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Dosimetric evaluation of ^{153}Sm-EDTMP, ^{177}Lu-EDTMP and ^{166}Ho-EDTMP for systemic radiation therapy: Influence of type and energy of radiation and half-life of radionuclides

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HIGHLIGHTS

- The radial dose and cumulative dose of ^{153}Sm, ^{177}Lu and ^{166}Ho are calculated.
- The effect of half-life of the radionuclide on the suitable activity for injection is studied.
- Dose delivery is fast for the short half-life radionuclides (^{153}Sm and ^{166}Ho).
- The results are in good accordance with clinical observations.
- The combination of different radionuclides with different characteristics could be more advantageous.

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ABSTRACT

In radiopharmaceutical therapy, delivered doses to critical organs must be below a certain threshold therefore internal radiation dosimetry of radiopharmaceuticals is essential. Advantages and disadvantages of radionuclides with different characteristics were evaluated for selection of appropriate radionuclide. The Monte Carlo MCNPX simulation program was used to obtain radial dose and cumulative dose of ^{153}Sm, ^{177}Lu and ^{166}Ho used in radiotherapy of bone metastases. A cylindrical geometry with constant density materials was supposed for simulation of femur bone. The radius of bone marrow, bone, and surrounding soft tissue was considered 0.6 cm, 1.3 cm and 4 cm, respectively. It was assumed that the radionuclides were uniformly distributed throughout the tumor. "continuous energy spectrum" of beta particle was used instead of mean beta energy. Our simulations show that absorbed dose in target organ (bone) is greater than other organs and ^{166}Ho gives a higher dose to the critical organ of bone marrow than either ^{153}Sm or ^{177}Lu. Absorbed dose versus time demonstrate faster dose delivery for the short half-life radionuclides (^{153}Sm and ^{166}Ho). These results are in good agreement with clinical observations which show a pain relief within 1 week after intravenous administration of ^{153}Sm-EDTMP, whereas it occurs within 2 week in the case of ^{177}Lu-EDTMP. According to the results, combination of different radionuclides with different characteristics such as ^{153}Sm-EDTMP and ^{177}Lu-EDTMP could be more advantageous to patients with painful bone metastasis.

1. Introduction

Metastasis is a complex event leading to the formation of new tumoral sites arising from a primary tumor (Lipton, 2010; Fizazi et al., 2009). It is responsible for more than 90% of fatality as documented in patients with solid tumors (Roodman, 2004). Metastasis is largely implicated in cancer aggressiveness and is a very common and often painful problem experienced by many cancer patients. In advanced stages, these are frequently associated with adverse clinical effects including pain, fractures, and hypercalcemia causing significant morbidity and affect functional status and quality of life (Pandit-Taskar et al., 2014).

A number of metastasis therapeutic modalities are available, including bisphosphonates, chemotherapy and external beam

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radiotherapy. Due to several limitations of previous therapies, radiopharmaceutical therapy has an important role in palliation of pain from bone metastases (Ayati et al., 2013). The goal of radiopharmaceutical therapy is to deliver a sufficiently large dose to the target organ while minimizing dose to the surrounding healthy tissue (Ranjbar et al., 2014). This kind of therapy have many benefit including the ability to treat multiple sites of metastases involvement simultaneously, lack of significant conflict with other treatments and ease of administration and the potential to be used repetitively.

Ethylenediamine tetra methylene phosphonic acid (EDTMP) is one of the most widely used ligands which forms stable complexes with various radiometals (Laznicek et al., 1994) such as samarium-153 (^{153}Sm) (Beiki et al., 2013; Correa-González et al., 2014), Lutetium-177 (^{177}Lu) (Shinto et al., 2014; Yuan et al., 2013) and Holmium-166 (^{166}Ho) (Rajendran et al., 2002) that these complexes have been tested and employed for human studies.

^{153}Sm emits beta particles with maximum energy of 0.81 MeV, mean energy of 0.23 MeV, maximum soft tissue range of 3.4 mm, average range of 0.6 mm and 28% abundant gamma emissions with a photopeak of 103 keV. It has a physical half-life of 1.9 days or 46.3 h (Aktolun and Goldsmith, 2013).

^{177}Lu decays with emissions of both gamma and beta particles. The maximum beta particle energy is 0.497 MeV (mean of 0.133 MeV) with maximum soft tissue range of approximately 1.5 mm. The gamma photon has 11% abundance with a photopeak of 208 keV. It has a physical half-life of 6.71 days (Aktolun and Goldsmith, 2013).

