Journal of Radiation and Nuclear Applications
An International Journal

http://dx.doi.org/10.18576/jrna/070206

Comparison of Maximum Permissible Activity of I-131 Determined by Benua and Leeper Method and Blood Absorbed Dose Method in Differentiated Thyroid Carcinoma Patients

Touqir Ahmed Afridi[1,2], *Muhammad Waqar*[2*], *Ambreen Khawar*[1], *Naureen Marwat*[3], *Zubair Ahmed Soomro*[2]

[1] Pakistan Institute of Engineering and Applied Sciences (PIEAS) Islamabad, Pakistan.
[2]Medical Physics Division, Nuclear Medicine Oncology & Radiotherapy Institute Nawabshah (NORIN), Pakistan.
[3]Medical Physics Division, Atomic Energy Cancer Hospital Islamabad (NORI), Pakistan.

Received: 21 Feb. 2022, Revised: 22 Mar. 2022, Accepted: 24 Mar. 2022.
Published online: 1 May 2022.

Abstract:
Background: Iodine-131 NaI is the mainstay of treatment in patients with well differentiated carcinoma. Fixed versus dosimetrically determined doses for iodine therapy are long in debate. **Objectives**: In this study, two dosimetry methods for the calculation of maximum tolerable activity (MTA) of iodine-131 NaI for treatment of well-differentiated thyroid carcinoma patients were compared. **Materials & Methods**: The methods included blood dosimetry method based on the Medical and Internal Radiation Dosimetry (MIRD) and 48-hour retention limit method based on modified Benua and Leeper method. For dosimetric analysis whole-body scans were obtained using pre-calibrated dual head SPECT/CT gamma camera for I-131 along with 1 ml blood samples at 2, 24, and 48 h post administration of I-131. Percent activity uptake in whole body as well as blood samples were determined. MATLAB was used to generate time activity curves and to calculate cumulative activities for whole body and blood at all-time points. Using the published MIRD formalism radiation absorbed dose to blood was determined. For 48-h retention limit method, percent whole body retention activities at 2, 24, and 48 h were plotted against time to fit Bi-Exponential curve. MTA with blood dosimetry method was calculated by dividing 2 Gy absorbed dose limit to blood. MTA with 48 h retention method was calculated by using 4.4 GBq retention limit at 48 h in Bi-Exponential decay equation. **Results & Discussion**: The MTA range with blood dosimetry method was found to be 395 mCi to 923 mCi as compared to 894.6 mCi to 4490 mCi with 48-hour retention method. Higher estimation of MTA is consequent to low retention of I-131 as none of the patients had any residual/metastatic disease. **Conclusions:** For lower retentions at 48 hours (<5%), the MTA differed up to the factor of 5. However, for the retention of up to 10%, MTA differed by the factor of 3. Hence, 48-hour retention limit method was found to over-estimate the MTA as compared to blood dosimetry method.

Keywords: Maximum permissible activity, Well-differentiated thyroid carcinoma, blood dosimetry, 48-hour retention.

1 Introduction

Thyroid gland is found anterior to the trachea in the neck just below the larynx. Thyroid gland takes up iodine and synthesizes thyroid hormones necessary for the metabolism. The adequate amount of thyroid hormone is necessary for the human body for proper functioning. Symptoms of thyroid cancer include lump or swollen palpable mass in the neck. Most of the nodules in the thyroid are benign but 10-15% of all nodules are found malignant practically [1]. The thyroid cancer accounts for 2% of all cancers in men and women worldwide [2]. Bukhari et. al. (2009) reported that the ratio of incidence of thyroid cancer from women-to-men is 4.7:1 [3]. Table 1 contains the incidence, growth, and type of thyroid cancers.

A ten year follow up study on mortality rate of WDTC patients showed that in around13% cases, the progressive disease leads the patient to death [4]. Radioiodine (I-131) is used for the treatment of thyroid cancer and following are two methods of administration of radioactivity to the patient.

i. Fixed activity method or empiric activity
ii. Dosimetrically determined activity

*Corresponding author e-mail: phy.waqar@gmail.com

Table 1: Types of Thyroid Cancer.

