A COMPARATIVE STUDY OF PRELIMINARY DOSIMETRY FOR HUMAN BASED ON DISTRIBUTION DATA IN RATS WITH ^{111}In, ^{90}Y, ^{153}Sm, AND ^{177}Lu LABELED RITUXIMAB

by

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Radio immunotherapy is one of the most important and effective therapies for B-cell non Hoddgkin's lymphoma treatment. Today, anti CD-20 antibodies labeled with beta emitter radionuclides are used in radio immunotherapy. Various radionuclides for labeling anti CD-20 antibodies have been studied and developed for the treatment and diagnosis of malignancies. This paper describes the preparation, bio-distribution and absorbed dose rate of ^{111}In, ^{90}Y, ^{177}Lu, and ^{153}Sm labeled anti CD-20 antibodies (rituximab) in human organs, after injection to rats. The macro cyclic bifunctional chelating agent, N-succinimidyl-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid (DOTA-NHS) for conjugation to antibody, was used to prepare DOTA-rituximab. The conjugates were purified by molecular filtration, the average number of DOTA conjugated per mAb was calculated and total concentration was determined by spectrophotometric method. Radio-labeling was performed at 40 °C for 24 hours. After the quality control studies, the final radioactive solution was injected intravenously into rats through their tail vein. The tissue uptakes of each injection were measured. Then we calculated S values for ^{177}Lu and ^{153}Sm by using specific absorbed fractions and data used in the manner of radio-labeled analysis and dosimetry for humans. The absorbed dose rate of each organ was calculated in the specific time by medical internal radiation dose method with linear approximation in the activity measurements.

Key words: radio immunotherapy, bio-distribution, rituximab, dosimetry, MIRD

INTRODUCTION

Radio immunotherapy (RIT) is a targeted therapy combined from immunology and radiotherapy [1, 2]. In the United States, radio immunotherapy has been confirmed by FDA for the treatment of some kinds of lymphoma. Bexxar (tositumomb) is a labeled monoclonal antibody with ^{131}I, and Zevalin (ibritumomab tiuxetan) is a labeled monoclonal antibody with ^{90}Y. Both of them are anti CD-20 monoclonal antibodies [3].

Rituximab, a chimerical, mouse-human, monoclonal antibody is mainly used in the treatment of non-Hodgkin's lymphoma. Like the other common antibodies used against B-cell, rituximab binds with human B-lymphocyte-restricted differentiation antigen: CD-20. CD-20 is not shed from the cell surface and does not internalize upon antibody binding. Rituximab is thought to deplete CD-20-positive cells via antibody-dependent cell-cytotoxicity and complement mediated cell lysis. These properties make the CD-20 receptor a suitable target for targeted therapy. The uptake of antibody has been observed on lymphoid cells in the spleen, thymus, B-lymphocytes and lymph nodes and liver. Rituximab has been used successfully as an anti CD-20 radio-labeled antibody [2]. So far, many beta emitters such as ^{131}I, ^{90}Y, ^{153}Sm, and ^{177}Lu were widely used in various previous studies [4]. Due to an appropriate half-life and decay characteristics of these nuclides they can be used in antibody labeling for RIT. Some beta emitters decay gamma photons whose energy levels are in the range of SPECT cameras. These gamma irradiations are feasible for imaging with treatment and using in diagnostic/therapeutic studies [3].

Auger electron is another kind of electron irradiation which is not different from beta in nature, it just has a different source and energy. Auger electrons have wide energy range from lower than 1 keV to higher than 100 keV, so some of them can be used in treatment goals for molecular category. ^{111}In is an auger electron emitter and due to its gamma radiation

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with suitable energy, nowadays it has a diagnostic use as a tracer nuclide in treatment with Zevalin [5].

Although the bio-distribution of the radio-labeled antibodies is almost the same as bio-distribution of intact antibody, but as a bio-conjugate, the radio-labeled antibody would go through the metabolic processes in liver, lungs and other metabolic sites leading to the release of free cations in the stream. Thus, in the second step, the cationic portion accumulation would serve as a new radiochemical species leading to variety of bioaccumulation modes based on each radionuclide. Finally, amount of dose imposed to the different organs is related to the energy and type of radiation for each radioisotope. In the present article, the preparation and bio-distribution of ^{177}Lu, ^{153}Sm, ^{90}Y, and ^{111}In labeled anti CD-20 antibodies (rituximab) conjugates have been studied and followed by the calculation of preliminary dosimetry for humans, based on distribution data in rats by acceptable approximations. Table 1 demonstrates physical properties of ^{177}Lu, ^{153}Sm, ^{90}Y, and ^{111}In.

