Original Article

Dosimetric analysis for the selection of radionuclides in bone pain palliation targeted therapy: A Monte Carlo simulation

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(Received 21 July 2016, Revised 25 September 2016, Accepted 28 September 2016)

ABSTRACT

Introduction: The use of beta emitters is one of the effective methods for palliation of bone metastasis. The risk of normal tissue toxicity should be evaluated in the bone pain palliation treatment.

Methods: In this study, the Monte Carlo simulation code MCNPX was used for simulation a bone phantom model consisted of bone marrow, bone and soft tissue. Specific absorbed fractions were calculated for monoenergetic electrons, photons and eight beta emitters: ^{32}P, ^{89}Sr, ^{90}Y, ^{153}Sm, ^{166}Ho, ^{177}Lu, ^{186}Re and ^{188}Re. Beta and gamma S-factor, absorbed dose and cumulative dose of mentioned radionuclides were obtained to the selection of radionuclides with optimal radiation characteristics.

Results: The results show ^{177}Lu gives a higher local dose to source organ. ^{177}Lu has fewer side effects on critical organ including bone marrow in comparison with other radionuclides such as ^{89}Sr, ^{32}P and ^{90}Y. Cumulative dose versus time shows after a long time, long half-life radionuclides delivering a higher dose in comparison with the short-half radionuclides.

Conclusion: According to the results, low energy β-emitters^{177}Lu, ^{153}Sm and ^{186}Re can be used for bone pain palliation especially in vertebra. Different combination of these radionuclides can be used to improving therapeutic effects for tumors with different size.

Key words: Bone metastasis; Pain palliation; Monte Carlo simulation; Dose distribution; Beta emitter radionuclides

Iran J Nucl Med 2017;25(Suppl 1):40-46
Published: February, 2017
http://irjnm.tums.ac.ir

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INTRODUCTION

Bone metastasis is a major complication for the cancer patient. Spine due to its size, proximity and rich vascularization being the most common site that involves in the bone metastasis [1-3]. Bone metastasis is painful and can degrade bone strength, causes pathological fractures and serious neurological complications due to spinal cord compression [4, 5]. Palliative therapy of severe pain of bone metastasis is an important part in the treatment of this disease [6]. Radionuclide therapy that utilizes ionizing radiation has an essential role in treatment and palliation of bone metastasis and this kind of therapy has been used since 1942 [7]. Radionuclide therapy can be used in widespread and multiple sites of bone involvement, simultaneously [8, 9].

The major key to successful in the radionuclide therapy is delivering high doses to the lesions while limiting radiation dose to normal and critical surrounding organ [10]. This is particularly important in the bone pain palliation based on the radionuclide therapy. The bone marrow is the critical and dose-limiting organ in radionuclide therapy of metastatic bone [11]. Hence the main requirement in selecting an effective radionuclide is the energy emitted during its decay should be mainly deposited locally, while whole body irradiation must be as small as possible [12]. The physical factors such as energy, half-life and tissue penetration range of selected radionuclides for radionuclide therapy affect the therapy efficacy [13]. Several beta emitter radionuclides such as ^{32}P, ^{89}Sr, ^{90}Y, ^{153}Sm, ^{177}Lu, ^{186}Re and ^{188}Re are used for treating painful bone metastasis [14-21].

Currently, several of these β emitting radionuclides are commercially available for bone pain palliation as $^{89}SrCl_2$, ^{153}Sm-EDTMP and ^{186}Re-HDEP and other radionuclides ^{90}Y, ^{166}Ho, ^{177}Lu and ^{188}Re are under research for palliative treatment of bone metastasis [22]. The ^{32}P and ^{89}Sr were the first radioisotopes to be evaluated for the palliative treatment of bone metastasis .^{32}P should be used in the orthophosphate form and ^{89}Sr is typically used as calcium analog [23]. ^{53}Sm is prepared in high radionuclide purity by neutron bombardment of enriched $^{152}Sm_2O_3$ in a nuclear reactor [24, 25].

