

Dosimetry of Bone-Seeking Radiopharmaceuticals for Palliative Therapy of Bone Metastases: A Simulation Study Using GATE Monte Carlo Code

Saman Dalvand¹, Hossein Rajabi^{1*} , Ameneh Omid², Etesam Malekzadeh¹

¹ Department of Medical Physics, School of Medical Sciences, Tarbiat Modares University, Tehran, Iran

² Department of Anatomical Sciences, Tarbiat Modares University, Tehran, Iran

*Corresponding Author: Hossein Rajabi
Email: hrajabi@modares.ac.ir

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Abstract

Purpose: Radiopharmaceutical Therapy (RPT) is one of the effective methods for pain palliation of bone metastases. Bone marrow is a critical organ in bone structure whose absorbed dose should be kept below a certain threshold. The purpose of this study was to calculate and compare absorbed doses of bone-seeking radiopharmaceuticals used in the palliative treatment of bone metastases.

Materials and Methods: In this study, the GATE Monte Carlo code was used to simulate a femur bone, which consists of bone marrow, endosteal layer, bone, and soft tissue phantom model. Absorbed doses of the ¹⁵³Sm-EDTMP, ⁸⁹SrCl₂, ¹⁷⁷Lu-EDTMP, ¹⁸⁸Re-HEDP, and ²²³RaCl₂ radiopharmaceuticals were calculated in the femur phantom compartments.

Results: bone absorbed doses per disintegration from alpha particles of ²²³RaCl₂ is approximately 24 times higher than absorbed doses from beta particles of ⁸⁹SrCl₂. Also, absorbed dose per disintegration from beta particles of ⁸⁹SrCl₂ in the bone is approximately 12, 6 and 1.5 times higher than ¹⁷⁷Lu-EDTMP, ¹⁵³Sm-EDTMP, and ¹⁸⁸Re-HEDP, respectively. Moreover, the bone and bone marrow absorbed dose from beta particles of ¹⁵³Sm-EDTMP is approximately 2 times higher than ¹⁷⁷Lu-EDTMP. Besides, absorbed dose per disintegration from beta particles of ¹⁸⁸Re-HEDP in the bone marrow is approximately 40, 30, 7, and 4 times higher than ²²³RaCl₂, ⁸⁹SrCl₂, ¹⁷⁷Lu-EDTMP and ¹⁵³Sm-EDTMP, respectively.

Conclusion: Our results show that ²²³RaCl₂ could be a more efficient radiopharmaceutical for radionuclide therapy of bone metastases. Also, ¹⁷⁷Lu-EDTMP, due to low marrow toxicity and comparable bone absorbed dose with ¹⁵³Sm-EDTMP, can be used for achieving bone pain palliation. Moreover, significantly high bone marrow absorbed dose of ¹⁸⁸Re-HEDP should be considered for palliative therapy of metastatic bone patients.

Keywords: Dosimetry; Bone Metastasis; Radiopharmaceutical Therapy; Monte Carlo Simulation.

1. Introduction

Bone is one of the common metastatic sites of cancers [1]. Metastasis occurs due to a complex pathophysiological process that causes secondary lesion formation in bone [2, 3]. Most of the bone metastases originate from breast, prostate, thyroid, and lung primary cancers [4-6]. Patients with bone metastases are at the risk of complications, including severe pain, spinal cord compression, hypercalcemia, and bone fractures [1, 4, 7]. There are several therapeutic modalities for bony lesions and the associated complications, including surgery, chemotherapy, radiotherapy, and bisphosphonates [8-11]. However, pain relief is generally required in the advanced stages of bone metastasis. The objective of Radiopharmaceutical Therapy is toxicity limitation to the secondary lesions with minimizing dose to the surrounding healthy tissues to improve the patients' life quality [12, 13].

The development of effective radiopharmaceuticals for maximum pain palliation and minimum damage to bone marrow is a major challenge. Phosphorous-32 was the first radionuclide used for palliative treatment of multiple bone metastases. However, due to the long-range of its beta particles in tissues and the high myelotoxicity, its use is limited now [14]. The $^{89}\text{SrCl}_2$ and $^{153}\text{Sm-EDTMP}$ are beta-emitting radiopharmaceuticals approved by the USA Food and Drug Administration (FDA) and nowadays are widely used in clinical practice [15, 16]. The $^{188}\text{Re-HEDP}$ and $^{177}\text{Lu-EDTMP}$ are beta-emitting radiopharmaceuticals yet under investigation [17]. Alpha-emitting radionuclides have also shown promising results due to short-range and high LET (Linear Energy Transfer) of its particles. As an example, $^{223}\text{RaCl}_2$ is a radiopharmaceutical that successfully passed the phase III of clinical trial for palliative management of metastatic bone patients and approved by the FDA for treatment of metastatic castration prostate cancer (mCRPC patients) with symptomatic bone metastases without visceral metastatic disease [18, 19].

