Radiobiological Principles

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Keywords: Experimental in-vivo studies, experimental in-vitro studies, inactivation of stem cells, inhibition of cell proliferation, apoptosis of lymphocytes, induction of differentiation, leukocyte adhesion, radiation effects on macrophages, monocytes, membranes, genes, autonomous nerve systems; abscess, arthritis, Graves' orbitopathy, heterotopic ossification, restenosis, neovascularisation; clinical study design

1.1 Historical Classification of Suggested Mechanisms

Radiotherapy has been given successfully to patients suffering from a wide variety of benign diseases, such as eczema and psoriasis, abscess, insertion tendinitis and osteoarthritis, ankylosing spondylitis and endocrine orbitopathy and for the prevention of heterotopic ossification or of restenosis after transluminal dilatation of blood vessels. Doses given for the different indications range from those given in cancer therapy to less than 1% of those doses. This suggests that very different radiobiological mechanisms are involved in the therapeutic action of radiotherapy on the different pathological processes. Textbooks on this topic [71, 132] tend to group these largely hypothetical mechanisms into classes that are also associated with different dose ranges. We prefer the following classification of mechanisms [115, 117]:

anti-proliferative radiation effects that may play a role in the prevention of heterotopic ossification, restenosis or keloids or of progression of Dupuytren's contracture or in the treatment of benign tumours such as fibromas. Doses are generally 10 Gy or higher.

anti-inflammatory radiation effects that may also be involved in the analgesic effects of radiotherapy for, e.g., periartthritis humeroscapularis or ankylosing spondylitis or osteoarthritis. Doses range from 2 to 6 Gy.
functional radiation effects that are poorly defined and that are assumed to work by modulating the responses of the autonomous nerve system or interfering with gene activation processes. Doses are usually lower than 2 Gy.

Many other radiation-induced changes were observed in various experimental investigations up to 1970, but their role in the therapeutic effectiveness of radiotherapy of benign diseases remains as speculative as those mechanisms listed above. They have been extensively documented by Zuppinger and Ruckensteiner [132].

1.2 Experimental Investigations in Vivo

The wide range of effective doses used for different pathological processes is evidence that different radiobiological mechanisms are likely to be involved in the therapeutic action and that it would be inappropriate to concentrate on just one mechanism that would be common for all effects. For this reason, experimental studies have to be performed specifically on the different types of pathological conditions that might be indications for radiotherapy using those animal models that share important pathological features with the respective condition in patients and that yield to quantitative analysis.

For most benign conditions treated by radiotherapy, no perfect animal model is available for experimentation. It has to be remembered, however, that rodent tumours are not very good models of human cancer, either. Yet, despite that, all fundamental radiobiological principles of radiotherapy have been derived from careful quantitative studies in rodent tumours by concentrating on the elucidation of basic mechanisms rather than on designing optimal treatment schedules in the respective animal experiment. In the same way, mechanistic studies in different animal models of benign disease may be suitable to elucidate specific mechanisms that are also working in the different human diseases. The following animal models for benign disease have been used for examinations of the mechanisms of radiotherapy of benign diseases such as arthritis, inflammatory granuloma, heterotopic ossification and restenosis.

1.2.1 Arthritis

Animal models for the assessment of novel anti-rheumatic or anti-inflammatory drugs are widely used in pharmacological research [37]. Various agents when injected into a knee joint of rabbits or rats can cause acute arthritis via different pathogenetic mechanisms. Some of these models have also been used to examine the effect of radiotherapy on experimental arthritis (Table 1.1).

The first study was performed by Pannewitz [84] in rabbits. An arthrosis was induced by electrocoagulation of the knee joint cartilage or by mechanical bone destruction. Irradiation given after injury had no effect on the morphology of the degenerative changes, which is consistent with the clinical observations that radiotherapy does not affect the progression of the structural injury, although it improves the clinical symptoms of painful degenerative joint diseases.

Several studies used antigen-induced arthritis in rabbits as an experimental model for rheumatoid arthritis. Meier-Ruge et al. [77] studied antigen-induced experimental arthritis 2 weeks, 4, 6 and 12 months after intra-articular injection of 0.2–0.4 mCi $^{90}$Y as a model for the effect of radiation-synovectomy. In non-arthritic knee joints, this led to degenerative changes of the lining cell layer, fibrosis and obliteration of vessels. Two weeks after injection of radionuclides, the inflammatory oedema had disappeared, the lining cell layer of the synovial membrane had decreased, and hyalin changes were present in the subsynovial connective tissue. Four months after treatment and later, this evolved into fibrosis without inflammatory changes. External X-irradiation with three daily fractions of 2 Gy 100 days after the induction of arthritis reduced the severity of antigen-induced experimental arthritis in rats [107]. Steffen et al. [113] induced an acute arthritis by intra-articular injection of ovalbumin into the knees of pre-immunized rabbits. Irradiation with a single dose of 6 Gy was given 12 days after the induction of arthritis. This had no effects on inflammatory cell numbers up to 3 weeks after irradiation, yet proliferation of the synovial membrane was temporarily inhibited.

Budras et al. [18] induced an acute arthritis in rabbit knees by intra-articular injection of Granugenol, which elicits the inflammatory response by a foreign body effect. Five weekly fractions of 1.5 Gy were given immediately or 6 or 12 weeks later, and histological