Volume 14, No 2 | International Journal of Radiation Research, April 2016

Bone marrow radiation dosimetry of high dose ^{131}I treatment in differentiated thyroid carcinoma patients

Y. Parlak[1], M. Demir[2*], I. Cavdar[3], S. Ereees[4], G. Gumuser[5], B. Uysal[6], G. Capa Kaya[6], M. Koç[6], E. Sayit[4]

[1]*Department of Nuclear Medicine, Medical Faculty, Celal Bayar University, Bozkoy Campus, 45030, Manisa, Turkey*
[2]*Department of Nuclear Medicine, Cerrahpasa Medical Faculty, Istanbul University, Cerrahpasa, Istanbul, Turkey*
[3]*Department of Nuclear Physics, Science Faculty, Istanbul University, Istanbul, Turkey*
[4]*Department of Nuclear Physics, Science Faculty, Celal Bayar University, 45140, Manisa, Turkey*
[5]*Department of Nuclear Medicine, Medical Faculty, Celal Bayar University, 45030, Manisa, Turkey*
[6]*Department of Nuclear Medicine, Medical Faculty, Dokuz Eylul University, 35340, İzmir, Turkey*

► *Original article*

Corresponding author:
Dr. Mustafa Demir,
Fax: *+90 212 141 31 06*
E-mail: *demirm@istanbul.edu.tr*

Revised: June 2015
Accepted: July 2015

Int. J. Radiat. Res., April 2016; 14(2): 99-104

DOI: 10.18869/acadpub.ijrr.14.2.99

ABSTRACT

Background: Radiation absorbed dose to the red bone marrow, a critical organ in the therapy of thyroid carcinoma, is generally kept below 2 Gy for non-myeloablative therapies. The aim of this study was to calculate bone marrow radiation dose by using MIRDOSE3 package program and to optimize the safe limit of activity to be administered to the thyroid cancer patients. ***Materials and Methods***: In this study, 83 thyroid cancer patients were divided into 3 groups based on the amount of activity administered into the body. In the groups, 3700 MBq, 5550 MBq and 7400 MBq activities were used respectively. The curves of time-activity were drawn from blood samples counts and effective half-life and residence time were calculated. Correlations of bone marrow radiation dose and radioiodine effective half-life were determined as a function of administered activity via ANOVA test. Tg levels and tumour diameters were compared using Spearman's correlation. ***Results:*** The effective half-lives of ^{131}I for three groups of whole-body, receiving 3700 MBq, 5550 MBq and 7400 MBq were calculated as 20.57±5.4, 17.8±5.8 and 18.7±3.9 hours, respectively. The average bone marrow doses for 3 groups of patients were 0.32±0.08 Gy, 0.42±0.14 Gy and 0.60±0.24 Gy, respectively. ***Conclusion:*** It was concluded that, the bone marrow dose to the patients still remains within the recommended level even after administering an activity of 7400 MBq of ^{131}I to the patients.

Keywords: *Radioiodine treatment, bone marrow dosimetry, MIRDOSE3, thyroid cancer.*

INTRODUCTION

Treatment of differentiated thyroid cancer (DTC) with radioiodine is a standard procedure for the ablation of remnant thyroid tissue following surgery and for the treatment of iodine-avid metastases [(1)].

The activity to be used for ^{131}I therapy still remains subject of discussion. Usually, patients are treated with fixed or standardized activities reflecting the physician's rating of the most safe or 'adequate' dosage rather than with an optimized treatment activity based on prior measurement of the patient's individual biokinetics [(2)]. The target dose is the determinant for successful therapy, and the decisive parameters are the therapeutic activity and the retention of ^{131}I in the target volume [(3)]. There is a broad range of fixed activities of ^{131}I recommended to be administered. In many cases, an activity between 1.1 and 3.7 GBq is prescribed for the radioiodine therapy after

[DOI: 10.18869/acadpub.ijrr.14.2.99]

thyroidectomy [3, 4]. Higher activity ^{131}I are given in subsequent therapies or in case of metastatic disease [2, 4, 5].

