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REVIEW ARTICLE

DEGRO guidelines for the radiotherapy of non-malignant disorders

Part II: Painful degenerative skeletal disorders

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Abstract
Background and purpose The purpose of this article is to summarize the updated DEGRO consensus S2e guideline recommendations for the treatment of benign painful degenerative skeletal disorders with low-dose radiotherapy.
Materials and methods This overview reports on the role of low-dose radiotherapy in the treatment of enthesiopathies (shoulder syndrome, trochanteric bursitis, plantar fasciitis, and elbow syndrome) and painful arthrosis (knee, hip, hand, and finger joints). The most relevant aspects of the DEGRO S2e Consensus Guideline Radiation Therapy of Benign Diseases 2014 regarding diagnostics, treatment decision, dose prescription as well as performance of radiotherapy and results are summarized.
Results For all indications mentioned above, retrospective and some prospective analyses have shown remarkable effects in terms of pain relief. Nevertheless, the Level of Evidence (LoE) and the Grade of Recommendation (GR) vary: LoE 1b–4 and GR A–C.
Conclusion Low-dose radiotherapy for painful degenerative skeletal disorders is effective in the majority of the patients and therefore it may be a reasonable therapeutic alternative when simple and non-invasive methods have been used without persistent success. For all discussed entities, single fraction doses of 0.5–1.0 Gy and total doses of 3.0–6.0 Gy/series applied with 2–3 fractions per week are recommended.

Keywords Enthesiopathy · Painful arthrosis · Benign degenerative disease · Low-dose radiotherapy · German S2e guideline

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DEGRO-S2e-Leitlinie für die Strahlentherapie von gutartigen Erkrankungen

Teil II: Schmerzhafte degenerative Skeletterkrankungen

Zusammenfassung

Hintergrund Zusammenfassung der Empfehlungen der DEGRO-S2e-Leitlinie zur Niedrigdosis-Radiotherapie von gutartigen schmerzhaften degenerativen Skeletterkrankungen.

Material und Methode Die vorliegende Zusammenfassung berichtet über die Bedeutung der Niedrigdosis-Radiotherapie in der Behandlung von Enthesiopathien (Schultersyndrom, Ellenbogensyndrom, Bursitis trochanterica, Fasciitis plantaris) und schmerzhaften Arthrosen (Knie-, Hüft, Hand- und Fingergelenksarthrosen). Die wichtigsten Aspekte der aktuellen DEGRO-S2e-Konsensus-Leitlinie Strahlentherapie gutartiger Erkrankungen bezüglich Diagnostik, Therapieentscheidungen, Dosisempfehlungen und Durchführung einer Radiotherapie werden zusammengefasst.

Ergebnisse Für alle genannten Entitäten wurde in zahlreichen retrospektiven und einigen prospektiven Untersuchungen ein bemerkenswerter Effekt der Niedrigdosis-Radiotherapie im Sinne einer Schmerzlinderung beschrieben. Je nach Entität wurden Evidenzlevel (LoE) von 1b–4 festgestellt, sodass unterschiedliche Empfehlungsgrade (GR) von A–C für den Einsatz der Radiotherapie ausgesprochen wurden.

Schlussfolgerung Die Niedrigdosis-Radiotherapie von benignen schmerzhaften degenerativen Skeletterkrankungen ist bei der Mehrheit der Patienten effektiv im Sinne einer Schmerzlinderung und ist daher insbesondere für Patienten, bei denen andere konservative Verfahren ohne Einsatz ionisierender Strahlung zu keiner anhaltenden Verbesserung der Schmerzsymptomatik geführt haben, eine gut begründbare therapeutische Alternative. Empfohlen wird die Durchführung der Bestrahlung mit Fraktionsdosen von 0,5–1,0 Gy bis zu Gesamtdosen von 3,0–6,0 Gy/Bestrahlungsserie sowie 2–3 Fraktionen pro Woche.

Schlüsselwörter Enthesiopathie · Schmerzhafte Arthrose · Gutartige degenerative Erkrankung · Niedrigdosis-Strahlentherapie · S2e-Leitlinie

Low-dose radiotherapy has been proven to be an effective tool in the treatment of painful degenerative skeletal disorders. This overview reports on the role of low-dose radiotherapy in the treatment of enthesiopathies (shoulder syndrome, trochanteric bursitis, plantar fasciitis, and elbow syndrome) and painful arthrosis (knee, hip, hand, and finger joints).

Enthesiopathies are usually described as painful degenerative disorders of the connective tissue located at specific tendon insertion areas of bones with some involvement of nearby soft tissues, e.g., tendons and bursae. Prevalence rates range from 1–10 % of the population. Enthesiopathies usually occur between the 4th and 6th decade and in most entities women are more frequently affected. Pathogenetic hypotheses are generally based on the assumption that mechanical overstressing, cyclic, repetitive, and intense movements with eccentric exposure will lead to submicroscopic structural damages with accompanying inflammatory, inflammatory–degenerative, degenerative, or microtraumatic changes [8]. The characteristic symptom is a localized load-dependent pain at the involved insertion area [21], which in some cases may spread in the distal or proximal direction [1]. The clinical examination should include inspection and palpation, and further functional tests if appropriate. Visible external signs of inflammation, motoric or sensible deficits, or perfusion disturbances are usually not associated with enthesiopathies.

Arthrosis is defined as a chronic, degenerative disorder of unknown cause characterized by a gradual loss of articular cartilage. Also involved in the disorder are joint structures, such as the bones, joint capsule, and near-joint musculature. Arthrosis is the most prevalent disease in Western societies but occurs worldwide. Approximately 10–15 % of adults over 60 years of age have some degree of arthrosis, and with an aging population it is becoming an increasingly important disease. Potential causes of arthrosis are mechanical overstressing and imbalance, acquired injuries, chronic arthropathies, congenital malformations, rheumatoid and bacterial arthritis, and others. The clinical lead symptom is pain during physical strain. Persistent pain at rest or during the night might be a sign of a more advanced stage of disease. The clinical examination should include inspection and palpation, joint mobility assessment, and further functional tests if necessary.

For all painful degenerative disorders, conventional X-ray diagnostic is routinely recommended to detect accidental neoplastic processes [2] and in unclear clinical situations additional ultrasound or magnetic resonance imaging (MRI) may be helpful.

More detailed information on all parts of this report including a comprehensive collection of the published data may be found in the complete version of the guideline, which is available at the DEGRO homepage (www.degro.org).

Non-radiotherapeutic treatment options

A large variety of treatment non-radiotherapeutic options is under ongoing discussion with no clear advantage of a single method: avoidance of mechanical stress, ultrasound or extracorporeal shock wave therapy, iontophoresis, laser therapy, various physiotherapeutic approaches, acupunc-

ture, steroid or hyaluronate injections and oral NSAIDs, Botox injections, surgical interventions up to joint replacement, etc.

Pain control after low-dose radiotherapy

Although an adequately powered placebo-controlled trial is lacking to formally prove the efficacy of radiotherapy in selected benign degenerative painful diseases and may never be performed due to ethical reasons, a huge body of evidence demonstrates low-dose radiotherapy as a very effective tool in the symptomatic treatment of benign degenerative diseases including enthesiopathies and painful arthrosis, especially in patients who did not persistently benefit from other non-radiation conservative therapies.

Shoulder syndrome

Response rates (complete and partial response: CR and PR) usually reached 58–100 % 2–3 months after radiotherapy [14, 17]. In 7928 retrospectively evaluated patients, Heyd et al. [6] reported response rates of 55 % with CR, and 33 % with PR; 12 % of the patients did not benefit. Early treatment less than 6 months after onset of pain seemed to be more effective than with chronic pain. Data about a higher success rate for patients with calcifications were inconsistent.

Elbow syndrome

Between 1923 and 2011, the outcome after low-dose radiotherapy for elbow syndrome had been reported in more than 2000 patients within 22 retrospective and prospective analyses. Approximately 82 % of the patients experienced significant pain reduction. The CR and PR rates were 45 % (range 5–94 %) and 35 % (range 7–73 %) [13].

Trochanteric bursitis

Glatzel et al. [3] reported on 34 patients who were treated with total doses of 6 Gy in single fractions of 1.0 Gy. After 3 months, 38 % had a CR, and 18 % had a PR. Olschewski and Klein [12] reported on another 26 patients. They found an overall response rate of 73 %, with 23 % CR and 50 % PR rates.

Plantar fasciitis

Retrospective analyses reported on CR rates in 12–81 %, and PR rates in 7–74 % [9, 15, 18]. In a randomized trial, Heyd et al. [7] randomly compared two dose regimens: 3.0 Gy/0.5 Gy vs. 6.0 Gy/1.0 Gy in 130 patients. Radiotherapy led to a highly significant reduction of pain symptoms in both groups, and the lower dose regimen was equally effective. In another randomized trial Niewald et al. [11] evaluated the efficacy of two other dose concepts in 62 evaluable patients: 6.0 Gy/1.0 Gy vs. 0.6 Gy/0.1 Gy. After one year, compared to the very low-dose arm the higher-dose arm led to a significant advantage in terms of pain control.

Gonarthrosis

Low-dose radiotherapy is an effective therapeutic option for painful Kellgren stage 2–3 arthrosis of the knee joint and can be recommended even if surgical interventions are not possible or desirable or if other conservative treatment methods are associated with excessive side effects or contraindicated. The results from 10,046 patients treated with low-dose radiotherapy for painful arthrosis of the knee joint have been published. Of these patients, 5069 were surveyed within the framework of a German patterns of care study performed in 2010 [10]. A response to radiation therapy in terms of a marked and complete reduction of pain was shown in 58–91 % of the irradiated patients.

Coxarthrosis

Considering the results of the retrospective studies, low-dose radiotherapy may be an effective therapeutic option for painful Kellgren stage 2–4 arthrosis of the hip joint, even if surgical interventions are not possible or desirable, or if other conservative treatment methods are associated with excessive side effects or contraindicated. The results from 895 patients treated with low-dose radiotherapy for painful arthrosis of the hip joint have been published. A response to radiation therapy in terms of a marked and complete reduction of pain was shown in 24–89 % of the irradiated patients [19].

Arthrosis of the hand and finger joints

Considering the results of the retrospective studies, low-dose radiotherapy may be an effective therapeutic option for painful arthrosis of the hand and finger joints, even if other conservative treatment methods are associated with excessive side effects or contraindicated. The results from 809 patients treated with low-dose radiotherapy for painful arthrosis of the hand and finger joints have been published. A response to radiation therapy in terms of a marked and complete reduction of pain was shown in 63–75 % of the irradiated patients [4].

Current recommendations on radiotherapy

General recommendations

Because of general radiation protection considerations radiotherapy should be recommended if non-radiotherapeutic approaches did not succeed [5, 20]. Furthermore, patients < 40 years should be irradiated in very exceptional cases and after careful evaluation of the potential risk versus the expected benefit. Orthovoltage or megavoltage techniques may be applied. Generally, the target volumes for enthesiopathies should encompass the complete involved insertion area together with the nearby bony and muscular tissues, and for painful arthrosis the target volumes must include the articular cartilage, the nearby bony structures, the entire synovia, the surrounding muscles, and the periarticular connective tissue, as well. In case of persisting pain or insufficient pain relief 6–12 weeks after radiotherapy, a second series may be recommended [13, 16]. Radiotherapy recommendations were summarized in Table 1 including the Oxford Level of Evidence (LoE) and the Grade of Recommendation (GR).

Shoulder syndrome

The target volume comprises the whole shoulder joint including the nearby bone and muscular structures; lung and female breast should be spared. In case of exclusive acromioclavicular pain a more limited volume may be treated. If a linear accelerator is used, an opposing field technique should be applied with 6 MV photons. Orthovoltage technique is usually performed with two opposing fields (ventrodorsal and dorsoventral) directly positioned on the painful shoulder covering the whole joint. Single doses of 0.5–1 Gy up to total doses of 3–6 Gy/series should be applied 2–3 times a week.

Table 1 DEGRO guideline recommendations for the radiotherapy of painful degenerative skeletal disorders

Skeletal disorder	Total doses/ series [Gy]	Single doses/ fraction [Gy]	Frequency of fractions	LoE	GR
Shoulder syndrome	3.0–6.0	0.5–1.0	2–3/week	4	C
Elbow syndrome	3.0–6.0	0.5–1.0	2–3/week	2c	B
Trochanteric bursitis	3.0–6.0	0.5–1.0	2–3/week	4	C
Plantar fasciitis	3.0–6.0	0.5–1.0	2–3/week	1b	A
Gonarthrosis	3.0–6.0	0.5–1.0	2–3/week	2c	B
Coxarthrosis	3.0–6.0	0.5–1.0	2–3/week	4	C
Hand and finger joint arthrosis	3.0–6.0	0.5–1.0	2–3/week	4	C

Gy Gray, *LoE* Oxford Level of Evidence, *GR* Grade of Recommendation

Elbow syndrome

The target volume should encompass the complete lateral or medial epicondyle together with the nearby bony and muscular tissues. Using Orthovolt therapy, usually a single field is clinically positioned over the medial or lateral epicondyle. At the linear accelerator, usually two orthogonal fields with low photon beam energy are used or a single field with electrons of appropriate energy. The reference point is determined on the central beam with a half joint diameter in tissue depth. Single fraction doses of 0.5–1.0 Gy are recommended, with total doses of 3.0–6.0 Gy/series with 2–3 fractions per week.

Trochanteric bursitis

The target volume should include the superficial and deep, primary and secondary bursae of the gluteus maximus region. If a linear accelerator is used, ventrodorsal parallel opposing portals should be applied with 6–10 MV photons. Using Orthovolt therapy, usually a single field is positioned at the most painful pressure point (clinical examination) above the trochanter major region. Like in other degenerative diseases, single doses of 0.5–1 Gy up to total doses of 3–6 Gy should be applied 2–3 times per week.

Plantar fasciitis

Orthovoltage therapy or megavoltage therapy may be used. In the former, bolus material is recommended to be attached to the edge of the heel in order to avoid local underdosage. The reference point should be in a constant tissue depth. In the latter, 4–6 MV photons of a linear accelerator should be used, applying lateral opposing portals, and the reference point should be in the midpoint of the heel. A total dose in the range of 3–6 Gy is recommended, applied in 2–3 single fractions a week of 0.5–1.0 Gy.

Gonarthrosis

The target volumes for painful knee joint arthrosis must include the articular cartilage, the nearby bony structures, the entire synovia, the surrounding muscles, and the periarticular connective tissue as well. Two opposed ventro-dorsal or lateral fields offer reliable distribution in the target volume. The dosage has to be determined at a uniform depth (e.g., middle of the knee joint). Appropriate radiation energy should be selected depending on the diameter of the joint. Single doses of 0.5–1.0 Gy and total doses of 3.0–6.0 Gy/series with 2–3 fractions per week are recommended.

Coxarthrosis

The target volumes for painful hip joint arthrosis must include the articular cartilage, the nearby bony structures, the entire synovia, the surrounding muscles, and the periarticular connective tissue as well. Two opposed ventro-dorsal fields offer a reliable distribution in the target volume. The dosage has to be determined at a uniform depth (e.g., middle of the hip joint). Appropriate radiation energy should be selected depending on the diameter of the joint. Single doses of 0.5–1.0 Gy, total doses of 3.0–6.0 Gy/series with 2–3 fractions per week are recommended. Radiation protection measures for the gonads are recommended.

Arthrosis of the hand and finger joints

The target volumes for painful hand and finger joints arthrosis must include the articular cartilage, the nearby bony structures, the entire synovia, the surrounding muscles, and the periarticular connective tissue of the involved joints. One dorsal or ventral field offers a reliable distribution in the target volume. The dosage has to be determined at a uniform depth (e.g., middle of the joint). Appropriate radiation energy should be selected depending on the diameter of the joint. Single doses of 0.5–1.0 Gy and total doses of 3.0–6.0 Gy/series, and 2–3 fractions per week are recommended. Radiation protection measures for the nails are recommended.

Treatment response evaluation

Success rates for pain relief and freedom of pain should be assessed 2–3 months after radiotherapy because of delayed response effects. Symptomatic outcome should be graded according to the classification published by von Pannewitz [22, 23] and/or conventional visual analogue scales.

Summary

In all indications mentioned above, retrospective and some prospective analyses have shown a remarkable effect in terms of pain relief. Nevertheless, the Level of Evidence (LoE) and the Grade of Recommendation (GR) vary: LoE 1b–4 and GR A–C. In summary, low-dose radiotherapy for painful degenerative skeletal disorders is effective in the majority of the patients and therefore it may be a reasonable therapeutic alternative when simple and non-invasive methods have been used without persistent success. Considering general radiation protection recommendations patients should be aged >40 years, and the duration of the pain history should exceed 3 months to exclude self-limiting acute disorders. For all discussed entities single fraction doses of 0.5–1.0 Gy, and total doses of 3.0–6.0 Gy/series applied with 2–3 fractions per week are recommended.

Compliance with ethical guidelines

Conflict of interest Oliver J. Ott, Marcus Niewald, Hajo-Dirk Weitmann, Ingrid Jacob, Irenaeus A. Adamietz, Ulrich Schaefer, Ludwig Keilholz, Reinhard Heyd, and Ralph Muecke state that there are no conflicts of interest. The accompanying manuscript does not include studies on humans or animals.

References

1. Chard MD, Hazleman BL (1989) Tennis elbow—a reappraisal. Br J Rheumatol 28:186–190
2. Ciancio G, Gutierrez M, Colina M et al (2011) Ultrasonographic detection of a metastatic elbow lesion mimicking epicondylitis. J Clin Rheumatol 17:164
3. Glatzel M, Baesecke S, Krauss A et al (2000) Ergebnisse der Strahlentherapie bei therapierefraktärer Insertionstendopathie am Trochanter Major. Strahlenther Onkol 176 (Suppl. 1):92
4. Glatzel M FD, Bäsecke S et al (2002) Ergebnisse der Strahlentherapie bei Rhizarthrose. Diplodocus-Verlag, Altenberge
5. Heyd R, Seegenschmiedt MH (2010) Epicondylopathia humeri radialis: efficacy of radiation therapy. MMW Fortschr Med 152:37–39
6. Heyd R, Schopohl B, Bottcher HD (1998) Radiation therapy in humero-scapular peri-arthropathy. Indication, method, results obtained by authors, review of the literature. Röntgenpraxis 51:403–412
7. Heyd R, Tselis N, Ackermann H et al (2007) Radiation therapy for painful heel spurs: results of a prospective randomized study. Strahlenther Onkol 183:3–9
8. Meyer-Clement M (2005) Epicondylopathia humeri radialis et ulnaris — eine Berufskrankheit? In: Orthopädisches Forschungsinstitut (ed) Münsteraner Sachverständigengespräche: Beurteilung und Begutachtung Schulter-Arm-Schmerz. Steinkopf Verlag, Darmstadt, pp 89–110
9. Micke O, Ernst-Stecken A, Muecke R et al (2008) Calcaneodynia; plantar and dorsal heel spur/heel spur syndrome. In: Seegenschmiedt MH, Makoski HB, Trott KR et al. (eds) Radiotherapy for non-malignant disorders. Springer, Berlin, pp 295–316
10. Muecke R, Seegenschmiedt MH, Heyd R et al (2010) Radiotherapy in painful gonarthrosis. Results of a national patterns-of-care study. Strahlenther Onkol 186:7–17
11. Niewald M, Seegenschmiedt MH, Micke O et al (2012) Randomized, multicenter trial on the effect of radiation therapy on plantar fasciitis (painful heel spur) comparing a standard dose with a very low dose: mature results after 12 months' follow-up. Int J Radiat Oncol Biol Phys 84:e455–462
12. Olschewski T, Klein H (2010) Fuktionelle Radiotherapie bei der Bursitis trochanterica. Strahlenther Onkol 186 (Suppl. 1):40
13. Ott OJ, Hertel S, Gaipl US et al (2012a) Benign painful elbow syndrome. First results of a single center prospective randomized radiotherapy dose optimization trial. Strahlenther Onkol 188:873–877
14. Ott OJ, Hertel S, Gaipl US et al (2012b) Benign painful shoulder syndrome: initial results of a single-center prospective randomized radiotherapy dose-optimization trial. Strahlenther Onkol 188:1108–1113

15. Ott OJ, Jeremias C, Gaipl US et al (2013) Radiotherapy for calcaneodynia. Results of a single center prospective randomized dose optimization trial. Strahlenther Onkol 189:329–334
16. Ott OJ, Hertel S, Gaipl US et al (2014a) The Erlangen Dose Optimization trial for low-dose radiotherapy of benign painful elbow syndrome. Long-term results. Strahlenther Onkol 190:293–297
17. Ott OJ, Hertel S, Gaipl US et al (2014b) The Erlangen Dose Optimization Trial for radiotherapy of benign painful shoulder syndrome. Long-term results. Strahlenther Onkol 190:394–398
18. Ott OJ, Jeremias C, Gaipl US et al (2014c) Radiotherapy for benign calcaneodynia: long-term results of the Erlangen Dose Optimization (EDO) trial. Strahlenther Onkol 190:671–675
19. Ruppert R, Seegenschmiedt MH, Sauer R (2004) Radiotherapie von Arthrosen. Orthopäde 33:56–62
20. Seegenschmiedt MH, Keilholz L, Martus P et al (1997) Epicondylopathia humeri. The indication for, technic and clinical results of radiotherapy. Strahlenther Onkol 173:208–218
21. Shiri R, Viikari-Juntura E (2011) Lateral and medial epicondylitis: role of occupational factors. Best Pract Res Clin Rheumatol 25:43–57
22. Von Pannewitz G (1933) Roentgen therapy for deforming arthritis. In: Holfelder H, Holthausen, H., Juengling, O., Martius, H, Schinz, HR (ed) Ergebnisse der Medizinischen Strahlenforschung. Thieme, Leipzig, p 61–126
23. Von Pannewitz G (1963) Degenerative Erkrankungen. In: Handbuch der Medizinischen Radiologie. Springer, Berlin, pp 96–98

Expanding the Scope of Radiation Therapy for Nonmalignant Diseases

What Goes Around Comes Around: Radiation Therapy of Nonmalignant Disorders
Presenter: David Roberge, MD
Moderator: Arshin Sheybani, MD

This session provides an overview of radiotherapy for nonmalignant indications from the lead co-editor of the 3rd edition of *Radiation Therapy of Benign Diseases*. The presentation touches on historical aspects as well as contemporary trends. Following the structure of this textbook, diseases irradiated are categorized as autoimmune, cutaneous, infectious, inflammatory, endocrine, musculoskeletal, neurological, lymphoid, pain-related, psychiatric, reproductive, tumoral, vascular or miscellaneous. The evidence supporting many indications is summarized and tips are shared for estimating treatment toxicity.

Cardiac Radioablation for Ventricular Tachycardia
Presenters: Daniel H. Cooper, MD; Geoff Hugo, PhD; Kaitlin Moore; Pamela Samson, MD, MPHS
Moderator: Malcolm Mattes, MD

Patients with high-risk ventricular tachycardia (VT) refractory to standard therapies (anti-arrhythmic drugs, catheter ablation) and multiple cardiovascular risk factors have poor survival and high rates of recurrent VT. Noninvasive cardiac radioablation using a single dose of SBRT to the VT substrate in the myocardium has shown promising results in a single Phase I/II trial and multiple case series. A number of elements of this new treatment remain in flux, including optimal patient selection, methods for targeting, methods for motion management, direct comparisons with catheter ablation, new findings around the biological underpinnings of cardiac radioablation, and evolving regulatory and billing issues.

A Pain in the Foot: Radiotherapy for Plantar Fasciitis
Presenter: Jarad Martin, DMed
Moderator: Malcolm Mattes, MD

This session provides an overview of the evidence and approach in managing patients with plantar fasciitis with radiotherapy.

An Overview of the Multidisciplinary Management of Dupuytren's and Ledderhose Diseases
Presenters: Gopal Bajaj, MD, MBA, FASTRO and M. Heinrich Seegenschmiedt, MD, PhD
Moderator: Bobby N. Koneru, MD, FASTRO

Dupuytren's and Ledderhose Diseases are very prevalent hyperproliferative disorders of the hands and feet that affect 3-5% of the population. When progressive, these conditions can result in pain, debility and loss of function. Radiation therapy is commonly utilized in Europe for the treatment of both of these conditions but much less commonly employed in North America. This session reviews the pathophysiology, diagnosis and management of Dupuytren's and Ledderhose Diseases and provide an overview of the expanding role of the radiation oncologist in the longitudinal and multidisciplinary management of these patients.

Low Dose Radiotherapy for Osteoarthritis
Presenters: Austin Dove, MD and Austin Kirschner, MD, PhD
Moderator: Bobby N. Koneru, MD, FASTRO

For several decades, low dose radiotherapy (LDRT) has been used in the treatment of osteoarthritis (OA) with significant success. Low dose radiotherapy has been established as an effective therapeutic alternative for patients with OA evidenced by multiple clinical trials with symptomatic pain relief shown in 70-90% of all irradiated patients. Given its low toxicity profile, proven effectiveness, non-invasive approach, and non-interference with other therapies, LDRT offers an excellent therapeutic option for refractory OA patients. In this session, we provide an overview of literature and techniques to effectively deliver LDRT for OA.

Expanding the Scope of Radiation Therapy for Nonmalignant Diseases

Overview

This series provides an overview of historical and contemporary indications for radiation therapy in the treatment of nononcological conditions such as ventricular tachycardia, plantar fasciitis, Dupuytren's and Ledderhose diseases, osteoarthritis, and functional brain disorders. The presenters review data supporting the use of radiation therapy for these conditions, describe the biological mechanisms of efficacy, and provide practical instructions on how to treat.

TOPICS COVERED:

Each topic is available as an onDemand recording.

- What Goes Around Comes Around: Radiation Therapy of Nonmalignant Disorders
- Cardiac Radioablation for Ventricular Tachycardia
- A Pain in the Foot: Radiotherapy for Plantar Fasciitis
- An Overview of the Multidisciplinary Management of Dupuytren's and Ledderhose Diseases
- Low Dose Radiotherapy for Osteoarthritis
- A Functional Radiosurgery Renaissance — Historical Perspectives & Future Applications

Please see the Program tab for session descriptions and presenters.

This activity is available from July 22, 2024, through 11:59 p.m. Eastern time on October 8, 2026.

The content was originally presented and recorded as a live webinar series August 28 - November 7, 2024.

Course summary

Available credit:
6.50 *AMA PRA Category 1 Credit™*
6.50 Certificate of Attendance

Course opens:	07/22/2024
Course expires:	10/08/2026
Cost:	$449.00
Rating:	

Target Audience

This activity is designed to meet the interests of radiation oncologists, radiation physicists, and radiation oncology residents.

Learning Objectives

Upon completion of this activity, participants should be able to do the following:

- Classify potential indications for radiotherapy of benign diseases.
- Identify trends and knowledge gaps in radiotherapy of benign diseases.
- Estimate the risk of treatment toxicity.
- Describe the key elements required to define a cardiac radioablation target volume.
- Describe expected efficacy and toxicity outcomes following cardiac radioablation.
- Describe plantar fasciitis, and know that it is common, and that traditional treatments can be ineffective.
- Discuss the evidence and mechanisms behind the use of radiotherapy for plantar fasciitis.
- Use radiotherapy effectively to treat plantar fasciitis.
- Describe and understand the unique pathophysiology of Dupuytren's and Ledderhose Disease.
- Analyze current data on the role of radiotherapy in the management of Dupuytren's and Ledderhose Disease.
- Discuss the role of the radiation oncologist in the multidisciplinary management of Dupuytren's and Ledderhose Disease.
- Articulate the evidence showing benefit of low dose radiotherapy (LDRT) for osteoarthritis as well as limitations.
- Identify appropriate patients who might benefit from LDRT and identify strategies for educating referring providers to develop thriving service line.
- Increase familiarity with the historical background of functional radiosurgery.
- Describe current applications of functional radiosurgery.
- Share a vision for future potential applications of functional radiosurgery.

Program

What Goes Around Comes Around: Radiation Therapy of Nonmalignant Disorders
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An Overview of the Multidisciplinary Management of Dupuytren's and Ledderhose Diseases
Presenters: Gopal Bajaj, MD, MBA, FASTRO and M. Heinrich Seegenschmiedt, MD, PhD
Moderator: Bobby N. Koneru, MD, FASTRO

Dupuytren's and Ledderhose Diseases are very prevalent hyperproliferative disorders of the hands and feet that affect 3-5% of the population. When progressive, these conditions can result in pain, debility and loss of function. Radiation therapy is commonly utilized in Europe for the treatment of both of these conditions but much less commonly employed in North America. This session reviews the pathophysiology, diagnosis and management of Dupuytren's and Ledderhose Diseases and provide an overview of the expanding role of the radiation oncologist in the longitudinal and multidisciplinary management of these patients.

Low Dose Radiotherapy for Osteoarthritis
Presenters: Austin Dove, MD and Austin Kirschner, MD, PhD
Moderator: Bobby N. Koneru, MD, FASTRO

For several decades, low dose radiotherapy (LDRT) has been used in the treatment of osteoarthritis (OA) with significant success. Low dose radiotherapy has been established as an effective therapeutic alternative for patients with OA evidenced by multiple clinical trials with symptomatic pain relief shown in 70-90% of all irradiated patients. Given its low toxicity profile, proven effectiveness, non-invasive approach, and non-interference with other therapies, LDRT offers an excellent therapeutic option for refractory OA patients. In this session, we provide an overview of literature and techniques to effectively deliver LDRT for OA.

A Functional Radiosurgery Renaissance — Historical Perspectives & Future Applications
Presenters: Markus Bredel, MD, PhD and Evan Thomas, MD, PhD
Moderator: Malcolm Mattes, MD

This session invites you to explore the history and revival of functional radiosurgery as it delves into the fascinating journey of a technique that revolutionized neurosurgery, from its inception to its current resurgence.

Discover how cutting-edge technology and advanced imaging are breathing new life into this precise, non-invasive treatment. Wel examine its evolving role in managing neurological disorders, chronic pain, and psychiatric conditions. From historical triumphs to contemporary breakthroughs, we chart the course of functional radiosurgery's remarkable resurgence.

Looking ahead, we unveil exciting future applications that promise to expand the horizons of neuroscience and patient care.

Faculty

- David Roberge, MD is employed by CHUM. Dr. Roberge receives honoraria and travel expenses as an Advisory Board member, consultant, and education/meeting faculty for Novocure; research funding (institution) from Novocure; honoraria and travel expenses as education/meeting faculty for Accuray; honoraria as a consultant and education/meeting faculty for Recordati; honoraria as an Advisory Board member for Roche Canada, Servier Canada, and AstraZeneca Canada. Dr. Roberge has ownership equity/warrants in MISO Chip, Croton Healthcare, and AFX Medical. Dr. Roberge is co-chair of the Brain Disease Site Committee for the Canadian Cancer Trials Group and President-elect of the Canadian Association of Radiation Oncology.
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- Bobby N. Koneru, MD, FASTRO is employed by FHN Memorial Hospital and Loyola University Stritch School of Medicine. Dr. Koneru serves on the Clinical Advisory Board of the International Organisation for Radiotherapy for Benign Conditions.

The person(s) above served as the developer(s) of this activity. Additionally, the Education Committee had control over the content of this activity. All relevant financial relationships have been mitigated.

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activity before its expiration date.

Required Hardware/software

One of the two latest versions of Google Chrome, Mozilla Firefox, Internet Explorer or Safari.

Radiation Therapy for Non-Cancerous Conditions - CAM 758HB

Category:	Radiology	**Last Reviewed:**	December 2024
Department:	Medical Affairs	**Next Review:**	December 2025
Original Date:	January 2024		

Description/Backgound

Radiation therapy may have appropriate use in several non-malignant conditions. The treatment goal in patients with non-malignant conditions is to achieve relief of the indicated condition with radiation therapy with minimal risk of radiation exposure to sensitive structures.

GENERAL INFORMATION

It is an expectation that all patients receive care/services from a licensed clinician. All appropriate supporting documentation, including recent pertinent office visit notes, laboratory data, and results of any special testing must be provided. If applicable: All prior relevant imaging results and the reason that alternative imaging cannot be performed must be included in the documentation submitted.

Where a specific clinical indication is not directly addressed in this guideline, medical necessity determination will be made based on widely accepted standard of care criteria. These criteria are supported by evidence-based or peer-reviewed sources such as medical literature, societal guidelines and state/national recommendations.

Policy

INDICATIONS FOR RADIATION THERAPY

2D or 3D Conformal (3D CRT) is considered medically necessary for several non-malignant conditions, including but not limited to:[1,2,3,4,5,6,7,8,9,10,11,12]

- Prevention of keloid scars as an adjunctive therapy following excisional surgery: superficial X-ray, electron beam, or conventional isodose technique photon beam therapy in 4 or fewer fractions.[13]
- Heterotopic ossification: 7 Gy to 8 Gy in a single fraction of 2D.
- Pterygium in cases that cannot be medically managed: contact beta brachytherapy in 3 fractions.
- Villonodular synovitis (recurrent after resection, or diffuse or bulky disease-causing bone destruction: 28 or fewer fractions of 2D/3D-CRT.
- Pinealoma (pineal parenchymal tumors): Postoperative radiation for incomplete resection, 45 – 60 Gy in 25 –30 fractions of 3D-CRT, and from 12 – 36 Gy of SRS/FSRT.
- Pituitary adenoma for medically inoperable cases, recurrence after surgery, incomplete resection, or persistence of elevated hormones after resection of functional adenomas: 3D-CRT, SRS, or IMRT, 45 – 54 Gy up to 30 fractions.
- Precancerous melanosis (lentigo maligna, Hutchinson's melanotic freckle, or circumscribed precancerous melanosis of Dubreuilh): for recurrence or more extensive lesions, superficial and orthovoltage therapy, 35 – 57 Gy in 5-23 fractions.
- Rosai-Dorfman disease for lesions involving the airway not responding to more conservative measures, up to 22 fractions of 2D/3D.
- Splenomegaly (hypersplenism): Very low doses of radiation on a less than daily basis, 10 or fewer fractions of 2D/3D.
- Total body irradiation (TBI): For non-malignant, pre-malignant and quasi-benign marrow disorders such as aplastic anemia or myelodysplastic disorders.[14,15]
    - 12 – 15 Gy given in 6 to 12 fractions over 3 – 5 days, fractionated in 2 to 3 treatments per day
    - Low-dose TBI, with doses of 2 – 6 Gy given in 1 to 4 fractions in combination with chemotherapy, is an effective conditioning regimen for hematopoietic stem cell transplantation in patients who cannot tolerate myeloablation due to age or comorbidities.
- Peyronie's disease (Morbus Peronie, Induratio penis plastica): 2D, orthovoltage, or electron beam radiation in 5 or fewer fractions.
- Parotid adenoma: for > 4 cm, positive margin status, and multinodularity, up to 30 fractions.
- Paraganglioma (chromaffin positive): for unresectable, recurrence, or as adjuvant therapy for incomplete resection, 25 – 28 fractions of 3D/IMRT, SRS 12 – 18 Gy.
- Orbital pseudotumor (lymphoid hyperplasia): Up to 10 fractions of 2D/3D.
- Orbital myositis (failed conservative therapy): up to 15 fractions of 2D/3D.
- Non-cutaneous neurofibromas: for symptomatic unresectable non-cutaneous lesions, up to 30 fractions.
- Lethal midline granuloma: for localized presentations or in conjunction with systemic therapy, 45 – 50 Gy up to 25 fractions.
- Lymphangiomas (capillary, cavernous, cystic hygromas, and lymphangial): for refractory lesions with repeated recurrence after resection (and chylothorax due to pleural involvement, 20 – 40 Gy in 10 – 20 fractions).
- Langerhans cell histiocytosis (LCH): for localized growth, up to 28 fractions of 3D.
- Inverted papilloma: for incomplete resection, or suspected malignant component, 45 – 70.4 Gy up to 39 fractions.
- Hyperthyroidism/thyroiditis: systemic 131-I.
- Hemangiomas (brain, spinal cord, subglottis, glottis, liver, GI tract, urinary tract, joints and orbit): Up to 30 fractions of IMRT.
- Gynecomastia: up to 5 fractions of electron beam therapy.
- Graves’ ophthalmopathy: up 20 10 fractions of 2D/3D.
- Gorham-Stout syndrome (disappearing bone syndrome): up to 25 fractions of 3D.
- Giant cell tumor of bone (osteoclastoma): for unresectable, up to 30 fractions.
- Dupuytren's contracture (fibromatosis) of hands/feet: up to 10 fractions of 2D or electron beam.
- Aneurysmal bone cyst: as the last resort, up to 10 fractions.
- Angiofibroma of nasopharynx (juvenile nasopharyngeal angiofibroma): for unresectable disease, up to 20 fractions.
- Angiomatosis retinae (von Hippel Lindau syndrome): beta plaque.
- Bowen's disease (squamous cell carcinoma in situ)/Erythroplasia of Queyrat: when typical alternatives (surgery, electrodessication and curettage, topical 5FU), are not possible, superficial radiation up to 20 fractions.
- Desmoid tumor: for inoperable cases, up to 28 fractions of 3D.
- Degenerative skeletal disorder: for symptomatic degenerative skeletal and joint disorders (i.e., plantar fasciitis, trochanteric bursitis) refractory to conventional treatments, up to 8 fractions of 2D.