Thyroid Cancer Type	Incidence	Category
Papillary Thyroid Cancer	High (80-85%) [4]	Differentiated
Follicular Thyroid Cancer	High (About 9.7%) [5]	Differentiated
Hurthle Cell Cancer	Low (0.5%) [6]	Differentiated
Medullary Thyroid Cancer	Low (About 3-5%) [7]	Undifferentiated
Anaplastic Thyroid Cancer	Low (About 1.6%) [8]	Undifferentiated

Empirical approach entails administration of fixed range of activity to the patients having thyroid remnants and metastasis, i.e., lung or bone metastasis. Table 2 shows the range of empiric activities.

Table 2: Summary of Fixed/Empiric Activities.

Expansion/extent of tumor	Empiric activities
Regional nodes: (surgery not possible)	150-175 mCi (5.6-5.7 GBq)
Metastasis in lungs	175-200 mCi (6.5-7.4 GBq)
Metastasis in bone	200 mCi (7.4 GBq)

In the other method, the amount of administered activity is calculated dosimetrically.

Benua et al. devised a formalism to determine the maximum activity which could be administered to the patient without exceeding the bone marrow tolerance limit. The maximum amount of activity that should be determined by not exceeding 2 Gy to the blood [10].

The blood dosimetry method uses whole body scans and blood samples to find the amount of radiation dose to the blood per Giga-Becquerel of radioactivity using MIRD scheme [11].

The dose to the blood is determined by the following expression.

$$\frac{D_{blood}}{A_o}\left[\frac{Gy}{GBq}\right] = 108 \times \tau_{per\ ml\ of\ blood}\,[h] + \frac{0.0188}{(wt[kg])^{2/3}} \times \tau_{total\ body}\,[h]$$

- D_{blood} is the average dose to blood.
- A_o is the amount of administered activity.
- τ are the Time-integrated activity coefficients obtained from the areas under the decay curve.
- w_t is the weight of the patient.

The aim of the study is to compare the maximum permissible activity of I-131 in WDTC patients

- That may result in 2 Gy blood dose limit with blood dosimetry-based analysis and;
- By extrapolating the retention limit of 3GBq and 4.4GBq (with and without diffused pulmonary metastasis) at 48 hours using the exponential function determined for whole body activity retention.

2 Methods & Materials

The study was performed at Nuclear Medicine, Oncology and Radiotherapy Institute (NORI) Islamabad. A flowchart of the methodologies under study is given in Figure 1.

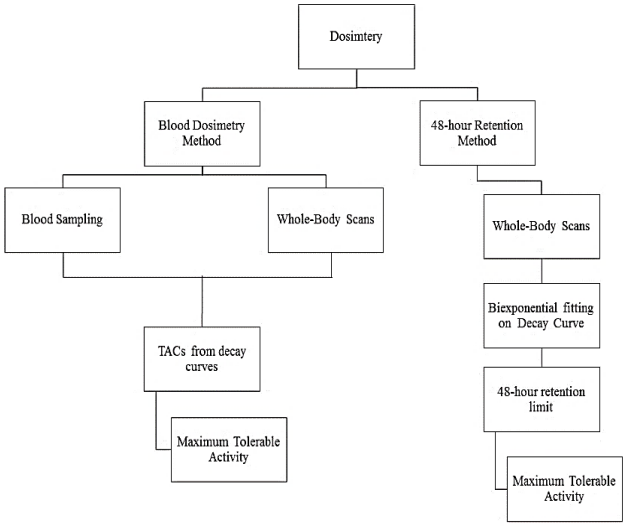

Fig. 1: Steps involved in both methodologies for determination of MTAs.

For calculation of maximum permissible activity, both blood dosimetry as well as 48-hour retention methods were employed in the study. Blood dosimetry is based on the principles of Medical and Internal Radiation Dosimetry (MIRD) and it gives the radiation dose absorbed in blood per GBq of I-131. The information obtained from data collected over 3 days following the administration of a small activity of Iodine-131 was used. The starting material is a computer, an internet connection, and large quantity of time and coffee.

