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Refresher course: Arthropathy and other benign conditions

# Anti-inflammatory effects of low-dose radiotherapy: Indications, dose and radiobiological mechanisms involved

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Low-dose radiotherapy (LD-RT) has been used for several benign diseases, including arthrodegenerative and inflammatory pathologies. Despite its effectiveness in clinical practice, little is still known about the mechanisms through which LD-RT modulates the various phases of the inflammatory response and about the optimal dose fractionation.

The objective is to summarize current knowledge on the radiobiological mechanisms underlying the anti-inflammatory effects of LD-RT in *in vitro* experiments, in *in vivo* experimental models and in clinical studies, and to provide recommendations on the most effective and safe LD-RT treatment schedules.

## 1. Introduction

Radiotherapy (RT) is recognized as one of the main modalities in the treatment of cancer. However, the use of RT to treat some benign diseases has received considerably less attention. The term "benign disease" in the radiotherapeutic context encompasses a series of non-neoplastic pathologies that have negative effects on quality of life. High-dose RT induces the production of pro-inflammatory cytokines, leading to an inflammatory response in the irradiated tissues. Paradoxically, RT administered at low doses has the ability to modulate an on-going inflammatory response, producing an anti-inflammatory effect. The efficacy of LD-RT has been demonstrated in the treatment of degenerative bone and inflammatory diseases, such as osteoarthritis, humeral epicondylitis, scapular-humeral periarthritis, or heel spurs. Despite the known efficacy of LD-RT, irradiation regimens are still not well established. Some protocols recommend doses between 0.3 and 1.5 Gy over 4–5 sessions per week for acute conditions (up to a total dose of 3–5 Gy) or 1–3 sessions per week for chronic conditions (up to a total dose of 12 Gy). Similarly, the radiobiological mechanisms involved in the anti-inflammatory action of LD-RT have not been completely elucidated. [1–6]

## 2. Role of RT in benign diseases. Accepted indications and clinical studies

The use of RT in benign pathology is not universal. Countries such as Germany use it extensively, whereas the use of RT for this purpose is anecdotal in other countries. The German Work Group on RT and Benign Diseases published a consensus on possible indications. Low doses should be used for the acute and chronic inflammatory diseases and for painful acute and chronic degenerative joint disease.

The efficacy of LD-RT for inflammatory/degenerative joint disorders has been confirmed in various clinical studies. In painful knee osteoarthritis, the administration of 3–6 Gy at a rate of 0.35–1 Gy/session led to 60–70% improvement in pain.

## 3. Anti-inflammatory mechanisms of LD-RT

LD-RT modulates the function of a variety of inflammatory cells, including endothelial cells, polymorphonuclear leukocytes, and macrophages. Various hypotheses have been offered to explain the mechanisms of LD-RT, such as a decreased adhesion of polymorphonuclear cells to

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endothelial cells, induction of apoptosis in the cells that comprise the inflammatory infiltrate, decreased expression of adhesion molecules (P-, L-, E-selectins, ICAM-1, VCAM-1), decreased iNOS that results in a decrease in NO and ROS, increased activation of Nuclear Factor-Kappa B (NF-kB) and increased expression of anti-inflammatory cytokines (IL-10, TGF-$\beta_1$).

The majority of *in vitro* studies have characterized the possible mechanisms that explain the anti-inflammatory effects of LD-RT, whereas *in vivo* studies have observed improvements in clinical parameters in diverse experimental models.[1–6]

## 4. Conclusions

RT administered at high doses induces production of pro-inflammatory cytokines in immune cells and endothelial cells. Paradoxically, LD-RT acts upon cells that participate in the inflammatory response, producing an anti-inflammatory effect. This anti-inflammatory effect has been demonstrated in *in vitro* studies, in experimental *in vivo* studies and in clinical studies. The efficacy of LD-RT has been demonstrated experimentally by lowering clinical inflammatory parameters and improving histological markers in various models of arthritis, with doses ranging from 0.5 to 1.5 Gy. *In vitro* studies suggest that LD-RT has a potent anti-inflammatory effect, inhibiting leukocyte–endothelium interactions at doses under 0.7 Gy. In contrast, inflammatory and degenerative bone diseases in humans are treated with doses ranging from 0.3 to 1.5 Gy. Thus, using lower doses in the range 0.1–0.3 Gy could maximize anti-inflammatory effects and minimize toxicity. With respect to mechanisms underlying the anti-inflammatory effect, potential mediators include a decrease in selectins, a decrease in NO production, an increase in apoptosis, an increase in NF-kB, and an increase in the expression of anti-inflammatory cytokines such as TGF-$\beta_1$. The effect of LD-RT over time has also been studied to establish an optimal radiotherapeutic treatment regimen; the effect is maintained up to 48 h after LD-RT and lost at 72 h. Therefore, clinical practice would likely require LD-RT treatments with fractions every 48–72 h. Properly designed and powered clinical studies are necessary to determine the most efficacious treatment dose and schedules, and to establish the role of LD-RT in the therapeutic algorithm of inflammatory conditions.

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