- Choroidal hemangioma: for diffuse lesions, especially if near the macula or papilla, and for those not responding to other treatments, LDR brachytherapy, or 2D/3D up to 20 fractions.
- Castleman's disease (giant lymph node hyperplasia): for orbital pseudotumor and Waldeyer's ring, LDR brachytherapy, or 2D/3D up to 25 fractions.
- Carcinoid tumors: for symptomatic unresectable non-secretory, or secreting tumors, up to 25 fractions.
- Hypersalivation of amyotrophic lateral sclerosis (ALS): when other means of management are ineffective or impractical, up to 4 fractions.

Stereotactic radiation therapy (SRS, SBRT) is considered **MEDICALLY NECESSARY** when used in the treatment of non-malignant cranial lesions, including the following (ASTRO, 2014):

- Arteriovenous malformation (AVM) of the brain or spine
- Trigeminal neuralgia that has not responded to other more conservative treatments
- Non-cancerous brain tumors such as acoustic neuroma, benign schwannomas, meningioma, hemangioma, pituitary adenoma, craniopharyngioma, neoplasm of the pineal gland and chordomas

TREATMENT OPTIONS REQUIRING PHYSICIAN REVIEW:
Treatment for other non-malignant conditions utilizing proton beam, stereotactic radiation therapy (SBRT) or intensity modulated radiation therapy (IMRT) modalities should be referred to physician review.

References

1. McKeown SR, Hatfield P, Prestwich RJ, Shaffer RE, Taylor RE. Radiotherapy for benign disease; assessing the risk of radiation-induced cancer following exposure to intermediate dose radiation. *Br J Radiol*. 2015;88(1056):20150405. doi:10.1259/bjr.20150405
2. Assembly of Life Sciences (U.S.). *Committee to Review the Use of Ionizing Radiation for the Treatment of Benign Diseases.* Bureau of Radiological Health. National Academies; 1977.
3. Eng TY, Boersma MK, Fuller CD, et al. The role of radiation therapy in benign diseases. *Hematol Oncol Clin North Am*. Apr 2006;20(2):523-57. doi:10.1016/j.hoc.2006.01.023
4. Meyer J. *The Radiation Therapy of Benign Disease: Current Indications and Techniques: 33rd San Francisco Cancer Symposium, San Francisco, Calif., April 3-4, 1999*. vol 35. Karger Medical and Scientific Publishers; 2001.
5. Micke O, Seegenschmiedt MH. Consensus guidelines for radiation therapy of benign diseases: a multicenter approach in Germany. *International Journal of Radiation Oncology* Biology* Physics*. 2002;52(2):496-513.
6. Order SE, Donaldson SS. Radiation Therapy of Benign Disease: A Clinical Guide (Medical Radiology). Springer; 2003.
7. Seegenschmiedt MH, Micke O, Muecke R. Radiotherapy for non-malignant disorders: state of the art and update of the evidence-based practice guidelines. *Br J Radiol*. Jul 2015;88(1051):20150080. doi:10.1259/bjr.20150080
8. Gunderson & Tepper. *Clinical Radiation Oncology, 2nd Edition*. Seegenschmiedt MH Nonmalignant Disease. Elsevier - Health Sciences Division; 2006.
9. Royal College of Radiologists. *A review of the use of radiotherapy in the UK for the treatment of benign clinical conditions and benign tumours*. Royal College of Radiologists; 2015.
10. US Department of Health, Education and Welfare, Public Health Service. Food and Drug Administration, Bureau of Radiological Health. A review of the use of ionizing radiation for the treatment of benign diseases. September 1977;Volume I. HEW Publication (FDA) 78-8043
11. Halperin EC, Brady LW, Wazer DE, Perez CA. *Perez & Brady's principles and practice of radiation oncology, 6th Edition*. Winkfield KM, Bazan JG, Gibbs IC, et al Nonmalignant Diseases. Lippincott Williams & Wilkins; 2013.
12. Gofman JW. *Preventing breast cancer: The story of a major, proven, preventable cause of this disease. 2nd Edition.* San Francisco: Committee for Nuclear Responsibility; 1996:243-254.
13. Borok TL, Bray M, Sinclair I, Plafker J, LaBirth L, Rollins C. Role of ionizing irradiation for 393 keloids. *Int J Radiat Oncol Biol Phys*. Oct 1988;15(4):865-70. doi:10.1016/0360-3016(88)90119-8
14. McKay C, Knight KA, Wright C. Beyond cancer treatment - a review of total lymphoid irradiation for heart and lung transplant recipients. *J Med Radiat Sci*. Sep 2014;61(3):202-9. doi:10.1002/jmrs.63
15. American College of Radiology, American Radium Society. ACR-ARS practic parameter for the performance of total body irradiation. American College of Radiology (ACR). Updated 2022. Accessed December 6, 2022. https://www.acr.org/-/media/ACR/Files/Practice-Parameters/tbi.pdf?la=en
16. American Society for Radiation Oncology. Model Policies: Stereotactic Body Radiation Therapy. American Society for Radiation Oncology (ASTRO). Updated June 2020. Accessed October 3, 2022. https://www.astro.org/ASTRO/media/ASTRO/Daily%20Practice/PDFs/ASTROSBRTModelPolicy.pdf
17. American Society for Radiation Oncology. Model Policies: Stereotactic Radiosurgery (SRS). American Society for Radiation Oncology (ASTRO). Updated 2014. Accessed October 13, 2022. https://www.astro.org/uploadedFiles/_MAIN_SITE/Daily_Practice/Reimbursement/Model_Policies/Content_Pieces/ASTROSRSModelPolicy.pdf

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross Blue Shield Association technology assessment program (TEC) and other nonaffiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

History From 2024 Forward

12/02/2024	Annual review, no change to policy intent.
01/01/2024	New Policy

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CRITICAL REVIEW

The Use of Low-Dose Radiation Therapy in Osteoarthritis: A Review

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Despite its clinical use and investigation in other countries, low dose radiation therapy (LDRT) in the treatment of osteoarthritis (OA) is minimally used in the United States (US). Numerous recent studies published outside the US have shown moderate to long-term pain relief and improvement of mobility after treatment with LDRT for joints affected by OA. Here, we review the most recent literature published on the use of LDRT in OA. We provide a brief outline on the epidemiology, pathophysiology, current treatments, and health care burden of OA within the US. We provide a brief history of the historic use of LDRT in the US as well as a history of LDRT within the modern era of radiation oncology, discuss criticisms of LDRT including recently published randomized trials questioning its benefit as well as the risk of secondary malignancy from LDRT, and provide an outline of treatment planning considerations and recommendations regarding dose and fractionation, energy, beam arrangements, and immobilization techniques. LDRT has been shown to be a cost-effective, noninvasive treatment with minimal side effects. Further investigation into the potential role in the treatment of OA with modern LDRT is recommended.

Introduction

Radiation therapy (RT) has been used worldwide to treat benign conditions for over a century. Since the discovery of x-rays and their rapid adoption for therapeutic purposes, many advancements have been made in our understanding of the benefits and risks of RT. Through several decades of investigation, it has become apparent that RT has different biologic effects at different doses. Conventional and hypofractionated RT have antiproliferative principles that are used in the treatment of malignant disorders. Alternatively, at doses of less than 1 Gray (Gy) per fraction, RT has been shown to have strong anti-inflammatory effects.[1] It should be noted that the dose-effect relationship in the range of small irradiation doses of less than 1 Gy cannot be assumed to be linear. By using anti-inflammatory properties, low dose radiation therapy (LDRT) has been used to successfully treat painful musculoskeletal conditions. Conditions such as plantar fasciitis, trochanteric bursitis, medial and lateral epicondylitis, tendinopathies of various joints, and osteoarthritis (OA) of both large and small joints have been shown to benefit from LDRT.[2] In this paper, we provide a critical review and summary of the literature focusing on the use of LDRT for OA.

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Disclosures: none.

Data sharing statement: All data generated and analyzed during this study are included in this published article (and its supplementary information files).

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Epidemiology

Osteoarthritis is the most common form of arthritis, affecting over 32 million Americans.[3] According to the World Health Organization, OA is the fastest increasing health condition and the second leading cause of disability in the United States (US).[4,5] Currently, 1 in 7 Americans have been diagnosed with OA, and the expected incidence and prevalence are predicted to continue to rise with an aging American population.[6] The estimated prevalence was 21 million in 1990, 27 million in 2010, and now over 32 million.[7] As a comparison, in 2018 the Surveillance, Epidemiology, and End Results Program database estimates there were just over 16 million Americans living with cancer of any site including skin and hematologic malignancies.[8] According to the Johnston County Osteoarthritis Project, which is an ongoing longitudinal population-based cohort study investigating the incidence, prevalence, and progression of OA for over 25 years, the lifetime risk of developing knee or hip OA is 46% and 25%, respectively.[9,10] Figure 1 outlines the lifetime incidence of OA for different joint sites.[11-13]

Presentation and pathophysiology

OA is characterized as a progressive disorder typically presenting with signs of joint stiffness, pain, and loss of mobility. Commonly, it affects both large and small joints, including the hands, hips, and knees. Although it is known that OA results from the degeneration of cartilage between bones in the joint, the underlying pathogenesis and mechanism of OA are complex and our understanding of exact mechanisms is evolving.[14] It is hypothesized that proinflammatory mechanisms drive the recruitment of proteolytic enzymes, which lead to degradation of extracellular matrix. This results in damage to bone, articular cartilage, menisci, ligaments, and synovium, which is further exacerbated by excessive joint loading.[15,16] Structurally, OA can lead to joint space narrowing, osteophytes, subchondral bony sclerosis, and bony deformation, which can be identified radiographically. Clinically, OA can be diagnosed if the following are present: persistent usage-related joint pain, age greater than 45 years, and morning stiffness lasting less than 30 minutes.[17] The American College of Rheumatology (ACR) endorses classification criteria for OA of the hand, hip, and knee, which incorporates history, physical examination, and laboratory findings.[18,19] Although the ACR does not endorse specific criteria for disease severity, it is commonly separated into mild, moderate, severe, and refractory based on clinical disease effect.

Risk factors

OA is more likely to be diagnosed in individuals with the following risk factors: older age, female sex, higher body mass index, family history of OA, anatomic factors including joint alignment and shape, or previous joint injury.[20] Almost 90% of affected patients are over the age of 45 with almost 50% of affected patients age 65 or older.[7] Women are disproportionately affected by OA, with studies showing an increased prevalence and severity of disease.[21] Obesity correlates significantly with increased risk, likely due to increased weight bearing of joints and a proinflammatory state.[22] Although poorly understood, there appears to be a genetic predisposition for OA in patients who have a family history of disease. Additionally, previous joint injury has been shown to increase risk of OA.[20]

Current treatment

Given that the exact disease mechanism is unknown and the etiology appears multifactorial, there is no definitive intervention for early stage degenerative OA, and treatment for late stages is focused on palliation of symptoms with the aim to restore the patient's mobility and thus improve their quality of life. Both the ACR and American Academy of

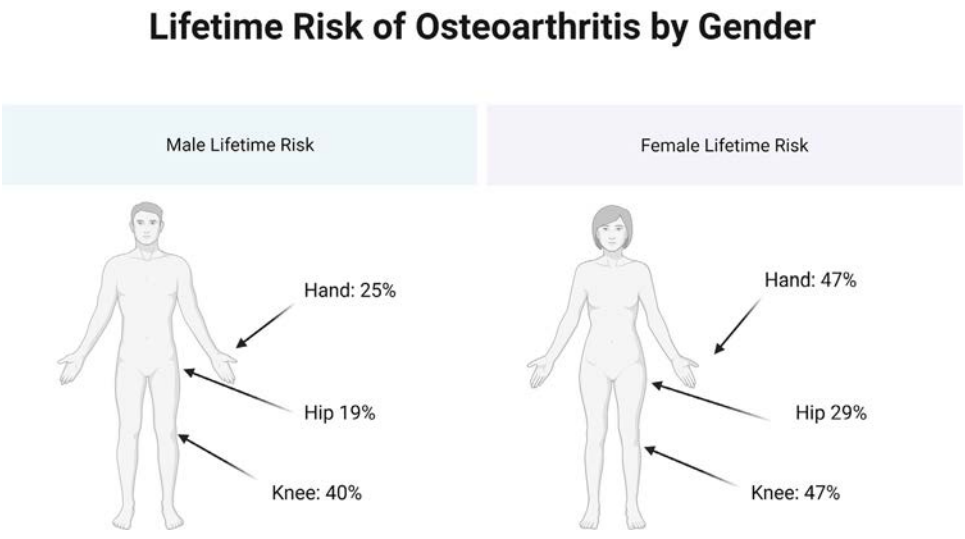

Fig. 1. Lifetime risk of osteoarthritis by sex and affected site.

Orthopedic Surgeons publish consensus guidelines for the management of OA.[23,24] Which interventions to implement varies among patients, and no universal guidelines exist for the specific sequencing or combination of interventions across all patients. Weight loss, moderate levels of physical activity, and physical rehabilitation approaches are some of the conservative therapies used.[25,26] Nonsteroidal anti-inflammatory drugs (NSAIDS) are usually the first-line treatment for OA after a trial of conservative management[23,27] and are typically helpful in alleviating pain, but also carry risks with long term use, including cardiovascular (CV) events, gastrointestinal bleeds, and chronic or acute renal failure.[28] In older patients who are more likely to be affected by OA, the risk of NSAID use has been shown to have an excess risk of 7 in 1000 nonfatal CV events per year, 2 in 1000 fatal CV events per year, and a 4-fold increased risk of gastrointestinal bleed.[29,30] Additionally, about 25% of all patients will not respond to these therapies or lose their responsiveness over time.[31] Intra-articular NSAIDs, corticosteroids, and biologic therapies can provide some relief. For a small portion of patients, surgical intervention such as joint lavage, debridement, synovectomy, radiofrequency ablation, or even prosthetic replacement might be indicated, carrying their own inherent risks of bleeding, infection, or other interventional complications. Figure 2 outlines the general treatment paradigm of OA.

Burden on health care system and patients

OA can present considerable challenges to affected patients when considering the sum of physical, psychological, and financial effects. OA commonly presents with pain and decreased range of motion of joints, which can lead to significant deficits in quality of life as well as decreased activity. Several studies have shown that patients with OA have greater pain, physical inactivity, and fatigue than the control population.[7] It is estimated that by the year 2040, over 10% of all adults will experience arthritis-related activity limitations.[32] Likely associated with decreased physical activity, OA has been shown to increase the risk of developing heart disease by 50%.[33] Additionally, with decreased activity, associated comorbid conditions, and adverse effects of medications, OA has been shown to increase all-cause mortality by 55%.[33] OA has also been associated with higher rates of depression and anxiety.[7] OA is the second-most costly health condition in the US and is responsible for over 4% of all total hospitalization costs.[34] One study suggests patients affected by arthritis make an average of $4000 less annually than those without,[34] with an estimated average direct cost of over $11,000 per person per year. Total US costs including indirect costs (lost earnings) and direct costs (medical expenditures) are 17 billion and 65 billion dollars, respectively, annually.[34] Considering the reduction of health-related quality of life in affected patients and the considerable socioeconomic costs due to multiple therapeutic procedures, OA is a significant burden on the US health system.

Overview of LDRT

In Germany over one-third of all RT treatments are for benign diseases, including over 15,000 patients with OA.[35] In the US, thousands of patients are treated each year for various benign diseases, such as intracranial meningioma,[36] vestibular schwannoma,[37] paraganglioma,[38] hidradenitis suppurativa,[39] orbital pseudotumor,[40] fascial fibromatosis,[41]

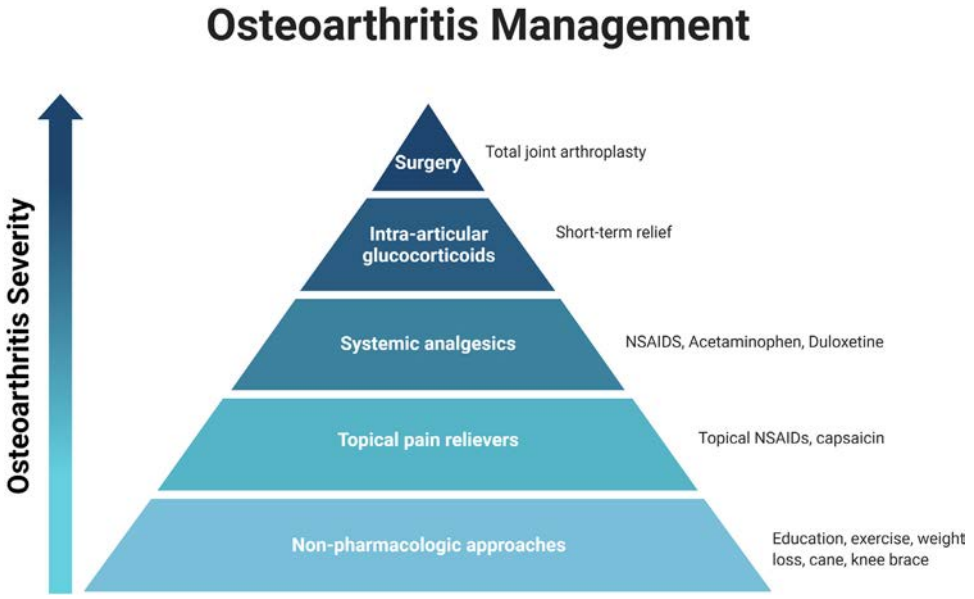

Fig. 2. Traditional management algorithm for osteoarthritis. Conservative management is first line, with progressively stronger (and potentially more toxic) pharmacologic management for persistent inflammation and pain. Surgery is reserved for patients who fail conservative and pharmacologic measures.

prevention of recurrent keloids,[42] and prevention of heterotopic ossification.[43] For several decades, LDRT has been used in the treatment of a wide variety of inflammatory conditions including symptomatic OA.[2,5] Low-dose RT has been positioned as an effective therapeutic alternative for patients with OA, evidenced by multiple clinical trials with symptomatic pain relief shown in 63% to 90% of all irradiated patients, with almost no acute side effects.[2,31]

Radiobiological mechanism

The precise pathophysiologic mechanisms of pain relief after RT are continuing to be investigated. Recent radiobiological studies show that low doses of radiation have anti-inflammatory efficacy based on the modulation of a multitude of inflammatory pathways and cellular components, including endothelial cells, leukocytes, and macrophages. Macrophages have been shown to play an integral role in the inflammatory pathway via multiple pathways, including ability to secrete proinflammatory cytokines, reactive oxygen species, and nitric oxide.[44] LDRT has been shown to significantly modulate macrophages via the nitric oxide pathway through inhibition of inducible nitric oxide synthase leading to reduced nitric oxide production.[44] Additionally, doses of radiation less than 1 Gy can polarize macrophages toward an anti-inflammatory M2 phenotype, although higher doses can bias toward a proinflammatory M1 phenotype.[45] LDRT has also been shown to modulate endothelial cells by reducing adhesion of leukocytes and thus migration of cells after doses between 0.3 and 1.0 Gy, as evidenced by multiple preclinical studies.[44,46] LDRT can also reduce production of proinflammatory cytokines from irradiated leukocytes as well as increase apoptosis of these cells.[47-49] Several studies using animal models of arthritis have shown that low dose irradiation with single doses of 0.5 to 1.5 Gy and total doses of 2.5 to 7.5 Gy clinically and histologically demonstrate anti-inflammatory efficacy.[48,50-52] Currently, there is an ongoing prospective study Immunophenotyping From Blood of Patients Suffering From Chronic Degenerating Joint diseases and receiving LDRT (IMMO-LDRT01) investigating the effects of LDRT on peripheral blood in patients irradiated for chronic degenerative and inflammatory conditions such as OA. In a recently published interim analysis of the study, investigators reported results of 125 patients of expected 250 patients that showed statistically significant improvement of pain as well as down-regulation of activated systemic immune cells determined by the measurement of expression of known activation markers such as CD25 and Human Leukocyte Antigen-DR isotype (HLA-DR).[53] Further studies are needed to characterize the exact mechanism of LDRT on inflammation. Figure 3 provides an outline of anti-inflammatory effects of LDRT in OA.

Risk of secondary malignancy

Low doses of ionizing radiation have the potential for the induction of secondary malignancy (SM), believed to occur as a stochastic effect with no threshold point and an increased risk proportional to increased dose.[54] When evaluating the carcinogenic risk of LDRT in the treatment of OA, factors such as age, sex, and anatomic location of treatment should be considered.[55] Multiple studies have tried to estimate the risk of SM from LDRT.[56-59] One challenge regarding estimating risk of SM is that much of our understanding of SM risks are based off cohort studies investigating the incidence in atomic bomb survivors and patients who developed SM after treatment with older RT techniques.[60-62] Multiple mathematical models exist to estimate risk; however, most models account for whole body radiation exposure, thus overestimating risk of SM from therapeutic radiation.[63] One study published in *Radiotherapy and Oncology* estimated the risk of fatal tumor induction in patients treated with RT for various benign conditions. In the study, the estimated lifetime risk for an induced fatal tumor for a patient receiving LDRT with total dose of 6 Gy for knee OA at the age of 25, 50, and 70 was 2 in 1000, 0.7 in 1000, and 0.3 in 1000 patients, respectively, when assuming an estimated effective dose of 13 mSv (which, of note, is an effective dose similar to an abdominopelvic computed tomography [CT] scan).[5,55,64] Although the knee is surrounded by tissues with lower carcinogenic susceptibility and thus lower tissue weighting factors when calculating effective dose, other joints such as the shoulder and hip are surrounded by organs with higher carcinogenic susceptibility. For example, in the same study, a 25-year-old female undergoing LDRT with a total dose of 6 Gy for shoulder OA has an estimated lifetime risk of fatal tumor of 20 in 1000 patients, with an estimated effective dose of 93 mSv. Despite these and other publications, a recent update of the German Society of Radiation Therapy and Oncology (DEGRO) guidelines for benign disease reports there have not been any known reported cases of SM from treatment of OA with LDRT.[2] A recently published retrospective study investigating the occurrence of breast cancer in female patients who underwent LDRT for nonmalignant disorders of the shoulder showed no increased risk of SM in comparison with the estimated spontaneous incidence of mammary carcinoma for this cohort.[64] In the study, a geographically defined district with a population of approximately 100,000 inhabitants was retrospectively analyzed as far back as 41 years with comprehensive review of radiologic diagnostics data, including mammography and RT records of patients with breast cancer and other nonmalignant disorders. Within this population, 158 women who underwent LDRT of the shoulder were investigated. RT was performed with cobalt-60 photons with an average cumulative dose of 6 Gy. Median age was 55 years old when RT of the shoulder was performed, with an average follow-up time of 21.3 years. Seven patients (4.4%) who were treated with LDRT for shoulder OA developed breast cancer. According to the incidence statistics, 5.9% breast cancer cases would have been expected in a control study population. The study concluded that neither the ipsilateral nor the contralateral breasts showed increased rates of breast cancer. Although the

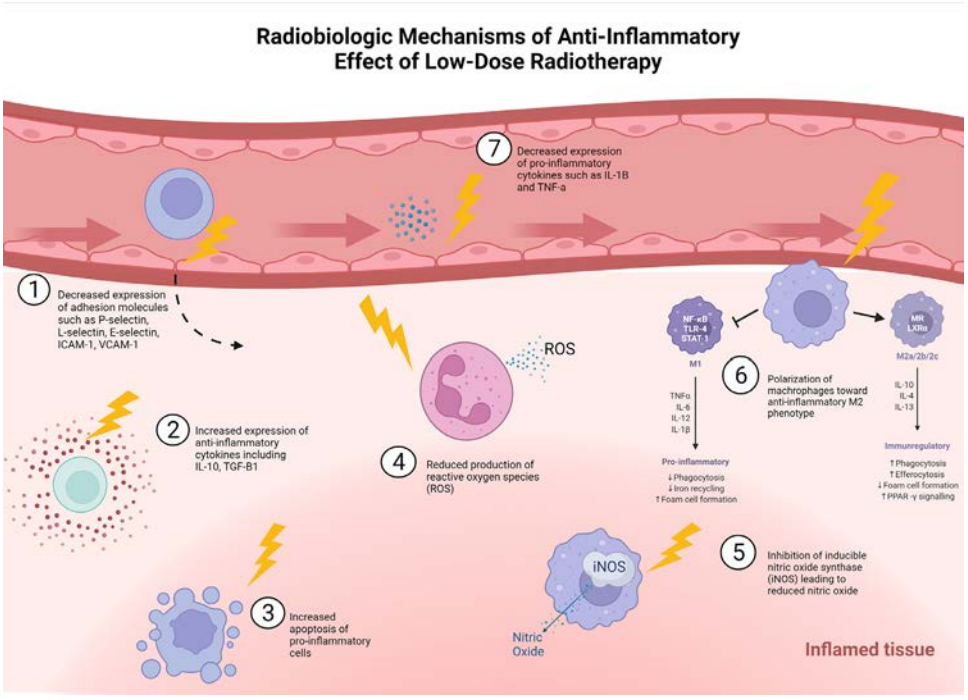

Fig. 3. Radiobiological mechanisms of anti-inflammatory effect of low-dose radiation therapy (LDRT). LDRT modulation of endothelial cells by reduced expression of adhesion molecules (1), resulting in a cascade of decreased cell migration and increased anti-inflammatory cytokines (2). Irradiated leukocytes result in a decrease of proinflammatory cytokines (7) and subsequent increased apoptosis (3); Reactive oxygen species (ROS) production is also reduced with irradiated leukocytes (4). Macrophage modulation by radiation (6) promotes regulatory immune cytokines while inhibiting proinflammatory cytokines and inducible nitric oxide synthase, downregulating nitric oxide production (5).

stochastic effects of radiation-induced SM are known, the exact risk of SM from LDRT is very difficult to define. In the 2018 DEGRO guidelines, LDRT for OA is recommended primarily for patients over the age of 40 to minimize risk of SM.[2]

Noncarcinogenic risks

LDRT has been shown to have very minimal acute side effects. In a review of several studies including over 1000 patients, only 1 patient reported mild skin redness. No other acute or late side effects were noted.[5,65-67] Additionally, LDRT does not negatively affect the function of healthy, noninflamed joints in preclinical studies,[68] and no literature exists to suggest LDRT could negatively affect a surgical procedure after irradiation for OA.

History of LDRT

Beginnings

In 1898, just 3 years after the discovery of x-rays, the first publication of RT use for arthritis was published by Sokolow, showing 4 patients treated with RT all having a complete pain response.[1,69] Subsequently, over the next 30 years, multiple studies were published showing significant pain relief in hundreds of patients treated for OA; however, in these studies, dose and fractionation schemes were highly variable, with some failing to detail radiation doses altogether.[70] After these initial publications, in 1933 the first well-described clinical investigation of RT for OA provided principles for field design, dose, and fractionation schemes.[70,71] After this seminal publication, subsequent studies were published over several decades further optimizing principles of radiation delivery and optimal dose and fractionation schemes.[70,72] Analyzing the historical data, about two-thirds of patients appeared to benefit from LDRT for OA with either improved pain or mobility.[70]

American experience

Historically, OA was commonly treated with LDRT in the US until the 1980s, when improved pharmacologic treatment options became available and studies questioned the benefit of treatment versus placebo, leading to decreased practice.[70] In 1998, a worldwide survey study analyzing practice patterns of radiation use for benign disease in over 1300 institutions in different countries found that less than 10% of providers in the US use RT for OA while over 85% of providers in Central European countries do.[73] Why are such significant practice patterns present? While being

vigilant to limit unnecessary radiation exposure, one explanation for differences in practice patterns could be the willingness to accept the small risk of SM for treatment of a benign disease,[5] with a historical context of RT for ankylosing spondylitis showing an increased risk of SM and mortality.[74] With the historic treatment of ankylosing spondylitis, it should be noted that the risk of SM was significantly increased, with the typical dose prescribed being 20 Gy in 1 Gy daily fractions with large fields including the sacro-iliac, lumbar, thoracic, and cervical spine irrespective of the symptomatic site of disease.[75]

In addition, 2 negative historical clinical trials were published in the 1970s that questioned the benefit of LDRT for OA.[70] In 1970, a randomized double-blind sham study investigating LDRT for a variety of painful locomotor conditions (125 out of 399 patients having OA) investigated doses of 4.5 Gy in 3 fractions or 6 Gy in 3 fractions over 1 week for the experimental group and lead shield for the sham group.[76] At 6 weeks, evaluation of pain showed nonsignificant statistical difference of 69% improvement for the treated group and 64% improvement for the sham group. In 1975, a randomized double-blind study of 104 patients with painful degenerative conditions (40 with OA) treated with radiation versus sham treatment found at 6 weeks no statistical difference in pain improvement in either group.[77] Although these 2 studies failed to show a benefit of RT for OA, it should be noted that the radiation dosing of these trials is not the same as modern day recommendations, as the understanding of the anti-inflammatory efficacy of LDRT suggests 1.0 Gy per treatment as the maximal dose per day with ideal dose per fraction between 0.3 and 0.7 Gy.[2,5] Additionally, it should be noted that in both trials, the majority of patients did not have OA and included other skeletal conditions, potentially contributing to nonsignificant statistical findings.

Modern Day LDRT

German pioneers

Modern era German investigators have pioneered the evidence-based treatment of OA. In 1995, the DEGRO formed a scientific task group called the German Cooperative Group on Radiotherapy for Benign Diseases (GCG-BD) to review several decades of German clinical experience using RT for nonmalignant disorders.[78] This task group systematically discussed and evaluated the relevant clinical data and subsequently published the first national guideline in 2000, developing prospective trials to improve the available levels of evidence for various nonmalignant disorders. In 2018, they published the most recent update, with levels of recommendation for different treatments based off available levels of evidence.[2] In published literature, LDRT has been shown to provide symptomatic pain relief in 60% to 90% of irradiated patients with almost no acute side effects.[2,31]

Recent literature for OA

Review articles have been published in the last decade describing both retrospective and prospective data showing efficacy of LDRT for OA pain and functional improvement.[5] One review including 20 studies discussed the results of pain reduction, functionality improvement, and side effects.[79] Herein, we review and outline studies with the highest quality of evidence published within the last few years using modern LDRT techniques and discuss current treatment planning recommendations. Table 1 outlines the most recent literature with the highest quality of evidence and modern RT planning.

Benefit of LDRT

One of the largest studies published is a retrospective analysis of 1185 anatomic sites in 970 elderly (≥65 years old) patients with OA of both large and small joints who were treated from 2008 to 2020 with LDRT given as 0.5 or 1 Gy dose 2 or 3 times weekly for 2 weeks.[81] Using the numerical rating scale, pain intensity was significantly decreased immediately, and at 8 weeks after completion of RT, 65.6% of patients reported a pain response associated with treatment. In cases of initial insufficient response, 384 courses of reirradiation were performed, with a pain response of 61.0% at 8 weeks after a second course of RT.

Another recent prospective study of 100 patients treated for hand OA assessed with visual analog scale (VAS) showed final significant pain improvement in 94% of patients, with median VAS score of 8 before treatment and median VAS score of 3 at 6 months after RT.[88] Of note, 63% of patients underwent a second course of treatment at 12 weeks due to inadequate initial response.

A recent planned interim analysis of prospective observational trial IMMO-LDRT01 reported on 125 of planned 250 patients with chronic degenerative disease. Pain as well as peripheral blood immune status were evaluated.[53] Pain relief was significantly improved, with mean VAS reduced from scores of 6.5 before treatment to 3.8 at 6 months after RT, with a statistical difference in immunophenotypes of peripheral blood cells.

In a retrospective analysis, pain response in 159 patients with 295 joints treated with LDRT showed a progressive reduction in median numerical rating scale scores up to 6 months after RT, and 64.8% maintained a decrease in pain 24 months after treatment completion.[82] Of note, 22.4% of sites received a second or third course of LDRT without a significant difference in long-term response rates compared with only 1 course of RT.

Another retrospective clinical study evaluated the efficacy of LDRT in 598 patients and found the mean VAS pain scores were significantly reduced from 7.0 before RT to 5.0 immediately after completing LDRT.[85] Long-term follow-up showed persistent pain response of 62.4% and a median VAS of 1.0 at a median follow-up of 38 months.

