

Original

Absorbed dose profiles for ^{32}P , ^{90}Y , ^{188}Re , ^{177}Lu , ^{153}Sm and ^{169}Er : radionuclides used in radiosynoviortheses treatmentM. Torres^{a,*}, E. Ayra^a, O. Albuerne^a and M.A. Montano Delgado^b^a Radiation Protection Department, Isotopes Centre, Carretera la Rada, Km 3 1/2 Havana, Cuba^b Hospital General Docente Enrique Cabrera, Havana, Cuba

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The main objective of this paper was to obtain the absorbed dose profiles for radionuclides of frequent or potential use in radiosynoviortheses. These profiles reveal the absorbed dose per activity of injected radionuclide (Gy/h*MBq) in the synovial membrane and the articular cartilage. The researched radionuclides were ^{32}P , ^{90}Y , ^{188}Re , ^{177}Lu , ^{153}Sm and ^{169}Er . The therapeutic range of each radionuclides in synovial tissue were also calculated. This range determines the synovial thickness that can be sufficiently irradiated and thus successfully treated. The S values for the synovial membrane and articular cartilage were calculated using as a model a cylinder with the source uniformly distributed in its volume. The synovial membrane was simulated varying the radius of the cylinder (from 0.5 cm to 9 cm) and its height (from 0.01 cm to 0.04 cm). The area in the base of the cylinder represents different sizes of the synovial surface (small, medium and large joints). The height of the cylinder represents different stages of the progression of the rheumatoid arthritis. The same model was used to simulate the articular cartilage but, the source was uniformly distributed into a cylindrical slab (0.01 cm height and 1 cm of radius). The results obtained allow the estimation of the dose that will be delivered to the synovial membrane and the articular cartilage for different joint sizes and different stages of progression of the rheumatoid arthritis (RA).

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Perfiles de dosis absorbida para ^{32}P , ^{90}Y , ^{188}Re , ^{177}Lu , ^{153}Sm y ^{169}Er : radionuclidos usados en el tratamiento de radiosinoviortesis

R E S U M E N

El principal objetivo de este trabajo fue obtener los perfiles de dosis para los radionúclidos de uso frecuente en radiosinoviortesis. Estos perfiles revelan la dosis absorbida impartida por unidad de actividad del radionúclido inyectado (Gy/h*MBq) en la membrana sinovial y el cartilago articular. Los radionúclidos seleccionados fueron ^{32}P , ^{90}Y , ^{188}Re , ^{177}Lu , ^{153}Sm and ^{169}Er . También fue calculado el rango terapéutico de cada radionúclido en el tejido sinovial. Este rango determina el grosor sinovial que puede ser irradiado suficientemente y por lo tanto, tratado con éxito. Los valores S para la membrana sinovial y el cartilago articular fueron calculados usando como modelo un cilindro con la fuente distribuida uniformemente en su volumen. La membrana sinovial fue simulada variando el radio del cilindro (rango 0.5 cm–9 cm) y su altura (rango 0.01 cm–0.04 cm). La variación del radio del cilindro representa varios tamaños de superficie sinovial (articulaciones pequeñas, medianas y grandes), y se define como el área de la base del cilindro; la variación de la altura, representa diferentes estados de progresión de la artritis reumatoide. El mismo modelo fue empleado para la simulación del cartilago articular, pero la fuente fue uniformemente distribuida dentro de una capa cilíndrica (0.01 cm) y 1 cm de radio. Los resultados obtenidos permiten la estimación de la dosis que será entregada a la membrana sinovial y el cartilago articular para diferentes tamaños de articulación y diferentes estados de progresión de la artritis reumática.