After administration of I-131, the first scanned image represented 100% of administered activity. Further images were acquired at 24 and 48 hours after patient had voided, to observe the clearance of activity from the body. To convert the number of counts into percent radioactivity, two different "standards" for SPECT/CT and gamma counter were used. The standard corrects for variations in detector sensitivity from measurement to measurement and absolute calibrations are not needed. The retained activity is calculated by using equation 2 below:

$$Retained\ Activity = Counts \times C.F$$

- C.F is the calibration factor having units of mCi/counts.

A rectangular region of interest (ROI) was drawn around the whole body on the anterior image. Counts/pixel in anterior and posterior images and number of total pixels were obtained. The geometric mean of the counts per pixel for whole body scan (cpp) was determined using equation 3

$$Geometric\ Mean = \sqrt{Anterior\ Counts \times Posterior\ Counts}$$

The G.M helps eradicating the uncertainty associated with the geometry and shape of the patient. For background radiation correction, a whole-body image was taken without patient on the couch at same standard scan speed. Any nearby radiation source was removed to have a good approximation of background. The anterior and posterior background images were analyzed to determine the count/pixel.

The retained activity is calculated by using following equation.

$$Retained\ Activity = C.F \times \{(GM\ of\ cpp - backgound\ cpp) \times no.of\ pixels\}$$

- Cpp is counts per pixel and C.F is the conversion factor.

Time-integrated activity coefficient is calculated by integrating the time activity curve. The curve is obtained by plotting the percentage activity against the time lapse between the administration of activity and scanning time. this gives an exponential fall which is inherent to radioactive decay.

$$\tau = \int_0^t A(t)dt$$

For the analysis of blood,1 ml blood samples of the patients at the time of scans were prepared and analyzed in gamma counter to calculate the background corrected counts. To deal with the time lapses between administration time, sampling time and analyzing time, decay correction was applied. In our protocol, we analyze the blood samples at the third day and thus, we apply the decay correction to every single measurement.

$$Counts_{decay\ corrected} = Counts_{Total} \times e^{\lambda t}$$

Percent activity in 1 ml blood sample was calculated by using the calibration factor and decay corrected counts. the percent activity is further used to plot against the sampling time. The area under this curve gives the blood residence time which we use to calculate the maximum tolerable activity. With the help of equation (1), blood absorbed dose was calculated which uses both TACs and weight of the patient. This equation gives dose absorbed to blood per GBq of the I-131 administered. By measuring the maximum activity that could deliver the radiation absorbed dose of 2 Gy to blood, maximum activity to be administered to the patient can be calculated as given in equation 7

$$MTA = \frac{2\ Gy}{Calculated\ Radiation\ Absorbed\ Dose\ to\ Blood\ \left[\frac{Gy}{GBq}\right]}$$

In the 48-hour retention method, also known as modified Benua and Leeper method, the maximum tolerable activity is calculated by using the whole-body percent activity of I131 determined at different time points. In the modified Benua and Leeper method, the diagnostic dose of I-123 was used to determine the therapeutic dose of the I-131. In our study, we used the diagnostic dose of I-131 instead of I-123 to project the 48-hour retention target of 4.4 GBq and 3 GBq to find the safe therapeutic dose of I-131. To determine MTA with this method we employed a backward decay correction on bi-exponential equation by using the 48-hour retention limit of 4.4 GBq and determining the initial activity to be administered.

3 Results and Discussion

The study included four WDTC patients with female to male ratio 3:1 with history of thyroidectomy before the administration of the diagnostic dose of radioiodine. Patients were given 5 mCi radioiodine for whole-body scans and blood sampling. I-131 Whole-body diagnostic scans at 2, 24, and 48 hours were analyzed

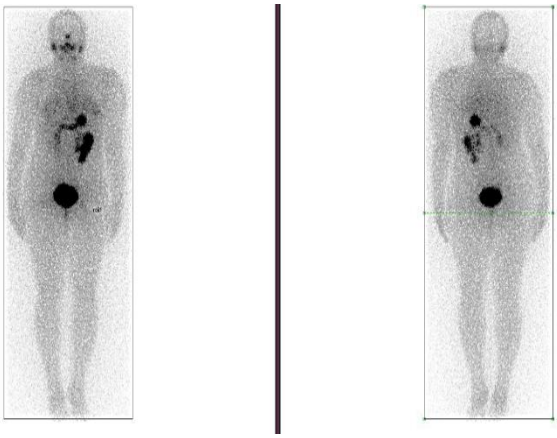

Fig. 2: Anterior and posterior 2-hour images of patient.

