Cellular dosimetry of beta emitting radionuclides-antibody conjugates for radioimmunotherapy

Original Article

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ABSTRACT

Introduction: The choice of optimal radionuclides for radioimmunotherapy depends on several factors, especially the radionuclide and antibody. The dosimetric characteristics of a non-internalizing and an internalizing monoclonal antibody (MAb) labeled with beta emitting radionuclides were investigated.

Methods: Using Geant4-DNA Monte Carlo simulation, we carry out dosimetric calculations for different subcellular distributions of beta-emitting radionuclides; ^{131}I, ^{177}Lu, ^{64}Cu, ^{186}Re and ^{153}Sm.

Results: The dependency of the radial dose profiles on the energy spectra of electrons (beta particles and Auger and internal conversion electrons) and also their relative yield of emission is clear. The highest difference between the radionuclides tested was observed when the activity was localized in the nucleus. There was not considerable difference in the nucleus dose when radionuclides were localized in cytoplasm and over the cell membrane.

Conclusion: There is a very significant increase in the dose deposited to the nucleus if ^{153}Sm localized at the nucleus. Although subcellular localization of activity isn't a critical factor for beta emitting radionuclides, but the use of internalizing MAbs leads to an increase in nucleus dose and to the killing of single cells in addition to the tumors.

Key words: Radioimmunotherapy; Cellular dosimetry; Monte Carlo; Beta emitter; Radionuclides

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INTRODUCTION

Radioimmunotherapy (RIT) is an excellent method for treatment of malignancies. Malignant cells normally over express antigens that induce immune response and production of antibodies. In RIT, a monoclonal antibody (MAb) that is against an over expressed antigen, is labelled with a radionuclide in order to target specific malignant cells. To reduce the immunoreaction in the patients, fragments (Fab) of antibodies can also be used [1]. In this technique, malignant cells are individually targeted and therefore the technique can be used for treatment of disseminated neoplasia and micro metastases. That is an advantage over external beam radiation therapy where visible tumors can be the subject of treatment [2].

In spite of great research activity during the last decade's only two radiopharmaceuticals, Zevalin® (yttrium-90 ibritumomab tiuxetan) and BEXXAR® (iodine-131 tositumomab) have been approved by the US food and drug administration (FDA). These radiopharmaceuticals have been effective in treatment of non-Hodgkin's lymphomas but no achievement in treatment of solid tumors. This may be blamed to radiation resistant of the tumor cells however; there are yet issues with RIT that need to be resolved [3]. Slow clearance of MAbs from plasma leads considerable exposure to bone marrow. In order to avoid severe damage to bone marrow, the administration of radiopharmaceuticals must be limited. However, it may be brought insufficient dose to the target cells and inefficient treatment. Currently, radionuclide treatment planning is subjective and activity administration is based on patient's weight or the whole body dose to the patients. Efficient treatment requires a comprehensive planning strategy, considering dosimetric and physical aspects of radiation matching the type of vector agent used [2].

DNA is the most sensitive component of the cells to ionizing radiation and the efficiency of a treatment protocol depends on the severity of damage to DNA. In external beam radiation therapy, target volumes are exposed uniformly and consequently dose to DNA and other organelles of the targeted cells are almost equal. As a result, the response to radiation is supposedly proportional to the absorbed dose in the target volumes [4]. However, in radionuclide therapy situation is rather different and dose to organelles of a cell can be considerably different depending on the type of radiation, penetration range of particles and distribution of radiopharmaceuticals around and inside the cells [5].

Currently, beta-emitting radionuclides are extensively under investigation in preclinical and clinical RIT studies. High-energy beta particles have long range of penetration and can deliver dose to large number of cells regardless of the radiopharmaceutical distribution. On the contrary, many radionuclides emit large number of low-energy Auger electrons that release the energy in short distances causing large dose to small volumes. Disintegration of Auger emitting radionuclides inside the cell nucleus can cause severe damage to DNA while the total dose to the cell can be negligible. Experimental studies showed that Auger emitting radionuclides internalized by the cells and located inside the nuclei are very toxic to the targeted cells [6].

