

Standard Operating Procedure for Prospective Individualised Dosimetry for ^{131}I -rituximab Radioimmunotherapy of Non-Hodgkin's Lymphoma

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Abstract

Radioimmunotherapy (RIT) is an attractive therapy for non-Hodgkin's lymphoma (NHL) as it allows targeted tumor irradiation which provides a cytotoxic effect significantly greater than that of the immune-mediated effects of a non-radioactive, or 'cold', antibody alone. Anti-CD20 antibodies such as rituximab are ideal for RIT, as not only is it easily iodinated, but the CD20 antigen is found on more than 95% of B-cell NHL. A standard operating procedure (SOP) has been formulated for personalized prospective dosimetry for safe, effective outpatient ^{131}I -rituximab RIT of NHL. Over five years, experience of treatment of outpatients with ^{131}I -rituximab was analyzed with respect to critical organ radiation dose in patients and radiation exposure of their carers. This radiation safety methodology has been refined; and offers the potential for safe, practical application to outpatient ^{131}I -rituximab RIT of lymphoma in general and in developing countries in particular. Given endorsement and sanction of this SOP by local regulatory authorities the personalized dosimetry paradigm will facilitate incorporation of RIT into the routine clinical practice of therapeutic nuclear oncology worldwide.

Key words: Dosimetry, I-131 rituximab, non-Hodgkin's lymphoma, standard operating procedure

Introduction

A standard operating procedure (SOP) has been formulated for personalized prospective dosimetry for safe, effective outpatient ^{131}I -rituximab radioimmunotherapy (RIT) of non-Hodgkin's lymphoma (NHL). Over five years, experience of treatment of outpatients with ^{131}I -rituximab was analyzed with respect to critical organ radiation dose in patients and radiation exposure of their carers.^[1] This radiation safety methodology was refined and offers the potential for safe, practical application to outpatient ^{131}I -rituximab RIT of lymphoma in developing countries. Given endorsement and sanction of this SOP by local regulatory authorities the personalized dosimetry

paradigm will facilitate incorporation of RIT into the routine clinical practice of therapeutic nuclear oncology worldwide.

Standard operating procedure

SOP for Prospective Individualized Iodine-131-rituximab Radioimmunotherapy of non-Hodgkin's lymphoma is described in this chapter. This comprehensive description would cover the following areas:

1. Rationale for dosimetric procedure
2. Patient preparation
3. Dosimetric tracer study and rituximab (non-radiolabeled) infusion
4. Dosimetry
5. Worked example
6. References

1. Rationale for dosimetric procedure

- 1.1 Radioimmunotherapy (RIT) is an attractive therapy for diseases such as non-Hodgkin's lymphoma (NHL) as it allows targeted tumor irradiation which provides a cytotoxic effect significantly

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greater than that of the immune-mediated effects of a non-radioactive, or 'cold', antibody alone.^[2] Targeted RIT not only provides a high radiation dose to the tumor as compared to normal tissue but by crossfire effects also kills neighboring malignant cells that do not express the target CD20 antigen.

- 1.2 Anti-CD20 antibodies such as rituximab are ideal for RIT, as not only is it easily iodinated,^[3,4] but the CD20 antigen is found on more than 95% of B-cell NHL.^[5,6] It is also found on circulating B-cells, but not on early progenitor B-cells or mature plasma cells.^[5,7] As the antigen is neither shed, nor modulated, and the antibody is not significantly internalized by the cell,^[8,9] the resulting stable antigen-antibody bond with a relatively long biological half-life of the antibody on the cell surface, provides a high radiation exposure probability to the tumor cells from the radiolabelled antibody.
- 1.3 The CD20 antigen is present on the tumor cells as well as circulating B-cells, both of which vary greatly in number in different patients. The clearance rate of an anti-CD20 antibody may therefore be expected to differ significantly between patients.^[6,10] The therapeutic activity requirement for effective safe therapy thus varies widely from one patient to another.
- 1.4 Dosing schema empirically based upon a MBq/kg or MBq/m², whilst simple to implement, are not appropriate for drugs such as radiolabeled anti-CD20 antibodies with highly variable individual bio-distribution and pharmacokinetics. Schema based upon a MBq/kg or MBq/m² for radiolabeled anti-CD20 antibodies will often result in either under-dosing of the patient and sub-optimal therapy, or the overdosing of the patient and consequent significant toxicity and myelosuppression.^[11] Individual prospective dosimetry is imperative.
- 1.5 Iodine-131 radiolabeled anti-CD20 antibodies have been shown to give a ten to fifteen-fold higher radiation dose to the targeted tumors than to the normal tissue.^[10] However, the tumoricidal radiation dose is limited by bone marrow-limited organ exposure, the maximum tolerated dose (MTD) being 2 Gy to the bone marrow.^[12]
- 1.6 Bone marrow dosimetry, based upon sequential gamma camera imaging, and the drawing of regions of interest (ROI) around bone marrow in each patient, is time-consuming and difficult. Bone marrow dosimetry based upon sequential blood sampling is also time consuming and may be unreliable.^[13-16] A safe radiation absorbed dose to the bone marrow of 2 Gy has been shown by dose escalation studies and bone marrow dosimetry to correspond to a whole-body radiation dose of approximately 0.75 Gy.^[7,11,17-20]

