

Organ doses from hepatic radioembolization with ^{90}Y , ^{153}Sm , ^{166}Ho and ^{177}Lu : A Monte Carlo simulation study using Geant4

N A A Hashikin^{1,2}, C H Yeong^{1,2}, S Guatelli³, B J J Abdullah^{1,2}, K H Ng^{1,2}, A Malaroda³, A B Rosenfeld³ and A C Perkins⁴

¹ Department of Biomedical Imaging and ² University of Malaya Research Imaging Centre, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

³ Centre for Medical Radiation Physics, Faculty of Engineering and Information Sciences, University of Wollongong, Wollongong, New South Wales, Australia

⁴ Radiological and Imaging Sciences, Medical Physics and Clinical Engineering, Medical School, University of Nottingham, Nottingham, United Kingdom

E-mail: chyeong@um.edu.my

Abstract. ^{90}Y -radioembolization is a palliative treatment for liver cancer. ^{90}Y decays via beta emission, making imaging difficult due to absence of gamma radiation. Since post-procedure imaging is crucial, several theranostic radionuclides have been explored as alternatives. However, exposures to gamma radiation throughout the treatment caused concern for the organs near the liver. Geant4 Monte Carlo simulation using MIRD Pamphlet 5 reference phantom was carried out. A spherical tumour with 4.3cm radius was modelled within the liver. 1.82GBq of ^{90}Y sources were isotropically distributed within the tumour, with no extrahepatic shunting. The simulation was repeated with ^{153}Sm , ^{166}Ho and ^{177}Lu . The estimated tumour doses for all radionuclides were 262.9Gy. Tumour dose equivalent to 1.82GBq ^{90}Y can be achieved with 8.32, 5.83, and 4.44GBq for ^{153}Sm , ^{166}Ho and ^{177}Lu , respectively. Normal liver doses by the other radionuclides were lower than ^{90}Y , hence beneficial for normal tissue sparing. The organ doses from ^{153}Sm and ^{177}Lu were relatively higher due to higher gamma energy, but were still well below 1Gy. ^{166}Ho , ^{177}Lu and ^{153}Sm offer useful gamma emission for post-procedure imaging. They show potential as ^{90}Y substitutes, delivering comparable tumour doses, lower normal liver doses and other organs doses far below the tolerance limit.

1. Introduction

Liver cancer is the second most common cause of death from cancer worldwide [1]. Radioembolization is widely used for palliative treatment of hepatocellular carcinoma (HCC), which is the most common type of liver cancer. The procedure involves intra-arterial administration of embolic Yttrium-90 (^{90}Y) microparticles directly to the tumour, delivering all the radiation in-situ. Two commercial radioembolic agents are available, the glass-based TheraSphere® (Nordion, Canada) and the resin-based SIR-Spheres (SIRTex, Australia) microspheres. ^{90}Y decayed 99.98 % via beta emissions, thus considered as a pure beta emitter. Since gamma emission is absent, verification of ^{90}Y -microsphere distribution following each procedure is a challenge. The post-procedure imaging is crucial for patient monitoring, in case



there is presence of extrahepatic deposition of the microparticles. Bremsstrahlung imaging can be utilised, but the images are very poor in resolution.

Several theranostic (therapy and diagnostic) radionuclides have been suggested as ^{90}Y alternative [2-5]. These include Samarium-153 (^{153}Sm), Holmium-166 (^{166}Ho), and Lutetium-177 (^{177}Lu). The physical characteristics are tabulated in table 1. Due to the presence of gamma emissions throughout the length of the treatment, the exposure from gamma radiation towards the organs in the proximity of the liver has been a concern. Moreover, in order to achieve similar therapeutic effect as ^{90}Y , higher activities may be required, increasing the gamma exposure to these organs. The aim of this study was to estimate the absorbed dose to these organs from the exposure of gamma radiations by the alternative radionuclides, as compared to ^{90}Y for hepatic radioembolization. The Geant4 Monte Carlo code was used to simulate the treatment.

Table 1. Physical characteristics of suggested radionuclides for radioembolization [6].