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Palabras claves:

Artritis

Reumatoide

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Método de Monte Carlo

Efectos de la radiación

Introduction

The treatment of inflammatory arthropathies is aimed to diminish the inflammation, relieve the pain, improve the functional capability and induce the remission of the disease. Although every case requires specific therapeutic guidelines¹, some joints may not experience clinical improvement, so other complementary therapies should be used. Most commons are intrarticular corticoids, chemical synovectomy, surgical synovectomy and radiosynoviortheses (RSV). An alternative to surgery is

RSV, which eliminates the inflamed tissue by means of beta radiation. The first published reports of this last treatment are as back as to 1924². In the clinical practice, the first results were published in 1952³ and were followed in the 60s with the inclusion of Y-90^{4,5}.

The RSV is the injection of a radioactive substance inside any synovial cavity, in such way that the injected radionuclide makes contact with the synovial membrane. This substance is rapidly phagocytized by the synovial lining cells. During the radioactive decay of the injected radionuclide, a therapeutic dose will be delivered to the synovial tissue destroying it. The energy of the beta emitters used in radiosynoviortheses range from 0.34 MeV (0.33 mm penetration in tissue) in the case of Er-169 to 2.27 MeV (3.6 mm penetration in tissue) for the Y-90. The half

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life of these isotopes goes from 2.3 hrs (Dy-165) to 27.8 days (Cr-51)⁶. Nowadays, the selection of the radionuclide to be used depends on the size of the joint to be treated. Thus, the smaller the joint, the lower should be the energy and therefore the penetration. These facts led to the use of fixed radionuclides for specific joints. The first works on the assessment of doses to the patients in RSV were published in the 80s and early 90s^{7–10}. As new radiopharmaceuticals offering many potential advantages for RSV are being developed in our centre, it seems prudent to evaluate the dose distribution of some radionuclides that have been used or tested in animal and human models: ³²P, ⁹⁰Y, ¹⁸⁸Re, ¹⁸⁶Re ¹⁷⁷Lu, ¹⁵³Sm and ¹⁶⁹Er.

The method used to assess the dosimetry in RSV is known as the Monte Carlo method. Nevertheless, while it provides an improved technique for calculating local dosimetry, there are still clear difficulties involved in relating this dosimetry to clinical outcome. Although the goal of radiation synovectomy procedure is ablation of the inflamed synovial tissue, very few studies have been performed to determine the dose required to reach this goal. The rationale for choosing a particular administered dose of a given isotope for a given joint is obscure. As with other form of therapy, clinical success in RSV will depend on the thickness of the synovium to be treated and the proximity of the non target organs to the joint (bone and articular cartilage), so it will be based in the absorbed dose and the penetration of the radiation emitted by the radionuclide.

The main objective of this paper was to obtain the absorbed dose profiles for radionuclides of frequent or potential use in radiosynoviortheses. These profiles reveal the absorbed dose per activity of injected radionuclide (Gy/h*MBq) in the synovial membrane and the articular cartilage. The radionuclides involved were those previously mentioned. The therapeutic range of each radionuclides in synovial tissue were also calculated. The therapeutic range is defined as the deepness at which the absorbed dose equals the 10% of the maximum dose deposited in the synovial surface. This range determines the synovial thickness that can be sufficiently irradiated and thus successfully treated.

Materials and methods

The synovial joint is basically the articular cartilage, bone and tissue (synovial membrane). In Table 1 is shown the composition and density of every constituent according to Johnson and Yanch⁸.

The energy of beta particles used in RSV should be enough as to deliver a dose of radiation good for destroying the synovial tissue and yet not as high as to expose unnecessarily the cartilage and bone. In Table 2 are listed the energetic characteristics of the radionuclides assessed in this work.

The MCNP4C Monte Carlo code was used to perform the dosimetry calculations. MCNP is a general-purpose Monte Carlo N-Particle code that can be used for neutron, photon, electron, or coupled neutron/photon/electron transport. MCNP4C is the first major release of MCNP since version 4B¹¹. The beta spectrum of

the radionuclides listed in Table 2 was downloaded from www.doseinfo-radar¹² and the characteristics of the gamma and/or electronic emission are the ones in the software Radiation Decay¹³.

