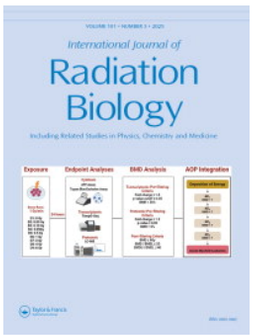

International Journal of Radiation Biology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/irab20

Effects of low dose rate radiotherapy on pain relief, performance score, and quality of life in patients with knee osteoarthritis; a double-blind sham-controlled randomized clinical trial

Danial Fazilat-panah, Seyed Alireza Javadinia, Ali Shabestani Monfared, Fahimeh Attarian, Mansour Babaei, Behnaz Yousefghahari, Saeed Najafzadeh Sadati, Nahid Ahmadi & Hamid Fallah Tafti

To cite this article: Danial Fazilat-panah, Seyed Alireza Javadinia, Ali Shabestani Monfared, Fahimeh Attarian, Mansour Babaei, Behnaz Yousefghahari, Saeed Najafzadeh Sadati, Nahid Ahmadi & Hamid Fallah Tafti (05 Mar 2025): Effects of low dose rate radiotherapy on pain relief, performance score, and quality of life in patients with knee osteoarthritis; a double-blind sham-controlled randomized clinical trial, International Journal of Radiation Biology, DOI: 10.1080/09553002.2025.2473975

To link to this article: https://doi.org/10.1080/09553002.2025.2473975

Published online: 05 Mar 2025.

INTERNATIONAL JOURNAL OF RADIATION BIOLOGY
https://doi.org/10.1080/09553002.2025.2473975

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Effects of low dose rate radiotherapy on pain relief, performance score, and quality of life in patients with knee osteoarthritis; a double-blind sham-controlled randomized clinical trial

Danial Fazilat-panah[a*], Seyed Alireza Javadinia[b*], Ali Shabestani Monfared[c], Fahimeh Attarian[d], Mansour Babaei[e], Behnaz Yousefghahari[f], Saeed Najafzadeh Sadati[g], Nahid Ahmadi[c] and Hamid Fallah Tafti[h]

[a]Cancer Research Center, Babol University of Medical Sciences, Babol, Iran; [b]Non-Communicable Diseases Research Center, Sabzevar University of Medical Sciences, Sabzevar, Iran; [c]Cancer Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran; [d]Department of Epidemiology and Biostatistics, School of Health, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran; [e]Clinical Research Development Unit of Rouhani Hospital, Babol University of Medical Sciences, Babol, Iran; [f]Department of Rheumatology, Ayatollah Rouhani Hospital, Babol University of Medical Sciences, Babol, Iran; [g]Private Section, Babol, Iran; [h]Radiotherapy Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

ABSTRACT

Introduction: Knee osteoarthritis (OA) is a prevalent chronic condition characterized by progressive damage to the articular cartilage, resulting in chronic pain, swelling, and reduced range of motion with a range of prevalence of 10-40%. This study aims to investigate the efficacy of low-dose radiation as a local treatment option for knee OA symptoms.

Methods: In this prospective study, patients with confirmed OA and older than 65 years were randomly assigned to treatment and control groups. The protocol plan IRCT20160706028815N6 was registered in Iranian registry of clinical trials system. The treatment group received 3 Gy radiation over six fractions, while the control group continued routine treatment without radiation. The pain intensity and functional levels were assessed at pretreatment and each month following completion of therapy for six consecutive months by Visual Analog Scale (VAS) and the Lysholm 100-point Scale, respectively. Analgesic medication usage and performance status (PS) were also assessed.

Results: The mean age of the patients was 77 years (range 72-89). All variables including VAS pain score, Lysholm scale, PS and analgesic consumption were improved following radiation from first month to the end of assessments (p value <0.01).

Conclusion: Results showed significant pain score improvements and enhanced joint function with no adverse effects. Findings were compared with previous studies, revealing mixed conclusions on low dose radiation therapy (LDRT) efficacy. Mechanistic hypotheses suggest LDRT may modulate inflammatory pathways. The study suggests LDRT at 3 Gy could benefit knee osteoarthritis patients and calls for further research on mechanisms of action in early-stage osteoarthritis.

ARTICLE HISTORY
Received 19 March 2024
Revised 21 February 2025
Accepted 24 February 2025

KEYWORDS
Knee; irradiation; low-dose radiotherapy; osteoarthritis; pain; performance status

Introduction

Knee osteoarthritis (OA) is a chronic condition that affects one or both knee joints, primarily causing progressive damage to the articular cartilage resulting in chronic pain, joint swelling and reduced range of knee joint motion, starting and worsening with aging process (Hunter and Bierma-Zeinstra 2019). Its prevalence is estimated to be a broad range of 10-40% in different parts of the world among different age groups (Losina et al. 2013; Driban et al. 2020; Hong et al. 2020; Li et al. 2020). Due to the increasing prevalence of its risk factors, the increase in the prevalence of knee OA has become a great trouble for the society. The primary risk factors include aging, obesity and higher body mass index, lower socioeconomic status and traumatic lesions of the joint (Moss et al. 2016; Callahan et al. 2021; Allen et al. 2022).

The primary treatment options of knee OA include lifestyle modification, systemic treatments as well as local treatments. Patients are usually advised to strengthen particular group of muscles by definite exercises and to minimize total and semi-total bending of the joint (Young et al. 2023). Systemic treatments typically consist of oral medication such nonsteroidal anti-inflammatory drugs (NSAIDs) which have been longtime recognized to have side effects specially among geriatric patients with probable comorbidities such as cardiac and gastric complications (Richard et al. 2023). OA is routinely treated locally by direct intra articular injection

CONTACT Hamid Fallah Tafti hmd_fallah@yahoo.com Radiotherapy Research Center, Shahid Ramazanzade Oncology Center, Shahid Sadoughi University of Medical Sciences, Shahid Motahari street, Yazd, Iran.
*Co-first authors.

of anti-inflammatory drugs, surgical manipulation and joint replacement (Postler et al. 2023; Richard et al. 2023).

