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LETTER

Low-dose radiotherapy for severe osteoarthritis refractory to conservative treatment in older adults: an underexplored option

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Abstract

Osteoarthritis is a chronic age-related disorder associated with persistent pain and progressive functional decline. Although arthroplasty is considered the definitive treatment for advanced disease, many older adults with severe symptomatic osteoarthritis are not candidates for surgery because of frailty, multimorbidity, or limited physiological reserve, and some decline operative intervention despite persistent symptoms after comprehensive conservative management. This scenario creates a therapeutic gap in patients whose primary goals are pain relief and preservation of function. Low-dose radiotherapy (LDRT), defined as localized anti-inflammatory irradiation delivered at total doses of approximately 3–6 Gy in small fractions, represents a non-invasive and largely underrecognized therapeutic option. Its biological effects differ from those of oncologic radiotherapy, acting mainly through immunomodulatory and anti-inflammatory mechanisms within the osteoarticular microenvironment. Observational studies and clinical cohorts have reported meaningful pain reduction and functional improvement, whereas randomized and pooled analyses have produced more heterogeneous results. These discrepancies may partly reflect differences in patient selection, baseline disease severity, and outcome assessment across studies. Despite remaining uncertainties, LDRT may represent a reasonable risk-adapted option for carefully selected older adults with severe osteoarthritis refractory to conservative therapy who are not eligible for arthroplasty or decline surgery. Greater clinical awareness and well-designed trials focused on this population are needed to clarify its role in multidisciplinary care.

Keywords: Low-dose radiationtherapy, osteoarthritis, pain management, joints, musculoskeletal pain disorders, aging, anti-inflammatory agents

In 2020, osteoarthritis affected 595 million people worldwide, primarily affecting the hip (78.6%), knee (74.9%), and hand (48.6%) [1]. Beyond being a purely degenerative disorder and projected to affect 7.6% of the global population by 2024, osteoarthritis is increasingly recognized as a chronic age-related disease whose prevalence rises alongside population aging [2–4]. It is currently understood as a state of low-grade chronic inflammation driven by osteoimmunological mechanisms and cytokine dysregulation, contributing to persistent pain and functional decline [1]. Its pathophysiology reflects the interaction between cumulative mechanical stress, chondrocyte senescence, and metabolic and genetic factors that progressively weaken the osteoarticular unit [3, 4].

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In older adults, osteoarthritis management follows a stepwise approach, with conservative measures typically followed by arthroplasty as the definitive treatment for advanced disease [1, 5]. However, the high prevalence of multimorbidity, frailty, sarcopenia, and/or malnutrition—conditions frequently encountered in geriatric populations—means that many older adults with severe symptomatic osteoarthritis remain refractory to conservative therapy yet are not candidates for arthroplasty, thereby creating a clinically meaningful therapeutic gap [6]. In this subgroup, where the primary goals are pain control and preservation of function rather than structural correction, therapeutic decisions should be proportionate to patient vulnerability and aligned with risk-adapted care in non-malignant conditions [7].

In this context, low-dose radiationtherapy (LDRT) delivered as localized anti-inflammatory irradiation operates through mechanisms fundamentally distinct from those of high-dose oncological radiotherapy [4, 7]. Unlike the latter, its therapeutic goal is not cytotoxicity or the induction of secondary inflammation, but rather the biological modulation of the inflammatory osteoarticular microenvironment [2]. At the molecular level, it regulates the inflammatory response by reducing pro-inflammatory cytokine expression, promoting macrophage polarization from a pro-inflammatory M1 phenotype towards an anti-inflammatory M2 profile, and attenuating degradative enzymatic activity, thereby exerting an immunomodulatory effect on cartilage, subchondral bone, synovium, and periarticular tissues [2, 4].

Clinically, LDRT is typically administered on an outpatient basis, with a total dose of 3–6 Gy delivered in fractions of 0.5–1 Gy per session over 6 applications, with the option of a second cycle after 8–12 weeks in cases of partial response [2, 8]. This modality has been employed in Germany for decades. It is supported by the *Radiotherapy for Benign Diseases* guideline issued by the German Society for Radiation Oncology (DEGRO), which recommends its use in severe gonarthrosis and coxarthrosis following failure of conservative management, particularly when surgical intervention is either not feasible or not desired by the patient [2, 9].