Most of the MAbs are attached to the antigens over the cell surface however, there are types of MAbs that are internalized by the cells and transfer into the cytoplasm after binding to the cell surface receptors. Internalizing MAbs attached with Auger emitters can be very efficient, particularly when the number of receptors on the cell surface is small [7]. The beta-emitting radionuclides also release a range of Auger and internal conversion electrons. For example, ^{131}I is a medium-range beta emitter but also emits low-energy Auger and internal conversion electrons. It has been shown that toxicity of ^{131}I dependents on the cell components it is accumulated [8, 9].

Maximum damage to DNA with minimum dose to the normal tissues can be a useful strategy in radionuclide therapy. Internalizing MAbs that enter the cytoplasm of targeted cells are excellent candidate for this goal however; proper selection of radionuclide is an essential issue. In the present study, we investigated the suitable radionuclides to bind the internalizing MAbs. An ideal agent should deliver high dose to nucleus when inside the cytoplasm and low cross dose to surrounding cells. We used Monte Carlo simulation to investigate the radionuclides from micro-dosimetry point of view.

METHODS

Radionuclides

Radionuclides ^{131}I, ^{177}Lu, ^{64}Cu, ^{186}Re and ^{153}Sm are radionuclides which release beta particles of low and intermediate energies and ^{111}In, ^{125}I and ^{123}I are the most commonly used Auger emitting radionuclides in therapeutic and diagnostic nuclear medicine. Following the radionuclide decay, beta particles, Auger and internal conversion electrons are emitted. Beta particles have continuous spectra of energy but energy spectra of Auger and internal conversion electrons are discrete.

Electron capture is a special form of beta decay, where the nucleus consumes one of its orbital electrons. Radionuclides ^{64}Cu and ^{186}Re decay by both β^- and EC. Auger electrons may release following an electron capture. Internal conversion is an alternative to the release of characteristic photon when excess energy of nucleus is transferred to an orbital electron [10].

Immediately after an EC or IC event, the atom will be excited and a vacancy is created in the inner atomic shell. Subsequently, the excited atom undergoes a series of transitions until the ground state of atom is reached. These transitions contain radioactive transitions, result in the emission of characteristic x ray, and nonradioactive transitions, the most common being of the Auger, Coster-Kronig and super Coster-Kronig types [11]. In this study, for all radionuclides, beta particles and monoenergetic electrons, consist of Auger and internal conversion electrons, are considered, and x-rays and gamma rays are neglected due to insignificant absorbed dose to the target volume. We used the radiation spectra have published by MIRD Committee (Table 1) [12]. Beta emitting radionuclides have a continuous energy spectrum of beta particles. The beta spectrums of ^{131}I, ^{177}Lu, ^{64}Cu, ^{186}Re and ^{153}Sm is shown in Figure 1. The spectrum of Auger/IC electrons of these radionuclides can also be seen in Figure 2.

Cell model

Based on the MIRD scheme, the cell model used in this study was two concentric homogeneous spheres of unit density water (G4_WATER) representing the cell and the cell nucleus. The radius of the cell and nucleus was 5 and 4 µm respectively. These are also typical dimensions for the V79 Chinese hamster cells which have been used in a large number of experimental studies [13] and also are generally used when modelling stimulated lymphocytes. The thickness of the cell membrane was considered 10 nm [14].

Monte Carlo simulation

Dose estimation performed in different cell compartments using Geant4 (version 10.04.p03). Geant4 is an open source, C++ based, Monte Carlo code to track different particles through matter [15]. In this study the Geant4-DNA physics list (G4EmDNAPhysics) was used to track the transport of particles in the liquid water during Mote Carlo simulation. For each type of electrons (beta, Auger and internal conversion) 5×10^6 primary electron considered and tracked down till complete stopping, i.e. down to cut-off energy of 10 eV. The photons emitted during the radionuclides decay were ignored in this study because of low probability of interaction inside small volumes. These photons could have less than 5% contribution to the absorbed dose in target volume. The point of origin is selected randomly within the specified source volume (whole cell, cytoplasm, nucleus, cell surface), while the initial direction is sampled isotopically. The absorbed dose was scored in spherical shells 0.1 µm thick. After calculation of the absorbed dose in each component of the cell form each type of emissions, the results were normalized based on the total yield of emission (Table 1).

Table 1: Decay information of radionuclides investigated in this study. Data were derived from the MIRD publication [12].

