Absorbed dose in fibrotic microenvironment models employing Monte Carlo simulation

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ABSTRACT

The presence or absence of fibrosis and yet more, the multimeric and multivalent nature of the radiopharmaceutical have recently been reported to have an effect on the radiation absorbed dose in tumor microenvironment models. Fibroblast and myofibroblast cells produce the extracellular matrix by the secretion of proteins which provide structural and biochemical support to cells. The reactive and reparative mechanisms triggered during the inflammatory process causes the production and deposition of extracellular matrix proteins, the abnormal excessive growth of the connective tissue leads to fibrosis. In this work, microenvironment (either not fibrotic or fibrotic) models composed of seven spheres representing cancer cells of 10 µm in diameter each with a 5 µm diameter inner sphere (cell nucleus) were created in two distinct radiation transport codes (PENELOPE and MCNP). The purpose of creating these models was to determine the radiation absorbed dose in the nucleus of cancer cells, based on previously reported radiopharmaceutical retain (by HeLa cells) percentages of the ^{177}Lu-Tyr^3-octreotate (monomeric) and ^{177}Lu-Tyr^3-octreotate-AuNP (multimeric) radiopharmaceuticals. A comparison in the results between the PENELOPE and MCNP was done. We found a good agreement in the results of the codes. The percent difference between the increase percentages of the absorbed dose in the not fibrotic model with respect to the fibrotic model of the codes PENELOPE and MCNP was found to be under 1% for both radiopharmaceuticals.

1. INTRODUCTION

Cancer aggressiveness is usually related to the fibrosis of tumors [1]. The extent of fibrosis in tumoral tissue may reduce the permeability of certain drugs [2]. The reactive and reparative mechanisms triggered during the inflammatory process cause the production and deposition of extracellular matrix proteins, the abnormal excessive growth of the connective tissue leads to fibrosis. The presence or absence of fibrosis and yet more the nature of the radiopharmaceutical, either monomeric system (^{177}Lu-Tyr^3-octreotate) or multimeric system (^{177}Lu-Tyr^3-octreotate-AuNP) was reported to have an effect on the radiation absorbed dose in tumor microenvironment models [3]. It was reported that the radiopharmaceutical retention (in a three-dimensional experimental model) of the monomeric system in a not fibrotic and fibrotic microenvironment was (approximately) 22% and 33% respectively. On the other hand, the retention of the multimeric system in a not fibrotic and fibrotic microenvironment was 75% and 97% respectively. The radiolabeled peptides attached in a double bonding, staple like effect, on the surface of the 20 nm gold nanoparticles (AuNP) leads to the

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multimeric nature of the radiopharmaceutical. The multimeric nature of the radiopharmaceutical is partially responsible for the increase of radiopharmaceutical retention percentage.

However, the radiation absorbed dose in the nucleus of cancer cells (HeLa) in fibrotic microenvironments caused by these radiopharmaceuticals (monomeric and multimeric) have not been investigated. Determining the radiation absorbed dose in the nucleus of cells is of vital interest since the nucleus contains the DNA, which is highly radiosensitive. Transport codes such as PENELOPE and MCNP based on the Monte Carlo methods can be used to calculate the radiation absorbed dose in the nucleus. The Monte Carlo method can be employed in the radiation transport of particles such as the beta particles emitted by ^{177}Lu. In Monte Carlo the individual particle tracks are faithfully reproduced with predetermined physical laws (such as the scattering and absorption cross sections) that govern the transport of particles in a medium [4].

2. METHODS

2.1. Computer Model

Cancer cell culture microenvironment computer models with absence or presence of fibrotic like material were created with the aim to determine and evaluate the radiation absorbed dose in the nucleus (implementing either the monomeric or multimeric radiopharmaceuticals). The cancer cell culture models are composed of 7 spheres representing 7 cells of 10 µm in diameter each with an inner sphere of 5 µm in diameter representing the cell nucleus. The 10 µm spheres (cells) were distributed in a 50 µm environment (either not fibrotic or fibrotic). The Cartesian coordinates of the spheres (cells) are listed in table 1 in micrometers. For the fibrotic environment, collagen composition was considered. On the other hand, water composition was considered for the cells and for the not fibrotic environment.

Table 1. Cartesian coordinates of the 10 µm in diameter spheres which represent tumor cells.