Table 1. Physical properties of ^{177}Lu, ^{153}Sm, ^{90}Y, and ^{111}In

	β-maximum energy [keV]	Probability [%]	Gamma energy [keV]	Probability [%]
^{177}Lu Half-life: 6.73 (d)	176.5 248.5 384.8 497.8	12.20 0.05 9.10 78.60	71.65 112.95 136.7 208.37 249.67 321.32	0.15 6.40 0.05 11.06 0.21 0.22
^{153}Sm Half-life: 1.92 (d)	635 705 808	32.2 49.6 17.5	69 103	4.85 29.8
^{90}Y Half-life: 2.67 (d)	2280 519.1	99.98 0.01	1760.7	0.01
^{111}In Half-life: 2.81 (d)	–	100	171.25 245.3	100 100

METHODS

^{111}In is produced in cyclotrons as a carrier-free radioisotope by the proton irradiation of ^{112}Cd-enriched targets through ^{112}Cd(p, 2n)^{111}In reaction. ^{111}In disintegrates by the electron capture via the excited level of 416.6 keV in ^{111}Cd. ^{111}In was produced at the Agricultural, Medical and Industrial Research School (AMIRS) 30 MeV cyclotron (Cyclone-30, IBA) Karaj, Iran [6, 7].

^{90}Y is obtained from the natural decay of its parent in ^{90}Sr ($t_{1/2}$ = 29 years) generator and is separated radiochemically from ^{90}Sr by a series of precipitation and filtration steps, or using a set of strontium-selective chromatographic columns. Obtained ^{90}Y is a carrier free radioisotope for the nuclear medicine from a research local generator. ^{90}Y decays with a physical $t_{1/2}$ of 64 hours by β^- emission to stable ^{90}Sr [8, 9] or can be produced in low specific activity by neutron activation [10].

^{153}Sm is a reactor product. ^{153}Sm was produced by the thermal neutron irradiation of enriched target of ^{152}Sm with 4 10^{13} cm^{-2}s^{-1} neutron flux for 3 days at Tehran Research Reactor. ^{153}Sm is produced according to the reaction ^{152}Sm(n, γ)^{153}Sm by σ = 206 b for thermal neutron and disintegrates via 3 main routes by 100% β^- emission to levels in ^{153}Eu. ^{153}Sm is not a carrier free radioisotope and its specific activity was 14.5-17 GBq/mg. ^{177}Lu is reactor-produced by the thermal neutron irradiation of ^{176}Lu enriched targets with the reaction ^{176}Lu(n, γ)^{177}Lu with σ = 2020 b. ^{177}Lu was obtained by exposure of natural Lu_2O_3 (^{175}Lu: 97.5% and ^{176}Lu: 2.5%) sample with a specific activity of 2.6-3 GBq/mg and radionuclide purity of 99.98% , to thermal neutron flux 4 10^{13} cm^{-2}s^{-1} for 5 days at Tehran Research Reactor. The irradiation targets were dissolved in 200 µL of 1.0 M HCl, in order to prepare $^{177}LuCl_3$ and $^{153}SmCl_3$.

Chemicals were purchased from Sigma-Aldrich Chemical Co. (UK). NHS-DOTA was purchased from Macrocycles (USA). Rituximab (Mabthera) was a pharmaceutical sample purchased from Roche Co. Radio-chromatography was performed by using a Bioscan AR-2000 radio TLC scanner instrument (Bioscan, Paris, France). A high purity germanium (HPGe) detector coupled with a Canberra™ (model GC1020-7500SL) multichannel analyzer and a dose calibrator ISOMED 1010 (Dresden, Germany) were used for counting distributed activity in rat organs. All values were expressed as mean standard deviation (Mean SD) and the data were compared using student's T-test. Statistical significance was defined as $P < 0.05$. Animal studies were performed in accordance with the United Kingdom Biological Council's Guidelines on the Use of Living Animals in Scientific Investigations, 2nd ed.

