



Red Marrow Absorbed Dose Calculation in Thyroid Cancer Patient Using a Simplified Excel Spreadsheet

Tiroid Kanseri Hastasında Basitleştirilmiş Bir Excel Elektronik Tablosu Kullanılarak Kırmızı İliğin Absorbe Ettiği Dozun Hesaplaması

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Abstract

Objectives: Absorbed dose to red marrow (D_{rm}) can be calculated using blood dosimetry. However, this method is laborious and invasive. Therefore, image-based dosimetry is the method of choice. Nonetheless, the commercial software is expensive. The goal of this work was to develop a simplified excel spreadsheet for image-based radioiodine red marrow dosimetry.

Methods: The serial whole-body images (acquired at 2nd, 6th, 24th, 48th, and 72th hours) of 29 patients from the routine pretherapeutic dosimetry protocol were retrospectively reanalyzed. The commercial OLINDA/EXM image-based dosimetry software was used to calculate the whole-body time-integrated activity coefficient ($TIAC_{wb}$) and D_{rm} [in terms of absorbed dose coefficient (d_{rm})]. For the simplified excel spreadsheet, the whole-body count was obtained from the vendor-supplied software. Then, the $TIAC_{wb}$ was computed by a fitting time-activity curve using an Excel function. S factor was taken from other publications and scaled according to the patient-specific mass. A comparison of the $TIAC_{wb}$ and d_{rm} from both methods was done using a non-inferiority test using a paired t-test or the Wilcoxon signed-rank test.

Results: The $TIAC_{wb}$ showed no significant difference between both methods ($p=0.243$). The calculated D_{rm} from a simplified Excel spreadsheet was assumed to be statistically non-inferior to the commercial OLINDA/EXM image-based dosimetry software with the non-inferiority margin of 0.02 ($p<0.05$).

Conclusion: The dose assessment from a simplified Excel spreadsheet is feasible and relatively low cost compared to the commercial OLINDA/EXM image-based dosimetry software.

Keywords: Red marrow absorbed dose, image-based dosimetry, radioiodine therapy, internal dosimetry

Öz

Amaç: Kırmızı iliğin absorbe ettiği doz (D_{rm}) kan dozimetresi kullanılarak hesaplanabilir. Ancak tam kan yöntemi zahmetli ve invaziftir. Bu nedenle, görüntü bazlı dozimetri tercih edilen yöntemdir. Bununla birlikte, ticari yazılım pahalıdır. Bu çalışmanın amacı, görüntü tabanlı radyoiodin kırmızı ilik dozimetresi için basitleştirilmiş bir excel elektronik tablosu geliştirmektir.

Yöntem: Yirmi dokuz hastanın rutin tedavi öncesi dozimetri protokolündeki seri tüm vücut görüntüleri (2, 6, 24, 48 ve 72. saatlerde elde edilen) retrospektif olarak yeniden analiz edilmiştir. Rutin olarak, ticari OLINDA/EXM görüntü tabanlı dozimetri yazılımı, tüm vücut zamana entegre edilmiş aktivite katsayısı ($TIAC_{wb}$) ve D_{rm} [absorbe edilen doz katsayısı (d_{rm})] hesabı için kullanıldı. Basitleştirilmiş bir Excel elektronik tablosu için, tüm vücut sayısı satıcı tarafından sağlanan yazılımdan elde edilmiştir. Daha sonra $TIAC_{wb}$, Excel işlevi kullanılarak oluşturulan zaman-aktivite eğrisi ile hesaplandı. S faktörü diğer yayınlardan alınarak hastaya özel kitleye göre ölçeklendirildi. İki yöntem ile elde edilen $TIAC_{wb}$ ve d_{rm} değerlerinin karşılaştırması, bağımlı örneklem t-testi veya Wilcoxon işaretli sıralar testine dayalı bir non-inferiority test kullanılarak analiz edildi.

Bulgular: $TIAC_{wb}$ iki yöntem arasında anlamlı bir fark göstermedi (eşleştirilmiş örneklem t-testi ile p değeri 0,243). Basitleştirilmiş bir Excel elektronik tablosundan hesaplanan d_{rm} değerinin, 0,02'lik non-inferiority payı ile ticari OLINDA/EXM görüntü tabanlı dozimetri yazılımı ile hesaplanan değerden istatistiksel olarak non-inferior olduğu görülmüştür (Wilcoxon işaretli sıralar testi ile p değeri <0,05).