In the United States, Koneru *et al*. conducted a retrospective analysis of 69 patients treated at 168 anatomical sites (mean age 74.1 years; range 59–94 years) who received a total dose of 3 Gy delivered in six fractions [8]. Pain intensity was assessed using the Numeric Rating Scale (NRS), which included both the total NRS (0–100 points), encompassing multiple domains related to functional impact, and the relevant NRS (0–10 points), focused on the patient's primary reported pain. The total NRS decreased from 40.4 ± 15.2 to 26.0 at the end of treatment and remained stable at 25.8 at 10 weeks ($p < 0.001$), representing an approximate absolute reduction of 14 points. The relevant NRS declined from 6.3 ± 2.1 to 4.0 and remained stable at follow-up ($p < 0.01$). The overall response was evaluated using the von Pannewitz Scale (VPS), with a score of ≤ 2 defined as a significant response. This threshold was achieved in 80% of treated joints at the end of therapy and was maintained in 72% at 10 weeks. Thirty-three per cent of joints received a second therapeutic cycle, resulting in additional pain reduction (total NRS from 28.3 to 16.8; relevant NRS from 5.2 to 3.7; $p < 0.01$) [8].

In Germany, Rühle *et al*. conducted a multicenter analysis of 970 patients aged ≥ 65 years, encompassing 1,185 treated anatomical sites (median age: 76 years; range: 65–98 years) [10]. Pain intensity, assessed using the total NRS, decreased from 66.0 ± 11.1 at baseline to 53.4 at the end of treatment and to 44.5 at 8-week follow-up ($p < 0.001$), corresponding to a cumulative reduction of approximately 21 points. Sixty percent of patients achieved a significant overall response, defined as a VPS ≤ 2, immediately post-treatment; this proportion increased to 65.6% at follow-up, suggesting a progressive analgesic effect and supporting deferred evaluation before determining definitive response. Efficacy was independent of age and was not influenced by sex, fractionation schedule, anatomical location, or prior treatments. A second therapeutic course was administered in 32.4% of cases, yielding a response rate of 61.0% that was consistent across age groups [10].

In Germany, the multicenter, randomized, single-blind ArthroRad trial evaluated 229 joints from 133 patients with painful osteoarthritis of the hand/fingers and knee (mean age 67 years) [11]. Joints were allocated either to a standard regimen of 3.0 Gy (0.5 Gy per fraction, twice weekly) or to an experimental ultra-low-dose regimen of 0.3 Gy (0.05 Gy per fraction, twice weekly), with follow-up extending to 12 months. Both groups demonstrated sustained pain relief, assessed using the Visual Analogue Scale (VAS, 0–100 points), with a mean reduction of 19.5 points in the standard group ($p < 0.001$) and 16.2 points in the experimental group ($p < 0.001$). A clinically relevant response was defined as a VAS reduction ≥ 30 points and was achieved in 41% of the standard-dose group and 44% of the ultra-low-dose group, with no statistically significant differences between regimens and no reported adverse events ($p = 0.641$). Baseline pain intensity was the only independent predictor of response, such that higher initial VAS scores were associated with a greater likelihood of improvement ($p = 0.001$) [11].

In contrast to the preceding observational evidence, the systematic review and meta-analysis by Hammadeh *et al*. examined whether low-dose radiotherapy is superior to placebo for pain relief and functional outcomes in osteoarthritis [9]. Twelve studies comprising 1,750 participants were included, of which six randomized controlled trials were eligible for quantitative meta-analysis. Overall risk of bias was low, and the certainty of evidence was rated as moderate for pain and function and high for adverse events. Regarding pain outcomes, the random-effects model demonstrated no statistically significant difference compared with placebo (standardized mean difference [SMD] −0.92; 95% CI −2.14 to 0.29; $p = 0.13$), with substantial heterogeneity ($I^2 = 96\%$; $p < 0.00001$). Similarly, no superiority of low-dose radiotherapy was observed for functional outcomes (SMD 0.22; 95% CI −0.13 to 0.56; $p = 0.22$), with low heterogeneity ($I^2 = 23\%$; $p = 0.27$).