Preparation of radio-labeled anti CD-20 antibodies (rituximab)

The radio-labeling of all radio-immunoconjugates are almost the same, this was mentioned in the related section. In the first step, lyophilized ritiximab (Roche) was purified with water for injection from excipients by ultra-filtration. Vivaspin-2 filters (30 kDa; Sartorius AG; 2 10 minute at 2.684 g) were used for all ultra-filtration purification steps. In short, trastuzumab was diluted with 0.2 M Na_2CO_3 (pH 9.2) buffer solution. The antibody concentration was measured using a biophotometer (Eppendorf) at OD = 280 nm. The solution was passed through a Vivaspin 2 (20 minute, 2.684 g) two times in order to remove the impurities. The antibody then can be removed from the upper part of the filter using bicarbonate buffer (0.2 M Na_2CO_3, pH 9.2). The final concentration was re-measured using biophotometric assay as well as structure integrity test using SDS-PAGE. Then DOTA-NHS (1.3 mg, excess 120 times) dissolved in bi-

carbonate buffer (400 µl, 0.2 M, pH 9.2) was added to the purified antibody solution (3.3 mg/ml) in a borosilicate vial and mixed gently for 20 times by pipetting. The mixture was gently shaken and incubated at room temperature for 24 hours. The mixture was then transferred on a Vivaspin 2 cut-off filter (30 KD) and centrifuged at 2.684 g for 15 minutes. In order to terminate the conjugation step and provide the suitable radiolabeling pH, the upper filter fraction is washed through using ammonium acetate buffer (0.2 M, pH 5.5) three times in order to remove excess of DOTA-NHS. In this stage, acetate buffer (1 ml) is added to the upper fraction, and the mixture is pippeted 10-20 times for immonoconjugate dissolution. The filter is then centrifuged upside-down at 2.684 g for 5 minute. The antibody concentration was measured using a biophotometer (Eppendorf) at OD = 280 nm. The spectrophotometric method for quantitation of micromolar concentrations of bifunctional DOTA-NHS ligand in DOTA-monoclonal antibody (mAb) conjugates is performed according to the reported method [11]. Briefly, the optical density of arsenaso yttrium (III) complex (2:1, 1 ml), prepared in 5.0 µM AAIII, 1.6 µM Y(III), 0.15 M sodium acetate buffer, pH 4.00, was measured at 652 nm. A standard curve was then plotted by the addition of multiple (8) 15 µl DOTA-NHS standard solutions (DOTA-NHS dissolved in 0.15 M sodium acetate buffer, pH 4.00), to the above mixture. In the second step, the optical density of 1:2 yttrium (III) complex of arsenaso (1 ml) was measured at 652 nm in the presence of conjugation product in order to determine DOTA-antibody attachments. For radiolabeling, typically, 370 MBq of radioisotope dissolved in 0.2 M HCl was added to a conical vial and dried under a flow of nitrogen. To the copper-containing vial acetate buffer (700 µl, pH 5.5) was added and the vial swirled for 10 minutes. The conjugate containing fraction (500 µg) in acetate buffer with the measured protein content was added to the vial and mixed gently for 5 minutes using pipetting (10-20). The mixture is then incubated at 40 ºC for 90 minutes followed by testing the radiochemical purity by ITLC using a radio TLC scanner (Whatman No. 1, 1 mM DTPA). Finally ETDA solution (10 µl, 10 mM) is added to the labeling mixture and incubated for 10 minutes in order to scavenge the unlabeled Cu cation. The mixture is then passed through the disposable PD10 De-salting column (Amersham) in order to further increase the radiochemical purity of the mixture. The final solution is then passed through a 0.22 micron biological filter for animal studies. The radio-immunoconjugate was analyzed for integrity by SDS-polyacrylamide gel electrophoresis (SDS-PAGE). The radio labeled mAb was evaluated with and without reduction by 2-mercaptoethanol. Approximately 200 000 cpm of each preparation was applied per lane and the 4-20% polyacrylamide were run according to the method of Laemmli [12]. The final radiochemical purity of the radio labeled monoclonal antibodies was checked by RTLC and HPLC as described earlier and in all cases it was >95% [4].

Bio-distribution data

^{177}Lu-DOTA-rituximab, ^{90}Y-DOTA-rituximab, ^{153}Sm-DOTA-rituximab, and ^{111}In-DOTA-rituximab were administered to the normal rats separately (15 rats) in order to determine bio-distribution. A volume (50-100 L) of final radioactive solution with 3.7 0.1 MBq activity was injected intravenously to the rats through their tail vein. The animals were killed at the exact time (3 rats in each time) and the specific activities of different organs were measured by using an HPGe detector (for ^{177}Lu, ^{111}In, and ^{153}Sm) and a beta scintillation detector (for ^{90}Y). Then the percentage of injected dose per gram (%ID/g) for each organ was calculated in each time point. It is necessary to calculate the %ID/g, since there are inherent limitations in measuring the activity of all tissues of each organ, such as bone and blood.