Table 1 Overview of clinical studies evaluating pain response after LDRT for OA

Reference	Study design (sample size)	Site	Total dose/dose per fraction (percentage of joints)	Fractionation schedule	Reirradiated (time after initial treatment)	Pain scoring	Follow-up	Outcome	Treatment device
Weissmann et al (2022)[80]	Retrospective (n = 196)	Foot and ankle	3.0 Gy/0.5 Gy (90%) 6.0 Gy/1.0 Gy (10%)	Twice weekly for 3 wk	84% (12 wk)	Subjective patient-reported pain reduction as percentage of improvement; response = at least 20% improvement	3 and 6 mo	75% response rate by 6 mo; 37% had 80%-100% reduction in pain	Orthovoltage
Ruhle et al (2021)[81]	Retrospective (n = 1185)	Multijoint	6.0 Gy/1.0 Gy (77.3%); 3.0 Gy/0.5 Gy (21.7%)	Given 2-3 times per week over 2-3 wk	32.4% (not reported)	VPS	8 and 8 wk after reirradiation	65.6% response at 8 wk; reirradiation: 61.0% response at 8 wk	Linac
Donaubauer et al (2020)[31]	Retrospective (n = 483)	Fingers and thumb	3.0 Gy/0.5 Gy (95.4%); 6.0 Gy/1.0 Gy (4.6%)	6 fractions over 3 wk	94.0% (12 wk)	Percent reduction in pain as scored by the patient	12 and 24 wk	Subjective reduction in 70% at end of RT	Orthovoltage
Hautmann et al (2020)[82]	Retrospective (n = 295)	Multijoint	6.0 Gy/1.0 Gy (77.6%); 5.0 Gy/1.0 Gy (1.0%); 1.0 Gy/1.0 Gy (0.3%); 3.0 Gy/0.5 Gy (19.0%); 5.0 Gy/0.5 Gy (1.4%); 1.5 Gy/0.5 Gy (0.7%)	Given over 2-3 wk	22.4% (12 wk)	NRS	19 mo (median)	64.8% response at 6 and 24 mo; reduction in median NRS from 5-3 at 24 mo	Linac
Hautmann et al (2019)[83]	Retrospective (n = 66)	Ankle and tarsal joints	3.0 Gy/0.5 Gy (60.6%); 6.0 Gy/1.0 Gy (36.4%); 5.0 Gy/1.0 Gy (3.0%)	Given over 2-3 wk	40.9% (6-12 wk)	NRS	31 mo (median)	75.0% response rate at 6 mo; 76.1% response rate at 12 mo; 70.0% response rate at 24 mo	Linac
Hautmann et al (2019)[84]	Retrospective (n = 217)	Reirradiated multijoint	3.0 Gy/0.5 Gy (55.3%); 1.5-2.0 Gy/0.5 Gy	Given 2-3 times per week over 2-3 wk	100% (median 14 wk)	NRS	25 mo (median)	57.6% response rate at 6 mo; 47.0%	Linac

(*Continued*)

Table 1 (*Continued*)

Reference	Study design (sample size)	Site	Total dose/dose per fraction (percentage of joints)	Fractionation schedule	Reirradiated (time after initial treatment)	Pain scoring	Follow-up	Outcome	Treatment device
			(1.4%); 6.0 Gy/1.0 Gy (43.3%)					response rate at 24 mo	
Juniku et al (2019)[85]	Retrospective (n = 598)	Multijoint	5.0 Gy/0.5 Gy (94.3%); 3.0 Gy/0.5 Gy (5.7%)	5 d per week	43.3% (not reported)	VAS	38 mo (median)	62.4% response (VAS 0-2) at 38 mo; reduction in median VAS from 7.0-1.0 at 38 mo	Linac
Kaltenborn et al (2016)[86]	Retrospective (n = 101)	Thumb	6.0 Gy/1.0 Gy	Twice weekly for 3 wk	10.9% (mean, 5 mo)	Subjective patient-reported response: CR, PR, or NC; response = CR or PR	3 and 12 mo	63% response rate at 3 mo (CR or PR); 70.3% response rate at 12 mo	Linac
Keller et al (2013)[87]	Retrospective (n = 1037)	Knee	0.5-10 Gy/0.5-1.5 Gy	Given 1-2 times per week (99.8%) 5 d per week (0.2%)	36.2% (not reported)	VPS	2 mo	79.3% response rate at 2 mo	Linac orthovoltage Cs-137
Alvarez et al (2021)[88]	Prospective (n = 100)	Hand	6.0 Gy/1.0 Gy (83%); 3.0 Gy/0.5 Gy (17%)	3 fractions per week for 2 wk	50.4% (median 12 wk)	VAS	10.5 mo (median)	94% response at 12 mo	Linac
Donaubauer et al (2021)[53]	Prospective (n = 125)	Multijoint	3.0 Gy/0.5 Gy	6 fractions over 3 wk	61.6% (3 mo)	VAS	6 mo	Planned interim analysis: reduction in mean VAS from 6.5-3.8 at 6 mo	Orthovoltage
Rogers et al (2020)[89]	Prospective (n = 99)	Fingers	4.0 Gy/0.5 Gy	Twice weekly for 4 wk	81.8% (2-12 mo)	VAS	12 mo	Reduction in VAS during activity by 3.0 (median) at 12 mo	Orthovoltage
Koc et al (2019)[90]	Prospective (n = 16)	Knee and hip	6.0 Gy/1.0 Gy	6 fractions given over 2 wk	0%	NRS	52 wk	50% response rate at 6 wk; 25% response rate at 52 wk	Linac

(*Continued*)

Table 1 (*Continued*)

Reference	Study design (sample size)	Site	Total dose/dose per fraction (percentage of joints)	Fractionation schedule	Reirradiated (time after initial treatment)	Pain scoring	Follow-up	Outcome	Treatment device
Micke et al (2018)[66]	Prospective (n = 703)	Multijoint	6.0 Gy/0.5 Gy (84.8%); 6.0 Gy/1.0 Gy (15.2%)	Not reported	7.3% (3 mo)	VAS and VPS	33 mo (median)	Reduction in mean VAS from 7.0-4.5 at the end of RT; 37.6% response rate at end of RT; 58.4% response rate at 33 mo	Linac orthovoltage
Micke et al (2017)[91]	Prospective (n = 166)	Multijoint	6.0 Gy/0.5 Gy (77.8%); 6.0 Gy/1.0 Gy (22.2%)	Not reported	8.4% (3 mo)	VAS and VPS	29 mo (median)	Reduction in mean VAS from 6.38-4.49 at the end of RT; 37.3% response at end of RT; 49.6% response at 29 mo	Linac orthovoltage
Niewald et al (2021)[92]	Randomized clinical trial (n = 229)	Hand and knee	3.0 Gy/0.5 Gy vs 0.3 Gy/0.05 Gy	Twice weekly for 3 wk	0%	VAS	3 mo and 1 year	Closed early owing to slow recruitment; 59% response rate at 3 mo; no significant difference between treatment arms	Linac
Mahler et al (2019)[93]	Randomized clinical trial (n = 55)	Knee	6.0 Gy/1.0 Gy vs sham radiation	6 fractions given every other day over 2 wk	0%	OMERACT-OARSI criteria	3 mo	44% response rate in treatment group at 3 mo; 43% response rate in sham group at 3 mo	Linac
Minten et al (2018)[94]	Randomized clinical trial (n = 56)	Hand	6.0 Gy/1.0 Gy vs sham radiation	6 fractions given every other day over 2 wk	0%	OMERACT-OARSI criteria	3 mo	29% response rate in treatment group at 3 mo; 36% response rate in sham group at 3 mo	Linac

Abbreviations: CR = complete response; LDRT = low-dose radiation therapy; linac = linear accelerator; NRS = numerical rating scale; OA = osteoarthritis; OMERACT-OARSI = Outcome Measures in Rheumatology—Osteoarthritis Research Society International; PR = partial response; NC = no change; RT = radiation therapy; VAS = visual analog scale; VPS = von pannwitz score.

In a retrospective study of 483 patients undergoing LDRT according to German guidelines, 70% of patients treated were found to have an improvement in their pain after LDRT.[31] Of note, patients who received 0.5 Gy per fraction reported a significantly better outcome in comparison to patients receiving 1 Gy per fraction. Given the principle of "as low as reasonably achievable," these data suggest using 0.5 Gy per fraction as opposed to 1 Gy to limit SM risk.

Recently, the ArthroRad Trial, a multicentric prospective randomized trial, evaluated the effect of LDRT on OA (3 Gy total in twice weekly 0.5 Gy fractions) versus very low dose (0.3 Gy total in twice weekly 0.05 Gy fractions), with patients blinded to the dose. Several in vitro studies have shown that due to the nonlinear dose-effect relationship in the range of less than 1 Gy fractions, anti-inflammatory effects can occur in doses much smaller than 0.5 Gy per fractions and thus the rationale for the study.[95,96] Unfortunately, the study was reported to close prematurely due to slow recruitment. Nevertheless, the results 3 months after RT from 244 treated joints showed improvement in both arms with no statistically significant differences found.[92] The authors concluded that further investigation should be performed studying conventional dose as well as very low dose radiation versus placebo.

Criticisms of LDRT

Recently published studies from the Netherlands have tested LDRT versus placebo. In 2017, European Society for Radiotherapy and Oncology presented and has since published the results of 2 randomized, double-blinded trials investigating the role of LDRT for pain relief and functional improvement of degenerative OA of the hand and knee joints. They provided the first clinical studies that compared modern LDRT with a sham irradiated group.

One study[94] looked at 56 patients with OA of the hand while the other study[93] looked at 55 patients with OA of the knee applying the same randomized, double-blinded design of RT at low dose (6 Gy in fractions of 1 Gy, 3 fractions per week) versus sham RT. In both studies, the authors evaluated the clinical response at 3 months of treatment according to the Outcome Measures in Rheumatology −Osteoarthritis Research Society International response criteria, including evaluation of pain and functionality of the treated joints. They noted no difference between the treated group and sham group at 3 months. In a subsequent publication, they reported outcomes at 6 and 12 months, which did not find significant difference in outcomes between the placebo and LDRT groups.[97]

After publication of these 2 trials, the GCG-BD published a response outlining the limitations of the studies.[98] The most obvious criticism of both studies was the low patient numbers that were powered for an expected benefit of 40% as part of the study design. Additionally, they note that a second series of RT is recommended at 6 to 12 weeks if insufficient response is achieved, with studies showing about 40% of patients requiring additional treatment to see benefit.[2] In the 2 studies, 1 Gy per fraction for total of 6 Gy was used, while newer data may suggest more anti-inflammatory response with 0.5 Gy per fraction for a total of 3 Gy rather than 1 Gy per fraction.[99,100] Although they note that both studies were well designed and conducted and add to preexisting literature, the studies do not provide definitive evidence to suggest no benefit of LDRT for OA.

Future directions of LDRT for OA

Currently, there are several ongoing prospective studies outside the US investigating LDRT for OA. In Germany, the ongoing prospective observational IMMO-LDRT01 clinical trial aims to study the changes in immune status before, during, and after LDRT using multicolor flow cytometry-based assays for over 30 immune cell subsets and their activation status.[101] In addition to clinical efficacy, this trial will elucidate the key immune-related mechanisms involved in response to LDRT for OA and other chronic degenerative joint diseases. Recently, an interim analysis of 125 was published, as described previously. In Spain, Radiotherapy 3 vs 6 Gy in Gonarthrosis and Coxarthrosis, an ongoing prospective randomized trial, is a noninferiority study randomizing patients with OA of the hip or knee to either 3 Gy (0.5 Gy per fraction, 3 fractions per week) or 6 Gy (1 Gy per fraction, 3 fractions per week) to determine optimal dosing, with anticipated completion date in 2023.

Treatment Planning

Overview

Currently, there is limited literature for consensus guidelines for treatment planning using LDRT for OA. We outline the current recommendation from the 2018 update from DEGRO as well as a recently published proposal from a Spanish group, which contains a 3-dimensional (3D) planning treatment atlas.[2,102] Figure 4 shows representative radiation fields for various sites of OA. Table 2 lists treatment planning recommendations including dose, energy, beam arrangements, immobilization techniques, and other considerations for planning. Of note, these are meant to serve as a primer for treatment planning, not consensus recommendations.

Small joints

In the 2018 update of DEGRO guidelines, the most recent German LDRT for OA recommendations were published.[2] For small joints, treatment energies recommended include orthovoltage in the range of 100 to 200 kV or 6 MV linear accelerator based treatment with parallel opposed beams or single Posterior-Anterior (PA) beam. If 6 MV energy is

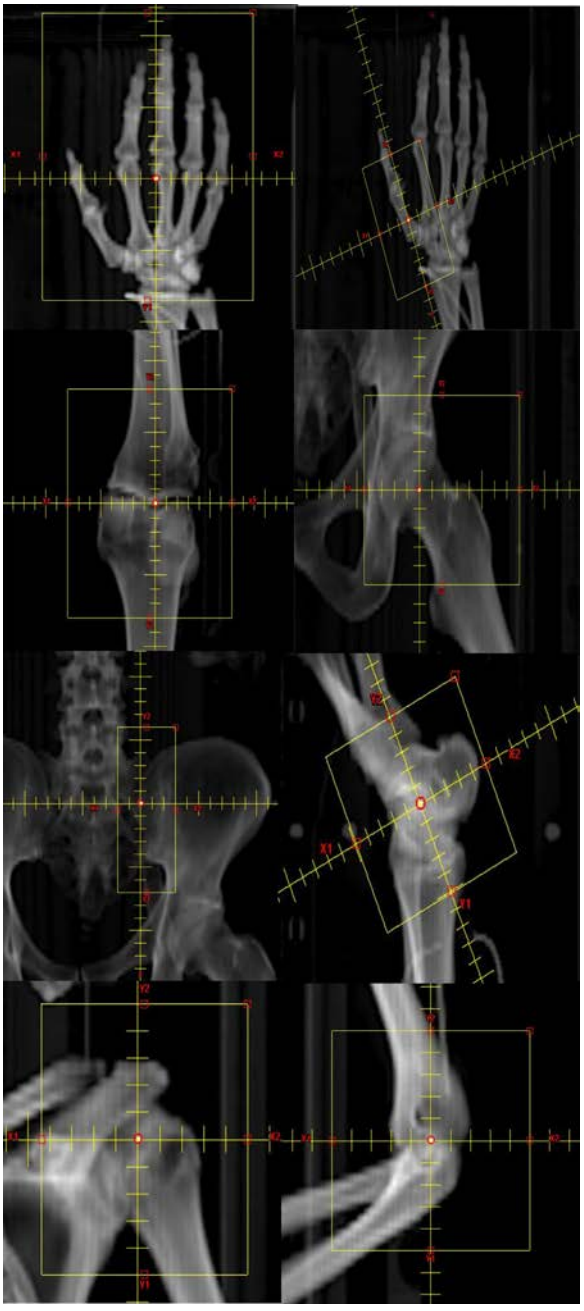

Fig. 4. Representative radiation fields for various sites of osteoarthritis (OA). Targets include third metacarpophalangeal (MCP) joint, first carpometacarpal joint, patellofemoral joint, acetabulofemoral joint, sacroiliac (SI) joint, glenohumeral joint, and humeroulnar joint. Center red circles represent isocenter. Hashmarks represent a distance of 1 cm. Solid unhatched yellow represents radiation treatment field.

used, it is recommended to consider a 5-mm bolus material to obtain homogenous dose distribution. Dose recommendations are 0.5 to 1.0 Gy per fraction for total doses of 3 to 6 Gy delivered twice a week. Target volume is recommended to be the entire affected joint with prescription to midpoint with limited additional recommendations regarding field sizes. If inadequate pain relief is achieved, retreatment can be considered 6 to 8 weeks later with the same dose and fractionation. Nail shielding should be considered to prevent growth defects.

The recently published 3D planning atlas recommends including the entire joint and cartilage as well as surrounding bursa, muscular insertion sites, and surrounding soft tissue structures within the treatment volume. The atlas additionally provides detailed recommendations for planning target volumes (PTVs) for each individual joint site.[102] CT-based cross-sectional imaging is suggested as optional for small joints if the target can be adequately defined clinically. Additional imaging such as magnetic resonance imaging can be used for target delineation, if available. It is suggested to consider immobilization devices such as extremity thermoplastic masks or vacuum-form custom-molded bags for treatment reproducibility. Consider bolus material of 5- to 10-mm thickness if inhomogeneous dose distribution is anticipated near the surface interface. Shielding nail beds is recommended to avoid growth defects. Caution is emphasized about limiting field sizes with too restrictive PTVs that can possibly limit pain reduction.[86] However, applying the radiation safety principle of "as low as reasonably achievable," radiation exposure with more precise PTV guidelines can be achieved as outlined in the atlas. Additionally, LDRT is recommended only for OA patients 40 years and older to limit the risk of SM.

Large joints

The 2018 DEGRO guidelines update also includes treatment planning guidelines for LDRT for OA of both the hip and knee.[2] For the knee, anterior-posterior or laterally opposed beams using at least 4 MV energy prescribed to joint midpoint are recommended. Additionally, orthovoltage can be considered with energies in the range of 100 to 200 kV. For hip treatment, anterior-posterior parallel opposed beams using higher energies of 10 MV or greater with prescription to mid-joint are recommended. As with other joint sites, both hip and knee dose recommendations are 0.5 to 1 Gy per fraction with total doses of 3 to 6 Gy with treatments given 2 to 3 times per week. Consideration for gonadal shielding should be made with hip treatment.

Recommended target volumes for large joints include the entire joint and cartilage as well as surrounding bursa, muscular insertion sites, and surrounding soft tissue structures, similarly to small joints.[102] CT-based cross-sectional imaging with 3D planning is suggested if the target cannot be adequately defined clinically. Immobilization for treatment should be considered using devices similar to those for oncologic treatment planning.

Treatment indications

According to the 2018 DEGRO update, LDRT for treatment of OA of the knee is recommended as category B (shall be

Table 2 OA disease sites and target volumes with associated technical specifications and setup for LDRT

Disease site	Target volume	Dose	Energy	Beam arrangement	Bolus	Immobilization technique	Shielding	Considerations
Hand	Proximal: Head of ulna Distal: 1.5-cm distal to DIP Medial: 1.5-cm flash Lateral: 1.5-cm flash	0.5 Gy in 6 fractions QOD or BIW prescribed to midpoint	6 MV*	Single posterior beam	5- mm bolus	Patient standing with hand on treatment couch	Consider lead fingernail shielding	
Thumb (alone)	Proximal: 1-cm proximal to radial styloid process Distal: Interphalangeal joint of thumb Medial: 2-cm medial from meta carpophalangeal joint Lateral: 2 cm from head of first metacarpal bone	0.5 Gy in 6 fractions QOD or BIW prescribed to midpoint	6 MV*	Single posterior beam	5- mm bolus	Patient standing with hand on treatment couch	Consider lead fingernail shielding	
Knee	Superior: 8-cm superior to joint space Inferior: 8-cm inferior to joint space Medial: 3-cm medial to medial femoral condyle Lateral: 3-cm lateral to lateral tibial condyle	0.5 Gy in 6 fractions QOD or BIW prescribed to midpoint	6 MV*	Parallel opposed AP beams	N/A	Patient supine, feet first, knee support		
Hip (acetabulofemoral joint)	Superior: 2 cm above femoral head Inferior: Superior aspect of lesser trochanter Medial: Inner pelvic brim Lateral: 1.5-cm lateral to femur	0.5 Gy in 6 fractions QOD or BIW prescribed to midpoint	10 MV or higher	Parallel opposed AP beams	N/A	Patient supine, headfirst, frog leg	Consider gonadal shielding if fertility preservation desired	Consider CT-based planning to determine dose distribution
Hip (sacroiliac)	Superior: 2 cm above SI joint Inferior: 2 cm below SI joint Medial: 2-cm medial SI joint space Lateral: 3-cm lateral SI joint space	0.5 Gy in 6 fractions QOD or BIW prescribed to midpoint	10 MV or higher	Parallel opposed AP beams	N/A	Patient supine, headfirst, frog leg	Consider gonadal shielding if fertility preservation desired	Consider CT-based planning to determine dose distribution

(*Continued*)

Table 2 (*Continued*)

Disease site	Target volume	Dose	Energy	Beam arrangement	Bolus	Immobilization technique	Shielding	Considerations
Ankle (tibiotalar joint)	Superior: 5-cm distal joint Inferior: 5-cm proximal joint Medial: 5-cm medial joint Lateral: 5-cm lateral joint	0.5 Gy in 6 fractions QOD or BIW prescribed to midpoint	6 MV*	Parallel opposed AP beams		Patient supine, feet first, consider extremity thermoplastic mask	Consider nail shielding if treatment forefoot	
Shoulder	Superior: 2 cm above coracoid process (AP)/ acromion (PA) Inferior: 2 cm below surgical neck of humerus Medial: 2-cm medial to glenoid cavity Lateral: 2-cm lateral to humeral greater tuberosity	0.5 Gy in 6 fractions QOD or BIW prescribed to midpoint	6 MV*	Parallel opposed AP beams	N/A	Patient supine, headfirst, blue block between feet or vac lock bag	Consider thyroid shield	Consider rotating collimator to keep breast out of field for female patients
Elbow	Superior: 5 cm above joint space Inferior: 5 cm below joint space Medial: 3-cm medial of humeral medial epicondyle Lateral: 3-cm lateral of humeral lateral epicondyle	0.5 Gy in 6 fractions QOD or BIW prescribed to midpoint	6 MV*	Parallel opposed AP beams	N/A	Patient supine, headfirst, consider extremity thermoplastic mask or arm akimbo		

Abbreviations: AP = anterior-posterior; PA = posterior-anterior; BIW = bi-weekly; CT = computer tomography; DIP = distal intraphalangeal joint; LDRT = low-dose radiation therapy; N/A = not applicable; OA = osteoarthritis; QOD = every other day; SI = sacroiliac.

* Can consider orthovoltage.

Table 3 Overview of indications and DEGRO level of recommendations for LDRT for musculoskeletal disease

Suggested criteria for treatment with LDRT for OA	
Appropriate after the exhaustion of other medical interventions or before more aggressive interventional treatments such as joint replacement (if more conservative treatment is desired)	
Older than age 40	
No known contraindications to radiation (pregnancy, active connective tissue disorder)	
2018 DEGRO level of recommendation	
Knee OA	Level recommendation B
Hip OA	Level recommendation C
Hand OA	Level recommendation C
Ankle OA	No level recommendation given
Shoulder OA	Level recommendation C
Plantar fasciitis	Level recommendation A
Elbow syndrome	Level recommendation B

Abbreviations: DEGRO = German Society of Radiation Therapy and Oncology; LDRT = low-dose radiation therapy; OA = osteoarthritis.

performed), which is the same recommendation given for keloids after surgical excision, a commonly practiced treatment within the US. LDRT as OA treatment of the hip, shoulder, and small joints is recommended as category C (can be given). Treatment of lower and upper ankle are not given a recommendation category due to insufficient data, although more recent data suggest good response to LDRT, and recommendations could likely be adjusted in future updates.[47,81,80,83] Table 3 provides an overview of treatment indications and DEGRO level of recommendations. Further clinical investigation and collaboration with other specialties, including rheumatology, orthopedics, and pain specialists, can help clarify appropriate indications for LDRT within the US. Currently, LDRT seems appropriate as a refractory treatment option after the exhaustion of other medical interventions or before more aggressive interventional treatments such as joint replacement (if more conservative treatment is desired).

Discussion

Despite its clinical use and investigation in other countries, LDRT in the treatment of OA is minimally used in the US. Numerous recent studies published outside the US have suggested moderate to long-term pain relief and improvement in mobility after treatment with LDRT for joints affected by OA.[2] LDRT has been shown to be a cost-effective, noninvasive treatment with minimal side effects. Although LDRT historically was used within the US and subsequently abandoned, advancements in our understanding of the radiobiology of LDRT and its anti-inflammatory effects should lead to prospective reinvestigation of the efficacy of LDRT for OA in the US.

There is a strong need for clearly defined treatment scheduling, including dosing, fractionation, and technique, to ensure the quality of LDRT. Additionally, there is a need to develop appropriate clinical endpoints of treatment and standardized response evaluation to improve outcome evaluation. With increased collaboration and investigation, adequate sample sizes for clinical trials can be achieved to truly determine the effectiveness of LDRT for OA. Therefore, we would recommend consideration of treating patients in prospective clinical trials to further evaluate and expand on the current existing literature.

We also encourage re-evaluation of the use of RT in other historically treated benign conditions. Currently, there are strong data to suggest a benefit of LDRT in plantar fasciitis, with about 80% efficacy in pain reduction.[103–105] Additionally, there are data to suggest benefit in other musculoskeletal disorders, such as trochanteric bursitis, medial and lateral epicondylitis, tendinopathies of various joints, Dupuytren contracture, Ledderhose disease, heterotopic ossification, and other disorders.[2] Although much modern data exist outside the US to support the benefit of radiation in these conditions, US investigation and use of radiation for these conditions are more limited.

Similar to the formation of the DEGRO scientific task force, the GCG-BD, to evaluate use of RT in benign disease, we recommend that a task force within the US be created to re-evaluate and develop consensus recommendations for treatment of these conditions. New, innovative treatments and clinical trials could be developed to promote investigation of new indications. Over the last decade, we have seen growth regarding the innovative use of RT for noncancer diseases in the US. In 2017, a landmark case series showed that stereotactic body RT is effective for cardiac ablation of refractory ventricular tachycardia (VT).[106] In a subsequent phase I/II clinical trial, EP-guided Noninvasive Cardiac Radioablation for Treatment of Ventricular Tachycardia, stereotactic body RT for refractory VT was shown to be both effective and safe.[107] Multiple studies have been published on the

safety and effectiveness of stereotactic radiosurgery for tremor movement disorders.[108,109] Other innovative RT treatments currently under investigation include the use of RT to inhibit amyloid plaque formation in Alzheimer disease,[110,111] radiosurgery for neuropsychiatric disorders,[112] radiosurgery for intractable pain[113] and trigeminal neuralgia,[114] and whole-lung irradiation for COVID-19 treatment.[115]

The aim of treating these nonmalignant conditions is to restore function and improve quality of life. With the creation of a cooperative group on RT within the US, consensus, evidence-based recommendations regarding treatments can be developed and collaboration among members can elevate the quality of research for the innovative use of functional RT in nonmalignant conditions.

Conclusions

Despite its clinical use and investigation in other countries, LDRT in the treatment of OA is minimally used in the US. Numerous recent studies published outside the US have suggested moderate to long-term pain relief and improvement in mobility after treatment with LDRT for joints affected by OA. LDRT has been shown to be a cost-effective, noninvasive treatment with minimal side effects. Further investigation into the potential role of modern techniques in the treatment of OA is recommended.

References

1. Torres Royo L, Antelo Redondo G, Árquez Pianetta M, et al. Low-dose radiation therapy for benign pathologies. *Rep Pract Oncol Radiother* 2020;25:250–254.
2. Mücke , Seegenschmiedt, & Micke. (n.d.). *Fachgruppenspezifische evidenzbasierte s 2e-Leitlinie der ... - degro*. Available at: https://www.degro.org/wp-content/uploads/2018/11/S2-Leitlinie-Strahlentherapie-gutartiger-Erkrankungen-update-2018-Endversion.pdf. Accessed January 8, 2022.
3. Centers for Disease Control and Prevention. (2020, July 27). *Osteoarthritis (OA)*. Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/arthritis/basics/osteoarthritis.htm#:~:text=Osteoarthritis%20(OA)%20is%20the%20most,underlying%20bone%20begins%20to%20change. Accessed January 8, 2022.
4. Sebbag E, Felten R, Sagez F, et al. The world-wide burden of musculoskeletal diseases: A systematic analysis of the World Health Organization Burden of Diseases Database. *Ann Rheum Dis* 2019;78:844–848.
5. Abdus-Salam AA, Olabumuyi AA, Jimoh MA, et al. The role of radiation treatment in the management of inflammatory musculoskeletal conditions: A revisit. *Radiat Oncol J* 2020;38:151–161.
6. Cisternas MG, Murphy L, Sacks JJ, et al. Alternative methods for defining osteoarthritis and the impact on estimating prevalence in a US population-based survey. *Arthritis Care Res (Hoboken)* 2016;68:574–580.
7. Osteoarthritis: A Serious Disease. 2016. Available at: https://oarsi.org/sites/default/files/library/2018/pdf/oarsi_white_paper_oa_serious_disease121416_1.pdf. Accessed January 8, 2022.
8. Cancer of any site - cancer stat facts. SEER. (n.d.). Available at: https://seer.cancer.gov/statfacts/html/all.html. Accessed January 8, 2022.
9. Johnston County Osteoarthritis Project – pioneering population based research. Thurston Arthritis Research Center. 2021. Available at: https://www.med.unc.edu/tarc/research/clinical-and-epidemiological-science-1/johnston-county-osteoarthritis-project/. Accessed January 8, 2022.
10. Osteoarthritis. (n.d.). Available at: https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Osteoarthritis#:~:text=Osteoarthritis%20(also%20known%20as%20OA,lining%2C%20ligaments%2C%20and%20bone. Accessed January 8, 2022.
11. Murphy L, Schwartz TA, Helmick CG, et al. Lifetime risk of symptomatic knee osteoarthritis. *Arthritis Rheum* 2008;59:1207–1213.
12. Qin J, Barbour KE, Murphy LB, et al. Lifetime risk of symptomatic hand osteoarthritis: The Johnston County Osteoarthritis Project. *Arthritis Rheumatol* 2017;69:1204–1212.
13. Murphy LB, Helmick CG, Schwartz TA, et al. One in four people may develop symptomatic hip osteoarthritis in his or her lifetime. *Osteoarthritis Cartilage* 2010;18:1372–1379.
14. Chow YY, Chin K-Y. The role of inflammation in the pathogenesis of osteoarthritis. *Mediators Inflamm* 2020;2020 8293921.
15. Loeser RF, Goldring SR, Scanzello CR, et al. Osteoarthritis: A disease of the joint as an organ. *Arthritis Rheum* 2012;64:1697–1707.
16. Wang X, Hunter DJ, Jin X, et al. The importance of synovial inflammation in osteoarthritis: Current evidence from imaging assessments and clinical trials. *Osteoarthritis Cartilage* 2018;26:165–174.
17. National Collaborating Centre for Chronic Conditions (UK). *Osteoarthritis: National Clinical Guideline for Care and Management in Adults*. London: Royal College of Physicians (UK); 2008.
18. Altman R, Alarcón G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601–1610.
19. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986;29:1039–1049.
20. Blagojevic M, Jinks C, Jeffery A, et al. Risk factors for onset of osteoarthritis of the knee in older adults: A systematic review and meta-analysis. *Osteoarthritis Cartilage* 2010;18:24–33.
21. Srikanth VK, Fryer JL, Zhai G, et al. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage* 2005;13:769–781.
22. King LK, March L, Anandacoomarasamy A. Obesity & osteoarthritis. *Indian J Med Res* 2013;138:185–193.
23. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol* 2020;72:220–233.
24. *Management of osteoarthritis of the knee (non-arthroplasty) evidence-based clinical practice guideline*. American Academy of Orthopedic Surgeons. (n.d.). Available at: https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/oak3cpg.pdf. Accessed January 8, 2022.
25. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the nonsurgical management of knee osteoarthritis. *Osteoarthritis Cartilage* 2014;22:363–388.
26. Fernandes L, Hagen KB, Bijlsma JWJ, et al. EULAR recommendations for the nonpharmacologic core management of hip and knee osteoarthritis. *Ann Rheum Dis* 2013;72:1125–1135.
27. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)* 2020;72:149–162.
28. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the nonsurgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019;27:1578–1589.
29. Coxib and traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: Meta-analyses of individual participant data from randomised trials. *Lancet* 2013;382:769-779.
30. Masclee GMC, Valkhoff VE, Coloma PM, et al. Risk of upper gastrointestinal bleeding from different drug combinations. *Gastroenterology* 2014;147:784–792 e9quiz e13-14.

31. Donaubauer A-J, Zhou J-G, Ott OJ, et al. Low dose radiation therapy, particularly with 0.5 Gy, improves pain in degenerative joint disease of the fingers: Results of a retrospective analysis. *Int J Mol Sci* 2020;21:E5854.
32. Hootman JM, Helmick CG, Barbour KE, et al. Updated projected prevalence of self-reported doctor-diagnosed arthritis and arthritis-attributable activity limitation among US adults, 2015-2040. *Arthritis Rheumatol* 2016;68:1582–1587.
33. Cost of osteoarthritis. Osteoarthritis Action Alliance. Available at: https://oaaction.unc.edu/policy/cost-of-osteoarthritis/. Accessed January 8, 2022.
34. Murphy LB, Cisternas MG, Pasta DJ, et al. Medical expenditures and earnings losses among US adults with arthritis in 2013. *Arthritis Care Res (Hoboken)* 2018;70:869–876.
35. Kriz J, Seegenschmiedt HM, Bartels A, et al. Updated strategies in the treatment of benign diseases-a patterns of care study of the German cooperative group on benign diseases. *Adv Radiat Oncol* 2018;3:240–244.
36. Marchetti M, Sahgal A, De Salles AAF, et al. Stereotactic radiosurgery for intracranial noncavernous sinus benign meningioma: International Stereotactic Radiosurgery Society systematic review, meta-analysis and practice guideline. *Neurosurgery* 2020;87:879–890.
37. Thai NLB, Mai NY, Vuong NL, et al. Treatment for vestibular schwannoma: Systematic review and single arm meta-analysis. *Am J Otolaryngol* 2021;43:103337.
38. Fatima N, Pollom E, Soltys S, et al. Stereotactic radiosurgery for head and neck paragangliomas: A systematic review and meta-analysis. *Neurosurg Rev* 2021;44:741–752.
39. Thompson AM, Seivright J, Atluri S, et al. Radiotherapy for hidradenitis suppurativa: A systematic review. *Dermatology* 2021;237:357–364.
40. Fionda B, Pagliara MM, Lancellotta V, et al. The role of radiotherapy in orbital pseudotumor: A systematic review of literature. *Ocul Immunol Inflamm* 2021;1–6.
41. Grenfell S, Borg M. Radiotherapy in fascial fibromatosis: A case series, literature review and considerations for treatment of early-stage disease. *J Med Imaging Radiat Oncol* 2014;58:641–647.
42. Xu J, Yang E, Yu N-Z, et al. Radiation therapy in keloids treatment: History, strategy, effectiveness, and complication. *Chin Med J (Engl)* 2017;130:1715–1721.
43. Georhakopoulos I, Kouloulias V, Kougiountzopoulou A, et al. Radiation therapy for the prevention of heterotopic ossification: Efficacy and toxicity of single fraction radiotherapy. *Orthop Rev (Pavia)* 2020;12:8577.
44. Hildebrandt G, Seed MP, Freemantle CN, et al. Mechanisms of the antiinflammatory activity of low-dose radiation therapy. *Int J Radiat Biol* 1998;74:367–378.
45. Calabrese EJ, Dhawan G, Kapoor R, et al. Radiotherapy treatment of human inflammatory diseases and conditions: Optimal dose. *Hum Exp Toxicol* 2019;38:888–898.
46. Trott KR, Kamprad F. Radiobiological mechanisms of anti-inflammatory radiotherapy. *Radiother Oncol* 1999;51:197–203.
47. Reichl B, Block A, Schäfer U, et al. DEGRO practical guidelines for radiotherapy of non-malignant disorders: Part I: Physical principles, radiobiological mechanisms, and radiogenic risk. *Strahlenther Onkol* 2015;191:701–709.
48. Arenas M, Gil F, Gironella M, et al. Anti-inflammatory effects of low-dose radiotherapy in an experimental model of systemic inflammation in mice. *Int J Radiat Oncol Biol Phys* 2006;66:560–567.
49. Lödermann B, Wunderlich R, Frey S, et al. Low dose ionising radiation leads to a NF-κB dependent decreased secretion of active IL-1β by activated macrophages with a discontinuous dose-dependency. *Int J Radiat Biol* 2012;88:727–734.
50. Hildebrandt G, Radlingmayr A, Rosenthal S, et al. Low-dose radiotherapy (LD-RT) and the modulation of iNOS expression in adjuvant-induced arthritis in rats. *Int J Radiat Biol* 2003;79:993–1001.
51. Rödel F, Keilholz L, Herrmann M, et al. Radiobiological mechanisms in inflammatory diseases of low-dose radiation therapy. *Int J Radiat Biol* 2007;83:357–366.
52. Fischer U, Kamprad F, Koch F, et al. Effekte einer niedrig dosierten Co-60-bestrahlung auf den verlauf einer aseptischen arthritis am kniegelenk des kaninchens [The effects of low-dose Co-60 irradiation on the course of aseptic arthritis in a rabbit knee joint]. *Strahlenther Onkol* 1998;174:633–639 [in German].
53. Donaubauer A-J, Becker I, Weissmann T, et al. Low dose radiation therapy induces long-lasting reduction of pain and immune modulations in the peripheral blood - interim analysis of the IMMO-LDRT01 trial. *Front Immunol* 2021;12:740742.
54. Hamada N, Fujimichi Y. Classification of radiation effects for dose limitation purposes: History, current situation and future prospects. *J Radiat Res* 2014;55:629–640.
55. Jansen JTM, Broerse JJ, Zoetelief J, et al. Estimation of the carcinogenic risk of radiotherapy of benign diseases from shoulder to heel. *Radiother Oncol* 2005;76:270–277.
56. Brenner DJ, Doll R, Goodhead DT, et al. Cancer risks attributable to low doses of ionizing radiation: Assessing what we really know. *Proc Natl Acad Sci U S A* 2003;100:13761–13766.
57. Cardis E, Vrijheid M, Blettner M, et al. Risk of cancer after low doses of ionising radiation: Retrospective cohort study in 15 countries. *BMJ* 2005;331:77.
58. Sachs RK, Brenner DJ. Solid tumor risks after high doses of ionizing radiation. *Proc Natl Acad Sci U S A* 2005;102:13040–13045.
59. Sachs RK, Shuryak I, Brenner D, et al. Second cancers after fractionated radiotherapy: Stochastic population dynamics effects. *J Theor Biol* 2007;249:518–531.
60. Land CE. Studies of cancer and radiation dose among atomic bomb survivors. The example of breast cancer. *JAMA* 1995;274:402–407.
61. Leuraud K, Richardson DB, Cardis E, et al. Risk of cancer associated with low-dose radiation exposure: Comparison of results between the INWORKS nuclear workers study and the A-bomb survivors study. *Radiat Environ Biophys* 2021;60:23–39.
62. Pierce DA, Preston DL. Radiation-related cancer risks at low doses among atomic bomb survivors. *Radiat Res* 2000;154:178–186.
63. Trott K-R, Kamprad F. Estimation of cancer risks from radiotherapy of benign diseases. *Strahlenther Onkol* 2006;182:431–436.
64. Zwicker F, Kirchner C, Huber PE, et al. Breast cancer occurrence after low dose radiotherapy of non-malignant disorders of the shoulder. *Sci Rep* 2019;9:5301.
65. Niewald M, Fleckenstein J, Naumann S, et al. Long-term results of radiotherapy for periarthritis of the shoulder: A retrospective evaluation. *Radiat Oncol* 2007;2:34.
66. Micke O, Ugrak E, Bartmann S, et al. Radiotherapy for calcaneodynia, achillodynia, painful gonarthrosis, bursitis trochanterica, and painful shoulder syndrome - Early and late results of a prospective clinical quality assessment. *Radiat Oncol* 2018;13:71.
67. Ott OJ, Hertel S, Gaipl US, et al. The Erlangen dose optimization trial for low-dose radiotherapy of benign painful elbow syndrome. Long-term results. *Strahlenther Onkol* 2014;190:293–297.
68. Deloch L, Rückert M, Fietkau R, et al. Low-dose radiotherapy has no harmful effects on key cells of healthy non-inflamed joints. *Int J Mol Sci* 2018;19:E3197.
69. Sokolow N. Roentgenstrahlen gegen Gelenkrheumatismus. *Fortschr Röntgenstrahlen* 1898;1:209–213.
70. Seegenschmiedt MH, Makoski H-B, Trott KR, et al. *Radiotherapy for Non-Malignant Disorders*. Berlin, Heidelberg: Springer; 2008.
71. Von Pannewitz G. Roentgen therapy for deforming arthritis. Ergebnisse der medizinischen Strahlenforschung. *Leipzig: Thieme* 1933;61–126.
72. von Pannewitz G. Strahlentherapie der arthrosis deformans. Technik und ergebnisse [Radiotherapy of arthrosis deformans. Method and results]. *Radiologe* 1970;10:51–54 [in German].
73. Leer JW, van Houtte P, Davelaar J. Indications and treatment schedules for irradiation of benign diseases: A survey. *Radiother Oncol* 1998;48:249–257.
74. Darby SC, Doll R, Gill SK, et al. Long term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. *Br J Cancer* 1987;55:179–190.