In radionuclide therapy of skeletal metastases, dose to bone marrow should be below a certain limit. The absorbed dose to bone marrow depends on both pharmaceutical distribution and the associate radionuclide particle/energy. The physical and biological properties of radiopharmaceuticals (half-life, the energy of

particles, and spatial distribution) should be carefully considered for dose estimation. As an example for radiopharmaceutical distribution, the $^{89}\text{SrCl}_2$ and $^{223}\text{RaCl}_2$ are distributed in the whole volume of the bone (bone volume-seeker), whereas $^{153}\text{Sm-EDTMP}$, $^{188}\text{Re-HEDP}$, and $^{177}\text{Lu-EDTMP}$ are primarily localized in endosteal surfaces due to phosphonate agents (bone surface-seeker) [20-22].

In recent years, interest in developing effective radiopharmaceuticals has increased for both treatment and palliative therapy of bone metastases. Dosimetry evaluation of bone-seeking radiopharmaceuticals and comparison to each other is important for identifying the most appropriate radiopharmaceutical among them. Although there are some Monte Carlo simulation studies for this purpose, realistic radiopharmaceuticals distribution is not considered. In a study by Ranjbar *et al.* [23], dosimetry was performed for $^{153}\text{Sm-EDTMP}$, $^{177}\text{Lu-EDTMP}$, and $^{166}\text{Ho-EDTMP}$ in a cylindrical femur phantom using MCNPX Monte Carlo code. In their study, they distributed radiolabeled phosphonates in bone volume of femur phantom and calculated absorbed doses in the femur compartments. In another study by Bagheri *et al.* [24], dosimetry was performed for some beta-emitting radiopharmaceuticals in a femur phantom using MCNP4C Monte Carlo code. In the previous studies, there is no realistic comparison between absorbed doses of alpha-emitting and beta-emitting radiopharmaceuticals in the human femur bone. In order to evaluate the risk versus the benefit of palliative radiopharmaceuticals, it is useful to have a more realistic comparison between absorbed doses of radiopharmaceuticals used in the palliative therapy of bony lesions, especially between new alpha-emitting $^{223}\text{RaCl}_2$ and commonly beta-emitting radiopharmaceuticals. Also, absorbed doses of $^{188}\text{Re-HEDP}$ and $^{177}\text{Lu-EDTMP}$, as under investigation radiopharmaceuticals for palliative treatment of secondary lesions, should be calculated and compared with other radiopharmaceuticals. The Monte Carlo simulation using an appropriate phantom is one of the accurate and efficient methods for dose estimation of internal emitters. The aim of the present study was to calculate and compare absorbed doses of $^{153}\text{Sm-EDTMP}$, $^{89}\text{SrCl}_2$, $^{177}\text{Lu-EDTMP}$, $^{188}\text{Re-HEDP}$, and $^{223}\text{RaCl}_2$ in radionuclide therapy of bone metastases. We used an analytical bone phantom model and the GATE Monte Carlo code for the calculation.

2. Materials and Methods

2.1. Geometry of Femur Phantom

According to reported size and morphology for human femur bone, a cylindrical geometry was assumed for simulating a part of the femur structure [25]. Three coaxial sub-cylinders with 1.2, 2.6, and 8.0 cm in diameter were supposed for bone marrow, bone (cortex), and soft tissue, respectively [25]. The length of the cylinders was considered 5.0 cm along the z-axis (Figure 1) [26]. The cylindrical geometry is a good approximation of femur bone, one of the most common sites of metastatic lesions. The endosteal layer was assumed 50.0 μm based on ICRP133 [27].