To determine the therapeutic range (X_{90}), an isotropic point source was simulated in the centre of various concentric spheres of different radii. These radii ranged from 1 mm to 10 mm (increasing 1 mm at a time) for all radionuclides but for Er-169. In this case, the radii ranged from 0.1 mm to 1 mm (0.1 mm at a time).

The S values for the synovial membrane and articular cartilage were calculated using as a model a cylinder with the source uniformly distributed in its volume. The synovial membrane was simulated varying the radius of the cylinder (from 0.5 cm to 9 cm) and its height (from 0.01 cm to 0.04 cm). The area in the base of the cylinder represents different sizes of the synovial surface (small, medium and large joints). The synovium area can be estimated through computer tomography (CT)⁷. The height of the cylinder represents different stages of the progression of the rheumatoid arthritis (RA)⁸. The same model was used to simulate the articular cartilage but, the source was uniformly distributed into a cylindrical slab (0.01 cm height and 1 cm of radius). The S value as a function of distance into the diseased synovium and articular cartilage for each of the 6 beta emitting radionuclides mentioned earlier were simulated incorporating very thin cylindrical slabs of tissue and articular cartilage to the original model.

The S (Gy/h*MBq) values have been calculated for different pair of source-target organs and for some radionuclides of interest in Nuclear Medicine¹⁴. In this paper, using Monte Carlo computer calculations, the S values for each proposed model were obtained calculating the mean absorbed energy (E) per disintegration deposited in a target mass (synovial membrane and articular cartilage), divided by the tissue mass (m) and multiplied by 576.7E-03 to obtain the absorbed dose level per cumulated activity in the source region, Gy/h*MBq. The basic equation for this situation is:

$$S = \frac{E}{m} * 576.7 * 10^{-3} \quad (1)$$

where m : tissue mass (g), E : mean absorbed energy (E) per disintegration deposited in a target mass (MeV).

If we consider that the radionuclide decays completely in the joint, so no leakage effect is taken into account, important aspect to keep in mind, the dose absorbed in the synovial membrane is obtained through the Eq. (2).

$$D_t = S \times 1.44 \times T_{1/2\text{fisico}} \times A_0 \quad (2)$$

where S : S-value (Gy/h*MBq), $T_{1/2}$: half life, A_0 : injected activity into the articular cavity.

For all cases, a sufficient number of electron and photon transport histories were generated to produce statistically reliable energy tallies, with relative errors less than 0.10. Also, the Bremsstrahlung radiation was considered in the calculations.

Table 1
Composition and density of components of the synovial joint

Elements	H	C	N	O	Na	Mg	P	S	Ca	Cl	ρ (g/cm ³)
Bone (%)	3.4	15.5	4.2	43.5	0.1	0.2	10.3	0.3	22.5	–	1.92
Articular cartilage (%)	9.6	9.9	2.2	74.4	0.5	–	2.2	0.9	–	0.3	1.1
Tissue (%)	10.0	14.9	3.5	71.6	–	–	–	–	–	–	1.0

Table 2
Energetic characteristic of the assessed radionuclides

Radionuclides	Y-90	P-32	Re-188	Lu-177	Sm-153	Er-169
$T_{1/2}$	64.1 h	14.3 days	16.98 h	6.71 days	46.7 h	9.4 days
Emission type	Beta	Beta	Beta, gamma, electron	Beta, gamma, electron	Beta, gamma, electron	Beta, gamma, electron

Table 3
S-Values (Gy/MBq·h) for different synovium sizes and thickness of synovial lining cells.

