Personalized radiosynoviorthese: dosimetry treatment planning

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Abstract. This work is devoted to the quantitative dosimetric support method for endoradyotherapy of inflammatory joints diseases. To reduce inflammation in synovium radiopharmaceutical is injected intraarticularly and provides local ablation of excessive synovial tissue. Present-day guidelines give empirical approaches to therapeutic activity selection. Such approaches lead to 20% untreated patients. Article shows way to improvement of cure level by introduction of dosimetric support.

1. Introduction

For over 40 years radiosynoviorthese (RSO) successfully used for treatment of arthritis [1], inter alia rheumatoid arthritis (RA). This approach had an extensive development in a recent decade. Clinical evaluation of RSO effectiveness and clinical statistic of RSO application to arthritis and osteoarthritis are described in works [2-4].

Main role in the development of inflammation and soreness is played by lining cells of the synovial membrane, that lost ability of contact inhibition. Normally, these cells produce synovial fluid, ensuring the wettability and the restoration of hyaline cartilage surface. Excess of lining cells leads to joint effusion and loss of movement function.

During RSO microparticles with β-radioactive isotope, ranging from 0.05 to 2 mm in diameter, injects in the cavity of immobilized joint. The microparticles are captured by a lining cells of the synovial membrane, as a result β-particles destroy layer of lining cells that produces excess of lubricant and its vascular supply layer. It is known that after administration of standard activity ^{90}Y (185-220 MBq) disease remission is observed in 80% of clinical cases [4]. The value of required dose D for target tissue is defined by the radiologist on the basis of synovial tissue radiosensitivity.

When there are several organs of known activity, according to MIRD-method a dose in the target organ can be represented as the sum of the individual components:

$$D_i = \sum_j \tilde{A}_j \times S(i \leftarrow j) \tag{1}$$

where *i, j* – the indexes of targets and sources respectively. Each component directly proportional to the cumulated activity in the source organ $\tilde{A}_j = \int A_j(t)dt$. The proportionality factor (S-factor) depends on the properties of radionuclide radiation and on the relative geometrical characteristics of

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the source and target. In the case of RSO there are one target (intima) and two source regions (intima and sinovial fluid):

$$D_{\text{int}} = \tilde{A}_{\text{int}} \times S_{\text{int}} + \tilde{A}_{sf} \times S_{sf} \quad (2)$$

RSO as any other therapeutic technique of nuclear medicine requires dosimetry treatment planning that takes into account the structural features of the particular joint and the stage of the disease. The existing "EANM Procedure Guidelines for Radiosynovectomy" contains only limited list of radionuclides - ^{90}Y (large joints), ^{186}Re (medium joints), ^{169}Er (small joints) with fixed activities. The further development of the method requires the expansion of available radionuclide list and optimization of assigning activities of radiopharmaceutical depending on the individual characteristics of the patient.

Dosimetric support is divided into two related tasks: dosimetric planning and dosimetric control of side irradiation. Dosimetry planning is based on the MIRD-formalism principles [5]. According to MIRD-formalism medical physicist should take into account the pharmacokinetics of the radiopharmaceutical and anatomic parameters of joint. Current model of synovial joint does not consider other structures of organism. We believe that the entire radiopharmaceutical localized in synovial joint. Important role here plays a pharmaceutical form containing the radionuclide. It must be microparticles, which is not eliminated from joint capsule during treatment and effectively captured by macrophages. Range of beta-particles has to be about 2-4 mm.

In the current paper we propose the method of calculating administered activity of ^{188}Re-colloid for RSO of the knee joint, developed on the basis of dose simulation by toolkit GATE/Gean4.

2. Materials and methods

For absorbed dose calculation open-source software GATE/GEANT4 [7-8] based on Monte-Carlo technique was used. Model of the joint (see Figure 1) consists of ranked cylindrical disks, representing the main elements of the synovial joint: bone, articular cartilage, synovium, layer of lining cells (intima), synovial fluid (cavity). The synovium is divided into two zones: the intima (0.3 ÷ 0.6 mm), which has a contact with synovial fluid, and sub-intima (1 ÷ 9mm). Diameter R equals to intercondylar distance (2 ÷ 9 cm).