^{166}Ho emits beta particles with maximum energy of 1.85 MeV, mean energy of 0.65 MeV, maximum soft tissue range of 8.5 mm and average range of 2 mm. It also emits a 6.5% abundant gamma photon of 80.5 keV that can be used for imaging and dosimetry. Its physical half-life is 26.8 h (Aktolun and Goldsmith, 2013).

In radiopharmaceutical therapy, delivered doses to critical organs must be below a certain threshold therefore internal radiation dosimetry of radiopharmaceuticals is essential. The bone marrow is a main critical organ for metastatic bone pain palliation therapy (Lewington, 2005). Therefore, it is an important tissue in absorbed dose calculations. The dependence of the absorbed dose in the tumor and critical organs on the properties of the radiopharmaceutical (physical and biological) demonstrates the importance of the calculation of absorbed dose by using the Monte Carlo simulation. The Monte Carlo simulation of the radiation transport in an appropriate phantom is the most accurate method for dose computation in radiotherapy (Mostaar et al., 2003; Stabin and Flux, 2007).

The aim of this study was to obtain radial dose and cumulative dose of ^{153}Sm, ^{177}Lu and ^{166}Ho used in radiotherapy of bone metastases. Advantages and disadvantages of radionuclides with different radiation energy and half-life were evaluated for selection of appropriate radionuclide. The radial dose distribution of target and critical organs (bone marrow, bone and soft tissue) due to beta-gamma emitters were calculated with the MCNPX code for all three radionuclides. Also the effect of half-life of the radionuclide on the suitable activity for injection was studied. In this work continuous energy spectrum of beta particle was used instead of mean energy.

2. Materials and methods

The three radionuclides normally used in bone metastases therapy were chose to investigate of dose distribution with MCNPX code. MCNPX (Hughes et al., 2002) is a general purpose Monte Carlo code which permits the description of the transport of different particles in arbitrary materials. Photons, electrons and neutrons, as well as other 29 particles can be considered. The upper energy limits for electrons and photons are 1 and 100 GeV, respectively. A lower limit of 1 keV is fixed for these particles.

2.1. Geometry

The cylindrical geometry is a good approximation of femur bone, one of the most common sites of secondary lesions (Coleman, 2006). A cylindrical geometry with constant density materials was supposed for simulation of femur structure. The minimum and maximum radii of the cylindrical bone were 0.6 cm, 1.3 cm and 4 cm for bone marrow, bone, and surrounding soft tissue, respectively, and a length of 5 cm was assumed along the z axis (Giladi et al., 1987).

2.2. Source specifications

MCNP requires the source for a particular problem to be specified in a user-defined input file. The source includes type of particle, position, energy, and direction of starting particles. It was assumed that the radionuclides were uniformly distributed throughout the tumor. The radionuclides used in this work are beta-gamma emitters. Beta particles are high energy electrons that are emitted from an unstable nucleus. Beta particles are not monoenergetic, and have a broad energy spectrum from zero to the maximum energy so in this work “continuous energy spectrum” of beta particle was used instead of mean beta energy (Fig. 1).

