Absorbed dose profiles for ^{32}P, ^{90}Y, ^{188}Re, ^{177}Lu, ^{51}Cr, ^{153}Sm and ^{169}Er: radionuclides used in radiosynoviortheses treatment

Mirta Torres[a] **, Enrique Ayra**[a] **, Omar Albuerne**[a] **, Montano Delgado**[b]

[a] Radiation Protection Department, Isotopes Centre, Carretera la Rada, Km 16 1/2
Havana, Cuba

[b]Hospital General Docente Enrique Cabrera, Havana, Cuba

Abstract: The remarkable advances in the design and synthesis of radiopharmaceuticals has created the opportunity of generating new agents for the treatment of radiosynoviortheses (RSV) which exhibit a minimum leakage from the synovial joint reducing, this way, the non desired absorbed doses to non target organs such as liver, spleen, kidney. Nowadays, the variety of beta emitters used in RSV ranges between 0.34 MeV – 0.33 mm penetration in tissue (^{169}Er) and 2.27 MeV – 3.6 mm penetration in tissue (^{90}Y). The half life of these isotopes goes from 2.3 hours (^{165}Dy) to 27.8 days (^{51}Cr). The selection criterion on which radionuclide should be used, in modern clinics, depends on which joints are to be treated. Thus, the smaller the joint, the lowest should be the energy of the beta emitted and the penetration in soft tissue of these particles. This leads to the use of fixed radionuclides and doses for each kind of joint. In the Isotopes Centre, we've been carrying on studies for the development of radiopharmaceuticals for the radiosynoviortheses treatment and focused our attention in the following radionuclides: ^{32}P, ^{90}Y, ^{188}Re, ^{177}Lu, ^{51}Cr, ^{153}Sm and ^{169}Er. 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 imparted per unit activity of injected radionuclide (Gy/h*MBq) in the synovial membrane and the articular cartilage. The researched radionuclides were those previously mentioned. Also were calculated the therapeutic range of each radionuclides in synovial tissue. 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. The synovial membrane model consisted on a cylinder with the source uniformly distributed in its volume. This model was simulated varying the radius of the cylinder (from 0.5cm to 9cm, with 0.5cm increments) and its height (from 0.01cm to 0.04cm with 0.005cm increments). The radii represent different sizes of the synovial surface (the area in the base of the cylinder) for small, medium and large joints. The height represents different stages of the progression of the rheumatoid arthritis (RA). The same model was employed for the simulation of the articular cartilage but, the source was uniformly distributed into a cylindrical slab (0.01 cm) and 1cm of radio. The results obtained allow the estimation of the dose that will be delivered to the synovial membrane and the articular cartilage for different sizes of the joint and different stages of the disease.

KEYWORDS: inflammatory arthropathies, radiosynoviorthesis, synovial membrane, articular cartilage, beta and gamma emitter radionuclides, MCNP4C code.

1. 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 illness requires specific therapeutic guidelines [1], 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 1924 [2]. In the clinical practice, the first results were published in 1952 [3] and were followed during the 60s with the inclusion of the 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 beta emitters used in radiosynoviortheses range energies between 0.34 MeV (0.33 mm penetration in tissue) in the case of Er-169 and 2.27 MeV (3.6 mm penetration in tissue) for the Y-90. The half 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 beginning of the 90s [7-11]. As new particulate radiopharmaceuticals offering many potential advantages 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: ^{32}P, ^{90}Y, ^{188}Re, ^{186}Re ^{177}Lu, ^{51}Cr, ^{153}Sm and ^{169}Er.

The method used to assess the dosimetry in RSV is known as the Monte Carlo method. Nevertheless, while it provides an improved method of calculating local dosimetry, there are still clear difficulties involved in relating calculated dosimetry to clinical outcome. While 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 isotopes 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 of 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 imparted per unit activity of injected radionuclide (Gy/h*MBq) in the synovial membrane and the articular cartilage. The radionuclides involved were those previously mentioned. Also were calculated the therapeutic range of each radionuclides in synovial tissue joint. 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.