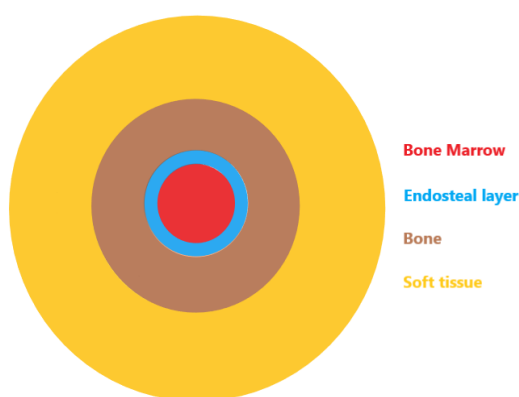


Figure 1. The geometry of femur phantom

2.2. Radionuclide Radiation Spectra

Radiopharmaceuticals considered in this study were ^{153}Sm -EDTMP, $^{89}\text{SrCl}_2$, ^{177}Lu -EDTMP, ^{188}Re -HEDP, and $^{223}\text{RaCl}_2$. The required data of radionuclides was derived from the "MIRD radionuclide data and decay scheme" and presented in Table 1 [28]. Radiopharmaceuticals were assumed distributed in the bone compartments based on known biodistribution features [21].

2.3. Monte Carlo Simulations

Simulations were performed using GATE (version 8.1). The elemental composition of tissues was defined based on ICRU-44 publication [29]. Livermore physics model was selected for the simulations. In this model, electron and photon cut-off energies are 100.0 eV and 250.0 eV, respectively [30]. That means, when the energy of particles falls below these threshold values during simulation, the tracking is terminated, and the remaining energy of the particle is deposited at that spot. Based on the GATE procedure, dose actors were attached to each bone compartment (bone marrow, endosteal layer, bone, and soft tissue). Actors are tools to interact with simulation and extract the required data; in this case, the absorbed dose unit to the bone compartments is in Gy. The number of histories was set so that to have uncertainties below <0.01 .

Table 1. Physical properties of Radiopharmaceuticals considered in this study

Radionuclide	Radiopharmaceutical	Decay Mode	$t_{1/2}$	Average Beta Energy (Mev)	Average Alpha Energy (Mev)
^{89}Sr	$^{89}\text{SrCl}_2$	Beta	50.5 d	0.584	-
^{153}Sm	^{153}Sm -EDTMP	Beta	1.9 d	0.223	-
^{177}Lu	^{177}Lu -EDTMP	Beta	6.7 d	0.132	-
^{188}Re	^{188}Re -HEDP	Beta	0.7 d	0.762	-
^{223}Ra	$^{223}\text{RaCl}_2$	Alpha	11.43 d	-	5.66
^{219}Rn	-	Alpha	3.96 s	-	6.75
^{215}Po	-	Alpha	1.78 ms	-	7.38
^{211}Pb	-	Beta	36.1 m	0.090	-
^{211}Bi	-	Beta, Alpha	2.17 m	0.035	6.56
^{207}Tl	-	Beta	4.77 m	0.113	-

3. Results

The results obtained from the simulations are presented in Table 2. It was found that the bone, endosteal layer, and soft tissue absorbed dose per disintegration from beta particles of ¹⁵³Sm-EDTMP, ¹⁷⁷Lu-EDTMP, and ¹⁸⁸Re-HEDP are approximately similar to each other (see Table 2 and Figure 2). On the other hand, absorbed dose per disintegration from beta particles of ⁸⁹SrCl₂ in the bone is approximately 12, 6, and 1.5 times higher than ¹⁷⁷Lu-EDTMP, ¹⁵³Sm-EDTMP, and ¹⁸⁸Re-HEDP, respectively. In addition, the bone and bone marrow absorbed dose from beta particles of ¹⁵³Sm-EDTMP is approximately 2 times higher than ¹⁷⁷Lu-EDTMP.

As can be seen from the Table 2, the most striking result to emerge from the data is that the bone absorbed doses per disintegration from alpha particles of ²²³RaCl₂ is approximately 24 times higher than absorbed doses from beta particles of ⁸⁹SrCl₂. Interestingly, while the absorbed dose per disintegration for the bone from alpha emitters was extremely higher than from beta emitters, this value

was significantly low in the bone marrow: 0.19 pGy/Bq for ²²³RaCl₂ versus 7.64 pGy/Bq for ¹⁸⁸Re-EDTMP. On the other hand, this difference is not significant for the gamma and x-ray absorbed dose (see Figure 3 and Figure 4). Besides, absorbed dose per disintegration from beta particles of ¹⁸⁸Re-HEDP in the bone marrow is approximately 40, 30, 7, and 4 times higher than ²²³RaCl₂, ⁸⁹SrCl₂, ¹⁷⁷Lu-EDTMP, and ¹⁵³Sm-EDTMP, respectively.