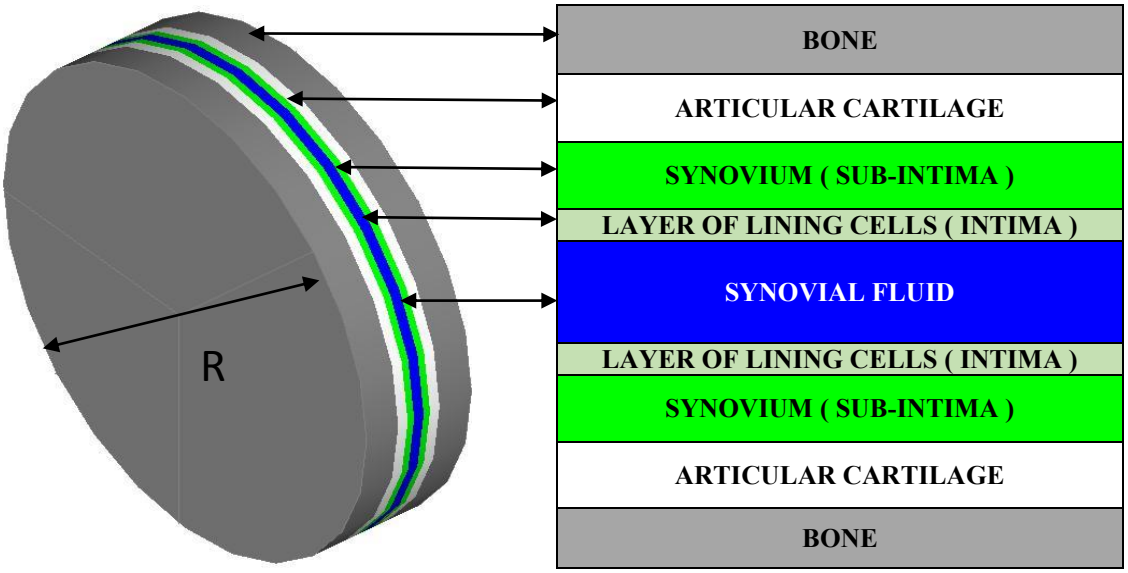


Figure 1. Geometrical model of synovial joint.

The elemental composition of [9] synovial joint tissues applied in this work is shown in Table 1.

Table 1. Synovial joint tissue elemental composition

Element	H	C	N	O	Na	Mg	P	S	Cs	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
Soft tissues	10,0	14,9	3,5	71,6	-	-	-	-	-	-	1,0

If the radioisotope is localized in the layer of lining cell (intima) and synovial fluid dose in the intima according to Eq.2 can be expressed as

$$D_{\text{int}} = \int A_{\text{int}}(t)dt \cdot S_{\text{int}} + \int A_{SF}(t)dt \cdot S_{SF} \tag{3}$$

where $A_{\text{int}}(t)$, $A_{SF}(t)$ – activities localized in intima and synovial fluid respectively.

$$A_{\text{int}}(t) = A_0^{\text{int}} \cdot e^{-\frac{t \cdot \ln 2}{T_{1/2}}}, \quad A_{SF}(t) = A_0^{SF} \cdot e^{-\frac{t \cdot \ln 2}{T_{1/2}}}$$

Effective elimination half-life is considered here as isotope decay half-life $T_{1/2}$. Leakage of pharmaceutical during the exposure is considered negligible. Considering that $A_0^{\text{int}} + A_0^{SF} = A_0$ initial activities in intima and in synovial fluid can be expressed as:

$$A_0^{\text{int}} = A_0 \cdot \delta_{\text{int}}, \quad A_0^{SF} = A_0 \cdot \delta_{SF} = A_0 \cdot (1 - \delta_{\text{int}}) \tag{4}$$

Where δ_{int} – share of total activity captured by intima (int); δ_{SF} – share of total activity captured by synovial fluid (SF). Then

$$D_{\text{int}} = A_0 \cdot \delta_{\text{int}} \cdot K \cdot S_{\text{int}} + A_0 \cdot (1 - \delta_{\text{int}}) \cdot K \cdot S_{SF} \tag{5}$$

where K – exposition coefficient, which describes reduction of activity during the exposure due to decay of radionuclide:

$$K = \int_0^{T_{\text{exp}}} e^{-\frac{t \cdot \ln 2}{T_{1/2}}} dt = \frac{T_{1/2}}{\ln 2}\left(1 - e^{-\frac{T_{\text{exp}} \cdot \ln 2}{T_{1/2}}}\right) \tag{6}$$

Where T_{exp} –time of exposure. Immobilization of the joint ensures that leakage is insignificant and the radioisotope remains inside the joint. Therefore the exposure time T_{exp} is considered as the time of immobilization.