- 1.7 The individualized dosimetry scheme predicated upon a whole body radiation dose of 0.75 Gy for patients with a platelet count $\geq 100 \times 10^9/L$ and neutrophils $\geq 1.5 \times 10^9/L$ minimizes the risk of significant myelosuppression. For patients who have previously undergone autologous stem cell transplantation, a lower prescribed radiation whole body dose may be desirable.^[10,20]
- 1.8 Preliminary research into a simplified dosimetric protocol used daily gamma camera imaging or NaI scintillation probe monitoring after administration of a tracer activity of radioiodine-131 labeled anti-CD20 antibody. However it was found that the residence time of radiolabeled anti-CD20 antibodies in patients followed a mono-exponential function and whole-body imaging or counting at three time intervals over a period of 6 to 7 days provided sufficient information to allow the residence time of the radiolabeled antibody to be calculated, and hence the prescribed activity to give a whole body dose of 0.75 Gy.^[10,11,18]
- 1.9 The antibody does not accumulate in fatty tissue^[10] and the patient's effective mass (related to lean body mass) is relevant for the dosimetry calculation. If the effective mass is less than the patient's actual weight, then it is used in determining the therapeutic activity. However if the patient's actual weight is less than the calculated effective mass, then the patient's actual weight is used in determining the therapeutic activity.
- 1.10 In our more than 400 patients undergoing ¹³¹I-rituximab RIT, the residence time ranged from 38.9 hours to 219.6 hours, (mean 138 hours). For very short residence times, the calculated therapeutic activities may exceed 5 GBq, in which case the prescribed therapeutic activity should be limited to no more than 5 GBq.

2. Patient preparation

- 2.1 Patients with NHL are referred by hematologist/oncologists for consultation with the nuclear medicine physician for consideration of ¹³¹I-rituximab radioimmunotherapy to assess eligibility for outpatient treatment. The rationale and logistics are explained to the patient, and their accompanying carer and information forms are provided by the nuclear physician during the consultation.
- 2.2 Written consent is obtained from the patient after sufficient time has elapsed to allow their due consideration.
- 2.3 In conformity with prevailing local regulatory agency requirements, signed declarations by patients, carers and back-up carers, to minimize radiation exposure to the public, after appropriate explanation by the nuclear physician and the

physicist and following formal risk assessment on behalf of the regulatory agency, are obtained.

- 2.4 Radiation safety, details of the therapy and logistics are discussed with the patient, the patient's carer, family members and any other household residents. All carers and co-residents sign a formal consent to 'knowingly and willingly receive up to 5 mSv radiation exposure per treatment episode' according to the local and international guidelines.^[21-23]
- 2.5 Arrangements are made for minimization of contact between the patient and children, and women who may be pregnant, for a period of one week following outpatient therapy.
- 2.6 In the event that a patient is deemed unsuitable for outpatient therapy, the ¹³¹I rituximab may be administered as an inpatient therapy in a hospital radiation isolation room, under confinement until the regulatory agency release limit is attained. The international release guideline of less than 25 μ Sv/h at 1 m^[22,23] would be expected to be satisfied after 5 to 7 days of hospital isolation.