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Sonuç: Basitleştirilmiş bir Excel elektronik tablosundan doz değerlendirmesi yapılabilir ve ticari OLINDA/EXM görüntü tabanlı dozimetri yazılımına kıyasla nispeten düşük maliyetlidir.

Anahtar kelimeler: Kırmızı iliğin absorbe ettiği doz, görüntüye dayalı dozimetri, radyoyot tedavisi, internal dozimetri

Introduction

The red marrow is considered as one of the critical organs in radioiodine treatment (^{131}I -sodium iodide) of differentiated thyroid cancer (DTC). In radioiodine treatment, the absorbed dose to the blood as a surrogate for red marrow is often kept below 2 Gy to avoid hematological toxicity. This safety limit has been defined by blood dosimetry from blood sampling since the original work of Benua et al. (1) in 1962. Such a limit is still widely accepted, even though many new approaches have been introduced to calculate the red marrow absorbed dose such as external whole-body counting using a gamma probe and quantitative imaging using serials of whole-body scans obtained from nuclear medicine imaging modality (2,3,4).

Currently, quantitative imaging is the method of choice due to its non-invasive procedures excluding serial blood collections. Several commercial dosimetry softwares include the function to calculate the time-integrated activity coefficient (TIAC) and absorbed dose in organs using either serial planar whole-body scans or single photon emission computed tomography (SPECT) acquisitions (3,4). However, the image-based commercial dosimetry software is expensive, limiting its use in routine clinical practice. The objectives of this study were to develop a simplified excel spreadsheet for an image-based radioiodine bone marrow dosimetry and to compare the results of this spreadsheet with the commercial OLINDA/EXM image-based dosimetry software.

Materials and Methods

Patient Data Selection

Twenty-nine DTC patients who participated in the routine pretherapeutic dosimetry protocol between May 2017 to March 2019 for radioiodine treatment at the Surin Hospital (Surin Province, Thailand) were included in this retrospective study. Five patients were male and 24 were female. The mean age was 48.8 years (range: 19.0-76.0 years) at the time of the treatment. Ethics Committee Approval was obtained from the Ethical Review Board of the Surin Hospital with the approval number: 12/2562 and date: 9th April 2019.

The inclusion criteria for this routine pretherapeutic dosimetry protocol were DTC patients who had a near-total

or total thyroidectomy, with withdrawn thyroid hormone for 4-6 weeks, low iodine diet intake, and serum thyroid-stimulating hormone >30 mIU/L before administration of radioiodine.

Dosimetry and Imaging Protocol

The pretherapeutic dosimetry protocol at the Surin Hospital was performed following European Association of Nuclear Medicine (EANM) standard operational procedures (3). Radioiodine ranging from 74 to 185 MBq was administered to patients. The whole-body data in this protocol were obtained from anterior and posterior conjugate views acquired at 2nd, 6th, 24th, 48th, and 72th hours postadministration. The gamma camera used for imaging was Symbia T16 SPECT/CT (Siemens Medical Solutions USA) and equipped with parallel-hole high energy collimators, using a 10% energy window set at 364 keV. The table speed for the whole-body images was 8 cm/min and the latter were acquired using a 256x1024 matrix. These protocol settings were applied to all patients and time points.

The Commercial OLINDA/EXM Image-based Dosimetry Software

In the pretherapeutic dosimetry protocol, the whole-body calculations were performed using a commercial HERMES OLINDA/EXM image-based dosimetry software (HERMES Medical Solution, Stockholm, Sweden). This software is the OLINDA/EXM version 1.1.

In this commercial software, the whole-body region of interest (ROI) in the anterior image was automatically mirrored and copied to the posterior image. The whole-body ROIs that had been defined in one of the whole-body scans were automatically copied to all other timepoints belonging to the same patient. Examples of image data and whole-body ROI are demonstrated in Figure 1a.

