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 (Drm) 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 radiiodine 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 (TIACWB) and Drm [in terms of absorbed dose coefficient (dRM)]. For the simplified excel spreadsheet, the whole-body count was obtained from the vendor-supplied software. Then, the TIACWB 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 TIACWB and dRM from both methods was done using a non-inferiority test using a paired t-test or the Wilcoxon signed-rank test.

Results: The TIACWB showed no significant difference between both methods (p=0.243). The calculated Drm 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 (Drm) kan dozimetresi kullanılarak hesaplanabilir. Ancak tam kan yöntemi zahmetli ve invaziftir. Bu nedenle, görüntü bazlı dozimetri tercih edilmektedir. Bu çalışmanın amacı, görüntü tabanlı radyoiyot kırmızı iliğin ilk dozimetresi için basitleştirilmiş bir excel elektronik tablosu geliştirilme

Yöntem: Yirmi dokuz hastanın rutin tedavi için dosimetre protokolündeki serit tüm vücut görüntülerini (2, 6, 24, 48 ve 72. saatlerde elde edilen) retrospektif olarak yeniden analiz edildi. Rutin olarak, ticari OLINDA/EXM görüntü tabanlı dozimetri yazılımı, tüm vücut zamana entegre edilmiş aktivite katsayısı (TIACWB) ve Drm [absorbe edilen doz katsayısı (dRM)] hesaplandı. Basitleştirilmiş bir Excel elektronik tablosu, tüm vücut sayısını satıcı tarafından sağlanan yazılımdan elde edilmiştir. Daha sonra TIACWB Excel ileki kullanım olarak oluşturulmuş zamanda良かったır eğrili ile hesaplandı. S faktörü diğer yayınlar arasında alınması bir fark göstermedi (esetleştirmek için t-testi ile p değerleri 0,243). Basitleştirilmiş bir Excel elektronik tablosunun hesaplanan dRM değerinin, 0,02’lik non-inferiority payı ile ticari OLINDA/EXM görüntü tabanlı dozimetri yazılımı ile hesaplanan değerden statistiksel olarak non-inferor olduğunu göstermiştir (Wilcoxon testi ile p değeri <0,05).

Bulgular: TIACWB iki yöntem arası anlamlı bir fark göstermedi (esetleştirmek için t-testi ile p değerleri 0,243). Basitleştirilmiş bir Excel elektronik tablosunun hesaplanan dRM değerinin, 0,02’lik non-inferiority payı ile ticari OLINDA/EXM görüntü tabanlı dozimetri yazılımı ile hesaplanan değerden statistiksel olarak non-inferor olduğu görülmüştür (Wilcoxon testi ile p değeri <0,05).

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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.
The whole-body TIAC\textsubscript{WB} (formally called residence time) is calculated from the area under TAC\textsubscript{WB}. The exponential extrapolation with a numerical trapezoidal integration is employed in this OLINDA/EXM image-based dosimetry software. In this software, D\textsubscript{rm} was calculated in terms of the absorbed dose coefficient (d\textsubscript{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\textsubscript{av}) was subtracted from the average activity in the whole-body ROI (WB\textsubscript{av}) and multiplied by the number of pixels in the whole-body image (N\textsubscript{WB}) as illustrated in equation (1).

\[
\text{WB}\textsubscript{net} = N\textsubscript{WB} \times (WB\textsubscript{av} - BKG\textsubscript{av}) \quad \text{equation (1)}
\]

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

\[
\text{WB}\textsubscript{GM} = \sqrt{WB\textsubscript{net(ant)} \times WB\textsubscript{net(post)}} \quad \text{equation (2)}
\]

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)].

\[
\text{FAA}(t) = A(t) = A \times e^{-\lambda t} \quad \text{equation (3)}
\]

Where, FAA(t) is the fraction of administered activity (A\textsubscript{0}) as a function of time t and A and \(\lambda\) are fit constants. The TIAC\textsubscript{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 (4).

\[
\text{TIAC}\textsubscript{WB} \int_0^\infty \text{FAA}(t) dt \quad \text{equation (4)}
\]

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

\[
\text{Drm} = D\textsubscript{rm-ECF} + D\textsubscript{rm-RoB} \quad \text{equation (5)}
\]

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\textsubscript{blood}) assuming that 14% of the TIAC\textsubscript{WB} can be attributed to blood as shown in equation (6). Thereby, the D\textsubscript{rm-ECF} can be calculated by the activity concentration in blood and the red marrow ECF fraction (RMEECF) as shown in equation (7). The RMEECF was 0.19, based on Sgouros studied using...
a theoretical investigation of radiolabeled monoclonal antibodies (9). For $D_{\text{ECF} \rightarrow \text{rm}}$, the patient-specific bone marrow mass is not necessary as it is canceled out when the $S$ value is scaled (2). For the $S$ value for red marrow to red marrow, the C&E phantoms were also used (10).