3. Dosimetric tracer study and rituximab (non-radiolabelled) infusion

- 3.1 Lugol's iodine (10 drops a day of 50 mg/ml iodine in potassium iodide solution) is commenced the day before the tracer activity administration of 250 MBq ¹³¹I rituximab, in order to protect the thyroid from irradiation by free radioiodine. The Lugol's iodine is taken in a small quantity of juice or other drink every day for three weeks or at least two weeks following the therapy administration.
- 3.2 The patient receives standard immunotherapy with 375 mg/m² rituximab in the morning prior to administration of a radiolabelled tracer on the same day. The infusion typically takes two to four hours. The infusion of cold antibody enhances tumor uptake of radiolabelled ¹³¹I-antibody.^[24,25]
- 3.3 After the intravenous infusion of the cold rituximab antibody, the tracer activity of 250 MBq ¹³¹I rituximab is administered intravenously. The radioactive tracer may be injected using a shielded syringe in the same canula, which is then removed.
- 3.4 Whole body quantitative anterior and posterior gamma imaging is performed on a gamma camera 10 to 60 minutes post injection, the patient having voided before commencement of the ¹³¹I rituximab tracer injection. Imaging is acquired using high energy general-purpose collimators set at 20% energy window and centered on the 364 keV ¹³¹I photopeak. No contouring is used. Step mode acquisition is recommended at an equivalent rate of 13 cm/minute or at a speed appropriate for the camera in use. If step mode is not available, whole body images should be acquired at a rate of 13 cm/min or at an appropriate speed. Matrix size of 1024 \times 1024, or the largest available, and with the same geometry for each image by recording length of scan from start to finish (cm) with an allowance of 10 cm above head and below feet, height of both detectors and bed height are recorded for reproduction at each subsequent scan. Extremities are included in the scans and the arms must not cross over the body. Total scan time is between 15 and 20 minutes and the scan terminates on preset. It is mandatory for each of the three scans, that the same camera, collimator, scanning speeds, window settings, geometry and patient positioning be used.
- 3.5 Background counts are acquired over the same length (cm) as the whole body scan. The background scan may be acquired at a faster rate (e.g., 39 cm per minute) but the counts must be multiplied proportionately to give effective counts in the anterior and posterior for the same time period as the patient images were acquired.
- 3.6 The intermediate gamma camera scan is performed after three or four days using exactly the same settings as the initial gamma camera scan. The patient is requested to void their bladder immediately prior to the scan. A background scan is also performed in the absence of the patient.
- 3.7 A final gamma camera scan is performed, using the same settings as the previous scans, and after the patient has voided. This scan is normally performed 7 days after the tracer administration. However the final scan may be performed up to 14 days after the administration of the tracer. A further background scan is performed in the absence of the patient.
- 3.8 If only a single-head gamma camera is available, then the total-body residence time may be calculated using only anterior counts, corrected for background counts.^[18]
- 3.9 It is also possible to use a simple NaI scintillation probe (e.g., thyroid probe) to determine the three data points necessary for the whole body dosimetry.^[18] Anterior and posterior counts can be made using a NaI probe over a period of two or three minutes. Background counts should also be taken shortly before the patient is present. The probe should be placed at a distance of 2 to 3 meters from the patient and it is important that the same geometry and count time period be used for each count—that is, the position of the patient and the location of the probe be identical for all of the counts. This simple method gives equivalent dosimetric results to using a gamma camera for the whole body counts.^[18]
- 3.10 Seven days after the initial rituximab infusion, the patient receives another standard immunotherapy

with 375 mg/m² rituximab in the morning prior to administration of the therapy activity on the same day.

4. Dosimetry

- 4.1 Prospective individualized dosimetry is based upon a whole body radiation absorbed dose of 0.75 Gy which limits marrow exposure to within the safe threshold of 2 Gy for a patient with sufficient hemopoietic marrow reserve.
- 4.2 The therapeutic activity may be calculated from:^[10,18]

$$\text{Therapeutic Activity (MBq)} = \left(\frac{\text{Activity.h (MBq.h)}}{\text{Residence Time (h)}} \right) \times \left(\frac{\text{Desired Total Body Dose (Gy)}}{0.75 \text{ Gy}} \right)$$

- 4.3 In order to calculate the therapeutic activity (MBq), it is first necessary to calculate:
 - (a) Activity.h (MBq.h), which is dependent on the properties of the radionuclide (¹³¹I), and patient's actual weight or the patient's effective mass—see Section 4.4.2.
 - (b) The Residence Time (h) of the ¹³¹I-rituximab is calculated from data obtained from the dosimetric gamma camera scans or scintillation probe counts—see Section 4.5.
- 4.4 Activity.h (MBq.h). Based upon the MIRD schema and assuming a simplified ellipsoidal volume for the patient and a heterogeneous distribution of the radioiodinated antibody in the patient, the Activity.h (MBq.h) may be derived from the simplified and semi-empirical formula:

$$\text{Activity.h}_{\text{MBq.h}} = (3624.59 \times \text{Weight}_{\text{kg}}) + 29283.65$$

This is only valid for iodine-131 and must not be used for other radioisotopes.