2. 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 Yanch [9]

Table 1: Composition and density of components of the synovial joint.

ELEMENTS	H	C	N	O	Na	Mg	P	S	Ca	Cl	ρ (g/cm3)
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

The energy of beta particles used in RSV should be enough to destroy the synovial tissue 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.

Table 2: Energetic characteristic of the assessed radionuclides

Radionuclides	Y-90	P-32	Re-188	Lu-177	Sm-153	Er-169	Cr-51
$T_{1/2}$	64.1 hours	14.3 days	16.98 hours	6.71 days	46.7 hours	9.4 days	27.7 days
Emission type	Beta	Beta	Beta, gamma, electron	Beta, gamma, electron	Beta, gamma, electron	Beta, gamma, electron	electron, gamma

The MCNP4C Monte Carlo code was used to perform the dosimetry calculations. The beta spectrum of each of these radionuclides was downloaded from www.doseinfo-radar [12] and the characteristics of the gamma and/or electronic emission are the ones in the software RADIATION decay [13].

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 went from 1 mm to 10 mm with 1 mm increment for all radionuclides but for Er-169 and Cr-51. In the case of the Erbium, the radii went from 0.1 mm to 1 mm with 0.1 mm increments. For Chromium, from 0.1 µm to 1 µm with 0.1 µm increments.

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. For the synovial membrane were simulated varying the radius of the cylinder (from 0.5cm to 9cm, with 0.5cm increments) and its height (from 0.01cm to 0.04cm with 0.005cm increments). The radii represent different sizes of the synovial surface (the area in the base of the cylinder) for small, medium and large joints. The synovium area can be estimated by mean of computer tomography (CT). The height represents different stages of the progression of the rheumatoid arthritis (RA) [8]. The same model was employed to simulate the articular cartilage but, the source was uniformly distributed into a cylindrical slab (0.01 cm) and 1cm of radio. The S value as a function of distance into the diseased synovium and articular cartilage for each of the 7 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 a number of radionuclides of interest in Nuclear Medicine. Here, the S factors for each proposed model was obtained by the calculation of the mean absorbed energy by disintegration (tally f8*) in the volume of the cell, thru the equation (1):

$$S = \frac{f8^*}{m} * 576.7 * 10^{-3} \qquad (1)$$

Where:
m: mass in grams of the cell.
*f8: results of the tally (MCNP).

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 by means of the equation (2).

$$D_t = S \times 1.44 \times T_{1/2\ fisico} \times A_o \qquad (2)$$

Where:

S: S-value (Gy/h*MBq)
T1/2: Half life
A_0: Injected activity into the articular cavity

For all the cases, a sufficient number of electron and photon transport histories were generated to produce statistically reliable energy tallies, with relative errors les than 0.10. Was included the Bremsstrahlung radiation.

3. Analysis and Discussion of Results.

3.1 Synovial membrane

S-values for the synovial membrane 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 ^{90}Y usually employ an average administered activity of 5 mCi for arthritic knee patients with synovium area of 250 cm^2. This value of administered activity will deliver approximately 130 Gy in the synovial membrane according to model employed (S-value = 0.007). If we want to obtain the same therapeutic effect in the synovial membrane of an arthritic wrist with 50 cm^2 of synovium area (S-value=0.035), it only will be necessary to inject 1 mCi of ^{90}Y. In this case it is considered that the radionuclide decays completely in the joint (equation 2),

Table 3: S -Values (Gy/MBq*h) for different synovium size and thickness of synovial lining cells at the tissue surface.