Accurate estimation of absorbed dose is required to evaluation the risk versus the benefit of different radionuclides that are used in humans. Absorbed dose (D) is one of the most important factors in the assessment of radiation damage to tissue. According to the Medical Internal Radiation Dose (MIRD) approach [26], the average dose to the target organ can be calculated as;

$$D_t = \sum_s \tilde{A}_s S(t \leftarrow s) \qquad (1)$$

Where ($\tilde{A}_s$) is the cumulated activity in the source organ and S (t←s) is defined as;

$$S(t \leftarrow s) = \sum \Delta_i \frac{\phi_i (t \leftarrow s)}{M_t} \qquad (2)$$

Where (Δ_i) is the mean energy emitted as (i^{th}) radiation per decay, (Φ_i) is the absorbed fraction in the target organ (t) from the (i^{th}) radiation emitted in the source organ (s), and (M_t) is the mass of the target organ in kg.

Since pain is the main symptoms of bone metastasis and the bone pain palliation based on the radionuclide therapy has been proven to be an effective treatment modality for both palliative therapy and treatment, interest in designing an effective radiopharmaceutical for bone metastasis has increased in recent years. Computational simulation is a powerful tool for dosimetric evaluation of different radionuclides in targeted radionuclide therapy. The aim of this study is for assessment and comparison of absorbed dose factors for mentioned radionuclides in different tissues by using Monte Carlo simulation code. A mathematical bone phantom of a typical thoracic vertebrae in the Monte Carlo simulation, MCNPX code was simulated to analyze the dosimetric distribution within three regions including bone, bone marrow and soft tissues. The absorbed and specific absorbed fractions for electrons and photons distributed uniformly throughout the source region are calculated for electrons and photons with energy of 0.1–3 MeV. The absorbed fraction and absorbed dose for all investigated radionuclides are presented.

METHODS

Simulations were carried out for six beta emitter radionuclides as radioactive sources; ^{32}P, ^{89}Sr, ^{90}Y, ^{153}Sm, ^{177}Lu and ^{186}Re in MCNPX code. The main physical characteristics of these radionuclides are listed in Table 1 [21, 27]. MCNP is a general purpose Monte Carlo code for transporting neutrons, photons, electrons, and other particles in various geometries. The Monte Carlo simulations were performed using MCNPX code version 2.4. The code contains flexible source and tally options and variance reduction schemes. Several tally cards can be used to estimate dose or energy deposition for typical simulation runs [28]. The simulations were performed in both photon and electron modes and all physics processes were taken into account by choosing the default PHYS cards with the default cut-off energy at 1 keV for electrons and photons. *F8 and F6 tally were used to score deposited energy in defined cells. The outputs were converted to dose in Gy by multiplying it by the corresponding conversion coefficients.

Table 1: Radionuclides are used for palliative treatment of bone metastases.

Radionuclide	Mean β-ray energy (keV)	γ-ray energy (keV)	$T_{1/2}$ (days)	Tissue penetration range (mm)
^{32}P	694.9	—	14.30	8.10
^{89}Sr	583.0	—	50.50	6.60
^{90}Y	934.0	—	2.68	3.90
^{166}Ho	694.6	80.5(6.7%)	1.10	3.20
^{153}Sm	229.0	103 (30%)	1.96	1.20
^{177}Lu	133.0	208 (11%)	6.70	0.67
^{186}Re	359.0	137 (9.4%)	3.70	1.80
^{188}Re	744.0	155 (15%)	0.70	3.50

For each radionuclide, 10^6 particles were simulated to keep the relative errors of the calculated quantities below 1% and to pass the ten statistical tests provided by the MCNP package [29, 30]. In simulations, a uniform distribution of monoenergetic particles and interested radionuclides within the source region is assumed. The average energy of beta particles was used in MCNPX data card for energy definition of particles.

Geometry

The simulation model is a cylindrical geometry with constant density materials for modeling a vertebra. The minimum and maximum radii of three coaxial sub-cylinders were 0.8 cm, 2 cm and 5 cm for bone marrow, bone, and surrounding soft tissue, respectively, and a length of 2 cm was assumed along the z-axis for cylindrical shell and surrounding soft tissue [31]. Elemental compositions and mass densities for bone marrow, bone and soft tissue were taken from Report 46 of the International Commission on Radiation Units and Measurements (ICRU) [32].