75. Richmond JJ. The importance of radiotherapy in the treatment of ankylosing spondylitis. *Proc R Soc Med* 1951;44:443–447.
76. Goldie I, Rosengren B, Moberg E, et al. Evaluation of radiation treatment of painful conditions of the locomotor system. A double blind study. *Acta Radiol Ther Phys Biol* 1970;9:311–322.
77. Valtonen EJ, Lilius HG, Malmio K. The value of roentgen irradiation in the treatment of painful degenerative and inflammatory musculoskeletal conditions. A double-blind study. *Scand J Rheumatol* 1975;4:247–249.
78. Seegenschmiedt MH, Micke O, Muecke R, et al. Radiotherapy for non-malignant disorders: State of the art and update of the evidence-based practice guidelines. *Br J Radiol* 2015;88:20150080.
79. Javadinia SA, Nazeminezhad N, Ghahramani-Asl R, et al. Low-dose radiation therapy for osteoarthritis and enthesopathies: A review of current data. *Int J Radiat Biol* 2021;97:1352–1367.
80. Weissmann T, Rückert M, Zhou J-G, et al. 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* 2021;12:777792.
81. Rühle A, Tkotsch E, Mravlag R, et al. Low-dose radiotherapy for painful osteoarthritis of the elderly: A multicenter analysis of 970 patients with 1185 treated sites. *Strahlenther Onkol* 2021;197:895–902.
82. Hautmann MG, Rechner P, Neumaier U, et al. Radiotherapy for osteoarthritis-an analysis of 295 joints treated with a linear accelerator. *Strahlenther Onkol* 2020;196:715–724.
83. Hautmann MG, Hipp M, Neumaier U, et al. Radiotherapy for osteoarthritis of the ankle and tarsal joints-analysis of 66 joints. *Strahlenther Onkol* 2020;196:569–575.
84. Hautmann M, et al. Re-irradiation for osteoarthritis-retrospective analysis of 217 joints. *Strahlenther Onkol* 2019;195(12):1060–1067.
85. Juniku N, Micke O, Seegenschmiedt MH, et al. Radiotherapy for painful benign skeletal disorders: Results of a retrospective clinical quality assessment. *Strahlenther Onkol* 2019;195:1068–1073.
86. Kaltenborn A, Bulling E, Nitsche M, et al. The field size matters: Low dose external beam radiotherapy for thumb carpometacarpal osteoarthritis: Importance of field size. *Strahlenther Onkol* 2016;192:582–588.
87. Keller S. Efficacy of low-dose radiotherapy in painful gonarthritis: experiences from a retrospective East German bicenter study. *Radiation Oncology* 2013;8:29.
88. Álvarez B, Montero A, Alonso R, et al. Low-dose radiation therapy for hand osteoarthritis: Shaking hands again? *Clin Transl Oncol* 2022;24:532–539.
89. Rogers S, et al. Prospective Evaluation of Changes in Pain Levels, Quality of Life and Functionality After Low Dose Radiotherapy for Epicondylitis, Plantar Fasciitis, and Finger Osteoarthritis. *Frontiers in Medicine* 2020;7:195.
90. Koc B, et al. 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. *European Journal of Orthopaedic Surgery & Traumatology* 2019;29:843–847.
91. Micke O, Seegenschmiedt MH, Adamietz IA, Kundt G, Fakhrian K, Schaefer U, Muecke R, German Cooperative Group on Radiotherapy for Nonmalignant Diseases (GCG-BD). Low-Dose Radiation Therapy for Benign Painful Skeletal Disorders: The Typical Treatment for the Elderly Patient? *Int J Radiat Oncol Biol Phys* 2017;98:958–963.
92. Niewald M, Müller LN, Hautmann MG, et al. ArthroRad trial: Multicentric prospective and randomized single-blinded trial on the effect of low-dose radiotherapy for painful osteoarthritis depending on the dose-results after 3 months' follow-up. *Strahlenther Onkol* 2022;198:370–377.
93. Mahler EAM, Minten MJ, Leseman-Hoogenboom MM, et al. Effectiveness of low-dose radiation therapy on symptoms in patients with knee osteoarthritis: A randomised, double-blinded, sham-controlled trial. *Ann Rheum Dis* 2019;78:83–90.
94. Minten MJM, Leseman-Hoogenboom MM, Kloppenburg M, et al. Lack of beneficial effects of low-dose radiation therapy on hand osteoarthritis symptoms and inflammation: A randomized, blinded, sham-controlled trial. *Osteoarthritis Cartilage* 2018;26:1283–1290.
95. Wunderlich R, Ernst A, Rödel F, et al. Low and moderate doses of ionizing radiation up to 2 Gy modulate transmigration and chemotaxis of activated macrophages, provoke an antiinflammatory cytokine milieu, but do not impact upon viability and phagocytic function. *Clin Exp Immunol* 2015;179:50–61.
96. Eckert D, Rapp F, Tsedeke AT, et al. ROS- and radiation source-dependent modulation of leukocyte adhesion to primary microvascular endothelial cells. *Cells* 2021;11:72.
97. van den Ende CHM, Minten MJM, Leseman-Hoogenboom MM, et al. Long-term efficacy of low-dose radiation therapy on symptoms in patients with knee and hand osteoarthritis: Follow-up results of two parallel randomised, sham-controlled trials. *Lancet Rheumatol* 2020;2:e42–e49.
98. Ott OJ, Micke O, Mücke R, et al. Low-dose radiotherapy: Mayday, mayday. We've been hit! *Strahlenther Onkol* 2019;195:285–288.
99. Rödel F, Frey B, Manda K, et al. Immunomodulatory properties and molecular effects in inflammatory diseases of low-dose x-irradiation. *Front Oncol* 2012;2:120.
100. Deloch L, Derer A, Hueber AJ, et al. Low-dose radiotherapy ameliorates advanced arthritis in hTNF-α tg mice by particularly positively impacting on bone metabolism. *Front Immunol* 2018;9:1834.
101. University of Erlangen-Nürnberg Medical School. Immunophenotyping from blood of patients suffering from chronic degenerating joint diseases and receiving local low dose radiation therapy (LDRT). Available at: https://clinicaltrials.gov/ct2/show/NCT02653079. Accessed January 8, 2022.
102. Alvarez B, Montero A, Hernando O, et al. Radiotherapy CT-based contouring atlas for non-malignant skeletal and soft tissue disorders: A practical proposal from Spanish experience. *Br J Radiol* 2021;94 20200809.
103. Micke O, Seegenschmiedt MH. German Cooperative Group on Radiotherapy for Benign Diseases. Radiotherapy in painful heel spurs (plantar fasciitis)—results of a national patterns of care study. *Int J Radiat Oncol Biol Phys* 2004;58:828–843.
104. Niewald M, Seegenschmiedt MH, Micke O, et al. Randomized, multicenter trial on the effect of radiation therapy on plantar fasciitis (painful heel spur) comparing a standard dose with a very low dose: Mature results after 12 months' follow-up. *Int J Radiat Oncol Biol Phys* 2012;84:e455–e462.
105. Canyilmaz E, Canyilmaz F, Aynaci O, et al. Prospective randomized comparison of the effectiveness of radiation therapy and local steroid injection for the treatment of plantar fasciitis. *Int J Radiat Oncol Biol Phys* 2015;92:659–666.
106. Cuculich PS, Schill MR, Kashani R, et al. Noninvasive cardiac radiation for ablation of ventricular tachycardia. *N Engl J Med* 2017;377:2325–2336.
107. Robinson CG, Samson PP, Moore KMS, et al. Phase I/II trial of electrophysiology-guided noninvasive cardiac radioablation for ventricular tachycardia. *Circulation* 2019;139:313–321.
108. Niranjan A, Raju SS, Kooshkabadi A, et al. Stereotactic radiosurgery for essential tremor: Retrospective analysis of a 19-year experience. *Mov Disord* 2017;32:769–777.
109. Khattab MH, Cmelak AJ, Sherry AD, et al. Noninvasive thalamotomy for refractory tremor by frameless radiosurgery. *Int J Radiat Oncol Biol Phys* 2022;112:121–130.
110. Chung M, Rhee HY, Chung WK. Clinical approach of low-dose whole-brain ionizing radiation treatment in Alzheimer's disease dementia patients. *J Alzheimers Dis* 2021;80:941–947.
111. Cuttler JM, Abdellah E, Goldberg Y, et al. Low doses of ionizing radiation as a treatment for Alzheimer's disease: A pilot study. *J Alzheimers Dis* 2021;80:1119–1128.
112. Martínez-Álvarez R. Radiosurgery for behavioral disorders. *Prog Neurol Surg* 2019;34:289–297.

113. Franzini A, Rossini Z, Moosa S, et al. Medial thalamotomy using stereotactic radiosurgery for intractable pain: A systematic review. *Neurosurg Rev* 2022;45:71–80.
114. Tuleasca C, Régis J, Sahgal A, et al. Stereotactic radiosurgery for trigeminal neuralgia: A systematic review. *J Neurosurg* 2018;130:733–757.
115. Ganesan G, Ponniah S, Sundaram V, et al. Whole lung irradiation as a novel treatment for COVID-19: Final results of the prospective randomized trial (WINCOVID trial). *Radiother Oncol* 2021;167:133–142.

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Original article

Orthovoltage x-ray therapy significantly reduces disability risk in knee osteoarthritis patients: A decade-long cohort study

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Abstract:
Introduction — Osteoarthritis (OA) of the knee and hip joints affects 13% of the adult population in the Russian Federation. While medications can provide some relief from the pain associated with OA, they are often not enough. An alternative treatment option is orthovoltage radiation therapy (OVRT), which not only relieves pain, but can also help prevent disability. However, there is little evidence for the long-term effectiveness of OVRT.
Objective — We compared the incidence of disability among patients with OA who received standard treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) in combination with the symptomatic slow-acting drugs for osteoarthritis (SYSADOA), or in combination with OVRT for knee OA in the setting of an open randomized controlled trial with long-term follow-up.
Material and Methods — The sampling frame included patients with confirmed OA of the knee *sensu* Altman (1991), with radiographic grades of OA from 0 to 2 *sensu* Kellgren-Lawrence. A total of 292 patients were randomly distributed among two groups of equal sizes. The control group received combination therapy with NSAIDs and SYSADOA. In the experimental group, OVRT was additionally performed at a total dose of 4.5 Gy. Relationships between treatment regimen and time to disability were studied using actuarial analysis, Kaplan-Meier plots. Crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI), as well as attributable fraction (AF) and population attributable fraction (PAF) were calculated.
Results — The cumulative time at risk for disability was 2,304.9 person-years. In total, 9.5% of patients in the experimental group became disabled during the observation period vs. 17.8% in the control group. In the experimental group, the level of disability was lower (HR=0.49, 95% CI: 0.26-0.95). Differences became more pronounced after adjusting for sex, age, radiographic grade of OA, pain intensity, and duration of OA before treatment (HR=0.24, 95% CI: 0.11-0.48). AF and PAF were 49.9% and 25.8%, respectively.
Conclusion — It has been shown that the introduction of OVRT in the treatment regimen can reduce the disability of patients with knee OA by almost 50%. One in four disability cases could be prevented if OVRT were used universally in the treatment of knee OA. Our results indicate that combining OVRT with standard care is a more effective approach to preventing disability in patients with knee OA than standard treatment alone.

Keywords: osteoarthritis, knee, disability, survival analysis, orthovoltage radiation therapy.

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Introduction

Osteoarthritis (OA) of the knee joint is a common musculoskeletal disease. According to a meta-analysis of 88 epidemiological studies, approximately 654.1 million people 40 years of age worldwide were diagnosed with gonarthrosis [1]. In Russia, the prevalence of OA of the knee and hip joints was estimated at 13% in people 18 years of age and older [2].

OA is a painful condition that is typically treated with nonsteroidal anti-inflammatory drugs (NSAIDs) [3, 4]. The uncontrolled use of NSAIDs can lead to serious gastrointestinal complications [5]. In accordance with the clinical recommendations by the Association of Rheumatologists of Russia, symptomatic slow-acting drugs for osteoarthritis (SYSADOA), such as chondroitin sulfate, glucosamine, and other tissue repair stimulants and correctors of bone and cartilage metabolism, can also be used to treat knee OA [4]. However, meta-analyses of studies conducted without the support of pharmaceutical companies did not confirm the benefits of using both chondroitin and glucosamine sulfates, and therefore their use was not recommended by most of the international professional rheumatology communities. [3, 4, 7].

OA often progresses steadily, leading to high rates of disability and referrals for surgical treatment. Up to 15% of patients with OA become disabled. Furthermore, OA patients account for about a

third of all patients with permanent disability due to joint diseases [8].

An alternative noninvasive treatment for OA is orthovoltage radiation therapy (OVRT). According to our randomized controlled trial, OVRT had a significant advantage over standard treatment, such as NSAIDs and SYSADOA, both in terms of immediate results [9] and long-term effects over a period of three years [10]. In Germany and Spain, radiation therapy is already included in the standards of pain management in OA and is recommended for the treatment of knee OA [11, 12]. However, it is not yet included in the therapeutic standards for the treatment of OA in Russia and many other countries. Its long-term analgesic effect has the potential to prevent disability and delay the need for surgery, but the lack of evidence regarding the long-term efficacy of OVRT is the main reason why it is not universally recommended for the treatment of OA [3, 4], which requires further research.

In publications examining the efficacy of OVRT, its safety was pointed out [13, 14], but its effect on disability was not reported.

We conducted a 10-year follow-up of patients with knee OA participating in a previously published randomized controlled trial (RCT) [3, 4] to assess whether the use of OVRT in addition to standard therapy reduces the risk of disability, compared with conventional treatment.

Material and Methods

Group recruitment procedure

This was a randomized controlled study with a long-term follow-up. Our study included all patients with confirmed knee OA sensu 1991 Altman criteria [15], with or without laboratory and radiographic manifestations, with radiographic grades of OA 0-2 sensu Kellgren-Lawrence [16], and an initial pain level of 30 mm or more based on the visual analog scale (VAS). Patients were recruited from outpatient clinics in Arkhangelsk, Northwestern Russia, between October 2012 and October 2014. Exclusion criteria were as follows: post-traumatic osteoarthritis, systemic connective tissue disease, a history of knee arthroplasty, and any condition precluding participation in the study. The selected patients were randomly assigned to two groups by blind randomization. Patient details and randomization procedure have been described previously [9, 10].

A total of 292 patients were included in the analysis, 146 in each group. The patients of the groups were comparable in terms of age and sex composition (*Table* 1).

Participants in the control group received conventional therapy with a combination of SYSADOA glucosamine (500 mg) and chondroitin (400 mg) sulfates according to the following scheme: 1 capsule 3 times a day for three weeks, then 1 capsule 2 times a day for up to twelve weeks. After an eight-week break, a second course was prescribed for twelve weeks according to the same scheme.

In the experimental group, in addition to standard conservative drug therapy, patients underwent orthovoltage X-ray therapy. The single focal dose was 0.45 Gy. A total of 10 sessions 48 hours apart resulted in a cumulative dose of 4.5 Gy. Both groups of patients were allowed to take selective NSAIDs.

Measuring the effect

The clinical endpoint of the follow-up was the established disability due to the knee joint OA. Data on the onset of disability were obtained from the Unified State Information System in the Field of Healthcare in Arkhangelsk. Patients without disabilities were censored by the date of the last check-up or by the date of their last registered visit to the doctor, or else by the specified date of 31 December 2021.

Statistical data processing

The incidence of disability in both groups was calculated per 100 person-years. Attribute fraction (AF) and population attributable fraction (PAF) were calculated to estimate the proportion of disability that could be prevented if all patients received OVRT in addition to standard treatment in the study and in the general population. Disability-free survival in the experimental and control groups was assessed using actuarial analysis. Differences between groups were assessed using the Gehan-Wilcoxon procedure. Cumulative disability risks were plotted using Kaplan-Meier plots. Although the groups were similar in age, radiographic grade of OA, body mass index, pain intensity, and duration of OA prior to study entry, we additionally controlled for these characteristics in proportional hazards analysis. Crude and adjusted hazard ratios (HR) were calculated. Survival analysis results were presented with 95% confidence intervals due to their superiority over traditional p-values [17].

For all calculations, the Stata software package version 17 (Stata Corp., TX, USA) was employed [18].

Results

The cumulative time at risk for disability was 2,304.9 person-years. In total, 9.5% (n=14) of patients became disabled in the experimental group vs. 17.8% (n=26) in the control group. The total numbers of disabled OA patients at baseline by radiographic grade are presented in *Table 2*.

Table 1. Demographic and clinical characteristics of the patients at the beginning of the trial

Characteristics	*Experimental group*	*Control group*	*P*
Numeric variables, mean (95% CI)			
Age, years	37.3 (35.1–39.4)	39.8 (37.7–41.9)	0.103
Body mass index, kg/m^2	27.0 (25.9–28.2)	26.6 (25.8–27.5)	0.667
Duration of OA, months	9.7 (8.8–10.6)	9.2 (8.1–10.4)	0.068
Pain intensity as measured by VAS, mm	57.1 (54.7–59.9)	55.7 (52.7–58.8)	0.574
Categorical variables, n (%)			
Proportion of females	64 (43.8)	77 (52.7)	0.274
Radiographic grade 0 of OA, n (%)	15 (10.3)	24 (16.4)	0.346
Radiographic grade 1 of OA, n (%)	89 (60.9)	86 (58.9)	
Radiographic grade 2 of OA, n (%)	42 (28.8)	36 (24.7)	

CI, confidence interval; OA, osteoarthritis; VAS, visual analog scale.

Table 2. Absolute numbers and proportion of patients who developed disability over the follow-up period, by radiographic grades of knee osteoarthritis (OA)

Radiographic grade of OA	*Experimental group*	*Control group*
Grade 0, n (%)	0/15 (0.0%)	1/24 (4.2%)
Grade 1, n (%)	1/89 (1.1%)	5/86 (5.8%)
Grade 2, n (%)	13/42 (30.9%)	20/36 (55.6%)

The incidence of disability due to knee OA was 1.17 per 100 person-years in the experimental group vs. 2.34 per 100 person-years in the control group. The incidence rate ratio was 0.50 (95% CI: 0.25-0.99), p=0.018. The AF and PAF were 50% and 24%, respectively, suggesting that only one in four disability cases would occur if all patients received OVRT in addition to standard care.

The actuarial analysis yielded the following results: 96.6% (95% CI: 92.0%-98.6%) and 90.2% (95% CI: 84.0%-94.1%) of patients in the treatment group had no disability through 5 and 10 years of follow-up, respectively, while the corresponding proportions in the control group were 91.1% (95% CI: 85.2%-94.7%) and 79.6% (95% CI: 70.9%-86.0%), p=0.030. The cumulative risks of developing disability in both groups are shown in *Figure* 1.

Crude HR estimated via proportional hazards analysis was 0.49, 95% CI: 0.26-0.95, p=0.033. Adjusting for differences between groups in age, sex, radiographic grade of OA, pain intensity, and duration of OA prior to treatment significantly increased the effect of OVRT in addition to standard treatment, compared with standard treatment alone (HR=0.24, 95% CI: 0.11-0.48). This implies that OVRT with standard care is a more effective treatment option in preventing disability than standard treatment alone.

Discussion

This is the first article analyzing long-term follow-up of patients with grade 0-2 gonarthrosis in our RCT until the establishment of a disability. Our findings suggest that OVRT in combination with conventional therapy significantly delays disability and has potential for clinical practice. The incidence of disability in our study is comparable with worldwide data [19].

Radiation therapy is not a widely accepted approach to the treatment of OA due to conflicting data on its effectiveness. A double-blind, randomized study involving 55 patients with knee OA conducted in the Netherlands showed that after three months of low-dose radiation, there was no reduction in pain in the radiation therapy group (HR 1.09; 95% CI 0.37-3.19). Furthermore, the authors found no changes in the synovial membrane according to ultrasound and MRI examination in both groups [20].

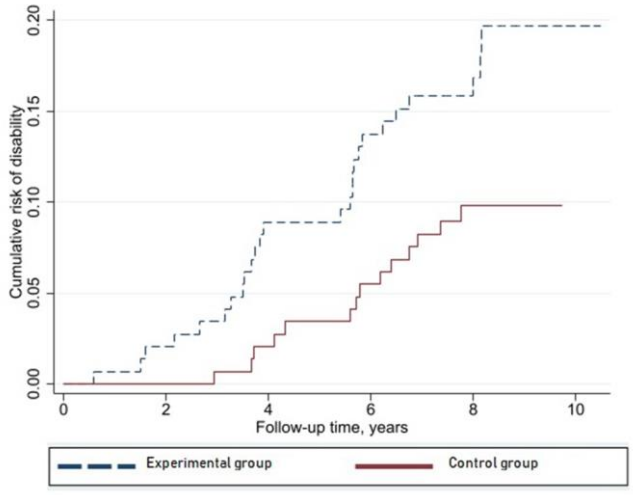

Figure 1. Cumulative risk of disability in the experimental group (solid line) and in the control group (dashed line).

A systematic review of 26 studies on the analgesic efficacy and safety of low-dose radiation therapy revealed a lack of high-quality studies, as well as a high heterogeneity in the used doses, schemes, and study designs [21]. Besides, published data on long-term side effects were nonexistent. Hence, the effectiveness of low-dose radiation therapy as a treatment for OA in clinical practice still needs confirmation through well-planned RCTs [3, 11].

On the other hand, in several countries, long-term use of radiation therapy for knee OA has already entered practice, as evidenced by the data of non-randomized trials included in national recommendations [11]. In our study, we observed the most pronounced effect from the use of radiation therapy for a longer period after the end of treatment: it persisted for at least three years [9, 10]. We believe that the long-term analgesic effect of OVRT significantly contributed to the reduction of persistent pain syndrome and objective pathological changes in the affected joints, which are drivers of disability.

The frequency of detecting disability in our study was significantly influenced by the initial radiographic grade of OA. When determining the disability grade, we considered the limitation of vital activities in patients with persistent disorders of static and dynamic functions (grades 3 and 4), because these disorders progressed faster with more severe radiographic grade of OA at baseline [22].

Several studies demonstrated that weight loss led to a decrease in the risk of developing OA of the knee joint and was associated with a decrease in pain and improved function of the knee joint [23, 24]. In our research, patients of the experimental group did not differ from those in the control group in terms of body mass index; however, adjustment for BMI and other characteristics substantially facilitated the detection of associations.

Patient outcomes were tracked over a long period, which was a major strength of our study. Most of the other studies had a limited follow-up period of one to three years [7, 8] without examining the long-term effects of treatment.

The main limitation of this study was its relatively small sample size (292 patients). However, this was enough to show the superiority of the experimental treatment over the control group. Moreover, it was sufficient to include five potential confounding factors in a multivariate proportional hazards analysis. Although our results provided sufficient evidence in favor of experimental treatment, it is necessary to replicate these findings in other clinical settings. In addition, longer follow-up is required.

Another limitation was the lack of mandatory registration of patients with OA, which can be considered as a dropout risk. However, as a risk reduction strategy, we had access to patients' medical records, and they were regularly called in for appointments to assess long-term outcomes of treatment. The use of medical information systems for dynamic monitoring of patients or the development of a register of patients with OA using a model of population-based cancer registers [25] can be useful for studying the long-term effects of treatment.

Conclusion

We established that the introduction of OVRT into treatment regimens reduced the disability of patients with OA of the knee joint by almost 50%. One in four disability cases could be

prevented if OVRT were used universally in the treatment of knee OA. Our findings suggested that combining OVRT with standard care is a more effective approach to preventing disability in patients with knee OA than conventional treatment alone.

Ethical approval

The study was approved by the local Ethics Committee of the Northern State Medical University (Protocol No. 10 of 21 December 2011). All procedures complied with the 1964 Declaration of Helsinki and its later amendments.

Conflict of interest

The authors declare no conflicts of interest.

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References

1. Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. *EClinicalMedicine* 2020; 29-30: 100587. https://doi.org/10.1016/j.eclinm.2020.100587.
2. Alekseeva LI, Taskina EA, Kashevarova NG. Osteoarthritis: epidemiology, classification, risk factors, and progression, clinical presentation, diagnosis, and treatment. *Modern Rheumatology Journal* 2019; 13(2): 9-21. Russian. https://doi.org/10.14412/1996-7012-2019-2-9-21.
3. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res* 2020; 72(2): 149-162. https://doi.org/10.1002/acr.24131.
4. Gonarthrosis. Clinical recommendations of the Ministry of Healthcare of the Russian Federation. 2021. Russian. https://cr.minzdrav.gov.ru/schema/667_1.
5. Tai FWD, McAlindon ME. Non-steroidal anti-inflammatory drugs and the gastrointestinal tract. *Clin Med (Lond)* 2021; 21(2): 131-134. https://doi.org/10.7861/clinmed.2021-0039.
6. Pyrikova NV, Antropova ON, Osipova IV. Adverse reactions of the cardiovascular system when taking nonsteroidal anti-inflammatory drugs and ways to reduce them. *Rational Pharmacotherapy in Cardiology* 2019; 15(5): 750-758. Russian. https://doi.org/10.20996/1819-6446-2019-15-5-750-758.
7. Zhu X, Sang L, Wu D, Rong J, Jiang L. Effectiveness and safety of glucosamine and chondroitin for the treatment of osteoarthritis: a meta-analysis of randomized controlled trials. *J Orthop Surg Res* 2018; 13(1): 170. https://doi.org/10.1186/s13018-018-0871-5.
8. Primorac D, Molnar V, Matišić V, Hudetz D, Jeleč Ž, Rod E, et al. Comprehensive review of knee osteoarthritis pharmacological treatment and the latest professional societies' guidelines. *Pharmaceuticals (Basel)* 2021; 14(3): 205. https://doi.org/10.3390/ph14030205.
9. Makarova MV, Titova LV, Valkov MYu. Orthvoltage X-ray therapy for the treatment of 0-2 gonarthritis stages: long-term results of a randomized trial. The dynamics of a pain syndrome. *Diagnostic radiology and radiotherapy* 2019; (3): 86-93. Russian. https://doi.org/10.22328/2079-5343-2019-10-3-86-93.
10. Makarova MV, Chernykh IA, Titova LV, Valkov MYu. The dynamics of morphological changes by MRI at orthovoltage x-ray therapy in patients with gonarthritis stage 0-2: long-term results of a randomized trial. *Diagnostic radiology and radiotherapy* 2019; (4): 71-79. Russian. https://doi.org/10.22328/2079-5343-2019-10-4-71-79.
11. Seegenschmiedt MH, Micke O, Niewald M, Mücke R, Eich HT, Kriz J, Heyd R. DEGRO guidelines for the radiotherapy of non-malignant disorders: Part III: hyperproliferative disorders. *Strahlenther Onkol* 2015; 191(7): 541-548. https://doi.org/10.1007/s00066-015-0818-2.
12. Torres Royo L, Antelo Redondo G, Árquez Pianetta M, Arenas Prat M. Low-dose radiation therapy for benign pathologies. *Rep Pract Oncol Radiother* 2020; 25(2): 250-254. https://doi.org/10.1016/j.rpor.2020.02.004.
13. Leuraud K, Richardson DB, Cardis El, Daniels RD, Gillies M, Haylock R, et al. Risk of cancer associated with low-dose radiation exposure: Comparison of results between the INWORKS nuclear workers study and the A-bomb survivors study. *Radiat Environ Biophys* 2021; 60(1): 23-39. https://doi.org/10.1007/s00411-020-00890-7.
14. Deloch L, Ruckert M, Fietkau R, Frey B, Gaipl US. Low-dose radiotherapy has no € harmful effects on key cells of healthy non-inflamed joints. *Int J Mol Sci* 2018; 19(10): 3197. https://doi.org/10.3390/ijms19103197.
15. Altman R, Alarcn G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the knee. *Arthritis Rheum* 1990; 33(11): 1601-1610. https://doi.org/10.1002/art.1780340502.
16. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. *Ann Rheum Dis* 1957; 16(4): 494-502. https://doi.org/10.1136/ard.16.4.494.
17. Grjibovski AM, Gvozdeckii AN. Interpretation of and alternatives to p-values in biomedical sciences. *Human Ecology* 2022; 29(3): 209-218. Russian. https://doi.org/10.17816/humeco97249.
18. Unguryanu TN, Grjibovski AM. Introduction to STATA – software for statistical data analysis. *Human Ecology* 2014; 21(1): 60-63. Russian. https://doi.org/10.17816/humeco17275.
19. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study. Lancet 2018; 392(10159): 1789-1858. https://doi.org/10.1016/S0140-6736(18)32279-7.
20. Mahler EAM, Minten MJ, Leseman-Hoogenboom MM, Poortmans PMP, Leer JWH, Boks SS, et al. Effectiveness of low-dose radiation therapy on symptoms in patients with knee osteoarthritis: A randomised, double-blinded, sham-controlled trial. *Ann Rheum Dis* 2019; 78(1): 83-90. http://doi.org/10.1136/annrheumdis-2018-214104.
21. Minten MJ, Mahler E, den Broeder AA, Leer JW, van den Ende CH. The efficacy and safety of low-dose radiotherapy on pain and functioning in patients with osteoarthritis: A systematic review. *Rheumatol Int* 2016; 36(1): 133-142. http://doi.org/10.1007/s00296-015-3337-7.
22. Drapkina OM, Skripnikova IA, Shepel RN, Kaburova AN. Osteoarthritis in a therapist's practice: the diagnostic and treatment algorithm. *Profilakticheskaya Meditsina* 2018; 21(6): 12-22. Russian. http://doi.org/10.17116/profmed20182106112.
23. Salis Z, Sainsbury I, Keen H, Gallego B, Jin X. Weight loss is associated with reduced risk of knee and hip replacement: A survival analysis using Osteoarthritis Initiative data. *Int J Obes (Lond)* 2022; 46(4): 874-884. https://doi.org/10.1038/s41366-021-01046-3.
24. Hall M, Castelein B, Wittoek R, Calders P, Van Ginckel A. Diet-induced weight loss alone or combined with exercise in overweight or obese people with knee osteoarthritis: A systematic review and meta-analysis. *Semin Arthritis Rheum* 2019; (48): 765-777. http://doi.org/10.1016/j.semarthrit.2018.06.005.
25. Valkov MYu, Karpunov AA., Coleman MP, Allemani C, Pankratieva AYu, Potekhina EF, et al. The population-based cancer registry as a resource for research and practical healthcare. *Human Ecology* 2017; 24(5): 54-62. Russian. https://doi.org/10.33396/1728-0869-2017-5-54-62.

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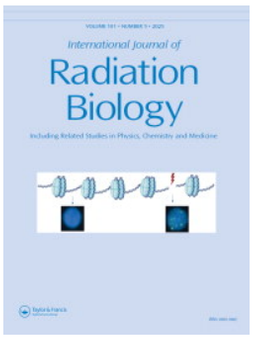

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Effects of low dose rate radiotherapy on pain relief, performance score, and quality of life in patients with knee osteoarthritis; a double-blind sham-controlled randomized clinical trial

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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

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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.

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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

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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 ($p < 0.001$).

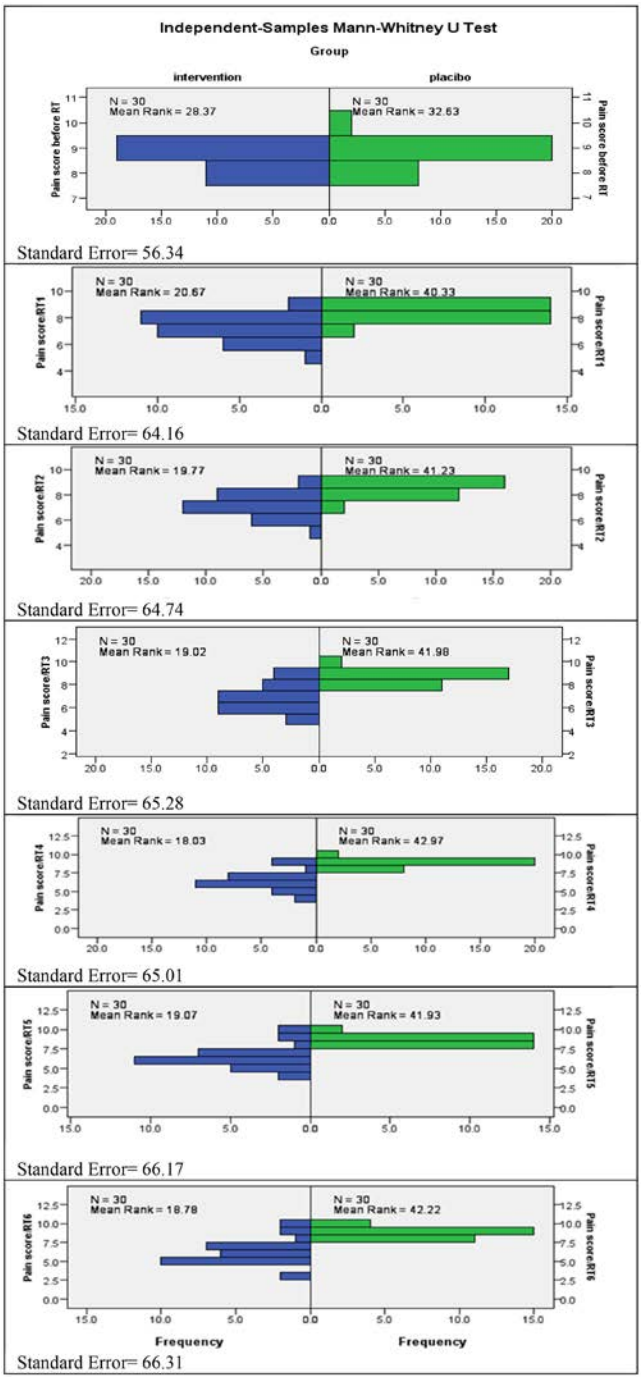

Figure 1. Changes of mean rank VAS pain score in two treatment and placebo groups before intervention (p = .25) during 6 months post intervention (p < .001).