	0.01 cm							0.015 cm						
A(cm^2)	^{90}Y	^{32}P	^{188}Re	^{177}Lu	^{153}Sm	^{51}Cr	^{169}Er	^{90}Y	^{32}P	^{188}Re	^{177}Lu	^{153}Sm	^{51}Cr	^{169}Er
13	0.152	0.154	0.325	0.335	0.294	0.013	0.295	0.144	0.146	0.291	0.277	0.243	0.010	0.240
20	0.098	0.099	0.208	0.214	0.188	0.008	0.189	0.092	0.094	0.186	0.177	0.156	0.006	0.154
28	0.068	0.069	0.145	0.149	0.131	0.006	0.131	0.064	0.065	0.130	0.123	0.108	0.004	0.107
38	0.050	0.051	0.106	0.109	0.096	0.004	0.096	0.047	0.048	0.095	0.091	0.080	0.003	0.078
50	0.038	0.039	0.081	0.084	0.074	0.003	0.074	0.036	0.037	0.073	0.069	0.061	0.002	0.060
64	0.030	0.031	0.064	0.066	0.058	0.003	0.058	0.029	0.029	0.058	0.055	0.048	0.002	0.047
79	0.024	0.025	0.052	0.054	0.047	0.002	0.047	0.023	0.024	0.047	0.044	0.039	0.002	0.038
95	0.020	0.020	0.043	0.044	0.039	0.002	0.039	0.019	0.019	0.039	0.037	0.032	0.001	0.032
113	0.017	0.017	0.036	0.037	0.033	0.001	0.033	0.016	0.016	0.032	0.031	0.027	0.001	0.027
133	0.014	0.015	0.031	0.032	0.028	0.001	0.028	0.014	0.014	0.028	0.026	0.023	0.001	0.023
154	0.013	0.013	0.027	0.027	0.024	0.001	0.024	0.012	0.012	0.024	0.023	0.020	0.001	0.020
177	0.011	0.011	0.023	0.024	0.021	0.001	0.021	0.010	0.010	0.021	0.020	0.017	0.001	0.017
201	0.010	0.010	0.020	0.021	0.018	0.001	0.018	0.009	0.009	0.018	0.017	0.015	0.001	0.015
227	0.008	0.009	0.018	0.019	0.016	0.001	0.016	0.008	0.008	0.016	0.015	0.013	0.001	0.013
254	0.008	0.008	0.016	0.017	0.015	0.001	0.015	0.007	0.007	0.014	0.014	0.012	0.000	0.012
	0.02 cm							0.025 cm						
A(cm^2)	^{90}Y	^{32}P	^{188}Re	^{177}Lu	^{153}Sm	^{51}Cr	^{169}Er	^{90}Y	^{32}P	^{188}Re	^{177}Lu	^{153}Sm	^{51}Cr	^{169}Er
13	0.138	0.140	0.264	0.237	0.211	0.008	0.197	0.134	0.136	0.244	0.207	0.189	0.007	0.166
20	0.089	0.090	0.170	0.151	0.135	0.005	0.126	0.086	0.087	0.156	0.132	0.121	0.004	0.106
28	0.062	0.063	0.118	0.105	0.094	0.003	0.088	0.060	0.061	0.109	0.092	0.084	0.003	0.074
38	0.045	0.046	0.087	0.077	0.069	0.003	0.064	0.044	0.045	0.080	0.068	0.062	0.002	0.054
50	0.035	0.035	0.066	0.059	0.053	0.002	0.049	0.034	0.034	0.061	0.052	0.047	0.002	0.042
64	0.028	0.028	0.056	0.047	0.042	0.002	0.039	0.027	0.027	0.048	0.041	0.037	0.001	0.033
79	0.022	0.023	0.043	0.038	0.034	0.001	0.032	0.022	0.022	0.039	0.033	0.030	0.001	0.027
95	0.018	0.019	0.035	0.031	0.028	0.001	0.026	0.018	0.018	0.032	0.027	0.025	0.001	0.022
113	0.016	0.016	0.030	0.026	0.024	0.001	0.022	0.015	0.015	0.027	0.023	0.021	0.001	0.018
133	0.013	0.013	0.025	0.022	0.020	0.001	0.019	0.013	0.013	0.023	0.020	0.018	0.001	0.016
154	0.011	0.012	0.022	0.019	0.017	0.001	0.016	0.011	0.011	0.020	0.017	0.015	0.001	0.014
177	0.010	0.010	0.019	0.017	0.015	0.001	0.014	0.010	0.010	0.017	0.015	0.013	0.000	0.012
201	0.009	0.009	0.017	0.015	0.013	0.000	0.012	0.008	0.009	0.015	0.013	0.012	0.000	0.010
227	0.008	0.008	0.015	0.013	0.012	0.000	0.011	0.007	0.008	0.014	0.011	0.010	0.000	0.009
254	0.007	0.007	0.013	0.012	0.010	0.000	0.010	0.007	0.007	0.012	0.010	0.009	0.000	0.008