The following equation was used to extrapolate bio-distribution data of radio labeled compounds from rats to humans

$$\frac{\%\mathrm{ID}}{\mathrm{g}_{\text{human organ}}} \quad \frac{\%\mathrm{ID}}{\mathrm{g}_{\text{animal organ}}} k \tag{1}$$

$$k \quad \frac{\text{Body mass}_{\text{animal}}}{\text{Body mass}_{\text{human}}} \tag{2}$$

The equation shows that the bio-distribution ratio of activity per each gram of each organ in the rat and human is a constant value which depends on the total tissue weight to body weight for rat and for humans. The above equation is obtained from the following equation with an algebraic formula [13]

$$\%\mathrm{ID}_{\text{human organ}} \quad \%\mathrm{ID}_{\text{animal organ}} \quad \frac{\dfrac{\text{Organ mass}_{\text{human}}}{\text{Body mas}_{\text{human}}}}{\dfrac{\text{Organ mass}_{\text{animal}}}{\text{Body mas}_{\text{animal}}}} \tag{3}$$

Dose estimates

Before therapeutic or investigation use on humans, some knowledge of the absorbed dose for patients is essential in radiotherapy. Medical internal radiation dose (MIRD) method is a standard one for calculating the dose estimates when radionuclides enter the human body and accumulate there. This method is based on the absorbed fractions (φ) and specific absorbed fractions of energy (Φ) [14].

$$D(r_{\mathrm{k}} \quad r_{\mathrm{h}})[\mathrm{mGy}] \quad \widetilde{A}_{\mathrm{h}}[\mathrm{MBq\,s}]\, S(r_{\mathrm{k}} \quad r_{\mathrm{h}}) \tag{4}$$

$$S(r_k \quad r_h)[\mathrm{mGyMBq^{-1}s^{-1}}] \quad \Delta_i \Phi_i(r_k \quad r_h) \tag{5}$$

$$\Delta_i[\mathrm{kg\ mGyMBq^{-1}s^{-1}}] \quad 1.6\ 10^{-13}\, n_i\, \overline{E}_i[\mathrm{MeV}] \tag{6}$$

$$\Phi \quad \frac{\varphi}{m} \tag{7}$$

The absorbed fraction is represented by the emitted energy of source which is absorbed in place of the target organ. In order to calculate the dose estimates based on this method, we should measure the cumulated activity in each organ as a source of radiation.

Bio-distribution data for human was determined by eq.1 based on distribution data in rats. There is a linear equation between ID and injected activity (IA), so %ID = %IA

Therefore %ID can be used for calculating the dose estimates instead of %IA when %ID/g (or %IA/g) was calculated in terms of initial injection activity values. In order to calculate the cumulated activity accurately for each organ, it is essential to know the pharmacokinetic model of each radio labeled compound. The pharmacokinetic model for each organ is based on complicated mathematical function forms. These functions are often multi-exponential ones for the antibodies [15]. In this study, the researchers used a linear approximation between the two experimental points of times in which the %ID/g had been measured before. In order to reduce the error of the method, the experimental points should be increased.

The total activity of each organ in each time point, is equal to %ID/g of the organ multiplied by the mass of organ. In this study, the mean weights for human organs with standard weight (70 kg) were used [16-18]. The authors point out that the organ weights vary in different sexes, races, and other individual parameters. The present study restricts itself to a general standard case shown in tab. 2 [19, 20].

Table 2. The standard weights of organs for humans with standard weight

Organ	Mass [g]
Adrenals	14
Blood	5500
Bone	10000
Kidneys	310
Liver	1800
Lungs	1000
Ovaries	11
Pancreas	100
Red marrow	1500
Spleen	180
Stomach wall	150
Thyroid	20
Total body	70000

RESULTS AND DISCUSSION

Bio-distribution

Absorption and bio-distribution of radio labeled compounds in organs of rats were determined by measuring %ID/g at different times. The uptakes were observed in the limited organs such as the liver, spleen and lungs and barely in the kidneys, bone and blood.

Cumulated activity

Bio-distribution data for humans were determined by eq. 1 based on the distribution data in rats. The activity value in human organs with linear approximation was calculated and represented diagrammatically as in the following charts.

The cumulated activity in each organ for 100 Bq of each radionuclide injection was shown in the following table (for ^{111}In and ^{90}Y in 72 hours, ^{153}Sm in 48 hours, and ^{177}Lu in 168 hours).