One of local treatments that has received attention in recent decades for OA is radiotherapy. Overall, studies have shown that LDRT for OA can be an effective treatment to improve quality of life and reduce pain particularly in patients who are not surgical candidates or cannot tolerate pharmacologic therapies due to side effects. Using this treatment modality is cost effective and noninvasive tool with minimal side effects which can lead to a reduction of pain and improvement of the quality of life for the patient (Dove et al. 2022). In this trial, we assessed the effect of low dose radiation therapy on symptoms of knee OA.

Methods

This survey was a double-blind sham-controlled randomized clinical trial which have been approved by the ethics committees of Babol University of Medical Sciences and Sabzevar University of Medical Sciences (IR.MEDSAB.REC.1399.121 and IR.MUBABOL.REC.1399.453). The protocol plan with code IRCT20160706028815N6 has been registered in the Iranian Registry of Clinical Trials (IRCT) system (https://irct.behdasht.gov.ir/). Patients in academic centers of Vasei Hospital and Shahid Rajaee Hospitals affiliated to Sabzevar University of Medical Sciences and Babol University of Medical Sciences, respectively, with knee OA were assessed. Inclusion criteria included patients age 65 years or older with OA confirmed by rheumatologist using history, physical examination and proper imaging older than 65 years old. While written consent was obtained from each patient separately, patients with history of lower limb radiation therapy due to any reason and with radiation interruption of at least two fractions, were excluded from the study.

After obtaining demographic data from patients, they were randomly assigned to treatment and control arm. The two groups were stratified by sex, age group and comorbidities including diabetes mellitus, cardiovascular disease and hypertension. In the treatment arm, patients performed CT scan of involved knee joint as CT sim, then images were delineated and planned by single radiation oncologist and dosimetrist using Lina Tech treatment planning system v.1.0.8.545. Treatment volume was both surfaces of involved knee joint. Afterwards, patients received exposure to total of 3 Gy photon beam by 6mv Elekta linear accelerator during 6 consecutive daily fractions, 0.5 Gy each day. Patients in control arm were simulated to undergo both CT scan and radiation therapy but none were exposed to X-ray.

Both groups were visited and examined by a single rheumatologist who was blind to the group; during multi visits before treatment, and monthly after completion of treatment for 6 consecutive months. OA severity was classified by Kellgren-Lawrence classification method, in which grading is as follows: grade 0: No joint space narrowing (JSN) or reactive changes, grade 1: Doubtful JSN, possible osteophyte lipping, grade 2: Definite osteophytes, possible JSN, grade 3: Moderate osteophytes, definite JSN, some sclerosis, possible bone-end deformity and grade 4: Large osteophytes, marked JSN, severe sclerosis, definite bone ends deformity (Kohn et al. 2016). Pain intensity was assessed using the Visual Analog Scale (VAS) [0 for no pain to 10 for the most severe pain] (Delgado et al. 2018). Functional level based on the Lysholm 100-point Scale [91 to 100 points is considered excellent; 84 to 90, good; 65 to 83, fair; and 64 or less, unsatisfactory] were also assessed (E Albuquerque et al. 2011; RP et al. 2011). Consumption and dosage of medications for knee OA including steroids and NSAIDs, as well as performance status (PS) of patients were also recorded during these visits.

All data was analyzed by SPSS 24 software using mainly Chi-Square and Fisher Exact tests to compare differences in periodic patient assessments between treatment and control arms.

Results

In this randomized clinical trial, 60 patients with knee OA were enrolled. The mean age of the patients was 76.77 ± 3.86 years with a range from 72 to 89 years. All participants were randomly allocated to intervention and placebo groups. The characteristics of the two study groups were compared in Table 1. The explicit result of Table 1 shows that the two groups were exactly comparable (Intervening variables were similar $p > .05$).

Table 2 shows that prior to the commencement of the trial, the pain score, the Lysholm score, and the number of daily medications in the RT and placebo groups did not have a statistically significant difference ($p > 0.05$). Since the distribution of pain score, Lysholm index, number of daily medications, and functional level was not normal between the two groups ($p < .05$), we used non-parametric tests to compare these two groups.

Table 3 shows a significant decrease in the mean rank VAS pain scores in the intervention group compared to the placebo. Notably, the median pain score significantly decreased over the 6-month period within intervention group (9 to 6, $p < .001$), while not seen any change in median pain score in placebo group during time (9 to 9, $p = .99$). The mean rank of VAS pain scores in the RT group decreased every month after radiation, and there is a statistically significant difference in the RT treatment group compared to the placebo ($p < 0.001$), while the difference of the total pain scores before RT intervention were not statistically significant between two groups ($p = 0.25$). The same happened to Lysholm score, in which an insignificant difference in the score between two study groups before intervention ($p = .06$) and become significant change in every monthly assessment ($p < .001$). Also an increase in mean rank Lysholm score was observed in intervention group (6 related sample) during the study (2.52 to 4.74, $p < .001$), while there wasn't any mean rank change in the placebo group during time (4.12 to 3.88, $p = .35$).

Figure 1 shows the changes in the mean rank VAS pain scores over the course of the study. The mean rank pain score in the radiotherapy treatment group decreased gradually during six months, while the mean rank of pain score during the placebo treatment did not show any significant changes ($p < 0.001$).

Table 1. Distribution of background variables and intervening factors were similar in both treatment groups of radiotherapy and placebo ($P > 0.05$).