Radionuclide	Decay mode	Radiation	Yield per disintegration	Mean energy (MeV)
^{131}I	β^-	β^-	1.000E+00	1.819E-01
		Int. Conv.	6.458E-02	1.481E-01
		Auger	6.975E-01	5.919E-04
^{177}Lu	β^-	β^-	1.00E+00	1.333E-01
		Int. Conv.	1.548E-01	8.737E-02
		Auger	1.117E+00	1.014E-03
^{64}Cu	β^-, β^+, EC	β^-	3.900E-01	1.904E-01
		β^+	1.741E-01	2.782E-01
		Int. Conv.	5.777E-07	1.338E+00
		Auger	1.807E+00	1.134E-03
^{186}Re	β^-, EC	β^-	9.253E-01	3.466E-01
		Int. Conv.	1.323E-01	1.051E-01
		Auger	1.393E+00	1.191E-03
^{153}Sm	β^-	β^-	1.000E+00	2.236E-01
		Int. Conv.	8.053E-01	5.003E-02
		Auger	6.578E+00	9.157E-04
^{123}I	EC	Int. Conv.	1.591E-01	1.317E-01
		Auger	1.371E+01	5.278E-04
^{125}I	EC	Int. Conv.	9.447E-01	7.706E-03
		Auger	2.301E+01	5.198E-04
^{111}In	EC	Int. Conv.	1.586E-01	1.761E-01
		Auger	7.431E+00	9.262E-04

Electrons were tracked to the few microns outside the cell since it is possible for the electrons to re-enter the scoring volume. Due to the isotropic emission of the primary particles, not all of the electrons emitted from the surface-bound radionuclide will enter the cell.

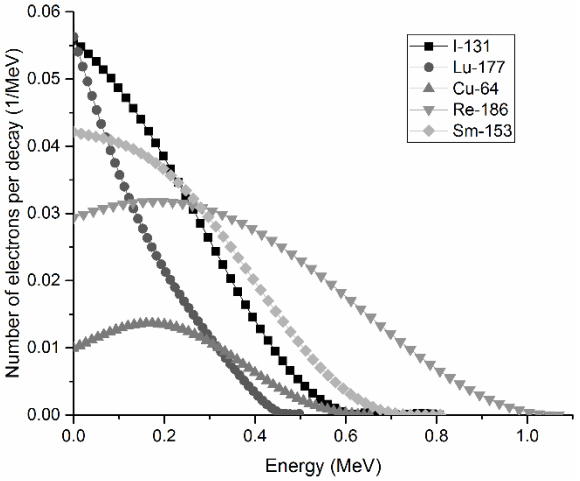

Fig 1. Beta spectra of beta emitting radionuclides which investigated in this study.

RESULTS

The calculated dose distribution of ^{111}In, ^{123}I and ^{125}I, using Geant4-DNA, inside and out of a cell as a function of the distance from the nucleus center are shown in Figure 3. The present results are compared with those simulated by MC4 code by Bousis et al. [13]. The dose profile was calculated by scoring the dose rate delivered per decay in thin, concentric, spherical shells around the nucleus center. The cell and nucleus dimensions are 5 and 4 µm, respectively. Radionuclides are distributed uniformly in different cell components (including nucleus, cytoplasm, whole cell and cell surface). The activity has uniform distribution of 1 MBq/cm^3 in the nucleus, cytoplasm and whole cell or 1 MBq/cm^2 on the cell surface. For the distribution at the cell surface, the vertical axis is shown in logarithmic scale, as the study by Bousis, et al. There is a significant difference ($p < 0.05$) between our data and the values obtained by MC4, using Mann-Whitney test.

For these Auger emitting radioisotopes, dose delivered to the nucleus was also calculated. As it is expected, when the radionuclides placed in the nucleus, a very high dose delivered to the nucleus, which is very significant compared to cytoplasm and cell surface distribution of activity.

For beta emitting radioisotopes, the mean dose delivered to the cell nucleus per decay was calculated when activity distributed at the different cell components and for beta particles and Auger/IC electrons, separately. The results are compared in Figure 4. Simulations were done and the total dose per decay was weighted by the probability of beta, Auger and internal conversion electrons according to Table 1. The highest dose is delivered to the nucleus when the radionuclide is distributed in the nucleus. The nucleus dose is high in the case of radionuclide distribution in the whole cell, cytoplasm and membrane.