Table 3. Cumulated activity in each organ for 100 Bq

Source of activities	^{111}In in 72 hours [Bq]	^{90}Y in 72 hours [Bq]	^{153}Sm in 48 hours [Bq]	^{177}Lu in 168 hours [Bq]
Liver	1.00E+07	7412794	6240141	1.50E+07
Spleen	1273493	486673	354265	1799396
Kidney	356347	32971.1	132562	91604
Lung	2314346	5674364	1001479	2681656
Bone	61873.7	1307319	1740421	5188390
Blood	649794	606337	227472	849008

Dose estimates

S values for ^{111}In and ^{90}Y were adopted from MIRD pamphlet no. 11 [21], then *S* values were calculated for ^{177}Lu and ^{153}Sm by using specific absorbed fractions [22], after that the absorbed dose rate in the specific time for various organs was calculated. In order to calculate *S* values of ^{177}Lu and ^{153}Sm, the researchers used the specific absorbed fractions for each gamma and beta energy of these radionuclides for any source/target organ. The specific absorbed fractions for beta decays will be 1, if both the source and the target refer to only one organ, otherwise they will be zero. *S* values (for some source organs) of ^{153}Sm and ^{177}Lu which were calculated in the article are shown in the tabs. 4 and 5

The point is that since blood flows through the human bodies, then its activity is considered as the part of activity of the carcass.

The sums of absorbed dose rates in specific time for each organ from uptakes of each radio labeled compounds are demonstrated in the following table.

