Review article

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Anti-inflammatory effects of low-dose radiotherapy

Indications, dose, and radiobiological mechanisms involved

Radiotherapy (RT) is recognized as one of the main modalities in the treatment of cancer, and approximately 60% of patients with cancer require RT during the course of their treatments. 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. This inflammatory response, as well as the associated side effects triggered by the inflammation, limit the total radiation dose that can be administered. Paradoxically, RT administered at low doses (LD-RT) modulates the 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 [25, 59, 60, 61, 63]. Despite the known efficacy of LD-RT, irradiation regimens are still not well established. Some protocols recommend doses between 0.3–1.5 Gy over 4–5 sessions per week for acute pathology (up to a total dose of 3–5 Gy) or 1–3 sessions per week for chronic processes (up to a total dose of 12 Gy) [59]. Similarly, the radiobiological mechanisms involved in the anti-inflammatory action of LD-RT have not been completely elucidated. The objective of this review is to provide more in-depth knowledge about optimal radiotherapeutic regimens and about the radiobiological mechanisms involved in the anti-inflammatory effects of LD-RT.

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. Reasons for the limited use of RT for treating benign diseases include fear of causing radiation-induced tumors and a lack of controlled studies investigating this application. In Germany, 37,400 cases are treated annually; two-thirds of these patients have inflammatory or degenerative osteoarticular diseases [14, 29, 35, 37, 38, 47, 61]. In 2002, the German Work Group on RT and Benign Diseases published a consensus on possible indications and there are several studies published about these indications [1, 4, 23, 38, 41, 44].

The total recommended doses vary from around 50 Gy to less than 10 Gy, and they suggest that low doses should be administered for the acute and chronic inflammatory diseases and painful acute and chronic degenerative joint disease [38].

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 in 151 patients [19]. Other studies

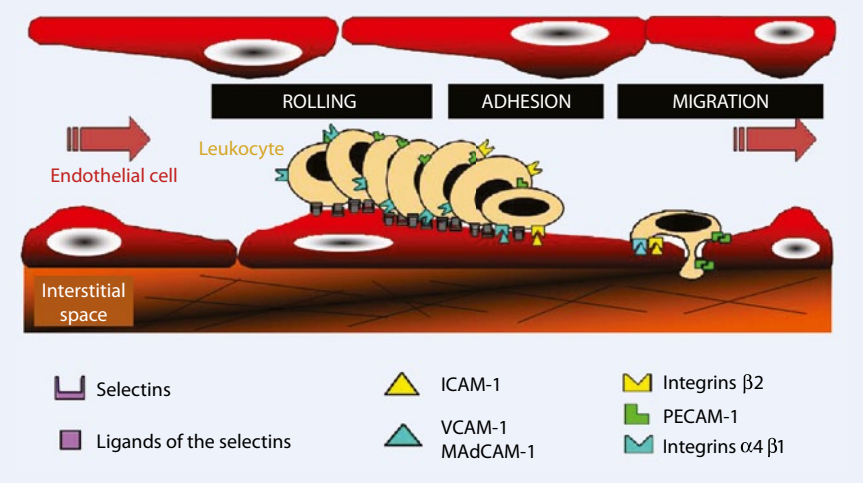

Fig. 1 ▲ Diagram of phases of recruitment of circulating leukocytes. *ICAM-1* intercellular adhesion molecule 1, *VCAM-1* vascular cellular adhesion molecule 1, *MAdCAM-1* mucosal addressin cell adhesion molecule-1, *PECAM-1* platelet/endothelial cell adhesion molecule 1

have described 50–90% improvement in pain, depending on joint affected and the duration of the symptoms prior to irradiation, with complete response in 12–25% of cases [30, 55].

The administration of 5 Gy, fractionated to 0.5 Gy/session (3 sessions/week), resulted in an improvement in pain (partial or complete) in 84–89% of patients with heel spurs [40, 42, 60].

