7.01.179	Low-Dose Radiotherapy for Non-Oncologic Indications		
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Policy Statement

I. Low-dose radiotherapy is considered **investigational** for the treatment of osteoarthritis.

II. Low-dose radiotherapy is considered **investigational** for the treatment of plantar fasciitis.

III. Adjuvant low-dose radiotherapy may be considered **medically necessary** for the prevention of heterotopic ossification following surgery in individuals who are determined to be at high risk for the development of heterotopic ossification (see Policy Guidelines section).

IV. Adjuvant low-dose radiotherapy may be considered **medically necessary** following surgical excision for the treatment of keloids (see Policy Guidelines section).

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Individuals at a high risk for heterotopic ossification may present with one or more risk factors:

- Age over 65 years
- Arthroplasty of the hip, knee, elbow, and shoulder
- Deep vein thrombosis
- Diffuse idiopathic skeletal hyperostosis
- Long bone fractures
- Male gender
- Paget's disease
- Pre-existing rheumatologic conditions such as ankylosing spondylitis
- Pressure ulcers
- Prior episodes of heterotopic ossification
- Prior injury to the same area
- Severity of injury
- Spasticity
- Spinal canal stenosis
- Traumatic brain injury

Individuals with functionally impairing keloids may present with:

- Keloids near eyes, mouth, or ears that impede vision, speech, facial expressions, communication, respiration, eating, or swallowing
- Keloids on the trunk or extremities limiting range of motion or manual dexterity
- Keloid formation that distorts nearby body parts
- Keloids that cause physical, social, or psychological impairment
- Keloids that cause chronic pain or intractable pruritus
- Keloids that compromise skin integrity
- Keloids treated as part of a comprehensive reconstructive plan following cutaneous trauma

The evidence base for the use of low-dose radiotherapy for prevention of keloid recurrence reports the initiation of treatment beginning immediately post-surgery to 48 hours post-surgery. Total

radiation doses ranged from 7 Gy to 20 Gy and were delivered as a single dose or as up to 4 fractions daily or weekly.

Coding
See the Codes table for details.

Description

Low-dose radiation therapy (LDRT) for non-oncologic indications is a non-invasive treatment modality that uses radiation at lower doses than traditional cancer radiotherapy. Targeted LDRT is proposed to modulate cellular processes in benign conditions by leveraging radiation's anti-inflammatory and anti-proliferative effects to inhibit abnormal tissue growth and remodeling after conventional therapies have failed.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

The Food and Drug Administration (FDA) regulates medical devices, including radiotherapy products such as linear accelerators (product codes IYE, JAD, KPQ, and MUJ) and brachytherapy (product code KXK), ensuring their safety and effectiveness before market approval. This oversight includes setting manufacturing quality control standards and conducting post-market surveillance to monitor ongoing safety of these devices. The most common modalities of low-dose radiotherapy used for the treatment or prevention of heterotopic ossification, keloids, osteoarthritis, and plantar fasciitis typically involve external beam radiation therapy. This approach often utilizes X-rays or electron beams, delivered in fractionated doses over multiple sessions, with the specific energy levels and treatment protocols tailored to each condition and patient.

Rationale

Background
Low-Dose Radiotherapy
Radiation therapy (RT) is a standard treatment for many types of cancer. Low-dose RT (LDRT), doses of less than 1 Gray (Gy) per fraction, has been shown to have anti-inflammatory effects and has been explored as a treatment for a variety of noncancerous inflammatory and degenerative musculoskeletal, orthopedic, and soft tissue diseases, typically after conventional medical treatments fail.[1,] These indications include the use of prophylactic LDRT for the prevention of heterotopic

ossification (HO) after total hip arthroplasty (THA) or fracture and keloids after surgical resection, as well as the treatment of painful inflammatory diseases such as osteoarthritis (OA) and plantar fasciitis. LDRT is commonly used for benign inflammatory and degenerative musculoskeletal diseases in Germany, where an estimated 10-30% of RT is applied to individuals with noncancerous conditions. However, in the United States, LDRT is infrequently used to treat benign conditions. For benign conditions, treatment schedules often involve multiple fractions, such as 0.5 Gy twice weekly for 3 weeks or 1.0 Gy once weekly for 6 weeks, with total doses generally below 20 Gy. Various types of ionizing radiation may be used and are most commonly delivered externally via photon or heavier particle beams. This therapeutic approach has a long history, with renewed interest in recent decades due to an improved understanding of LDRT's biological effects and advancements in radiation delivery techniques.[2,] Current research focuses on optimizing dose fractionation, understanding long-term outcomes, and exploring new treatment indications.