In OLINDA/EXM image-based dosimetry software, the activity in the images is converted from the counts using either standard activity or equipment detection efficiency. In this work, the camera detection efficiency was investigated and used for activity determination for all patients. Then, a bi-exponential function was fitted to the data. Consequently, the whole-body time-activity curve whole-body (TAC_{WB}) was generated. An example of TAC_{WB} is shown in Figure 1b.

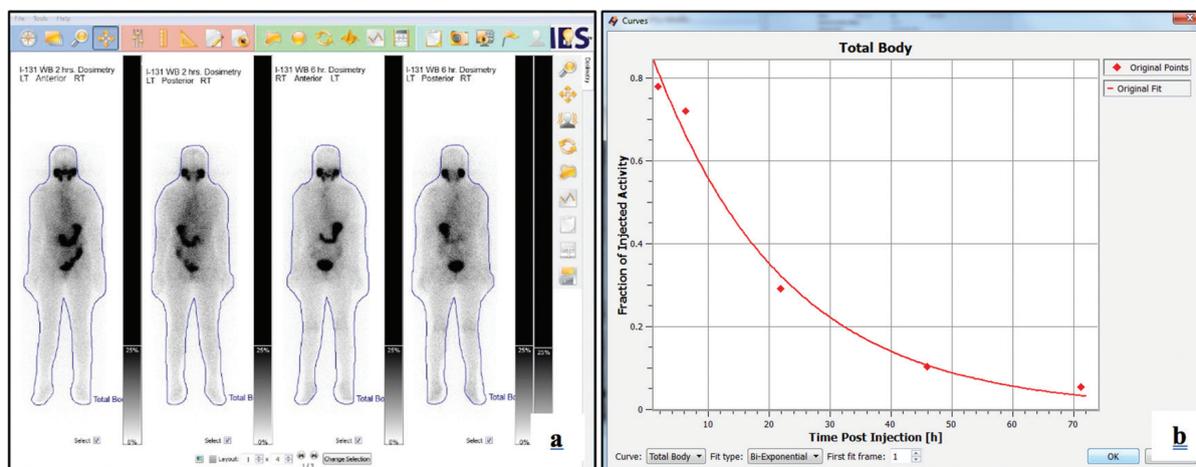


Figure 1. a) Sample screenshot of the image data and whole-body ROI of the commercial OLINDA/EXM image-based dosimetry software. **b)** The bi-exponential fit of the TAC

ROI: Region of interest, TAC: Time-activity curve, OLINDA/EXM: Organ Level Internal Dose Assessment/Exponential Modelling

The whole-body $TIAC_{WB}$ (formally called residence time) is calculated from the area under TAC_{WB} . The exponential extrapolation with a numerical trapezoidal integration is employed in this OLINDA/EXM image-based dosimetry software. In this software, D_{rm} was calculated in terms of the absorbed dose coefficient (d_{rm}) (mGy/MBq). This commercial software uses the medical internal radiation dose schema and the Cristy and Eckerman (C&E) phantoms (5). In our work, doses were scaled using the patient-specific mass at the time of radioiodine treatment.

A Simplified Excel Spreadsheet

The serial whole-body images of 29 DTC patients were reanalyzed using the vendor-supplied Syngo software (Siemens Medical Solutions, USA) as illustrated in Figure 2a. Data were exported to an Excel spreadsheet (Microsoft Corp., Redmond, WA). For background correction, the average activity in the whole-body background ROIs (BKG_{av}) was subtracted from the average activity in the whole-body ROI (WB_{av}) and multiplied by the number of pixels in the whole-body image (N_{WB}) as illustrated in equation (1).

$$WB_{net} = N_{WB} \times (WB_{av} - BKG_{av}) \quad \text{equation (1)}$$

Then, the whole-body geometric mean (WB_{GM}) was calculated from the whole-body net anterior ($WB_{net(ant)}$) and whole-body net posterior ($WB_{net(post)}$) as shown in equation (2).

$$WB_{GM} = \sqrt{WB_{net(ant)} \times WB_{net(post)}} \quad \text{equation (2)}$$

In the excel spreadsheet, the equipment efficiency was also used to determine the activity similar to the OLINDA/EXM image-based software. Then, the whole-body activity of each time point was computed to the fraction

of administered activity (FAA) using a mono-exponential function in MS Excel [as illustrated in equation (3)].