Effects of RT on cellular integrity

Dose–response curves. Effects at low dose

Various mathematical models have been proposed to explain dose–effect curves:

- A *linear model without threshold*, where a linear relationship between radiation dose and risk is assumed. This is the most accepted and used hypothesis at present, and it takes into account the worst-case situation, assuming that any dose of radiation, however low, is potentially harmful to the organism.
- A *linear model with threshold*, which includes a dose threshold below which adverse effects are not seen. This model is based on studies that suggest that repair and defense mechanisms are highly effective for low-dose radiation, which makes it possible to neglect adverse effects for such doses [5, 63].
- The *hormesis model*, first described by Luckey in 1980 [36], postulates cellular adaptative processes at low doses of RT. It deals with an adaptive response and could explain the observed phenomenon that cells submitted to a very low-dose RT exposure can later resist exposure to higher doses of RT [56, 68].

It is to remark that the potential existence of a dose threshold below which harmful effects do not exist and beneficial effects could be potentially observed would imply a fundamental change in the premises of the current radiological protection system.

Limitations of the applicability of RT in benign illnesses: carcinogenesis. Epidemiological studies

The main concern that impedes validation and acceptance of RT for benign illnesses is the risk of carcinogenesis. This issue is truly complex, as epidemiological studies with low doses have overall not detected a significant increase in the incidence of cancer due to statistical and methodological limitations. Thus, the lack of evidence about carcinogenic effects at low doses suggests two possibilities: either such effects do not exist or they are too weak to appear as statistically significant.

In most studies, the presumed risk of radiation-induced cancer is extrapolated from observations of the effects at high or moderate doses with calculations based on the linear model without threshold, which is the most conservative approach. This hypothesis has been controversially discussed; there are groups supporting the existence of a dose threshold under which RT has no effect [5, 65, 66].

Epidemiological studies characterizing the effects of acute exposures to radiation in humans include follow-up of the following: survivors of the atomic bomb explosions in Hiroshima and Nagasaki, survivors of the nuclear plant accident in Chernobyl, patients irradiated for ankylosing spondylitis in Great Britain, and patients with tuberculosis who received repeated fluoroscopic examinations in Canada [8, 13, 28, 46, 62]. Analyses of these groups have demonstrated an increase in the incidence of radiation-induced cancer with the years since exposure [46]. The most important risk factor is age at the time of exposure. The risk of carcinogenesis is higher in people who were young when exposed (<30 years old), while when radiation is given to patients older than 60 years, the risk of cancer is three times lower [6, 8].

Epidemiological studies in populations exposed to elevated levels of natural radiation, in the USA, China, Japan, India, Iran, Austria, and the United Kingdom, have shown, in some cases, a decrease in mortality and in the incidence of cancer [11, 12, 17, 18, 43]. In addition, positive effects have been seen, such as a lower frequency of cellular chromosomal aberrations and decreased induction of chromosomal abnormalities after irradiating the cells with high doses of RT in the population of Ramsa (Iran) [17, 18].

Most epidemiological studies performed on nuclear plant workers exposed to low-dose radiation do not have adequate statistical power. The results of these individual studies are inconsistent regarding an increased risk of cancer [9, 10]. Therefore, taking into account discrepancies in the epidemiological data, we believe that the carcinogenic potential of low-dose radiation is reduced. Moreover, it is important to note that this hypothetical risk has been extrapolated from epide-

miological studies with exposure to much higher doses [33].

Mechanisms of inflammatory response: role of leukocytes and adhesion molecules

The inflammatory response of LD-RT is a tightly regulated process that involves a sequence of leukocyte–endothelium interactions, called rolling, adhesion, and migration to the interstitial space (**Fig. 1**). Initially, circulating leukocytes enter into a weak interaction with endothelial cells through a rolling movement across the walls of venules. This phenomenon of rolling is transitory and reversible, but it produces leukocyte activation through the action of local inflammatory mediators. Activated leukocytes adhere to endothelial cells and finally migrate across the endothelial cell junctions into the interstitial space [45]. Each of these stages is regulated by known membrane-bound receptors such as cellular adhesion molecules, which are expressed on the surface of endothelial cells, leukocytes, and platelets [45]. The next phase of the inflammatory response is characterized by accumulation of a variety of immunocompetent cells such as lymphocytes (B and T), granulocytes (neutrophils, eosinophils, and basophils), and monocytes/macrophages. Subsequently, the immune cells perform functions such as phagocytosis, cytotoxicity, antigen presentation, cytokine secretion, release of reactive oxygen species (ROS), and expression of inducible NO-synthetase (iNOS) that result in the production of nitric oxide (NO). Activation of macrophages is an important step in inflammation because once they are activated, macrophages produce NO and pro-inflammatory cytokines responsible for pain, erythema, and edema. Endothelial cells have a decisive role in the inflammatory process because of their ability to recruit leukocytes and express various cytokines and growth factors. Whereas some cytokines, such as interleukin (IL)-1, tumor necrosis factor-α (TNF-α), IL-6, IL-8, and IL-12, have pro-inflammatory effects, others have anti-inflammatory effects, as it occurs with transforming growth factor (TGF)- β_1, IL-10, and IL-4. Pro-inflammatory cytokines are important for inducing expression of adhesion molecules and other inflammatory mediators, such as NO.