Variable	category	n	Intervention group n (%)	Placebo group n (%)	*p* value
Gender	Female	47	27 (90.0)	20 (66.7)	0.06*
	Male	13	3 (10.0)	10 (33.3)	
Age (years)	76≥	38	19 (63.3)	19 (63.3)	0.50*
	>76	22	11 (36.7)	11 (36.7)	
Wight (kg)	78≥	32	18 (60.0)	14 (46.7)	0.30*
	78<	28	12 (40.0)	16 (53.3)	
Height (cm)	166 ≥	27	13 (43.3)	14 (46.7)	0.79*
	166<	33	17 (56.7)	16 (53.3)	
Diabetes mellitus	Yes	20	10 (33.3)	10 (33.3)	0.99
	No	40	20 (66.7)	20 (66.7)	
Hypertension	Yes	34	18 (60.0)	16 (53.3)	0.60*
	No	26	12 (40.0)	14 (46.7)	
Cardiovascular disease	Yes	11	4 (13.3)	7 (23.3)	0.31*
	No	49	26 (86.7)	23 (76.7)	
duration of osteoarthritis	6≥ month	38	21 (70.0)	17 (56.7)	0.28*
	6< month	22	9 (30.0)	13 (43.3)	
Kellgren-Lawrence score	Grade 1	13	9 (30.0)	4 (13.3)	0.23**
	Grade 2	43	20 (66.7)	23 (76.7)	
	Grade 3	4	1 (3.3)	3 (10.0)	
	Hip	2	0	2 (6.7)	

*Chi Square Test, **Fisher Exact Test.

Table 2. Baseline clinical characteristics of participated in intervention and placebo groups.

Variable	Score/ number	n	Intervention group n (%)	Placebo group n (%)	*p* value*
VAS pain score	8	19	11 (36.7)	8 (26.7)	0.42
	9	39	19 (63.3)	20 (66.7)	
	10	2	0 (0)	2 (6.7)	
Lysholm score	1= <65	2	2 (6.7)	0 (0)	0.06
	2=65-83	46	18 (60.0)	28 (93.3)	
	3=84-90	12	10 (33.3)	2 (6.7)	
	4=90-100	0	0 (0)	0 (0)	
Daily number use of drug	3	7	4 (13.3)	3 (10.0)	0.25
	4	23	13 (43.3)	10 (33.3)	
	5	25	11 (36.7)	14 (46.7)	
	6	3	0 (0)	3 (10.0)	
	8	2	2 (6.7)	0 (0)	

*Fisher Exact Test.

Table 3. Comparison of VAS pain and lysholm score assessed prior and during 6 months intervention treatment in participant.

Time of assessment	Group	N	Mean rank of VAS pain score	Sum of Mean rank VAS pain score	*P* value*	Mean rank of Lysholm scores	Sum of Mean rank Lysholm scores	*p* value*
Prior to radiation	placebo	30	32.63	979.00	0.25	27.43	823.00	0.06
	intervention	30	28.37	851.00		33.57	1007.00	
	Total	60						
1 month later	placebo	30	40.33	1210.00	<0.001	23.00	690.00	<0.001
	intervention	30	20.67	620.00		38.00	1140.00	
	Total	60						
2 months later	placebo	30	41.23	1237.00	<0.001	19.50	585.00	<0.001
	intervention	30	19.77	593.00		41.50	1245.00	
	Total	60						
3 months later	placebo	30	41.98	1259.50	<0.001	17.50	525.00	<0.001
	intervention	30	19.02	570.50		43.50	1305.00	
	Total	60						
4 months later	placebo	30	42.97	1289.00	<0.001	17.93	538.00	<0.001
	intervention	30	18.03	541.00		43.07	1292.00	
	Total	60						
5 months later	placebo	30	41.93	1258.00	<0.001	18.50	555.00	<0.001
	intervention	30	19.07	572.00		42.50	1275.00	
	Total	60						
6 months later	placebo	30	42.22	1266.50	<0.001	17.50	525.00	<0.001
	intervention	30	18.78	563.50		43.50	1305.00	
	Total	60						

*Mann-Whitney Test.

Figure 2 illustrates an increase in the mean rank Lysholm score, monthly after treatment with RT, while in the placebo group, this score decreased over time, indicating a worsening natural history of OA. The total Lysholm score also increased in consequent monthly assessments, while in the placebo group, monthly scores decreased over time, and this difference was statistically significant ($p < 0.001$).