$$FAA(t) = \frac{A(t)}{A_0} = A \times e^{-\lambda \times t} \quad \text{equation (3)}$$

Where, $FAA(t)$ is the fraction of administered activity (A_0) as a function of time t and A and λ are fit constants. The $TIAC_{WB}$ (as shown in Figure 2b) in this spreadsheet were calculated by integrating the equation (3) from zero to infinity as shown in the following equation (3, 4).

$$TIAC_{WB} \int_0^{\infty} = FAA(t) dt \quad \text{equation (4)}$$

As recommended in the EANM guideline for bone marrow and whole-body dosimetry in radioiodine therapy for thyroid cancer, the contributors to D_{rm} were the activity in the extracellular fluid (ECF) ($D_{rm \leftarrow ECF}$) and the remainder of the body (RoB) ($D_{rm \leftarrow RoB}$) as illustrated in equation (4,5).

$$D_{rm} = D_{rm \leftarrow ECF} + D_{rm \leftarrow RoB} \quad \text{equation (5)}$$

The contribution from the activity in the ECF is also called the blood method and assumes that the activity distribution in ECF is equal to the activity distribution in the plasma. However, the completed blood method is laborious, invasive, and resource consuming. Many groups have published using this method to avoid blood sampling (2,6,7,8).

In this spreadsheet, the method introduced by Thomas et al. (2) was used to estimate the blood $TIAC$ ($TIAC_{blood}$) assuming that 14% of the $TIAC_{WB}$ can be attributed to blood as shown in equation (6). Thereby, the $D_{rm \leftarrow ECF}$ can be calculated by the activity concentration in blood and the red marrow ECF fraction (RMECF) as shown in equation (7). The RMECF was 0.19, based on Sgouros studied using

Dosimetric parameter	The commercial OLINDA/EXM image-based dosimetry software		A simplified excel spreadsheet	
	Mean \pm SD	Range	Mean \pm SD	Range
$TIAC_{WB}$ (h)	24.42 \pm 8.71	9.61-46.03	23.28 \pm 5.00	13.24-31.49
d_{rm} (mGy/MBq)	0.0653 \pm 0.0233	0.0268-0.1280	0.0798 \pm 0.0220	0.0356-0.1433

SD: Standard deviation, $TIAC_{WB}$: Whole-body time-integrated activity coefficient, d_{rm} : Absorbed dose coefficient, OLINDA/EXM: Organ Level Internal Dose Assessment/ Exponential Medelling

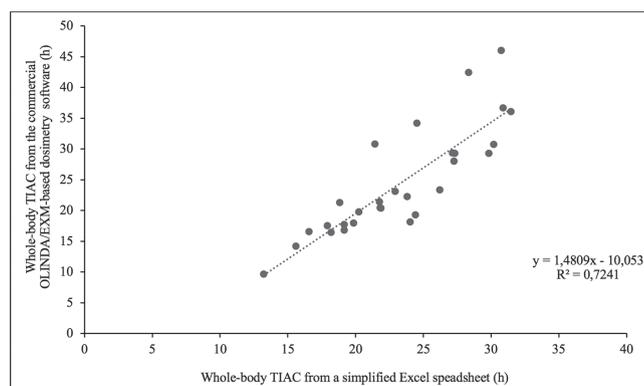


Figure 3. Correlation of the $TIAC_{WB}$ calculated from a simplified Excel spreadsheet and the commercial OLINDA/EXM image-based dosimetry software

$TIAC_{WB}$: Whole-body time-integrated activity coefficient

OLINDA/EXM image-based dosimetry software with a non-inferiority margin of 0.02 (p value <0.05 using the Wilcoxon signed-rank test because non-normality was assumed). The non-inferiority margin of 0.02 was set based on SD of d_{rm} from the commercial OLINDA/EXM image-based dosimetry software that was used in the pretherapeutic dosimetry protocol. Pearson's correlation coefficient was 0.737 (p value <0.001) as illustrated in Figure 4.