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 endothelial cells, induction of apoptosis in the cells that comprise the inflammatory infiltrate, decreased expression of adhesion molecules (P-, L-, E-selectins, ICAM, VCAM), decreased iNOS that results in a decrease in NO and ROS, increased activation of nuclear factor-kappa B (NF-κB), increased expression of anti-inflammatory cytokines (IL-10, TGF-β_1), hampered the expression of cellular total AKT and the chemokine CCL20 from PMN, and increased activator protein 1 (AP-1) activity [16, 21, 22, 24, 25, 26, 27, 31, 32, 39, 48, 49, 50, 51, 52, 53, 54, 58].

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

In vitro studies

Studies in vitro (**Tab. 2**) suggest that doses ≤0.7 Gy modulate the expression of adhesion molecules and the production of cytokines, leading to a decrease in leukocyte adherence to endothelial cells [25, 31, 32, 51, 53]. In these studies, the role of LD-RT has been investigated at different steps of the inflammatory response. Some of the in vitro studies analyzed the duration and timing of the anti-inflammatory response to LD-RT. Decreases in adhesion were observed at 4, 24, and 48 h after RT, and in two studies an increase in leukocyte adherence to endothelial cells was ob-

Abstract · Zusammenfassung

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

Abstract
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 known about the mechanisms through which LD-RT modulates the various phases of the inflammatory response and about the optimal dose fractionation. The objective of this review is to deepen knowledge about the most effective LD-RT treatment schedule and radiobiological mechanisms underlying the anti-inflammatory effects of LD-RT in various in vitro experiments, in vivo studies, and clinical studies.

Keywords
Low-dose radiotherapy · Leukocyte · Endothelium · Adhesion molecules · Benign diseases

Entzündungshemmende Effekte von niedrigdosierter Strahlentherapie. Indikationen, Dosis und zugrundeliegende radiobiologische Mechanismen

Zusammenfassung
Niedrigdosierte Strahlentherapie (LD-RT) wird für die Behandlung verschiedener gutartiger Erkrankungen, einschließlich für arthrodegenerative und entzündliche Erkrankungen verwendet. Obwohl diese in der Praxis effektiv sind, wissen wir noch sehr wenig über die zugrundeliegenden Mechanismen der entzündungshemmenden Wirkung und die optimale Dosisfraktionierung. Das Ziel des Artikels ist es, unser Wissen über LD-RT und die zugrundeliegenden entzündungshemmenden Effekte in verschiedenen In-vitro-Versuchen und In-vivo-Studien sowie in klinischen Studien zu vertiefen.

Schlüsselwörter
Niedrigdosierte Strahlentherapie · Leukozyten · Endothelium · Adhäsionsmoleküle · Gutartige Erkrankungen

Tab. 1 Summary of radiobiological mechanisms of LD-RT

Mechanism	Dose tested
Immunoglobulin superfamily	No change in expression of ICAM-1 or VCAM-1 (dose 0.1–1 Gy) [21, 24, 25, 31]
Selectins	↓ expression L-selectin (minimum dose of 0.3 Gy), no change in E-selectin or P-selectin [31]
	↓ expression E-selectin (minimum dose of 0.7 Gy) [25, 53]
	↑ E-selectin (0.5 Gy) [21]
iNOS	↓ iNOS (≤1.25 Gy) [24, 26]
ROS	↓ ROS (0.3–0.6 Gy) [58]
NF-κB	↑ NF-κB (maximum of 0.5 Gy), ↓ 0.6 Gy-0.8 Gy and ↑ again at 1–3 Gy [54]
TGF-β_1	↑ TGF-β_1 (maximum of 0.5 Gy) [54]
AP-1	↑ AP-1 (maximum of 0.3 Gy)), ↓ 0.5–1 Gy and ↑ again at 3 Gy [52]