Due to that electron emission energies and spectral shapes differ between β- active radionuclides, the absorbed dose penetration range can vary substantially from radionuclide to radionuclide. 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 from the source at which the 90 % of the absorbed dose is deposited in the tissue slabs (X_{90}). The X_{90} values for each of the seven beta-emitting radionuclides investigated are included in table 4.

Table 4: Therapeutic range (X_{90}) for ^{90}Y, ^{32}P, ^{188}Re, ^{177}Lu, ^{153}Sm, ^{51}Cr and ^{169}Er

X_{90} (mm)						
^{90}Y	^{32}P2	^{188}Re	^{177}Lu-	^{153}Sm	^{51}Cr	^{169}Er
2.22	2.1	2.1	1.3	1.6	0.0012	0.18

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} = 2mm, the second group (^{177}Lu and ^{153}Sm) between 1< X_{90} < = 2 mm and third (^{51}Cr and ^{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 joint with a thin synovial membrane, this penetration represents an unnecessary radiation hazard to other normal structures around the joitn.

For example, for an arthritic knee, with thick synovium, the suited radionuclides to impart a therapeutic dose in the synovial depth are ^{90}Y, ^{32}P and ^{188}Re. An average administered activity of 5 mCi 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 treatment [14], other investigator have used a "calculated ^{90}Y dose equivalent" when administering other radionuclide.

The following table shows the activity values of ^{188}Re and ^{32}P to obtain the "^{90}Y dose equivalent" in the synovial membrane (synovial linning cells- 0.2 mm and 250 cm^2 of synovium area).

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

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 of 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 [16], has the advantage of a tissue penetration equivalent to that of ^{90}Y but a shorter half –life, important for leakage reduction. 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 a ^{188}W-^{188}Re generator would greatly extend its availability.

Following the same procedures 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 minor X_{90}. The following table shows the activity values of ^{177}Lu and ^{153}Sm to obtain the "^{90}Y dose equivalent" in the synovial membrane of an arthritics wrist.

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 arthritics wrist (synovial membrane thickness- 0.1 mm and 50 cm^2 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 the disease. On the other hand ^{169}Er and ^{51}Cr are used to treat small joints only.

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

10 to 20 MBq for proximal or distal interphalangeal joints
20 to 40 MBq for metacarpophalangeal or metatarsophalangeal joints
20 to 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 of ^{169}Er in proximal and distal interphalangeal joints at a synovial depth of 0.1 mm with activity injected of 10 to 20 MBq is from 910 to 1820 Gy [18]. This aspect should be taken into account to prescribe the activity with other radionuclides.

Following the same procedure previously described for median and large joints, is shown in table 7 the activity values of ^{177}Lu and ^{153}Sm to obtain the "^{169} Er dose equivalent" in the synovial membrane of small joints (thickness of synovial lining cells is 0.1 mm and 13 cm^2 of synovium area).