- (a) If the patient's effective mass is less than the patient's actual weight, then the effective mass is used to determine the Activity.h. However if the patient's actual weight is less than the calculated effective mass, then the patient's actual weight is used to determine the Activity.h.
- (b) In order to determine the patient's effective mass, the patient actual height and weight are measured and recorded. The patient's effective mass is calculated using one of the commonly used formula, for example:

$$\text{Effective Mass}_{(\text{kg})} = 65.76 + (1.452 \times (\text{Patient Height}_{\text{cm}} - 152)) \text{ for males}$$

$$\text{Effective Mass}_{(\text{kg})} = 62.34 +$$

$$(1.247 \times (\text{Patient Height}_{\text{cm}} - 152)) \text{ for females}^{[18]}$$

- 4.5 The Residence Time for a patient may be obtained in one of three ways:

- (a) By plotting the percent of Injected Tracer Activity versus time on a semi-logarithmic graph and graphically obtaining the point at which the line has decreased to 36.78% (i.e., 1/e or 1/2.718282). (See section 5.1.5.1)
- (b) By plotting the percent of Injected Tracer Activity versus time on a linear-linear graph and obtaining the slope of the line, for example, by using the 'Trendline' and 'Display Equation on Chart' options in Microsoft Excel. (See section 5.1.5.2) The Residence time is then given by:

$$\text{Residence Time}_h = \frac{\left(\text{Log}_{10} \left(\frac{1}{e} \right) \right)}{\text{Slope of Curve}}$$

- (c) By calculating the Residence Time directly using the Percentage Activity remaining at each time point from:

$$\text{Residence Time}_{\text{hours}} = \frac{t_2 \left(1 - \frac{C_2}{C_1} \right) + \frac{C_2}{C_1} (t_3 - t_2)}{\text{Ln} \left(\frac{C_1}{C_2} \right) + \text{Ln} \left(\frac{C_2}{C_3} \right)}$$

Where

- t₁ = Time in hours from initial scan—i.e., 0;
- t₂ = Time in hours from initial scan to second scan;
- t₃ = Time in hours from initial scan to third scan;
- C₁ = Initial percentage of tracer in patient at t₁, i.e., 100%;
- C₂ = Percentage of tracer remaining in patient at t₂;
- C₃ = Percentage of tracer remaining in patient at t₃.^[18]

Alternatively the background-corrected geometric mean of the counts at each time point may be used instead of the percentage of tracer remaining (i.e., C₁, C₂ and C₃).

The use of the non-graphical method is not recommended as a stand-alone procedure. If the numeric calculation is performed, the data should be graphed to ensure linearity and avoid errors which may arise from faulty data entry and only become apparent on a plot.

4.5.1 The geometric mean of the anterior and posterior whole body image counts, corrected for background, for each time point for the three scans, is used to plot the time-activity curve. The geometric mean is calculated by taking the square root of the anterior whole-body count, minus the background count, multiplied by the posterior whole-body count, minus the background count.

$$\text{Count}_{geom} = \sqrt{\left[\left(\begin{array}{c} \text{Whole Body Count}_{ant} - \\ \text{BGnd Count}_{ant} \end{array} \right) \times \left(\begin{array}{c} \text{Whole Body Count}_{post} - \\ \text{BGnd Count}_{post} \end{array} \right) \right]}$$

It is important that 'raw' counts of photons detected are used in the calculation rather than any idiosyncratic camera acquisition-corrected count which may introduce non-linearity.

- 4.6 Once the Activity. Hours and the Residence Time have been determined, the Therapeutic Activity in MBq may be calculated using the equation in 4.2.
- 4.7 All these calculations may be semi-automated by devising a relatively simple spreadsheet into which the raw data such as patient height, weight, sex, and required whole body dose (nominally 0.75 Gy) and scan data including anterior, posterior patient and background counts are entered. The output then represents the prescribed therapeutic activity of ¹³¹I-rituximab to give the required whole body dose.