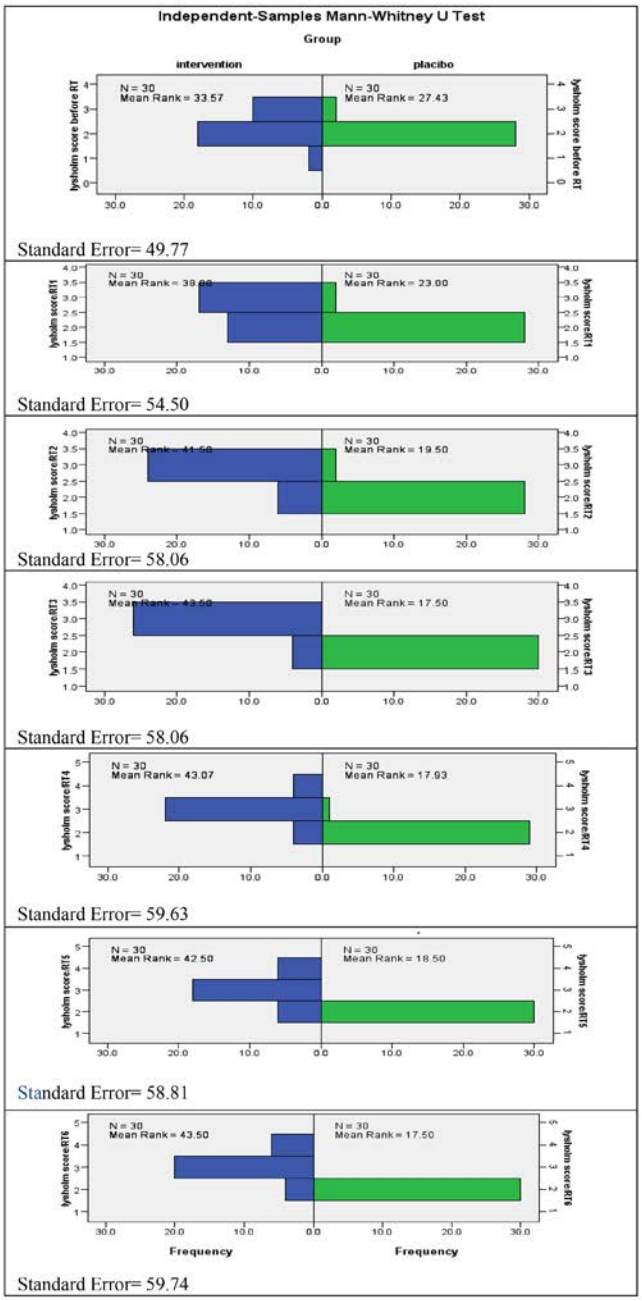

Figure 2. Changes of mean rank lysholm score in the treatment and placebo groups before intervention (p = .06) and during 6 months after intervention (p < .001).

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.

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Disclosure statement

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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.

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Clinical Investigation

Prospective Randomized Comparison of the Effectiveness of Radiation Therapy and Local Steroid Injection for the Treatment of Plantar Fasciitis

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Summary

Based on retrospective and prospective data, radiation therapy is effective for the treatment of plantar fasciitis. Local injections of corticosteroids are used to control pain when other conservative treatments have failed. We performed a randomized, prospective trial to compare the effects of radiation therapy with those of local corticosteroid injections. We show the superiority of radiation therapy concerning pain relief and recommend radiation therapy for treating plantar fasciitis.

Purpose: The purpose of this study was to conduct a randomized trial of radiation therapy for plantar fasciitis and to compare radiation therapy with local steroid injections.

Methods and Materials: Between March 2013 and April 2014, 128 patients with plantar fasciitis were randomized to receive radiation therapy (total dose of 6.0 Gy applied in 6 fractions of 1.0 Gy three times a week) or local corticosteroid injections a 1 ml injection of 40 mg methylprednisolone and 0.5 ml 1% lidocaine under the guidance of palpation. The results were measured using a visual analog scale, a modified von Pannewitz scale, and a 5-level function score. The fundamental phase of the study was 3 months, with a follow-up period of up to 6 months.

Results: The median follow-up period for all patients was 12.5 months (range, 6.5-18.6 months). For the radiation therapy patients, the median follow-up period was 13 months (range, 6.5-18.5 months), whereas in the palpation-guided (PG) steroid injection arm, it was 12.1 months (range, 6.5-18.6 months). After 3 months, results in the radiation therapy arm were significantly superior to those in the PG steroid injection arm (visual analog scale, $P<.001$; modified von Pannewitz scale, $P<.001$; 5-level function score, $P<.001$). Requirements for a second treatment did not significantly differ between the 2 groups, but the time interval for the second treatment was significantly shorter in the PG steroid injection group ($P=.045$).

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Conclusion: This study confirms the superior analgesic effect of radiation therapy compared to mean PG steroid injection on plantar fasciitis for at least 6 months after treatment.

Introduction

Plantar fasciitis is included in the heterogeneous group of degenerative benign diseases involved with osseous and tendinous structures of spurs. Approximately 15% of patients visiting a podiatrist's office complain of heel pain. In nearly 73% of cases, spur formation is radiologically detectable (1, 2). An abnormal pronation in the back foot due to increased body weight, varus deformity, or inappropriate shoes chronically stretch the plantar aponeurosis, causing microlesions that consequently result in chronic inflammation and formation of a bony heel spur (3). Bony heel spurs are more common in women than in men, most commonly between 40 and 49 years of age (4). Diagnosis is based on clinical examination, radiography, ultrasonography, scintigraphy, and magnetic resonance imaging (5).

Generally, plantar fasciitis can be effectively treated with a combination of conservative modalities such as nonsteroidal anti-inflammatory medications, steroid injections, phonophoresis, night splints, orthotic devices, shoe modifications, extracorporeal shock-wave therapy, and/or stretching exercises (6-9). These methods are used alone or in various combinations, and no single method clearly stands out as superior. However, 10% of patients do not respond to these treatments or combination of treatments and require surgery to relieve their symptoms (10).

Because of its known anti-inflammatory effects, radiation therapy has been used for at least 60 years. However, its exact mechanism remains unknown. The probable mechanisms of action of radiation therapy in nonmalignant disease are the anti-inflammatory effects of low-dosage ionizing radiation: modulation of E-selectin adhesion on endothelial cells, decreased leukocyte adhesion, apoptosis in endothelial cells and leukocytes are enhanced, and reduced oxidative burst in activated macrophages (11-13). The antiproliferative and immunomodulatory effects which play a role in irradiation with fraction doses higher than 2 Gy are likely less important (14). The reported results of plantar fasciitis radiation therapy vary from 50% to 70% of patients reporting complete pain relief (15, 16). Fractional doses of 0.5 to 1.0 Gy and total doses of 3 to 6 Gy are commonly applied for plantar fasciitis (17, 18).

Conservative treatment for plantar fasciitis frequently involves corticosteroid injection into the heel. Local corticosteroid injection is used to control pain when other conservative treatments have failed. Local corticosteroid injections have been used with ultrasonograpy-guided (UG), palpation-guided (PG), or scintigraphy-guided techniques. PG injection is an effective and common treatment. Some studies favor the UG injection method, whereas other studies favor the PG or scintigraphy-guided techniques (19, 20). Kane et al (20) reported no statistical differences in outcome between patients who underwent UG and those who had PG injection. Likewise Yucel et al (5) reported no statistical differences in outcome between UG- and PG-injected patients.

To our knowledge, no previous single study has compared radiation therapy with PG steroid injections for plantar fasciitis. The aim of the present study was to compare radiation therapy with PG steroid injections for the conservative treatment of plantar fasciitis.

Methods and Materials

Patients

Between March 2013 and April 2014, 128 patients were enrolled in our study and randomized to 2 groups. Matching patients with the criteria defined in the study protocol were randomized to 2 groups by the same orthopedist (F.C.) according to their order of admission. Patient assessment by scoring their pain was performed after randomization by the same radiation oncologist (E.C.). Of these, 58 patients received a total dose of 6.0 Gy given in 3-weekly fractions of 1 Gy (radiation therapy arm); 2 patients received a total dose of 6.0 Gy given in 2-weekly fractions of 1 Gy; and 64 patients received an injection of 40 mg (1 ml) of methylprednisolone and 0.5 ml of 1% lidocaine in the painful heel spur, using palpation (PG steroid injection arm). The trial design and Consolidated Standards of Reporting Trials (CONSORT) flow chart is summarized in Figure 1 (21).

In this prospective, randomized trial, patients were included if they met the following criteria: (*1*) symptoms and clinical diagnosis of a painful heel spur; (*2*) duration of symptoms longer than 6 months; (*3*) radiologically proven heel spur; (*4*) Karnofsky performance status $\geq$70; and (*5*) age $\geq$40 years. Patients who had previous radiation therapy, trauma to the foot, severe psychiatric disorders, rheumatic and/or vascular diseases, or were pregnant or breastfeeding were excluded from the study. The use of analgesics before enrollment was not restricted. Patients were referred to our institution by orthopedists, and all had recurrent symptoms after previous conservative treatments.

All procedures were in accordance with the ethical standards of the Responsible Committee on Human Experimentation (institutional and national) and with the Helsinki Declaration of 1975 (revised in 2008). The trial was approved by the local ethics committee. All patients were informed about the side effects of both treatment regimens as well as the possible carcinogenic risk of radi-

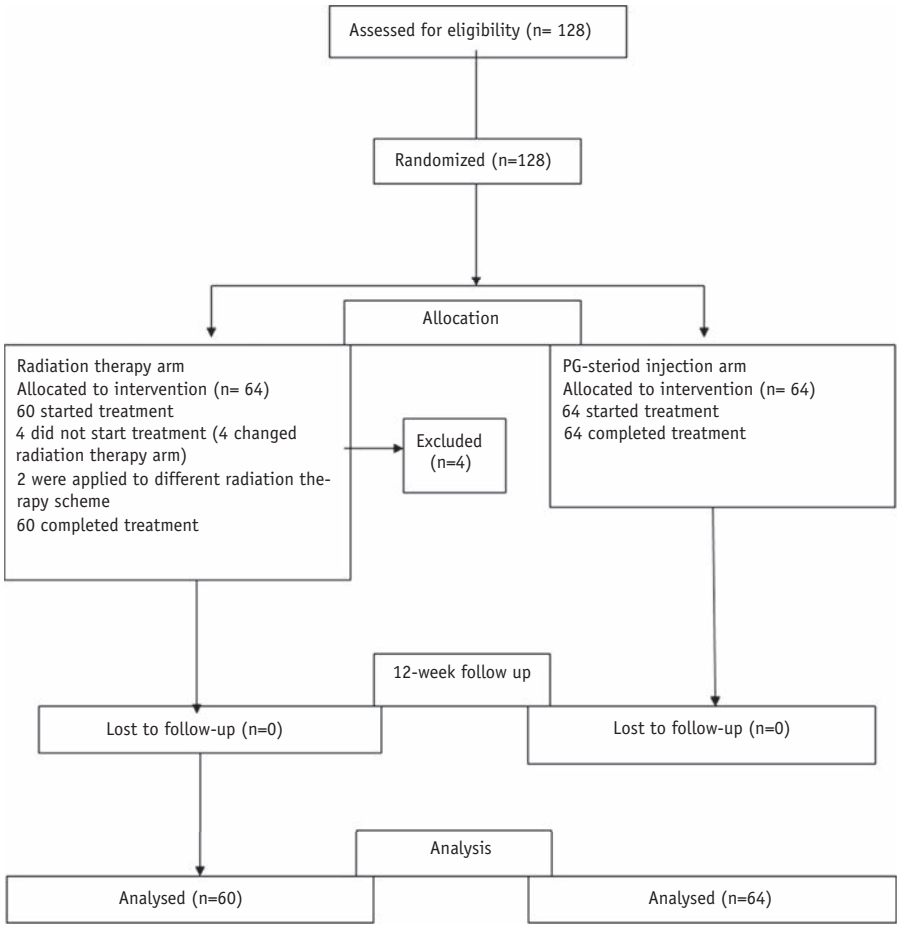

Fig. 1. Trial design and CONSORT flow chart. CONSORT = Consolidated Standards of Reporting Trials.

ation therapy. All patients provided written informed consent before entering the trial.

Treatment

Radiation therapy was performed using a 6-MV photon beam of a linear accelerator, applying lateral parallel opposing portals. All patients receiving radiation therapy underwent planning using a simulator, and each patient was put in a supine position with the affected leg immobilized. The same target volume definition was used for all patients in the radiation therapy arm. We used standardized treatment portals localized at the simulator. Standard treatment volume included the whole calcaneus, plantar fascia insertion, and the Achilles tendon insertion with appropriate fall off. The target volume consisted of the calcaneus and the region of the plantar aponeurosis (Fig. 2). The size varied from 7.0 × 8.0 cm to 9.0 × 10.0 cm. Radiation therapy fractions generally were administered 2 to 3 times per week, adding up to a whole-treatment time of 2 to 3 weeks. We chose to complete the scheme applied 3 times per week for 2 weeks in this study. This scheme was preferred because it is more suited to our clinic schedule. Radiation therapy sessions were performed on Monday, Wednesday, and Friday (Fig. 2).

All PG steroid injection applications were conducted by a single orthopedist to avoid the effects of person-related differences on the results. PG steroid injections were applied to 79 heels in 68 plantar heel spur patients. Patients were put into a prone position with the ankle in a neutral position and knee flexed 90°. A 22-gauge 1.5-inch needle was connected to a 3-cm^3 syringe filled with 40 mg of methylprednisolone (1 ml) mixed with 0.5 ml of 1% lidocaine. The painful area and medial tubercle of calcaneus were determined by palpation. The skin was sterilized with alcohol and iodine. The needle was inserted 2 to 3 cm anteromedially to the tenderest point in the inferior heel, near the calcaneal tuberosity, and moved toward the tenderest area.

All patients were followed in our clinic. Follow-up examinations were performed every 6 weeks by examining the patient in the clinic, mailing questionnaires to the patients, or interviewing the patient on the telephone.

Endpoint and statistics

The endpoint of this clinical trial was pain reduction. Pain levels were measured using a standardized questionnaire

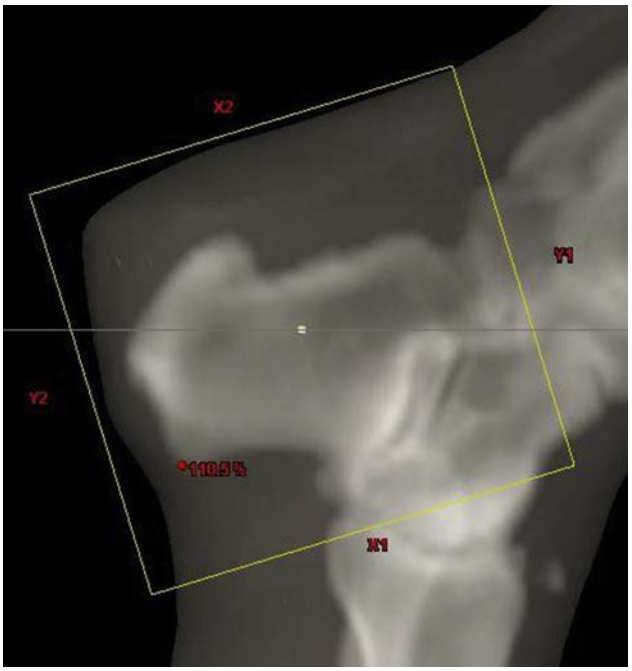

Fig. 2. Simulator radiograph of radiation therapy for plantar fasciitis.

immediately before and after both treatment schemes, as well as during a follow-up visit 6 weeks after completion of treatment. All patients were followed for 6 months. In the case of an unfavorable response to radiation therapy or PG-steroid injection after 12 weeks, the patient was offered a second treatment series applying radiation therapy, steroid injection, or other treatment (eg, extracorporeal shock-wave therapy or ultrasound applications). The patient chose the treatment option. Regardless of the outcome of this second series, these patients remained in their treatment arms, with their results classified as unsatisfactory. The 6-month follow-up duration was chosen based on the retrospective experience that most beneficial effects are observed within 6 months.

Pain levels were determined using a graphic visual analog scale (VAS) with levels ranging from 0 (no pain) to 10 (maximum conceivable pain); a modified von Pannewitz pain score (where complete response [CR] = pain free; partial response [PR] = substantial pain improvement; minor response [MR] = pain improvement; and no change = pain unchanged or increased or worsening); and a 5-level function score (where excellent = 90-100 points; good = 70-85 points; fair = 40-69 points; and poor = 0-39 points) (3). Events were defined as the requirement for second treatment.

The compatibility of variables to normal distribution was investigated using visual (histogram and probability graphs) and analytical methods (One-Sample Kolmogorov-Smirnov). After examining the distribution of variables, Student *t* tests, Mann-Whitney U tests, χ^2 tests, and Fisher exact tests were used to compare data. Event-free probabilities were estimated and graphically represented as time-to-event curves using the Kaplan-Meier method. The influence of cofactors was assessed using log-rank tests for censored survival data. Variables that were significant in the univariate analyses were entered into multivariate analyses.

In univariate analysis, disease and treatment associated with the dependent and independent variables were determined according to relevant published reports. In multivariate analysis, the significance in the univariate analysis or P value $<.25$ variables or likely to impact on the results reported in previous studies have shown that the variables were included in the analysis. P values of $<.05$ were considered statistically significant. SPSS version 13 software was used for all statistical analyses.

Results

A total of 128 patients were included in this trial. Four patients in the radiation therapy arm changed their mind after consenting, and they were included to PG steroid arm. We chose to complete the scheme applied 3 times per week for 2 weeks in this study. The treatment was 2 times per week for 3 weeks for 2 patients, and these patients were included. A total of 4 patients had to be excluded after randomization. Of these 124 patients, 60 were assigned to the radiation therapy arm, and 64 were assigned to the PG steroid injection arm. The trial design and CONSORT flow chart are summarized in Figure 1 (21).

Follow-up examinations were completed in October 2014; the median follow-up duration was 12.5 months (range, 6.5-18.5 months). The median follow-up duration for the radiation therapy arm was 13 months (range, 6.5-18.5 months), whereas for the PG steroid arm, it was 12.1 months (range, 6.5-18.6 months). Therefore, the durations of the follow-up period were not statistically different between the groups ($P=.282$).

The mean age of patients at enrollment was 52.6 years (range, 40-74 years of age) for the radiation therapy arm compared with 54.7 years (range, 40-74 years of age) for the PG steroid injection arm. Before therapy, we determined that patients in the 2 groups were comparable with respect to age, sex, body mass index (BMI), history of pain, limitations in their daily work and physical activity before treatment, treatment modalities used before radiation therapy or PG steroid injection, and performance of simple tests such as walking on their heels or toes. However, the mean duration of pain was significantly prolonged in the radiation therapy arm compared to the PG steroid arm (0.018). The patients' characteristics are summarized in Table 1.

Pretreatment VAS scores were higher in the radiation therapy arm. The pretreatment VAS score was 7.6 in the radiation therapy arm and 6.9 in the PG steroid arm. The pretreatment 5-level function score was 41.6 in the radiation therapy arm and 48.4 in the PG steroid arm. These differences were significantly different ($P=.009$ and

Table 1 Patient characteristics

Characteristic	Radiation therapy group	PG steroid group	*P*
No. of patients (%)	60 (48.4%)	64 (51.6%)	
Age (y)			.814
Mean	52.6 (40-74)	54.7 (40-74)	
Sex			.850
Female	46 (76.7%)	51 (79.7%)	
Male	14 (23.3%)	13 (20.3%)	
Body mass index			.336
Mean	34	33.1	
Range	21.9-48	21.3-43.8	
Occupation			.313
Standing	54 (90%)	61 (95.3%)	
Sitting	6 (10%)	3 (4.7%)	
Cigarette smoker			.886
Yes	9 (15%)	8 (12.5%)	
No	51 (85%)	56 (87.5%)	
No. of locations of spur (%)			.614
Plantar	41 (68.3%)	42 (65.6%)	
Dorsal	9 (15%)	11 (17.2%)	
Both	10 (16.7%)	11 (17.2%)	
Duration of pain (mo)			.018
Mean	18.6	14	
Range	6-48	6-48	
≤6 months	12 (20%)	22 (34.3%)	
>6 months	48 (80%)	42 (65.6%)	
Localization of pain			.413
Right	17 (28.3%)	21 (32.8%)	
Left	19 (31.7%)	22 (34.4%)	
Right = left	4 (6.7%)	5 (7.8%)	
Right > left	12 (20%)	9 (14.1%)	
Right < left	8 (13.3%)	7 (10.9%)	
Extension of pain			.169
None	17 (28.3%)	8 (12.5%)	
Sole of foot	14 (23.3%)	20 (31.3%)	
Calf	22 (36.7%)	26 (40.6%)	
Sole of foot and calf	7 (11.7%)	10 (15.6%)	
Start of pain			.545
Unknown	5 (8.3%)	6 (9.4%)	
Sudden	28 (46.7%)	26 (40.6%)	
Insidious	27 (45%)	32 (50%)	
Impact of pain on quality of life			.923
No impact	9 (15%)	10 (15.6%)	
Leisure	1 (1.7%)	6 (9.4%)	
Work	30 (50%)	24 (37.5%)	
Leisure and work	20 (33.3%)	24 (37.5%)	
Effects on daily work			.087
Able to work	40 (66.7%)	33 (51.6%)	
Unable to work	19 (31.7%)	29 (45.3%)	
No occupancy	1 (1.7%)	2 (3.1%)	
Effects on leisure or sports			.295
Unlimited	-	1 (1.6%)	
Limited	6 (10%)	7 (10.9%)	
Impossible	1 (1.7%)	4 (6.3%)	
No sports	53 (88.3%)	52 (81.3%)	
Previous therapy			.246
Ice/heat	6 (10%)	7 (10.9%)	
Extracorporeal shock wave	12 (20%)	14 (21.9%)	
Oral medication	9 (15%)	8 (12.5%)	
Injection	21 (35%)	17 (26.6%)	
Insole support	9 (15%)	12 (18.7%)	
Ultrasound application	3 (5%)	6 (9.4%)	
Test			.883
Standing on toes	9 (15%)	8 (12.5%)	
Walking on toes	11 (18.3%)	10 (15.6%)	
Standing on heel	13 (21.7%)	15 (23.4%)	
Walking on heel	27 (45%)	31 (48.5%)	
VAS			.009
Mean	7.6	6.9	
Minimum	4	4	
Maximum	10	10	
Median	8	7	
Five-level function score			.001
Mean	41.6	48.4	
Minimum	20	30	
Maximum	70	85	
Median	40	50	

Abbreviations: PG = palpation guide; VAS = visual analog scale.

$P = .001$, respectively). These data are summarized in Table 1.

The mean differences in VAS scores after 3 months was 2.8 in the radiation therapy arm and 4.6 in the PG steroid injection group. Therefore, patients in the radiation therapy arm had superior results ($P < .001$). A similar result was observed upon evaluation of the 5-level function scores: the mean difference was 78.3 in the radiation therapy arm and 60 in the PG steroid injection group ($P < .001$). Treatment outcome after radiation therapy was significantly better than treatment outcome after PG steroid injection (Table 2).

The mean differences in VAS scores after 6 months compared with the values before radiation therapy was 2.7 in the radiation therapy arm and 4.6 in the PG steroid injection group, resulting in superior results after radiation therapy ($P < .001$). A similar result was observed when evaluating the 5-level function: the mean difference amounted to 78.7 in the radiation therapy and 59 in the PG steroid injection group ($P < .001$) (Table 2).

Overall, 93 patients were event-free during the follow-up period. With a total number of 25% (31) events (second treatment requirement), 1-year event-free probability of radiation therapy arm was 95%, whereas the event-free probability in the PG steroid arm was 90.2% according to Kaplan-Meier analysis (Fig. 3). The time interval required for the second treatment ranged from 4 months to 15.2 months (mean, 9 months) after radiation therapy and

Table 2 Comparison of pain data after 3 months and 6 months

Measurement	Value	RT group for 3 month	PG steroid group for 3 month	*P*	RT group for 6 month	PG steroid group for 6 month	*P*
VAS	Mean	2.8	4.6	<.001	2.7	4.6	<.001
	Minimum	0	0		0	0	
	Maximum	9	10		10	10	
	Median	2	5		2	5	
Five-level function score	Mean	78.3	60	<.001	78.7	59	<.001
	Minimum	30	6		35	0	
	Maximum	100	100		100	100	
	Median	85	57.5		80	60	
	Excellent	24 (40%)	10 (15.6%)		23 (38.3%)	10 (15.6%)	
	Good	24 (40%)	12 (18.8%)		23 (38.3%)	14 (21.9%)	
	Moderate	12 (20%)	32 (50%)		13 (21.7%)	29 (45.3%)	
	Poor	-	10 (15.6%)		1 (1.7)	11 (17.2%)	
Modified von Pannewitz pain score	Complete response	23 (38.3%)	10 (15.6%)	<.001	21 (35%)	10 (15.6%)	<.001
	Partial response	17 (28.3%)	6 (9.4%)		20 (33.3%)	8 (12.5%)	
	Minor response	11 (18.3%)	22 (34.4%)		12 (20%)	20 (31.3%)	
	No change	8 (13.3%)	20 (31.3%)		6 (10%)	20 (31.3%)	
	Increased pain	1 (1.7)	6 (9.4%)		1 (1.7%)	6 (9.4%)	

Abbreviations: PG = palpation guide; RT = radiation therapy; VAS = visual analog scale.

from 3.1 months to 14.1 months (mean, 6.4 months) after PG steroid injection. The time interval for the second treatment was significantly longer in the radiation therapy group than in the PG steroid injection group ($P = .045$).

In 1 patient in the PG steroid injection arm, acute infection was observed at the injection site. The patient was treated with antibiotic therapy. Acute side effects or long-term toxicity did not occur in the radiation therapy arm.

In univariate and multivariate analyses, age ($\leq$50 or >50 years), sex, BMI, pain onset ($\leq$6 months or >6 months), and treatment group were investigated as prognostic factors for pain relief. Results of the univariate analyses indicated that only age was considered a significant prognostic factor ($P = .015$). None of these factors was statistically significant in multivariate analyses. Results of univariate and multivariate analyses are shown in Table 3.

Discussion

Up to 10% of adults will suffer heel pain during their lifetime, and plantar fasciitis causes approximately 80% of all heel pain (22). Plantar fasciitis commonly presents as sharp, stinging pain. It develops upon initially straining the planter aponeurosis, followed by development of persistent inflammatory reactions (23). The pain is worse during weight-bearing activities such as walking, jogging, and lifting (24). Treatment of the heel spurs is primarily nonsurgical, including use of nonsteroidal anti-inflammatory drugs, ultrasound diathermy, physical therapy, night splinting, corticosteroid injection, and shock-wave therapy (6-9).

The aim of this study was to compare the analgesic effects of radiation therapy with that of PG steroid injections. Furthermore, this trial was randomized but not blinded to the patient or physician. There was a clear superiority of radiation therapy treatment over PG steroid injection in terms of pain relief as well as quality of life. The improvement persisted for at least several months after therapy.

Corticosteroid injection in the heel for pain relief is considered if other conservative modalities fail. PG injection is an effective and common treatment (25). In all studies to date, regardless of the method used, VAS values are improved by steroid injection: 5.4 to 2.4 (range, 3.3-7.5 and 0.8-4.8, respectively) for PG steroid injection (26), 6.4 to 2.2 (range, 3.7-9.1 and 0.7-4.7, respectively) for PG steroid injection (5), and 59.7 to 18.2 (range, 48-71.5 and 5.5-30.9, respectively) for PG steroid injection (19). In another study, there were statistically significant differences between the preinjection and follow-up VAS values. Genc

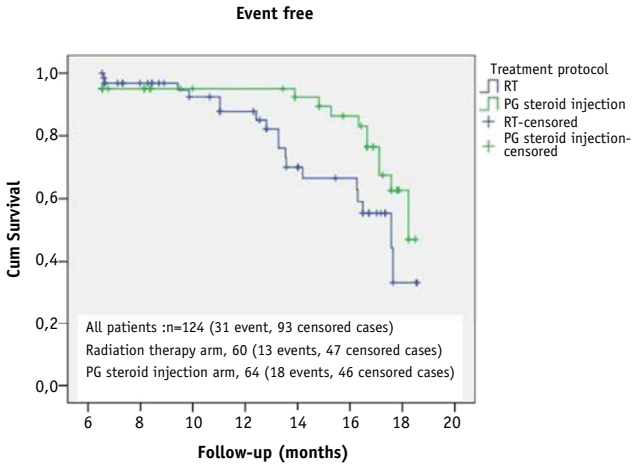

Fig. 3. Kaplan-Meier curve for pain control used for all patients. Cum = cumulative; PG = palpation guide; RT = radiation therapy.

Table 3 Univariate and multivariate analyses of prognostic factors

Variable	No. of patients	Univariate analyses		Multivariate analyses	
		Event-free probability (follow-up, mo)	*P*	Hazard Ratio (95% CI)	*P*
Age (y)					
≤50	52	22.5% (17.8)	.015	0.45 (0.20-1.02)	.053
>50	72	59% (18.6)			
Sex			.326		
Male	27	43% (18.6)		0.83 (0.27-2.56)	.751
Female	97	45.3% (18.5)			
BMI			.784		.948
<25	3	66.7% (17.6)		0.52 (0.05-5.47)	.584
25-29.9	26	33.7% (18.5)		0.56 (0.06-5.13)	.612
30-39.9	23	47% (18.6)		0.65 (0.06-7.18)	.725
>40	12	29.6% (18.5)			
Duration of pain (mo)					
≤6	36	16.8% (17.6)	.244	0.84 (0.33-2.09)	.702
>6	88	47.2% (18.6)			
Treatment scheme					
Radiation therapy	60	47% (18.5)	.065	1.89 (0.88-4.04)	.102
PG-steroid injection	64	33.3% (18.6)			

Abbreviations: BMI = body mass index; PG = palpation guide.

et al (25) found that with PG steroid injections, plantar fascia thickness and mean VAS values decreased significantly 6 months after steroid injection. In the present study, there were statistically significant differences between the preinjection and follow-up VAS values. A response rate of 59.4% was obtained at the 6-month follow-up in the PG steroid injection arm.

Application of radiation therapy in benign disorders has been used for nearly 100 years in central Europe. Patients with plantar fasciitis constitute an important proportion of patients undergoing radiation therapy. A recent randomized trial published by Niewald et al (18) compared a standard radiation therapy dose with a very low dose. In terms of pain relief and quality of life, those authors showed the superiority of the standard dose over the low dose. Thus, it can be assumed that administration of 6 Gy, as used in our study, is a sufficient dose. In the radiation therapy arm, response rates of 84.9% were obtained at the 6-month follow-up examination. Our results are comparable to previous data that reported response rates ranging from 65% to 100%. In another study that included 3472 patients, complete pain relief was noted in 53.2% of patients and partial pain relief in 30.9%, and 15.9% of patients were unchanged (27). In the current study, 35% of patients in the radiation therapy arm had complete responses, 33.3% had partial responses, 20% had minor responses, and 10% were unchanged. In the PG steroid injection arm, 15.6% of patients had complete responses, 12.5% had partial responses, 31.3% had minor responses, and 31.3% were unchanged. In the radiation therapy arm, we observed a significantly increased rate of patients who responded to treatment, which was significantly in favor of radiation therapy. Ott et al (28) reported mean VAS pain values 6 weeks after completion of their study in the 1.0-Gy treatment group was 28.9. With the use of standard dose, Niewald et al (18) found a mean difference in VAS scores of −43.39 after 3 months compared with the values before radiation therapy. Moreover, another study reported the mean VAS pain value after completion of radiation therapy was 2.15 (29). In the current study, the mean VAS pain values 3 months after completion of the study treatment were 2.8 for radiation therapy arm and 4.6 for the PG steroid arm. These results are statistically significant in favor of radiation therapy.

Crawford et al (30) demonstrated that steroid injection relieved heel pain after 1 month, which did not persist at the 3-month follow-up. That study therefore concluded that steroid injections provide only short-term relief. In our study, there were no differences between the 2 arms regarding the need for secondary treatment. However, the duration until the second treatment was significantly shorter in the injection arm. PG injection might have been the cause of inaccurately guided injections. In addition, repeated corticosteroid injections tend to cause fat pad atrophy and plantar fascia rupture (31). However, in our study, no patients who underwent steroid injections experienced fat pad atrophy and plantar fascia rupture.

The possible carcinogenic risks of radiation therapy have been investigated in many trials, and it has been determined that the risk is not as high as originally feared (32, 33). Radiation therapy fields used to treat plantar fasciitis are too small and the total doses are much lower than those used for malignant disease. We observed no acute and or long-term side effects in this study in the radiation therapy arm.

In our analyses of prognostic factors that predict pain relief, age was determined to be statistically significant based on univariate analysis. No factors were significant in the multivariate analyses. Sex, BMI, pain onset ≤6 months versus >6 months, and treatment modality were not significant prognostic factors for pain relief. In a study by

Hermann et al (34), age, length of heel spur $\leq$6.5 mm, and onset of pain $<$12 months before radiation therapy were prognostic factors that affected pain relief. In another study, multivariate analyses indicated that age, prior treatment, and high-voltage photons were prognostic factors for pain relief (32).

Conclusions

Our prospective study provides high-level evidence that demonstrates radiation therapy yields pain relief in patients with plantar fasciitis compared to PG steroid injection.