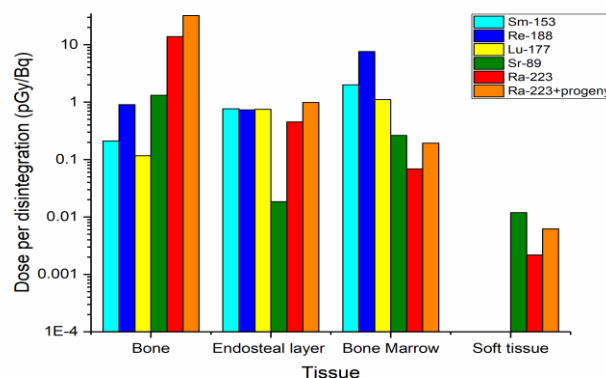


Figure 2. Absorbed dose from alpha and beta particles in the femur phantom (y-axis is in logarithmic scale)

Table 2. Absorbed dose per disintegration (pGy/Bq) in the femur for radiopharmaceuticals considered in this study

Tissue	Radiations	²²³ Ra	²²³ Ra+progeny	¹⁵³ Sm	¹⁷⁷ Lu	⁸⁹ Sr	¹⁸⁸ Re
Bone	Alpha	13.90	32.24	-	-	-	-
	Beta	-	-	0.21	0.11	1.32	0.90
	Gamma	1.38E-2	3.77E-2	1.0E-2	5.23E-3	1.14E-5	8.38E-3
	x-ray	14.20E-2	1.44E-1	3.0E-2	2.78E-3	1.83E-8	2.29E-3
Endosteal Layer	Alpha	0.45	0.99	-	-	-	-
	Beta	-	-	0.76	0.75	0.01	0.73
	Gamma	2.81E-4	6.82E-4	4.09E-4	3.93E-4	2.33E-7	5.84E-4
	x-ray	9.83E-4	1.00E-3	5.41E-3	1.12E-3	5.33E-11	1.45E-3
Bone Marrow	Alpha	6.89E-2	0.19	-	-	-	-
	Beta	-	-	2.00	1.11	0.26	7.64
	Gamma	1.43E-2	3.58E-2	1.11E-2	1.03E-2	1.31E-5	1.85E-2
	x-ray	4.10E-2	4.16E-2	2.29E-2	3.83E-3	1.73E-9	3.93E-3
Soft Tissue	Alpha	2.18E-3	6.19E-3	-	-	-	-
	Beta	-	-	8.82E-5	6.81E-6	2.45E-7	1.19E-2
	Gamma	2.88E-3	7.21E-3	9.39E-4	8.55E-4	2.67E-6	1.58E-3
	x-ray	7.96E-3	8.08E-3	7.93E-4	9.26E-5	9.87E-11	8.59E-5

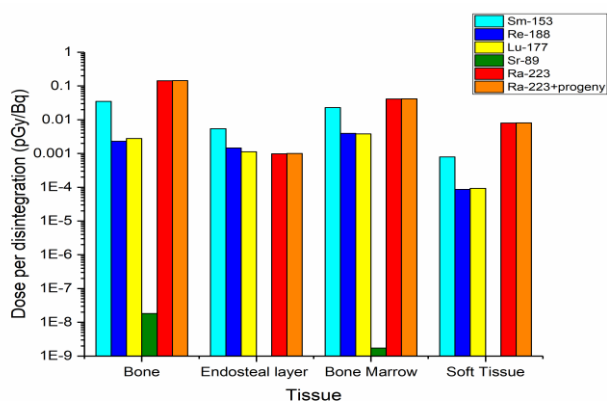


Figure 3. Absorbed dose from gamma emissions in the femur phantom (y-axis is in logarithmic scale)