The radial dose profiles, in which only the beta particles are emitted, are compared when the radionuclide distributed in the different cell compartments (Figure 5). The variation of dose distribution with beta spectrums, mean energy of beta particles and probability of beta decay is clear and is significant ($p < 0.05$) using Kruskal-Wallis test. The dose profiles, inside and outside the cell, of ^{131}I and ^{177}Lu are very similar for beta emission when the radionuclides distributed at the nucleus ($p = 0.219$, 0.390), at the cytoplasm ($p = 0.720$, 0.577) and at the cell surface ($p = 0.445$, 0.596), and the dose profile of ^{153}Sm outside the cell is close to these radionuclides.

The results obtained in the case of emission of Ag/IC electrons presented in Figure 6. The energy spectrums of Ag/IC electrons and the probability of their emission by radionuclides are different, and there is a significant difference ($p < 0.05$) dose delivered by these electrons, depending on their spectrum. Ag/IC electrons emitted by ^{153}Sm delivered a significant dose to all distances. The dose profiles outside the cell for ^{131}I and ^{186}Re are similar when Ag/IC electrons emitted from the nucleus ($p = 0.514$) and the whole cell ($p = 0.375$).

DISCUSSION

The selection of radionuclide for radioimmunotherapy depends upon its physical properties, availability and labeling characteristics. Historically monoclonal antibodies incorporated beta particle emitting radionuclides with emission ranges of a few millimeters in tissue [16]. There are two disadvantages for alpha emitters, including their very short half-live and non-specific toxicity before reaching to the target cells. For diseases disseminated in the body and micrometastases, the use of Auger and internal conversion electrons is more appropriate. But this is effective when a large number of tumor cells are targeted by carrier molecules and for high-density antigens [17]. In the other hand, due to the very short range of auger electrons, they can be effective when the disintegration take place intracellularly, and a large number of decays are required to kill the cell. Therefore, the use of beta emitting radioisotopes is preferred.

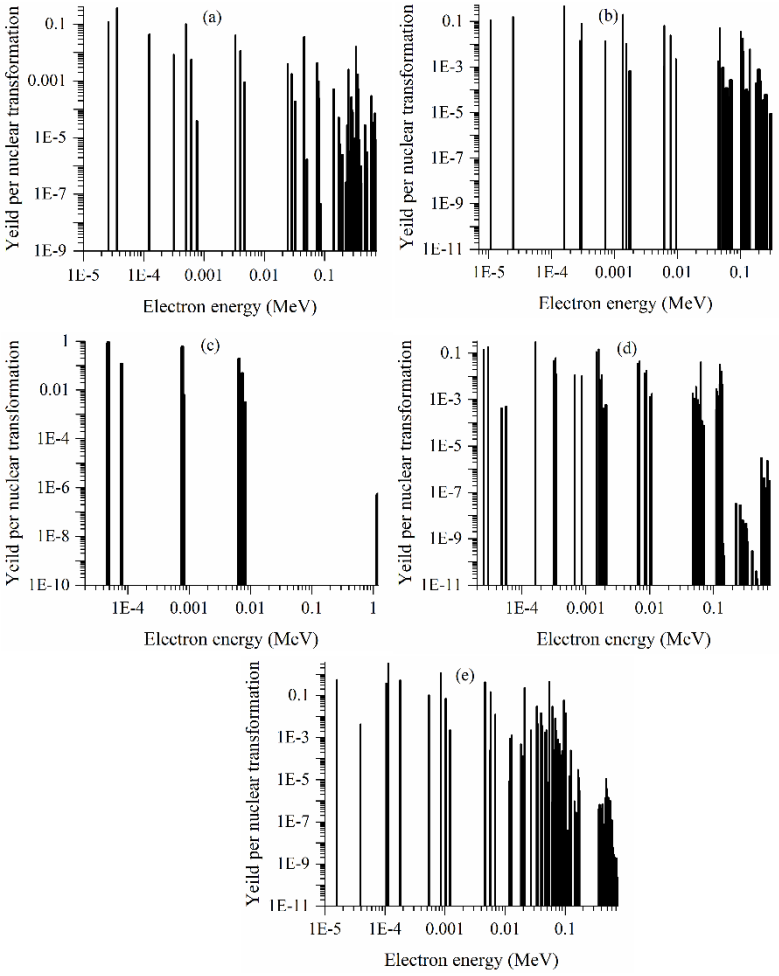

Fig 2. The energy spectrum of Auger and Internal Conversion electrons of beta emitting radionuclides (a) I-131, (b) Lu-177, (c) Cu-64, (d) Re-186 and (e) Sm-153.