From the retained activity against the time of imaging after administration, decay curves were drawn. The area under decay curve at gave the Time-Integrated Activity Co-efficient TIAC for the whole-body retention. MATLAB was used to calculate the TIAC for whole-body as well as blood activity curves. Blood samples of the patient were taken at 2, 24, and 48 hours after the oral administration of I-131 and 1 ml of blood was stored in Eppendorf tubes for each sample. The samples were analyzed in gamma counter at 3rd day after the decay correction.

Similarly, using retained activity at different time points Error! Reference source not found. and plotting it against

respective time, we get TIAC for blood samples. The decay curve is shown following.

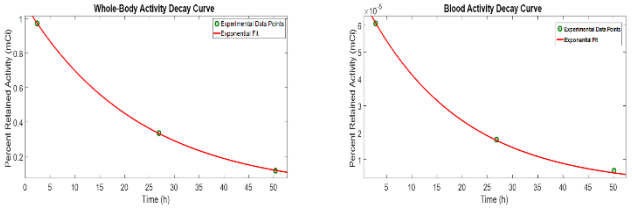

Fig. 3: Decay curve of blood retained activity.

Decay of radioactivity from blood data as well as image data has been represented in Figure 3 above. Table 3 shows the comparison of the maximum tolerable activities calculated with both methods.

Table 3: Maximum Tolerable Activities calculated from Blood Dosimetry method and 48-hour retention method.

Percent 48-hour Retention	MTA by Blood Dosimetry	MTA by 48-hour Retention method
3.5 %	922.67 mCi	3102 mCi
3.8 %	808.82 mCi	2043 mCi
11.8 %	397.39 mCi	894.6 mCi
2.2 %	779.19 mCi	4489 mCi

Our results agree with the literature as it has been reported that 48-hour retention method overestimates the MTA values. Figure 4 shows the comparison of MTAs.

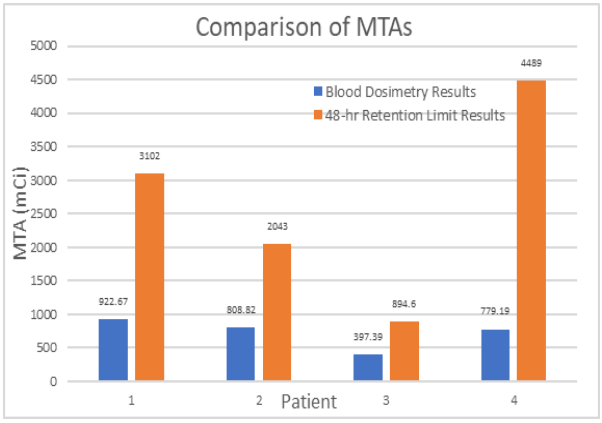

Fig. 4: Comparison of Maximum Tolerable Activities.

The approximation becomes better if the patient has higher retentions at 48 hours. It has been reported in the literature that for the retentions less than 5%, 100% of the patients get overdoses by the factor of 2.5 or more. Thus, our results are concordant with the literature.

Table 4: Comparison of MTAs obtained using blood dosimetry method.

Studies	No: of Patients	Age (Mean ± SD)	Weights Kg (Mean ± SD)	% Retention (Mean ± SD)	MTA mCi (Mean ± SD
Current Study	04	32.75±7.63	71±13.73	5.325±3.79	727.02±197.7
Nostrand et. al. [12]	142	47.8±16.2	81.7±20.6	14.4±8.9	448.9±150.8

In Table 4 Error! Reference source not found. The results of blood dosimetry are compared with the results reported by D. V. Nostrand et. al [12].

Table 5: Comparison of MTAs using 48-h retention limit method.

Studies	No: of Patients	% Retention (48 hours) (Mean ± SD)	MTA mCi (Mean ± SD
Current Study	04	2.2 – 11.8	894.6 – 4489
Frank Atkins et al. [13]	170	3.8 - 66.1	62.16 – 1110.8

The results compared in Table 5 show a significant difference between MTA in current study and Frank Atkins et al. The reason apparent is higher retention in patients of this study as compared to current study owing to different patient characteristics. Even if we have high retentions, the MTA calculated by the 48-hour retention method will still be higher and cause over-treatment. Therefore, it is suggested that lesion-based dosimetry should be employed and compared with the blood dosimetry.