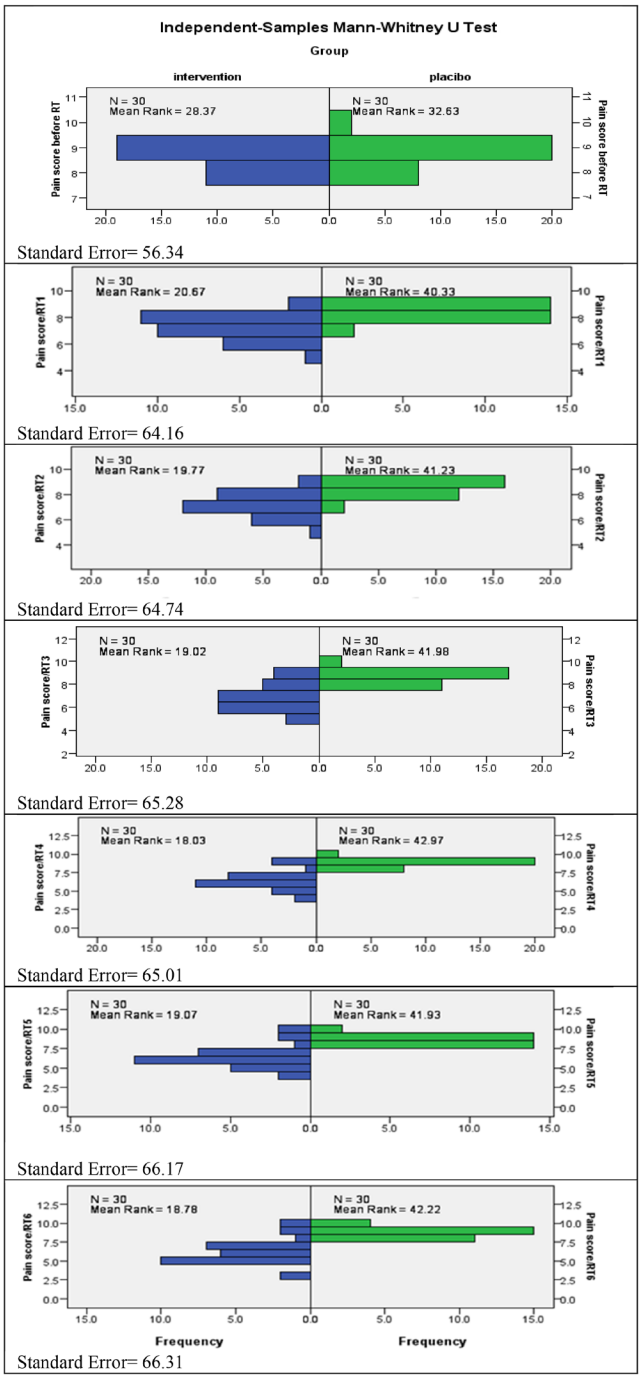

Figure 1. Changes of mean rank VAS pain score in two treatment and placebo groups before intervention (p = .25) during 6 months post intervention (p < .001).

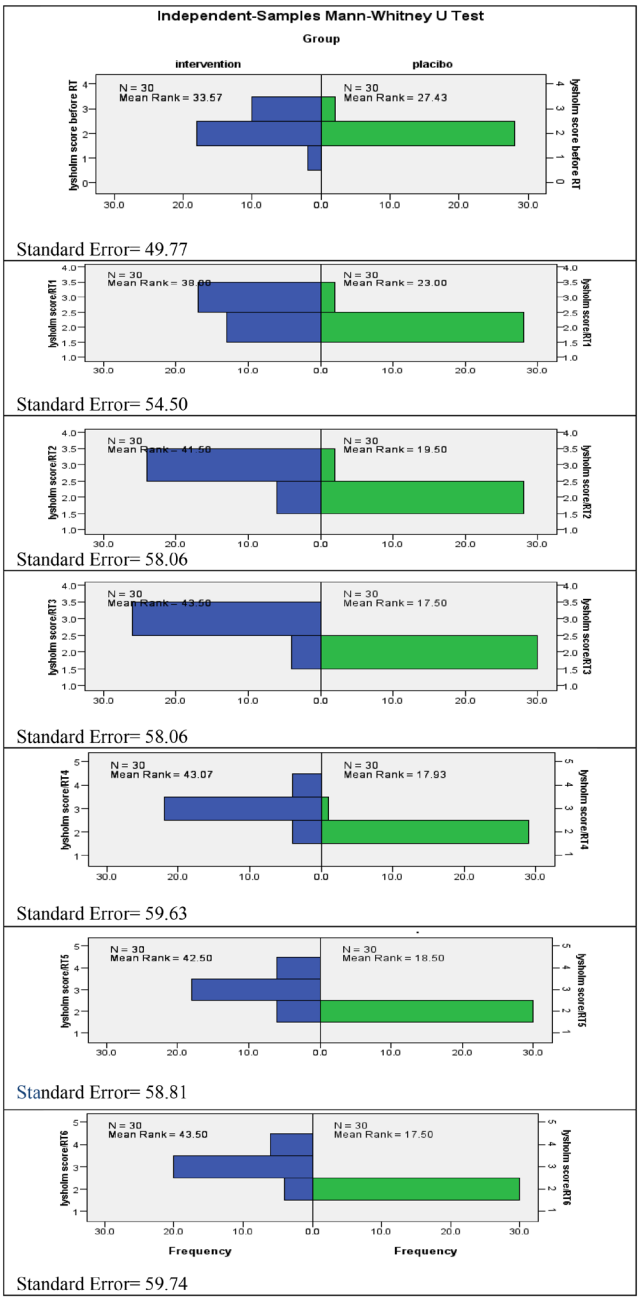

Figure 2. Changes of mean rank lysholm score in the treatment and placebo groups before intervention (p = .06) and during 6 months after intervention (p < .001).

Table 4 shows the statistical significance changes in the mean rank daily consumption of pain-relief medication between participants in two groups, monthly (p < .001). This table also shows that in the intervention group receiving radiotherapy, the mean rank daily intake of pain-relief medications decreased from 6.18 to less than 3 (p < .001), while vice versa incremental changes in daily medication consume occurred in the placebo group (mean rank from 3.84 to 4.84) during same period (p = .02).

The performance status of patients in both groups was assessed monthly for six months after radiation treatment and placebo. Table 5 shows the results of changes in the performance status during treatment compared to placebo. This table shows statistically significant changes in performance status after treatment in the two groups receiving radiotherapy and placebo. After one month, 53.3% and 46.7% of the RT treatment group experienced relative improvement and stable PS, respectively; while in the placebo treatment group, 13.3% and 86.6% had relative PS improvement and stable PS, respectively. Assessment of the treatment effect in the two groups after six months post radiotherapy and placebo showed that in the RT intervention group, 23.3% of individuals showed improvement after treatment, 63.4% had relative improvement in the functional level, and 13.3% reported no effect, whereas in the placebo treatment group, no change in the functional level was observed (p<0.001).