Spheres	X [µm]	Y [µm]	Z [µm]
1	0	5	0
2	0	10	-11
3	0	-11	10
4	0	-12	-7
5	14	-7	0
6	16	0	10
7	10	11	9

A 3 dimensional (3D) drawing was done to visualize the geometrical structure of the computer model. An image of the 3D drawing taken from the location x = 80 µm, y =94 µm,

and z =61 µm at a virtual camera angle rotation X: 63.5º, Y: 0.6º, Z: 46.7º (based on XYZ Euler rotation) is shown in figure 1.

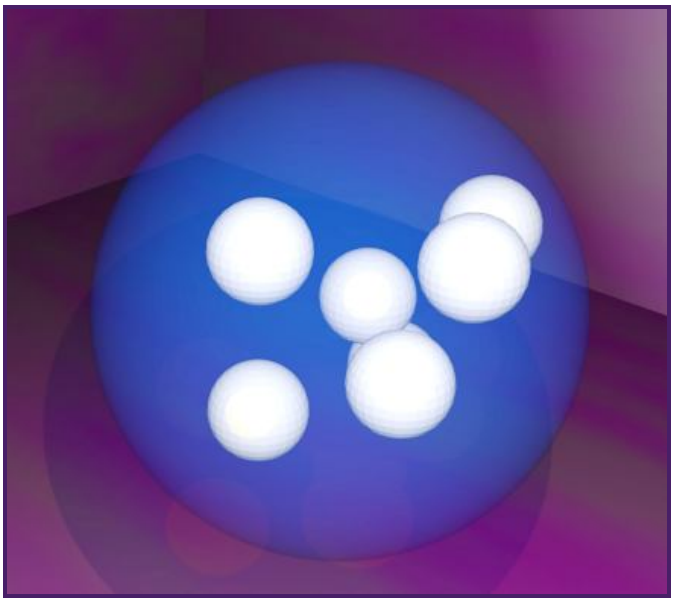

Figure 1. Illustration of the computer cell culture model composed of 7 spheres (cells) of 10 µm in diameter immersed in a 50 µm sphere representing the environment (either not fibrotic or fibrotic).

2.2. Monte Carlo simulation

The computer models served as the geometrical structures for the computer simulations. The computer simulation PENELOPE and MCNP codes were used for the transport simulation of the most important electrons and beta particles emitted by ^{177}Lu (convoluted spectrum of the emission probabilities higher than 1.5 and with energies higher than 1 keV) in two different microenvironments (not fibrotic, considering water as the chemical composition, and fibrotic in which collagen chemical composition was included). An initial 1,000,000 particles were simulated in both codes. The source was located between the 10 µm in diameter sphere and the 5 µm in diameter sphere which represents the cytoplasm, (each cytoplasm was considered a source) simulating the internalization of the target specific radiopharmaceuticals (^{177}Lu-Tyr^3-octreotate or ^{177}Lu-Tyr^3-octreotate-AuNP). Also in the case of the fibrotic environment model, the source was placed in the environment since it was found that such radiopharmaceuticals are retained in the fibrotic microenvironment [3].

2.3. Radiation absorbed dose calculation

The average deposited energy was estimated in each cell nucleus via Monte Carlo simulation, and the mass of the nucleus was calculated by multiplying the material (water) mass density

by its volume ($m = \rho V$). The average deposited energy in each nucleus was divided by the mass of the nucleus to determine the average deposited energy per unit of mass (radiation absorbed dose). Multiple simulations were done to simulate the source in each cell cytoplasm and the fibrotic microenvironment. The simulations were added and given the appropriate weight according to the retained fraction (see introduction) for each type of radiopharmaceutical and microenvironment. The results were normalized to an initial activity of total 1 Bq, that is, a cumulative activity of 82,112 Bq·s for a 24 h irradiation time period). The average radiation absorbed dose to a region target (the nucleus) r_T due to the region sources r_s (cytoplasms and fibrotic environment) is calculated as follow,

$$D_{rT} = \sum_{r_S}^{N_S} \tilde{A}_{r_S\,Norm} \sum_{i} \frac{E_i Y_i \phi(r_T \leftarrow r_S)}{m_{r_T}} \qquad (1)$$

where,

- E_i is the energy of the i[th] nuclear transition, Y_i is the number of i[th] nuclear transitions per nuclear transformation.
- $\tilde{A}_{r_S\,Norm}$ is the normalized cumulated activity in the source region (r_s).
- m_{r_T} is the mass of the region target (nucleus).
- $\phi(r_T \leftarrow r_S)$. is the radiation energy absorbed fraction of a target region due to the emissions of a region source (r_s).
- N_s is the total number of region sources.
- m is the mass of the target (r_T)

The E_i and the Y_i were supplied to the computer codes by means of the emission spectrum of ^{177}Lu.