Osteoarthritis

OA is the most common form of arthritis globally, affecting approximately 3.3-3.6% of the population worldwide and causing moderate to severe disability in 43 million people. It can be classified as primary (idiopathic) or secondary (due to a predisposing condition).[2,] Management includes non-pharmacologic approaches (e.g., exercise, weight loss) and pharmacologic interventions (e.g., acetaminophen, NSAIDs, intra-articular corticosteroid injections). For severe cases unresponsive to conservative measures, surgical options like joint replacement may be considered. OA is characterized by joint pain, stiffness, and locomotor restriction, but its presentation and progression vary greatly between individuals. Diagnosis is primarily clinical, based on symptoms and physical examination findings, with imaging studies used for confirmation and staging. The pathophysiology involves an interplay of risk factors, mechanical stress, and abnormal joint mechanics, leading to pro-inflammatory markers and proteases that mediate joint destruction. Management includes non-pharmacologic approaches (e.g., exercise, weight loss) and pharmacologic interventions (e.g., acetaminophen, NSAIDs, intra-articular corticosteroid injections). For severe cases unresponsive to conservative measures, surgical options like joint replacement may be considered. In some settings, LDRT has been explored as a treatment option for OA, typically involving the application of radiation to affected joints in multiple fractions over a short period.[3,]

Plantar Fasciitis

Plantar fasciitis is a common cause of heel pain resulting from degenerative irritation of the plantar fascia and surrounding structures. It affects approximately 1 million patients annually in the United States, with peak incidence between ages of 40 to 60 years.[4,] Diagnosis is primarily clinical, based on localized heel pain that is worst with initial steps in the morning or after prolonged rest. While imaging is not typically needed for diagnosis, ultrasound may reveal thickening and heterogeneity of the plantar fascia. Treatment generally begins with conservative measures such as rest, NSAIDs, stretching exercises, orthotics, and night splints. For recalcitrant cases, more advanced therapies like extracorporeal shock wave therapy, botulinum toxin injections, platelet-rich plasma, prolotherapy, or corticosteroid injections have been considered. Surgery is reserved as a last resort for cases that fail to respond to at least 6-12 months of non-operative management. LDRT represents another alternative to surgical treatment for plantar fasciitis and typically involves the application of fractionated doses of radiation to the affected area. Total doses generally range from 3 to 6 Gy, delivered in fractions of 0.5 to 1 Gy, 2-3 times per week. The mechanism of action is thought to involve anti-inflammatory effects, including decreased expression of certain enzymes and reduction in the adhesion of peripheral blood mononuclear cells.[5,]

Keloid

Keloids are benign raised scars that form due to excessive tissue proliferation and collagen deposition during abnormal wound healing. They result from pathological wound healing and excess dermal fibrosis, characterized by an imbalance in the destruction and deposition of extracellular matrix.[6,] Keloids can appear months to years after injury and continue to grow indefinitely without regression, expanding beyond the original borders of injury and invading surrounding tissue. They

affect 30-90% of patients, with higher prevalence in darker-skinned individuals (African-Americans, Hispanics, and Asians) and those with a family history. Facial keloids, particularly those near the eyes, nose, or mouth, may impair vision, speech, and facial expressions, while keloids on the trunk or extremities can restrict range of motion and dexterity, potentially diminishing quality of life.[7,] Keloids can also cause varying degrees of pain, often correlating with the keloid's size, growth rate, and depth of tissue involvement. When located in high-tension areas, over joints, or in regions with dense nerve innervation, the pain associated with keloids may be severe and impede daily activities. While numerous treatment options exist, including intra-lesional corticosteroid injections, pressure therapy, and cryotherapy, surgical excision followed by immediate adjunctive postoperative LDRT has emerged as an effective approach to recurrence prevention. Radiation is typically indicated for recurrent keloids or those at high risk of recurrence, such as marginal resections, wider spread, and unfavorable locations. Treatment usually targets the scar plus a 1 cm radial margin to a depth of 0.5-1 cm. Electrons are the most commonly used modality, though superficial x-rays and brachytherapy are also options. The recommended total radiation dose ranges from 12 to 20 Gy.