ICAM-1 intercellular adhesion molecule 1, **VCAM-1** vascular cellular adhesion molecule 1, **iNOS** inducible NO-synthetase enzyme, **ROS** reactive oxygen species, **NF-κB** nuclear factor kappa B, **TGF-** β_1 transforming growth factor β_1, **AP-1** activator protein 1

Tab. 2 Summary of in vitro low-dose radiotherapy studies

Author	Dose (Gy)	Results
Kern [31]	0.1–10	0.1–0.5 Gy: ↓ adhesion 70%. ↓ L-selectin expression (minimum of 0.3 Gy)
		No change in expression of ICAM-1 or VCAM-1 with dose 0.1–1 Gy
		No change in expression of E-selectin, P-selectin
		↑ apoptosis (maximum 0.3–0.7 Gy)
Roedel [49, 51, 52, 54]	0.3–10	0.3–0.7 Gy: ↓ adhesion, ↓ E-selectin, ↑ TGF-β_1 and ↑ IL-6, ↑ NF-κB, ↑ AP-1
Hildebrandt [24, 25, 27]	0.3–10	0.3–0.6 Gy: ↓ adhesion. ↓ expression of E-selectin. No change in ICAM-1
		≤1.25 Gy: ↓ iNOS
Schaue [58]	0.3–10	0.3–0.6 Gy: ↓ oxidative stress
Mirzaie-Joniani [39]	0.5–10	<2 Gy and lower dose rate: ↑ apoptosis
Hallahan [21]	0.5–50	↑ expression of E-selectin (observed with dose of 0.5 Gy)
		ICAM-1 unchanged with dose <5 Gy
Hertveldt [22]	0.1–5	<1 Gy: ↑ apoptosis
Prasad [48]	0.25–50	↑ NF-κB (maximum of 0.5 Gy)

ICAM-1 intercellular adhesion molecule 1, **VCAM-1** vascular cellular adhesion molecule 1, **TGF-** β_1 transforming growth factor β_1, **IL-6** interleukin, **NF-κB** nuclear factor kappa B, **AP-1** activator protein 1, **iNOS** inducible NO-synthetase enzyme.

served 12 h after irradiation, showing an inverse correlation with concentrations of TGF-β_1 and activation of NF-κB [25, 54].

In vivo studies

In vivo studies (**Tab. 3**) using animal models of arthritis demonstrated a reduction in clinical and histological parameters of arthritis after administering radiation doses between 0.5–1.5 Gy [7, 15, 26, 34, 64]. In animal models, LD-RT led to an improvement of clinical symptoms, inflammatory signs, and pain [64, 67]. Decreases in inflammatory proliferation of synovial cells, as well as decreases in the synthesis of synovial fluid and joint swelling were also observed. In a similar manner, LD-RT leads to a decrease in inflammatory signs, bone loss, and degradation of cartilage [64]. The various therapeutic regimens employed in different studies are described in **Tab. 3**.

Timing of anti-inflammatory efficacy was assessed in some of the in vivo studies, and decreases in clinical arthritis parameters were observed up to 15–19 days after the maximal inflammatory response [34]. In addition, histological changes were characterized over time, demonstrating histological improvement 10–30 days after irradiation with 0.5–1 Gy during the acute inflammatory phase [15, 26, 34].

The systemic effect of local irradiation was demonstrated by irradiating one extremity in rabbits with a dose between 0.1 and 10 Gy. A significant increase in phagocytic activity of *E. aureus* was observed in peripheral blood cells 48 h after 1 Gy, but decreased phagocytic activity was observed at higher doses [20]. In a model of granulomatous disease, the anti-inflammatory effect of irradiation correlated with decreased iNOS activity and increased expression of heme oxygenase-1 (HO-1) [27]. The results from a pro-inflammatory stimulus demonstrate that LD-RT induces an increase in levels of TGF-β_1, which is maximal 24 h after irradiation and decreases to basal levels at 72 h. LD-RT also induces decreased levels of pro-inflammatory cytokines such as TNF-α, interleukin-1 beta (IL-1β), and iNOS at 24 and 48 h and increased levels of HO-1 and inducible heat shock protein 70 (HSP70) [57].

