Risk of Cancer Induction

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10.1 Introduction

Medical use of radiation is now an indispensable part of modern healthcare, and correct risk estimation is essential for justification of radionuclide therapy especially in benign disease. Radiosynoviorthesis is a local intra-articular injection of radiopharmaceuticals for radionuclide therapy. It has now been applied for more than 50 years for treatment of resistant synovitis of the different joints in various inflammatory joint diseases. While there is growing interest in the use of radiosynoviorthesis especially in patients with rheumatoid arthritis and hemophilic synovitis, concerns regarding potential toxicity including a fear of genotoxic effects and carcinogenesis still exist. Throughout this chapter, we will describe specific studies of radiosynoviorthesis and risk of carcinogenesis, touching on strengths and limitations, the need for caution interpretation, and implications for risk assessment.

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10.2 Radiation Carcinogenesis

Biological effects of ionizing radiation result largely from DNA damage, caused directly by ionizations within the DNA molecule or indirectly from the action of chemical radicals formed as a result of local ionizations. Ordinarily, a high proportion of radiation-induced DNA damage is repaired by the cell, with long-term biological consequences related to a defective DNA repair system [1]. Exposure to ionizing radiation may cause both deterministic and stochastic biologic effects. Deterministic effects are those that typically occur soon after exposure and that increase in magnitude with increasing doses above a threshold dose level. Deterministic doses such as the intended dose on the synovial surface result in cell death. Stochastic effects of radiation typically occur later after exposure, and the probability but not the magnitude of the effects is dose dependent. A threshold dose level for stochastic effects is generally not assumed. Examples of stochastic effects include cancer induction and genetic changes.

Epidemiological studies which attempt to determine the association between radiation exposure and a health outcome have been the main source of information defining the radiation risk. Today, there is also growing interest in biodosimetry techniques to assist in long-term epidemiologic investigations so that radiation-related cancer risks can be estimated as well as possible [2]. These studies have demonstrated that children are considerably more sensitive to the carcinogenic effects of ionizing radiation than adults. Furthermore, children live longer and thus have a larger window of opportunity for expressing radiation damage. Based on epidemiological studies of Japanese atomic bomb survivors and children and infants irradiated for benign diseases such as tinea capitis and skin hemangioma, a distinct pattern of risk for radiation-related tumors has emerged. Dose-related increased risks for cancers of the thyroid gland, breasts, brain, nonmelanoma skin cancer, and leukemia have been observed in adults who were irradiated for benign diseases in childhood [3]. These studies show that the risk of getting cancer rises in a straight line with exposure exceeding doses of 100 mSv. Below that 100-mSv level, however, the risk of cancer induction becomes uncertain.

Both epidemiological and biodosimetric studies of cancer risks associated with exposure to ionizing radiation have some limitations. A major limitation is related to exploring risks to a population from low doses of radiation from high-dose exposure studies, for example, in studies of the survivors of atomic bombing in Japan and in Chernobyl recovery operation workers. There are typically other uncertainties in evaluating the association between radiation exposure and cancer risk. There may be uncertainties in the "transfer" of risk estimated from one population to another, uncertainties in the effect of confounding factors, and uncertainties in the uptake and metabolism of specific radionuclides. Additionally, many factors contribute to the risk for radiation carcinogenesis, some specific to the patient and some of which are specific to radiation treatment. Various kinds of ionizing radiation like electromagnetic (X-rays, gamma rays) or particulate (alpha, beta, neutrons) show remarkable differences of their biological effectiveness. For instance, thyroid cancer has been the single largest health impact of the Chernobyl nuclear disaster, with

6,000 cases identified by 2005, according to an UNSCEAR report, but there is no likelihood of a thyroid cancer being induced by nuclides other than radioiodine [4].

10.3 Risk of Radiosynoviorthesis

Concerns about radiosynoviorthesis include the risks from exposure to ionizing radiation and cancer induction. Since it is a local form of radionuclide therapy, there should be a differentiation of tumor entities and their likelihood of being theoretically induced by radiosynoviorthesis agents. Its safety will depend on the fact which normal structures are in the target of the radiation and the percentage of the dose delivered. Beta-emitting colloidal particles are phagocytized by inflamed hypertrophic synovial tissue, including that part of the synovial lining which lies adjacent to hyaline cartilage at margins. It is therefore an inevitable event that there will be some irradiation of cartilage and subchondral bone during radiosynoviorthesis. Nevertheless, it is established that different tissues (or organs) of the body have different sensitivities for the induction of cancer by radiation. Bone marrow is very sensitive, but hyaline cartilage and muscle tissue tolerate a very high-dose radiation [5]. The dose to the bone marrow in large- or midsize joints is considered negligible owing to the fact that the distance to the radiation source is greater than the mean tissue penetration of radionuclides used for radiosynoviorthesis. Radiocolloid particles which leak out of the treated joints could potentially accumulate in the regional lymph nodes, reticuloendothelial system, bone marrow, and liver [6]. In this context, leakage of beta emitters causes little stochastic exposure especially in the hematopoietic system. No published studies have directly attributed any cancer risk to radiosynoviorthesis. But it is important to recognize how difficult it would be to perform such a study. Because low-dose risks are small and difficult to detect, epidemiological studies with sufficient statistical power would require extremely large populations and careful matching of the subjects in the study to ensure an accurate result.