This discrepancy between observational studies and ran-

domized trials may partly reflect differences in patient selection and study design. Randomized trials often use stricter inclusion criteria that exclude frail older adults with multimorbidity or functional impairment, patients commonly seen in routine geriatric practice. In contrast, observational cohorts often include these more clinically complex populations, which may better represent real-world candidates for LDRT. As a result, differences in baseline disease severity and functional vulnerability may contribute to the variability in reported outcomes. Although much of the clinical experience with LDRT comes from Germany, interest in this approach has also grown in other settings, including North America and additional European centers. Broader international evidence and trials specifically aimed at older, medically complex patients could help clarify its role in multidisciplinary pain management [9].

In terms of safety, low-dose radiotherapy for osteoarthritis typically employs total doses of 3–6 Gy, approximately tenfold lower than those used in oncological radiotherapy for macroscopic disease (60–66 Gy), and is therefore associated with a favorable overall toxicity profile [9]. In placebo-controlled trials, the proportion of responders did not differ significantly up to 12 months (RR 1.15; 95% CI 0.87–1.51), with no statistically significant differences observed at months 1, 2, 3, 6, and 12 ($p = 0.13$, 0.33, 0.91, 0.70, and 0.54, respectively; $I^2 = 0\%$). Overall, adverse events were more frequent in the low-dose radiotherapy group (RR 1.44; 95% CI 1.08–1.92; $p = 0.01$; $I^2 = 0\%$), predominantly nail reactions (RR 2.24; 95% CI 1.13–4.45; $p = 0.02$). However, these were largely grade 1 toxicity—mild and transient in nature—without a significant increase in serious adverse events or toxicity ≥ grade 3 [9]. The carcinogenic risk is largely theoretical and depends on patient age, cumulative dose, irradiated volume, and the presence of genetic predisposition syndromes [12]. Given the low exposure associated with low-dose radiotherapy and the prolonged latency required for the development of radiation-induced malignancies, the absolute risk is considered extremely low in individuals over 40 years of age and clinically marginal in geriatric populations, with no evidence of a significant increase in secondary neoplasms in the available series [9, 12].

Although placebo-controlled evidence has yielded inconsistent results [9, 11], the magnitude of benefit observed in clinical cohorts [8, 10], together with its favorable safety profile [7, 9] and biological plausibility, supports the need for further investigation using rigorous study designs [1, 4]. Future trials should focus on older adults with severe osteoarthritis who are unresponsive to comprehensive conservative management—including physical therapy, lifestyle changes, multimodal pain relief, interventional procedures (such as corticosteroid or local anesthetic injections, platelet-rich plasma, hyaluronic acid), nerve blocks, or radiofrequency denervation [1, 2, 6]—and are not candidates for arthroplasty. This group often includes individuals characterized by frailty, multiple health conditions, osteosarcopenia, as well as patients who decline surgical treatment [1, 6, 7, 10].

Although additional studies are needed to more precisely define optimal candidate selection, standardized protocols already exist and are supported by guidelines such as those of the German Society for Radiation Oncology, DEGRO, which have demonstrated clinical effectiveness and feasibility [1, 7, 9]. In this context, LDRT may serve as a risk-adjusted approach for symptom control in older adults with severe osteoarthritis who do not respond to conservative treatments and are not candidates for arthroplasty. These patients prioritize pain relief and functional preservation as their therapeutic goals. Outcomes are reported using either the Numeric Rating Scale (NRS) or the Visual Analogue Scale (VAS), depending on the original study's instruments. Although these scales differ methodologically, they measure similar aspects of pain intensity and functional impact; thus, results should be interpreted mainly in terms of meaningful symptom improvement. These findings support further investigation of LDRT in carefully selected older adults as part of multidisciplinary pain management strategies.

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