A(cm ²)	Thickness of synovial lining cells											
	0.01 cm						0.015 cm					
	⁹⁰ Y	³² P	¹⁸⁸ Re	¹⁷⁷ Lu	¹⁵³ Sm	¹⁶⁹ Er	⁹⁰ Y	³² P	¹⁸⁸ Re	¹⁷⁷ Lu	¹⁵³ Sm	¹⁶⁹ Er
13	0.152	0.154	0.325	0.335	0.294	0.295	0.144	0.146	0.291	0.277	0.243	0.240
20	0.098	0.099	0.208	0.214	0.188	0.189	0.092	0.094	0.186	0.177	0.156	0.154
28	0.068	0.069	0.145	0.149	0.131	0.131	0.064	0.065	0.130	0.123	0.108	0.107
38	0.050	0.051	0.106	0.109	0.096	0.096	0.047	0.048	0.095	0.091	0.080	0.078
50	0.038	0.039	0.081	0.084	0.074	0.074	0.036	0.037	0.073	0.069	0.061	0.060
64	0.030	0.031	0.064	0.066	0.058	0.058	0.029	0.029	0.058	0.055	0.048	0.047
79	0.024	0.025	0.052	0.054	0.047	0.047	0.023	0.024	0.047	0.044	0.039	0.038
95	0.020	0.020	0.043	0.044	0.039	0.039	0.019	0.019	0.039	0.037	0.032	0.032
113	0.017	0.017	0.036	0.037	0.033	0.033	0.016	0.016	0.032	0.031	0.027	0.027
133	0.014	0.015	0.031	0.032	0.028	0.028	0.014	0.014	0.028	0.026	0.023	0.023
154	0.013	0.013	0.027	0.027	0.024	0.024	0.012	0.012	0.024	0.023	0.020	0.020
177	0.011	0.011	0.023	0.024	0.021	0.021	0.010	0.010	0.021	0.020	0.017	0.017
201	0.010	0.010	0.020	0.021	0.018	0.018	0.009	0.009	0.018	0.017	0.015	0.015
227	0.008	0.009	0.018	0.019	0.016	0.016	0.008	0.008	0.016	0.015	0.013	0.013
254	0.008	0.008	0.016	0.017	0.015	0.015	0.007	0.007	0.014	0.014	0.012	0.012
A(cm ²)	0.02 cm						0.025 cm					
	⁹⁰ Y	³² P	¹⁸⁸ Re	¹⁷⁷ Lu	¹⁵³ Sm	¹⁶⁹ Er	⁹⁰ Y	³² P	¹⁸⁸ Re	¹⁷⁷ Lu	¹⁵³ Sm	¹⁶⁹ Er
	⁹⁰ Y	³² P	¹⁸⁸ Re	¹⁷⁷ Lu	¹⁵³ Sm	¹⁶⁹ Er	⁹⁰ Y	³² P	¹⁸⁸ Re	¹⁷⁷ Lu	¹⁵³ Sm	¹⁶⁹ Er
13	0.138	0.140	0.264	0.237	0.211	0.197	0.134	0.136	0.244	0.207	0.189	0.166
20	0.089	0.090	0.170	0.151	0.135	0.126	0.086	0.087	0.156	0.132	0.121	0.106
28	0.062	0.063	0.118	0.105	0.094	0.088	0.060	0.061	0.109	0.092	0.084	0.074
38	0.045	0.046	0.087	0.077	0.069	0.064	0.044	0.045	0.080	0.068	0.062	0.054
50	0.035	0.035	0.066	0.059	0.053	0.049	0.034	0.034	0.061	0.052	0.047	0.042
64	0.028	0.028	0.056	0.047	0.042	0.039	0.027	0.027	0.048	0.041	0.037	0.033
79	0.022	0.023	0.043	0.038	0.034	0.032	0.022	0.022	0.039	0.033	0.030	0.027
95	0.018	0.019	0.035	0.031	0.028	0.026	0.018	0.018	0.032	0.027	0.025	0.022
113	0.016	0.016	0.030	0.026	0.024	0.022	0.015	0.015	0.027	0.023	0.021	0.018
133	0.013	0.013	0.025	0.022	0.020	0.019	0.013	0.013	0.023	0.020	0.018	0.016
154	0.011	0.012	0.022	0.019	0.017	0.016	0.011	0.011	0.020	0.017	0.015	0.014
177	0.010	0.010	0.019	0.017	0.015	0.014	0.010	0.010	0.017	0.015	0.013	0.012
201	0.009	0.009	0.017	0.015	0.013	0.012	0.008	0.009	0.015	0.013	0.012	0.010
227	0.008	0.008	0.015	0.013	0.012	0.011	0.007	0.008	0.014	0.011	0.010	0.009
254	0.007	0.007	0.013	0.012	0.010	0.010	0.007	0.007	0.012	0.010	0.009	0.008