Dosimetric parameters calculations

Based on Monte Carlo simulation tally *F8 was used for calculation energy deposition in each cylindrical layer which gives results in MeV per particle. The output of tally was used to calculate the absorbed fraction (AF) as follows:

$$AF = \frac{*F8}{E_0}. \quad (3)$$

Where E_0 is the initial energy of the particle in MeV. Specific absorbed fraction (SAF) was calculated as;

$$SAF = \frac{AF}{M_t}. \quad (4)$$

Where M_t is the mass of the target organ in g. The SAF describes the mean absorbed fraction of energy per unit mass in a target organ. S-value for source (s) and target organ (t) is defined as follow;

$$S_{(t \leftarrow s)} = 1.602 \times 10^{-10} \frac{\sum_i (*F8)_i N_i}{M_t}. \quad (5)$$

Where N_i is the number of emitted particles per disintegration and 1.602×10^{-10} converts MeV into joules and gives S-factor in Gy Bq^{-1} S^{-1}. The S-factor values describe the fraction of radiation energy absorbed per unit mass within a target organ.

The total dose during a time interval *t* after deposition of the radionuclide was calculated as;

$$D = \frac{D_0}{\lambda_E}(1 - e^{-\lambda_E t}). \quad (6)$$

Where D_0 (Gyd^{-1}) is the initial dose rate and λ_E (d^{-1}) is called the effective elimination constant.

RESULTS

The specific absorbed fraction for monoenergetic electrons and photons as a function of initial particles energy when activity is located in the bone volume for three tissues are shown in Figure 1.

Figure 2 shows the self-absorbed fraction as a function of particles energy in the source regions. It is evident from figure for the same energy, the bone with bigger volume and density gives the larger self-absorption in comparison with the marrow as a region with smaller volume and density.

To evaluate the energy deposited within the target volume, a uniform distribution of interesting radionuclides was considered in the bone volume as source region. Figures 3a and 4a show the variation of the energy deposition for investigated radionuclides within different tissues for β-particles and γ-rays, respectively. Figures 3b and 4b show the percentage of deposited energy per source energy for the tissues.

In Table 2 the S-factors are shown separately for γ-rays and β-particles for all radionuclides and different tissues when activity is located in the bone volume.

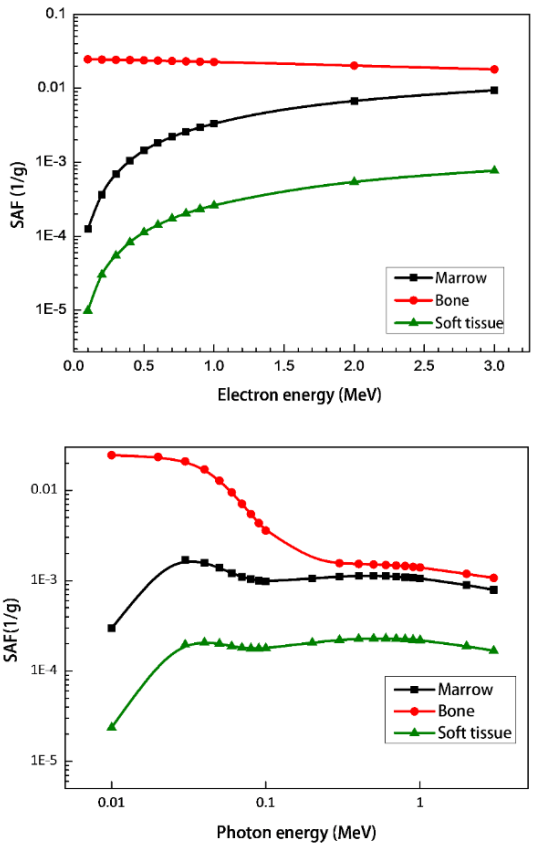

Fig 1. Specific absorbed fractions (SAF) for electron (above) and photons (below) in the different tissues for bone as source region.