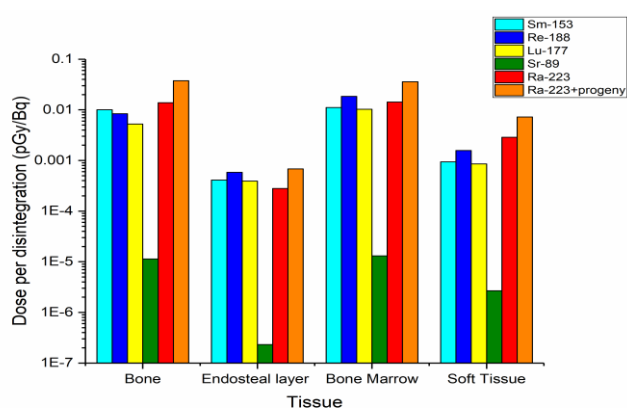


Figure 4. Absorbed dose from x-ray emissions in the femur phantom (y-axis is in logarithmic scale)

The bone, endosteal layer, and bone marrow absorbed dose per disintegration from beta particles of $^{153}\text{Sm-EDTMP}$ and $^{177}\text{Lu-EDTMP}$ is over 20 times higher than gamma and x-ray emissions, while this value for $^{188}\text{Re-HEDP}$ and $^{89}\text{SrCl}_2$ is more than 100 times. Also, bone and endosteal layer absorbed dose per disintegration from Alpha particles of $^{223}\text{RaCl}_2$ is over 20 times higher than gamma and x-ray emissions, whereas bone marrow absorbed dose is approximately 5 times higher. In contrast, for all beta-emitting radiopharmaceutical except $^{89}\text{SrCl}_2$, soft tissue absorbed dose per disintegration from gamma and x-ray emissions is over 10 times higher than beta particles. Also, for $^{223}\text{RaCl}_2$ alpha particles and gamma and x-ray emissions approximately have the same absorbed dose per disintegration in the soft tissue. Furthermore, having considered the progeny of alpha emitters, its absorbed dose per disintegration approximately increases by 2.3, 2.2, 2.8, and 2.8 times for the bone, endosteal layer, bone marrow, and soft

tissue, respectively (see Table 2 and Figure 2). On the other hand, no significant difference was found for the gamma and x-ray absorbed dose (see Figure 3 and Figure 4).

4. Discussion

Radiopharmaceuticals $^{89}\text{SrCl}_2$, $^{188}\text{Re-HEDP}$, $^{153}\text{Sm-EDTMP}$, $^{177}\text{Lu-EDTMP}$, and $^{223}\text{RaCl}_2$ are developed for palliative treatment of bone metastases. For accurate dosimetry, it is necessary to consider the differences between radiopharmaceutical spatial distributions.

According to the results, $^{223}\text{RaCl}_2$ has the highest absorbed dose in the bone and lowest absorbed dose in the bone marrow in comparison to other radiopharmaceuticals considered in this study. Figure 2 demonstrates that alpha particles mainly deliver dose to the bone, and the absorbed dose, due to those particles, is low in the bone marrow and endosteal layer. It seems possible that this result is due to the short-range penetration and high LET of the alpha particles in combination with the bone-volume seeking feature of this radiopharmaceutical that causes absorbed dose from those particles is localized in the source compartment. It was found that considering progenies of the $^{223}\text{RaCl}_2$ increases the absorbed dose of the bone tissues on average by 2.5 times. However, because of the short half-life of these radionuclides, the accumulated absorbed doses are negligible in comparison with an accumulated absorbed dose of the $^{223}\text{RaCl}_2$. The high bone absorbed dose from beta particles of $^{89}\text{SrCl}_2$ in comparison to $^{153}\text{Sm-EDTMP}$, $^{177}\text{Lu-EDTMP}$, and $^{188}\text{Re-HEDP}$ is because of its bone-volume seeking feature. Besides, high bone marrow absorbed dose from beta particles of $^{188}\text{Re-HEDP}$ in the bone marrow is due to its high beta energy and long tissue penetration range. As can be seen from Figure 2, $^{177}\text{Lu-EDTMP}$ and $^{153}\text{Sm-EDTMP}$ have a close absorbed dose in bone, but $^{177}\text{Lu-EDTMP}$ absorbed dose is lower in case of bone marrow. The reason for this is that the average beta energy of $^{177}\text{Lu-EDTMP}$ is lower than $^{153}\text{Sm-EDTMP}$. Figure 3 shows that the absorbed dose from gamma emission of $^{223}\text{RaCl}_2$ is higher than other radiopharmaceuticals. For $^{153}\text{Sm-EDTMP}$, $^{177}\text{Lu-EDTMP}$, and $^{188}\text{Re-HEDP}$, the bone marrow absorbed dose due to gamma photons is