Table 4. Changes of mean rank daily consumption of pain-relief medication within intervention groups during 6 months ($p < .05$) and between intervention groups before ($p = .34$) and during 6 months intervention ($p < .05$).

	Mean rank: k related sample		Mean rank: 2 independent sample		
Variable	Placebo N = 30	Intervention N = 30	Placebo N = 30	Intervention N = 30	*p* value**
use of pain-relief medication before RT. n = 60	3.83	6.18	32.50	28.50	0.34
Use of pain-relief medication /RT1. n = 60	3.37	5.45	34.87	26.13	0.04
Use of pain-relief medication /RT2. n = 60	3.83	4.62	38.50	22.50	<0.001
Use of pain-relief medication /RT3. n = 60	4.07	3.52	40.20	20.80	<0.001
Use of pain-relief medication /RT4. n = 60	3.83	3.17	41.25	19.75	<0.001
Use of pain-relief medication /RT5. n = 60	4.53	2.80	41.30	19.70	<0.001
Use of pain-relief medication /RT6. n = 60	4.53	2.27	41.20	19.0	<0.001
p value*	0.02	<0.001			

*Friedman Test: k related sample.
**Mann-Whitney Test.

Table 5. Changes the performance status during 6 months intervention treatment in participant.

Time of assessment	Status	Intervention group n (%)	Placebo group n (%)	*p* value*
1 month later	Improve	0	0	0.02
	Improve Slightly	16 (53.3)	4 (13.3)	
	stable	14 (46.7)	25 (83.3)	
	deterioration	0	1 (3.3)	
2 months later	Improve	0	0	<0.001
	Improve Slightly	26 (86.7)	6 (20.0)	
	stable	4 (13.3)	23 (76.7)	
	deterioration	0	1 (3.3)	
3 months later	Improve	4 (13.3)	0	<0.001
	Improve Slightly	22 (73.3)	3 (10.0)	
	stable	4 (13.3)	27 (90.0)	
	deterioration	0	0	
4 months later	Improve	6 (20.0)	0	<0.001
	Improve Slightly	22 (73.3)	5 (16.7)	
	stable	2 (6.7)	25 (83.3)	
	deterioration	0	0	
5 months later	Improve	7 (23.3)	0	<0.001
	Improve Slightly	19 (63.3)	2 (6.7)	
	stable	4 (13.3)	28 (93.3)	
	deterioration	0	0	
6 months later	Improve	7 (23.3)	0	<0.001
	Improve Slightly	19 (63.4)	0	
	stable	4 (13.3)	30 (100.0)	
	deterioration	0	0	

*Fisher Exact Test.

Discussion

This study enrolled 60 patients with knee osteoarthritis (OA) and demonstrated significant improvements in pain relief and functional status following low-dose radiotherapy (LDRT), as evidenced by the reduction in Visual Analog Scale (VAS) pain scores and the improvement in Lysholm scores ($p < .001$).

As depicted in figures 1 and 2, the average VAS pain score as well as the Lysholm score have improved in all of the monthly assessments, significantly ($p < .001$). Koc et al. in 2019, in a small volume non-randomized study, assessed the effect of 6 Gy radiation on 16 osteoarthritic hip and knee joints in 12 patients and reported significant improvement in half of the joints after 6 weeks regarding pain score (Koc et al. 2019). Another non-randomized retrospective trial issued by Rühle et al. in 2021, demonstrated that 6 Gy radiation could reduce pain significantly, assessed by a numeric rating scale (NRS) and the Pannewitz scoring system (Rühle et al. 2021). Our study was a prospective single blind randomized trial which included only knee joints. A similar result was seen in the report of Hautmann et al. trial in which radiation of 295 patients mostly included knee osteoarthritis, resulted in pain score improvement in 33.8% of patients after 12 months (Hautmann et al. 2020).

In contrast, some other randomized trials have concluded that low dose radiation therapy (LDRT) in OA does not have a beneficial effect. Mahler et al. in their randomized, double-blinded, sham-controlled trial in 2018, concluded that 6 Gy radiation to osteoarthritic knee join have no effect on pain symptom nor inflammation (Mahler et al. 2019). In a quit similar trial on hand OA in 2018, Minten et al. concluded that LDRT has no significant effect on symptoms and inflammation of the joint (Minten et al. 2018). Both trials finally advised against the use of LDRT as a treatment for knee OA. Small sample size is the common specificity of these trials, which could be one reason for this conclusion.

Osteoarthritic joints other than knee joints were also the target of radiation in some trials and, surprisingly, the results were promising. In 2019, Hautman et al. released the report of a multi-center single arm trial in which they radiated tarsal and ankle joints of 66 patients diagnosed with OA. In 56.7% of them, improvement in joint mobility occurred, the response which lasted at least for 24 months (Hautmann et al. 2020). Niewald et al. in 2024, following a randomized clinical trial, concluded that patients with OA of hand, finger and knee joints could tolerate radiation and had a good improvement regarding pain, function and quality of life (Niewald et al. 2024).

Regarding the mechanism through which LDRT could improve joint function and pain, there are several hypotheses. Hildebrandt et al. in 2009 introduced the nitric oxide pathway as an inflammation induction pathway. They found that LDRT inhibits this pathway, whereas high-dose conventional radiation therapy does not (Hildebrandt et al. 1998). The same pathway as well as modulation of cytokine and adhesion molecule expression on activated endothelial cells and leukocytes are introduced by Rödel et al. as the mechanism in which LDRT could suppress inflammation and subsequently improve joint symptoms (Rödel et al. 2007). Other trials and review articles during recent years have identified the reduction of inflammatory markers such as IL4 and IL17, a shift from CD8+ to CD4+ T cells, and the activation of Nrf2 as significant factors contributing to the anti-inflammatory and analgesic effects of LDRT (Weitmann and Niewald 2013; Javadinia et al. 2021; Weissmann et al. 2021, 2023).