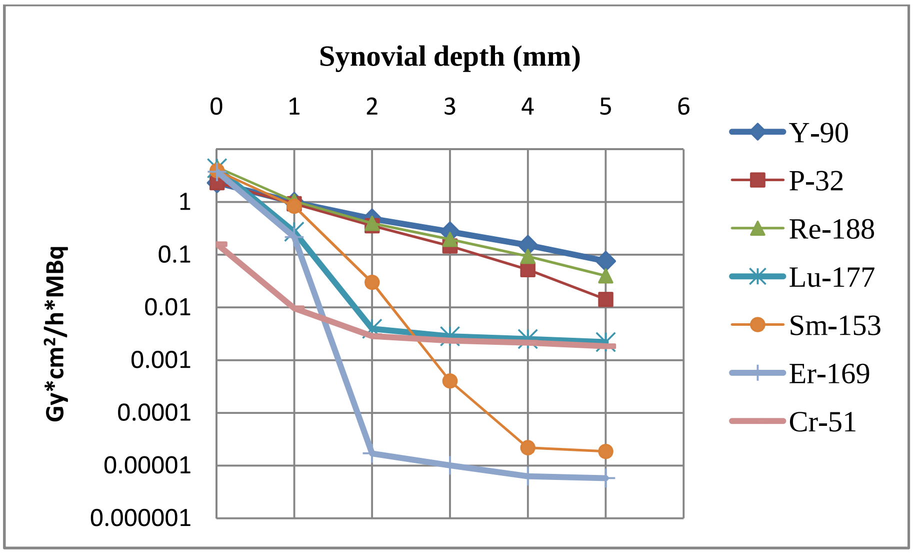
Table 7: Values of activity administered of ^{177}Lu and ^{153} Sm to obtain the "^{169} Er dose equivalent" in the synovial membrane of an arthritics small joint (thickness of synovial lining cells, 0.1 mm and 10 cm^2 of synovium area).

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

This empirical approach to calculating the administered dose of a new radionuclide appears to provide basis for initiation of new investigations with different radionuclides [15]. However, the nonexistence of one theoretical sustentation of these calculations still provokes that the researcher should determine the dose of a new radionuclide that will be effective for the treatment. The clinical trials constitute the final objective 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 seven beta-emitting radionuclides investigated (Figure 1). Having selected the appropriated radionuclide, these curves can then be used by the clinician to predict the amount of activity required to deliver sufficient dose to a give synovial depth.

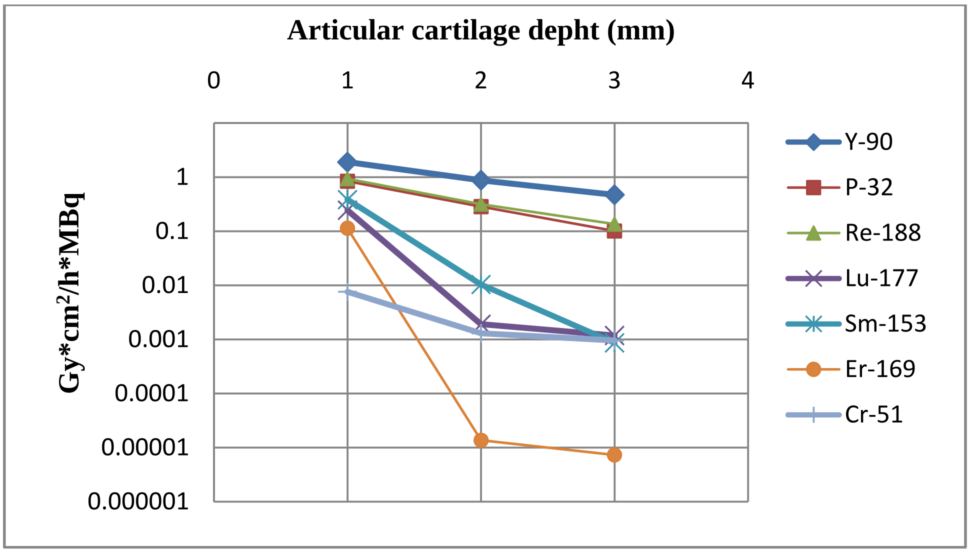
Figure 1: Absorbed doses profiles (Gy*cm^2/h*MBq) as a functions of distance into the diseased synovium.



3.2 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 al [10], 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 ^{90}Y. Thus, the β radiation induces no systemic effect. Absorbed doses profiles in the articular cartilage versus distance are presented in Figure 2.

Figure 2: Absorbed doses profiles (Gy*cm^2/h*MBq) as a functions of distance into the articular cartilage.



