referral centers in Brazil concur the most with our results, as they demonstrated that properly selected cases of low and intermediate risk patients, there was no statistical difference in high dose and low dose therapy in both low risk and intermediate risk groups. This research further highlighted that irrespective of initial risk stratification, low dose therapy should also only be utilized when it is necessary and that it is acceptable to follow patients without RAI therapy if their postoperative non-stimulated thyroglobulin levels were negative.[9] Studies by Durante, Schvartz and Vaisman all have shown to have statistically insignificant differences in complete clinical response rates between groups treated with low dose and no dose RAI therapy, particularly in low and intermediate risk groups.[9]

However, the results of a similar study conducted by Gomez *et al*. in Spain only partially validate our results. While their experience also suggested that low-dose iodine and even no RAI therapy may be an effective strategy for low-risk DTC cases, the low dose was associated with non-excellent responses and recurrences (38.5% with low dose vs. 8.8% with high dose therapy) if utilized in patients with intermediate risk tumours.[6] Furthermore, Kim and Colleagues in Seoul demonstrated that there was no significant difference in recurrence between intermediate risk and high risk patients being treated intermediate-dose (100 mCi) and high-dose (150 mCi) RAI therapy, however, they did not study the effect of using lower doses than 100 mCi.[8] Finally, Wongsurawat *et al*. in Thailand also focused on the most efficacious dose of RAI therapy for intermediate risk patients and found that high dose therapy provided a better prognosis in terms of risk of recurrence than low dose RAI treatment. Despite similar percentage difference of remission between the two doses, the adjusted odds ratio for vital characteristics affecting remission rates such as type of DTC, nodal stage, tumour stage, patient age, and baseline levels of stimulate thyroglobulin and anti-thyroglobulin showed that high dose treatment was more effective. The study did, however, maintain that low dose therapy was appropriate for low risk of recurrence patients.[12]

Overall, there are many benefits of judicious use of RAI therapy for residual disease in patients with low and intermediate risk cancers including but not limited to decreased cost of treatment and reduced hospital stay making it convenient for the patient. It also leads to fewer side effects such as post-therapy thyroiditis, sialadenitis and most importantly the risk of secondary malignancy.[12]

LIMITATIONS

The limitations of this study include the retrospective nature of the study design and the short interval to follow up of 1 year which may not be adequate in generalizing our results to patients of thyroid cancer. Hence, it is imperative that the patients are reassessed at other times during the follow-up interval. Moreover, we did not study the adverse effects of the low dose and high dose RAI treatments. The small sample size of the study will also contribute to the lack of generalizability of these results, hence it is imperative that we conduct similar research and collect further data from other centers and regions in our country in order to increase the validity of the research. It is also possible that the patients presenting to our center for RAI therapy do not represent the true depiction of the disease prevalence in our country.

CONCLUSION

This study concludes that the low dose of RAI provided an excellent response of treatment in contrast to patients who had no RAI dose. After 1 year of follow up, the ultrasound imaging also showed negative structural recurrence in majority of the patients which proves that the low dose of RAI can increase the chances for a disease free follow-up.

Ethical Approval and Consent to participate:

The research adhered to the guidelines set forth in the Declaration of Helsinki as well as those for Good Clinical Practice (GCP) and all relevant regulatory requirements. The Ethical Review Committee of Aga Khan University granted an ethical review exemption (ERC number), with data privacy and ERC regulatory

authorizations obtained. Prior to data acquisition, all participants provided informed consent

Consent for publication

Not Applicable

Availability of supporting data

Some or all datasets generated during and/ or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declaration of Conflicting Interests

The authors have no relevant conflicting interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgments

Not Applicable

AUTHORS' CONTRIBUTION

NR, NI: Contributed to the design and implementation of the research. AJ: Data collection, data analysis, write-up. FK: Data analysis and interpretation. MK: Literature search, write-up, proof reading.

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Submitted: December 27, 2023	*Revised: November 21, 2024*	*Accepted: December 4, 2024*

Address for Correspondence:

Nanik Ram, Assistant Professor, Department of Medicine, Aga Khan University Hospital, Karachi-Pakistan
Email: nanikkhatwani@yahoo.com