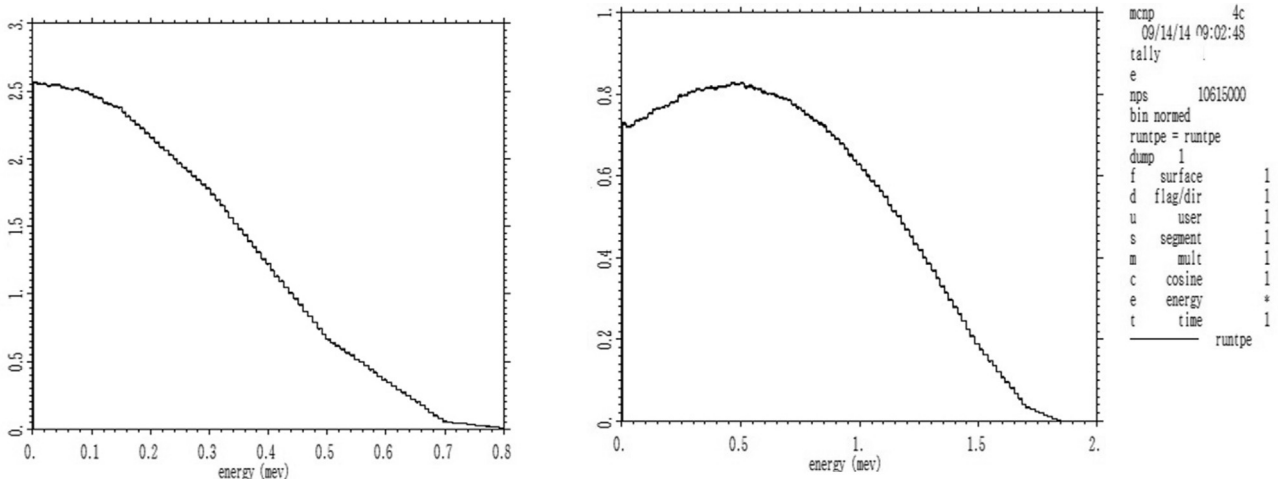

Fig. 1. Energy spectrum of electrons in beta decay of ^{153}Sm (left) and ^{166}Ho (right).

2.3. Materials and tallies

To simulate the dose rate distribution, the volume of the phantom was subdivided into cylindrical layers. Both the F6 and *F8 tallies can be used for calculation of absorbed dose by MCNP method, but since F6 tallies is not defined for electrons and since ^{153}Sm, ^{177}Lu and ^{166}Ho emit beta particles, in this study *F8 was used to calculate absorbed dose in the cylindrical layers. The bone marrow density was assumed to be 1.03 g cm^{-3}, and the bone tissue was simulated with a density of 1.92 g cm^{-3}. The material composition of the bone marrow, bone and soft tissue was taken from the International Commission on Radiation Units and Measurements (ICRU, 1989). For decrease of statistical error (below 4%) about 4–5 $\times$ 10^7 particles were simulated.

3. Results and discussion

Systemic administration of beta-emitting radiopharmaceuticals for pain palliation in advanced metastatic bone disease is an effective and established therapy. Bone is a composite material of inorganic crystals bound to protein. The mineral phase, built of crystals containing mainly calcium and phosphate, is called hydroxyapatite (Wong and Piert, 2013). Bone-seeking radiopharmaceuticals accumulate in the skeletal tissue as it undergoes adsorption on the surface of the newly formed hydroxyapatite crystals (Orsini et al., 2013).

Because biologic responses to radiation are complicated processes that depend on both total dose and dose rate, investigation of both dose and dose rate is necessary. Radial dose distribution and absorbed dose per one radionuclide disintegration for uniform cylindrical activity distribution are shown for X-ray and gamma emissions of ^{153}Sm, ^{177}Lu and ^{166}Ho (Fig. 2).

Despite higher energy of gamma rays of the ^{177}Lu-EDTMP, the absorbed dose related to photon emissions of ^{153}Sm-EDTMP is more than other radionuclides in the three tissues (bone marrow, bone, soft tissue) because the photoelectric interactions are most probable for low photon energy as well as gamma-ray branching ratio of ^{153}Sm-EDTMP is higher than the branching ratios of other radionuclides.

Fig. 3 shows the dose distribution and absorbed dose per disintegration in the femur phantom for beta particles of studied radiopharmaceuticals.

This figure demonstrates that beta absorbed dose in source location (bone) is greater than other tissues as it was expected. Regarding the absorbed doses that are obtained in this study, under the same conditions, ^{166}Ho-EDTMP gives a higher dose to the critical organ of bone marrow than either ^{153}Sm or ^{177}Lu.

The comparison between Figs. 3 and 2 indicates that deposited energy due to beta particles is much larger than the energy which gamma emissions deposit in the bone marrow, bone and soft tissue. Beta particles have the greater proportion in absorbed dose of the tissues in comparison with gamma radiations. The reason for this is that absorbed fractions from beta particles distributed uniformly in the bone are greater than absorbed fractions from photon radiations.

In addition to the delivered dose, other factors exist that may influence the biologic response to irradiation such as the dose rate. Therefore the delivered dose to the tissue as a function of time is evaluated. To make a better analogy, in Figs. 4 and 5 we illustrate the dose delivered to the bone and to the bone marrow as a function of time for each of the radiopharmaceuticals investigated.

Absorbed dose to the bone is almost similar for the three radionuclides Fig. 5. Unlike the previous situation, dose delivered to the bone marrow is different for the three radionuclides Fig. 4.

It can also be seen that at short times, ^{153}Sm-EDTMP and ^{166}Ho-EDTMP deliver a higher dose to the bone than ^{177}Lu-EDTMP, while for longer times the converse is true.

In other words, absorbed dose versus time shows faster dose delivery for the short half-life radionuclides (^{153}Sm and ^{166}Ho). Dose rates varied, suggesting a longer response duration for ^{177}Lu than for the other radionuclides.