The results of the present study show the potential use of LDRT in mitigating the burden of symptoms in patients with OA. These interventions, along with newly introduced integrated therapies in malignant conditions such as crocin and melatonin, can significantly improve the quality of life in patients (Ebrahimi et al. 2024; Sedighi Pashaki et al. 2023; Sedighi Pashaki et al. 2021; Salek et al. 2021).

Despite these promising findings, there are several limitations and considerations regarding the interpretation of these results and the application of LDRT in clinical practice. First, the sample size in this trial is relatively small (n = 60), which could limit the generalizability of the findings. Larger multicenter trials would be necessary to validate these results and to establish the long-term effects of LDRT in a broader population. Additionally, our study was limited to knee OA; thus, extrapolating these results to other joint types or to OA patients with comorbidities may require further investigation. Given that the participants were predominantly elderly (mean age 76.77 years), the results may not be applicable to younger individuals or those with less severe OA. Another limitation is the lack of long-term follow-up. Although the six-month follow-up period revealed significant improvements, the durability of these benefits over time remains unclear. Longer follow-up is required to assess whether the improvements in pain relief and functional status are sustained, and if any long-term adverse effects arise.

Regarding the potential risks of LDRT, while this treatment was well-tolerated in our study, it is important to acknowledge that radiation, even at low doses, carries inherent risks. The potential long-term risks include radiation-induced malignancies, particularly in older patients with a history of cancer or those with prolonged exposure to radiotherapy. The cumulative radiation dose over time, particularly in patients requiring multiple treatments, could increase the risk of carcinogenesis. Although our study found no significant adverse effects, further research is needed to monitor for any delayed radiation-related side effects, such as tissue fibrosis, bone necrosis, or joint deformities, especially in high-risk populations. Additionally, radiation therapy has known side effects, including fatigue, skin irritation, and potential exacerbation of comorbidities such as cardiovascular disease in elderly patients. It is crucial to carefully weigh these risks against the potential benefits, particularly in patients with advanced OA or those with multiple underlying health conditions.

While our study demonstrates promising results, the potential for side effects must be considered, and further research is necessary to determine the optimal dosage and frequency of LDRT to minimize risks while maximizing therapeutic benefits.

Conclusion

In this randomized study, we demonstrated that LDRT at 3 Gy can provide significant analgesic effects, as evidenced by improvements in pain scores, reduced daily pain medication consumption, and enhanced performance status among patients with knee osteoarthritis (OA). This dose appeared to have no adverse effects, aligning with findings from previous trials (Koc et al. 2019; Mahler et al. 2019). While the results are promising, it is important to consider the potential long-term risks of LDRT, such as radiation-induced complications, which were not observed in this study but should be closely monitored in future trials. Future research should explore whether lower doses of LDRT could also be effective and continue to investigate the precise analgesic and anti-inflammatory mechanisms underlying its therapeutic effects. Furthermore, studies evaluating the efficacy of LDRT in the earlier stages of OA could help expand its potential applications beyond advanced disease, providing new avenues for patient care and management.

Acknowledgements

We would like to express our special thanks of gratitude to radiotherapy stuff of Shahid Rajaei oncology center, Babolsar, Mazandaran, Iran. We extend our thanks to the Clinical Research Development Unit of Vasei Hospital, affiliated with Sabzevar University of Medical Sciences, for their kind support

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This study was supported by Babol University of Medical Sciences (grant number 724133253) and Sabzevar University of Medical Sciences (grant number 99151).

Notes on contributors

Danial Fazilat-panah, MD, is an Assistant Professor of Radiation Oncology, Shahid Rajaei Educational Hospital, Babol University of Medical Sciences, Babolsar, Mazandaran, Iran.

Ali Shabestani Monfared, PhD, is a Professor of Medical Physics, Shahid Rajaei Educational Hospital, Babol University of Medical Sciences, Babolsar, Mazandaran, Iran.

Fahimeh Attarian, MSc, is a Lecturer of Epidemiology and Biostatistics, School of Health, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Razavi Khorasan, Iran.

Seyed Alireza Javadinia, MD, is an Assistant Professor of Radiation Oncology, Vasei Educational Hospital, Sabzevar University of Medical Sciences, Sabzevar, Razavi Khorasan, Iran.

Mansour Babaei, MD, is an Assistant Professor of Rheumatology, Rohani Educational Hospital, Babol University of Medical Sciences, Babol, Mazandaran, Iran.

Behnaz Yousefghahari, is an Assistant Professor of Rheumatology, Rohani Educational Hospital, Babol University of Medical Sciences, Babol, Mazandaran, Iran.

Saeed Najafzadeh Sadati, is an Assistant Professor of Rheumatology, Rohani Educational Hospital, Babol University of Medical Sciences, Babol, Mazandaran, Iran.

Nahid Ahmadi, MD, is a Radiation Oncologist, Shahid Rajaei Educational Hospital, Babol University of Medical Sciences, Babolsar, Mazandaran, Iran.

Hamid Fallah Tafti, is a Radiation Oncologist, Shahid Ramazanzade Cancer Center, Shahid Sadoughi University of Medical Sciences, Yazd, Yazd, Iran.