To estimate S-factors absorbed dose distribution were simulated in GATE for two different cases: 1) radionuclide is uniformly distributed only in the intima; 2) radionuclide is uniformly distributed only in the synovial fluid (SF). Then S-factors are calculated according to formula (2):

$$S_{\text{int}} = \frac{D_{\text{int}}^1}{\int A_{\text{int}}(t)dt} = \frac{D_{\text{int}}^1}{A_0^{\text{int}} \cdot K}, \quad S_{SF} = \frac{D_{\text{int}}^2}{\int A_{SF}(t)dt} = \frac{D_{\text{int}}^2}{A_0^{SF} \cdot K} \tag{7}$$

Where D_{int} – dose in intima [Gy], A_{int} – activity of radionuclide in intima [MBq], A_{SF} - activity of radionuclide in synovial fluid [MBq]. S_{int} and S_{SF} were simulated for various thickness of sub-intima and sizes of synovial joint. Results are presented in Tables 3 and 4. Using S_{int} and S_{SF} it is possible to calculate required activity of radionuclide for the case, when a part of total activity is absorbed in

intima. If D_{int} [Gy] - therapeutic dose for the target tissue, administered activity A_0 [MBq] of radionuclide can be calculated according to Eq.5 as follows:

$$A_0 = \frac{\mathrm{D_{int}}}{\mathrm{K} \cdot (\mathrm{S_{int}} \delta_{\mathrm{int}} + S_{SF}(1 - \delta_{\mathrm{int}}))} \quad (8)$$

where S_{int} и S_{SF} – S-factors for activity accumulated only in intima or only in synovial fluid (Eq.8), δ_{int} – share of total activity captured by layer of lining cell, K [h] – exposition coefficient (Eq.6). .

3. Model validation

For validation of mathematical model the physical phantom of the joint was manufactured (Figure 2) from tissue-equivalent material (ABS-plastics). Tissue-equivalence of material was confirmed by measuring Hounsfield number for ABS-plastics on Philips Precedence 16 SPECT/CT system.

Central volume of the phantom imitating the synovial capsule was filled with water solution containing 40 MBq of ^{188}Re activity measured by dose-calibrator "RADMEDRIG-04P".

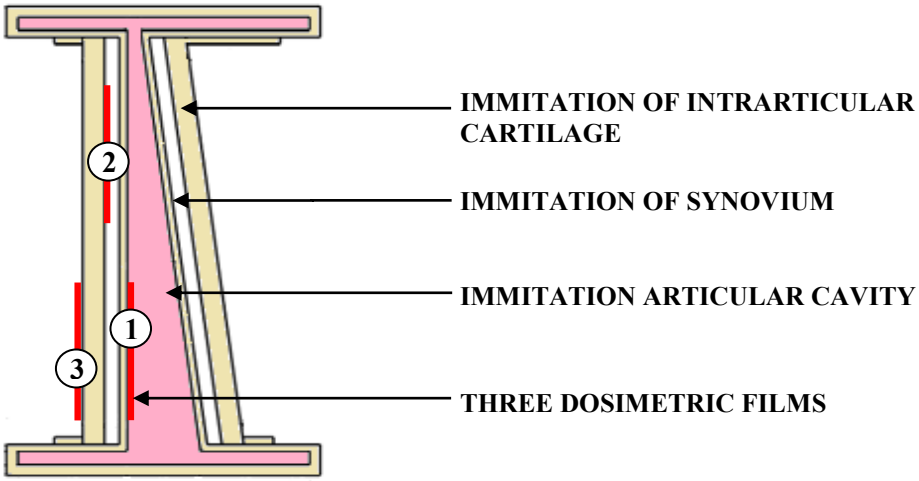


Figure 2. Working drawing of synovial joint phantom and film dosimeters positioning.

The dose at the surface of phantom after 24-hour exposition were measured by film dosimeters GafChromic EBT [10]. Dynamic range of the dosimetric film is from 0.5 to 16 Gy. Three dosimetric films were arranged so that not to overlap each other to measure dose at various distances from the source distributed in articular cavity (positions 1, 2 and 3).

Table 2. Experimentally measured and simulated absorbed doses at different detector positions in phantom with ^{188}Re-source distributed in articular cavity.

Detector position	Absorbed dose, Gy	
	Film dosimeter GafChromic, Gy	GATE simulation, Gy
1	3,5±0,5	3,8
2	2,0±0,3	2.2
3	0,5±0,2	0,7

Table 2 contains experimentally measured absorbed dose values in dosimetric films placed at different distances from the phantom cavity filled with radioactive solution (pos. 1, 2, 3 on Figure2), and GATE simulated absorbed doses. The simulated values are in good agreement with experiment.