Radionuclides	^{90}Y	^{153}Sm	^{166}Ho	^{177}Lu
Physical half-life, $T_{1/2}$ (days)	2.67	1.93	1.12	6.65
Maximum E_{β^-} (keV) (% yield)	2279.8 (99.98)	807.6 (19.5)	1854.5 (48.2)	498.3 (79.3)
Principal E_{γ} (keV) (% yield)	-	103.2 (29.2)	80.6 (6.6)	208.4 (10.4)
Maximum beta range (mm) in soft tissue	11.4	4.0	9.3	2.5

E_{β^-} : energy of beta; E_{γ} : energy of gamma

2. Materials & Methods

2.1. Simulation with ^{90}Y

Monte Carlo simulation using Geant4.9.6.p03 advanced example *human_phantom* was carried out. The 70 kg, 1.74 m tall human phantom adopted from MIRD Pamphlet 5, and a spherical tumour of radius $r = 4.3$ cm, simulated within the liver volume are shown in figure 1 (a) and (b), respectively. The tumour size was chosen since it was the largest spherical tumour able to be constructed within the liver, without interceptions between the tumour and liver boundaries. The tumour and liver volumes are 333 and 1833 cm^3 , respectively, which correspond to 18.2 % tumour involvement.

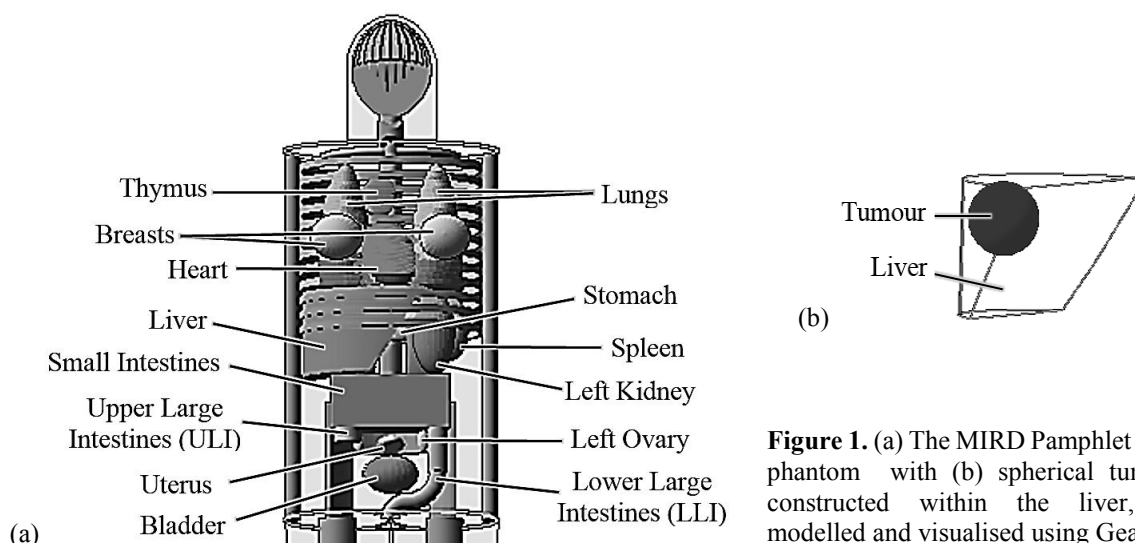


Figure 1. (a) The MIRD Pamphlet 5 [7] phantom with (b) spherical tumour constructed within the liver, as modelled and visualised using Geant4.

The total activity, A of 1.82 GBq ^{90}Y was prescribed to the tumour, as determined using equation (1) [8], which incorporates the Body Surface Area (BSA) value calculated from equation (2) [9]. The ^{90}Y sources were assumed to be fully taken by the tumour, with no lung and extrahepatic shunting. The

number of events, N corresponding to the total ^{90}Y activity was 6.07×10^{14} events, as determined using equation (3) where decay constant, λ of ^{90}Y is $3.00 \times 10^{-6} \text{ s}^{-1}$.

$$A \text{ (GBq)} = \text{BSA (m}^2\text{)} - 0.2 + (\% \text{ tumour involvement} / 100) \quad (1)$$

$$\text{BSA (m}^2\text{)} = 0.20247 \times \text{height}^{0.725} \text{ (m)} \times \text{weight}^{0.425} \text{ (kg)} \quad (2)$$

$$A \text{ (Bq)} = \lambda \text{ (s}^{-1}\text{)} N \quad (3)$$

The electromagnetic interactions of particles were modelled using the Low Energy Livermore and Radioactive Decay Physics List. The threshold of production of secondary particles was fixed to 1 mm. The Geant4 General Particle Source was used to generate the decay of the radionuclide in the tumour. ^{90}Y point-like sources were isotropically distributed within the tumour volume with randomised direction of emissions. Approximately 6.07×10^7 events were generated in each simulation to obtain a statistical accuracy of less than 1 % in the results. The energy deposited (MeV) to all organs were multiplied to 10^7 , converted to Joules (J), and divided by each organ mass (kg) to obtain the total absorbed dose (Gy).