higher than bone, endosteal layer, and soft tissue. In contrast, the absorbed dose from gamma rays of $^{89}\text{SrCl}_2$ is negligible in all compartments. The reason is that gamma-ray energy and yield of $^{89}\text{SrCl}_2$ is very low compared to other radiopharmaceuticals. As can be seen from Figure 4, $^{223}\text{RaCl}_2$ and $^{89}\text{SrCl}_2$ have the highest and lowest absorbed dose due to their x-rays in the bone and bone marrow, respectively. The absorbed dose due to x-ray emissions of $^{223}\text{RaCl}_2$ and $^{153}\text{Sm-EDTMP}$ in bone is high compared to other tissues. The density of bone tissue is higher than the endosteal layer and bone marrow. Therefore, the photoelectric interactions between low energy x-ray emissions of this radiopharmaceuticals and bone are most probable. Also, the reason for the high soft tissue absorbed dose per disintegration from gamma and x-ray emissions compared to beta and alpha particles for all radiopharmaceutical, except $^{89}\text{SrCl}_2$, is that gamma and x-ray emissions have high penetration in materials.

Ranjbar *et al.*'s study [23] is comparable to our study. There is a discrepancy between absorbed-dose per disintegration results, but for comparison between $^{153}\text{Sm-EDTMP}$ and $^{177}\text{Lu-EDTMP}$, the results are in agreement. Their reported bone absorbed dose per disintegration from $^{153}\text{Sm-EDTMP}$ and $^{177}\text{Lu-EDTMP}$ and our calculated dose differed by 2.2 and 1.3 pGy/Bq, respectively. However, bone absorbed dose from beta particles of $^{153}\text{Sm-EDTMP}$ is 1.72 times higher than $^{177}\text{Lu-EDTMP}$ in their study, whereas this value is 1.90 in our study. The Relative difference between the results is 10%, which is justifiable. The discrepancy could be due to differences between radionuclide data and geometrical and theoretical assumptions. Their phantom is not included in the endosteal layer. Furthermore, they distributed all three radiopharmaceuticals in entire bone volume, whereas we distributed radiolabeled phosphonates in the endosteal layer. Also, another reason could be due to differences between the energy cut-off of two codes. The MCNPX energy cut-off is 1keV for both electron and photon radiations. In contrast, in Livermore physics of GATE, as mentioned earlier, electron and photon cut-off energies are 100 eV and 250 eV, respectively.

We are aware that our research may have two limitations. The first is the geometrical consideration,

in which a simple model of the femur was used instead of a voxelized phantom. The second is ignoring the Auger and internal conversion electron's dose that is an important issue for future research. Further studies, which should take these limitations into account, will be needed to be undertaken.

The results show that $^{223}\text{RaCl}_2$ has the highest absorbed dose in the bone volume with minimal bone marrow absorbed dose compared to the beta-emitting radiopharmaceuticals considered in this study. On the other hand, $^{89}\text{SrCl}_2$ deposits highest absorbed dose to the bone and lowest absorbed dose to the bone marrow in comparison with other beta-emitting radiopharmaceuticals. Also, $^{188}\text{Re-HEDP}$ has the highest bone marrow absorbed dose compared to other radiopharmaceuticals. The results are in good agreement with clinical observations. Clinical outcome data demonstrated that $^{223}\text{RaCl}_2$ has higher therapy efficiency and lower myelotoxicity than $^{153}\text{Sm-EDTMP}$ and $^{89}\text{SrCl}_2$ [31, 32]. Experimental studies have indicated the safety and efficacy of $^{223}\text{RaCl}_2$ for palliative therapy of bone metastases [33, 34]. Also, clinical results suggest that $^{153}\text{Sm-EDTMP}$ and $^{177}\text{Lu-EDTMP}$ can be used interchangeably [35, 36].

5. Conclusion

$^{223}\text{RaCl}_2$ delivers an intense and highly localized dose to the bone with sparing the bone marrow in comparison with the beta emitter radiopharmaceuticals used in the palliative therapy of bone metastases. According to the results, $^{223}\text{RaCl}_2$ could be a more efficient radiopharmaceutical for radionuclide therapy of bone metastases. Moreover, $^{177}\text{Lu-EDTMP}$, due to low marrow toxicity and comparable bone absorbed dose with $^{153}\text{Sm-EDTMP}$, can be used for achieving bone pain palliation. Also, high bone marrow absorbed dose of $^{188}\text{Re-HEDP}$ should be considered for palliative therapy of metastatic bone patients.