These radionuclides possess the advantage that being able to deliver cross-doses to neighboring cells which have not been targeted, but they also damage healthy tissue [18]. So, the more specific irradiation of tumor tissue with less radiation exposure to normal cells by selecting the appropriate radiopharmaceutical is desirable.

In this study, we calculate the radial dose profile of three Auger emitting radionuclides, ^{123}I, ^{125}I and ^{111}In, which are widely used in diagnostic and therapeutic nuclear medicine using Geant4-DNA (Figure 1) and were compared with the similar values obtained by Bousis et al. [13]. They have perused the dosimetric features of several Auger emitting radionuclides using the MC4 track structure code. There is a significant difference between our data and this study which is due to the differences between two simulation codes. MC4 is an in-house code in which electron transport above 10 keV is based on a condensed-history scheme whereas for electrons below 10 keV event-by-event simulation is carried out. In this study we used Geant4-DNA physics model that is uses event-by-event algorithm to track electrons below 1 MeV. This is likely one reason for the observed differences between the results of this paper and those published by Bousis et al. [13]. Another differences between the results of two studies can be the different radionuclides decay schemes used in the simulations. They used AAPM Nuclear Medicine Task Group Report [11], while in our study MIRD radionuclides decay schemes was used [12].

The dose delivered to the nucleus was also calculated (Figure 3) and one can clearly see the increase in nucleus dose when radionuclides located in the nucleus. It has been demonstrated in many theoretical and experimental investigations [19] for Auger electrons.

Contrary to Auger-emitters, it has been reported that the cytotoxicity of ^{131}I is independent of intracellular localization [20]. However, Neti et al. observed that self-dose from ^{131}I attached to DNA could lead to high radiotoxicity [9].