4. Results and discussions

Calculated S-factors for two different distributions of ^{188}R and for the various sizes of joints, intraarticular gap and layer of lining cells are shown in Table 3 (a), 3 (b) and 4.

Table 3 (a). S-factor for ^{188}Re activity distributed only in intima, $S_{int}\left[\frac{Gy}{MBq \cdot h}\right]$.

Intraarticular gap, mm	Thickness intima, mm	Joint area, cm^2							
		13	28	50	79	113	154	201	254
1	0.35	0,102	0,046	0,026	0,017	0,012	0,009	0,007	0,007
	0.45	0,094	0,043	0,024	0,015	0,011	0,008	0,006	0,006
	0.55	0,088	0,040	0,022	0,014	0,010	0,007	0,006	0,006
3	0.35	0,088	0,040	0,022	0,014	0,010	0,007	0,006	0,006
	0.45	0,081	0,037	0,021	0,013	0,009	0,007	0,005	0,005
	0.55	0,077	0,034	0,019	0,012	0,009	0,006	0,005	0,005

Table 3 (b). S-factor for ^{188}Re activity distributed only in intima, $S_{int}\left[\frac{Gy}{MBq \cdot h}\right]$.

6	0.35	0,084	0,038	0,021	0,014	0,010	0,007	0,005	0,005
	0.45	0,078	0,035	0,020	0,013	0,009	0,007	0,005	0,005
	0.55	0,073	0,033	0,019	0,012	0,008	0,006	0,005	0,005

Table 4. S-factor for ^{188}Re activity distributed only in synovial fluid, $S_{SF}\left[\frac{Gy}{MBq \cdot h}\right]$.

Intraarticular gap, mm	Thickness intima, mm	Joint area, cm^2							
		13	28	50	79	113	154	201	254
1	0.35	0,095	0,043	0,024	0,016	0,011	0,008	0,006	0,006
	0.45	0,090	0,041	0,023	0,015	0,010	0,008	0,006	0,006
	0.55	0,086	0,039	0,022	0,014	0,010	0,007	0,006	0,006
3	0.35	0,050	0,023	0,013	0,006	0,006	0,004	0,003	0,003
	0.45	0,048	0,022	0,012	0,006	0,006	0,004	0,003	0,003
	0.55	0,046	0,021	0,012	0,005	0,005	0,004	0,003	0,003
6	0.35	0,027	0,012	0,007	0,005	0,003	0,002	0,002	0,002
	0.45	0,026	0,012	0,007	0,004	0,003	0,002	0,002	0,002
	0.55	0,025	0,011	0,006	0,004	0,003	0,002	0,002	0,002

Figure 3A presents dependence of S-factor (δ_{int} =0.5) on intraarticular gap for different intercondylar distances R: 40, 60, 80 and 100 mm. Increasing the intraarticular gap from 1 to 6 mm leads to S-factor reduce by 1.2 times at R = 40 mm, and 1.3 times at R = 100mm. The width of the intraarticular gap and intercondylar distance can be estimated using computer tomography.

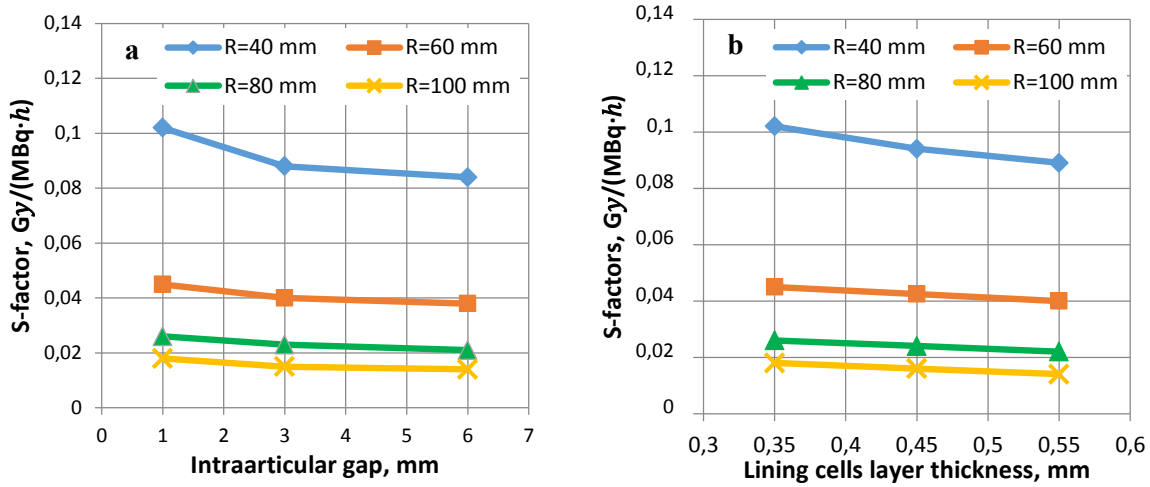


Figure 3. S-factor dependences on intraarticular gap width (a) and on thickness of the lining cells layer (b) for the number of intercondylar distances R: 40, 60, 80 and 100 mm.

