Dosimetry in Radiosynoviorthesis

DOSIMETRY IN RADIOSYNOVIORTHESIS: ^{90}Y VS. ^{153}SM

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Abstract—**Although there are several radionuclides suitable for radiosynoviorthesis (RSO), not all of them can irradiate deeper synovium. Yttrium-90 (^{90}Y) is the beta radionuclide with more penetration range; therefore, it is predominantly used to treat knees. The aim of this paper is to highlight several dosimetry concepts to compare ^{90}Y and ^{153}Sm, also discussing the feasibility of implementing a dose planning methodology for both in RSO. The MCNPX Monte Carlo nuclear code version 2.6 was used for calculating S-values from which the activity to be injected into the joint was obtained. This activity is considered sufficient to deliver a 100-Gy absorbed dose in 1 mm of synovial tissue. The simulated mathematical model consisted of a system formed by several cylindrical slabs of 1-mm thickness, aligned consecutively. The different areas of the cylinder base simulate several synovial membrane sizes. The effective treatment range for each radionuclide was also calculated. Quantification of the synovial joint features (synovial thickness and synovial surface) by diagnostic imaging, such as magnetic resonance (MRI) combined with a Monte Carlo simulation, can be used to achieve a treatment planning strategy in RSO with the available radionuclides. Health Phys. 114(1):1–6; 2018**

Key words: radiosynoviorthesis; beta particles; Monte Carlo; dosimetry, absorbed dose; beta particles; dose, absorbed; dosimetry, beta; Monte Carlo

INTRODUCTION

ALTHOUGH THERAPEUTIC nuclear medicine (TNM) is frequently associated with oncological disease treatment (cancer treatment), its field also covers the treatment of non-oncological disease. Radiosynoviorthesis (RSO) or radioactive synovectomy is a TNM procedure developed as an alternative to surgical and chemical synovectomy. RSO is the destruction of the inflamed synovial membrane or pannus tissue by the use of radionuclides (RN) (Kampen et al. 2002). It could be applied for treatment of different inflammatory diseases of joints such as rheumatoid arthritis (RA), osteoarthritis, and in hemophilia patients when prophylaxis with coagulation factors (CF), allied to physiotherapy, fail to control synovitis (Thomas et al. 2011).

The main benefits from RSO in Hemopilic Arthropathy (HA) are the reduction of joint bleeds, pain relief, and mobility improvement in treated joints, consequently improving the quality of life of the patients (Rodriguez-Merchan et al. 2014).

There are several RN beta emitters commonly used in RSO (Deutsh et al. 1993; Van der Zant, 2008). The maximum beta radiation energy ranges from 0.34 MeV (^{169}Er) for minor joints (hands and feet) to 2.28 MeV (^{90}Y) for large joints (knee). The RN physical half-life used for RSO ranges from 17.1 h (^{188}Re) to 342.25 h (^{32}P).

Yttrium-90 (^{90}Y), in the forms of citrate or silicate colloids, is the most used radiopharmaceutical (RP) for RSO (Thomas et al., 2013a; Van der Zant, 2008; Kampen et al. 2002). More recently, hydroxyapatite has been used as a carrier to ^{90}Y and ^{153}Sm in HA patients (Calegaro et al. 2014). In RSO, an average of 185 MBq of ^{90}Y is considered adequate to deliver an absorbed dose of 100 Gy per 100 g of synovium, usually found on adult knees. This calculation, performed in the 1990s, considered the area of knee joints from adult patients with RA (Jonhson and Yanch 1991).

Among other factors, the RSO success depends on a therapeutic dose effectively delivered to the target tissue, the inflamed synovium, and it is a function of the area and thickness of the synovium. Good results also depend on the minimization of radiation exposure of non-target structures, such as articular cartilage and sub-chondral bones, besides extra-articular tissues and organs.

The aim of this paper is to highlight several dosimetry concepts to compare the use of ^{90}Y to ^{153}Sm, discussing the feasibility of implementing a dose planning methodology for both RN in RSO.

MATERIALS AND METHODS

Since the goal of RSO is to produce the pannus ablation, the physical characteristics of the available RN (physical

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The authors declare no conflicts of interest.