4 Conclusions

We conclude that MTA obtained by the 48-hour retention method strongly depends upon the percentage retention of radioiodine in the body in comparison to blood based dosimetric method. The MTA results were not reliable for retention less than 5% at 48 h post administration. This method gave very high values, which are not applicable in the practical life and may results in overtreatment of the patient. For higher retentions at 48 hours, the method gives better results and values of MTA decrease accordingly. But as compared to blood dosimetry method, the over-estimation still exists.

Although, MTA obtained through blood dosimetry method which also seems to be retention dependent were in close approximation to the activities used at centers which establish much safer doses for patient. Thus, blood dosimetry method is more reliable method of calculating maximum tolerable activity.

Acknowledgement

We would like to thank the staff members of AECH-NORI

Islamabad & AECH-NORIN Nawabshah, and faculty of Department of Physics & Applied Mathematics and Department of Nuclear Medicine PIEAS Islamabad for their support and assistance.

References

[1] L. Wartofsky and D. van Nostrand, "Thyroid Cancer: A Comprehensive Guide to Clinical Management." Soc Nuclear Med, 2017.

[2] J. P. Brito, I. D. Hay, and J. C. Morris, "Low risk papillary thyroid cancer," Bmj., **348**, 2014.

[3] U. Bukhari, S. Sadiq, J. Memon, and F. Baig, "Thyroid carcinoma in Pakistan: a retrospective review of 998 cases from an academic referral center," Hematol. Oncol. Stem Cell Ther., **2(2)**, 345–348, 2009.

[4] H. Salehiniya, R. Pakzad, S. Hassanipour, and M. Mohammadian, "The incidence and mortality of thyroid cancer and its relationship with HDI in the world," World Cancer Res. J., **5(2)**, 1–6, 2018.

[5] F. Limaiem, A. Rehman, and T. Mazzoni, "Cancer, papillary thyroid carcinoma (PTC)," 2019.

[6] S. K. Grebe and I. D. Hay, "Prognostic factors and management in thyroid cancer--consensus or controversy?," West. J. Med., **165(3)**, 156, 1996.

[7] L. J. DeGroot, E. L. Kaplan, M. S. Shukla, G. Salti, and F. H. Straus, "Morbidity and mortality in follicular thyroid cancer," J. Clin. Endocrinol. Metab., **80(10)**, 2946–2953, 1995.

[8] C. Durante et al., "Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy," J. Clin. Endocrinol. Metab., **91(8)**, 2892–2899, 2006.

[9] F. D. Gilliland, W. C. Hunt, D. M. Morris, and C. R. Key, "Prognostic factors for thyroid carcinoma: A population-based study of 15,698 cases from the Surveillance, Epidemiology and End Results (SEER) Program 1973–1991," Cancer Interdiscip. Int. J. Am. Cancer Soc., **79(3)**, 564–573, 1997.

[10] R. S. BENUA, N. R. CICALE, M. SONENBERG, and R. W. Rawson, "The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer," Am. J. Roentgenol. Radium Ther. Nucl. Med., **87**, 171–182, 1962.

[11] N. Alan Selcuk, T. Toklu, S. Beykan, and S. I. Karaaslan, "Evaluation of the dosimetry approaches in ablation treatment of thyroid cancer," J. Appl. Clin. Med. Phys., **19(4)**, 134–140, 2018.

[12] D. Van Nostrand et al., "Utility of the radioiodine whole-body retention at 48 hours for modifying empiric activity of 131-iodine for the treatment of metastatic well-differentiated thyroid carcinoma," Thyroid., **19(10)**, 1093–1098, 2009.

[13] F. Atkins, D. Van Nostrand, S. Moreau, K. Burman, and L. Wartofsky, "Validation of a Simple Thyroid Cancer Dosimetry Model Based on the Fractional Whole-Body Retention at 48 Hours Post-Administration of 131I," Thyroid., **25(12)**, 1347–1350, 2015.