The results show S-factors of γ-rays are lower than that of β-particles and therefore β-particles have main contribution in the total S-factor. ^{90}Y, ^{32}P, ^{89}Sr, ^{188}Re and ^{166}Ho are high energy β-emitters and they have higher S-factors, respectively. For gamma emissions, ^{153}Sm has higher S-factor values than other radionuclides in the three tissues because the photons with low energy have lower chance to escape and as it is seen in Table 1 the γ-ray branching ratio of ^{153}Sm is higher than that of other radionuclides.

Total Absorbed dose for all three tissues per 1 Bq activity of radiopharmaceuticals deposited in bone tissue is shows in Figure 5.

Finally, the delivered dose to the bone is shown as a function of time for the eight radionuclides in Figure 6.

DISCUSSION

We studied the radiation dose distribution within the vertebrae phantom for selected radionuclides. It was assumed that all radionuclides uniformly distributed in the source target (bone and bone marrow). As it is seen from Figures 1a and 1b, electrons SAFs are much higher than that of photons for the same energy, volume and tissue. The photons SAF values in target regions increase at energy ranging of 0.01-0.02 MeV and then decreases. The β-particles and electrons interact through coulomb forces with atomic nuclei and orbital electrons of absorber. In electron encounter, energy losses incurred in ionization and excitation events, whereas those incurred in nuclear encounters, resulting in bremsstrahlung production. In the nuclear medicine energy range, ionization and excitation events are domain. The photons, on the other hand, deposit their energy indirectly and through complex interactions with atoms, nuclei and electrons. Hence photons escaping probability from the target volume without any interaction is greater [33, 34]. The SAFs for bone in the case of source and target decreases with increasing particles energy, however, SAFs for other target regions including marrow and soft tissue increase as the particles energy increase. Lower energy particles deposit most of their energy in source and when the particles energy increases, tissue penetration would be enough to escape from the source area and into the surrounding tissue.

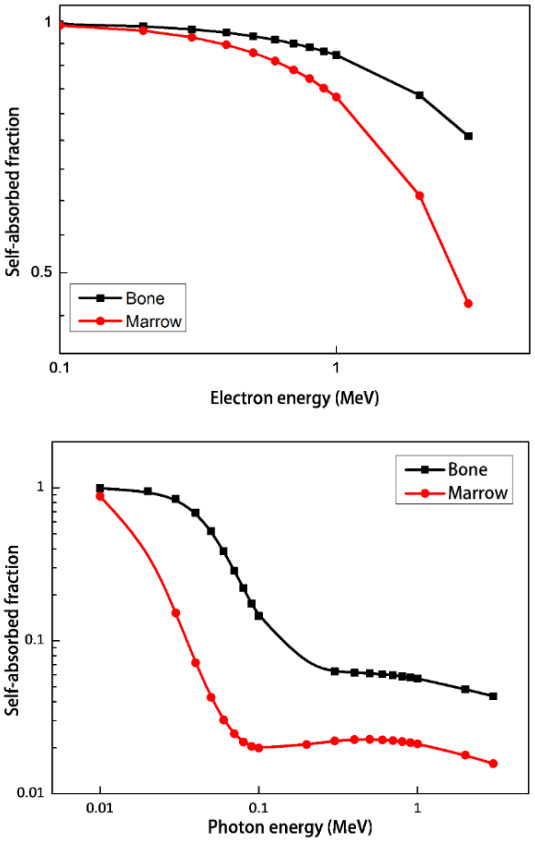

Fig 2. Self-absorbed fractions for electron (above) and photons (below) in the source regions.

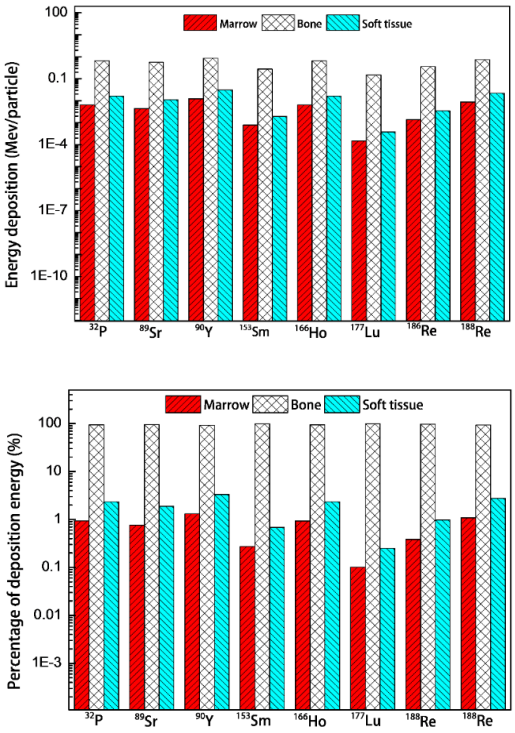

Fig 3. Beta absorbed energy (above) and percentage of the absorbed energy (below) in various tissues for different radionuclides.