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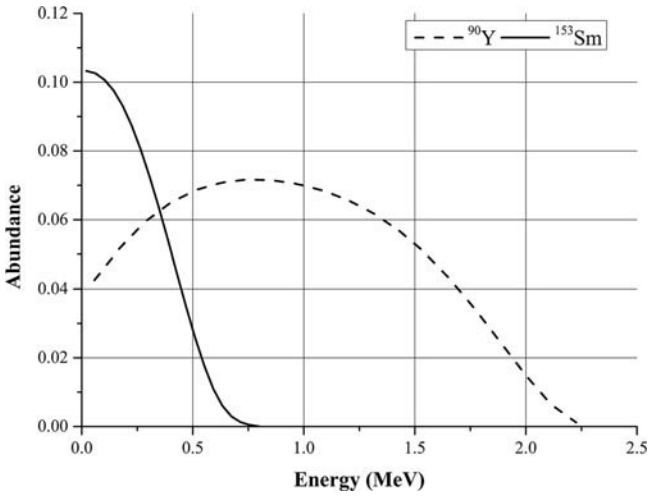

Fig. 1. Beta spectra of ^{90}Y and ^{153}Sm.

half-life, energy, and type of particle) should be the first items to consider in treatment planning. Fig. 1 depicts the beta spectra of ^{90}Y and ^{153}Sm. The physical and nuclear characteristics of ^{90}Y and ^{153}Sm are shown in Table 1.

Monte Carlo simulation

MCNPX version 2.6 was used for calculating S-values. The modeling with this code followed these steps: modes, geometric specification, source configuration, material specification, tally choice, and number of histories to run (Briesmeister 1997). Each assessed radionuclide (^{90}Y and ^{153}Sm) was simulated according to decay data from Brookhaven National Laboratory database (Stabin et al. 2001). The average deposited energy calculated through the available command code in MCNP (tally)*f8 (Briesmeister 1997) was independently scored to calculate the S-values considering contributions from photons and electrons.

The mathematical model considered (Fig. 2) consisted of a 5.1 mm height cylinder divided into six cylindrical slices, the first one with 0.1 mm, representing the synovial surface, and the other slices with 1-mm height mimicking the synovial thickness (ranging from 1 to 5 mm). The different areas of the cylinder base simulate several synovial membrane sizes, from 10 to 500 cm^2 (radius ranging from 1.8 to 12.6 cm). The uniform particle position sampling in the first slice of the model (0.1 mm) defined the source configuration, assuming a homogeneous radiopharmaceutical distribution in the synovial surface according to different sizes of the simulated mathematical model.

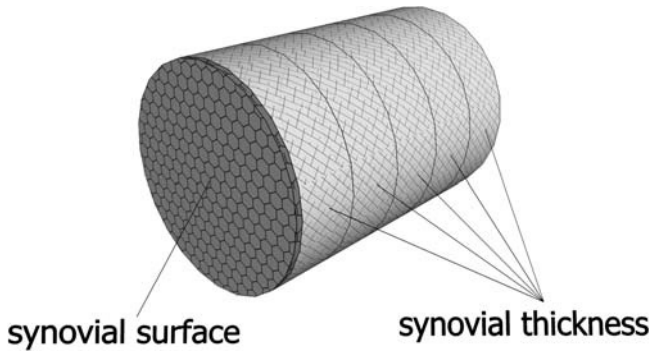

Fig. 2. Representation of the simulated geometry with the Monte Carlo code MCNP 2.6e.

Calculations of the effective treatment range (ST_{90}) in the synovial membrane were determined using the same mathematical model described before but considering a synovial surface of 250 cm^2. The compositions and density (ρ) of synovium were modeled according to Johnson and Yanch (1991). S-value was calculated complying with the Medical Internal Radiation Dose (MIRD) (Snyder et al. 1975).

The average energy per disintegration deposited in tissue volume was calculated through the available command code in MCNP (tally)*f8 (Briesmeister 1997). The activity to be injected (IA) (without considering leakage from the joint cavity) to deliver an average absorbed dose of 100 Gy at the determined ST was determined by eqn (1):

$$\mathrm{IA} = 69.44\ \mathrm{S}^{-1}\left(\mathrm{T}_{1/2}\right)^{-1}. \qquad (1)$$

If possible, readjustment of dose estimates should be done by determining the residence time. In this case, the biodistribution study should cover a period over three times the physical half-life of the injected RN (Cremonesi et al. 2006). Five hundred thousand (500,000) histories were simulated to produce an error below 5%.

RESULTS

The ST_{90} calculated values for ^{90}Y and ^{153}Sm are shown in Table 2.

Fig. 3 shows the electron tracks depicted with Vised code (Visual Editor for Creating MCNPX input file) for ^{90}Y (A), ^{153}Sm (B), and for ^{90}Y + ^{153}Sm cocktail (C). In the figures, the arrows denote the starting of the electron tracks

Table 1. Physical characteristics such as half-life ($T_{1/2}$), decay data, energy of beta and gamma emission, and composition of RP containing ^{90}Y and ^{153}Sm.