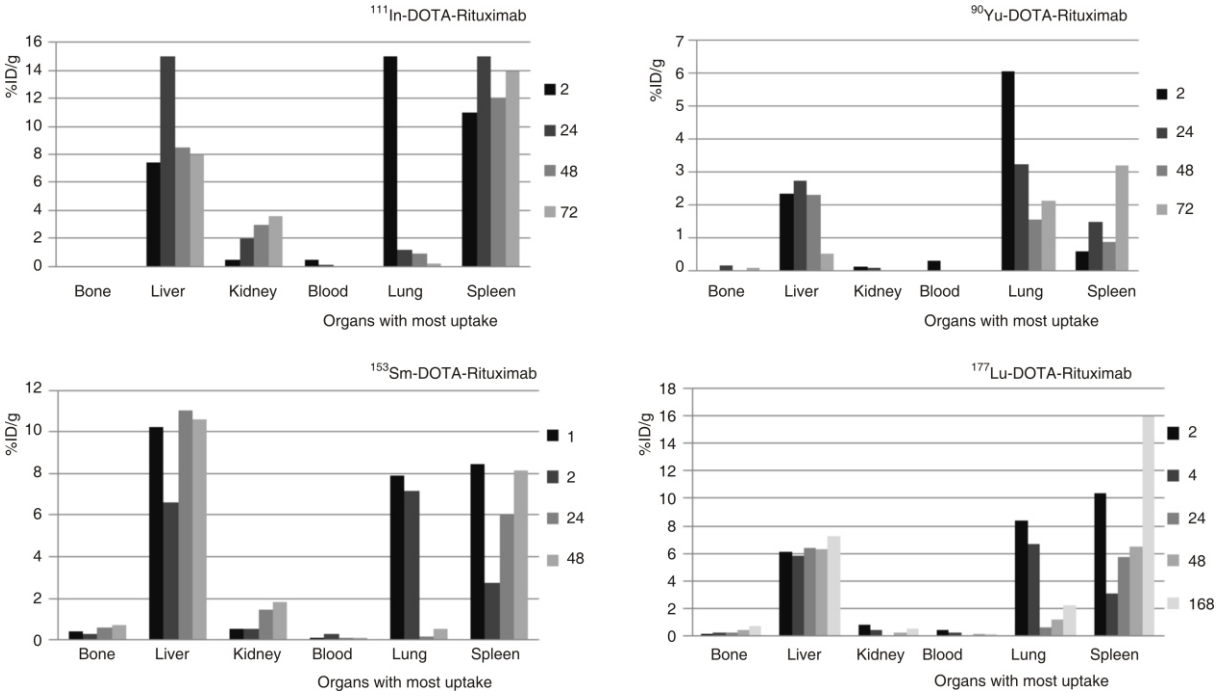

Figure 1. Biodistribution of radiolabeled in the organs of rats

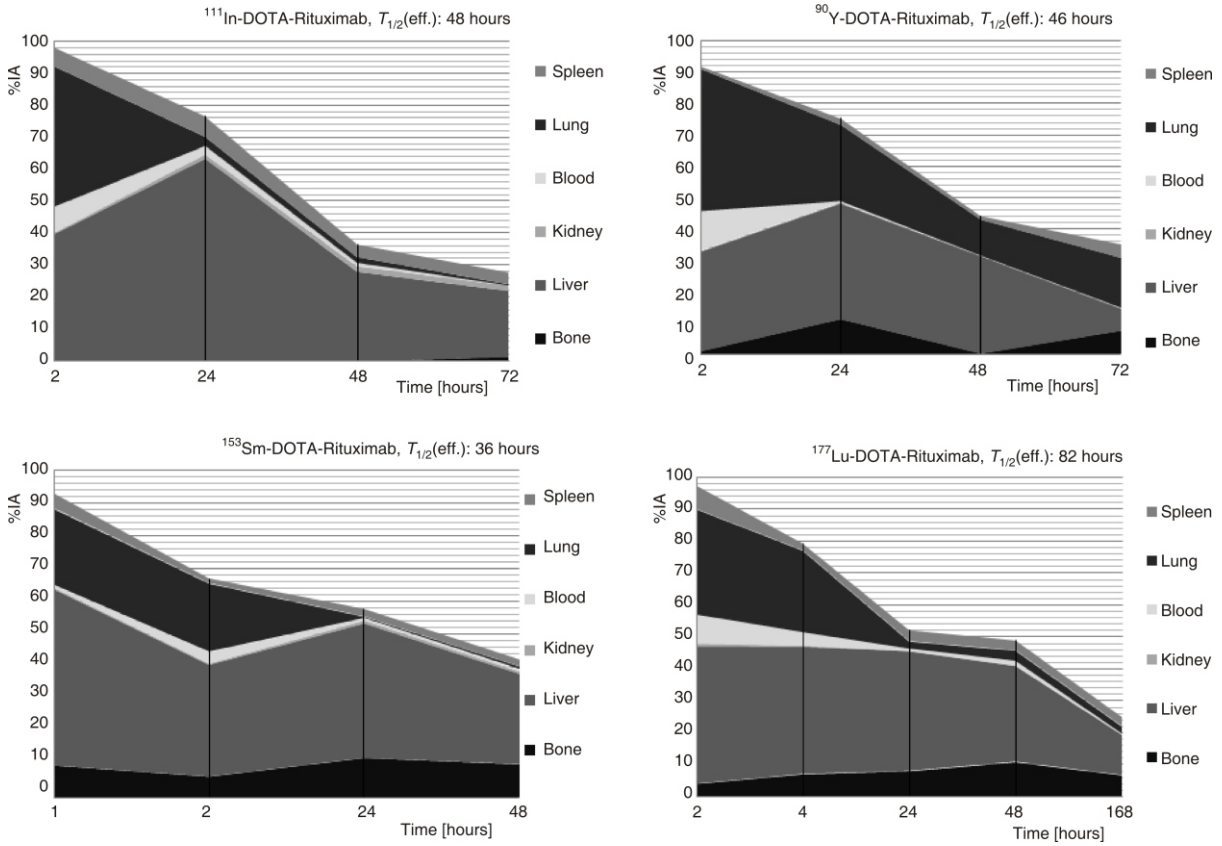

Figure 2. The activity value in human organs

In the present study, the researchers investigated four radio labeled anti CD-20 antibodies (rituximab) and studied the preparation, QCs and bio-distribution of them in the normal rats. Bio-distributions of radio

Table 4. *S* values of ^{177}Lu [mGyMBq^{-1}s^{-1}]

Target \ Source	Liver	Spleen	Kidneys	Lungs	Bone	Carcass
Adrenals	1.02E-07	1.06E-07	1.68E-07	5.54E-08	5.81E-08	3.74E-07
Bladder wall	8.70E-08	2.68E-09	1.88E-09	9.05E-08	8.65E-09	3.71E-07
Bone surfaces	2.43E-08	2.47E-08	3.17E-08	3.26E-08	2.47E-06	3.86E-07
Brain	2.40E-10	1.96E-10	4.87E-11	2.02E-09	2.80E-08	3.63E-07
Breasts	1.65E-08	1.09E-08	5.12E-09	5.40E-08	1.27E-08	3.58E-07
Stomach wall	3.44E-08	1.75E-07	5.87E-08	2.76E-08	1.99E-08	3.69E-07
Heart wall	5.46E-08	3.76E-08	1.89E-08	1.02E-07	2.59E-08	3.73E-07
Kidneys	6.84E-08	1.52E-07	7.82E-05	1.66E-08	1.56E-08	3.71E-07
Liver	1.37E-05	1.74E-08	6.78E-08	1.88E-08	1.18E-08	3.71E-07
Lungs	1.26E-08	3.95E-08	1.88E-07	2.39E-05	1.71E-08	3.66E-07
Ovaries	9.23E-09	9.70E-09	1.69E-08	1.26E-09	1.23E-08	3.75E-07
Pancreas	8.83E-08	2.98E-07	1.16E-07	3.96E-08	3.55E-08	3.76E-07
Red marrow	2.01E-08	2.05E-08	4.14E-08	6.24E-08	2.45E-06	3.68E-07
Skin	8.67E-09	8.56E-09	9.43E-09	9.72E-09	1.03E-08	3.56E-07
Spleen	1.73E-08	1.35E-04	1.52E-07	1.78E-08	1.10E-08	3.71E-07
Testes	6.25E-10	6.60E-10	9.35E-10	1.28E-10	1.12E-08	3.65E-07
Thyroid	2.34E-09	2.08E-09	9.61E-10	4.56E-09	1.54E-08	3.69E-07
Uterus	7.96E-09	6.67E-09	1.53E-08	1.18E-09	3.66E-08	3.76E-07
Total body	3.74E-07	3.71E-07	3.68E-07	3.74E-07	3.66E-07	3.66E-07