These results are in good agreement with clinical observations, which show a pain relief within 1 week after intravenous administration of ^{153}Sm-EDTMP (Fischer and Kampen, 2012), whereas it occurs within 2 weeks in the case of ^{177}Lu-EDTMP (Alavi, 2010).

Different injected activities would lead to different absorbed doses. Therefore, to make an excellent comparison, the required injected activity for each of the radionuclides are also investigated by considering of the threshold doses of bone marrow which is used in bone pain palliation therapy by ^{153}Sm-EDTMP: 57 mGy/mCi (Guidelines, 2003).

Under the same conditions, for each specified dose in bone marrow, the required activity A increases in the following order:

$$A_{\text{required}}\left(^{153}\text{Sm}\right) > A_{\text{required}}\left(^{177}\text{Lu}\right) > A_{\text{required}}(^{166}\text{Ho})$$

The required activity and the half-life of radionuclides are directly proportional to each other ($A \propto T_{1/2}$), whereas the needed activity and particles energy of each radionuclide are inversely related ($A \propto (1/E)$).

The required activity for injection of ^{166}Ho was very low because ^{166}Ho has the higher beta particles energy than ^{153}Sm and ^{177}Lu.

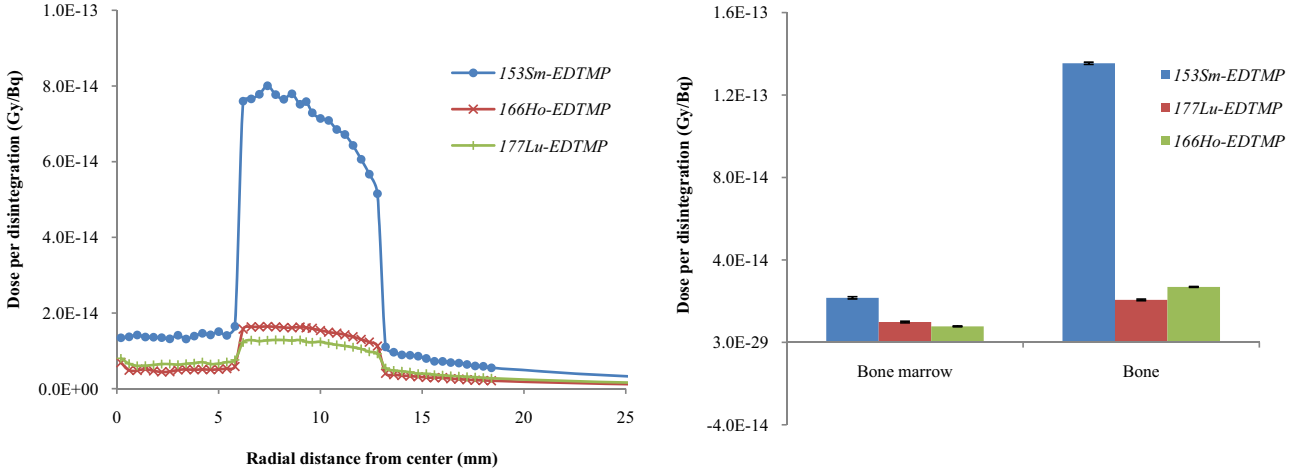

Fig. 2. Radial dose distribution (left) and absorbed dose (right) for X-ray and gamma emissions.