RN	$T_{1/2}$ (h)	Decay data	Maximum/mean beta energy (MeV)	Gamma emission energy MeV (%)	RP	Joint
^{90}Y	64.1	Beta	2.28/0.93	None	Citrate, Silicate, Hydroxyapatite	Medium, Large
^{153}Sm	46.5	Beta, electron, gamma	0.80/0.23	0.10 (28)	Hydroxyapatite	Medium

Table 2. ST_{90} for RN ^{90}Y and ^{153}Sm.

RN	X_{90} (mm)
^{90}Y	2.93
^{153}Sm	1.01

from the source (0.01 cm thickness) to ST range from 1 to 5 mm in a 250 cm^2 SS.

Fig. 4 shows the ratio between deposited energy (E_{dep}) for ^{90}Y (a) and ^{153}Sm (b) in ST range from 1 to 5 mm.

Fig. 5 shows the activity to be injected (IA) values to deliver 100 Gy at 1 mm of ST as a function of SS (cm^2) for ^{90}Y and ^{153}Sm. These values were obtained without considering extraarticular leakage from joint cavity.

DISCUSSION

Although there are several RN suitable for RSO, not all of them can irradiate the deeper synovium. Yttrium-90 (^{90}Y) is the beta RN with more penetration range, which is the reason why it is predominantly used to treat knees. However, Hydroxyapatite − ^{153}Sm (HA − ^{153}Sm) and Hydroxyapatite [−^{90}Y (HA-^{90}Y)] exhibit different prices, with HA-^{90}Y being 10 times more expensive than HA-^{153}Sm. Therefore, the controversy regarding the use of HA-^{153}Sm to treat knees might be more related to a financial convenience than to an evidence-based discussion. This circumstance makes dose planning a necessity.

According to the results, the ST_{90} values do not exceed 3 mm in depth. Therefore, for the treatment of thick synovium (>2 mm), ^{90}Y or other radionuclides with ST_{90} as high as 2 mm, such as ^{32}P and ^{188}Re (Torres et al. 2009), are recommended.

In 2014, some authors reported good results using ^{153}Sm (Calegaro et al. 2014). They applied 740 MBq of hydroxyapatite ^{153}Sm to 20 knees of patients with HA and 185 MBq of the same RP to another 20 knees, with better results being achieved with higher activities. They do not explain the rationale on which the two doses were based. Previously, in 1999, Clunie et al. (1999), in a randomized controlled trial with rheumatoid arthritis (RA) knees, showed inferior results for ^{153}Sm with 555 MBq of injected activity when compared to triamcinolone alone. Dos Santos et al. (2009), on a similar controlled trial with RA knees, showed that 555 mBq of ^{153}Sm was also inferior to triamcinolone. Thomas et al. (2013b) showed the results of RSO in 697 joints from 400 hemophilic patients, using either HA-^{153}Sm, HA-^{90}Y, or ^{90}Y citrate, with better results in those patients treated with ^{90}Y- citrate. The odds ratio of ^{90}Y-citrate vs. HA-^{153}Sm was 9.4 in knees, although it was not significant in elbows and ankles.

As depicted in Figs. 2 and 4, a synovial thickness with more than 2 mm cannot be properly irradiated using ^{153}Sm. It is noteworthy that the pannus thickness in patients with HA knees is often superior to 4 mm (Pirich et al. 1999). Therefore, a low penetration RN might not achieve the desired effect of synovial irradiation.

In the present study, using the values plotted in Fig. 5, it would be necessary to administer 481 MBq of HA-^{153}Sm to deliver 100 Gy at 1-mm synovial thickness in knee size of