As shown in Figure 2, electrons self-absorbed fractions decrease uniformly as energy increases and electrons with energy 0.1 MeV or less absolutely are absorbed in the source regions. Figure 2 shows the photons self-absorbed fractions are highly sensitive at energy range of 0.01–0.1 MeV and present a steep decrement with a minimum in 0.1 MeV and then slightly increase and then turn to decrease. This behavior shows, in this energy range, the steep variation in photons absorbed fractions can be attributed to an increase in photon escaping probability from the source region due to an increase in energy. It is evident from figure for a same energy, the bone with bigger volume and density gives the larger self-absorbed in comparison with the marrow as a region with smaller volume and density. As could be expected, the results confirm the self-absorbed fractions are proportional to the volume and to the density of the source organ.

It is seen in Figure 3a the energy deposition in target organ with bigger volume is more than that with smaller volume. According to results shown in Figure 3b, most of β-particles energy is deposited in the source volume and on average, 95.6% of these particle energy is deposited within the bone. Figure 4a shows the most of γ-rays energy is deposited outside the source. For gamma radiation of these radionuclides, only an average of 0.6% of gamma energy is deposited in the bone volume and about an average of 34% of these particle energy is deposited within the marrow. The results show most of the energy deposited within vertebrae phantom is from β-particles.

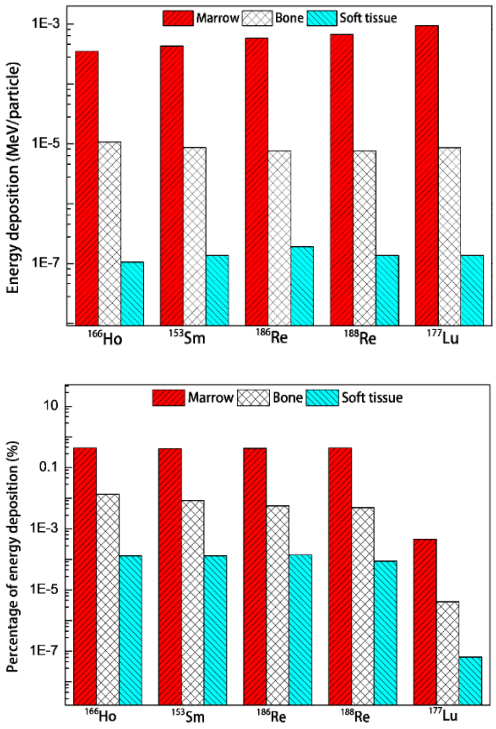

Fig 4. Gamma absorbed energy (above) and percentage of the absorbed energy (below) in various tissues for different radionuclides.

The absorbed dose of different tissues is calculated for uniformly distribution of radionuclide in the bone volume as the sources. As Figure 5 indicates dose in the bone volume, source region, has higher uptake than other tissues. ^{90}Y, ^{32}P and ^{89}sr deliver the higher dose to the bone in comparison with other radionuclides but they also cause bone marrow to receive a higher dose indicating a higher marrow toxicity. ^{177}Lu and ^{153}Sm deliver the lower dose to the marrow indicating a lower marrow toxicity. These simulated results are in good agreement with clinical trials demonstrating both ^{177}Lu and ^{153}Sm are suitable β-emitting radionuclides for bone pain palliation therapy [35-37]. Other factors such as physical half-life affect the advantage and side effect of one radionuclide compared to another. The physical half-life affects the duration of pain relief and determines the total amount of injected activity [38]. According to the type of radiation, radionuclides can be divided into two groups, the first consists pure β-emitters namely ^{90}Y, ^{32}P and ^{89}Sr and the second includes ^{153}Sm, ^{166}Ho, ^{177}Lu, ^{188}Re and ^{186}Re.