References

1. Michetti ML, Jacobs SA. Calcaneal heel spurs: Etiology, treatment, and a new surgical approach. *J Foot Surg* 1983;22:234-239.
2. McCarthy DJ, Gorecki GE. The anatomical basis of inferior calcaneal lesions. A cryomicrotomy study. *J Am Podiatry Assoc* 1979;69:527-536.
3. Micke O, Ernst-Stecken A, Mücke R, et al. Calcaneodynia: Plantar and dorsal heel spur/heel spur syndrome. In: Seegenschmiedt MH, Makoski HB, Trott KR, et al., editors. Radiotherapy for Nonmalignant Disorders. Berlin: Springer; 2008:295-315.
4. Schroeder BM. Diagnosis and treatment of heel pain. *Am Fam Physician* 2002;65:1686-1688.
5. Yucel I, Yazici B, Degirmenci E, et al. Comparison of ultrasound-, palpation-, and scintigraphy-guided steroid injections in the treatment of plantar fasciitis. *Arch Orthop Trauma Surg* 2009;129:695-701.
6. Akfırat M, Sen C, Gunes T. Ultrasonographic appearance of the plantar fasciitis. *Clin Imaging* 2003;27:353-357.
7. Dasgupta B, Bowles J. Scintigraphic localisation of steroid injection site in plantar fasciitis. *Lancet* 1995;346:1400-1401.
8. Evans A. Podiatric medical applications of posterior night stretch splinting. *J Am Podiatr Med Assoc* 2001;91:356-360.
9. Hammer DS, Adam F, Kreutz A, et al. Ultrasonographic evaluation at 6-month follow-up of plantar fasciitis after extracorporeal shock wave therapy. *Arch Orthop Trauma Surg* 2005;125:6-9.
10. Barrett SL, Day SV. Endoscopic plantar fasciotomy: Two portal endoscopic surgical techniques—Clinical results of 65 procedures. *J Foot Ankle Surg* 1993;32:248-256.
11. Hildebrandt G, Seed MP, Freemantle CN, et al. Mechanisms of the antiinflammatory activity of low-dose radiation therapy. *Int J Radiat Biol* 1998;74:367-378.
12. Schaue D, Marples B, Trott KG. The effect of low dose X irradiation on the oxidative burst in stimulated macrophages. *Int J Radiat Biol* 2002;78:567-576.
13. Hildebrandt G, Maggiorella L, Rödel F, et al. Mononuclear cell adhesion and cell adhesion molecule liberation after X-irradiation of activated endothelial cells in vitro. *Int J Radiat Biol* 2002;78:315-325.
14. Trott KR, Kamprad F. Radiobiological mechanism of antiinflammatory radiotherapy. *Radiother Oncol* 1999;51:197-203.
15. Miszczyk L, Jochymek B, Wozniak G. Retrospective evaluation of radiotherapy in plantar fasciitis. *Br J Radiol* 2007;80:829-834.
16. Seegenschmiedt MH, Keilholz L, Katalinic A, et al. Radiotherapy of plantar heel spurs: Indications, technique, clinical results at different dose concepts. *Strahlenther Onkol* 1996;172:376-383.
17. Heyd R, Tselis N, Ackermann H, et al. Radiation therapy for painful heel spurs: Results of a prospective randomized study. *Strahlenther Onkol* 2007;183:3-9.
18. Niewald M, Seegenschmiedt MH, Micke O, et al. Randomized, multicenter trial on the effect of radiation therapy on plantar fasciitis (painful heel spur) comparing a standard dose with a very low dose: Mature results after 12 months' follow-up. *Int J Radiat Oncol Biol Phys* 2012;84:455-462.
19. Kane D, Greaney T, Shanahan M, et al. The role of ultrasonography in the diagnosis and management of idiopathic plantar fasciitis. *Rheumatology (Oxford)* 2001;40:1002-1008.
20. Porter MD, Shadbolt B. Intralesional corticosteroid injection versus extracorporeal shock wave therapy for plantar fasciopathy. *Clin J Sport Med* 2005;15:119-124.
21. Rennie D. CONSORT revised—Improving the reporting of randomized trials. *JAMA* 2001;285:2006-2007.
22. Young C. In the clinic. Plantar fasciitis. *Ann Intern Med* 2012;156:1-16.
23. Schepsis AA, Leach RE, Gorzyca J. Plantar fasciitis. *Clin Orthop* 1991;266:185-196.
24. Barry LD, Barry AN, Chen Y. A retrospective study of standing gastrocnemius-soleus stretching versus night splinting in the treatment of plantar fasciitis. *J Foot Ankle Surg* 2002;41:221-227.
25. Genc H, Saracoglu M, Nacir B, et al. Long-term ultrasonographic follow-up of plantar fasciitis patients treated with steroid injection. *Joint Bone Spine* 2005;72:61-65.
26. Tsai WC, Hsu CC, Chen CP, et al. Plantar fasciitis treated with local steroid injection: Comparison between sonographic and palpation guidance. *J Clin Ultrasound* 2006;34:12-16.
27. Micke O, Seegenschmiedt MH. German Cooperative Group on Radiotherapy for Benign Diseases. Radiotherapy in painful heel spurs (plantar fasciitis). Results of a national patterns of care study. *Int J Radiat Oncol Biol Phys* 2004;58:828-843.
28. Ott OJ, Jeremias C, Gaipl US, et al. Radiotherapy for calcaneodynia. Results of a single center prospective randomized dose optimization trial. *Strahlenther Onkol* 2013;189:329-334.
29. Koca T, Aydın A, Sezen D, et al. Painful plantar heel spur treatment with Co-60 teletherapy: Factors influencing treatment outcome. *Springerplus* 2014;3:1-4.
30. Crawford F, Atkins D, Young P, et al. Steroid injection for heel pain: Evidence of short-term effectiveness. A randomized controlled trial. *Rheumatology (Oxford)* 1999;38:974-977.
31. Kane D, Greaney T, Bresnihan B, et al. Ultrasound guided injection of recalcitrant plantar fasciitis. *Ann Rheum Dis* 1998;57:383-384.
32. Muecke R, Micke O, Reichl B, et al. Demographic, clinical and treatment related predictors for event-free probability following low-dose radiotherapy for painful heel spurs—A retrospective multicenter study of 502 patients. *Acta Oncol* 2007;46:239-246.
33. Surenkok S, Dirican B, Beyzadeoğlu M, et al. Heel spur radiotherapy and radiation carcinogenesis risk estimation. *Radiat Med* 2006;24:573-576.
34. Hermann RM, Meyer A, Becker A, et al. Effect of field size and length of plantar spur on treatment outcome in radiation therapy of plantar fasciitis: The bigger the better? *Int J Radiat Oncol Biol Phys* 2013;87:1122-1128.

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Clinical Oncology
The Royal College of Radiologists

Recommendations for using radiotherapy for benign disease in the UK

March 2023

Contents

Foreword

Radiotherapy has multiple potential uses in the treatment of non-cancerous conditions but there is much variation in how it is employed in the UK. Many clinical oncologists will use radiation for one or two of these indications but there are few, if any, experts in the use of radiation for benign diseases as a whole. The Royal College of Radiologists (RCR) therefore published an evidence-based review and guideline for the use of radiotherapy for benign disease in 2015 under the leadership of Professor Roger Taylor with the intention of harmonising practice and explaining the utility of radiotherapy for these conditions.

The evidence base in this field is slow to change, so there are relatively few major updates in this second edition. There is a new chapter on total lymph node irradiation in patients who have rejection of solid organ transplants. We have removed chapters covering diseases where radiotherapy is rarely, if ever, used in the UK.

Many thanks to Roger Taylor, Tom Roques, Norma Sidek and Robin Prestwich for undertaking the review and rewriting of this document. We are also grateful to Karl Butterworth, Sara Erridge, John Frew, Sarah Jefferies, Agata Rembielak, Maria Vassilou, Richard Shaffer, Gillian Whitfield and James Wylie for helping to review and redraft relevant sections.

We would also like to thank members of the original 2014 working group whose effort has provided such a secure basis for this update: Roger Taylor, Paul Hatfield, Stephanie McKeown, Robin Prestwich and Richard Shaffer.

This guidance should prove a valuable resource for departments to review and develop their protocols for these rare indications for radiotherapy, which nonetheless can provide patients with considerable benefits.

Nicky Thorp

Introduction

There are two basic mechanisms that can be exploited for the treatment of benign conditions with radiotherapy (RT). First, the anti-proliferative effect of RT, which can be used, for example, to reduce the risk of heterotopic ossification (HO) following hip replacement or the recurrence of pigmented villonodular synovitis following a synovectomy. Second, the anti-inflammatory effect of RT can be used to treat soft-tissue inflammatory conditions such as Graves' orbitopathy (GO). RT doses employed for the treatment of benign conditions are often well below the range used to treat cancer. For example, a so-called 'anti-inflammatory dose' of RT is often around 20 Gray (Gy) in ten fractions or its equivalent and, for most patients, acute toxicity is not a problem.

In recent decades, the use of RT for benign conditions in the UK has declined. It is likely that this is largely due to the increased availability of alternative medical therapies, advances in surgery and concerns as to the potential, if very small, risk of radiation-induced cancer (RIC). In Germany, RT is still widely used for a range of benign conditions. A 2018 patterns of care study suggests that as many as 68% of all patients receiving RT in that country do not have cancer.[1] A 2014 survey of UK RT departments conducted by the RCR, discussed in the first edition of this guidance, established that the numbers treated in the UK are much smaller and they vary considerably from one department to another. There is also a paucity of formal guidance documents about the use of RT in benign disease – the last published German guidelines are from 2015.[2–5] The International Organisation for Radiotherapy for Benign Conditions (https://iorbc.com) has recently been established.

Interpretation of the literature is problematic. Reports of the use of RT for many benign conditions comprise mainly case reports or small single-institution retrospective series. Follow-up tends to be relatively short term in comparison with the life expectancy of patients with benign conditions and it is often difficult to ascertain the long-term benefits and risks of treatment. On the other hand, for some conditions such as GO, randomised trials have been conducted recently and there is ongoing clinical research in the use of RT for other benign conditions.

For some conditions there are large follow-up studies on the risks of RIC but many of these studies are for conditions that are no longer being treated with RT; for example, tinea capitis, peptic ulcers and ankylosing spondylitis. It is very likely that one of the reasons for the decline in the use of RT for benign conditions is the fear of radiation and, in particular, concern about the risk of RIC, exemplified by the increased incidence of leukaemia following RT for ankylosing spondylitis. Bearing in mind the age range of most patients and the relatively low RT doses employed – often to peripheral areas of the body – the risks of RT may be lower than the risks of alternative pertinent therapies such as anti-inflammatory drugs and other interventions.[6]

The first edition of this document included a comprehensive section on the radiobiology of treating benign disease and chapters on all benign conditions for which RT was thought to be in use in the UK. This second edition has been streamlined to focus on the most common benign conditions for which RT is established as a treatment modality. It is hoped that the document will provide a useful resource for clinical oncologists who receive referrals for patients with these conditions. The evidence for use of radiation in benign disease continues to evolve so this document should not be viewed as a proscriptive list of the only benign conditions that can be treated with RT in the UK. The evidence base for any other indications should be carefully considered before local protocols are developed and approved.

Meningiomas are no longer included as they are managed by neuro-oncology multidisciplinary teams (MDTs) together with other central nervous system (CNS) tumours. Other chapters have been removed from this second edition in light of the fact that RT is no longer or rarely used to treat them in UK practice: orbital pseudotumour/idiopathic orbital inflammation; pterygium; age-related macular degeneration; choroidal haemangioma; cerebral arteriovenous malformations; hidradenitis suppurativa; psoriasis; chronic eczema; Peyronie's disease; vertebral haemangioma and aneurysmal bone cyst. A new section on total lymphatic irradiation (TLI) has been added.

Many of the recommendations in the remaining sections are largely unchanged from the first edition; however, the latest evidence is now included. Much of the evidence base for use of RT in benign disease is Grade C level, although randomised studies and systematic reviews exist in some areas.

References

1. Kriz J, Seegenschmeidt HM, Bartels A *et al*. Updated strategies in the treatment of benign diseases—a patterns of care study of the german cooperative group on benign diseases. *Adv Radiat Oncol* 2018; **3**: 240–244.
2. Reichl B, Block A, Schäfer U *et al*. DEGRO practical guidelines for radiotherapy of non-malignant disorders. Part I: physical principles, radiobiological mechanisms, and radiogenic risk. *Strahlenther Onkol* 2015; **191**: 701–709.
3. Ott O, Niewald M, Weitmann H *et al*. DEGRO guidelines for the radiotherapy of non-malignant disorders. Part II: painful degenerative skeletal disorders. *Strahlenther Onkol* 2015; **191**: 1–6.
4. Seegenschmiedt MH, Micke O, Niewald M *et al*. DEGRO guidelines for the radiotherapy of non-malignant disorders. Part III: hyperproliferative disorders. *Strahlenther Onkol* 2015; **191**: 541–548.
5. Reinartz G, Eich HT, Pohl F. DEGRO practical guidelines for the radiotherapy of non-malignant disorders. Part IV: symptomatic functional disorders. *Strahlenther Onkol* 2015; **191**: 295–302.
6. McKeown SR, Hatfield P, Prestwich RJD *et al*. Radiotherapy for benign disease: assessing the risk of radiation-induced cancer following exposure to intermediate dose radiation. *Br J Radiol* 2015; **88**: 20150405.

Summary of recommendations

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Scottish Intercollegiate Guidelines Network (SIGN) (see appendix 2).

1 Orthopaedic/musculoskeletal

1.1 Dupuytren's disease of the hand

1.1.1 RT is effective in the early stages of Dupuytren's disease, where there is no contracture (stage N) or a contracture of up to ten degrees (N/I) (Grade B).

1.1.2 Patients with more advanced disease should not be treated with RT but may be offered surgical release (Grade C).

1.1.3 Due to the variable progression of this disease, only patients whose disease has progressed within the last 6–12 months should be treated (Grade C).

1.1.4 The aim is to treat nodules and cords to the periosteum of the hand bones, for a depth of 5–15 mm. Therefore, 120–15 kV photons, or up to 6 mega-electron volts (MeV) electrons with appropriate bolus would be reasonable. Proximal and distal margins of 1–2 cm on palpable nodules and cords, with 0.5–1 cm lateral margins should be used (Grade D).

1.1.5 RT dose: the regimen of choice is 30 Gy in ten fractions, consisting of two phases of 15 Gy in five fractions with a gap of 6–12 weeks between the two phases. An alternative fractionation is 21 Gy in seven fractions on alternate days over two weeks (Grade B).

1.2 Plantar fibromatosis (Ledderhose disease)

1.2.1 RT seems to be an effective modality of treatment for plantar fibromatosis, with good local control and symptomatic benefit (Grade B).

1.2.2 The recommended total dose would be 30 Gy in ten fractions, given in two separate phases of 15 Gy in five daily fractions, with 12 weeks between the two phases (Grade B). The RT can be delivered using orthovoltage photons or electrons as described above for Dupuytrens RT.

1.3 Plantar fasciitis

1.3.1 RT is effective and may be considered for patients who have had plantar fasciitis for more than six months and who have failed conservative management (Grade A).

1.3.2 Dose and technique: 3–6 Gy in six fractions (0.5–1 Gy per fraction) over three weeks delivered using a single lateral field, a parallel-opposed pair of lateral fields or 200–250 kV photons (Grade A).

1.4 Heterotopic ossification of the hip

1.4.1 RT and non-steroidal anti-inflammatory drugs (NSAIDs) are both effective in the prevention of HO but NSAIDs are more cost-effective (Grade A).

1.4.2 RT should be considered in people who are unable to take NSAIDs or who are at risk of more severe HO. It should be avoided in younger patients (for example <50 years).

1.3 Plantar fasciitis

Background

The plantar fascia is a band of fibrous tissue that runs along the plantar surface of the foot and extends from the calcaneus bone to the metatarso-phalangeal joints. Plantar fasciitis is a very common condition, which causes heel pain in approximately 10% of the population and is a combination of inflammation and degeneration of the plantar fascia. It is most common in people between the ages of 40–60 years. However, it can occur at any age. It is twice as common in women as it is in men and is also common in athletes. It is caused by mechanical overload, which may be due to a combination of obesity, prolonged standing and walking or intense exercise, and biomechanical disturbances of the foot or lower leg. In 80% of patients complete resolution is achieved in 12 months, but some patients have more prolonged and disabling symptoms.

Management

Plantar fasciitis is a clinical diagnosis, but an ultrasound scan may be useful to rule out other causes of heel pain. In most patients, simple conservative measures are all that is required, including resting, weight loss, analgesia, icing, stretching exercises, footwear changes and orthotics.

For those cases where symptoms do not resolve with simple measures, various other treatments may be considered, including:

1. Steroid injections: these may provide short-term relief from pain but carry a risk of plantar fascia rupture.
2. Extracorporeal shockwave treatment (ESWT): this is a non-invasive treatment in which a device is used to pass acoustic shockwaves through the skin to the affected area. Local anaesthesia may be used as high-energy ESWT can be painful. Five randomised controlled trials (RCTs) compared ESWT in chronic plantar fasciitis with sham ESWT – one with conservative treatment, and one with a single corticosteroid injection. Overall, the results of studies were inconclusive, and there was evidence of a substantial placebo response.[1]
3. Ultrasonic tissue repair: this uses ultrasound imaging to guide a needle-like probe into the damaged plantar fascia tissue. Using ultrasound energy, the probe tip vibrates rapidly to break up the damaged tissue, which is suctioned out. There is scant evidence only for this method and its outcome.
4. Surgery: this should only be considered in patients who have failed adequate conservative treatment. Techniques include open or endoscopic plantar fascia division and gastrocnemius release. There is case series evidence of success, but no randomised evidence, and it may be associated with complications such as flattening of the longitudinal arch and plantar fascia rupture.[2–5]

Radiotherapy

RT has been used since 1924 for the treatment of plantar fasciitis.[6] Many retrospective studies have shown heel pain response to RT; for example, a German study reported on 7,947 patients and found a 70% pain response three months after RT.[7]

Heyd *et al* randomised 130 patients between low-dose (LD) RT (3 Gy in six fractions over three weeks) and high-dose (HD) RT (6 Gy in six fractions over three weeks).[8] Patients' feet

were treated with a single lateral field. If there was insufficient pain response, a second course of treatment was administered. Before treatment, 90.8% had severe pain and 9.8% had moderate pain. Six weeks after RT there was a response in 80% in the LD group and 84.6% in the HD group. Toxicity was minimal, with 28% experiencing a slight increase in pain during RT. Overall, at six-month follow-up, 87.7% had an improvement in pain, with no significant difference between the two groups.

Niewald *et al* performed a trial randomising patients between standard-dose (SD) RT (6 Gy in six fractions over three weeks) and LD RT (0.6 Gy in six fractions over three weeks).[9] Inclusion criteria were: clinical diagnosis of plantar fasciitis; symptoms for more than six months; heel spur seen on X-ray; Karnofsky Performance Status >70; and age >40 years. The RT was delivered using 4–6 megavolt (MV) photons using a lateral parallel-opposed pair of fields, although the protocol also allowed treatment using 200–250 kV photons.[10] The target volume was the calcaneus and plantar aponeurosis. If there was a poor response at 12 weeks, a second treatment, at the standard (6 Gy) dose, was administered. It was intended to randomise 200 patients, but only 62 patients were treated as the trial was prematurely closed due to such a large treatment effect, with a statistically significant improvement in pain and quality of life at three months in the SD group compared with the LD group.

Similar results were seen in other quality-of-life and pain scores. Of note, reirradiation was necessary in 63.6% of the LD group compared with 17.2% of the SD group, with those in the LD group who were reirradiated showing equally good results to those primarily in the SD group. Efficacy was maintained at 48 weeks, and there were no acute or chronic side-effects.

Potential long-term effects of radiotherapy

The risk of RIC after RT for plantar fasciitis will be similar to that estimated for Dupuytren's disease (0.02%) since the doses and age range are similar (see section 1.1 on Dupuytren's disease). This estimate is based on a field size of 60 cm^2 but the risk increases or decreases with the field size. The risk decreases with increasing age at treatment. As a matter of course, patients should be counselled as to the risk of RIC, which should be more strongly emphasised in younger patients.

The risk of other cancers outside the irradiated field, assuming adequate shielding for the remaining parts of the body, should be small due to the location of the radiation field at the extremity of the leg. Other possible consequences of radiation exposure at the recommended dose will be similar to those indicated for Dupuytren's disease.

Recommendations

1.3.1 RT is effective and may be considered for patients who have had plantar fasciitis for more than six months and who have failed conservative management (Grade A).

1.3.2 Dose and technique: 3–6 Gy in six fractions (0.5–1 Gy per fraction) over three weeks delivered using a single lateral field, a parallel-opposed pair of lateral fields or 200–250 kV photons (Grade A).

References

1. National Institute for Health and Care Excellence. *NICE interventional procedures guidance IPG311 (2009)*. London: National Institute of Health and Care Excellence, 2013.
2. Marafkó C. Endoscopic partial plantar fasciotomy as a treatment alternative in plantar fasciitis. *Acta Chir Orthop Traumatol Cech* 2007; **74**(6): 406–409.
3. Sinnaeve F, Vandeputte G. Clinical outcome of surgical intervention for recalcitrant infero-medial heel pain. *Acta Orthop Belg* 2008; **74**(4): 483–488.
4. Bazaz R, Ferkel RD. Results of endoscopic plantar fascia release. *Foot Ankle Int* 2007; **28**(5): 549–556.
5. Maskill JD, Bohay DR, Anderson JG. Gastrocnemius recession to treat isolated foot pain. *Foot Ankle Int* 2010; **31**(1): 19–23.
6. Richarz A. Die Rontgenbehandlung der Epikondylitis und der Kalkaneodynie. *Fortschr Rontgenstr* 1924; **32**: 460.
7. Micke O, Seegenschmiedt MH, German Cooperative Group on Radiotherapy for Benign Diseases. Radiotherapy in painful heel spurs (plantar fasciitis) – results of a national patterns of care study. *Int J Radiat Oncol Biol Phys* 2004; **58**(3): 828–843.
8. Heyd R, Tselis N, Ackermann H, Röddiger SJ, Zamboglou N. Radiation therapy for painful heel spurs. *Strahlentherapie und Onkologie* 2007; **183**(1): 3–9.
9. Niewald M, Seegenschmiedt MH, Micke O *et al*. Randomized, multicenter trial on the effect of radiation therapy on plantar fasciitis (painful heel spur) comparing a standard dose with a very low dose: mature results after 12 months' follow-up. *Int J Radiat Oncol Biol Phys* 2012; **84**(4): e455–e462.
10. Niewald M, Seegenschmiedt MH, Micke O *et al*. Randomized multicenter trial on the effect of radiotherapy for plantar fasciitis (painful heel spur) using very low doses – a study protocol. *Radiat Oncol* 2008; **18**(3): 3–27.

1.4 Heterotopic ossification of the hip

Background

HO is the abnormal formation of mature bone within extraskeletal soft tissues. It occurs most commonly after trauma or surgical procedures, for example after total hip arthroplasty. The origin of the new bone is not entirely clear, but it is thought to result from the inappropriate differentiation of pluripotential mesenchymal cells into osteoblastic stem cells. Under the influence of inductive agents (bone morphogenic proteins), these cells form new bone. HO can occur at any age, although most hip replacements occur between the ages of 50–80 years.

In many patients HO is asymptomatic, but in some patients the new bone may cause symptoms such as swelling and tenderness, pain and limited range of motion. Risk factors include prior HO, trauma and muscle injury, and disorders such as Paget's disease and ankylosing spondylitis.

The commonly used Brooker classification of HO at the hip is based on antero–posterior plain X-ray findings (see Table 3). Broadly, Brooker grades 3 and 4 represent severe HO, which often leads to functional disability.[1]

Surgery and NSAIDs

Symptomatic HO is treated with surgery, which is delayed until at least six months after the traumatic episode to allow the bone to mature and for the inflammation to settle. Preventative measures, either NSAIDs or RT, may be used to minimise the risk of recurrence or to reduce the initial occurrence rate in high-risk situations.

Table 3. Brooker classification of heterotopic ossification around the hip joint

Age	Description
1	Bone islands within the soft tissues
2	Bone spurs from the pelvis or proximal end of the femur, with at least 1 cm between opposing bone surfaces
3	Bone spurs from the pelvis or proximal end of the femur, with <1 cm between opposing bone surfaces
4	Apparent bone ankylosis of the hip

NSAIDs are thought to prevent the formation of heterotopic bone by inhibiting the post-traumatic inflammatory response and by inhibiting the differentiation of mesenchymal cells into osteogenic cells.

Meta-analyses have shown a mean overall reduction in the risk of HO after total hip arthroplasty (THA) with NSAIDs (apart from aspirin) from 61% to 27% when compared with a placebo.[2,3] Non-selective (for example indomethacin) and selective (for example celecoxib) NSAIDs are equally effective. Side-effects of NSAIDs may include gastric irritation and bleeding, and renal dysfunction. They may also increase the non-union of concomitant fractures.[4]

Radiotherapy dose and fractionation

RT is thought to reduce the formation of ectopic bone by acting on osteoprogenitor cells, perhaps via inhibition of bone morphogenic protein signal transduction pathways. These cellular changes usually begin to happen 16 hours after surgery and peak at 32 to 48 hours postoperatively. RT was first used in 1981 in patients at high risk of HO. It was delivered using a parallel-opposed pair of photon fields to a dose of 20 Gy in ten fractions.[5] Due to worries about radiation-induced malignancy, studies were performed to investigate lower total doses of radiation for this purpose. These showed that a single fraction of RT of 7–8 Gy given within 3–4 days postoperatively was as effective as a fractionated course.[6,7]

Three recent meta-analyses from two different groups provide excellent summaries of the literature and come to broadly concordant conclusions about the evidence on dose and timing of RT. They all contain summary tables of individual RCTs.[8–10]

Overall, 20–30% of joints receiving RT progress to HO, with Brooker grades 1 or 2 much more common than grades 3 or 4. Hip joints were the most commonly irradiated – there is no evidence to suggest that rates differ with other joints. A single fraction of 7 Gy delivered postoperatively within 96 hours of surgery is the most commonly used regimen. There is some evidence of a dose response compared with lower doses than 7 Gy but there is no compelling evidence for higher doses. There is some evidence that fractionated RT is more effective than a single fraction, but it is hard to know whether this reflects the number of fractions or the total dose in the few studies where this comparison was made. The convenience of a single fraction probably outweighs any potential small benefit of multiple fractions.

The delivery of postoperative RT can present significant logistical barriers due to postoperative pain and the need to minimise early postoperative mobilisation of the joint. Preoperative RT has therefore been used, and though the optimum time interval has not been studied in depth, treatment within four hours of surgery has emerged as a standard. Studies comparing pre- and postoperative RT contain small numbers but there is no good evidence for a difference in efficacy.

RT and NSAIDs appear equally effective at reducing HO with some evidence that RT may be better at preventing more severe disease.[11] NSAIDs are considerably more cost-effective than RT.[12] RT is therefore recommended to prevent HO in people who are not able to take NSAIDs or who are at very high risk of severe HO.

Radiotherapy fields

Anterior–posterior fields are used and the dose is prescribed to the mid-point. The RT portal should encompass the regions that are most likely to form heterotopic bone, particularly the neck of the femur, the tip of the greater trochanter, between the greater trochanter and the ilium and between the lesser trochanter and the ischial ramus. Reference to preoperative plain X-rays can aid planning. Shielding (of the acetabular component or proximal to the base of the greater and lesser trochanter) has been suggested due to fears of reduction of bony ingrowth into cementless prostheses; however, shielding increases the likelihood of developing HO and does not reduce the risk of prosthetic loosening.[13] An attempt should however be made to shield the central pelvic organs to reduce the risk of RIC.

Potential long-term effects of radiotherapy

Since there are several drug treatment options for HO, it is normally wiser to restrict use of RT to individuals older than 50 since the risk of RIC will be small. However, given the low dose recommended, if there are contraindications or lack of response to NSAIDs, RT could be considered for younger patients, with appropriate counselling regarding the risk of radiation-induced malignancy and infertility.

A study using male and female anthropomorphic phantoms has estimated the risk of a RIC arising from RT for HO to range from ~2% to 4%. It was notable that the effective doses were 4–26% higher in the female phantom due to its smaller size; this increased the amount of at-risk tissue being included in the radiation field (principally lower large intestine, red marrow and gonads). As expected, the risk was also increased as the age at treatment decreased.

The effect of radiation quality and technique also modified the risk. For example, higher photon energies (15 Mv versus 6 Mv) reduced the effective dose by 1% in females or increased the effective dose by 9% in males. Individualised shielding blocks reduced the effective dose to at-risk tissues by ~26%; this dose reduction was especially found for lower large intestine and in the female phantom for the gonads. When comparing the effective dose per unit field size, the male phantom had a relatively small range (1.51–1.74 millisievert [mSv]/cm^2) compared with the female phantom (1.82–2.14 mSv/cm^2). The equivalent gonadal doses were 57–93 mSv (male) and 39–167 mSv (female); consequently, heredity effects would be important in patients who choose subsequently to have children. However, since treatments are more usually performed in older patients this is unlikely to be a major issue. The authors stressed that the range of effective doses for the different treatments at various body sites is large and they advised that clinicians should optimise treatment protocols to reduce the effective dose and thus the related risk of RIC.[14]

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Radiation Therapy for Benign Conditions

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to conduct timely, rigorous, and independent systematic reviews to support VA clinicians, program leadership, and policymakers improve the health of Veterans. ESP reviews have been used to develop evidence-informed clinical policies, practice guidelines, and performance measures; to guide implementation of programs and services that improve Veterans' health and wellbeing; and to set the direction of research to close important evidence gaps. Four ESP Centers are located across the US. Centers are led by recognized experts in evidence synthesis, often with roles as practicing VA clinicians. The Coordinating Center, located in Portland, Oregon, manages program operations, ensures methodological consistency and quality of products, engages with stakeholders, and addresses urgent evidence synthesis needs.

Nominations of review topics are solicited several times each year and submitted via the ESP website. Topics are selected based on the availability of relevant evidence and the likelihood that a review on the topic would be feasible and have broad utility across the VA system. If selected, topics are refined with input from Operational Partners (below), ESP staff, and additional subject matter experts. Draft ESP reviews undergo external peer review to ensure they are methodologically sound, unbiased, and include all important evidence on the topic. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. In seeking broad expertise and perspectives during review development, conflicting viewpoints are common and often result in productive scientific discourse that improves the relevance and rigor of the review. The ESP works to balance divergent views and to manage or mitigate potential conflicts of interest.

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Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

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Technical Expert Panel

To ensure robust, scientifically relevant work, the technical expert panel (TEP) guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members included:

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Disclosures

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The findings and conclusions in this document are those of the author(s) who are responsible for its contents and do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. The final research questions, methodology, and/or conclusions may not necessarily represent the views of contributing operational and content experts. No investigators have affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

Executive Summary

KEY FINDINGS

We identified 48 studies on the use of low-dose radiation therapy (RT; <60 Gy) for the treatment of 9 prioritized benign diseases: heterotopic ossification, keloids, plantar fasciitis, pterygium, osteoarthritis, Dupuytren's contracture, Ledderhose disease, Peyronie's disease, and hidradenitis suppurativa.

Heterotopic Ossification (10 Randomized Controlled Trials [RCTs])

- RT may reduce the occurrence of heterotopic ossification. There was no significant difference in function (all with low confidence). Studies provided insufficient evidence (no conclusion) for radiologic failure, side effects, and patient satisfaction, experience of care, or quality of life.

Keloids (4 RCTs and 2 Nonrandomized Comparative Studies [NRCS])

- There was no significant difference in pain after RT (low confidence). Studies provided insufficient evidence (no conclusions) for recurrence of keloids, cosmetic outcomes, skin condition, or side effects and complications. No study reported data on patient satisfaction, experience, or quality of life.

Plantar Fasciitis (5 RCTs)

- RT may improve function. There was no significant difference in plantar fasciitis thickness, a composite measure of pain and function, and side effects (all with low confidence). Studies provided insufficient evidence (no conclusion) for pain or use of secondary treatment. No study reported data on patient satisfaction, experience, or quality of life.

Pterygium (Brachytherapy – 2 RCTs, 2 NRCS, and 1 Single Group Study)

- Studies provided insufficient evidence (no conclusion) for the recurrence of pterygium, symptomatic improvement, cosmetic results, or side effects. No study reported data on patient satisfaction, experience, or quality of life.

Pterygium (Non-Brachytherapy – 1 Single Group Study), Osteoarthritis (2 RCTs, 3 Single Group Studies, and 1 Systematic Review of Single Group Studies), Peyronie's Disease (5 Single Group Studies), Dupuytren's Contracture (5 Single Group Studies), Ledderhose Disease (1 RCT and 3 Single Group Studies), and Hidradenitis Suppurativa (1 Single Group Study)

- Mostly single group studies found disease-related symptoms improved after RT. Side effects were sparsely reported but included skin reactions. Some studies found patients were satisfied with treatment (certainty of evidence not assessed for these diseases and outcomes).

INTRODUCTION

RT targets inflammatory parameters, impedes cell growth, and is frequently used to treat cancer. Low-dose RT has been proposed as a treatment for benign inflammatory and degenerative musculoskeletal diseases, typically when conventional therapy fails. This includes the use of RT for the treatment (or prevention) of heterotopic ossification, keloids after surgical resection, osteoarthritis, and plantar fasciitis.

Benign inflammatory and degenerative musculoskeletal diseases can cause physical limitations and decreased quality of life. Veterans are at increased risk for some benign inflammatory and degenerative

musculoskeletal, orthopedic, and soft tissue conditions due to the physical demands and injuries related to military service. RT is commonly used for the treatment of benign diseases in Germany. Outside of Germany, RT is rarely used to treat benign conditions. The Veterans Affairs (VA) Evidence Synthesis Program (ESP) was asked by the Veterans Health Administration (VHA) National Radiation Oncology Program for an evidence review on radiation treatment for benign conditions. In collaboration with VA partners, we developed the following Key Question (KQ): *What are the benefits and harms of low-dose radiation therapy for the treatment or prevention of benign hyperproliferative and degenerative skin/epithelial, and musculoskeletal disorders such as keloid scars, hidradenitis suppurativa, Dupuytren's contracture, Ledderhose disease, Peyronie's disease, plantar fasciitis, heterotopic ossification, pterygium, or osteoarthritis in adults?*

METHODS

We searched for peer-reviewed articles in Medline (via PubMed), Embase, and ClinicalTrials.gov from inception to April 1, 2023. One included study was identified by the peer reviewers and was published in May 2023. Eligible studies evaluated the effect of low-dose RT for the 9 prioritized benign diseases (heterotopic ossification, keloids, plantar fasciitis, pterygium treated with and without brachytherapy, osteoarthritis, Dupuytren's contracture, Ledderhose disease, Peyronie's disease, and hidradenitis suppurativa). We excluded studies where participants were <18 years of age, where the majority of patients received re-irradiation of the same anatomic site, where brachytherapy (except for pterygium) was used, and where the majority of patients were treated before 1980. We followed a best evidence approach and prioritized comparative studies (*ie,* RT vs no RT) within each condition of interest. RCTs were given priority over NRCS. Single group studies were included when there were fewer than 5 comparative studies within a disease. When only single group studies were available, we reviewed those studies with the largest sample sizes (up to 5 studies per disease based on study budget). Prioritized outcomes included disease-related symptoms, side effects, and patient satisfaction, experience, and quality of life. Where there were at least 3 studies reporting results from sufficiently similar analyses (based on population, interventions, comparators, and outcomes), we conducted meta-analyses using random-effects models. When there were at least 3 comparative studies per disease, we used GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology to determine certainty of evidence. The review protocol was registered in PROSPERO (CRD42023447241).

RESULTS

Forty-eight studies reported on the effectiveness of low-dose RT for the treatment of heterotopic ossification (N = 10), keloids (N = 6), plantar fasciitis (N = 5), pterygium treated with brachytherapy (N = 5) and without brachytherapy (N = 1), Peyronie's disease (N = 5), Dupuytren's contracture (N = 5), Ledderhose disease (N = 4), hidradenitis suppurativa (N = 1), and osteoarthritis. For osteoarthritis, we included 1 systematic review of 7 single group studies and 5 studies identified from the updated search. Across all 48 studies, there was variation in the total dose of RT (in 47 studies range = 0.5 to 40 Gy and in 1 study <5% of patients received up to 70 Gy), sample size (range = 17 to 2,164), and follow-up (range = 1 to 144 months). ES Table shows summary results by disease.

