Physica Medica 47 (2018) 64–72

Contents lists available at ScienceDirect

Physica Medica

journal homepage: www.elsevier.com/locate/ejmp

Original paper

Dosimetry perspectives in radiation synovectomy

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ARTICLE INFO

Keywords:
Radiation synovectomy
Radionuclide
Dosimetry
Contamination

ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory disease that can potentially damage the synovial joints. One of the effective treatment modality for RA is radiation synovectomy (RSV) where properly selected radionuclide is injected into the joint space, enabling controlled destruction of diseased synovial membrane via radiation exposure. Radiation dosimetry in RSV appears challenging due to the heterogeneous nature of synovial membrane, nonuniform distribution and leakage of radionuclide from the synovial cavity. This article reviews the dosimetric perspective pertaining to RSV. Specifically, characteristics of radionuclide for RSV and radiation dose to target and non-target (i.e., articular cartilage, bone, bloodstream, gonads, etc.) tissues of patient have been discussed. The personal dose $H_p(0.07)$ to the hands of medical staff (i.e., radiochemist, therapist physician, nurse) may be considerably high due to handling of high specific activities (~500 MBq/ml for Y-90); such doses are typically measured using thermoluminescence dosimeters (TLD) ring dosimeters and ranges from 1 to 21.5, 0.1 to 40 and 0.1 to 5 μSv/MBq for the radiochemist, therapist physician and the nurse, respectively. Methods to minimize radiation doses to the patient, medical staff and public are elaborated. Contamination risks and precautionary measures are also reported.

1. Introduction

Radiation synovectomy (RSV) refers to the radio-ablation of inflamed synovium by injecting a beta-emitting radionuclide inside the synovial joint cavity. The surface lining of synovium consists of phagocytes that are capable of absorbing the injected radionuclide, where radioactive decay of the radionuclide imparts radiation dose to the synovial tissue. The injected radionuclide is titrated in such a way as to deliver the required therapeutic radiation dose to the synovial tissue, creating a permanently destroyed synovium, enabling improved joint movement and reduced pain, swelling, and effusion. Afterwards, the regenerated tissue is supposed to be asymptomatic [1]. The effectiveness of RSV varies for the given radionuclides used, joint and diseases. However, on the average, RSV has been found effective in up to 80% of patients [2].

RSV was arguably first proposed by Fellinger and Schmid [3] and comprehensively described by Ansell et al. [4]. Specifically, an intra-articular injection of colloidal Au-198 (370 MBq) was used for treating rheumatoid arthritis (RA) of the knees. Although, the symptoms were relieved, the procedure also resulted in significant local and distant side effects, necessitating improved dosimetry techniques for delivering the desired radionuclide dose. However, when performed properly, RSV is safe with very low rate of complications and side effects. Most common side effect of RSV is intensification of inflammatory symptoms (radiosynovitis). Leakage of the radionuclide outside the joint cavity is also assumed as a major side effect, which results in increased irradiation of the patient. Rare complications of RSV include temporarily greater pain, allergy, local infection, fever, malaise, ulceration with local skin radiation necrosis, increased oedema and joint effusion, septic arthritis and hemorrhage [2,5,6].

Initial dosimetry investigations were carried using Au-198, injected 24 h prior to the surgical synovectomy; the synovial membrane and fluid were analyzed for radioactivity after surgery. Measurements showed that synovium and fibrin clot were highly radioactive, as opposed to the synovial fluid. More specifically, Au-198 was present in the outer cells (thickness ~1 mm) of synovium, indicating that Au-198 (mean range < 1 mm) would not deliver the desired/uniform dose to the full thickness of inflamed synovium (often ~1 cm). Thereafter, Y-90 having a higher beta energy (mean range ~4 mm) was suggested for RSV [7]. Moreover, the relatively small particle sizes of colloid Au-198 and high energy gamma emissions resulted in excessive loss of the radionuclide into the lymphatic system and doses to remote non-target tissues, respectively. The frequency of damaged circulating lymphocytes was 8.5%, compared with 0.48% for controls [8]. Compared to Au-198, no leakage of Y-90 to the knees, pelvis and abdomen, the groin lymph nodes or liver was observed with scintigraphy study [7,9];