Heterotopic Ossification

Heterotopic ossification (HO) is the abnormal formation of mature, lamellar bone in extraskeletal soft tissues where bone does not normally exist.[8,] It is a common complication in rehabilitation settings, affecting patients with burns, stroke, spinal cord injury (SCI), traumatic amputation, joint replacement, and traumatic brain injury (TBI). The exact incidence varies by population, with rates as high as 90% in high-risk total hip arthroplasty (THA) patients, 20-30% in adult SCI patients, and 10-20% in adult TBI patients. The hip is the most commonly affected site for HO, followed by the elbow. Diagnosis is primarily clinical, based on pain, decreased range of motion, and local signs like edema and erythema, typically occurring 3-12 weeks after the inciting event. Management focuses on prevention in high-risk patients through range of motion exercises, NSAIDs, bisphosphonates, and LDRT in joint replacement cases. LDRT is typically prescribed as 7-8 Gy in a single fraction, given either preoperatively within 24 hours or postoperatively within 72 hours.[9,] Treatment consists of mobilization with ROM exercises, pharmacological interventions (NSAIDs, bisphosphonates), and surgical resection for mature HO causing functional limitations, typically performed 12-18 months after initial presentation to allow for full maturation of the ectopic bone. While several studies have reported similar HO prevention effectiveness for LDRT compared to NSAIDs, concerns remain regarding the risk of secondary malignancies, nonunion, and wound healing complications.

Low-Dose Radiotherapy for Other Indications

Several other dermatologic or benign tissue disorders, including achillodynia, Dupuytren's contracture, medial and lateral epicondylitis, Graves ophthalmopathy, hidradenitis suppurativa, ledderhose disease, Peyronie's disease, pterygium, tendinopathies, and trochanteric bursitis have some published evidence for the use of LDRT [1,10,3,] However, these conditions are not addressed in this medical policy due to limited high-quality evidence, varying clinical practices, or the availability of alternative standard treatments. The use of LDRT for these and other unlisted non-oncologic conditions should be considered on a case-by-case basis, taking into account the specific clinical context, potential risks and benefits, and current clinical guidelines. It is important to note that the absence of these conditions from this medical policy does not necessarily indicate a lack of efficacy or appropriateness of LDRT in these cases but reflects the focused scope of this policy. Additional indications may be added when the accrual of higher-quality evidence permits a decision regarding the net health benefit of LDRT.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Osteoarthritis

Clinical Context and Therapy Purpose

The purpose of low-dose radiotherapy (LDRT) in individuals who have osteoarthritis (OA) is to provide a treatment option that is an alternative to or an improvement on medical therapy or conservative treatments (e.g., physical and occupational therapy, education and lifestyle modification, non-steroidal anti-inflammatory drugs [NSAIDs], supportive devices, or transcutaneous electrical stimulation), in individuals with treatment-resistant OA.

The following PICO was used to select literature to inform this review.

Populations

The relevant population(s) of interest are individuals with OA that is unresponsive to optimal medical therapy.

Interventions

The therapy being considered is LDRT administered either as a course of multiple small fractions (1-3 Gy) OR as a single treatment of up to 8 Gy.

LDRT for OA is believed to modulate inflammatory processes and reduce pain in affected joints. It is thought to work by suppressing pro-inflammatory cytokines and activating anti-inflammatory pathways although the underlying mechanisms are still not completely understood.[11,]

Comparators

Comparators of interest include physical therapy, medication, surgery, and intra-articular corticosteroids. Medications used for treatment include nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, dietary supplements, and narcotics. Surgeries for OA include arthroscopy (a procedure to diagnose and treat joint problems using a tiny camera inserted through a small surgical opening) and joint replacement.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, medication use, and treatment-related morbidity. Specifically, outcomes of interest include pain and medication usage, and improvement in functional outcomes and QOL. Reductions in pain and medication use can be observed within a week. The duration of pain relief with corticosteroids is rarely longer than 3 months, so outcomes should be measured within this window.

The WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) is a self-administered questionnaire evaluating knee and hip OA across three dimensions: pain (5 items), stiffness (2 items), and physical function (17 items).[12,] Patients rate their symptoms using either a Likert scale or Visual Analog Scale (VAS) with a higher score indicating worse limitations or symptoms:

- Likert scale: 0 (none) to 4 (extreme) per item; total range 0-96
- VAS: 0-100 mm per item; total range 0-2400 mm

The AUSCAN (Australian/Canadian Osteoarthritis Hand Index) is a self-administered questionnaire evaluating hand OA across three dimensions: pain (5 items), stiffness (1 item), and physical function (9 items).[12,] Patients rate their symptoms over the past 48 hours using either a Likert scale or Visual Analog Scale (VAS) with a higher score indicating worse limitations or symptoms:

- Likert scale: 0 (none) to 4 (extreme) per item; total range 0-60
- VAS: 0-100 mm per item; total range 0-1500 m

The Numeric Rating Scale (NRS) and Visual Analog Scale (VAS) are self-administered tools for assessing pain intensity.[13,] The NRS uses a single item with whole numbers, while the VAS uses a continuous line. Patients rate their current pain level or pain over a specified period (e.g., the past 24 hours) using either scale, with a higher score indicating worse pain:

- NRS: 0 (no pain) to 10 (worst pain imaginable); total range 0-10
- VAS: 0 mm (no pain) to 100 mm (worst pain imaginable); total range 0-100 mm

The OMERACT-OARSI (Outcome Measures in Rheumatology-Osteoarthritis Research Society International) responder criteria are standardized measures used to assess treatment response in OA clinical trials.[14,] A patient is considered a responder if they meet either of the following conditions:

- High improvement in pain or function:≥50% relative improvement and ≥20 points absolute improvement (on a 0-100 scale) in either pain or function
- Improvement in at least two of the three following domains:Pain: ≥20% relative improvement and ≥10 points absolute improvement (0-100 scale)
- Function: ≥20% relative improvement and ≥10 points absolute improvement (0-100 scale)
- Patient's global assessment: ≥20% relative improvement and ≥1 point absolute improvement (0-10 scale)

The PGA (Patient Global Assessment) is a self-administered single-item scale evaluating the patient's overall perception of their disease activity or health status.[15,] Patients rate their condition considering the ways their disease affects them. The PGA is commonly used in rheumatological conditions, including rheumatoid arthritis and OA. Patients typically rate their status over a recent time period (e.g., the past week) using either a Numeric Rating Scale (NRS) or Visual Analog Scale (VAS), with a higher score indicating worse disease activity or health status:

- NRS: 0 (very well) to 10 (very poor); total range 0-10
- VAS: 0 mm (very well) to 100 mm (very poor); total range 0-100 mm

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

A systematic review by the Veteran Affairs Administration's Evidence Synthesis Program was published in 2024, which evaluated radiotherapy (RT) for benign conditions, including the treatment of OA.[1,] The review searched databases through April 2023, including 2 RCTs and 10 single-arm studies (N=1410) for the treatment of OA. The total radiation dose ranged from 0.5 to 12 Gy, with

outcome assessment at 1 year for both trials. One RCT focused on knee OA, while the other examined hand OA; both compared RT to sham procedures. Neither RCT found significant differences in pain scores between RT and sham RT through 12 months of follow-up, using either the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) or the Numerical Rating Scale (NRS). However, several single-arm studies reported decreased pain levels on the Visual Analog Scale (VAS) and modified Von Pannewitiz scores up to 6 months post-treatment. Similarly, the RCTs showed no differences in functional outcomes using WOMAC or Australian/Canadian Hand Osteoarthritis Index (AUSCAN) scores compared to sham procedures. Multiple single-arm studies found significant improvements in site-specific measurements (e.g., Harrison hip score, Constant score, Japanese knee score, Tegner-Lysholm score, Insall Knee score, Knee Injury and Osteoarthritis Outcome Score, or investigator-derived instruments) from baseline. Both RCTs assessed stiffness, Patient Global Assessment, patient satisfaction, and treatment response (based on a composite of pain and function), finding no differences between RT and sham RT. The authors did not assess the certainty of evidence for this indication due to the lack of 3 comparative studies.