Epidemiological cohorts continue to play an important role in low-dose radiation research and health risk evaluation in medical exposures as well as other cohorts with high-dose radiation exposure. Unfortunately, there are only two retrospective cohorts published specific to research on cancer incidence among patients treated with radiosynoviorthesis. One small study on the long-term risks of cancer in patients with rheumatoid arthritis who have been treated with Y-90 was reported by Vuorela et al. [7]. It included 143 rheumatoid arthritis patients with a single radiosynoviorthesis of the knee with Y-90, between the years 1970 and 1985, and other rheumatoid arthritis patients not treated with radiosynoviorthesis. The incidence of cancer in patients with and without radiosynoviorthesis was compared with that of the local population during the period starting in 1979 and ending in 1999. Adjusting for age, gender, and calendar period, the study reported no excess cancers in either of the two cohort groups (treated and not treated with radiosynoviorthesis) in comparison with the reference population. More precisely, the standardized incidence ratio for all cancers was 0.6 (95 % confidence interval (CI) 0.3–1.1) for the treated patients and 1.1 (95 % CI 0.9–1.3) for patients not treated with radiosynoviorthesis.

In a larger cohort, Infante-Rivard C et al. studied cancer incidence in patients with rheumatoid arthritis or haemophilic synovitis receiving one or more radiosynoviortheses. Follow-up covered over 25 years and compared the incidence in this group with background rates from the province of Quebec and from other parts of Canada [8]. This study reached similar conclusions with Vuorela et al., but it was substantially larger; it included subjects who had received more than a single treatment and was able to consider quantitative estimates of exposure such as dose and number of radiosynoviorthesis. A total of 4,860 radiosynoviortheses were recorded for the cohort, with subjects receiving between 1 and 16 treatments and a majority (79 %) getting 1 or 2. Treatments were most often administered to the knee joint. Most procedures were done with Y-90 (71 %) or P-32 (29 %). Category-specific rates in this cohort including 2,412 adult patients were compared with rates in similar categories from the general population generating standardized incidence ratios (SIR). No increase in the risk of cancer was observed (SIR 0.96; 95 % CI 0.82–1.12). Additionally, there was no dose–response relationship with the amount of radioisotope administered or number of radiosynoviorthesis.

Epidemiological evidence that low doses of radiation may induce cancer in humans is only available for doses higher than 100 mSv [4]. The effective doses for radiosynoviorthesis given in the dosimetric studies seem to be in the low-dose range (<50 mSv) [9–11]. For example, the effective dose with Re-186 remains approximately 30 times lower than with other treatments such as I-131 in benign thyroid diseases [12]. Also, effective doses in radiological imaging range easily in the same magnitude of 20 mSv, when computed tomography (CT) is used repeatedly. It is almost twice the dose of an abdominal CT image [13]. But that risk is very low overall and may be difficult to measure with epidemiologic techniques.

There have been two cases of acute lymphocytic leukemia reported in hemophilia patients receiving chromic phosphate-32 [14]. Both children, aged 9 and 14 years, had uncomplicated radiosynoviorthesis and developed leukemia within 1 year. Interestingly, both patients had a history of autoimmune disorder, and the interval between exposure and the development of leukemia was less than the expected peak of radiation-induced leukemia. A recent survey of hemophilia treatment centers in the United States (US) identified that approximately 1,100 P-32 radiosynoviortheses were performed in 700 patients with hemophilia, both adults and children, since 1988. While the overall cancer rate in persons with hemophilia is not known, according to one prospective study of malignancy in over 3,000 individuals with hemophilia in the United States, the rate of leukemia was low, less than 1 in 33,000 person-years [15]. Pediatric ALL has a yearly incidence of 1 in 2,500 children under age 15. Estimates from the US national registry would suggest that there should have been 1.5 cases of ALL in the hemophilia population over the last 10 years [16]. It is also kept in mind that there are differences in radiation sensitivity between individuals, depending on their gender, age, genetic factors, lifestyle, and concomitant exposures to other agents. As a consequence of these arguments, the Medical and Scientific Advisory Council of the National Hemophilia Foundation recommends discussion about the risk–benefit ratio of radiosynoviorthesis, including the potential risk of cancer, with all individuals or with their parents considering

the procedure, and written informed consent should be obtained which clearly documents that these two cases of malignancy were discussed [17]. Today, Y-90, Re-186, and Er-169 have gained widespread acceptance for radiosynoviorthesis in Europe, and P-32 is no longer mentioned in European guidelines because it has disadvantages such as half-life and high lymphatic transport [18]. Until now, an increased risk of cancer after radiosynoviorthesis with Y-90, Re-186, and Er-169 radiocolloids has not been reported.