The remainder of the body TIAC ($\text{TIAC}_{\text{RoB}}$) can be calculated as the difference between the TIAC$_{\text{WB}}$ and the other source organs which is only in this case. In this spreadsheet was calculated by subtracting the TIAC$_{\text{blood}}$ from the TIAC$_{\text{WB}}$ as shown in equation (8). $S$ value for the remainder of the body to red marrow was taken from the C&E phantoms ($S_{\text{RoB} \rightarrow \text{rm}, \text{phantom}}$). In this case, there were only two source organs. The patient-specific $S$ value for the remainder of the body to red marrow ($S_{\text{RoB} \rightarrow \text{rm}, \text{patient}}$) was calculated using a linear scaling as recommended in the EANM guideline illustrated in equation (9) (4).

$$D_{\text{RoB} \rightarrow \text{rm}} = (A_0 \times (\text{TIAC}_{\text{WB}} - \text{TIAC}_{\text{blood}})) \times S_{\text{RoB} \rightarrow \text{rm}, \text{patient}}$$

$$S_{\text{RoB} \rightarrow \text{rm}, \text{phantom}} = \frac{m_{\text{m, phantom}}}{m_{\text{WB, phantom}} - m_{\text{m, phantom}}}$$. $m_{\text{m, phantom}}$ and $m_{\text{WB, phantom}}$ are the red marrow mass, the whole-body mass of the C&E phantoms, and the whole-body mass of the patient respectively (10). In the same manner, $d_{\text{rm}}$ was computed from the $D_{\text{rm}}$ normalized by administered activity $A_0$. The unit of $d_{\text{rm}}$ is mGy/MBq.

### Statistical Analysis

SPSS version 20 (IBM Inc., NY, USA) was used for statistical analysis. The TIAC$_{\text{WB}}$ and the $d_{\text{rm}}$ calculated from the commercial OLINDA/EXM image-based dosimetry software and a simplified excel spreadsheet were expressed as mean ± standard deviation (SD). A comparison of the TIAC$_{\text{WB}}$ and the $d_{\text{rm}}$ from both methods was statistically assessed using a non-inferiority test based on the paired t-test when normality was assumed or the Wilcoxon signed-rank test for the case of non-normality (11). Pearson’s correlation was also used to study the correlation between both methods (12).

### Results

This retrospective study included 29 patients who participated in the pretherapeutic dosimetry protocol for radioiodine therapy. In this work, the TIAC$_{\text{WB}}$ and the $d_{\text{rm}}$ were reanalyzed using a simplified excel spreadsheet. The mean (± SD) and range (minimum-maximum) of the TIAC$_{\text{WB}}$ and the $d_{\text{rm}}$ are summarized in Table 1. The calculated TIAC$_{\text{WB}}$ showed no statistically significant difference between the two methods ($p$ value 0.243 using a two-sided paired t-test because normality was assumed). The Pearson correlation coefficient was 0.851 ($p$ value <0.001) (Figure 3).

The calculated $d_{\text{rm}}$ from the commercial OLINDA/EXM image-based dosimetry software was 0.0653±0.0233 mGy/MBq (range: 0.0268 to 0.1280 mGy/MBq). After reanalysis with a simplified excel spreadsheet, the mean (± SD) of the $d_{\text{rm}}$ was 0.0798±0.0220 mGy/MBq (range: 0.0356 to 0.1433 mGy/MBq). For $d_{\text{rm}}$, the statistical results showed that the calculated $d_{\text{rm}}$ from a simplified excel spreadsheet was statistically non-inferior to that from the commercial
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.

### Table 1. The mean (mean ± SD) and range (minimum - maximum) of the TIAC$_{WB}$ in hours and $d_{rm}$ in mGy/MBq calculated from the commercial OLINDA/EXM image-based dosimetry software and a simplified excel spreadsheet

| Dosimetric parameter | The commercial OLINDA/EXM image-based dosimetry software | A simplified excel spreadsheet |
|----------------------|---------------------------------------------------------|--------------------------------|
|                      | Mean ± SD | Range | Mean ± SD | Range |
| TIAC$_{WB}$ (h)      | 24.42±8.71 | 9.61-46.03 | 23.28±5.00 | 13.24-31.49 |
| $d_{rm}$ (mGy/MBq)   | 0.0653±0.0233 | 0.0268-0.1280 | 0.0798±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 Assessmant/ Expanential Medelling

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

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

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 $d_{rm}$ (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.

| Previous studies | TIAC<sub>WB</sub> (h) mean ± SD |
|------------------|---------------------------------|
| 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 |

It was found that most publications reported a large SD in the TIAC<sub>WB</sub> like our findings. The possible explanations for high SD for TIAC<sub>WB</sub> 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<sub>rm</sub> is the ratio between the bone marrow absorbed dose and administered activity. In this study, the difference in the d<sub>rm</sub> from a simplified excel spreadsheet and the commercial OLINDA/EXM image-based dosimetry software was -26.98%. Many factors affect d<sub>rm</sub>, 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<sub>rm</sub> 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<sub>rm</sub> 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<sub>rm</sub> calculated from both methods were compared with the values reported by other groups as demonstrated in Table 3.

In this study, the mean and SD of d<sub>rm</sub> from the simplified excel spreadsheet was 0.0798±0.0220 mGy/MBq. Traino et al. (21) and Miranti et al. (22) calculated the d<sub>rm</sub> using the reference data from the RADAR website with an estimated d<sub>rm</sub> of 0.0739±0.0217 mGy/MBq and 0.0845±0.0385 mGy/MBq, respectively. Willegaignon et al.(23) also computed the d<sub>rm</sub> from whole-body images using the OLINDA/EXM software with a mean of 0.0660±0.0550 mGy/MBq. Similarly, the d<sub>rm</sub> 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<sub>rm</sub>. 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<sub>rm</sub> 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 TIAC₂₀₀₀ calculated from a simplified excel spreadsheet was non-inferior to that of the software. The calculated dₘ in 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 dₘ in radiiodine 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.

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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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