Randomized Controlled Trials

Mahler et al (2019) conducted a randomized, double-blind, sham-controlled trial evaluating the efficacy of LDRT in patients with symptomatic knee OA.[16,] Patients were randomized to receive 6 fractions of 1 Gy LDRT (n=27) or sham treatment (n=28) over 2 weeks. The primary outcome was the proportion of OMERACT-OARSI responders (individuals with either a relative improvement in pain or function ≥ 50% and an absolute improvement of ≥ 20 points or 2 of the following: ≥ 20 points improvement in pain or function and ≥ 1 point absolute improvement on PGA) at 3 months. No significant difference was found between LDRT and sham groups in the proportion of responders (44% vs. 43%; 95% CI, -25% to 28%; p=.9). Secondary outcomes (WOMAC pain, function, and stiffness) also showed no significant differences between groups. A summary of RCT study characteristics and outcomes are presented in Tables 1 and 2, respectively.

Minten et al (2018) performed a similar randomized, double-blind, sham-controlled trial evaluating LDRT in patients with symptomatic hand OA.[17,] Patients received 6 fractions of 1 Gy LDRT (n=28) or sham treatment (n=28) over 2 weeks. The primary outcome was the proportion of OMERACT-OARSI responders at 3 months. No significant difference was found between LDRT and sham groups in the proportion of responders (mean difference, -7%; 95% CI, -31% to 17%). Secondary clinical and inflammatory outcomes also showed no significant differences between groups.

Van den Ende et al (2020) reported open-label, 12-month follow-up results for both the knee and hand OA trials by Mahler et al (2018) and Minten et al (2019).[18,] For knee osteoarthritis, the proportion of responders at 12 months was 52% in the LDRT group versus 44% in the sham group (OR, 1.41; 95% CI, 0.45 to 4.48). For hand OA, the proportion of responders at 12 months was 31% in the LDRT group versus 27% in the sham group (OR, 1.23; 95% CI, 0.37 to 4.12). No significant differences were found between groups in other clinical outcomes at 6 or 12 months for either knee or hand OA. The studies were limited primarily by small sample sizes but suggest LDRT is not substantially effective for knee or hand OA symptoms compared to sham treatment.

Table 1. Summary of Key RCT Characteristics for Osteoarthritis

Study; Trial	Countries	Sites	Dates	Participants[2]	Interventions[1]	
Minten et al (2018)[17,]; Ende et al (2020)[18,]	The Netherlands	2	2016-2017	Individuals with hand OA with a mean age of 65 years and an NRS pain score of 6.1 who did not respond to conservative therapy	1 Gy x 6 in 2 weeks (n=28)	Sham: 0 Gy x 6 in 2 weeks (n=28)

Study; Trial	Countries	Sites	Dates	Participants[2]	Interventions[1]	
Mahler et al (2018)[16]; Ende et al (2020)[18],	The Netherlands	2	2000-2015	Individuals with knee OA with a mean age of 65 years and an NRS pain score of 5.1 who did not respond to conservative therapy	1 Gy x 6 in 2 weeks (n=27)	Sham: 0 Gy x 6 in 2 weeks (n=27)

Gy: gray; NR: not reported; NRS: numeric rating scale; OA: osteoarthritis; RCT: randomized controlled trial; VAS: visual analogue scale.
[1] Number randomized; intervention; mode of delivery; dose (frequency/duration).
[2] Key eligibility criteria