The bone marrow dosimetry is used to predict the level of toxicity from radionuclide therapy thus allowing one to deliver the most efficient therapy with a minimal level of adverse effects for patients. Bone marrow is one of the most radiosensitive tissues in the body and without stem cell support; it is commonly the dose-limiting tissue for radionuclide therapy. The bone marrow dose limited approach was originally described by Song and Sgouros [6, 7]. This concept basically aims to guarantee the safety of treatment. Blood, as a surrogate of the organ at risk the red bone marrow, was considered as the critical organ in this approach. In order to avoid a serious myelotoxicity, a threshold value for the absorbed dose in blood is considered as 2 Gy [2,8,9].

To calculate the bone marrow absorbed dose, the maximum tolerated activity for an individual, an understanding of the pharmacokinetics of the radioiodine (^{131}I) is necessary [10].

According to MIRD (Medical Internal Radiation Dose) principle, calculation of the radiation absorbed dose for a target organ is based on the distribution of radioactive material (radioisotope) in a single or multiple source organ or system [11,12].

A computer package program MIRDOSE3, which has been developed by the MIRD committee (Radiation Internal Dose Information Center, Oak Ridge Institute of Science and education), USA is used in this study as a widely approved standard for internal dosimetry method [13]. In this method, the geometry of the source and target organs and the attenuation properties of the tissues in the body are presumed on the radionuclide and its various decay pathways.

The fraction of radiation energy emitted from the source organ that is deposited in the target organ called absorbed fraction, φ, with paired arguments, target-source. The specific absorbed fraction, Φ, is defined as φ, divided by the mass (m) of the target organ. S has been evaluated for each radionuclide of interest for a large number of source organs, O_s, and target organs O_t, by the following relationship [14].

$$S(O_t \leftarrow O_s) = \Sigma\varphi\ (O_t \leftarrow O_s)\ \Delta/m$$

The total dose to the target organ due to radioactivity in the source organ is equal to the product of S and cumulative activity, Ã. Cumulative activity, Ã, is the area under the time-activity curve. The residence time (τ) is the area under a source organ's time-activity curve divided by the administered activity if τ is the residence time and A_0 is the initial activity administered to the patient, then the final equation for the dose, D, to the target organ is

$$D(O_t \leftarrow O_s) = \tilde{A}S(O_t \leftarrow O_s) = A_0\ \tau\ S(O_t \leftarrow O_s)$$

The objective of the study, was to calculate bone marrow radiation dose in by using MIRDOSE3 package program and to optimize the safe limit of activity to be administered to the non-metastatic differentiated thyroid carcinoma patients.

MATERIALS AND METHODS

Patient groups

In this study, 83 thyroid cancer patients were divided into 3 groups based on the amount of administered activity (table 1). In the first group, there were 48 non metastatic thyroid cancer patients (14 male, 34 female with age range from 22 to 79 year) that was received 3700 MBq. There were 18 patients with lymph node metastases (3 male, 15 female with age range from 28 to 67 year) in the second group that was received 5550 MBq. In the third group, there were 17 patients with distal metastases lung, bone or other organ metastases (5 male, 12 female with age range from 23 to 71 year) treated by 7400 MBq.

The experimental design of the present study was previously approved by the local ethics committee and written informed consent from all patients was obtained.

All patients in the study had previously

[DOI: 10.18869/acadpub.ijrr.14.2.99]

Table 1. The age and gender of all patients versus administered activity.

Groups	Administered Activity (MBq)	Number of Patients	Mean Age
1	3700	48 (14 male, 34 female)	50.8±12
2	5550	18 (3 male, 15 female)	41.1±10
3	7400	17 (5 male, 12 female)	53.0±16
Total		83	49.8±12

undergone a total thyroidectomy for papillary or follicular variant thyroid cancer and thyroid hormone replacement therapy had been discontinued for appropriate periods to assure adequate hypothyroidism when the ^{131}I was administered. The patients were without documented kidney disease or other medical conditions that would lower normal urinary excretion.