Analysis and discussion of results

Synovial membrane

S-values for synovial membranes with different synovium size are shown in Table 3. As the area of the inflamed synovium increases, diminishes the value of the absorbed dose rate in the synovial membrane. Studies with ⁹⁰Y usually apply an average administered activity of 185 MBq for arthritic knee patients with synovium area of 250 cm². This value of administered activity will deliver approximately 130 Gy in the synovial membrane according to our model (S-value = 0.007). If we wish to obtain the same therapeutic effect in the synovial membrane of an arthritic wrist with 50 cm² of synovium area (S-value = 0.035), it only will be necessary to inject 37 MBq of ⁹⁰Y. In this case it is considered that the radionuclide decays completely in the joint (Eq. 2).

Since electron emission energies and spectral shapes differ between β-active radionuclides, the absorbed dose penetration

Table 4
Therapeutic range (X₉₀) for ⁹⁰Y, ³²P, ¹⁸⁸Re, ¹⁷⁷Lu, ¹⁵³Sm, and ¹⁶⁹Er

X ₉₀ (mm)					
⁹⁰ Y	³² P	¹⁸⁸ Re	¹⁷⁷ Lu	¹⁵³ Sm	¹⁶⁹ Er
2.22	2.1	2.1	1.3	1.6	0.18

range can vary substantially from one radionuclide to another. Essentially, this effective penetration ranges determine the thickness of inflamed synovium that can be treated successfully. One way of evaluating this range is to establish the distance at which the absorbed dose equals the 10% of the dose deposited in the synovial membrane (X₉₀). The X₉₀ values for each of the six beta-emitting radionuclides considered in this paper are included in Table 4.

Note that X_{90} can be divided in three groups. The first group formed by ^{90}Y , ^{32}P and ^{188}Re with $X_{90} = 2 \text{ mm}$, the second group (^{177}Lu and ^{153}Sm) with $1 < X_{90} < 2 \text{ mm}$ and the third one (^{169}Er); $X_{90} < 1$. These variations can be used to help the clinician performing RSV in selecting the best radionuclide for individual joint and synovium condition. No single radionuclide is ideally suited for use in every radiation synovectomy, since the thickness of inflamed synovium will differ from joint to joint and from patient to patient. In a large joint with thick synovial membrane, for example, deep penetration of the beta particles is desirable in order to sufficiently treat the inflamed tissue. In small joints with thin synovial membrane, this penetration represents an unnecessary radiation hazard to other normal structures around the joint.

For example, for an arthritic knee, with thick synovium, the suited radionuclides to deliver a therapeutic dose in the synovial depth are ^{90}Y , ^{32}P and ^{188}Re . An average administered activity of 185 MBq of ^{90}Y delivers a radiation absorbed dose of approximately 100 Gy to 100 g-synovium. Since this dose of ^{90}Y was shown to be efficacious in the treatment¹⁵, other investigators have used a “calculated ^{90}Y dose equivalent” when administering other radionuclide.

The Table 5 shows activity values of ^{188}Re and ^{32}P to obtain the “ ^{90}Y dose equivalent” in the synovial membrane (0.2 mm thickness of synovial lining cells and 250 cm² of synovium area).