References

- 1- Kimura, T., "Multidisciplinary approach for bone metastasis: a review," *Cancers*, vol. 10, no. 6, pp. 156, 2018.
- 2- Mundy, G.R., "Metastasis to bone: causes, consequences and therapeutic opportunities," *Nature Reviews Cancer*, vol. 2, no. 8, pp. 584-593, 2002.

- 3- Florencio-Silva, R. *et al.*, "Biology of bone tissue: structure, function, and factors that influence bone cells," *BioMed research international*, Article ID 421746, 2015.
- 4- Coleman, R.E., "Clinical features of metastatic bone disease and risk of skeletal morbidity," *Clinical cancer research*, vol. 12, no. 20, pp. 6243s-6249s, 2006.
- 5- Costa, L. and P.P. Major, "Effect of bisphosphonates on pain and quality of life in patients with bone metastases," *Nature Reviews Clinical Oncology*, vol. 6, no. 3, pp. 163-174, 2009.
- 6- Selvaggi, G. and G.V. Scagliotti, "Management of bone metastases in cancer: a review", *Critical reviews in oncology/hematology*, vol. 56, no. 3, pp. 365-378, 2005.
- 7- Tsuzuki, S., *et al.*, "Skeletal complications in cancer patients with bone metastases," *International Journal of Urology*, vol. 23, no. 10, pp. 825-832, 2016.
- 8- Dennis, K., *et al.*, "Management of bone metastases: recent advances and current status," *Journal of Radiation Oncology*, vol. 1, no. 3, pp. 201-210, 2012.
- 9- Janjan, N., *et al.*, "Therapeutic guidelines for the treatment of bone metastasis: a report from the American College of Radiology Appropriateness Criteria Expert Panel on Radiation Oncology," *Journal of palliative medicine*, vol. 12, no. 5, pp. 417-426, 2009.
- 10- Sartor, O., P. Hoskin, and Ø.S. Bruland, "Targeted radio-nuclide therapy of skeletal metastases," *Cancer treatment reviews*, vol. 39, no. 1, pp. 18-26, 2013.
- 11- Michael, H.-H., Y.-Y. Tsai, and S.E. Hoffe, "Overview of diagnosis and management of metastatic disease to bone," *Cancer Control*, vol. 19, no. 2, pp. 84-91, 2012.
- 12- Lewington, V.J., "Bone-seeking radionuclides for therapy," *Journal of nuclear medicine*, vol. 46, no. 1 suppl, pp. 38S-47S, 2005.
- 13- Handkiewicz-Junak, D., *et al.*, "EANM guidelines for radionuclide therapy of bone metastases with beta-emitting radionuclides," *European journal of nuclear medicine and molecular imaging*, vol. 45, no. 5, pp. 846-859, 2018.
- 14- Paes, F.M. and A.N. Serafini, "Systemic metabolic radiopharmaceutical therapy in the treatment of metastatic bone pain," in *Seminars in nuclear medicine*, vol. 40, no. 2, pp. 49-104, 2010.
- 15- Hirabayashi, H. and J. Fujisaki, "Bone-specific drug delivery systems," *Clinical pharmacokinetics*, vol. 42, no. 15, pp. 1319-1330, 2003.
- 16- Tomblyn, M., "The role of bone-seeking radionuclides in the palliative treatment of patients with painful osteoblastic skeletal metastases," *Cancer Control*, vol. 19, no. 2, pp. 137-144, 2012.
- 17- Lange, R., *et al.*, "Pharmaceutical and clinical development of phosphonate-based radiopharmaceuticals for the targeted treatment of bone metastases," *Bone*, vol. 91, pp. 159-179, 2016.
- 18- Body, J.-J., S. Casimiro, and L. Costa, "Targeting bone metastases in prostate cancer: improving clinical outcome," *Nature reviews Urology*, vol. 12, no. 6, pp. 340, 2015.
- 19- Parker, C.C., *et al.*, "Three-year safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases from phase 3 randomized alphasradin in symptomatic prostate cancer trial," *European urology*, vol. 73, no. 3, pp. 427-435, 2018.
- 20- Johnson, J.C., *et al.*, "Calculation of radiation dose at a bone-to-marrow interface using Monte Carlo modeling techniques (EGS4)," *Journal of nuclear medicine: official publication, Society of Nuclear Medicine*, vol. 33, no. 4, pp. 623-628, 1992.
- 21- Strigari, L., *et al.*, "Radiopharmaceutical therapy of bone metastases with 89 SrCl 2, 186 Re-HEDP and 153 Sm-EDTMP: a dosimetric study using Monte Carlo simulation," *European journal of nuclear medicine and molecular imaging*, vol. 34, no. 7, pp. 1031-1038, 2007.
- 22- Appelbaum, F., *et al.*, "Myelosuppression and mechanism of recovery following administration of 153Samarium-EDTMP," *Antibody Imunoconjug Radiopharm*, vol. 1, pp. 263-270, 1988.
- 23- Ranjbar, H., *et al.*, "Dosimetric evaluation of 153Sm-EDTMP, 177Lu-EDTMP and 166Ho-EDTMP for systemic radiation therapy: Influence of type and energy of radiation and half-life of radionuclides," *Radiation Physics and Chemistry*, vol. 108, pp. 60-64, 2015.
- 24- Bagheri, R., *et al.*, "Study of bone surface absorbed dose in treatment of bone metastases via selected radiopharmaceuticals: using MCNP4C code and available experimental data," *Cancer Biotherapy and Radiopharmaceuticals*, vol. 30, no.4, pp. 174-181, 2015.
- 25- Husmann, O., *et al.*, "Three-dimensional morphology of the proximal femur," *The Journal of arthroplasty*, vol. 12, no. 4, pp. 444-450, 1997.
- 26- Giladi, M., *et al.*, "Stress fractures and tibial bone width. A risk factor," *The Journal of bone and joint surgery. British volume*, vol. 69, no. 2, pp. 326-329, 1987.
- 27- Bolch, W., *et al.*, "ICRP publication 133: The ICRP computational framework for internal dose assessment for reference adults: specific absorbed fractions," *Annals of the ICRP*, vol. 45, no. 2, pp. 5-73, 2016.