Bone marrow dosimetry

In the standart MIRD approach, the general expression for RM (Red Marrow) absorbed dose is [15],

$$D_{RM} = \tilde{A}_{RM} \times S_{(RM \leftarrow RM)} + \Sigma \tilde{A}_h \times S_{(RM \leftarrow h)} + \tilde{A}_{RB} \times S_{(RM \leftarrow RB)}$$

Where D_{RM} is the mean absorbed dose in RM. $\tilde{A}_{RM}$, $\tilde{A}_h$, $\tilde{A}_{RB}$ are cumulated radioactivity in red marrow (RM), other organ source (h) and the reminder of body (RB), respectively. $S_{(RM \leftarrow RM)}$, $S_{(RM \leftarrow h)}$ and $S_{(RM \leftarrow RB)}$ are the S values from RM, h and RB to RM respectively.

Radiation dose from residual thyroid tissue to red marrow should be neglected because is low in non-metastatic thyroid carcinoma patients. When calculating radiation absorbed dose for bone marrow (RM-red marrow), the BM dose formula is used [16].

$$D_{(BM)} = [\tilde{A}_{(RM)} \times S_{(RM \leftarrow RM)}] + [\tilde{A}_{(RM)} \times S_{(RM \leftarrow RB)}]$$

Blood samples were collected at 2, 19, 24, 48, 72, 96, 120 and 144 hours after ^{131}I administration, and tubes were filled with 1 ml of blood and measured in a well counter (Capintec CRC 25). The resultant data's were used to generate time-activity curves for blood activity. The curves of time-activity were drawn from blood samples counts and effective half-life and residence time were calculated.

MIRDOSE3 requires three data as input: (1) a radionuclide, (2) a phantom specification and (3) some source and target organs with associated residence time. In the present study, ^{131}I and adult female non-pregnant phantom were selected in the input form. Finally, all the values were transferred to Microsot Excel for further calculation.

Correlations of bone marrow radiation dose and radioiodine effective half-life were determined as a function of administered activity via ANOVA test. Study data were analysed using the SPSS software version 11.0. The level of significance was set at below 0.05.

RESULTS

In all patients, the TSH levels were increased to over 40 mIU/L after the interruption of thyroid hormone replacement. Effective half-life of ^{131}I in patients receiving 3700, 5550 and 7400MBq were calculated as 20.57±5.4, 17.75±5.8 and 18.70±3.9 hours, respectively. The average effective half-life for all three groups was calculated as 19.00±5.0 hours. Bone marrow doses for patients receiving 3700, 5550 and 7400MBq administered activities were found to be 0.32±0.1, 0.42±0.1 and 0.60±0.2 Gy, respectively (table 2).

No statistically significant difference was found between the effective half-lives as a function of administered activity, and between the effective half-lives and bone marrow radiation dose ($p>0.05$). According to the ANOVA statistic, significant differences were found between administered activity and bone marrow radiation dose ($p<0.05$).

Patients were grouped on the basis of their Tg levels and tumor diameters were compared using Spearman's correlation. Significant correlations were found between administered activity, Tg levels and tumor diameters (table 3).

[DOI: 10.18869/acadpub.ijrr.14.2.99]

Table 2. Correlation with effective half-life and bone marrow doses of activity.

Groups	Effective Half Life (h)	Bone Marrow Dose(Gy
1	20.57±5.4	0.32±0.1
2	17.75±5.8	0.42±0.1
3	18.70±3.9	0.60±0.2

DISCUSSION

Nuclear medicine physician should calculate the necessary activity to be administered to patients in order to obtain successive treatment. There are three methods for determining the ^{131}I activity. The are fixed empirical dose method, dosimetry based approach and fractional dose method [3].

The most common and simplest method is to administer a fixed empirical dose regardless of ^{131}I uptake of tumour lesion. Doses are usually determined by disease extent. Conventional doses are 3.7–6.5 GBq (100–175 mCi) for cervical lymph node metastasis, and 5.5–7.4 GBq (150–200 mCi) for distant metastasis [17]. In our clinic, doses of treatment are 3.7 GBq dose for non-metastatic, 5.5 GBq dose for lymph node metastasis, 7.4 GBq for distant metastasis.