2.1.1. Comparison between Geant4 and the partition model. The tumour absorbed dose calculated by means of Geant4 was compared to the tumour dose estimated using the MIRD based partition model [10] as shown in equation (4). This was done to quantify the agreement between the two models for internal dosimetry.

$$\text{Absorbed dose (Gy)} = \frac{49670 \times A \text{ (GBq)}}{\text{mass (g)}} \quad (4)$$

2.2. Simulations with ^{153}Sm , ^{166}Ho and ^{177}Lu .

2.2.1. Determination of dose factor. The activities corresponding to 10^7 events calculated using equation (3), are shown in table 2 for each radionuclide. A pilot run simulation with 10^7 events, uniformly distributed throughout the liver volume were carried out for each radionuclide. The energy deposited (J) to the liver were converted to absorbed dose (Gy) and divided by the corresponding activity to obtain the dose per activity (Gy/GBq) for each radionuclide. The dose per activity value was then normalised to that of ^{90}Y to obtain the dose factor.

Table 2. Radionuclide activity corresponding to 1×10^7 events.

Radionuclides	Decay constant, $\lambda \text{ (s}^{-1}\text{)}$	Corresponding activity, $A \text{ (Bq)}$
^{90}Y	3.00E-6	30
^{153}Sm	4.16E-6	41.6
^{166}Ho	7.18E-6	71.8
^{177}Lu	1.21E-6	12.1

2.2.2. Simulations with other radionuclides as compared to ^{90}Y . The total ^{90}Y activity of 1.82 GBq were divided by each dose factor to determine the activity needed for each radionuclide to deliver identical tumour dose as ^{90}Y . These activities were then applied into the tumour and the simulation setup as in section 2.1 were repeated for each radionuclide. The dose to the tumour, normal liver and other organs were recorded and compared with ^{90}Y .

3. Results and discussion

The activity of each alternative radionuclide used to achieve the same tumour dose of (262.9 ± 0.6) Gy, are shown in table 3. The dose estimated using the partition model was 271.5 Gy. The 3 % dose difference between the two methods can be explained due to presence of cross-over radiation at the tumour edge, which escaped from the tumour volume and recorded by the Geant4 simulation. This fraction of radiation was neglected by the partition model because of the assumption that beta particles are fully absorbed by the source volume, due to the small beta penetration depth.

Table 3. Radionuclide activities to deliver 263 Gy tumour dose.

Radionuclides	Dose per activity (Gy/GBq)	Dose factor	Equivalent activity (GBq)
^{90}Y	27.62	1	1.82
^{153}Sm	6.04	0.219	8.32
^{166}Ho	8.62	0.312	5.83
^{177}Lu	11.30	0.409	4.44

The remaining radiation that escaped from the tumour was absorbed by the normal liver. As shown in table 4, the other radionuclides contribute to lower normal liver doses which are advantageous as it allows for normal liver tissue sparing. This was due to the shorter beta ranges (lower beta energies), and thus, only a small fraction of these energies reaching the normal liver volume as compared to ^{90}Y .

Table 4. Normal liver dose (Gy) as a result of 263 Gy tumour dose.

Radionuclides	Absorbed dose (Gy)
^{90}Y	2.92 ± 0.05
^{153}Sm	2.30 ± 0.01
^{166}Ho	2.20 ± 0.06
^{177}Lu	1.59 ± 0.02