Figure 3B presents dependence of S-factor ($\delta_{Int} = 0.5$) on thickness of the lining cells layer of synovium for different intercondylar distances R: 40, 60, 80 and 100 mm. It can be seen that increase of the lining cells layer thickness from 0.35 to 0.55 mm leads to S-factor reduction by 1.2 times at R = 40 mm, and 1.3 times at R = 100 mm. Lining layer thickness could be measured by ultrasound scanner or by MRI.

5. Dosimetric protocol

The next steps of dosimetric planning may be used for clinical applications of RSO:

1. CT scanning for evaluation of intercondylar distance and width of intraarticular gap;
2. US scanning for evaluation of intima and effusion thickness;
3. Determination of S-factor using Table 3 and 4.
4. Leakage control (WB scintigraphy);
5. Evaluation of radionuclide distribution (SPECT-CT).
6. Determination of immobilization time;
7. Calculation of administered activity using formula 3 and 4.

6. Conclusion

Study of the S-factor dependence on geometrical parameters of synovial joint carried out using GATE simulation shows that dose planning procedure for RSO must take into account the individual characteristics of each patient. Increase of intercondylar distance, intraarticular gap width and thickness of lining cells layer requires to increase administered activity of the radiopharmaceutical.

The proposed approach for dosimetry planning of RSO meets the modern requirements of clinical practice. Such approach allows calculation of required activity based on individual anatomical structure of synovial joint. It is possible to calculate S-factors for any parameters of synovial joint on the base of Monte-Carlo simulation and present them in a convenient form for clinical use. Necessary parameters can be determined by complex of diagnostic procedures.

Presented method has high flexibility and reproducibility and provides an opportunity for physicians to conduct extensive retrospective analysis. thus such approach will lead to improvement of RSO effectiveness.

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References

[1] Deutsch, E., Brodack, J.W., Deutsch. K.F. Radiation synovectomyrevisted. European Journal of Nuclear Medicine 199320: 1113-1 127
[2] ChrapkoB, ZwolakR, NocunA, GolebiewskaR, MajdanM. Radiationsynovectomy with 90Y colloid in the therapy of recurrent knee joint effusions in patients with inflammatory joint diseases. RheumatolInt 2007;27:729–34.
[3] Zuderman L, Liepe K, Zöphel K, et al. Radiosynoviorthesis (PCO): influencing factors and therapy monitoring. Ann Nucl Med. 2008;22(9):735–41. DOI: 10.1007/s12149-008-0167-7. Epub 2008 Nov 28.
[4] Liepe K, Zaknun JJ, Padhy A, et al. Radiosynovectomy usingyttrium-90, phosphorus-32 or rhenium-188 radiocolloids vs. corticoid instillation for rheumatoid arthritis of the knee. Ann NuclMed. 2011;25(5):317–23. DOI: 10.1007/s12149-011-0467-1.Epub 2011 Feb 19.
[5] B. R. B. Walters, I. Kawrakow, and D. W. O. Rogers, "History by historystatistical estimators in the beam code system,"Med. Phys.29, 2745–2752(2002).
[6] LANL,MCNPX 2.6.0 Users's Guide, Technical Report No. LA-CP-071473, 2008.
[7] G. Battistoni, S. Muraro, P. Sala, F. Cerutti, A. Ferrari, S. Roesler,A. Fasso, and J. Ranft, "The FLUKA code: Description and benchmarking," inHadronic Shower Simulations Workshop, edited by M. Albrowand R. Raja (AIP Conference, Fermilab, Batavia, IL, 2006), Vol. 896, pp.31–49.
[8] A. Ferrari, P. Sala, A. Fasso, and J. Ranft,FLUKA: A Multi-Particle Trans-port Code, Technical Report No. INFN/TC 05/11, SLAC-R-773, CERN-2005-10, 2005.
[9] International Commission on Radiation Units and Measurements. ICRU-44: Tissue Substitutes in Radiation Dosimetry and Measurements, 1989.
[10] // GafChromic: http://gafchromic.ru/.[2015]