Using fix-administered activity fails to consider the individuality of patients in which there is no consideration for patient specific factors; such as reliable and universal adjustments based on the patient weight, age or gender of the patient or any other patient specific factors for that matter. In addition to this, in the limitations of fix-administered activity, it lacks the description of the radioiodine biodistribution in the body, slow and long component of radioiodine clearance from the kidneys, and the transport of radioiodine in the blood stream are not determinant factors. However, literature shows that all of these factors are critical to the efficiency of treatment [18-20]. Excessive radioiodine administration can lead to side effects in the short or in the long term such as the induction of bone marrow suppression. As bone marrow is very sensitive to the radiation; it seems that in some patients who are subjected to low activity administration less than the standard dose formula must decrease the absorbed dose to bone marrow. Lassman has investigated the same methodology in his 2010 study [2] and mentioned the disadvantages of fix dose formula and the serious potential side effects that arise from lackness the patient-specific parameters.

Table 3. Tg levels and tumor diameters of patients.

	Administered Activity (MBq)	Number of Patients	Tg levels and tumour diameters (Mean±SD)	P Value
Thyroglobulin (Tg) levels (ng/ml)	3700	48	12±12.5	0.010
	5550	18	399±185.1	
	7400	17	313±586	
Tumor diameters (cm)	3700	45	0.87±1.75	0.04
	5550	26	1.50±3.06	
	7400	12	1.44±4.16	

Some studies proposed that, the dose-limiting toxicity of RAI treatment is mainly on the bone marrow (BM), and the limit has been set involve the dose (administered activity) that delivers 2 Gy (200 rad) to the blood as an equivalent of BM and whole-body retention of <4.44 GBq (<120 mCi) at 48 h, and lung uptake should be less than 3 GBq (~80 mCi) [7,21].

At present, differential thyroid cancer is treated with standard empirical activities with significant disadvantages. Exposure to radiation resulting from standard activities is heterogeneous and the radiation dosage absorbed by the blood changeable due to variety of many factors such as (patients' Body Mass Index, renal clearance) [20]. In thyroid cancer patients treated during hypothyroidism, blood dose may increase above 2 Gy after the administration of 7.4 GBq (200 mCi) [22]. In case of a low blood dose and high renal clearance inadequate accumulation of radioiodine should be expected in the target tissue. Hence, this situation can be resolved by increasing the therapeutic activity.

Patient specific therapy depending on pre-treatment dose calculations for bone marrow absorbed dose and the target dose per activity enhance the possibility to calculate the optimum activity to ablate all remnant thyroid lesions without exceeding the bone marrow tolerated dose and also to determine the

[DOI: 10.18869/acadpub.ijrr.14.2.99]

necessary activity to fullfil effective tumor regression. Hanscheid conducted a study in 2006, and studied the blood samples of patients for blood doses finding a range between 0.064 and 0.35 mGy/MBq. Bone-marrow absorbed dose was found 0.074 mGy/MBq by Willegaignon after the 3.7 GBq. In the our study, bone-marrow absorbed dose was found 0.086 mGy/MBq for 3.7 GBq, 0.075 mGy/MBq for 5.5 GBq and 0.081 mGy/MBq for 7.4 GBq.

De Keizer *et al.* conducted a study on bone marrow dosimetry in 2004 [10], none of the patients in the present study went over the limit of 2 Gy. They collected samples of blood and urine from thyroid cancer patients and analyzed the samples for renal clearance of iodine and bone marrow absorption of radiation. Four patients, in their study, were reported to have a whole-blood absorbed dose higher than the threshold level of 2 Gy. The doses of bone marrow radiation have been calculated using the MIRD method and their results were between the ranges of 0.28 Gy to 1.91 Gy [10] which is slightly higher than our results. In the study, MIRDOSE3 program was used for total body and red marrow dosimetry for dosages reduction in a patient with hemodialysis who presented as a case report and done by Kaptein [23].