Our group analyzed the effects of LD-RT on an experimental model of acute systemic inflammation induced by lipopolysaccharide (LPS) in mice. The abdominal region of mice was irradiated with a single dose of RT at 0.1, 0.3, or 0.6 Gy 1 h before administration of the pro-inflammatory stimulus. Leukocyte–endothelium interactions were analyzed using intravital fluorescent microscopy. Expression of the endothelial adhesion molecule ICAM-1 was quantified by a marked double antibody technique, and plasma and intestinal levels of TGF-β_1 were determined by ELISA. Five hours after irradiation, we observed that LD-RT caused decreased adhesion of leukocytes in intestinal venules at three studied dose levels. The lowest effective dose was 0.3 Gy, and the anti-inflammatory action of RT did not depend on changes in ICAM-1 expression in response to LPS. Moreover, LD-RT induced overexpression of TGF-β_1, and increased expression of this cytokine is, at least in part, responsible for the anti-inflammatory effect of RT. This anti-inflammatory effect was maintained for 48 h after irradiation and lost

Tab. 3 Summary of experimental studies of LD-RT

Author	Experimental model	RT dose/time	Results
Van Pannewitz [67]	Rabbit knee arthritis (electrocoagulation)	1 Gy	↓ inflammation symptoms
		Different	
Glenn [20]	Healthy rabbit leg	0.1–10 Gy (90–400 KV)	↑ phagocytic index at 1 Gy
		24 h–2 weeks before study	↓ phagocytic index at doses >1 Gy
Budras [7]	Rabbit knee arthritis (intraarticular granugenol injection)	5 fractions of 1.5 Gy	↓ inflammation (↓ cellular proliferation at sinovial membrane; ↓ synovial fluid)
		Immediately, 6 or 12 weeks after injection	
Trott [64]	Rat knee arthritis (intraarticular *Mycobacterium TBC* injection)	5 Gy 4 fractions of 1 Gy (daily)	↓ inflammation (4 fractions of 1 Gy) (↓ articular swelling, ↓ destruction of cartilage and bone)
		3 h after injection	
Fischer [15]	Rabbit knee arthritis	5 fractions of 1 Gy (daily)	↓ inflammation (also histological)
	(Intraarticular injection of papaín)	1 day post-injection	(↓ articular diameter, ↓ synovial membrane thickness, ↓ synovial membrane cells)
Hildebrandt [27]	Mice granulomatous disease	2 Gy day 2	↓ inflammation (also histological)
		2 Gy day 6	↓ iNOS and ↑ HO-1
		5 fractions of 0.5 Gy from day 2 to day 6	
Hildebrandt [26]	Rat knee arthritis (*Mycobacterium TBC*)	5 fractions of 1 Gy 5 fractions of 0.5 Gy	↓ inflammation (also histological) ↓ iNOS and ↑ HO
		15–19 days post-induction	
Liebmann [34]	Rat leg arthritis (*Mycobacterium TBC*)	5 fractions of 1 Gy 5 fractions of 0.5 Gy	↓ inflammation (more effective 5 fractions of 1 Gy)
		10–26 days post-induction	
Schaue [57]	Mice superficial dorsal air cell model	0–5 Gy	↓ iNOS, ↑ HSP-70 and ↑ HO-1
		6 h after induction	
Arenas [2, 3]	Mice systemic inflammation model with lipopolysaccharide (LPS)	0.1, 0.3, 0.6 Gy	↓ leukocyte adhesion
		5, 24, 48, 72 h	ICAM-1 not modified
			↑ TGF-β_1

iNOS inducible NO-synthetase enzyme, **HO-1** hemoxygenase-1, **HSP70** inducible heat shock protein 70.

at 72 h. We have also observed a correlation with TGF-β_1 levels in the first 24 h [2, 3].

Conclusion

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 various 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 0.5–1.5 Gy. In vitro studies suggest that LD-RT has a potent anti-inflammatory effect, inhibiting leukocyte–endothelium interactions at doses <0.7 Gy. In contrast, inflammatory and degenerative bone diseases in humans are treated with doses ranging from 0.3–1.5 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 (L-, E-), a decrease in NO, an increase in apoptosis, an increase in NF-κB, and an increase in the expression of anti-inflammatory cytokines such as TGF-β_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 establish the role of LD-RT in the therapeutic algorithm of inflammatory conditions.

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