Discussion

Image-based red marrow dosimetry calculation in radioiodine therapy is performed to maximize the radiation dose to remnant thyroid or metastasis CT while considering the patient's safety by minimizing bone marrow toxicity. The primary parameter requested for internal dosimetry is often the $TIAC$ (13). In this study, the calculated from a simplified excel spreadsheet was slightly shorter than that using the commercial OLINDA/EXM image-based dosimetry software. The mean percentage difference in $TIAC_{WB}$ between both methods was 0.41%. Many factors affect $TIAC$ estimation such as counts-to-activity conversion method, ROI delineation, background correction, and method of fit and integration of TAC.

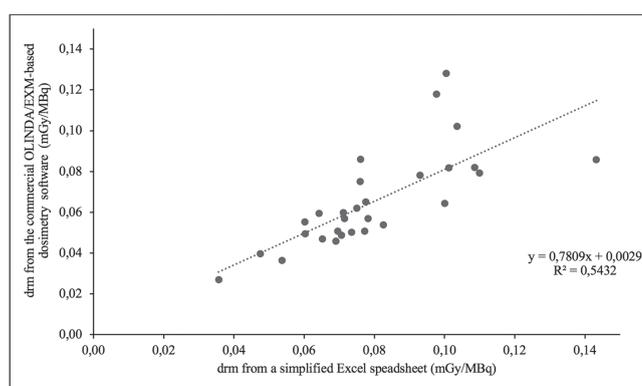


Figure 4. Correlation of the d_{rm} calculated from a simplified Excel spreadsheet and the commercial OLINDA/EXM image-based dosimetry software

d_{rm} : Absorbed dose coefficient

In this study, the counts-to-activity conversion was similar using equipment efficiency for both methods. For ROI delineations, there were drastic differences between the commercial OLINDA/EXM image-based dosimetry software and a simplified excel spreadsheet. As regards illustration, the commercial OLINDA/EXM image-based dosimetry software has an advanced option to draw and automatically copy ROIs from the initial whole-body to all the other images belonging to the same patient. In contrast, the ROI in a simplified Excel spreadsheet was manually drawn using the vendor-supplied software. Many studies have reported that ROI delineation was one of the critical uncertainty factors for dose calculation in nuclear medicine (14,15,16). For the fit and integration method, a simplified excel spreadsheet was used; the mono-exponential fit (also called single exponential function) in MS Excel. The commercial OLINDA/EXM image-based dosimetry software was fitted using a bi-exponential fit function. According to the EANM guideline for pretherapeutic dosimetry in DTC, the bi-exponential fitting is suggested to determine the (3). Many simplified approaches have been developed and illustrate that the simple mono-exponential could be used in routine practice (17,18). However, errors of the mono-exponential might be higher since such a fitting

does not reflect realistic kinetics in the uptake and long-term retention phase of radioiodine kinetics (17). The most desirable next step is to include the bi-exponential fit in our excel spreadsheet to improve the accuracy of TIAC. Comparison of the presented in this work with other publications is tabulated in Table 2.

	TIAC _{WB} (h) mean ± SD
Previous studies	
Hänscheid (29) (2006)	24.10±7.80
Willegaignon et al. (25) (2012)	25.77±6.98
Willegaignon et al. (23) (2016)	29.18±18.14
Present study	
A simplified excel spreadsheet	23.28±5.00
The commercial OLINDA/EXM image-based dosimetry software	24.42±8.71
TIAC _{WB} : Whole-body time-integrated activity coefficient, DTC: Differentiated thyroid cancer, SD: Standard deviation, OLINDA/EXM: Organ Level Internal Dose Assessment/Exponential Modelling	

It was found that most publications reported a large SD in the TIAC_{WB}, like our findings. The possible explanations for high SD for TIAC_{WB} in radioiodine treatment might be related to the disease characteristic of ablation in DTC patients such as metastasis, iodine intake/uptake, hormonal level, age of the treated patient.