Note the great differences in the activity administered, but not in the effective penetration ranges in tissue. In this case the radionuclide selection to treat the damaged tissue will depend on its availability. ^{32}P and ^{90}Y are the two isotopes most widely used today as the basis for RSV agents; however, these isotopes do not emit imageable gamma rays and thus are very difficult to obtain quantitative dosimetric information on patients treated with agents based on ^{32}P and ^{90}Y . These radionuclides are available in our centre. ^{188}Re has the advantage of a tissue penetration equivalent to that of ^{90}Y but a shorter half-life, important for leakage reduction¹⁶. It has a 155 keV gamma ray, which would permit analysis of leakage to other organs by gamma camera imaging. The possibility of producing the isotope with an ^{188}W - ^{188}Re generator would greatly extend its availability.

Following the same procedure previously described with ^{90}Y , ^{32}P and ^{188}Re in median and small joints with thin synovium depth, the most appropriate radionuclides are those with less X_{90} . The Table 6 shows the activity values of ^{177}Lu and ^{153}Sm to obtain the “ ^{90}Y dose equivalent” in the synovial membrane of an arthritic wrist.

Table 5
Values of activity administered of ^{188}Re and ^{32}P to obtain the “ ^{90}Y dose equivalent” into the synovial membrane

Radionuclide	X_{90}	S-value Gy/h*MBq	Absorbed dose (Gy)	Administered activity (MBq)
Y-90	2.22	0.007	130	185
P-32	2.1	0.007	130	37
Re-188	2.1	0.013	130	407

Table 6
Values of activity administered of ^{177}Lu and ^{153}Sm to obtain the “ ^{90}Y dose equivalent” into the synovial membrane of an arthritic wrist (0.1 mm thickness of the synovial membrane and 50 cm² of synovium area)

Radionuclide	X_{90}	S-value Gy/h*MBq	Absorbed dose (Gy)	Administered activity (MBq)
^{177}Lu	1.3	0.084	130	6.7
^{153}Sm	1.6	0.074	130	26.1

Both ^{177}Lu and ^{153}Sm , by their energetic properties, can be used to treat small joints in advanced stages of arthritis. On the other hand ^{169}Er is used to treat small joints only¹⁷.

The amount of radioactivity for a single intra-articular injection with ^{169}Er depends on the joint size¹⁸:

10–20 MBq for proximal or distal interphalangeal joints,
20–40 MBq for metacarpophalangeal or metatarsophalangeal joints,
20–80 MBq for trapeziometacarpal joints.

Multiple joints may be treated simultaneously with a cumulative dose not exceeding 555 MBq per patient

The absorbed dose estimated for a ^{169}Er injected activity of 10 to 20 MBq at a synovial depth of 0.1 mm is 910 to 1820 Gy¹⁸. This aspect should be taken into account to prescribe the activity in case of other radionuclides.

In Table 7 are shown the activity values of ^{177}Lu and ^{153}Sm to obtain the “ ^{169}Er dose equivalent” in the synovial membrane of small joints (0.1 mm thickness of synovial lining cells and 13 cm² of synovium area).

This empirical approach to calculating the dose of a new radionuclide to be administered appears to provide basis to start new researches with different radionuclides. However, the nonexistence of theoretical sustentations for these calculations still make the clinical trials the only way to determine the dose of a new radionuclide that will be effective in a treatment. Thus, the clinical trials constitute the final bases to introduce new radionuclides for RSV.

Curves displaying absorbed dose as a function of distance into the diseased synovium have been generated for each of the six beta-emitting radionuclides investigated (Fig. 1). Having selected the appropriated radionuclide, these curves can then be used by

Table 7
Values of activity administered of ^{177}Lu and ^{153}Sm to obtain the “ ^{169}Er dose equivalent” in the synovial membrane of an arthritic small joint (0.1 mm thickness of synovial lining cells and 10 cm² of synovium area)

Radionuclide	X_{90}	S-value Gy/h*MBq	Absorbed dose (Gy)	Administered activity (MBq)
^{169}Er	0.2	0.295	958	10
^{177}Lu	1.3	0.335	958	12.3
^{153}Sm	1.6	0.294	958	48.4