ORCID

Danial Fazilat-panah http://orcid.org/0000-0003-4194-6575
Seyed Alireza Javadinia http://orcid.org/0000-0003-2467-837X
Ali Shabestani Monfared http://orcid.org/0000-0002-1457-7199
Fahimeh Attarian http://orcid.org/0000-0001-9752-0480
Mansour Babaei http://orcid.org/0000-0002-4179-7787
Behnaz Yousefghahari http://orcid.org/0000-0002-8416-6643
Saeed Najafzadeh Sadati http://orcid.org/0009-0000-7457-155X
Nahid Ahmadi http://orcid.org/0000-0003-2639-5779
Hamid Fallah Tafti http://orcid.org/0000-0002-8515-410X

Data availability statement

Raw data were generated at Babol Medical University. Derived data supporting the findings of this study are available from the corresponding author [Hamid Fallah Tafti] on request.

References

Allen KD, Thoma LM, Golightly YM. 2022. Epidemiology of osteoarthritis. Osteoarthritis Cartilage. 30(2):184–195. doi:10.1016/j.joca.2021.04.020.

Callahan LF, Cleveland RJ, Allen KD, Golightly Y. 2021. Racial/ethnic, socioeconomic, and geographic disparities in the epidemiology of knee and hip osteoarthritis. Rheum Dis Clin North Am. 47(1):1–20. doi:10.1016/j.rdc.2020.09.001.

Delgado DA, Lambert BS, Boutris N, McCulloch PC, Robbins AB, Moreno MR, Harris JD. 2018. Validation of digital visual analog scale pain scoring with a traditional paper-based visual analog scale in adults. J Am Acad Orthop Surg Glob Res Rev. 2(3):e088. doi:10.5435/JAAOSGlobal-D-17-00088.

Dove APH, Cmelak A, Darrow K, McComas KN, Chowdhary M, Beckta J, Kirschner AN. 2022. The use of low-dose radiation therapy in osteoarthritis: a review. Int J Radiat Oncol Biol Phys. 114(2):203–220. doi:10.1016/j.ijrobp.2022.04.029.

Driban JB, Bannuru RR, Eaton CB, Spector TD, Hart DJ, McAlindon TE, Lu B, Lo GH, Arden NK. 2020. The incidence and characteristics of accelerated knee osteoarthritis among women: the Chingford cohort. BMC Musculoskelet Disord. 21(1):60. doi:10.1186/s12891-020-3073-3.

Ebrahimi N, Javadinia SA, Salek R, Fanipakdel A, Sepahi S, Dehghani M, Valizadeh N, Mohajeri SA. 2024. Randomized, double-blind, placebo-controlled clinical trial of concurrent use of crocin during chemoradiation for esophageal squamous cell carcinoma. Cancer Invest. 42(2):155–164. Feb doi:10.1080/07357907.2024.2319754.

E Albuquerque RP, Giordano V, Calixto A, Malzac F, Aguiar C, do Amaral NP, Carvalho ACP. 2011. Analysis on the modified lysholm functional protocol among patients with normal knees. Rev Bras Ortop. 46(6):668–674. doi:10.1016/S2255-4971(15)30323-2.

Hautmann MG, Hipp M, Neumaier U, Steger F, Brockmann S, Treutwein M, Ernstberger A, Ettl T, Kölbl O, Süß C. 2020. Radiotherapy for osteoarthritis of the ankle and tarsal joints-analysis of 66 joints. Strahlenther Onkol. 196(6):569–575. doi:10.1007/s00066-019-01551-5.

Hautmann MG, Rechner P, Neumaier U, Süß C, Dietl B, Putz FJ, Behr M, Kölbl O, Steger F. 2020. Radiotherapy for osteoarthritis-an analysis of 295 joints treated with a linear accelerator. Strahlenther Onkol. 196(8):715–724. doi:10.1007/s00066-019-01563-1.

Hildebrandt MP, Seed CN, Freemantle CAS, Alam PR, Colville-Nash KR, Trott G. 1998. Mechanisms of the anti-inflammatory activity of low-dose radiation therapy. Int J Radiat Biol. 74(3):367–378. doi:10.1080/095530098141500.

Hong JW, Noh JH, Kim DJ. 2020. The prevalence of and demographic factors associated with radiographic knee osteoarthritis in Korean adults aged ≥ 50 years: The 2010-2013 Korea National Health and Nutrition Examination Survey. PLoS One. 15(3):e0230613. doi:10.1371/journal.pone.0230613.

Hunter DJ, Bierma-Zeinstra S. 2019. Osteoarthritis. Lancet. 393(10182):1745–1759. doi:10.1016/S0140-6736(19)30417-9.

Javadinia SA, Nazeminezhad N, Ghahramani-Asl R, Soroosh D, Fazilat-Panah D, PeyroShabany B, Saberhosseini SN, Mehrabian A, Taghizadeh-Hesary F, Nematshahi M, et al. 2021. Low-dose radiation therapy for osteoarthritis and enthesopathies: a review of current data. Int J Radiat Biol. 97(10):1352–1367. doi:10.1080/09553002.2021.1956000.

Koc BB, Schotanus MGM, Borghans R, Jong B, Maassen ME, Buijsen J, Jansen EJP. 2019. Short-term pain reduction after low-dose radiotherapy in patients with severe osteoarthritis of the hip or knee joint: a cohort study and literature review. Eur J Orthop Surg Traumatol. 29(4):843–847. doi:10.1007/s00590-019-02377-8.

Kohn MD, Sassoon AA, Fernando ND. 2016. Classifications in brief: Kellgren-Lawrence classification of osteoarthritis. Clin Orthop Relat Res. 474(8):1886–1893. doi:10.1007/s11999-016-4732-4.

Li D, Li S, Chen Q, Xie X. 2020. The prevalence of symptomatic knee osteoarthritis in relation to age, sex, area, region, and body mass index in China: A systematic review and meta-analysis. Front Med (Lausanne). 7:304. doi:10.3389/fmed.2020.00304.