Another study was conducted by Dorn *et al.* in 2003 [15] with thyroid cancer patients and using the MIRDOSE3 method that found dosimetry-guided high-dose (Bone marrow absorbed dose up to 3 Gy). In their study, no permanent BM suppression was observed in patients who received absorbed doses of <3 Gy to BM, the maximum administered dose was 38.5 GBq (1040 mCi) at one time with the BM dose limitation in metastatic thyroid cancer patiens., In our study, bone marrow doses were found to be 0.60±0.2 Gy for metastatic thyroid cancer receiving 7.4 GBq administered activities.. Even though was reached the critical limit of 3 Gy, 3,7 GBq (1000 mCi) dose is in the safety limits reported by Dorn *et al* in 2003 [16].

Iodine biokinetics in the body, residual thyroid tissue size, thyroid uptake and Tg values are known to play an important role in determining the dose of bone [3, 24, 25]. In the present study, patients were grouped on the basis of their Tg levels and tumor diameters, then the relation between two groups was examined by Spearman's correlation (table 3). In clinical practice, Tg levels are considered as a parameter in determining the amount of activity to be administered. However, the determination of treatment dose is not only dependent on the Tg level. For patients with a high Tg level, the blood doses were high, as well.

CONCLUSION

It is concluded that effective half-life of the radioiodine is not associated with the amount of activity, age and gender of patients. The amount of activity was correlated with bone marrow doses and our findings can be used as an extrapolation coefficient to determine the total bone marrow dose in metastatic and non-metastatic patients.

We used a dosimetric methodology based on the MIRD technique and our findings demonstrated that BM doses are in the safety limit. Despite of the administrated doses were within the radiation limits, it has been concluded that the first dose in the treatment may be increased in patients with metastatic thyroid cancer.

***Conflict of interest*:** *Declared none.*

REFERENCES

1. Verburg FA, De Keizer B, Lips CJ, Zelissen PM, De Klerk JM (2005) Prognostic significance of successful ablation with radioiodine of differentiated thyroid cancer patients. *Eur J Endocrinol,* ***15:*** *33-7.*
2. Lassmann M, Reiners C, Luster M (2010) Dosimetry and thyroid cancer: The individual dosage of radioiodine. *Endocrine-Related Cancer,* ***17:*** *61–72.*
3. Hänscheid H, Lassmann M, Luster M, Thomas SR, Pacini F, Ceccarelli C, *et al.* (2006) Iodine biokinetics and dosimetry in radioiodine therapy of thyroid cancer: Procedures and results of a prospective ınternational controlled study of ablation after rhTSH or hormone withdrawal. *J Nucl Med,* ***47:*** *648–54.*
4. Tuttle R M, Leboeuf R, Robbins RJ, Qualey R, Pentlow K, Larson SM *et al.* (2006) Empiric radioactive iodine dosing regimens frequently exceed maximum tolerated activity

[DOI: 10.18869/acadpub.ijrr.14.2.99]

levels in elderly patients with thyroid cancer. *J Nucl Med,* ***47:*** *1587–91.*