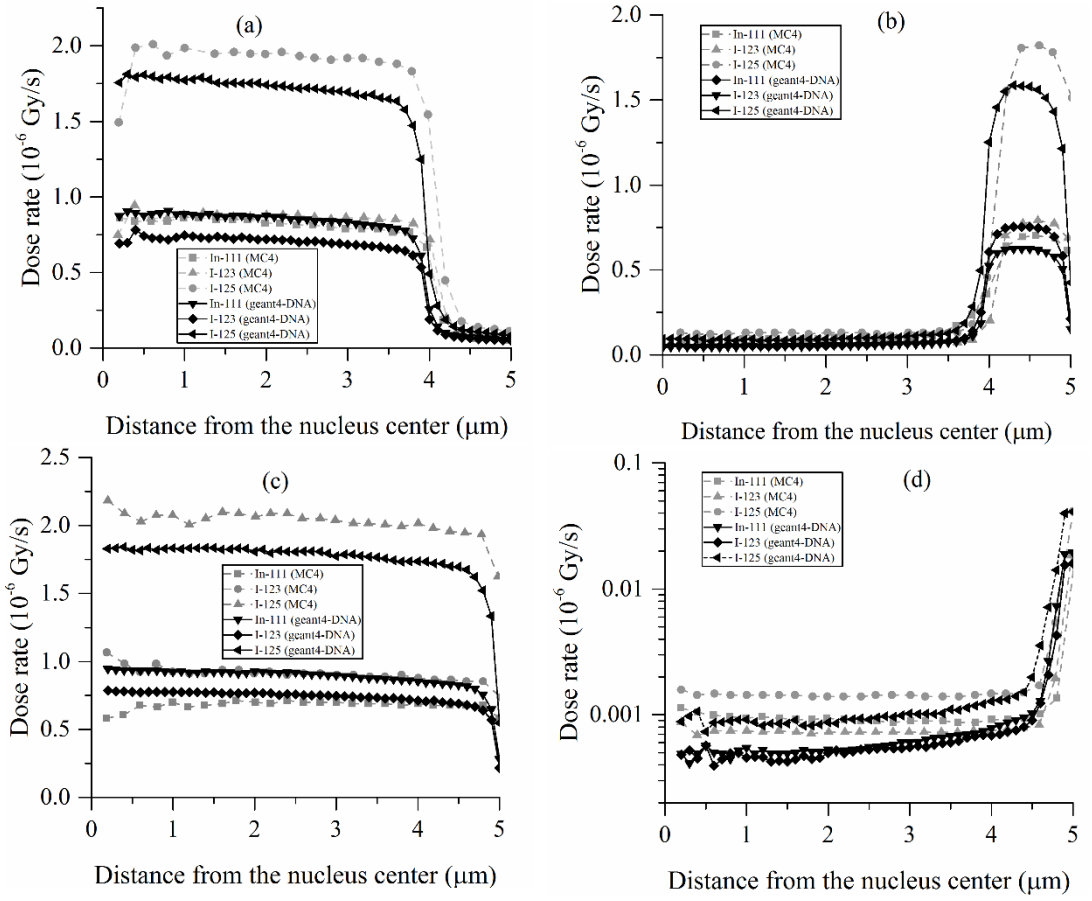

Fig 3. The absorbed dose rate as a function of the distance from the center of the cell for different intracellular localization of auger emitting radionuclides having a uniform distribution of 1 MBq cm^{-3} in the (a) nucleus, (b) the cytoplasm, (c) the whole cell and (d) 1 MBq cm^{-2} on the cell surface.

When ^{131}I was not internalized or internalized but not bound to DNA, has the cytotoxic effect similar (or higher) to that of Auger-emitters [21]. By attaching ^{131}I to internalizing monoclonal antibodies (MAbs), the dose delivered to the nucleus increases several times [8, 20]. It has been shown that the use of the internalizing MAbs antibodies labeled with ^{64}Cu [22] and ^{177}Lu [23] leads to an increase in the accumulation of radionuclides in the tumor and increases the toxicity.

A number of beta-emitters, such as ^{64}Cu and ^{186}Re, decay by electron capture mode in addition to beta decay, which results in the emission of Auger and internal conversion (Ag/IC) electrons. In addition, other beta-emitters that only decay by beta mode, also emit these electrons with different yields. ^{153}Sm is a radioisotope that emit these electrons with a high probability (7.4 per decay).

In this study the impact of cellular localization of various beta-emitters that are commonly used in clinic (^{131}I, ^{177}Lu, ^{186}Re, ^{64}Cu and ^{153}Sm) were investigated. We calculated the radial dose profile from center of nucleus to out of the cell when radionuclides located in the cell components, for beta particles and Ag/IC electrons separately.

The continuous beta spectra (Figure 1) and the discrete mono-energetic spectrum (Figure 2) of these radionuclides are different. The nucleus dose is maximum when the radionuclide is located at the nucleus (Figure 5). Ag/IC electrons of ^{186}Re and ^{64}Cu deliver more doses than beta particles, when activity distributed at the nucleus. For ^{153}Sm, the dose delivered to the nucleus by Ag/IC electrons is very significant when the activity is distributed in the nucleus, as well as in the cytoplasm and cell surface.

Dependence of the dose on the mean energy and the spectrum of beta particles, can be well seen in the dose deposited at the nucleus and also in the radial dose profile. The mean beta particle energy of ^{131}I and ^{177}Lu is closer together, which had led to similarity of their dose profiles, inside and outside the cell, when the radionuclide located at the nucleus (^{131}I (0.362 Gy in, 0.015 Gy out), ^{177}Lu (0.372 Gy in, 0.014 Gy out)), the cytoplasm ((0.121 Gy, 0.019 Gy), (0.121 Gy, 0.018 Gy)) and the cell surface ((0.011 Gy, 0.00029 Gy), (0.011 Gy, 0.00028 Gy)).