Losina E, Weinstein AM, Reichmann WM, Burbine SA, Solomon DH, Daigle ME, Rome BN, Chen SP, Hunter DJ, Suter LG, et al. 2013. Lifetime risk and age at diagnosis of symptomatic knee osteoarthritis in the US. Arthritis Care Res (Hoboken). 65(5):703–711. doi:10.1002/acr.21898.

Mahler EAM, Minten MJ, Leseman-Hoogenboom MM, Poortmans PMP, Leer JWH, Boks SS, van den Hoogen FHJ, den Broeder AA, van den Ende CHM. 2019. Effectiveness of low-dose radiation therapy on symptoms in patients with knee osteoarthritis: a randomised, double-blinded, sham-controlled trial. Ann Rheum Dis. 78(1):83–90. doi:10.1136/annrheumdis-2018-214104.

Minten MJM, Leseman-Hoogenboom MM, Kloppenburg M, Kortekaas MC, Leer JW, Poortmans PMP, van den Hoogen FHJ, den Broeder AA, van den Ende CHM. 2018. Lack of beneficial effects of low-dose radiation therapy on hand osteoarthritis symptoms and inflammation: a randomised, blinded, sham-controlled trial. Osteoarthritis Cartilage. 26(10):1283–1290. doi:10.1016/j.joca.2018.06.010.

Moss AS, Murphy LB, Helmick CG, Schwartz TA, Barbour KE, Renner JB, Kalsbeek W, Jordan JM. 2016. Annual incidence rates of hip symptoms and three hip OA outcomes from a U.S. population-based cohort study: the Johnston County Osteoarthritis Project. Osteoarthritis Cartilage. 24(9):1518–1527. doi:10.1016/j.joca.2016.04.012.

Niewald M, Moumeniahangar S, Müller LN, Hautmann MG, Dzierma Y, Fleckenstein J, Gräber S, Rübe C, Hecht M, Melchior P. 2024. ArthroRad trial: randomized multicenter single-blinded trial on the effect of low-dose radiotherapy for painful osteoarthritis-final results after 12-month follow-up. Strahlenther Onkol. 200(2):134–142. doi:10.1007/s00066-023-02152-z.

Postler AE, Lützner C, Goronzy J, Lange T, Deckert S, Günther KP, Lützner J. 2023. When are patients with osteoarthritis referred for surgery? Best Pract Res Clin Rheumatol. 37(2):101835. doi:10.1016/j.berh.2023.101835.

Richard MJ, Driban JB, McAlindon TE. 2023. Pharmaceutical treatment of osteoarthritis. Osteoarthritis Cartilage. 31(4):458–466. doi:10.1016/j.joca.2022.11.005.

Rödel F, Keilholz L, Herrmann M, Sauer R, Hildebrandt G. 2007. Radiobiological mechanisms in inflammatory diseases of low-dose radiation therapy. Int J Radiat Biol. 83(6):357–366. doi:10.1080/09553000701317358.

Rühle A, Tkotsch E, Mravlag R, Haehl E, Spohn SKB, Zamboglou C, Huber PE, Debus J, Grosu AL, Sprave T, et al. 2021. Low-dose radiotherapy for painful osteoarthritis of the elderly: a multicenter analysis of 970 patients with 1185 treated sites. Strahlenther Onkol. 197(10):895–902. doi:10.1007/s00066-021-01816-y.

Salek R, Dehghani M, Mohajeri SA, Talaei A, Fanipakdel A, Javadinia SA. 2021. Amelioration of anxiety, depression, and chemotherapy related toxicity after crocin administration during chemotherapy of breast cancer: a double blind, randomized clinical trial. Phytother Res. 35(9):5143–5153. doi:10.1002/ptr.7180.

Sedighi Pashaki A, Mohammadian K, Afshar S, Gholami MH, Moradi A, Javadinia SA, Keshtpour Amlashi Z. 2021. A randomized, controlled, parallel-group, trial on the effects of melatonin on fatigue associated with breast cancer and its adjuvant treatments. Integr Cancer Ther. 20:1534735420988343. doi:10.1177/1534735420988343.

Sedighi Pashaki A, Sheida F, Moaddab Shoar L, Hashem T, Fazilat-Panah D, Nemati Motehaver A, Ghanbari Motlagh A, Nikzad S, Bakhtiari M, Tapak L, et al. 2023. A randomized, controlled, parallel-group, trial on the long-term effects of melatonin on fatigue associated with breast cancer and its adjuvant treatments. Integr Cancer Ther. 22: 15347354231168624. doi:10.1177/15347354231168624.

Weissmann T, Rückert M, Putz F, Donaubauer AJ, Hecht M, Schnellhardt S, Schubert P, Roesch J, Höfler D, Ott OJ, et al. 2023. Low-dose radiotherapy of osteoarthritis: from biological findings to clinical effects-challenges for future studies. Strahlenther Onkol. 199(12): 1164–1172. doi:10.1007/s00066-022-02038-6.

Weissmann T, Rückert M, Zhou JG, Seeling M, Lettmaier S, Donaubauer AJ, Nimmerjahn F, Ott OJ, Hecht M, Putz F, et al. 2021. Low-dose radiotherapy leads to a systemic anti-inflammatory shift in the pre-clinical K/BxN serum transfer model and reduces osteoarthritic pain in patients. Front Immunol. 12:777792. doi:10.3389/fimmu.2021.777792.

Weitmann HD, Niewald M. 2013. [Radiotherapy of painful degenerative and inflammatory diseases of joints and soft tissue]. MMW Fortschr Med. 155(1):43–46. doi:10.1007/s15006-013-0042-x.

Young JJ, Pedersen JR, Bricca A. 2023. Exercise therapy for knee and hip osteoarthritis: is there an ideal prescription? Curr Treatm Opt Rheumatol. 1(4):1–17. doi:10.1007/s40674-023-00205-z.