5. Meier DA, Brill DR, Becker DV, Clarke SE, Silberstein EB, Royal HD, *et al.* (2002) Procedure guideline for therapy of thyroid disease with Iodine 131. *J Nucl Med,* ***43:*** *856–61.*
6. Song H, He B, Prideaux A, Du Y, Frey E, Kasecamp W, *et al.* (2006) Lung dosimetry for radioiodine treatment planning in the case of diffuse lung metastases. *J Nucl Med,* ***47:*** *1985–94.*
7. Sgouros G, Song H, Ladenson PW, Wahl RL (2006) Lung toxicity in radioiodine therapy of thyroid carcinoma: Development of a dose-rate method and dosimetric implications of the 80-mCi rule. *J Nucl Med,* ***47:*** *1977–84.*
8. Hanscheid H, Lassmann M, Luster M, Kloos RT, Reiners C (2009) Blood dosimetry from a single measurement of the whole body radioiodine retention in patients with differentiated thyroid carcinoma Endocrine-Related. *Cancer,* ***16:*** *1283–89.*
9. Lassmann M, Hänscheid H, Chiesa C, Hindorf C, Flux G, Luster M (2008) EANM Dosimetry Committee. Dosimetry EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy. *Eur J Nuc Med Mol Imaging,* ***35:*** *1405-12.*
10. De Keizer B, Hoekstra A, Konijnenberg MW, de Vos F, Lambert B, van Rijk PP, *et al.* (2004) Bone marrow dosimetry and safety of high ^{131}I activities given after recombinant human thyroid-stimulating hormone to treat metastatic differentiated thyroid cancer. *J Nucl Med,* ***45:*** *1549-54.*
11. Bolch WE, Eckerman KF, Sgouros G, Thomas SR (2009) MIRD Pamphlet No. 21: A Generalized Schema for Radiopharmaceutical Dosimetry Standardization of Nomenclature. J Nucl Med, 50: 477–84.
12. Shahbazi-Gahrouei D and Nikzad S (2011) Determination of organ doses in radioiodine therapy using medical internal radiation dosimetry (MIRD) method. *Iran J Radiat Res,* ***8(4):*** *249-252.*
13. Stabin M (1996) MIRDOSE-The personel computer software for use in internal dose assessment in nuclear medicine. *J Nucl Med,* ***37:*** *538-46.*
14. Sorenson JA and Phelps ME (1987) Physics in nuclear medicine, Orlando*: Grune & Stratton, 197-218.*
15. Shen S, DeNardo GL, Sgouros G, O'Donnell RT, DeNardo SJ (1999) Practical determination of patient-specific marrow dose using radioactivity concentration in blood and body. *J Nucl Med,* ***40:*** *2102-06.*
16. Dorn R, Kopp J, Vogt H, Heidenreich P, Carroll RG, Gulec SA (2003) Dosimetry-guided radioactive iodine treatment in patients with metastatic differentiated thyroid cancer: Largest safe dose using a risk-adapted approach. *J Nucl Med,* ***44:*** *451-56.*
17. Loevinger R, Budinger TF, Watson EE (1991) MIRD primer for absorbed dose calculations, revised edition, New York, Society of Nuclear Medicine.
18. Lee JJ, Chung JK, Kim SE, Kang WJ, Park DJ, Lee DS, *et al.* (2008) Maximal safe dose of I-131 after failure of standard fixed dose therapy in patients with differentiated thyroid carcinoma. *Ann Nucl Med,* ***22:*** *727–34.*
19. Ashok RS (2007) TNM classification of thyroid carcinoma World. *J Surg,* ***31:*** *879–87.*
20. Willegaignon J, Ribeiro VP, Sapienza M, Ono C, Watanabe T, Buchpiguel C (2010) Is it necessary to reduce the radioiodine dose in patients with thyroid cancer and renal failure? Arq. Bras. Endocrinol. *Metab,* ***54:*** *413-18.*
21. Benua RS and Leeper RD (1986) A method and rationale for treating thyroid carcinoma with the largest safe dose of I-131. In: Meideros-Neto GA, Gaitan E, eds. Frontiers of Thyroidology. Vol. II. New York, NY: *Plenum, 1317–21.*
22. Chiesa C, Castellani MR, Vellani C, Orunesu E, Negri A, Azzeroni R, *et al.* (2009) Individualized dosimetry in the management of metastatic differentiated thyroid cancer. *The Quarterly J Nucl Med Mol İmaging,* ***53:*** *546-61.*
23. Kaptein EM, Levenson H, Siegel ME, Gadallah M, Akmal M (2000) Radioiodine dosimetry in patients with end-stage renal disease receiving continuous ambulatory peritoneal dialysis therapy. *J Clin Endocrinol Metab,* ***85:*** *3058-64.*
24. Bal CS, Kumar A, Pant GS (2005) Radioiodine Dose for Remnant Ablation in Differentiated Thyroid Carcinoma: A Randomized Clinical Trial in 509 Patients. The *Journal of Clinical Endocrinology & Metabolism* ***89:*** *1666–73.*
25. De Hoekstra A, Konijnenberg MW, De Vos F, Lambert B, Van Rijk PP, Lips CJ, *et al.* (2004)Bone marrow dosimetry and safety of high ^{131}I activities given after recombinant human thyroid-stimulating hormone to treat metastatic differentiated thyroid cancer. *J Nucl Med,* ***45:*** *1549–54.*

[DOI: 10.18869/acadpub.ijrr.14.2.99]