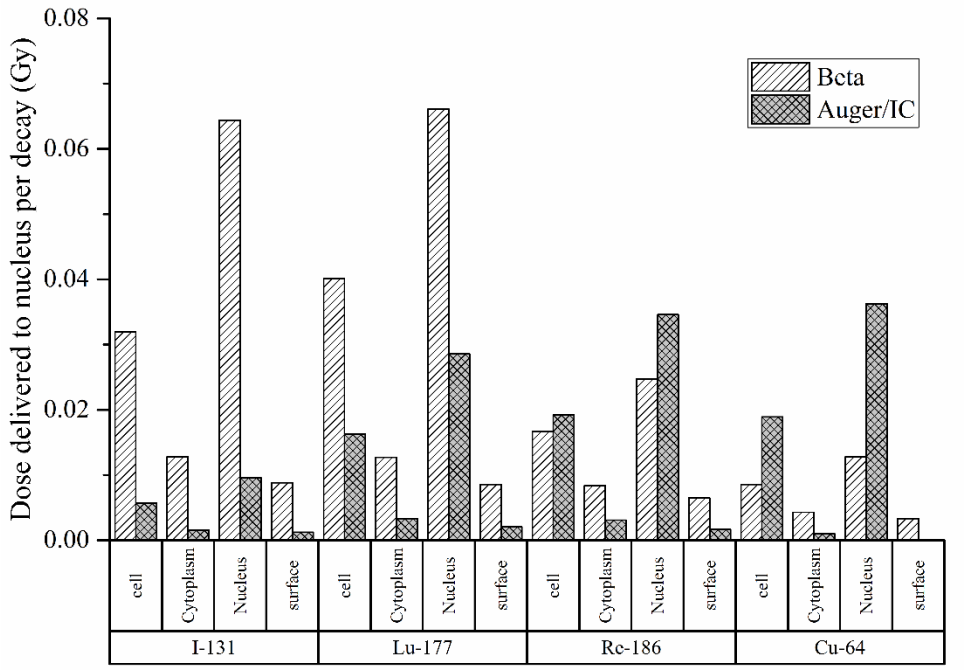

Fig 4. Dose delivered to the cell nucleus when beta emitting radionuclides distributed at different cell compartments (whole cell, cytoplasm, nucleus and cell surface).

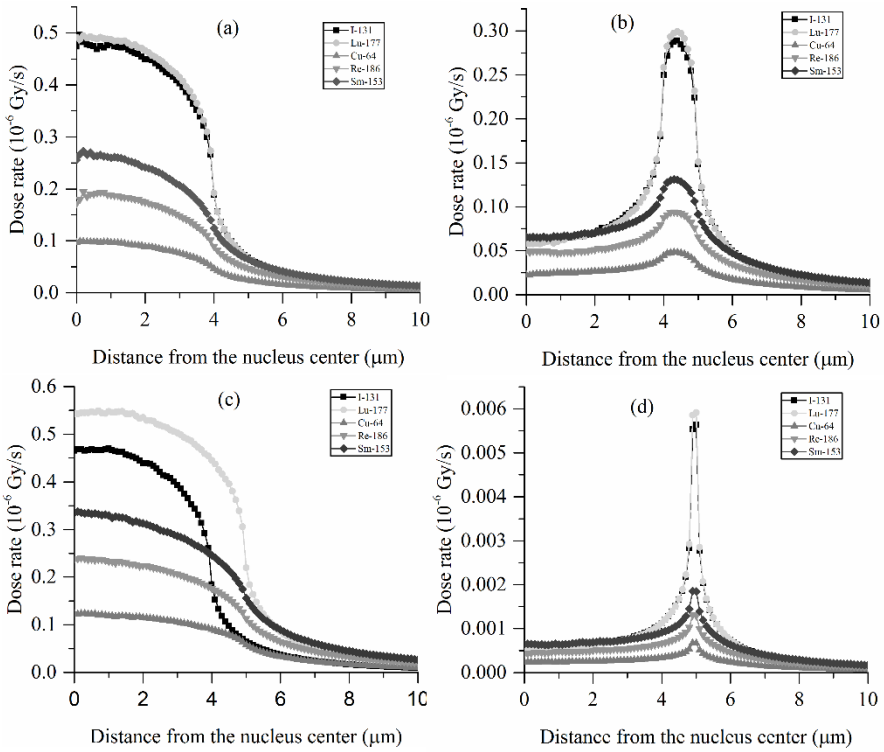

Fig 5. Dose distribution of ^{131}I, ^{177}Lu, ^{64}Cu, ^{186}Re and ^{153}Sm when these radionuclides were bound to the a) nucleus, b) cytoplasm, c) whole cell (MBq/cm^3) and d) cell surface (MBq/cm^2) and dose delivered by beta particles (not auger and IC electrons).