5. Worked example

5.1 Given a male NHL patient of height 175.5 cm and weight 97 kg, with platelet count of $160 \times 10^9/L$, neutrophils $2 \times 10^9/L$, and modest bone marrow involvement, what is the prescribed activity in MBq for ¹³¹I-rituximab radioimmunotherapy?

5.1.1 As the hemopoietic marrow reserve is sufficient and there is insignificant bone marrow infiltration, the full 0.75 Gy whole body dose will be prescribed.

5.1.2 The effective mass may be calculated using: Effective Mass_(kg) = 65.79 +

$$\begin{aligned} & (1.452 \times (\text{Patient Height}_{cm} - 152)) \text{ for males} \\ & = 65.76 + (1.452 \times (175.5 - 152)) \\ & = 99.88 \text{ kg} \end{aligned}$$

As the patients actual weight is less than the calculated effective mass, the actual weight will be used in the calculation.

5.1.3 The Activity.h (MBq.h) may be calculated using:

$$\begin{aligned} \text{Activity.h}_{MBq.h} &= (3624.59 \times \text{Weight}_{kg}) + 29283.65 \\ &= (3624.59 \times 97.0) + 29283.65 \\ &= 351585.2 + 29283.65 \\ &= 380868.9 \text{ MBq.h} \end{aligned}$$

5.1.4 A tracer activity of 250 MBq ¹³¹I-rituximab is injected intravenously after the cold mabthera infusion. Anterior and posterior planar gamma camera scans are performed within the hour. This is time zero, t_0 . A second set of scans is performed four days later and a third set of scans three days after that. Background scans are also performed. The photon counts from each scan are determined from the images. Table 1 gives the results.

The geometric mean count of each scan can now be calculated. In respect of the initial scan:

$$\begin{aligned} \text{Count}_{geom} &= \sqrt{\left[\left(\begin{array}{c} \text{Whole Body Count}_{ant} - \\ \text{BGnd Count}_{ant} \end{array} \right) \times \left(\begin{array}{c} \text{Whole Body Count}_{post} - \\ \text{BGnd Count}_{post} \end{array} \right) \right]} \\ &= \sqrt{[(57692 - 1809) \times (49750 - 1661)]} \\ &= \sqrt{[2,687,322,366]} \\ &= 51839 \end{aligned}$$

Similarly for the other scans, and by simple arithmetic, we obtain the results presented in Table 2.

5.1.5 The residence time may now be obtained by one of the three methods outlined in Section 4.5 [Figures 1 and 2].

5.1.5.1 First method-graphically by plotting

Table 1: Example gamma camera scan results

	Scan 1	Scan 2	Scan 3
	16 August	20 August	23 August
	2012 15:00	2012 09:05	2012 09:30
Hours since initial scan	0.0	90.1	162.5
Anterior	57692	31534	19289
Posterior	49750	26548	16307
Ant background	1809	1747	1737
Post background	1661	1599	1644

Table 2: Geometric mean count, fraction of tracer remaining, and log of activity

	Scan 1	Scan 2	Scan 3
Counts _{Geomean}	51,839	27,261	16,043
% injected activity remaining	100.0	52.6	30.9
Log ₁₀ (% injected activity)	2.0000	1.7208	1.4906