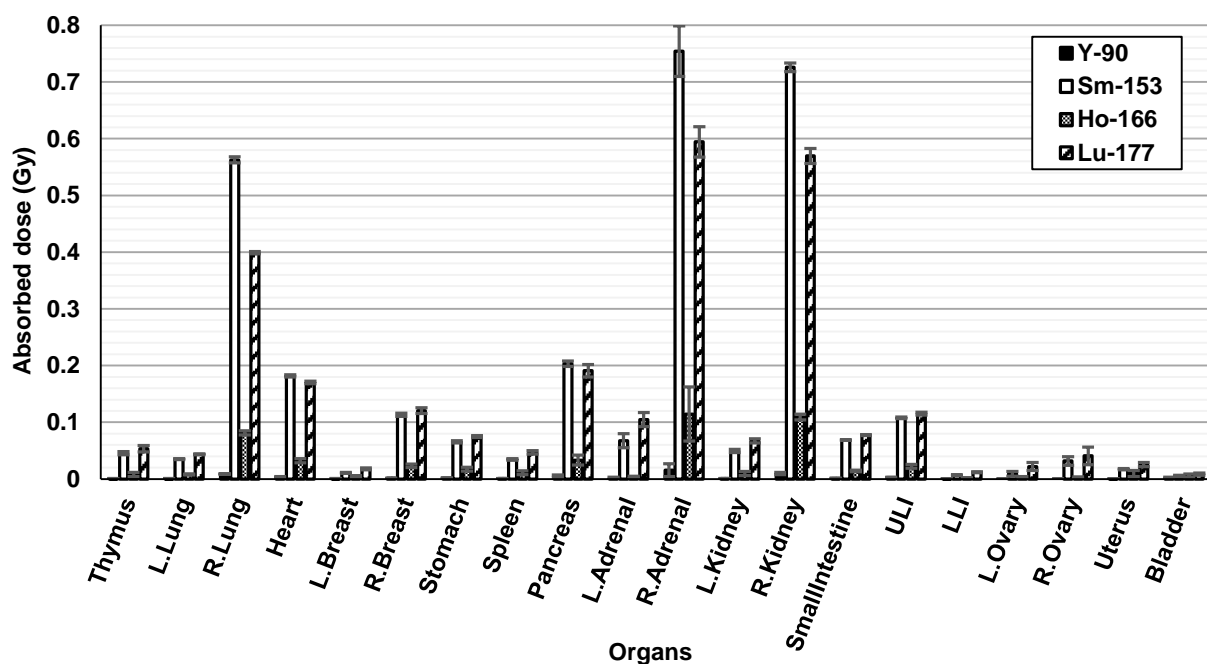


Figure 2. Organ doses as a result of 263 Gy tumour dose from ^{90}Y , ^{153}Sm , ^{166}Ho and ^{177}Lu . L: left, R: right, ULI: upper large intestines, LLI: lower large intestines.

The absorbed doses to the other organs from the various radionuclides are shown in figure 2. It was observed that the highest organ doses were from ^{153}Sm followed by ^{177}Lu , however all doses were still far below the maximum tolerance limit, i.e. 60, 23 and 17.5 Gy for adrenal glands, kidneys and lungs, respectively. The absorbed doses to these organs were found to be less than 1 Gy, and were affected by the energy of the gamma emissions, the half-life of the radionuclides, the distance from the liver and the organs masses.

Even though the absorbed doses to organs found in this study were lower than 1 Gy, it should be noted that they may be higher when more complicated cases are being simulated i.e. larger tumour hence higher activity, as well as the presence of normal liver uptake and lung or extrahepatic shunting. Further work to simulate more complex situations should be carried out and the maximum limit for treatment eligibility should be determined.

4. Conclusions

^{166}Ho , ^{177}Lu and ^{153}Sm offer the useful gamma emissions for post-procedure imaging. They show potential as ^{90}Y substitutes, delivering comparable tumour doses and lower normal liver doses, with other organ doses far below the maximum tolerance limit.

References

- [1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin D M, Forman D and Bray F 2015 *Int. J. Cancer* **136** E359-86
- [2] Hashikin N A A, Yeong C H, Abdullah B J, Ng K H, Chung L Y, Dahalan R and Perkins A C 2015 *PLoS One* **10** e0138106
- [3] Hashikin N A A, Yeong C H, Abdullah B J J, Ng K H, Chung L Y, Dahalan R and Perkins A C 2015 Samarium-153 labelled microparticles for targeted radionuclide therapy of liver tumor *World Congress on Medical Physics and Biomedical Engineering, June 7-12, Toronto, Canada (IFMBE Proc.)* ed Jaffray DA (Switzerland: Springer International Publishing) **51** pp. 471-4
- [4] Mumper R J, Ryo U Y and Jay M 1991 *J Nucl Med.* **32** 2139-43
- [5] Poorbaygi H, Reza Aghamiri S M, Sheibani S, Kamali-Asl A and Mohagheghpoor E 2011 *Appl. Radiat. Isot.* **69** 1407-14
- [6] Laboratoire National Henri Becquerel 2014 France http://www.nucleide.org/DDEP_WG/DDEPdata_by_Z.htm
- [7] Snyder W S, Ford M R and Warner G G 1978 *MIRD Pamphlet No. 5 Revised: Estimates of Specific Absorbed Fractions for Photon Sources Uniformly Distributed in Various Organs of a Heterogeneous Phantom* (New York: Society of Nuclear Medicine)
- [8] Sirtex 2004 [package insert] (Lane Cove, Australia: Sirtex Medical)
- [9] Dubois D and Dubois E 1916 *Arch. Int. Med.* **17** 863-71
- [10] Ho S, Lau W Y, Leung T W, Chan M, Ngar Y K, Johnson P J and Li A K 1996 *Eur. J. Nucl. Med.* **23** 947-52

Acknowledgements

This study was funded by the Ministry of Science, Technology and Innovation (MOSTI) Science Fund SF011-2014 and University of Malaya Postgraduate Research Fund PG104-2013B.