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https://doi.org/10.1016/j.ejmp.2018.02.015
Received 21 August 2017; Received in revised form 11 January 2018; Accepted 16 February 2018

however, very small amounts of activity were detected in the blood (< 0.2%), urine (< 0.4%) and faeces (< 0.13%) [4,7,10]. Moreover, the leakage was suspected to occur partially from the injecting needle track and was observed to decrease when it was flushed with normal saline after administration of the radionuclide (before withdrawing the needle from the joint) [11]. Later, absorbed dose profiles for six radionuclides (i.e., Au-198, Dy-165, P-32, Re-186, Y-90, and Ho-166) were analytically calculated. These profiles provided the dose imparted per unit activity of injected radionuclide (Gy/mCi) as a function of penetration distance (mm) and was aimed at estimating the necessary quantity of radionuclide (i.e., activity) and the extent and pattern of absorbed dose in the joint [12]. Moreover, handling of high quantities of unsealed activities are inevitable at each step of the RSV procedure, which pose risk of high local skin doses of beta radiations to the medical staff (i.e., radiochemist, physician, nurses) unless appropriate dosimetry measurements are adopted. Finally, radiation exposure and protective measures for dose reduction of the patient attendants, family members and public are also crucial [13–21].

In this review, we aim at the dosimetry perspective of RSV procedures. Specifically, we start with the properties of an *ideal* radionuclide for RSV procedures, frequently used radionuclides and their clinical selection for the treatment of small, medium and large joints. Afterwards, various dosimetry aspects of RSV procedures such as the radiation dose to the target (i.e., diseased synovial membrane) and non-target (i.e., articular cartilage, articular bone, gonads, lymph nodes, whole body, etc.) organs of patient are discussed. Radiation doses to medical staff (i.e., the therapist physician, radiochemist, nursing staff, etc.), relatives of the patient and general public are also discussed. Finally, contamination risks and precautionary measures are highlighted.

2. *Ideal* radionuclide for RSV procedures

The basic criteria for an *ideal* radionuclide for RSV applications, as defined in many studies [1,12,17,22,23], comprise of properties such as the radionuclide being a beta particle emitter with short physical half-life, little or no gamma-ray emission, high chemical purity, no toxicity, rapid and complete biodegradability and cost effectiveness. The most commonly used radionuclides in RSV clinics that qualifies the aforementioned criteria include Yttrium-90 (Y-90), Rhenium-188 (Re-188), Erbium-169 (Er-169), Phosphorous-32 (P-32), Lutetium-177 (Lu-177), Holmium-166 (Ho-166), Samarium-153 (Sm-153) and Dysprosium-165 (Dy-165). Table 1 summarizes the physical properties of these and other typically used radionuclides in RSV applications, respectively [24].

Complete tissue destruction of synovium within the extent of targeted boundaries of the diseased joint (and consequently, RSV success) is primarily determined by the ability to deliver a clinically relevant dose to the diseased synovium. Consequently, it is essential to plan activity titration based on the depth and volume of the target tissue. To this end, selection of the radionuclide for RSV would be critical. Specifically, energy characteristics of the emitted beta (β) particle and its linear energy transfer would play a crucial role towards defining the radiation dose profile in the target tissue [33]. That said, a summary of the frequently used radionuclides in RSV procedures along with typically injected activities, particle size, joint of application and primary mode of production is depicted in Table 2.

Table 1
Summary of physical properties of typically used radionuclides in RSV applications. Therapeutic range is the distance from the source within which 90% of the energies are absorbed.