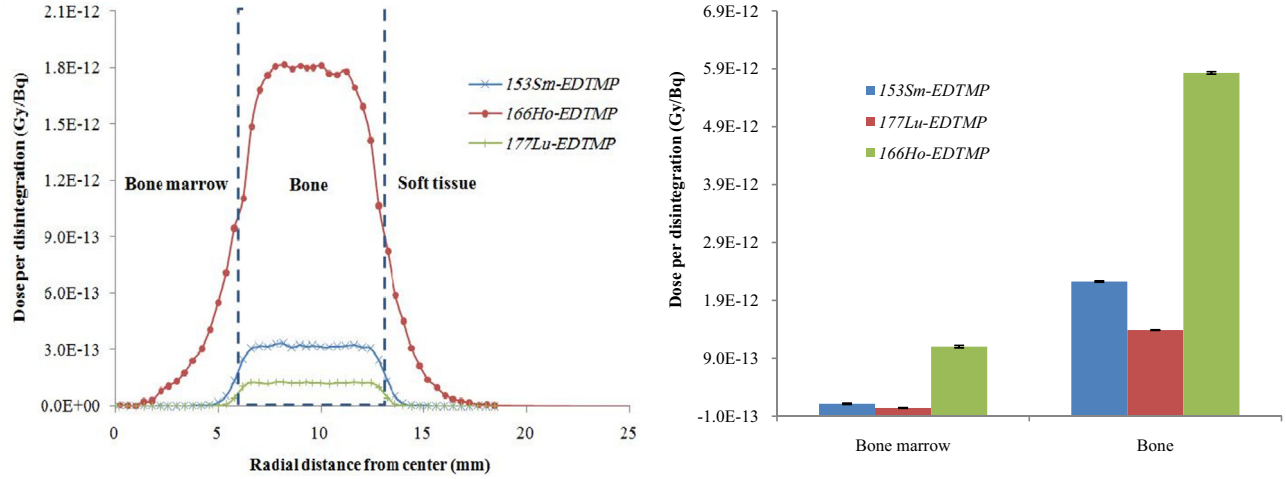

Fig. 3. Radial dose distribution (left) and absorbed dose (right) for beta particles.

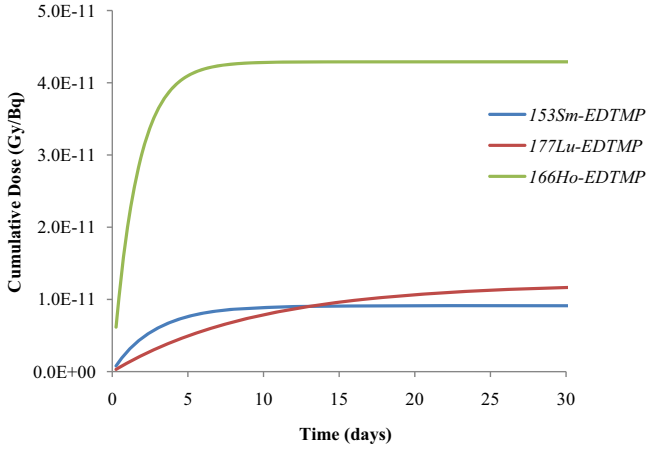

Fig. 4. Absorbed dose to the bone marrow versus time for ^{153}Sm-EDTMP, ^{177}Lu-EDTMP and ^{166}Ho-EDTMP.

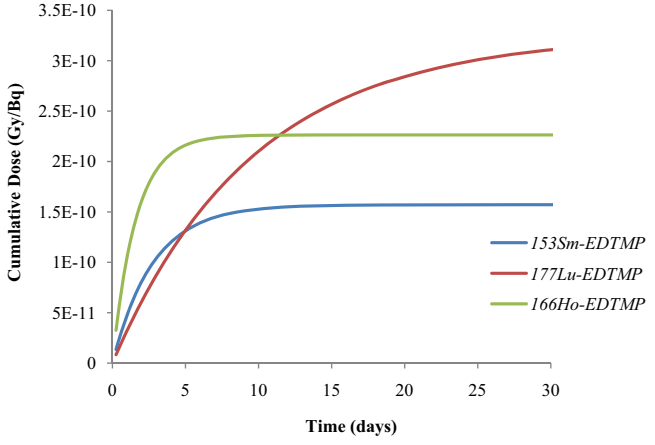

Fig. 5. Absorbed dose to the bone versus time for ^{153}Sm-EDTMP, ^{177}Lu-EDTMP and ^{166}Ho-EDTMP.

Although ^{153}Sm has the higher beta particles energy than ^{177}Lu, but the activity for injection is higher for ^{153}Sm than ^{177}Lu. The reason this is so, is the longer half-life of ^{177}Lu than ^{153}Sm.

4. Conclusions

Radiopharmaceutical therapy is an effective method for pain palliation in metastatic bone disease. Dosimetry of internal emitters has been one of the important topics to be studied in clinical nuclear medicine. Dosimetry also plays an important role in radiopharmaceutical therapy where estimates of activity necessary to produce tumor doses must be weighed against the risk to healthy tissue.

This study examined the influence of type and energy of radiation and half-life of radionuclides such as ^{153}Sm, ^{177}Lu and ^{166}Ho used in radiopharmaceutical therapy of bone metastases. For comparing the benefit and damage in using these radionuclides, dosimetry simulations were performed for all three radionuclides.

The results show that high-energy beta emitters have a long-range that allows for the deposition of high radiation doses in large targets. Low energy beta emitters have a short-range that allows concentration of most of their dose in small targets. Because of complementary characteristics of these radionuclides, we believe that the combination of different radionuclides with different characteristics (radiation energies and half-life) such as ^{153}Sm and ^{177}Lu could be more advantageous to patients with tumoral lesions of different sizes.

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