Table 5. *S* values of ^{153}Sm [mGyMBq^{-1}s^{-1}]

Target \ Source	Liver	Spleen	Kidneys	Lungs	Bone	Carcass
Adrenals	1.69E-07	1.87E-07	2.81E-07	8.72E-08	8.61E-08	5.83E-07
Bladder wall	3.65E-09	2.07E-09	6.11E-09	6.50E-10	1.39E-08	5.81E-07
Bone surfaces	6.00E-08	6.16E-08	7.92E-08	8.80E-08	3.93E-06	6.47E-07
Brain	1.70E-10	5.39E-11	2.87E-11	2.10E-09	3.98E-08	5.68E-07
Breasts	2.41E-08	1.47E-08	5.80E-09	8.77E-08	1.86E-08	5.56E-07
Stomach wall	5.45E-08	3.18E-07	9.50E-08	4.50E-08	2.73E-08	5.73E-07
Heart wall	8.88E-08	6.39E-08	2.77E-08	1.75E-07	3.80E-08	5.81E-07
Kidneys	1.15E-07	2.63E-07	1.22E-04	2.23E-08	3.02E-08	5.77E-07
Liver	2.14E-05	2.39E-08	1.12E-07	7.39E-08	2.02E-08	5.78E-07
Lungs	7.78E-08	6.77E-08	2.34E-08	3.75E-05	3.04E-08	5.74E-07
Ovaries	1.18E-08	1.05E-08	2.23E-08	1.71E-09	3.49E-08	5.84E-07
Pancreas	1.48E-07	5.23E-07	1.97E-07	6.74E-08	5.05E-08	5.86E-07
Red marrow	2.81E-08	2.90E-08	5.96E-08	5.48E-08	3.84E-06	5.69E-07
Skin	1.29E-08	1.25E-08	1.34E-08	1.43E-08	1.43E-08	5.53E-07
Spleen	2.35E-08	2.10E-04	2.63E-07	6.67E-08	1.80E-08	5.77E-07
Testes	1.06E-09	4.52E-10	6.66E-10	1.05E-10	1.54E-08	5.66E-07
Thyroid	2.37E-09	2.30E-09	5.17E-10	2.76E-08	2.07E-08	5.76E-07
Uterus	1.01E-08	7.30E-09	1.98E-08	9.25E-10	5.29E-08	5.85E-07
Total body	5.81E-07	5.80E-07	5.79E-07	5.75E-07	5.76E-07	5.72E-07

labeled compounds were in agreement with other radio labeled anti CD-20 antibodies species already reported [23, 24], moreover, they were in line with our previous studies.

High uptake in the spleen and reticoloendothelial organs due to the final accumulation of B-lymphocytes carrying the radio-immunoconjugate on their surface was observed. As a natural reaction to the depletion of the lymphocytes, the reticulloendothelial system including the spleen will be the final possible reservoir of the depleted lymphocytes. Observable accumulation in the lungs was also observed. Interestingly, we found reports of severe pulmonary reactions (pulmonary infiltrates or edema) during anti CD-20 antibodies therapy in the literature [4], [25-27]

The absorbed dose rate of each organ was calculated in the specific time by MIRD method with the linear approximation of measurement of activities. The dose rate estimation is based on more than 1.5 times of effective half-life of each radio labeled compound.

The results showed that the high absorbed dose is in the liver, lungs and spleen; and the absorbed dose of other organs (such as the red marrow and brain) is low as acceptable level values.