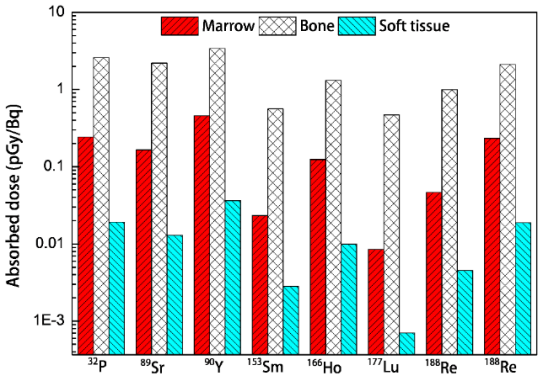

Fig 5. Absorbed doses in different tissues.

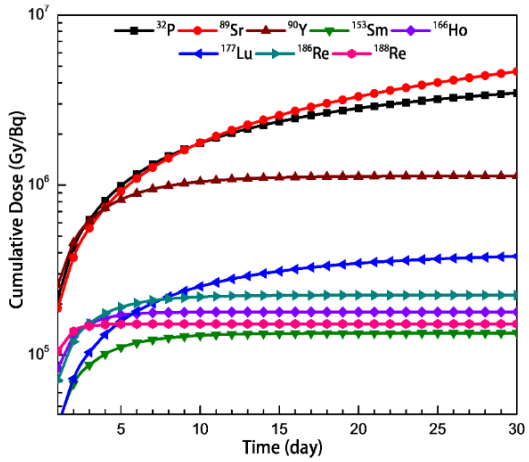

Fig 6. Delivered dose to the bone versus time for all radionuclides.

As seen in Figure 6, the first group shows higher cumulative dose than the second group at all times. It can see, in both groups, for short times, high-energy and short half-life radionuclides show faster dose delivery while for a longer time absorbed dose versus time shows higher dose delivery for the long half-life radionuclides. These results are in good agreement with clinical observations which show a typical response time within 2-3 weeks after injection of $^{89}SrCl_2$ and 2 weeks in case of ^{177}Lu- EDTMP [15] while ^{177}Lu- EDTMP response time is shorter than that of other radionuclides in later group [7]. Faster dose delivery for ^{90}Y and ^{188}Re indicate these irradiating agent may be more effective in the killing of metastatic cells than the other, but in the other hand this may decrease the therapeutic ratio or the ratio between killed malignant cell and normal cell repair. For delivery of 90% of the total dose of radiation requires approximately 3.5 half-lives of decay. The longer time period required to deliver therapeutic level dose may be a disadvantage for patients who have a short life-expectancy [13, 14, 21]. The total amount of injected activity is inversely proportional to the half-life and the energy of irradiating agent. A short physical half-life or a low energy radionuclide requires a larger amount of injected activity. The administered activity for injection of ^{89}Sr and ^{90}Y is very low because ^{89}Sr has longer half-life and ^{90}Y is a high energy β-emitter whereas the administered activity for injection of ^{177}Lu and ^{188}Re is high because ^{188}Re has shorter half-life and ^{177}Lu is a low energy β-emitter [6, 35, 39, 40].

CONCLUSION

In this study, we simulated a mathematical thoracic vertebra phantom and calculated dose parameters for six radionuclides that are employed in clinical used or under research for palliative of bone metastasis by using the Monte Carlo code MCNPX. High energy β-emitters, such as ^{90}Y, ^{89}Sr and ^{188}Re due their long penetration range are useful for treatment of bulky tumors. The results show using high energy radionuclides increase the deliver dose to the lesion with increase in absorbed dose of the surrounding tissues specially in critical organ; the bone marrow. On the other hand, low energy β-emitters such as ^{177}Lu ,^{153}Sm and ^{186}Re are alternatives for treatment of small tumors. The results show low energy β-emitters ^{177}Lu, ^{153}Sm and ^{186}Re can be used for bone pain palliation in the vertebra to improve therapeutic effects different combination of these radionuclides can be used in patients with tumors of various sizes.

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