Results presented in this paper are in agreement whit those found in the references [9-11, 17-18]

4. 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 penetrability. Each patient would have a MRI study prior to RSV in order to determine the tissue volume and to select the appropriated dose and radionuclides, eliminating the practice of fixed radionuclides and doses for the treatment of different kind of joints, methodology applied in many clinics in Europe [19].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 of 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 degree of radiation damage to articular cartilage.

REFERENCES

[1] MANUAL MERCK, 17.ª Edición 1999

[2] ISHIDO C. Über die Wirkung des radiothoriums auf die Gelenke. Strahlentherapie 1924;27:188-96

[3] FELLINGER K, SCHMID J. Local therapy of rheumatics diseases. Wien Z Inn Med 1952;33:351-63

[4] DELBARRE F, MENKES C ET AL, Synoviorthesis with radioisotopes, Press med. 76 (1968) 1045.

[5] DELBARRE F, LE GO A, MENHES C, AIGNAN M, ET AL, Double Blind statistical study of therapeutics effect of a radioactivity yttrium (90Y) charged colloid on rheumatoid arthritis of the knee. C R Acad Sci Hebd Seances Acad Sci D 1974;279:1051-4

[6] CLUNIE. G. A survey of radiation synovectomy in Europe, 1991-1993. European Journal of Nuclear Medicine. (Sep 1995) V.22 (9).p.970-976.

[7] MARTTI HANNELIN, A dosimetric study of Dysprosium-165 macroaggreagates used in treating rheumatoid arthritis, Commentationes physico-mathematicae 87/1988, Dissertationes No. 16, Central Hospital of Etela-Saimaa, Lappeenranta, Finland.

[8] HARLING ET AL. Radiation synovectomy. Treatment of rheumatoid arthritis. Nucleat scince and engineering. Vol 110 apr 1992

[9] L.SCOTT JOHNSON AND JACQUELYN C. YANCH, Absorbed dose profiles for radionuclides of frequent use in radiation synovectomy, Arthritis and Rheumatism, Vol 34. No 12, December 1991.

[10] JOHNSON L.S, YANCH J.C, SHORTKROFF S, ET.AL, Beta-particle dosimetry in radiation synovectomy, European Journal of Nuclear Medicine, (Sep 1995) V.22 (9).p.977-988.

[11] OTTO K HARLING, JACQUELYN C YANCH, ET AL, Boron neutron capture and radiations synovectomy research at the Massachusetts Institute of Tecnology Reactor, Nuclear Science and engineering: 110, 330-348 (1992).

[12] STABIN MG, SIEGEL J, HUNT J, SPARKS RB, LIPSZTEIN J AND ECKERMAN K. RADAR, The radiation dose assessment resource. An online source of dose information for nuclear medicine and occupational radiation safety. J Nucl Med, Supplement 42:243P, 2001

[13] CHARLES HACKER, Radiation decay version 2 March 1997. Engineering and Applied Science, Griffith University, Australia

[14] W. U. KAMPEN, ET AL. Therapeutics status of radiosinoviortesis of the knee with yttrium[90Y] colloid in rheumatoid arthritis and related indications. Rheumatology 2007, 46:16-24.

[15] E DEUTSCH, J W BRODACK, K F DEUTSCH. Radiation synovectomy revisited, European Journal of Nuclear Medicine, (1993) 20:1113-1127

[16] VENKATESAN PP, SHORTKROFF S, ZALUTSKY MR, SLEDGE CB, Rhenium heptasulfide: a potential carrier system for radiation synovectomy, Int rad Appl Instrum [B], 17:357-362, 1990.

[17] A BALSA BRETÓN J GARCÍA-ARROBA MUÑOZ, Sinoviortesis radioisotópica, Rev Esp Med Nucl 2004; 27: 49 – 55.

[18] SCHERING, A local quality treatment for arthritis diseases.

[19] CLUNIE. G, A survey of radiation synovectomy in Europe, European Journal of Nuclear Medicine,V.22(9).p.970-976,Sep1995