ES Table. Summary of Findings by Disease

Disease; Patients; Design (Studies)	Disease-Related Outcomes	Side Effects	Patient Satisfaction, Experience, QoL
Heterotopic ossification 1,530; RCT (10)	Low evidence for a difference in heterotopic ossification at follow-up (pooled OR = 0.47, 95% CI [0.19, 1.17]). No difference in function (low confidence). Insufficient evidence (no conclusion) for radiologic failure.	Insufficient evidence (no conclusion)	Insufficient evidence (no conclusion)
Keloids 599; RCT (4), NRCS (2)	Insufficient evidence (no conclusion) for a difference in keloid recurrence at follow-up (pooled OR = 1.32, 95% CI [0.40, 4.33]). No difference in pain (low confidence). Insufficient evidence (no conclusion) for cosmetic outcomes and skin conditions.	Insufficient evidence (no conclusion)	No evidence
Plantar fasciitis 1,153; RCT (2), NRCS (1), single group (2)	Function may improve after RT compared to alterative treatment (low confidence). No difference in plantar fasciitis thickness and a composite measure of pain and function (low confidence). Insufficient evidence (no conclusion) for pain, remission, or use of secondary treatment.	No difference (low confidence)	Insufficient evidence (no conclusion)
Pterygium (brachytherapy) 1,492; RCT (2), NRCS (2), single group (1)	Insufficient evidence (no conclusion) for recurrence of pterygium (pooled OR = 0.75, 95% CI [0.30, 1.92]), symptom improvement, cosmetic results.	Insufficient evidence (no conclusion)	No evidence
Pterygium (non-brachytherapy)[a] 65; single group (1)	Reduction in recurrence.	No evidence	No evidence
Osteoarthritis[a] 3662; RCT (2), single group (3), systematic review (1)	No difference in pain, function, stiffness, patient global assessment, composite measure of pain and function, and mental or physical health.	No difference	No difference
Peyronie's disease[a] 415; single group (5)	Symptoms improved after RT.	No long-term side effect; 39% reported erythema	Some satisfaction with sex life after RT. No evidence on patient satisfaction, experience or QoL.
Dupuytren's contracture[a] 653; single group (5)	Symptoms improved after RT.	Skin complications	Most patients were satisfied with RT. No evidence on QoL.
Ledderhose disease[a] 200; RCT (1) and single group (3)	Reduced pain and improved walking performance.	Skin complications and soft tissue fibrosis (mild)	Improved QoL. Most patients were satisfied with RT.
Hidradenitis suppurativa[a] 231; single group (1)	Symptoms improved after RT.	No evidence	No evidence

Notes. [a] Certainty of evidence not assessed.

Abbreviations. QoL=quality of life; RT=radiation therapy.

Heterotopic Ossification

Ten RCTs conducted between 1988 and 2008 (that analyzed 1530 participants) compared low-dose RT to surgery with or without non-steroidal anti-inflammatory drugs (NSAIDs). Three studies were conducted in US, 6 in Germany, and 1 in the Netherlands. Total radiation dose ranged from 5 to 12 Gy. Nine RCTs had medium risk of bias for poor reporting (unclear method of randomization, not reporting allocation concealment, and not reporting blinding). One RCT reported results from a per protocol analysis and excluded a large number of patients from the RT arm, raising concerns of selection bias (*ie,* high risk of bias).

In summary (ES Table), there was a clinical, but not statistically significant, reduction in the occurrence of heterotopic ossification after RT compared to surgery with or without NSAIDs (9 studies). There was no significant difference in function between RT and surgery with or without NSAIDs (3 studies). Studies provided insufficient evidence for radiologic failure, pain, side effects, and patient satisfaction, experience of care, or quality of life (imprecise and inconsistent estimates and methodological limitations).

Keloids

Six comparative studies (4 RCTs and 2 NRCS) conducted between 1991 and 2021 (that analyzed 599 participants) compared low-dose RT to surgery, surgery with 5-fluorouracil or a topical steroid, or a topical steroid alone. Two studies were conducted in the US, 2 in China, 1 in Nigeria, and 1 in Pakistan. Total radiation dose ranged from 7 to 32 Gy. Three RCTs had medium risk of bias (not blinding participants/personnel and not clearly reporting whether outcomes assessors were independent), 1 RCT had high risk (only reporting outcomes for 52% of treated patients), and 2 NRCS reported unadjusted crude analyses (*ie,* high risk of bias).

In summary (ES Table), studies provided insufficient evidence that RT affects the recurrence rate of keloids compared to alternative treatments (6 studies). There was no difference in pain after RT compared to alternative treatments (1 study). Studies provided insufficient evidence for cosmetic outcomes, skin conditions, or side effects and complications. No study reported quality of life, patient satisfaction, or experience of care outcomes.

Plantar Fasciitis

Five studies (2 RCTs, 1 NRCS, and 2 single group) conducted between 2007 and 2020 (that analyzed 1,153 participants) reported on the use of low-dose RT. The RCTs and NRCS compared RT to platelet-rich plasma therapy, palpation-guided steroid injection, or extracorporeal shock wave therapy. Two studies were conducted in Turkey, 1 in India, and 2 in Germany. Total radiation dose was either 3 or 6 Gy. Two RCTs had medium risk of bias (outcome assessor was not blinded or unclear whether outcome assessor was blinded). The NRCS reported unadjusted crude analyses (*ie,* high risk of bias). Single group studies are unable to estimate the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), function may improve for patients who receive RT (2 studies). There was no significant difference in plantar fasciitis thickness (2 studies), a composite measure of pain and function (1 study), and side effects (4 studies). Studies provided insufficient evidence for effect of RT on pain or use of secondary treatment. No study reported quality of life, patient satisfaction, or experience of care outcomes.

Pterygium (Brachytherapy)

Five studies (2 RCTs, 2 NRCS, and 1 single group) conducted between 1989 and 2009 (that analyzed 1,492 participants) evaluated the use of brachytherapy for the primary treatment or prevention of recurrence of pterygium after excision compared to excision alone, excision with fluorouracil, or excision with mitomycin C. One study was conducted in Brazil, 1 in Israel, 1 in Nigeria, 1 in Turkey, 1 in Japan, and 1 in Germany. In 4 studies, total radiation dose ranged from 10 to 35 Gy. In 1 study, total radiation ranged from 10 to 70 Gy, but we included this study since <4% of patients received >60 Gy. Both RCTs had no methodological concerns. One NRCS only conducted crude analyses (*ie,* high risk of bias) and 1 NRCS only matched for age and sex (*ie,* medium risk of bias). The single group study was unable to estimate the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), studies provided insufficient evidence for the effect of RT on recurrence of pterygium, symptomatic improvement, cosmetic results, or side effects. No study reported quality of life, patient satisfaction, or experience of care outcomes.

Pterygium (Non-Brachytherapy)

One single group study conducted between 1987 and 2000 (that analyzed 65 participants) evaluated the use of RT (5 to 30 Gy) for the primary treatment or prevention of recurrence of pterygium after excision. The study authors are from Germany, but the specific location of the study was unclear. The single group study had minimal methodological limitations, but the design was unable to estimate the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), 23.5% of lesions recurred after RT (1 study). No long-term side effects were reported. The study did not report symptoms, cosmetic outcomes, and patient satisfaction, experience, or quality of life. Certainty of evidence was not assessed for these outcomes.

Osteoarthritis

Six studies (2 RCTs, 3 single group, and 1 systematic review of 7 single group studies) conducted between 2004 and 2020 (that analyzed 3,574 participants) reported on low-dose RT for the treatment of osteoarthritis. Three studies were conducted in Germany and 2 in the Netherlands. Total radiation dose ranged from 0.5 to 6 Gy. The RCTs had no methodological weaknesses. The single group studies had minimal methodological limitations, but the study design was unable to estimate the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), 4 single group studies but not 2 RCTs reported improvements in pain, function, a composite measure, and somatic measure. Side effects including fatigue, local reactions, skin reactions, and nail reactions were comparable between RT and sham RT (2 RCTs). Single group studies, but not the 2 RCTs, reported improvements after RT on a version of the Short Form Health Survey. Certainty of evidence was not assessed for these outcomes.

Peyronie's Disease

Five single group studies conducted between 1982 and 2008 (that analyzed 415 participants) reported on the use of RT for the prevention or primary treatment of Peyronie's disease. Four studies were conducted in Germany and 1 in the Netherlands. Total radiation dose ranged from 12 to 40 Gy. The single group design was unable to determine the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), single group studies reported improvements or stabilization after RT in deviation/curvature (4 studies), foci quality (1 study), and an undefined measure of symptoms (3 studies), and a reduction in pain (4 studies) and number and size of foci (1 study). Between 36% and 51% of patients were satisfied with their sex life after RT (2 studies). Five studies reported different side effects that ranged from 0% (long-term) to 39% (erythema). Certainty of evidence was not assessed for these outcomes.

Dupuytren's Contracture

Five single group studies conducted between 1982 and 2013 (that analyzed 653 participants) reported on the use of RT for the primary treatment of Dupuytren's contracture. Four studies were conducted in Germany and 1 in Poland. Total radiation dose ranged from 21 to 32 Gy. The single group design was unable to determine the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), disease stage (3 studies) and nodules and symptoms (4 studies) either stabilized or regressed in most patients after RT. Skin-related complications were the most commonly reported side effect (5 studies). Most patients were satisfied with treatment (2 studies). No study reported quality of life or experience of care outcomes. Certainty of evidence was not assessed for these outcomes.

Ledderhose Disease

Four studies (1 RCT and 3 single group) conducted between 1996 and 2023 (that analyzed 200 participants) reported on the use of RT for treatment of Ledderhose disease. Two studies were conducted in Germany and 2 in the Netherlands. Total radiation dose ranged from 24 to 32 Gy. The RCT had no methodological concerns (*ie,* low risk of bias). The single group design was unable to determine the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), pain (4 studies), gait or walking speed (3 studies) and quality of life (1 study) improved after RT. Lesions and symptoms stabilized or improved and nodes and strands decreased or remained stable after RT (2 studies). Skin reactions were the most commonly reported side effect (13% to 25%; 4 studies). Most patients were satisfied with their treatment at follow-up (3 studies). Certainty of evidence was not assessed for these outcomes.

Hidradenitis Suppurativa

One single group study conducted between 1979 and 1997 (that analyzed 231 participants) reported on the use of RT for treatment of hidradenitis suppurativa. The study was conducted in Germany. The total radiation dose ranged from 3 to 20 Gy. The single group study was unable able to determine the effect of RT on outcomes (*ie*, high risk of bias).

In summary (ES Table), after RT 78% of patients had a resolution or improvement of symptoms and 39% of patients had resolution of all symptoms. Side effects and patient satisfaction, experience, or quality of life were not reported. Certainty of evidence was not assessed for these outcomes.

DISCUSSION

RT, which is typically used to treat cancer, can also been used to treat benign inflammatory and degenerative musculoskeletal disorders. We identified few comparative studies that evaluated the effect of RT for the treatment of the 9 prioritized diseases. Furthermore, we were only able to evaluate

the certainty of evidence for 4 of the 9 diseases. The effect of RT on clinical outcomes is mixed. RT shows promise for the treatment or prevention of heterotopic ossification and function for people with plantar fasciitis. Low-dose RT may be safe. Local skin reactions were the most commonly reported side effect, but studies did not consistently report adverse events and it was not always clear whether an adverse event was due to RT, co-occurring intervention (*eg*, surgery), or a natural feature of the lesion. Patients and providers are concerned about the risk of radiation-induced malignancies. No study reported cases of radiation-induced malignancies, but studies were not powered (sample sizes were too small) or designed (follow-up time was too short) to detect this rare outcome. Single group studies predominantly informed the synthesis of the majority of diseases. Findings (especially causal inference) from single group studies need to be interpreted with caution because it is challenging to differentiate treatment effect from symptom resolution that could have occurred naturally over the study observation period.

The evidence base on RT for the 9 prioritized diseases has several important limitations. Few comparative studies evaluate the effect of RT. RCTs had independent outcome assessors but did not blind participants or personnel. Three RCTs evaluating RT employed sham RT as a comparison group, which could serve as a model for future studies. There was heterogeneity among studies both within and across diseases. This included variation in radiation dosing, administration of radiation (*ie*, before or after surgery), comparator group (when included), and timing of follow-up assessments. These differences make it challenging to determine the effect of radiation on outcomes. In addition, there was inconsistent reporting of disease characteristics, disease-related outcomes, and side effects. Finally, few studies reported patient quality of life, satisfaction, or experience.

None of the articles focused on a Veteran or military population. Nevertheless, the clinical findings likely translate to the VA population, as the underlying biology of these conditions do not differ by patient population. Patient satisfaction, experience of care, and quality of life are more sensitive to health system features. Only a few studies reported these outcomes (mostly positive findings), but it remains unknown how Veterans would rate their experience. Veterans may or may not receive radiation from 1 of the 41 VHA-operated radiation oncology centers. The location of care (and burden associated with receiving care) could meaningfully impact satisfaction, experience, and quality-related outcomes. RT is typically used after conventional therapy fails and requires a referral from the primary treating provider. For RT to become part of standard care (inside and outside the VA) requires educating referring providers on the benefits and harms of RT. To increase uptake of RT, VA can take the lead on developing a benign disease care pathway. One of the biggest concerns for patients and providers when considering RT is the risk of radiation-induced malignancies. As noted above, few studies reported on this outcome and no study was adequately designed to detect radiation-induced malignancies. There is an opportunity for VA to help fill this gap. VA administrative data combined with efforts from the VA National Radiation Oncology Program (VA-NROP) could be used to develop a registry to monitor radiation-induced malignancies.

Research Gaps/Future Research

There is a need for well-designed, adequately powered comparative studies. RCTs should consider employing sham radiation as the comparison group or other conservative modalities such as steroid injections. Most observational studies used data from medical records, but they did not account for confounding between groups. Future observational studies, including studies of electronic health records, should at minimum conduct causally explicit analyses to counter confounding bias. There is also a need to better understand patient quality of life, experience, and satisfaction, including

treatment-related burden. Finally, and as noted above, there is a need for a registry to collect data on radiation-induced secondary malignancies.

Limitations

This evidence review has several limitations. We employed a best-evidence approach due to the number of prioritized diseases and published studies. Our review included the strongest available evidence (*ie,* comparative designs prioritized over single group studies). Nevertheless, we may have excluded studies with important data on the benefits and harms of RT for benign conditions. There was large variation in studies, and we were unable to investigate potential sources of heterogeneity of treatment effects. Sometimes it was unclear whether an adverse event was a negative consequence of the treatment. We sought to make minimal inference about adverse events and tried to stay true to how data were reported in the literature.

CONCLUSIONS

RT has been explored as a treatment (typically after conventional therapy fails) for a variety of benign diseases. There were few comparative studies on the use of RT for the treatment of the prioritized benign diseases. RT may reduce the occurrence of heterotopic ossification and improve function in plantar fasciitis. There was no significant difference in pain for people with keloids after RT compared to alternative treatments. We have low confidence in these conclusions due to methodological limitations of the studies, imprecision, and inconsistency. One RCT found pain, walking speed, step rate, and quality of life improved in people with Ledderhose disease after RT compared to sham RT (certainty of evidence was not evaluated). There was either insufficient (due to no comparative design, methodological limitations, inconsistent estimates) or no evidence for the effect RT on most other disease-related outcomes, side effects, or patient satisfaction, experience, or quality of life for people with keloids, pterygium, osteoarthritis, Peyronie’s disease, Dupuytren’s contracture, and hidradenitis suppurativa. Despite the gaps in the evidence, we found no indication that RT should not be used after conventional therapy fails for the 9 prioritized diseases. We assess that there is equipoise about the clinical utility of RT in patients failing conventional therapies. Future research should conduct comparative studies (RCTs or NRCS that control for confounders) for the use of RT for benign conditions.

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What is Low-Dose Radiotherapy (LDRT)?

Low-Dose Radiotherapy (LDRT) is a non-invasive, anti-inflammatory treatment that uses very low doses of radiation to reduce pain and improve joint function in patients with osteoarthritis (OA). This treatment has been used successfully in Europe and is gaining recognition in the United States for its effectiveness in managing OA symptoms, especially when other treatments have not provided sufficient relief.

How Does LDRT Work?

LDRT works by targeting the inflamed areas of the joint with precise, low doses of radiation. The radiation helps to reduce inflammation and modulate the immune response, leading to pain relief and improved mobility. Unlike higher doses of radiation used in cancer treatment, the low doses in LDRT focus specifically on reducing inflammation without significant risk of side effects.

Key Benefits of LDRT

- **Non-Invasive Treatment:** No surgery or needles involved; just targeted radiation therapy.
- **Outpatient Procedure:** Treatment involves six sessions, each lasting ~10 minutes.
- **High Success Rate:** Most patients experience significant pain relief after the initial course of treatment.
- **Re-treatment Option:** If necessary, the treatment can be repeated for sustained relief.
- **Covered by Insurance:** LDRT is covered by Medicare and many commercial insurance plans.

What to Expect During LDRT Treatment

- **Consultation**: Meet with the radiation doctor to discuss your condition and how LDRT can help.
- **Planning**: The treatment plan is customized for your specific joint(s) and level of discomfort.
- **Treatment Sessions:** (6) 10-minute outpatient treatments, with option to repeat treatment if needed. Majority of patients experience relief after initial course. Each session is quick and painless, similar to getting an X-ray.
- **Cost:** The treatments are covered by Medicare and many commercial insurances

Who Should Consider LDRT?

LDRT is recommended for patients with osteoarthritis who:

- Have not found relief with other treatments like physical therapy, medications, or injections.
- Interested in limiting or eliminating medication use for OA.
- Are looking for a non-surgical option to manage their OA pain.
- Are over 40 years old (to minimize any potential long-term risks).

Safety and Side Effects

LDRT is considered very safe with minimal side effects. The procedure does not affect healthy joints and has no known impact on future surgical procedures if needed. The risk of developing secondary conditions from LDRT is extremely low.

For more information or to schedule a consultation, contact our radiation oncology team at 310-825-9775.

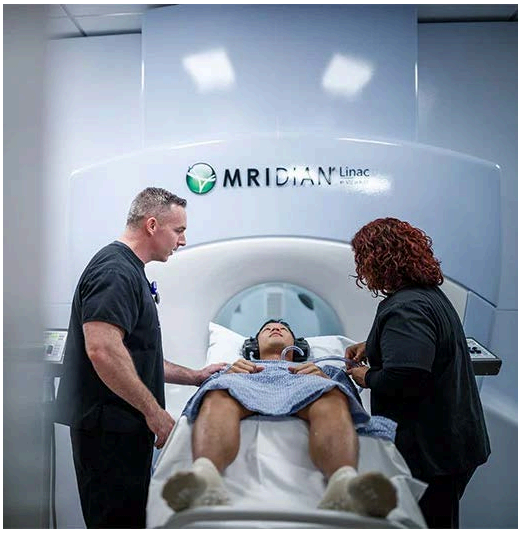
Radiation Therapy for Benign Diseases

July 18, 2023

Radiation therapy is well known for its use in the treatment of cancer. A large number of cancer patients receive radiation therapy at some point during their course of treatment, but radiation therapy may also be administered for benign diseases.

There are several benign conditions that are treated with radiation therapy. For these conditions, the level of evidence to recommend radiotherapy is strong and as such, health insurance providers consider radiotherapy treatment as medically necessary. However, in certain diagnoses, treatment is considered medically necessary when there is failure, intolerance, or contraindication to other established medical or surgical therapies.

Considered Medically Necessary



Desmoid Tumor

Desmoid tumor or aggressive fibromatosis is a non-malignant tumor that usually grows most commonly in the tissues of the abdomen, arms and legs. Although desmoid tumors are not malignant, they can be aggressive and grow into nearby organs or structures. Typical symptoms include a mass or swelling in the involved area, pain and functional impairment. Some desmoid tumors are slow growing and do not require immediate treatment. Otherwise, typical treatment includes surgery, chemotherapy, non-chemotherapy drugs and radiotherapy.

The goal of treatment is to eradicate the desmoid tumor and to improve the symptoms of mass, swelling, pain and functional and organ preservation.

Gynecomastia

Male breast enlargement is not a sign of breast cancer in men. Known as gynecomastia, breast growth in men can result from weight gain or taking certain types of medications. The first sign of gynecomastia is often a soft lump of fatty tissue that may be tender or sore. Just as women can develop noncancerous (benign) breast lumps, so can men. Examples of benign male breast lumps include cysts, lipomas, hematomas, Phyllodes tumors and fat necrosis.

Heterotopic Ossification (H.O.)

H.O. occurs when bone develops in the soft tissues. It usually happens after surgery or injury. There is a rare genetic disorder that predisposes to H.O. formation. Typical symptoms include hard bumps under the skin. This may be painful. If the bone formed is around a joint, it causes difficulty walking or functional impairment. Treatment includes surgery, steroid therapy, drug (non-steroidal) therapy and radiation therapy.

The goal of treatment is to improve or prevent functional impairment and pain, if present.

Dupuytren’s contracture

Dupuytren’s contracture is a type of fibromatosis that causes one or more fingers to bend toward the palm of the hand. These fingers cannot straighten. Knots form under the skin creating a thick cord that pulls the fingers toward the palm of the hand. The condition is painless and without treatment worsens over time. Typical symptoms include the formation of knots and then thick cords. The knots may be tender but not painful. Treatment consists of surgery, steroid injections, needling (a needle is inserted through the skin to break the cord that is contracting the finger), and radiation therapy.

The goal of the treatment is to release the contracted finger(s) and regain the functionality of the affected hand.

Ledderhose disease

Ledderhose disease is a type of fibromatosis that affects the plantar surface of the foot (bottom of the foot). The disease presents with small and hard growth in the bottom of the foot. The growths may be painful making walking difficult. Other symptoms include curling of the toes. Typical treatment includes steroid injections, oral medications, surgery and radiation therapy.

The goal of treatment is to improve walking with no pain or discomfort.

Pigmented villonodular synovitis (PVNS)

PVNS is a benign condition that arises from the soft connective tissue of the joints. Any joint can be affected but is most commonly found in the hip or knee. PVNS can be localized within one area of the joint or diffuse when the entire joint is involved. Typical symptoms include swelling of the affected joint, joint effusion (fluid within the joint), pain and difficulty walking. Treatment includes surgery, drug therapy and radiation therapy.

The goal of treatment is to improve pain, swelling and walking.

Considered Medically Necessary When There is Failure, Intolerance or Contraindication to Other Established Medical or Surgical Therapies

Degenerative skeletal and joint disorders

Degenerative diseases of the skeleton and joints include conditions such as osteoarthritis, plantar fasciitis and other inflammatory conditions affecting joints and tendons. These conditions create inflammation of the affected area which in turn causes pain, swelling, discomfort and functional impairment. Treatment includes oral anti-inflammatories, icing, weight loss, exercise, surgery, and radiation therapy.

The goal of treatment is the improvement of pain and functional impairment.

Keloid scar

A keloid is a raised thick scar that usually forms after skin injury. It can occur anywhere in the body. Typical symptoms are pain and discomfort. If the keloid is large and, depending on location, it can cause functional impairment. Treatment includes steroid injections, surgical removal and radiation therapy.

The goal of treatment is to improve symptoms of pain, discomfort and functional impairment.

Orbital pseudotumor

Orbital pseudotumor is swelling of the tissues behind the eyes. The eyes sit inside the orbits or eye sockets. Typical symptoms include pain, restricted eye movement, decreased eyesight, double vision, and proptosis or eye swelling protruding from the eye socket (proptosis). Treatment includes steroid therapy, surgery and radiation therapy. Mild cases may be observed without treatment and may resolve on their own.

The goal of treatment is to improve symptoms of pain, decreased eyesight, impaired eye motion, discomfort and proptosis.

If you'd like to refer a patient to receive radiation therapy at Moffitt Cancer Center, contact Dr. Jose Penagaricano at Jose.Penagaricano@moffitt.org or call 813-745-8830.

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ADVANCES IN ONCOLOGY

Low-Dose Radiation Therapy for Benign Musculoskeletal Disorders

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KEYWORDS

• Low-dose radiation therapy • Osteoarthritis • Plantar fasciitis • Benign musculoskeletal disorder

KEY POINTS

- Low-dose radiation therapy (LDRT) is experiencing a resurgence as a treatment for benign musculoskeletal disorders like osteoarthritis (OA) and plantar fasciitis (PF), due to its cost-effectiveness, non-invasiveness, and minimal side effects, with significant use in Europe and increasing interest in the United States
- LDRT exerts its therapeutic effects through complex biological mechanisms, primarily involving immune modulation, reduction of inflammatory cytokines, and alteration of cell adhesion and migration, contributing to its analgesic and anti-inflammatory properties.
- Clinical studies have demonstrated that LDRT provides significant pain relief and functional improvement in OA and PF, with benefits sometimes lasting beyond 24 months post-treatment, although some randomized trials have shown mixed results due to methodological limitations.
- Treatment planning for LDRT involves precise targeting of affected areas, utilizing modern imaging and delivery techniques to maximize efficacy while minimizing risks, with recommended doses typically 0.5 Gy per fraction for a total dose of 3 Gy.
- LDRT's potential benefits in refractory cases of OA and PF, along with ongoing research, suggest a growing role for this therapy.

INTRODUCTION

For over a century, radiotherapy (RT) has been employed on a global scale to treat benign conditions. There are at least 72 benign conditions treated with radiation over the years [1]. Since the discovery of X rays and their subsequent therapeutic application, our understanding of RT's benefits and risks has significantly evolved, such as RT has distinctive biologic effects at different doses. Conventional and hypofractionated RT, with its antiproliferative principles, are utilized in treating malignant and benign hyperproliferative disorders. Conversely, RT at doses of less than 1 Gy per fraction has displayed potent anti-inflammatory effects [2]. More recently, there has been a resurgence of the use of RT in treating benign musculoskeletal conditions primarily in the United States which has been widespread practice in

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ABBREVIATIONS	
3D	three-dimensional
DC	dendritic cell
EC	endothelial cell
IL-8	interleukin-8
LDRT	low-dose radiation therapy
MPH	macrophage
OA	osteoarthirits
OC	osteoclast
PF	plantar fasciitis
ROS	reactive oxygen species
RT	radiotherapy
TGF-β1	transforming growth factor-β1
TNF-α	tumor necrosis factor α
WHO	World Health Organization

some European countries. In this article, we will discuss the biological mechanism of how low-dose radiation therapy (LDRT) produces its effect in treating benign musculoskeletal diseases. Following this, we will discuss the data and clinical management of both osteoarthritis (OA) and plantar fasciitis (PF).

BIOLOGICAL MECHANISMS OF LOW-DOSE RADIOTHERAPY

In general, ionizing radiation can exert its effects either directly or indirectly. Direct effects can occur if charged particles, such as electrons, directly interact with components such as DNA, which is the most radiosensitive structure in our body, by causing single or double strand breaks. Likewise, DNA breakage can also occur indirectly via free radicals, such as reactive oxygen species (ROS), that can also damage DNA. While there is a higher chance of indirect damage than direct effects to critical cell components, as cells consist mostly of water, this also depends on the type of radiation, the administered dose, and the cellular composition [3–9].

While a lot of the single or double strand breaks are being repaired by a variety of repair mechanisms, there is a plethora of consequences, which can arise from these. Among these consequences are oxidative stress, cell death (apoptosis or necrosis), mitotic catastrophe, autophagy, cell cycle arrest, or senescence [6,8,9], that have also been observed after LDRT [10–12]. These so-called targeted effects of ionizing radiation are well known and, in general, also well understood. Nevertheless, there are also nontargeted effects that can arise as a result from the aforementioned targeted effects, that are often mediated by the immune system. These nontargeted effects arise mainly from cells that are not directly damaged by ionizing radiation. The so-called bystander effects are one form of nontargeted, indirect effects. Here, neighboring cells are modulated by cells that were directly exposed to and damaged by radiation either via cell-cell communication (gap junctions) or secreted factors [13,14].

The most important effects for the efficacy of low-dose radiotherapy (LDRT), however, seem to be immune-mediated effects. While the exact underlying mechanisms are not fully understood, a wide range of effects in immune cells, likely contributing to the observed analgesic effects [15], has been discovered over the past years [10,16,17]. With these discoveries, it is becoming clearer that a key aspect of LDRT's effectiveness likely involves the modulation of immune cell subsets and their activation status [10,18–21].

Endothelial Cells

Endothelial cells (ECs) play a crucial role in recruiting leukocytes to sites of inflammation. They further secrete various cytokines, chemokines, and adhesion factors when activated in an inflammatory state [22–24]. Post-LDRT, activated ECs exhibit a nonlinear dose-dependent regulation of secreted cytokines and their mRNA expression levels. Among these, especially interleukin-8 (IL-8), a cytokine that promotes proangiogenic and antiapoptotic effects, as well as EC migration into the extracellular matrix has shown to be modified by LDRT in a beneficial way [22]. When ECs were pretreated with tumor necrosis factor α (TNF-α) in order to simulate an inflammatory environment before LDRT, a transient reduction in the adhesion of peripheral blood mononuclear cells at doses of 0.3 to 0.6 Gy, accompanied by discontinuous expression of the anti-inflammatory cytokine transforming growth factor-β1 (TGF-β1), has been observed [15,16,21,24,25]. Further, LDRT also impacts ECs by reducing inducible nitric oxide synthase, leading to decreased EC-leukocyte interactions and the production of anti-inflammatory cytokines such as IL-10, along with reduced expression of various adhesion molecules.

The role of ROS and antioxidative factors in reducing leukocyte adhesion in primary human microvascular ECs after LDRT has also been examined: under laminar shear stress, mimicking physiologic conditions, LDRT resulted in increased mRNA expression of antioxidative factors (at 0.1, 0.5, and 1.0 Gy) and a reduction in ROS (at 0.1 Gy), as well as decreased leukocyte adhesion (at 0.1 Gy). However, no significant changes were observed

under static conditions following LDRT in a TNF-α-induced inflammatory state [15,26].

Leukocytes

Studies have shown that a cell line of immortalized human T cells (Jurkat cells) as well as peripheral blood lymphocytes exhibit increased adhesion to ECs after LDRT. This effect was accompanied by changes in ion channels and an increase in cell diameter for Jurkat cells at low radiation doses [27]. An interim analysis of the IMMO-LDRT01 trial including 125 patients, resembling 50% of expected patient numbers, found that among others, activation markers (cluster of differentiation 25 [CD25] and Human Leukocyte Antigen – DR isotype [HLA-DR]) on immune cells in peripheral blood were downregulated after LDRT [18,19]. In mouse models, the lowest observed effective dose to reduce leukocyte adhesion was found to be 0.3 Gy [15,28]. Abdominal irradiation of mice with 0.3 Gy, following an inflammatory stimulus, resulted in a significant reduction of adherent leukocytes in the LDRT-treated group for up to 48 hours postirradiation, with reduced leukocyte rolling ability observed up to 72 hours after LDRT [29]. In a murine model of OA, local LDRT at 0.5 Gy lead to altered immune cell levels in peripheral blood, whereas more pronounced effects were observed in the bone marrow, where there was a notable shift from inflammatory CD8+ T cells to anti-inflammatory CD4+ T cells in both the treated and the untreated leg [15,17].

Macrophages

Macrophages (MPHs), another cell type significantly involved in the inflammatory microenvironment and affected by LDRT, have also been studied extensively. Research on peritoneal MPHs isolated from Balb/c mice showed that LDRT reduced the release of inflammatory cytokines IL-1β and TNF-α depending on the dose [30]. Further studies examined the effects of LDRT (0.01–2.0 Gy) on activated peritoneal MPHs from Balb/c mice, revealing that while viability and phagocytosis were unaffected, migration was reduced, and chemotaxis was enhanced, potentially contributing to anti-inflammatory responses. An anti-inflammatory cytokine milieu was also observed [31]. Despite the ability of MPHs to perform proinflammatory or anti-inflammatory functions based on their phenotype, no significant phenotype alterations were found in bone marrow-derived MPHs exposed to LDRT doses of 0.1 to 2.0 Gy [32]. The ability of MPHs to stimulate other immune cells was also investigated: Here, it was found that activated MPHs cocultured with T cells showed reduced major histocompatibility complex class II (MHCII) surface expression at doses of 0.7 to 2.0 Gy. As MHCII is crucial for CD4 + T cell responses to inflammatory stimuli, CD4 + T cells exhibited reduced proliferation, potentially altering immune responses. Dendritic cells (DCs) coincubated with supernatants from irradiated MPHs showed reduced surface levels of CD40, a co-stimulatory molecule necessary for cell activation, but maintained their ability to induce CD4 + or CD8 + T cell proliferation, suggesting that while activated MPHs can modulate T cell-mediated immune reactions, they do not significantly alter DC-mediated T cell responses [15,31].

Osteoblasts and Osteoclasts

Next to immune cells, the bone is also affected by LDRT. However, unlike inflammatory factors, that can be found on a systemic level, the bone is only locally affected by LDRT [15,33]. Inflammatory mouse osteoblasts showed increased mineralization at 0.5 Gy and upregulated osteoclast (OC) regulatory factors at 0.5 and 1.0 Gy [33]. LDRT effects on ex vivo differentiated OCs from human blood, found no significant changes in apoptosis but reduced OC numbers, resorbing activity, and nuclei per OC, along with downregulation of NFATc1, a key transcription factor for osteoclastogenesis [34]. Similar effects were observed in OCs from an inflammatory mouse model, where OC numbers and resorptive activity were reduced at doses of 0.5 to 2.0 Gy [33]. In mice suffering from polyarthritis, a single local dose of 0.5 Gy led to decreased inflammatory areas and reduced bone erosions in the irradiated feet [15,33].

Cytokine Expression

Key effects observed after LDRT regarding cytokine expression include the overexpression of anti-inflammatory TGF-β1, reduced levels of inflammatory cytokines, and a decrease in inducible heat shock protein 70 (Hsp70), which collectively promote an anti-inflammatory response. Hsp70, recognized as a danger-associated molecular pattern, typically induces inflammation [16,18]. This has also been shown in in vivo settings, where for example, a mouse model of OA revealed that local LDRT at 0.5 Gy altered immune cells in peripheral blood and induced an anti-inflammatory shift in serum cytokines [18].

Taken together, there is a plethora of immune-modulating effects by LDRT that contribute to the observed analgesic and anti-inflammatory effects in OA and other degenerative diseases such as heel spur and PF.

OSTEOARTHRITIS AND THE USE OF LOW-DOSE RADIOTHERAPY

OA affects over 32 million Americans and is expected to continue rising as the population ages [35]. The World Health Organization (WHO) identifies OA as a rapidly increasing health condition and the second leading cause of disability in the United States [36]. OA presents significant challenges to affected patients, including the combined physical, psychological, and financial burdens, leading to decreased activity and quality of life. OA is the second-most costly health condition in the United States, responsible for over 4% of all total hospitalization costs.

OA is a progressive disorder that involves joint stiffness, pain, and mobility loss. It affects small and large joints, such as knees, hips, and hands. Driven by proinflammatory processes, the complex pathogenesis of OA leads to the degeneration of cartilage within joints, resulting in damage to bone, articular cartilage, menisci, ligaments, and synovium [37]. Several risk factors increase the likelihood of an OA diagnosis, including joint injury, anatomic factors such as joint alignment and shape, higher body mass index (BMI), older age, female gender, and family history of OA [38]. Current treatment for OA focuses on palliation of symptoms with the aim of restoring patient mobility and improving quality of life. Interventions vary among patients, and no universal guidelines exist for the specific sequencing or combination of interventions across all patients. First-line treatment for OA usually involves nonsteroidal anti-inflammatory drugs, following a trial of conservative management [39]. LDRT is likely an appropriate treatment option for refractory cases following exhaustion of other medical interventions or as noninvasive approach before the aggressive interventional treatments, such as joint replacement.

LDRT is a cost-effective, noninvasive treatment of OA with minimal side effects. LDRT as treatment for OA dates back to 1898, just 3 years after the discovery of X rays. LDRT provides symptomatic pain relief in 63% to 90% of patients [40]. There is no evidence that LDRT negatively impacts the function of healthy, noninflamed joints or that it could negatively influence a future surgical procedure. The use of LDRT for OA was commonplace in the United States until the 1980s, when improved pharmacologic treatment options became available and studies questioned the benefit of treatment versus placebo [41]. There is also potential concern for the very small risk of induced malignancy when using RT to treat a nonmalignant disease, which is traditionally viewed as a stochastic effect with increasing risk proportional to the increased dose. Although consideration is given to factors such as age, gender, and anatomic location of treatment, the exact risk of secondary malignancy from LDRT is challenging to define but is likely extremely low. In Germany, over one-third of all RT treatments are administered for benign diseases, including more than 15,000 OA patients annually [42], but in the United States the use of LDRT for OA is much less.