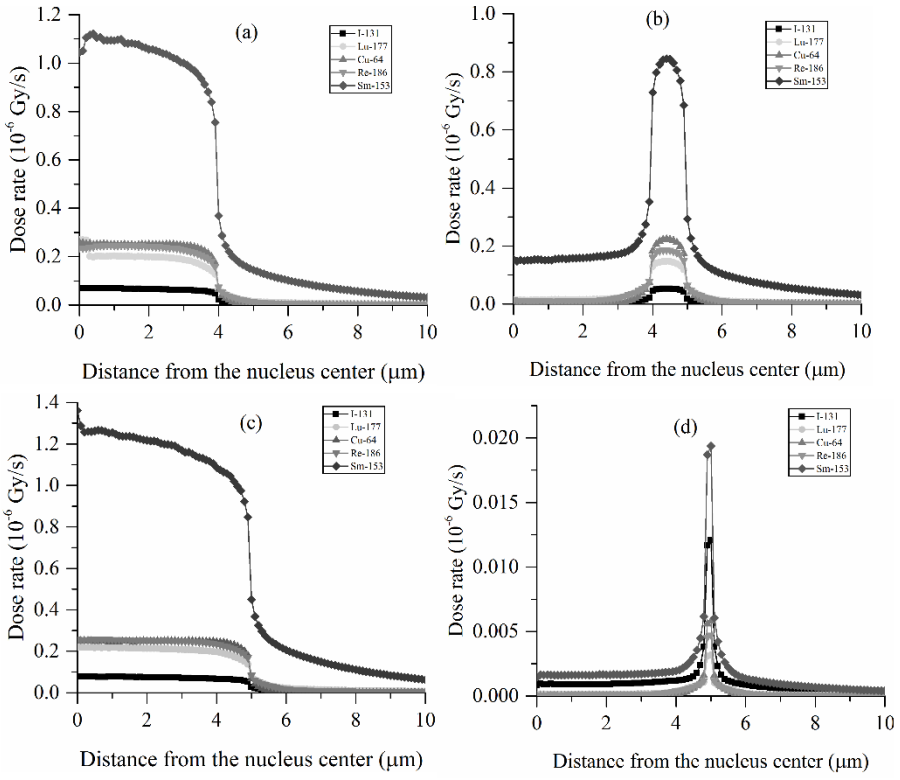

Fig 6. Absorbed dose delivered by auger and internal conversion electrons for beta emitting radionuclides which distributed at a) nucleus, b) cytoplasm, c) whole cell (MBq/cm^3) and d) cell surface (MBq/cm^2).

These values are higher for ^{153}Sm and are close to these radionuclides out of the cell. Although for ^{64}Cu, despite the similarity of beta energy, the lower emission yield has led to a decrease in dose. By increasing the average energy of beta spectra, the delivered dose decreases.

Each radionuclide has a unique spectrum of electron energies (Figure 2). The mono-energetic electron spectra of these radionuclides contains electrons with energy less than a few hundred keV. Auger electrons have energy less than 70 keV and internal conversion electrons are in the range from about 100 keV to 800 keV. Electrons with energy about 30 keV are optimal to kill single cell by Abs on the cell surface [24] which include the high energy auger electrons and lower energy internal conversion electrons. Mattes et al. [25] stated that for electrons with energies > 14 keV, there is a relatively small advantage of the cytoplasm. For electron energies of < 5 keV, localization to the cytoplasm isn't effective. And for electrons of 7-12 keV cytoplasm localization is a significant advantage. For most of the radionuclides there are few electrons in these range of energy. However, ^{153}Sm emit a large number of auger electrons which results in the deposition of a high dose to the nucleus, even for the cytoplasm or the cell surface localization of this radionuclide.

For all beta emitter radionuclides that we investigated, cytoplasm localization doesn't have many effect in nucleus dose relative to the cell surface localization, although when activity located in the nucleus, the deposited dose significantly increases. This increase is much higher for ^{153}Sm, which appears to be due to a much greater number and also a much higher yield of auger electrons being emitted by this radionuclide.

CONCLUSION

It is more appropriate to use auger-emitters to kill single cells. But these radionuclides are only effective if delivered to the nucleus. On the other hand, due to the self-absorbed dose of auger electrons, a large number of cells should be targeted by Abs. For beta emitters, in addition to cross-irradiation dose to cells which are not directly reached by Ab, they can kill single cells if enough Ab is bound to the cells. Thus, beta-particle emitters could kill single cells and be effect in large tumors. By using internalizing MAbs, the cytoplasmic accumulation of radionuclide increases and with delivering drugs to the nucleus, the nucleus deposited dose increases. This effect could be significant for ^{153}Sm. More theoretical and experimental studies are needed to further clarify the efficacy of these radionuclides.

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