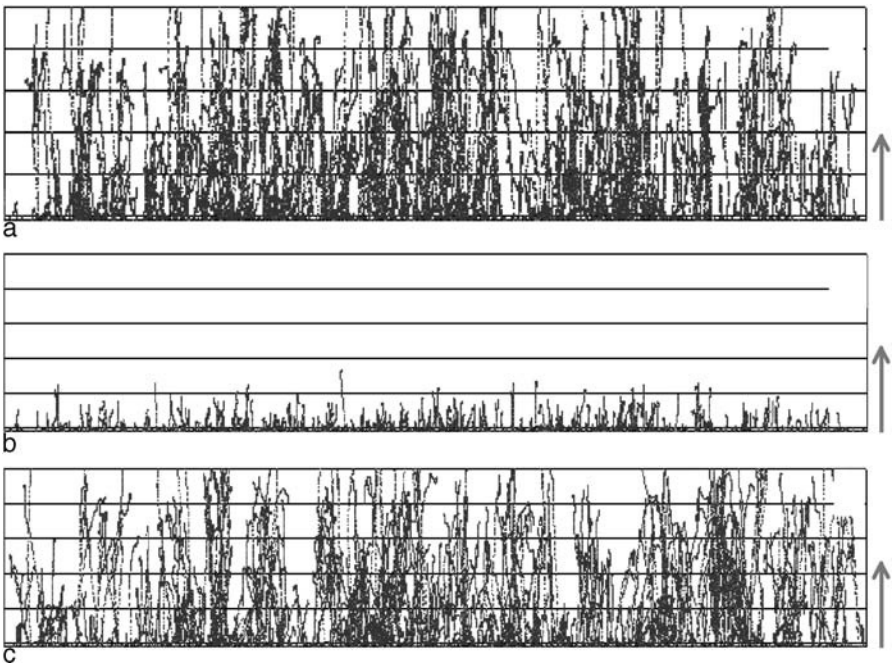

Fig. 3. Electron tracks for ^{90}Y (A), ^{153}Sm (B) and ^{90}Y (20%) + ^{153}Sm (80%) cocktail (C).

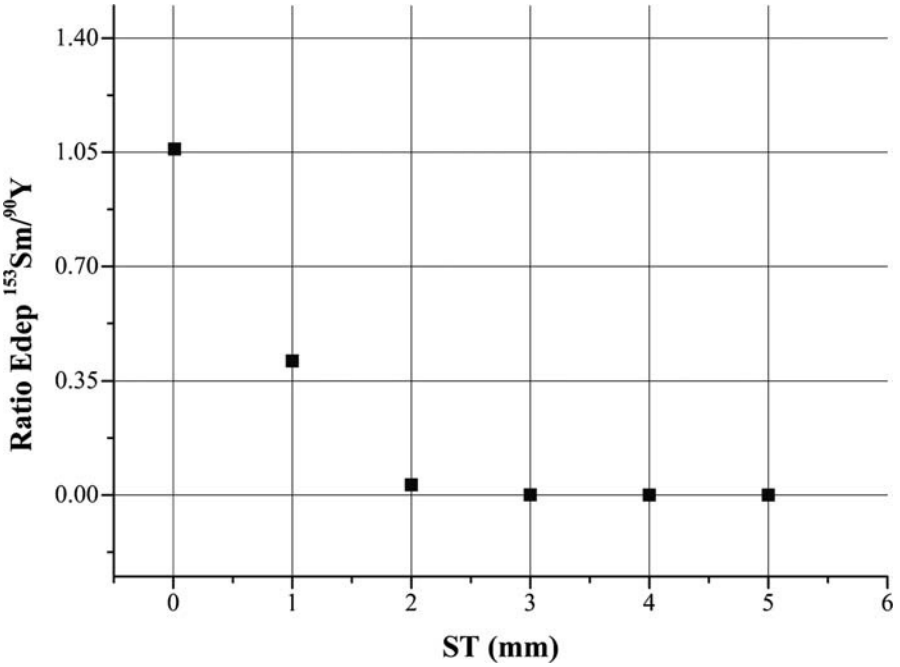

Fig. 4. Ratio between E_{dep} for ^{153}Sm and ^{90}Y in ST ranging from 1 to 5 mm.

250 cm^2. This activity value complies with the data published by previous authors (Dos Santos et al. 2009; Clunie et al. 1999), assuming that there was no RP leakage from the joint.

On the synovial thickness that can be effectively irradiated, the synovium size (SS) is also another important qualitative parameter to be considered in treatment planning. In RSV applied to RA, several authors have considered 250 cm^2 as the mean SS for adult knees (Li et al. 2004; Deutsh et al. 1993; Kampen et al. 2002). Historically, this synovial size is used as a reference to prescribe approximately 185 MBq of ^{90}Y to deliver 100 Gy in the SS of an adult knee. However, in HA the recurrent bleeding cycles can increase the SS in non-adult patients (children and adolescents). In these cases, a higher activity should be administered into the articular joint to avoid underdose to the pannus.

Despite the fact that ^{90}Y is more effective than ^{153}Sm to irradiate synovium more deeply, the absorbed dose delivered to articular cartilage is 10 times greater with ^{90}Y (Torres et al. 2009). Therefore, the maximum value of the activity to be injected should take into consideration the absorbed dose that could produce a deterministic effect on non-target tissues, such as the articular cartilage and bone.