The total cumulated activity was calculated as (for a 24h irradiation time period, and an initial activity of 1 Bq),

$$\tilde{A} = \int_0^t A_0 e^{-\lambda t}\, dt\, [Bq \cdot s]. \qquad (2)$$

and multiply by the retain fraction for each radiopharmaceutical for each environment case (not fibrotic or fibrotic) obtained in a previous work [3]. The contribution of each of the sources (the cytoplasms of the 7 cells, and the microenvironment for the case of the fibrotic model was considered. That is, self-dose, cross-dose, and environment contributions were considered.

3. RESULTS AND DISCUSSION

3.1. Radiation absorbed dose implementing the PENELOPE code

The average radiation absorbed dose in the nucleus for the cancer cell culture model was calculated by implementing the PENELOPE results and the corresponding retain activities for each case of microenvironment (not fibrotic and fibrotic) and type of radiopharmaceutical (either ^{177}Lu-Tyr^3-octreotate or ^{177}Lu-Tyr^3-octreotate-AuNP). The average radiation absorbed dose in each of the 7 nucleus of the cancer cells and the average to a single nucleus is listed in table 2 for the not fibrotic cancer cell culture model and in table 3 for the fibrotic model. These results were calculated for a 24 h irradiation time period and normalized to an initial activity of 1 Bq (cumulated activity of 82,112 Bq·s).

Table 2. Average radiation absorbed dose (Gy) for the not fibrotic cancer cell culture model derived from PENELOPE simulations.

Radiation Absorbed Dose (Gy) in the Nucleus for the Not Fibrotic Model (PENELOPE)							
^{177}Lu-Tyr^3-octreotate							
Nucleus	1	2	3	4	5	6	7
Total dose	1.86	1.73	1.71	1.72	1.81	1.83	1.77
Average dose	1.78 (σ = 0.05)						
^{177}Lu-Tyr^3-octreotate-AuNP							
Nucleus	1	2	3	4	5	6	7
Total dose	6.19	5.77	5.70	5.73	6.04	6.11	5.90
Average dose	5.92 (σ = 0.18)						

Table 3. Average radiation absorbed dose (Gy) for the fibrotic cancer cell culture model derived from PENELOPE simulations.

Radiation Absorbed Dose (Gy) in the Nucleus for the Fibrotic Model (PENELOPE)							
^{177}Lu-Tyr^3-octreotate							
Nucleus	1	2	3	4	5	6	7
Total dose	2.07	1.90	1.91	1.92	1.98	1.97	1.94
Average dose	1.96 (σ = 0.06)						
^{177}Lu-Tyr^3-octreotate-AuNP							
Nucleus	1	2	3	4	5	6	7
Total dose	6.64	6.11	6.13	6.15	6.39	6.38	6.24
Average dose	6.29 (σ = 0.18)						

The average radiation absorbed dose in the nucleus increases in the fibrotic model and is greater for ^{177}Lu-Tyr^3-octreotate-AuNP (not fibrotic = 5.92 Gy, fibrotic =6.29 Gy) than due to the ^{177}Lu-Tyr^3-octreotate (not fibrotic = 1.78 Gy, fibrotic = 1.96 Gy). The radiation absorbed dose to the nucleus increased by approximately 0.37 Gy (6.29 Gy - 5.92 Gy) that is, it increased 6% $\left(\%\ \text{increase} = \frac{|6.29-5.92|}{5.92} x100\right)$ due to fibrosis and about 0.18 Gy (1.96 Gy - 1.78 Gy) or about 10% $\left(\%\ \text{increase} = \frac{|1.96-1.78|}{1.78} x100\right)$ for the monomeric system. Such increase in the dose (0.37 Gy for the multimeric system and 0.18 Gy for the monomeric system) maybe of biological relevance since chromosome aberrations has been detected in doses as low as 0.1 Gy [5].

3.2. Radiation absorbed dose implementing the MCNP code

The average radiation absorbed dose in the nucleus for the cancer cell culture model was also calculated by implementing the MCNP simulation (same conditions as in the PENELOPE simulations) results for each case of microenvironment (not fibrotic and fibrotic) and type of radiopharmaceutical (either ^{177}Lu-Tyr^3-octreotate or ^{177}Lu-Tyr^3-octreotate-AuNP). The average radiation absorbed dose (derived from the MCNP) in each of the 7 nucleus of the cancer cells and the average to a single nucleus is listed in table 4 for the not fibrotic cancer cell culture model and in table 5 for the fibrotic model. These results were calculated for a 24 h irradiation time period and normalized to an initial activity of 1 Bq (cumulated activity of 82,112 Bq·s).