As previously explained, the d_{rm} is the ratio between the bone marrow absorbed dose and administered activity. In this study, the difference in the d_{rm} from a simplified excel spreadsheet and the commercial OLINDA/EXM image-based dosimetry software was -26.98%. Many factors affect d_{rm} , including the phantom and S factor. In our study, both methods used the C&E phantoms, but different versions. The simplified excel spreadsheet used the C&E phantoms from the study of Stabin et al. (19) in 1995 whereas, the commercial OLINDA/EXM image-based dosimetry software used the newer version from the study of Stabin et al. (5) in 2003. The latter version used the bone marrow specific absorbed fraction from the EGS4 Monte Carlo code.

Statistical comparison of the d_{rm} from both methods was analyzed using a non-inferiority test. Generally, this test is used to assess that a new drug or new treatment is not worse than the main comparator drug or a reference treatment by more than a non-inferiority margin (11,20). In this study, the non-inferiority margin of 0.02 was set.

This value was based on the SD of d_{rm} from the commercial OLINDA/EXM image-based dosimetry software and other published works (as illustrated in Table 3). The non-inferiority test showed that a simplified Excel spreadsheet software was no worse than the commercial OLINDA/EXM image-based dosimetry software at the non-inferiority margin.

For comparison, the mean values of d_{rm} calculated from both methods were compared with the values reported by other groups as demonstrated in Table 3.

	d_{rm} (mGy/MBq) mean ± SD
Previous studies	
Traino et al. (21) (2007)	0.0739±0.0217
Miranti et al. (22) (2015)	0.0845±0.0385
Willegaignon et al. (23) (2016)	0.0660±0.0550
Alan Selcuk et al. (24) (2018)	0.1079±0.0319
Present study	
A simplified excel spreadsheet	0.0798±0.0220
The commercial OLINDA/EXM image-based dosimetry software	0.0653±0.0233
d_{rm} : Absorbed dose coefficient, DTC: Differentiated thyroid cancer, SD: Standard deviation	

In this study, the mean and SD of d_{rm} from the simplified excel spreadsheet was 0.0798±0.0220 mGy/MBq. Traino et al. (21) and Miranti et al. (22) calculated the d_{rm} using the reference data from the RADAR website with an estimated d_{rm} of 0.0739±0.0217 mGy/MBq and 0.0845±0.0385 mGy/MBq, respectively. Willegaignon et al.(23) also computed the d_{rm} from whole-body images using the OLINDA/EXM software with a mean of 0.0660±0.0550 mGy/MBq. Similarly, the d_{rm} calculated by Alan Selcuk et al. (24) using the same software was 0.1079±0.0319 mGy/MBq.

From these results, the reference phantom and S factor value greatly impacted the d_{rm} . This is coherent with many studies and the difference in the dosimetry can be greater than 150% when using different phantoms and S factors (25,26,27,28). Hence, the selection of phantom is an important factor in the dosimetry calculation. Although the d_{rm} results showed some differences between both the software, the clinical outcome is still difficult to prove at this stage.

Study Limitations

The small number of patients and the heterogeneity of the stages of the disease (local or distant metastasis) in the patient group might have biased the outcome of this study.

Conclusion

The $TIAC_{VB}$ calculated from a simplified excel spreadsheet was not statistically different from that of the software. The calculated d_{m} using the simplified excel was non-inferior to that calculated by the software with an acceptable margin.

It can be concluded that a simplified excel spreadsheet can be used to calculate the d_{m} in radioiodine therapy of DTC patients. The dose assessment using this method is feasible and relatively low cost compared to the commercial OLINDA/EXM image-based dosimetry software. Hence, the simplified Excel spreadsheet should increase the number of dosimetry studies in low or middle-income countries, though it requires further validation with more patients. Also, a method for improving TAC integration and the updated phantom for S-factor should be further considered.

Ethics

Ethics Committee Approval: Ethics Committee Approval was obtained from the Ethical Review Board of the Surin Hospital with the approval number: 12/2562 and date: 9th April 2019.

Informed Consent: This retrospective study represents no more than minimal risk to subjects and will not adversely affect their rights and welfare. Due to the impracticality of contacting those individuals no longer in follow-up at Surin Hospital. Hence, the authors are requesting waiver of consent from the Ethical Review Board.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.R., Concept: K.C., Design: K.C., P.C., Data Collection or Processing: R.S., Analysis or Interpretation: R.S., K.R., Literature Search: R.S., P.C.,

Writing: K.C., P.C.

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