Biomarkers that could be used for molecular epidemiological studies in radiation-exposed cohorts are of particular interest. While the validation of potential biomarkers of low-dose ionizing radiation is questioned, there is extensive research in this field [19]. The measurement of chromosome aberrations in peripheral lymphocytes whether stable (balanced translocations) or unstable (dicentrics, ring chromosomes) has been frequently used in studies of patients treated with radiosynoviorthesis. Recently, we studied the cytogenetic analyses such as chromosomal aberration analysis, micronuclei, and sister chromatid exchange as indicators of radiation-induced cytogenetic damage in 38 hemophilic children undergoing radiosynoviorthesis using Y-90 or Re-186 [20, 21]. The results of our studies indicate that high radiation doses, which would induce genotoxic effects, are not obtained by peripheral blood lymphocytes in children after radiosynoviorthesis. Dicentric aberrations are the main interest in these types of studies as the formation of dicentric chromosomes in human peripheral lymphocytes is a specific effect of ionizing radiation [22]. We could not detect any persistent dicentric chromosomal aberrations after the therapy, and there was no statistically significant increase in the number of chromosomal aberrations in children who were treated with Y-90 or Re-186 radiosynoviorthesis. Several studies have confirmed that there was no significant increase in the number of dicentric chromosomes following radiosynoviorthesis in patients who were treated with different radioisotopes [23–25].

Kavakli et al. reported some chromosomal aberrations in 40 patients with hemophilia after radiosynoviorthesis using Y-90 and Re-186. Three months after radioisotope exposure, chromosomal breakages still continued in 21 patients of whom 15 already had chromosomal breakages prior to radiosynoviorthesis, and mean values of chromosomal breakages were not found to be significant. They also pointed out that, after 1 year following the radiosynoviorthesis, four patients had persistent same level chromosomal breakages [26]. Due to the high frequency of chromosomal breakages in the patient group before radiosynoviorthesis and concomitant factors during follow-up, it is difficult to establish a relation between these nonspecific chromosomal breakages and radiosynoviorthesis. Falcon de Vargas et al. carried out a study on 31 hemophilic patients (age range 9–24 years) with no chromosomal aberrations; only nonspecific chromosomal structural changes (breakages) were observed 6 months after Re-186 injection for radiosynoviorthesis, and these changes were reversible after 1 year postinjection [23]. In contrast to these findings, Manil et al. reported a significant cumulative increase in dicentric aberrations 7 days after radiosynoviorthesis in 45 rheumatoid arthritis patients treated with Re-186 [27]. However, as there was no follow-up after 7 days in this study, it is unclear whether this significant increase in dicentrics would be persistent afterward or not.

Even if the relationship of cancer risk with micronuclei is not well substantiated, as is that with chromosomal aberrations, this method has been proven to be useful as a "biologic marker of early effects" in biomonitoring studies on the human population exposed to genotoxic agents. Micronuclei represent small, additional nuclei formed by the exclusion of chromosome fragments or whole chromosomes lagging at mitosis. Micronuclei rates, therefore, indirectly reflect chromosome breakage or impairment of the mitotic apparatus. We have observed mildly increased frequency of micronuclei in the peripheral lymphocytes of hemophilic children 2 days after radiosynoviorthesis in both Y-90 and Re-186 group. But this effect was not persistent in the peripheral lymphocytes of the children in our study and had disappeared at the day 90 control. Kavakli et al. also confirmed these results, and they have reported that there was no significant difference between the hemophilic patients with and without radiosynoviorthesis with respect to micronuclei values [28]. Prosser et al. also analyzed 22 patients with rheumatoid or osteoarthritis of the knee treated with Y-90 silicate, and no significant increase in micronucleus frequency was observed [29].

The long-lasting clinical practice and the lack of any well-documented cases of malignancy resulting from radiosynoviorthesis suggest a very low and acceptable risk compared with the benefit for the patient. The tumor morbidity rate as a result of whole-body irradiation was calculated as 0.4 per 1,000 related to International Commission on Radiological Protection (ICRP) 60 risk data [30], and the genetic radiation risk related to United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) data was described as being several orders of magnitude below 1 per 1,000 [31]. On the other hand, because of the complexity of biomonitoring of genotoxicity, we need further investigations to understand the radiation effects in untargeted living systems exactly. Furthermore, radiation effects are thought to be cumulative, which is of particular importance in children diagnosed with hemophilia. Debate continues on what cumulative level is acceptable for cancer risks for the patients need recurrent radiosynoviorthesis due to chronic disease. Patients should understand that radionuclide therapies should only be performed when the effectiveness to be gained justifies the potential harm. Decision-making about radiosynoviorthesis should include a thorough conversation between patients and their doctors regarding the benefits and risks of the procedure. While the benefits of radiosynoviorthesis outweigh the risks of developing subsequent cancers, the presence of such risks could implicate the need for further investigation into methods of minimizing the radiation dose delivered to joint and surrounding tissues.

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