Table 4. Average radiation absorbed dose (Gy) for the not fibrotic cancer cell culture model derived from MCNP simulations.

Radiation Absorbed Dose (Gy) in the Nucleus for the Not Fibrotic Model (MCNP)							
^{177}Lu-Tyr^3-octreotate							
Nucleus	1	2	3	4	5	6	7
Total dose	2.09	1.79	1.79	1.78	1.88	1.90	2.00
Average dose	1.89 (σ = 0.11)						
^{177}Lu-Tyr^3-octreotate-AuNP							
Nucleus	1	2	3	4	5	6	7
Total dose	6.98	5.97	5.96	5.94	6.28	6.32	6.68
Average dose	6.30 (σ = 0.37)						

Table 5. Average radiation absorbed dose (Gy) for the fibrotic cell culture model derived from MCNP simulations.

Radiation Absorbed Dose (Gy) in the Nucleus for the Fibrotic Model (MCNP)							
^{177}Lu-Tyr^3-octreotate							
Nucleus	1	2	3	4	5	6	7
Total dose	2.36	1.98	1.99	1.99	2.06	2.04	2.17
Average dose	2.08 (σ = 0.13)						
^{177}Lu-Tyr^3-octreotate-AuNP							
Nucleus	1	2	3	4	5	6	7
Total dose	7.52	6.35	6.37	6.36	6.63	6.60	7.03
Average dose	6.69 (σ = 0.40)						

The average radiation absorbed dose in the nucleus increases in the fibrotic model and is greater for ^{177}Lu-Tyr^3-octreotate-AuNP (not fibrotic = 6.30 Gy, fibrotic = 6.69 Gy) than due to the ^{177}Lu-Tyr^3-octreotate (not fibrotic = 1.89 Gy, fibrotic = 2.08 Gy). Slightly higher results were obtained with MCNP. The radiation absorbed dose to the nucleus increased by approximately 6% $\left(\%\ \text{increase(multimeric)} = \frac{|6.69-6.30|}{6.30} x100\right)$ for the multimeric system and about 10% for the monomeric one $\left(\%\ \text{increase(monomeric)} = \frac{|2.08-1.89|}{1.89} x100\right)$, when fibrosis was present. Similar results were calculated in both radiation transport codes (PENELOPE and MCNP). However, a. There is less than a 1% difference in the increase percentages of the results derived from PENELOPE and MCNP, that is in both codes it increased 10% (for the monomeric case) and 6%(for the multimeric case) under the presence of fibrosis.

3.3. Comparison of the results of both codes

Similar results were calculated in both radiation transport codes (PENELOPE and MCNP). However, around 6% higher results were obtained with MCNP. This difference in the values can be explained by the uncertainties in the results, in PENELOPE there was a percent error of approximately 6% while in MCNP the error was smaller (around 3%) for both microenvironments. Hence, the true value may be somewhere in between the results of PENELOPE and MCNP. A summary of the average radiation absorbed dose in the nucleus for both transport codes are listed in table 6. On the other hand, both codes coincide that the multivalent and multimeric nature of the radiopharmaceutical increase the radiation absorbed dose approximately by 2.3 times

Table 6. Summary of values that compare the results derived from PENELOPE and MCNP.

PENELOPE				MCNP			
Not Fibrotic		Fibrotic		Not Fibrotic		Fibrotic	
Monomeric	Multimeric	Monomeric	Multimeric	Monomeric	Multimeric	Monomeric	Multimeric
1.78	5.92	1.96	6.29	1.89	6.30	2.08	6.69

4. CONCLUSIONS

The average radiation absorbed dose in the nucleus increases in the fibrotic model and is greater for ^{177}Lu-Tyr^3-octreotate-AuNP than due to the ^{177}Lu-Tyr^3-octreotate. The radiation absorbed dose to the nucleus increased by approximately 0.37 Gy that is, it increased 6% due to fibrosis and about 0.18 Gy or about 10% for the monomeric system. Such increase in the dose maybe of biological relevance since chromosome aberrations has been detected in doses as low as 0.1 Gy [5]. Furthermore, the multivalent and multimeric nature of the radiopharmaceutical increase the radiation absorbed dose approximately by 2.3 times.

5. REFERENCES

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