The articular cartilage is the most exposed non-target tissue on RSO, which makes it a matter of concern (Pirich et al. 1999; Kampen et al. 2007). The absorbed dose in cartilage has been calculated by various authors, using mathematical models (Torres et al. 2009; Johnson et al. 1995). Therefore, the volumetric quantification pre- and post-RSO by diagnostic imaging such as magnetic resonance (MR) can be useful to correlate the effect of the dose on the articular cartilage.

Based on future perspectives using RP cocktails such as ^{177}Lu and ^{90}Y in PRRT (PRRT-Peptide Receptor Radiotherapy) (De Jong et al. 2005), the development of ^{90}Y/^{153}Sm cocktail for RSO can be an innovator (Fig. 3).

The limitations of the suggested dose planning are related to the following assumptions considered during dose calculation: full retention of RP injected into the joint cavity (considering no leakage in Monte Carlo simulation), IA uniform distribution in synovial surface, and the use of a simple mathematical model to simulate the joint.

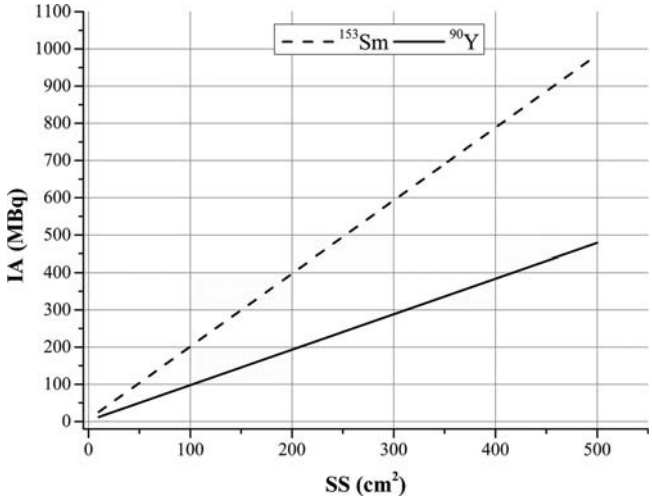

Fig. 5. IA values to deliver 100 Gy at 1 mm ST for ^{90}Y and ^{153}Sm vs. SS (cm^2).

The possible leakage of RP, which may cause significant exposure to radiation in the liver, spleen, and other organs (Kampen et al. 2002), depends on the characteristics of the synovial joint (rupture of the joint cavity, the presence of broken Baker's cyst) and the injected RP. Regarding the RP, the extra-articular leakage is mainly determined by the particle size (Van der Zant, 2008).

Development of RP with particle sizes in the range of 2–5 μm potentiates the extra-articular leakage reduction (Van der Zant, 2008; Clunie et al. 1995; Kampen et al. 2002). However, the immobilization of a treated joint is the safest procedure to prevent the injected RN leakage from the joint cavity (Silva et al. 2012; Turkmen 2009; Kampen et al. 2002).

To calculate IA, it was considered a homogenous distribution of the injected RP in SS. Specifically, RP uptake by synovium depends on the inflammatory activity of synovitis and the characteristics of RP.

Using SPECT (Single Photon Emission Computed Tomography) imaging, several pharmacokinetic studies showed that intra-articular distribution of injected RP in the joint cavity could be focal or diffuse (Van der Zant 2008; Gavin et al. 1995). However, the results did not show significant differences between both RP distributions, but a slight increase of extra-articular leakage was observed with the focal distribution (Van der Sant 2008).

Monte Carlo simulation of anatomical models obtained with real 3D imaging is the most accurate method to calculate the absorbed dose (Sgouros et al. 2008). However, this methodology requires a long computer time, making its implementation hardly feasible to be used in routine clinical practice.

Shortly, the use of Gate Monte Carlo simulation code in dosimetry calculations using the anatomic and functional information obtained through hybrid devices such as SPECT/CT and PET/CT (Sarrut et al. 2014) will probably allow a better dose-effect correlation in RSO.

CONCLUSION

Since the synovial thickness (ST) could determine the probability of therapeutic success of RSO, there is a limitation in patients with thicker synovium. In these cases, it is recommended to use RN with ST_{90} greater than 2 mm. Depending on radiological MRI findings such as SS and ST, the dose planning allows the development of protocols incorporating the use of multiple doses (activity) and RN in less than 6 mo. This methodology not only prevents possible adverse effects in the articular cartilage but also the pannus underdose, which can produce a low treatment response.

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