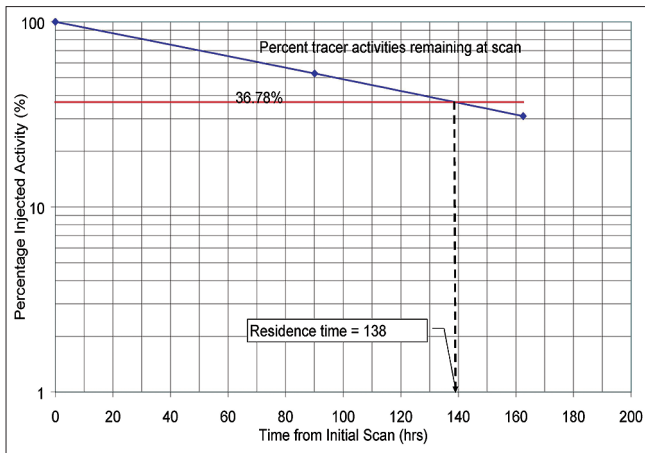


Figure 1: Total whole body residence time estimation

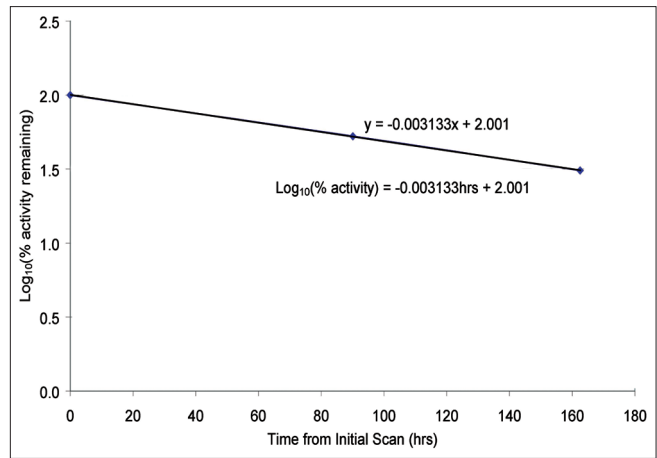


Figure 2: Total whole body residence time calculation

percentage injected activity remaining vs. time of scan on a semi-logarithmic graph and determining where the line crosses the 36.78% (1/e) level. The plot should be a straight line, or very nearly so. If it is not, the data needs to be verified. Common causes of error are:

- Time and/or date entered incorrectly;
- Counts measured incorrectly;
- Incorrect gamma camera settings (e.g., one scan was at a different speed, window setting etc.);
- Significant change in patient lifestyle during dosimetry examination period (exercise, work, diet, quantity of fluid drunk etc.).

5.1.5.2 Second method-by plotting Log_{10} of the percentage injected activity remaining vs. time of scan on a linear-linear graph and determining the slope of the line. The plotted curve should be a straight line, or very nearly so. If it is not, the data needs to be verified. Common causes of error are:

- Time and/or date entered incorrectly;
- Counts measured incorrectly;
- Incorrect gamma camera settings (e.g., one scan was at a different speed, window setting etc.);
- Significant change in patient lifestyle during dosimetry examination period (exercise, work, diet, quantity of fluid drunk etc.).

Using the spreadsheet Trendline/Display equation on chart, the slope of the line is the coefficient of the equation and equals -0.003133. The residence time is therefore:

$$\begin{aligned} \text{Residence Time}_h &= \frac{\left(\text{Log}_{10} \left(\frac{1}{e} \right) \right)}{\text{Slope of Curve}} \\ &= \frac{-0.43429}{-0.003133} \\ &= 138.62 \text{ hours} \end{aligned}$$

5.1.5.3 Third method-by using the data from Table 1 and the formula given in Section 4.5:

$$\begin{aligned} \text{Residence Time}_{\text{hours}} &= \frac{t_2 \left(1 - \frac{C_2}{C_1} \right)}{\text{Ln} \left(\frac{C_1}{C_2} \right)} + \frac{C_2 (t_3 - t_2)}{\text{Ln} \left(\frac{C_2}{C_3} \right)} \\ &= \frac{90.08 \left(1 - \frac{52.6}{100.0} \right)}{\text{Ln} \left(\frac{100.0}{52.6} \right)} + \frac{52.6 (162.5 - 90.08)}{\text{Ln} \left(\frac{52.6}{30.9} \right)} \\ &= \frac{42.6979}{0.6424} + \frac{38.093}{0.5319} \\ &= 138.6 \text{ hours} \end{aligned}$$

Slight differences may occur between the three methods due to rounding errors etc.

5.2 Finally, the therapeutic activity may be calculated using the equation given in Section 4.2:

$$\begin{aligned} \text{Therapeutic Activity (MBq)} &= \left(\frac{\text{Activity.h (MBq.h)}}{\text{Residence Time (h)}} \right) \times \\ &\quad \left(\frac{\text{Desired Total Body Dose (Gy)}}{0.75 \text{ Gy}} \right) \end{aligned}$$

$$= \left(\frac{380,868.88}{138.6} \right) \times \left(\frac{0.75}{0.75} \right)$$

= 2748 MBq of ¹³¹I-rituximab for a WBD of 0.75 Gy.

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