- 28- Eckerman, K.F. and A. Endo, MIRD: "radionuclide data and decay schemes," *Snmmti*, 2007.
- 29- ICRU, I., "Tissue substitutes in radiation dosimetry and measurement," *International Commission on Radiation Units and Measurements*, 1989.
- 30- Tajik-Mansoury, M., H. Rajabi, and H. Mozdarani, "A comparison between track-structure, condensed-history Monte Carlo simulations and MIRD cellular S-values," *Physics in Medicine & Biology*, vol. 62, no. 5, pp. N90, 2017.
- 31- Goyal, J. and E.S. Antonarakis, "Bone-targeting radiopharmaceuticals for the treatment of prostate cancer with bone metastases," *Cancer letters*, vol. 323, no. 2, pp. 135-146, 2012.
- 32- Pacilio, M., *et al.*, "Dosimetry of bone metastases in targeted radionuclide therapy with alpha-emitting ²²³Ra-dichloride," *European journal of nuclear medicine and molecular imaging*, vol. 43, no.1, pp. 21-33, 2016.
- 33- Parker, C., *et al.*, "Alpha emitter radium-223 and survival in metastatic prostate cancer," *New England Journal of Medicine*, vol. 369, no. 3, pp. 213-223, 2013.
- 34- Harrison, M.R., *et al.*, "Radium-223 chloride: a potential new treatment for castration-resistant prostate cancer patients with metastatic bone disease," *Cancer management and research*, vol. 5, pp. 1, 2013.
- 35- Sharma, S., *et al.*, "Comparative therapeutic efficacy of ¹⁵³Sm-EDTMP and ¹⁷⁷Lu-EDTMP for bone pain palliation in patients with skeletal metastases: patients' pain score analysis and personalized dosimetry," *Frontiers in medicine*, vol. 4, pp. 46, 2017.
- 36- Thapa, P., *et al.*, "Clinical efficacy and safety comparison of ¹⁷⁷Lu-EDTMP with ¹⁵³Sm-EDTMP on an equidose basis in patients with painful skeletal metastases," *Journal of Nuclear Medicine*, vol. 56, no.10, pp. 1513-1519, 2015.