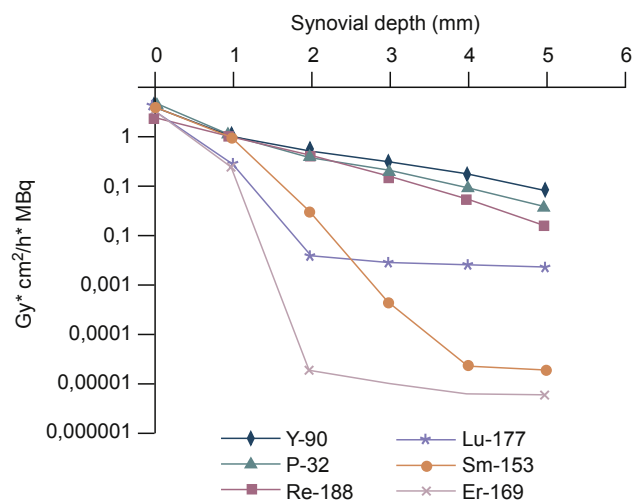


Fig. 1. Absorbed doses profiles (Gy*cm²/h*MBq) as a function of distance into the diseased synovium.

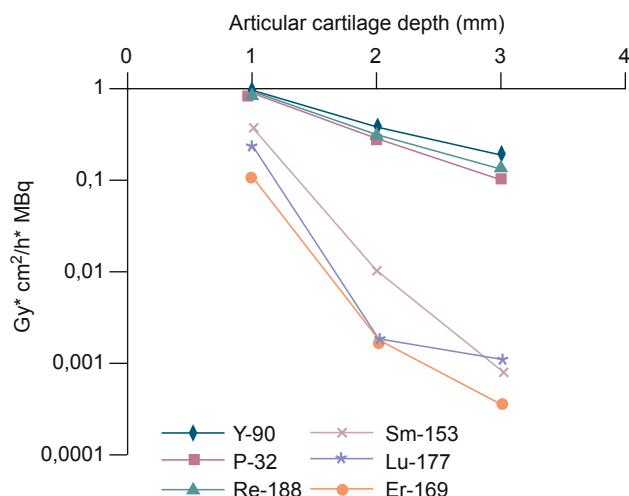


Fig. 2. Absorbed doses profiles ($\text{Gy} \cdot \text{cm}^2 / \text{h} \cdot \text{MBq}$) as a function of distance into the articular cartilage.

the clinician to predict the amount of activity required to deliver sufficient dose to a given synovial depth.

Articular cartilage

The presence of the healthy articular cartilage in the arthritic joint limits the prescribed treatment activity. The question of harmful effect of β radiation in the articular cartilage has always been a subject of debate. According to Johnson et al⁹, for a cartilage thickness of 2 mm, a dose of 1 Gy is reached at a depth of 1.5 mm in the adjoining bone with 185 MBq of ⁹⁰Y. Thus, the β radiation induces no systemic effect. Absorbed doses profiles in the articular cartilage versus distance are presented in Fig. 2.

Results presented in this paper are in agreement with those found in the references^{9–11,17,18}.

Conclusions

In RSV, the radionuclide choice is critical since the synovial thickness of different joints in the human body (e.g., finger, wrist, knee, etc.) vary substantially. Also, joints at different stages of the disease show different degrees of swelling and may also call for a beta emitter of different penetration. Each patient should have a MRI study prior to RSV in order to determine the tissue volume and to select the appropriated dose and radionuclides to be used, eliminating the practice of fixed radionuclides and doses for the

treatment of different kind of joints, methodology applied in many clinics in Europe^{19,20}. The selection of the radionuclide for the treatment will depend on the thickness of the synovium to be treated and the proximity of the non target organs to the joint (bone and articular cartilage). Values here presented can be a useful tool to prescribe adequate quantities of new radionuclides for RSV. Additionally, provide information about the radiation damage to articular cartilage.

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