Table 6. Absorbed dose [mGyMBq^{-1}]

Organ	^{111}In in 72 h	^{90}Y in 72 h	^{153}Sm in 48 h	^{177}Lu in 168 h
Adrenals	0.162	0.012	0.015	0.025
Bladder wall	0.008	0.012	0.001	0.019
Bone surfaces	0.037	0.238	0.074	0.136
Brain	0.001	0.012	0.002	0.004
Breasts	0.002	0.012	0.004	0.007
Stomach wall	0.090	0.012	0.006	0.013
Heart wall	0.004	0.012	0.009	0.016
Kidneys	0.267	0.171	0.171	0.089
Liver	1.036	6.136	1.335	2.114
Lungs	0.314	8.535	0.382	0.649
Ovaries	0.017	0.012	0.002	0.005
Pancreas	0.174	0.012	0.014	0.025
Red marrow	0.052	0.572	0.070	0.135
Skin	0.019	0.012	0.002	0.005
Spleen	0.915	4.033	0.746	2.432
Testes	0.004	0.012	0.001	0.003
Thyroid	0.012	0.012	0.002	0.004
Uterus	0.015	0.012	0.002	0.006
Total body	0.072	0.326	0.056	0.096

CONCLUSIONS

Therefore, according to the kind of decay and energy (only β^-, >2 MeV), it is observed that ^{90}Y impose the highest amount of absorbed dose to the body; the lungs (with the 42% of the total dose) receive a dose more than 8.5 mGy/MBq in 72 hours. The liver, spleen and red marrow with 6.1, 4.0, 0.5 (3%) mGy/MBq, respectively, have the highest amount of absorbed dose. The other organs receive the dose less than 5% of total one.

As the researchers expected, due to the highest abundance of gamma photon decay, ^{111}In has the largest share in organs that received dose. The liver and spleen received the dose about 1 mGy/MBq (around 30% of total one) in 72 hours. The absorbed dose of the lungs, kidneys, pancreas, and adrenals were 0.31, 0.26, 0.17, and 0.16 mGy/MBq, respectively. In comparison to ^{90}Y, ^{111}In imposes lower dose to the patients as a diagnostic/therapeutic radionuclide.

For ^{153}Sm in 48 hours, the highest absorbed dose was observed in the liver with 1.3 mGy/MBq (46%) followed by the spleen, lungs, kidneys, and bone tissues received 0.74 (26%), 0.38 (13%), 0.17 (6%), and 0.07 (3%) mGy/MBq, respectively.

^{177}Lu had the smallest share in organs that received dose. The highest absorbed dose was observed in the spleen with 2.5 mGy/MBq (42%), and in the liver with 2.1 mGy/MBq (37%) in 168 hours. The lungs comprised the only tissues that received more than 3% of total dose with 0.64 mGy/MBq (11%). The results showed that ^{177}Lu contributes more to dose than ^{153}Sm, so it can be said that the main reason is longer half-life of ^{177}Lu in comparison with ^{153}Sm.

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УПОРЕДНО ПРОУЧАВАЊЕ ПРЕЛИМИНАРНЕ ХУМАНЕ ДОЗИМЕТРИЈЕ ЗАСНОВАНО НА РАСПОДЕЛИ АНТИТЕЛА У ПАЦОВА МАРКИРАНИХ ^{111}In, ^{90}Y, ^{177}Lu, И ^{153}Sm

Радиоимунотерапија је једна од најважнијих и најефективнијих терапија за лечење Б-ћелија не-Хочкиновог лимфома, те се данас у њој користе анти-CD20 антитела маркирана са радионуклидима који су бета емитери. Овај рад приказује припрему, биорасподелу и јачину апосорбоване дозе анти-CD20 антитела (ритуксимаб) маркираних ^{111}In, ^{90}Y, ^{177}Lu, и ^{153}Sm. У припреми DOTA-rituximab-а за потребе везивања са антителима коришћена је *N-succinimidyl-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetraacetic* киселина (DOTA-NHS) која је макро-циклични челатин агенс. Коњуганти су прочишћени молекуларном филтрацијом, израчунат је средњи број DOTA-е коњуговане и одређена укупна концентрација применом спектрофотометријске методе. Радиомаркирање је трајало 24 сата при температури од 40 °C. После спроведене контроле квалитета, финални радиоактивни раствор је убризган пацовима кроз вену на репу. Мерена је прихваћена количина раствора у ткиву после сваког убризгавања. Потом су израчунате S вредности за ^{177}Lu и ^{153}Sm користећи специфичне апсорбоване фракције и податке као при анализи и дозиметрији радио-маркера код људи. Апсорбована јачина дозе одређена је за сваки орган у специфичном временском интервалу користећи медицинску интерну радијациону дозу са линеарном апроксимацијом за мерења активности.

Кључне речи: радиоимунотерапија, биорасподела, ритуксимаб, дозиметрија, медицинска интерна радијациона доза