Radionuclide	Max. Energy (MeV)	Half-life	Max. Range (mm)	Mean Range (mm)	Therapeutic Range (mm)	References
Y-90	2.25	2.7 days	11	3.6	2.8	[22]
Re-186	1.07	3.7 days	3.6	1.2	1.0	[24]
P-32	1.71	14.4 days	7.9	2.6	2.2	[25]
Dy-165	1.28	2.3 h	5.6	1.4	1.3	[26]
Au-198	0.962	2.7 days	3.9	0.8	0.9	[27]
Ho-166	1.85	1.13 days	8.7	2.2	2.1	[28,29]
Sm-153	0.263	1.93 days	3.1	0.7	0.7	[30]
Re-188	2.12	17 h	10	3.1	2.1	[31]
Er-169	0.34	9.4 days	1.0	0.3	0.24	[24]
Lu-177	0.5	6.73 days	2.0	0.67	0.6	[2,32]

It is important to note that the more relevant clinical index for the selection of a radionuclide is the therapeutic range defined as the depth at which the absorbed dose is equal to 10% of the maximum dose deposited in the synovial surface [33]. In other words, therapeutic range is the distance from the source within which 90% of the energies are absorbed.

For RSV purposes, the synovial joints are divided into three groups; small (e.g., fingers, toe), medium (e.g., wrist) and large (e.g., hip, knee) joints. For RSV of the small joints such as the metacarpophalangeal joints, Er-169 citrate colloid may be used with a maximum energy and maximum range in soft tissue of the β particles being 0.34 MeV and 1 mm, respectively, which closely correspond to the thickness of the inflamed synovium [34]. Holmium-166 (Ho-166) ferric hydroxide has also been used for RSV of metacarpophalangeal joints [28]. For bigger joints like the knee, Y-90 colloids are preferred as it offers greater soft-tissue penetration and a larger particle size resulting in less accumulation in regional lymph nodes [35,36].

3. Dosimetry perspectives in RSV procedures

The recommended therapeutic dose to the target tissue for successful RSV depends on the multiple factors such as size, thickness and the type of the *disease*; thereby, it appears challenging to ascertain the precise absorbed dose in a given treatment [2,34,43,44]. In this context, initial attempts focused on absorbed dose calculations assumed that the synovial joint is a continuous and homogeneous medium of constant density. However, this over-simplified assumption may not be completely consistent with what is practical, as the thickness of inflamed synovium is typically non-uniform and heterogeneous. The back-scattered radiation from articular cartilage and bone also confounds the situation [45]. In addition, the emission energy of β particles has been assumed monoenergetic, contrary to the more realistic spectrum of energies [35]. Finally, the distribution pattern of the radionuclide inside the joint, leakage from the joint, transport of energy by bremsstrahlung photons, etc. further inhibit our ability to calculate the absorbed dose in RSV procedures accurately [12]. To this end, adequate dosimetry, where the absorbed doses to the target and to non-target tissues are quantified, provides a valuable tool towards successful RSV procedures [35,46].

Previously, various methodologies to facilitate absorbed dose calculations have been proposed and implemented. For instance, absorbed dose profiles [12,23] and absorbed dose factors [33,34] for frequently used radionuclides (e.g., Y-90, Re-186, P-32, Ho-166, Au-198, Dy-165) in RSV procedures have been previously presented; these profiles/factors can be used to extrapolate the absorbed dose imparted to the synovial joint per unit activity of injected radionuclide as a function of penetration distance. Such factors also help to select the best suited radionuclide towards achieving the proper depth of penetration in target tissue. Importantly, these theoretical models are limited to monoenergetic β-emission; thereby caution may be exercised in extrapolating these algorithms for multiple β-energies or mixed β- and γ-emissions.

In general, the administered activity and type of radionuclide varies from patient to patient and due to the complex geometry of the individual joint with an unknown surface of the inflamed synovial tissue to be treated, it is very difficult to determine the radiation dose to target and non-target tissues accurately. Nonetheless, there has been a growing interest (and requirement) to improve the dosimetric