The specific mechanisms underlying pain relief after RT are complex and continue to be explored. Recent studies suggest that low doses of radiation exhibit anti-inflammatory efficacy by modulating several inflammatory pathways and cellular components, including ECs, leukocytes, and MPHs [43–45]. LDRT has been shown to significantly impact MPHs and modulate ECs, reducing leukocyte adhesion and cell migration. It also reduces the production of proinflammatory cytokines from irradiated leukocytes and increases their apoptosis [46–48].

Recent Clinical Research Data

In 2000, the German Society of Radiation Therapy and Oncology (DEGRO) scientific task group published the first national guideline and has since developed prospective trials to improve the available levels of evidence for RT to treat nonmalignant disorders. In 2018 and 2022, they published updated guidelines providing levels of recommendation based on the available evidence [49,50]. In the last decade, several review articles have been published, describing both retrospective and prospective data showing the efficacy of LDRT for OA pain and functional improvement. Notable recent reviews include high quality studies using modern LDRT techniques with current treatment planning recommendations [20,51].

LDRT benefits for OA include symptomatic pain relief in 60% to 90% of irradiated patients with almost no acute side effects [49]. Several studies, both retrospective and prospective, have demonstrated the efficacy of LDRT in providing significant pain relief and functional improvement in OA patients, with some reporting continued benefits beyond 24 months after treatment [52–58]. Some studies indicated a greater response using 0.5 Gy per fraction compared with 1 Gy per fraction [59,60].

Recent criticisms of LDRT for OA appeared from 2 randomized, double-blinded trials that tested LDRT versus placebo for pain relief and functional improvement of OA of the hand and knee joints. Both studies

reported no significant difference between the treated group and the sham group at 3, 6, and 12 months [61,62]. However, these studies have been criticized for low patient numbers (55 and 56 patients) causing insufficient power to show a difference between the groups and for not considering a second course of radiation therapy in initial nonresponders, which is often required to see benefits.

Clinical Set-up—Treatment Planning Overview

While consensus guidelines for treatment planning using LDRT for OA are not available, there are recommendations from the DEGRO 2018 update and a Spanish group, which includes a three-dimensional (3D) planning treatment atlas [50,63]. The target volume should encompass the entire affected joint and surrounding joint-related structures, with the prescription to the midpoint. Care should be taken to avoid overly restrictive treatment volumes that may limit efficacy [64]. For small joint treatments, radiation therapy energies include orthovoltage (100–200 kV) or 4 to 6 MV linear accelerator-based treatment with parallel opposed beams or a single beam. For large joints, radiation therapy energies include at least 4 MV for the knee and higher (10 MV or greater) for the hip. The recommended dose is 0.5 to 1.0 Gy per fraction for total doses of 3 to 6 Gy, delivered on nonconsecutive days 2 to 3 times per week. If the initial treatment does not provide adequate pain relief, retreatment can be considered 6 to 8 weeks later with the same dose and fractionation. The use of 3D imaging (CT or MRI) may help with target delineation. For treatment reproducibility, immobilization devices can be considered, such as extremity thermoplastic masks or vacuum-form custom-molded bags. A tissue-equivalent bolus material of 5 to 10 mm thickness should be considered if an inhomogeneous dose distribution is anticipated near the joint-surface interface. LDRT is generally recommended for patients aged 40 years and older to limit the small risk of RT-induced malignancy. RT fields are typically a parallel-opposed design and should include the entire affected joint and synovial sac with sufficient margin of at least 1 to 2 cm, including the bursa and joint-related structures (Fig. 1, eg, treatment fields). Fields that are too small may cause insufficient treatment response [64].

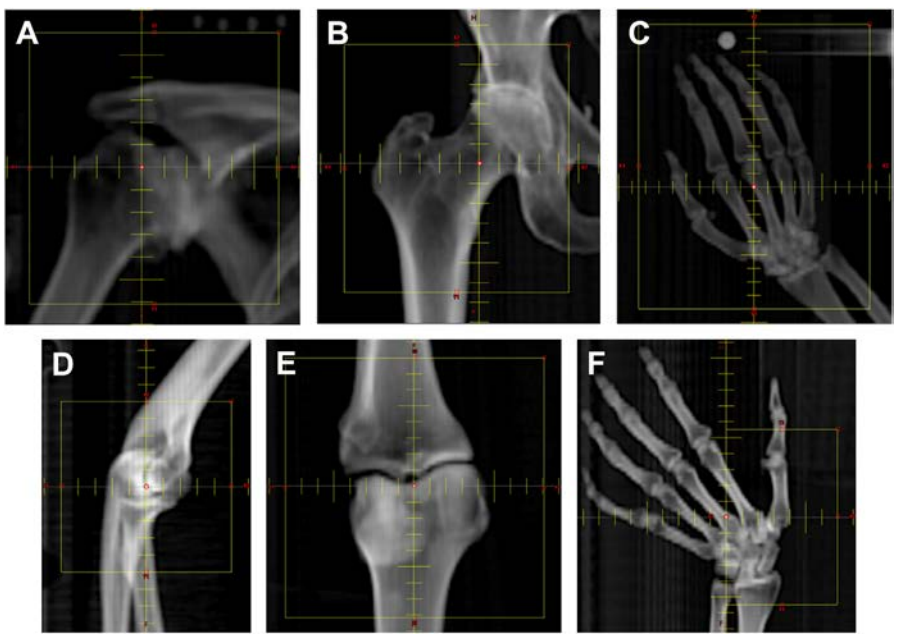

FIG. 1 LDRT fields for OA. Examples of parallel-opposed design with open fields to encompass affected joint with at least 1 to 2 cm surrounding margin. (**A**) Right shoulder [AP] 11 x 12 cm, (**B**) right hip [AP] 11 x 12 cm, (**C**) right hand whole [PA] 17 x 21 cm, (**D**) right elbow [AP] 10 x 10 cm, (**E**) left knee [AP] 16 x 16 cm, (**F**) right first metacarpal-carpal [AP] 7 x 11 cm.

PLANTAR FASCIITIS AND THE USE OF LOW-DOSE RADIOTHERAPY

PF is a common cause of heel pain, resulting from inflammation and degeneration of the plantar fascia, a thick band of tissue connecting the heel bone to the toes. The condition can be debilitating, significantly impacting quality of life and mobility. Conservative treatments such as rest, stretching, exercises, orthotics, analgesics, and corticosteroids are commonly employed as first-line therapies. However, these measures are not always effective, leaving many patients to seek alternative treatment options.

For those who do not respond to conservative management, RT has emerged as a promising treatment modality for PF. Several randomized multicenter trials have investigated the efficacy of RT, compared different dose fractionation schedules, and evaluated its long-term benefits. These studies have provided valuable insights into the potential of RT as a noninvasive and effective solution for managing this common debilitating condition.

Recent Clinical Research Data

In a randomized multicenter trial, Niewald and colleagues compared the effects of standard-dose RT (6 Gy in 6 fractions twice a week) with LDRT (0.5 Gy in 12 fractions given 3 times a week) in patients with painful heel spur (PF). The study demonstrated equivalence of both fractionation schemes. Earlier the same authors compared very low dose (0.6 Gy in 6 fractions of 0.1 Gy twice weekly) to standard dose (6 Gy in 6 fractions given twice weekly) which showed significant improvement with standard dose. These benefits were sustained at 48 weeks, with no reported acute or chronic side effects. The trial concluded that standard-dose RT is superior in providing long-term pain relief for PF [65].

Local steroid injection was compared with RT (6 Gy in 6 fractions over 2–3 weeks) in a prospective randomized trial of 128 patients with PF. The results indicated that RT had a significantly better analgesic effect, with 35% of patients achieving complete pain relief compared with 16% in the steroid injection group. The study highlighted the superior efficacy of RT over steroid injections for long-term pain management in PF [66].

Another randomized study of 130 patients, comparing LDRT (3.0 Gy in 6 fractions over 3 weeks) with high-dose RT (6.0 Gy in 6 fractions over 3 weeks). Both treatment groups exhibited significant pain reduction, with minimal toxicity and a high response rate at 6 months. The study underscored the effectiveness of both LDRT and high-dose RT in managing PF, suggesting that a lower total dose of 3 Gy might be the preferred dose for treatment [67].

Following these trials, Badakhshi and colleagues evaluated 171 patients treated with LDRT (3 Gy in 6 fractions) as this dose in the 2 prior trials had shown benefit. Results showed that 67.3% of patients reported no or mild pain 3 months post-treatment, and 61.4% maintained these results at a mean follow-up of 54 months. The study concluded that LDRT is effective and has minimal side effects, making it a viable treatment option for PF [68].

The collective evidence from these studies among others supports the use of RT as an effective treatment for PF, offering significant pain relief and improved quality of life with minimal side effects. RT demonstrated superior long-term efficacy compared with other conventional treatments such as corticosteroid injections.

Clinical Set-up—Treatment Planning Overview

The patient is positioned supine on the treatment table with the affected foot immobilized to ensure reproducibility. A computed tomography (CT) scan is obtained of the foot in the immobilization device to identify the treatment area accurately. The treatment plan is

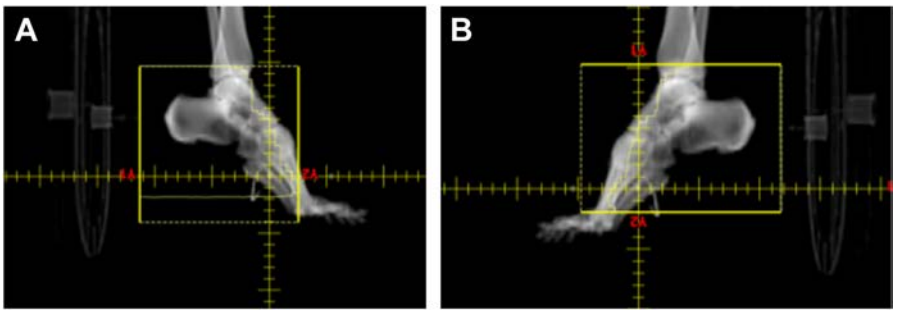

FIG. 2 LDRT fields for PF. Examples of parallel-opposed design with open fields to encompass joints with sufficient margin. (**A**) Left food medial 90° beam 20 x 20 cm. (**B**) Left foot lateral 270° beam 20 x 20 cm.

developed, generally using a parallel opposed pair of photon fields. The target volume includes the calcaneus and the plantar fascia to the tarso-metatarsal joints, to include tender areas with a 2-cm margin.

When treating with orthovoltage (200–250 kV photons), a clinical setup is performed without a CT scan. The patient is positioned supine, standing with a foot on stool, or in a prone position with the affected foot immobilized. Anatomic landmarks such as the calcaneus (heel bone), the medial and lateral malleoli (ankle bones), and the metatarsal heads (ball of the foot) are used to design the clinical treatment fields. The treatment field typically covers the plantar aspect of the foot, ensuring adequate coverage of the inflamed plantar fascia while sparing surrounding healthy tissues. The standard treatment protocol involves administering LDRT, typically 3 Gy in 6 fractions over 3 weeks.

Treatment is delivered using a parallel pair of lateral fields with 200 to 250 kV photons or 6 MV photons, [if a parallel pair, then dose prescribed to the midpoint] (Fig. 2, eg, treatment fields).

SUMMARY

LDRT is a cost-effective, noninvasive and painless treatment of benign musculoskeletal disorders like OA and PF with minimal side effects. It is an attractive therapeutic option for patients who do not want or cannot have surgery. We now have a better understanding of the mechanisms of LDRT in benign musculoskeletal disorders. Studies of LDRT have reported substantial reductions in pain scores and improvements in functionality, with some benefits persisting beyond 24 months after treatment completion. Randomized controlled trials have demonstrated its effectiveness in reducing pain and improving quality of life for patients unresponsive to conservative treatments in both OA and PF. There are ongoing trials for OA comparing LDRT to placebo that will provide more information regarding this treatment effectiveness. LDRT has shown to provide pain relief and functional improvement in most patients.

Despite its higher utilization in clinical use and investigation in other countries, the use of LDRT in the treatment of benign musculoskeletal conditions declined in the United States in 1980s with newer systemic anti-inflammatory therapies. More recently utilization of LDRT is having a resurgence in the United States. To improve the utility of LDRT for benign musculoskeletal disorders, increased collaboration among clinical specialties, such as Rheumatology, Orthopedics, and Pain Specialists, can help clarify the appropriate indications for LDRT. Further utilization and investigation into the potential role of LDRT in the treatment of benign musculoskeletal conditions using modern techniques is recommended.

Pearl: Immune Modulation

LDRT's effectiveness in treating conditions like osteoarthritis and plantar fasciitis is largely due to its ability to modulate immune responses, reducing inflammation and providing analgesic effects. Understanding the immune pathways involved can help optimize patient selection and treatment outcomes, which is an active area of research.

Pearl: Patient Selection

LDRT is particularly beneficial for patients who have not responded to conservative treatments or who are not candidates for surgery. LDRT offers a non-invasive alternative with minimal side effects, making it suitable for older patients or those with comorbidities. Patients with mild to moderate grade OA tend to respond better than those with severe grade OA, but all can be considered for LDRT.

Pitfall: Dose and Fractionation

Careful attention must be paid to the dose and fractionation schedule. Evidence suggests that lower doses (around 0.5 Gy per fraction) may be more effective than higher doses, and improper dosing could reduce efficacy or increase risks.

Pitfall: Risk of Secondary Malignancy

Although the risk is very low, clinicians should consider the potential for radiation-induced malignancy, especially in younger patients. Appropriate patient counseling and risk assessment are essential before initiating LDRT.

Pearl: Collaborating with Specialists

Collaboration with rheumatologists, orthopedists, and pain specialists can enhance patient care by ensuring comprehensive treatment plans and clarifying indications for LDRT use, thereby optimizing patient outcomes.

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DISCLOSURE

None.

REFERENCES

[1] Roberge D, Donaldson SS. Radiation therapy of benign diseases. Springer Nature Switzerland AG; 2023.

[2] Royo LT, Redondo GA, Pianetta MÁ, et al. Low-dose radiation therapy for benign pathologies. Rep Practical Oncol Radiother 2020;25(2):250–4.
[3] Reisz JA, Bansal N, Qian J, et al. Effects of ionizing radiation on biological molecules—mechanisms of damage and emerging methods of detection. Antioxidants Redox Signal 2014;21(2):260–92.
[4] Islam MT. Radiation interactions with biological systems. Int J Radiat Biol 2017;93(5):487–93.
[5] Nikitaki Z, Mavragani IV, Laskaratou DA, et al. Systemic mechanisms and effects of ionizing radiation: a new 'old' paradigm of how the bystanders and distant can become the players. Semin Cancer Biol; 2016. p. 37–8.
[6] Dagar G, Gupta A, Shankar A, et al. The future of cancer treatment: combining radiotherapy with immunotherapy. Front Mol Biosci 2024;11:1409300.
[7] Frey B, Rückert M, Deloch L, et al. Immunomodulation by ionizing radiation—impact for design of radio-immunotherapies and for treatment of inflammatory diseases. Immunol Rev 2017;280(1):231–48.
[8] Deloch L, Derer A, Hartmann J, et al. Modern radiotherapy concepts and the impact of radiation on immune activation. Front Oncol 2016;6:141.
[9] Derer A, Deloch L, Rubner Y, et al. Radio-immunotherapy-induced immunogenic cancer cells as basis for induction of systemic anti-tumor immune responses–pre-clinical evidence and ongoing clinical applications. Front Immunol 2015;6:505.
[10] Lumniczky K, Impens N, Armengol G, et al. Low dose ionizing radiation effects on the immune system. Environ Int 2021;149:106212.
[11] Falcke SE, Rühle PF, Deloch L, et al. Clinically relevant radiation exposure differentially impacts forms of cell death in human cells of the innate and adaptive immune system. Int J Mol Sci 2018;19(11). https://doi.org/10.3390/ijms19113574.
[12] Zahnreich S, Rösler HP, Schwanbeck C, et al. Radiation-induced DNA double-strand breaks in peripheral leukocytes and therapeutic response of heel spur patients treated by orthovoltage X-rays or a linear accelerator. Strahlenther Onkol 2020;196(12):1116–27.
[13] Lyng FM, Azzam EI. Abscopal effects, clastogenic effects and bystander effects: 70 Years of non-targeted effects of radiation. Radiat Res 2024;202(2):355–67.
[14] Buonanno M, Gonon G, Pandey BN, et al. The intercellular communications mediating radiation-induced bystander effects and their relevance to environmental, occupational, and therapeutic exposures. Int J Radiat Biol 2023;99(6):964–82.
[15] Niewald M, Moumeniahangar S, Müller LN, et al. 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 2024;200(2):134–42.
[16] Weissmann T, Rückert M, Putz F, et al. Low-dose radiotherapy of osteoarthritis: from biological findings to clinical effects-challenges for future studies. Strahlenther Onkol 2023;199(12):1164–72.
[17] Rödel F, Frey B, Manda K, et al. Immunomodulatory properties and molecular effects in inflammatory diseases of low-dose x-irradiation. Front Oncol 2012;2:120.
[18] Weissmann T, Rückert M, Zhou JG, et al. 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 2021;12:777792.
[19] Donaubauer AJ, Becker I, Weissmann T, et al. Low dose radiation therapy induces long-lasting reduction of pain and immune modulations in the peripheral blood - interim analysis of the IMMO-LDRT01 trial. Front Immunol 2021;12:740742.
[20] Dove APH, Cmelak A, Darrow K, et al. The use of low-dose radiation therapy in osteoarthritis: a review. Int J Radiat Oncol Biol Phys 2022;114(2):203–20.
[21] Staruch M, Gomez S, Rogers S, et al. Low-dose radiotherapy for greater trochanteric pain syndrome-a single-centre analysis. Strahlenther Onkol 2024;200(2):128–33.
[22] Schröder S, Juerß D, Kriesen S, et al. Immunomodulatory properties of low-dose ionizing radiation on human endothelial cells. Int J Radiat Biol 2019;95(1):23–32.
[23] Mantovani A, Bussolino F, Dejana E. Cytokine regulation of endothelial cell function. FASEB J 1992;6(8):2591–9.
[24] Speyer CL, Ward PA. Role of endothelial chemokines and their receptors during inflammation. J Invest Surg 2011;24(1):18–27.
[25] Roedel F, Kley N, Beuscher HU, et al. Anti-inflammatory effect of low-dose X-irradiation and the involvement of a TGF-beta1-induced down-regulation of leukocyte/endothelial cell adhesion. Int J Radiat Biol 2002;78(8):711–9.
[26] Eckert D, Rapp F, Tsedeke AT, et al. ROS- and radiation source-dependent modulation of leukocyte adhesion to primary microvascular endothelial cells. Cells 2021;11(1). https://doi.org/10.3390/cells11010072.
[27] Voos P, Fuck S, Weipert F, et al. Ionizing radiation induces morphological changes and immunological modulation of Jurkat cells. Front Immunol 2018;9:922.
[28] Torres Royo L, Antelo Redondo G, Arquez Pianetta M, et al. Low-Dose radiation therapy for benign pathologies. Rep Practical Oncol Radiother 2020;25(2):250–4.
[29] Arenas M, Gil F, Gironella M, et al. Time course of anti-inflammatory effect of low-dose radiotherapy: correlation with TGF-beta(1) expression. Radiother Oncol 2008;86(3):399–406.
[30] Frischholz B, Wunderlich R, Rühle PF, et al. Reduced secretion of the inflammatory cytokine IL-1β by stimulated peritoneal macrophages of radiosensitive Balb/c mice after exposure to 0.5 or 0.7 Gy of ionizing radiation. Autoimmunity 2013;46(5):323–8.
[31] Wunderlich R, Rühle PF, Deloch L, et al. Ionizing radiation reduces the capacity of activated macrophages to induce T-cell proliferation, but does not trigger dendritic

cell-mediated non-targeted effects. Int J Radiat Biol 2019; 95(1):33–43.
[32] Deloch L, Fuchs J, Rückert M, et al. Low-dose irradiation differentially impacts macrophage phenotype in dependence of fibroblast-like synoviocytes and radiation dose. J Immunol Res 2019;2019:3161750.
[33] Deloch L, Derer A, Hueber AJ, et al. Low-dose radiotherapy ameliorates advanced arthritis in hTNF-α tg mice by particularly positively impacting on bone metabolism. Front Immunol 2018;9:1834.
[34] Eckert D, Rapp F, Tsedeke AT, et al. Modulation of differentiation and bone resorbing activity of human (pre-) osteoclasts after X-ray exposure. Front Immunol 2022; 13:817281.
[35] CDC. 2024. Available at: https://www.cdc.gov/arthritis/osteoarthritis/?CDC_AAref_Val=https://www.cdc.gov/arthritis/types/osteoarthritis.htm.
[36] Sebbag E, Felten R, Sagez F, et al. The world-wide burden of musculoskeletal diseases: a systematic analysis of the World Health Organization Burden of Diseases Database. Ann Rheum Dis 2019;78(6):844–8.
[37] Chow YY, Chin K-Y. The role of inflammation in the pathogenesis of osteoarthritis. Mediat Inflamm 2020; 2020(1):8293921.
[38] Blagojevic M, Jinks C, Jeffery A, et al. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthr Cartil 2010;18(1):24–33.
[39] Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Rheumatol 2020;72(2):220–33.
[40] Hildebrandt G, Kamprad F-H. Degenerative joint disease activated osteoarthrosis deformans: hip, knee, shoulder and other joints. Radiotherapy for Non-Malignant Disorders. Berlin, Heidelberg: Springer-Verlag; 2008. p. 317–32.
[41] Trott K-R, Kamprad F-H. Side effects and long-term risks from radiotherapy of non-malignant diseases. Radiotherapy for Non-Malignant Disorders. Berlin, Heidelberg: Springer-Verlag; 2008. p. 29–43.
[42] Kriz J, Seegenschmiedt HM, Bartels A, et al. Updated strategies in the treatment of benign diseases-a patterns of care study of the German cooperative group on benign diseases. Adv Radiat Oncol 2018;3(3):240–4. https://doi.org/10.1016/j.adro.2018.02.008.
[43] Hildebrandt G, Seed MP, Freemantle CN, et al. Mechanisms of the anti-inflammatory activity of low-dose radiation therapy. Int J Radiat Biol 1998;74(3):367–78.
[44] Calabrese E, Dhawan G, Kapoor R, et al. Radiotherapy treatment of human inflammatory diseases and conditions: optimal dose. Hum Exp Toxicol 2019;38(8): 888–98.
[45] Rödel F, Keilholz L, Herrmann M, et al. Radiobiological mechanisms in inflammatory diseases of low-dose radiation therapy. Int J Radiat Biol 2007;83(6):357–66.
[46] Trott K-R, Kamprad F. Radiobiological mechanisms of anti-inflammatory radiotherapy. Radiother Oncol 1999; 51(3):197–203.
[47] Arenas M, Gil F, Gironella M, et al. Anti-inflammatory effects of low-dose radiotherapy in an experimental model of systemic inflammation in mice. Int J Radiat Oncol Biol Phys 2006;66(2):560–7.
[48] Lödermann B, Wunderlich R, Frey S, et al. Low dose ionising radiation leads to a NF-κB dependent decreased secretion of active IL-1β by activated macrophages with a discontinuous dose-dependency. Int J Radiat Biol 2012;88(10):727–34.
[49] Mücke R, Micke O, M Seegenschmiedt, Strahlentherapie gutartiger Erkrankungen. Fachgruppenspezifische evidenzbasierte S2e-Leitlinie der Deutschen, Gesellschaft für Radioonkologie (DEGRO) (2018). https://www.degro.org/wp-content/uploads/2018/11/S2-Leitlinie-Strahlentherapie-gutartiger-Erkrankungen-update-2018-Endversion.pdf.
[50] Mücke RMO, Seegenschmiedt MH, Kriz J, et al. DEGRO-AG "radiotherapie gutartiger erkrankungen" version 3.0. 2024. Available at: https://www.degro.org/wp-content/uploads/2022/12/20221130-Strahlentherapie-gutartiger-Erkrankungen-Version-3.0.pdf.
[51] Javadinia SA, Nazeminezhad N, Ghahramani-Asl R, et al. Low-dose radiation therapy for osteoarthritis and enthesopathies: a review of current data. Int J Radiat Biol 2021; 97(10):1352–67.
[52] Rühle A, Tkotsch E, Mravlag R, et al. Low-dose radiotherapy for painful osteoarthritis of the elderly: a multicenter analysis of 970 patients with 1185 treated sites. Strahlenther Onkol 2021;197(10):895–902.
[53] Álvarez B, Montero Á, Alonso R, et al. Low-dose radiation therapy for hand osteoarthritis: shaking hands again? Clin Transl Oncol 2022;24(3):532–9.
[54] Donaubauer A-J, Becker I, Weissmann T, et al. Low dose radiation therapy induces long-lasting reduction of pain and immune modulations in the peripheral blood–interim analysis of the IMMO-LDRT01 trial. Front Immunol 2021;12:740742.
[55] Hautmann MG, Rechner P, Neumaier U, et al. Radiotherapy for osteoarthritis—an analysis of 295 joints treated with a linear accelerator. Strahlenther Onkol 2020;196:715–24.
[56] Juniku N, Micke O, Seegenschmiedt MH, et al. Radiotherapy for painful benign skeletal disorders: results of a retrospective clinical quality assessment. Strahlenther Onkol 2019;195(12):1068.
[57] Hautmann MG, Hipp M, Neumaier U, et al. Radiotherapy for osteoarthritis of the ankle and tarsal joints—analysis of 66 joints. Strahlenther Onkol 2020;196:569–75.
[58] Hautmann MG, Rechner P, Hipp M, et al. Re-irradiation for osteoarthritis—retrospective analysis of 217 joints. Strahlenther Onkol 2019;195(12):1060–7.
[59] Abdus-Salam AA, Olabumuyi AA, Jimoh MA, et al. The role of radiation treatment in the management of

inflammatory musculoskeletal conditions: a revisit. Radiat Oncol J 2020;38(3):151.
[60] Donaubauer A-J, Zhou J-G, Ott OJ, et al. Low dose radiation therapy, particularly with 0.5 Gy, improves pain in degenerative joint disease of the fingers: results of a retrospective analysis. Int J Mol Sci 2020;21(16):5854.
[61] Mahler EA, Minten MJ, Leseman-Hoogenboom MM, et al. Effectiveness of low-dose radiation therapy on symptoms in patients with knee osteoarthritis: a randomised, double-blinded, sham-controlled trial. Ann Rheum Dis 2019; 78(1):83–90.
[62] Minten M, Leseman-Hoogenboom M, Kloppenburg M, et al. Lack of beneficial effects of low-dose radiation therapy on hand osteoarthritis symptoms and inflammation: a randomised, blinded, sham-controlled trial. Osteoarthr Cartil 2018;26(10):1283–90.
[63] Alvarez B, Montero A, Hernando O, et al. Radiotherapy CT-based contouring atlas for non-malignant skeletal and soft tissue disorders: a practical proposal from Spanish experience. Br J Radiol 2021;94(1124):20200809.
[64] Kaltenborn A, Bulling E, Nitsche M, et al. The field size matters: low dose external beam radiotherapy for thumb carpometacarpal osteoarthritis: importance of field size. Strahlenther Onkol 2016;192(8):582–8.
[65] Niewald M, Seegenschmiedt MH, Micke O, et al. Randomized, multicenter trial on the effect of radiation therapy on plantar fasciitis (painful heel spur) comparing a standard dose with a very low dose: mature results after 12 months' follow-up. Int J Radiat Oncol Biol Phys 2012; 84(4):e455–62.
[66] Canyilmaz E, Canyilmaz F, Aynaci O, et al. Prospective randomized comparison of the effectiveness of radiation therapy and local steroid injection for the treatment of plantar fasciitis. Int J Radiat Oncol Biol Phys 2015; 92(3):659–66.
[67] Heyd R, Tselis N, Ackermann H, et al. Radiation therapy for painful heel spurs. Strahlenther Onkol 2007;183(1):3.
[68] Badakhshi H, Buadch V. Low dose radiotherapy for plantar fasciitis. Treatment outcome of 171 patients. Foot 2014; 24(4):172–5.

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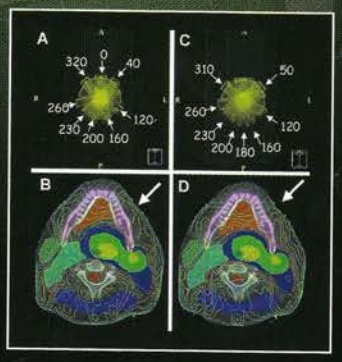

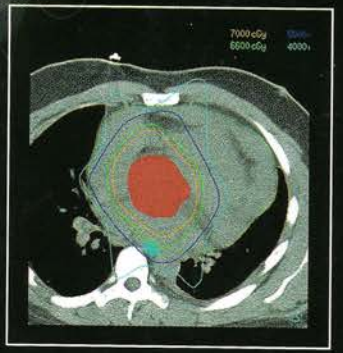

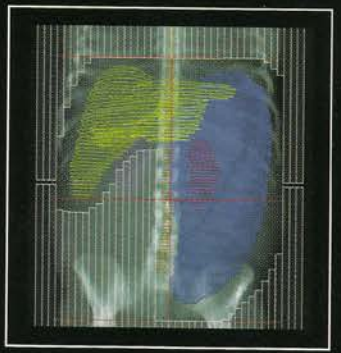

Table 89.13 RADIOLOGIC STAGING OF ARTHROSIS ACCORDING TO KELLGREN AND LAWRENCE (1957)

Stage	Description
I	No osteophytes No narrowing of joint space Low subchondral sclerosis
II	Commencing formation of osteophytes Slight narrowing of joint space Moderate irregularities of joint contours and surfaces
III	Pronounced formation of osteophytes Clear narrowing of joint space Clear irregularities of joint contours and surfaces Subchondral cyst formation
IV	Pronounced narrowing of joint space up to the point of complete destruction Deformation and necrosis of the respective counterjoint

and "stress capacity" of the joint, causing wear and typical degeneration of the joint. The course is enhanced by congenital (dysplasia) and acquired (deformity, axial deviation, trauma) disorders. Some metabolic dysfunctions may favor development of arthrosis as well (e.g., diabetes mellitus or hyperuricemia).

Localized pain is the key symptom of reactive synovialitis caused by chronic stress through cartilage abrasion (activated arthrosis). This is followed by irritation of joint capsule and tendon attachment sites (periarthrosis) causing joint-dependent muscle tension. Subjective symptoms and radiographic findings are often incongruent. Functional loss has an impact on professional and leisure activities and reduces quality of life. Objective findings are joint reddening, hyperthermia, and swelling due to effusion, joint grinding, deformity, reduced mobility, and typical radiologic signs (Fig. 89.8).

Nonradiotherapeutic Treatment

Prevention and early recognition are crucial; prearthrotic changes (axial malposition, incongruent joint surfaces) are treated with corrective osteotomy. Noninvasive measures are described in 6.1. Invasive measures include arthroscopic lavage, debridement of inflammatory synovial changes, and smoothing of chondral joint surface. Autologous cartilage replacement to repair damaged chondral surfaces is possible in individual cases for small joint areas. Partial or total joint replacement with an artificial implant is the last option, but the patency rate of implants is only 10 to 15 years.

Radiotherapeutic Options

Low-dose RT is indicated if noninvasive measures have failed and surgery is not compulsory. It may reduce pain and pain-related dysfunction, but does not remove pathomorphologic changes. The affected joints of the upper (shoulder, elbow, thumb, fingers) and lower (hip, knee, ankle) extremity are irradiated via enface, lateromedial or ventrodorsal opposing fields using the orthovolt (150 to 200 kV/20 mA, 4-mm Al filter) or linear accelerator low-energy photons (<6 MV). The dose reference point is always located in the center of the joint (for opposing field setup)

RT can lead to primary freedom from pain and secondary to improved joint function. Numerous uncontrolled studies have been published and almost all have reported long-term pain relief and functional gain in 50% to 75%. A pain record of >2 years and objective findings like joint grinding, deformity, radiologic OA stage IV, are indicators of unfavorable prognosis.

In a monocenter study, 103 painful joints received 6 to 12 Gy low-dose RT after failing available conservative treatments. Established orthopaedic scores were applied for response evaluation. A total of 63% joints improved significantly in long-term follow-up (19% free of symptoms; 44% pain relief, and functional gain of >50%). It was concluded that RT is a very effective treatment option for pain reduction in refractory OA compared with other methods. Because of very low risk of side effects and low costs, RT provides an excellent alternative to conventional conservative treatments and in case of inoperability. Joint replacement surgery might be delayed or completely avoided in individual cases. Results of RT and a literature review have been provided by Keilholz et al. (76).

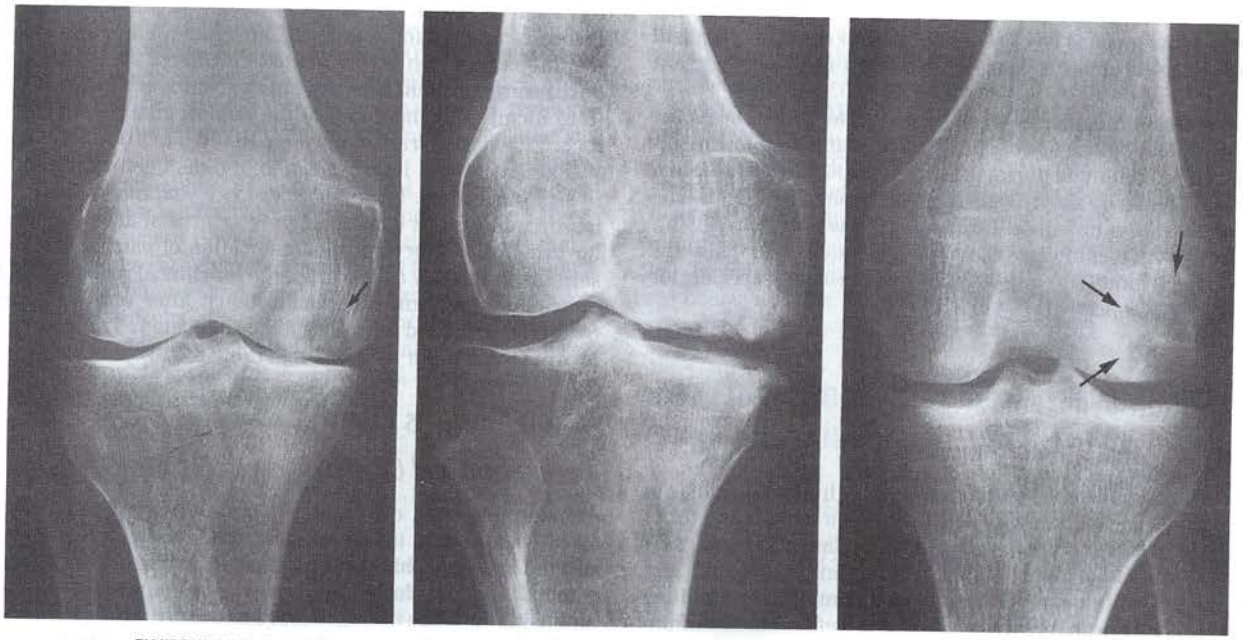

FIGURE 89.8. Typical signs of arthrosis: narrowing of joint space **(left,** *arrow***)**, incongruency and sclerosis of joint surfaces **(center)**, and subchondral cysts **(right,** *arrows***)**.