Table 2. Summary of Key RCT Results for Osteoarthritis

Study	Treatment Response	Pain	Functioning	Global Assessment	Adverse Events, n (%)
Minten et al (2018)[17]; Ende et al (2020)[18],	OMERACT-OARSI	AUSCAN pain	AUSCAN functioning	PGA	
LDRT (n=28)	3 mos: 29% 6 mos: 28% 12 mos: 31%			Any reaction: 21 (75%) Skin reactions: 14 (50%) Nail reactions: 10 (36%) Fatigue: 8 (29%) Other reactions: 9 (32%) Serious AEs: 2 (7%)	
Sham (n=28)	3 mos: 36% 6 mos: 41% 12 mos: 27%			Any reaction: 18 (64%) Skin reactions: 12 (43%) Nail reactions: 4 (14%) Fatigue: 8 (29%) Other reactions: 6 (21%) Serious AEs: 0%	
Summary	OR (95% CI): 3 mos: 0.69 (0.22 to 2.17) 6 mos: 0.57 (0.18 to 1.81) 12 mos: 1.23 (0.37 to 4.12)	Mean Treatment Difference (95% CI): 3 mos: -3.7 (-11.5 to 4.0) 6 mos: -6.4 (-11.9 to 0.3) 12 mos: 3.7 (-4.3 to 11.6)	Mean Treatment Differences (95% CI): 3 mos: -6.5 (-13.4 to 0.4) 6 mos: -3.6 (-10.7 to 3.5) 12 mos: -1.2 (-8.2 to 5.9)	Mean Treatment Differences (95% CI): 3 mos: -0.1 (-1.2 to 1.1) 6 mos: 0.3 (-0.9 to 1.5) 12 mos: -0.1 (-1.2 to 1.1)	NR
Mahler et al (2018)[16]; Ende et al (2020)[18],	OMERACT-OARSI	WOMAC Pain	WOMAC Function	PGA	
LDRT (n=27)	3 mos: 44% 6 mos: 41% 12 mos: 52%			Any reaction: 10 (37%) Skin reactions: 5 (19%) Nail reactions: 4 (15%) Fatigue: 6 (22%) Other reactions: 3 (11%) Serious AEs: 0%	
Sham (n=27)	3 mos: 43% 6 mos: 35% 12 mos: 44%			Any reaction: 10 (36%) Skin reactions: 5 (18%) Nail reactions: 3 (11%) Fatigue: 4 (14%) Other reactions: 4 (14%) Serious AEs: 3 (11%)	
Summary	OR (95% CI) 3 mos: 1.1 (0.4 to 3.2)	Mean Treatment Differences (95% CI):	Mean Treatment Differences (95% CI):	Mean Treatment Differences (95% CI):	NR

Study	Treatment Response	Pain	Functioning	Global Assessment	Adverse Events, n (%)
	6 mos: 1.3 (0.41 to 4.42) 12 mos: 1.41 (0.45 to 4.48)	3 mos: −2.9 (−10.7 to 4.8) 6 mos: 0.5 (-7.6 to 8.6) 12 mos: -3.3 (-11.2 to 4.6)	3 mos: 3.1 (−4.3 to 10.5) 6 mos: 3.2 (-4.6 to 10.9) 12 mos: -2.6 (-10.2 to 5.0)	3 mos: 0.2 (−1.0 to 1.5) 6 mos: -0.1 (-1.3 to 1.2) 12 mos: 0.2 (-1.1 to 1.4)	

AEs: adverse events; AOFAS: American Orthopaedic Foot and Ankle Society; AUSCAN: Australian/Canadian Hand Osteoarthritis Index; BL: baseline; CI: confidence interval; HR: hazard ratio; LDRT: lose-dose radiotherapy; mos: months; NNT: number needed to treat; OMERACT-OARSI: Outcome Measures in Rheumatology-Osteoarthritis Research Society International; OR: odds ratio; PGA: patient global assessment; RCT: randomized controlled trial; RR: relative risk; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

The purpose of the study limitations tables (see Tables 3 and 4) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 3. Study Relevance Limitations for Osteoarthritis

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Minten et al (2018)[17]; Ende et al (2020)[18]		5: No reirradiation for individuals who lacked a treatment response			
Mahler et al (2018)[16]; Ende et al (2020)[18]		5: No reirradiation for individuals who lacked a treatment response			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 4. Study Design and Conduct Limitations for Osteoarthritis

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Minten et al (2018)[17]; Ende et al (2020)[18]		2. Outcome assessors not blinded during the extended follow-up period reported by Ende et al (2020)		4. Power calculations used a large expected effect size; may not capture smaller changes in pain and function		
Mahler et al (2018)[16]; Ende et		2. Outcome assessors not blinded during the extended follow-up			Power calculations used a large expected effect size; may not capture smaller	

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
al (2020)[18,]		period reported by Ende et al (2020)			changes in pain and function and estimates at follow-up periods past 3 months	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Nonrandomized Studies

Several single-arm studies (N= 13 to 1145) have been published on the safety and efficacy of LDRT for OA at multiple sites (foot, ankle, fingers, hand, knee, hip) with varying dosages and fractionation schedules.[19,20,21,22,23,24,25,26,5,27,28,29,] Multiple authors reported decreased pain levels on the visual analog scale (VAS), numeric rating scale (NRS), and modified von Pannewitiz scores up to 6 months post-treatment; significant baseline improvements were also noted for site-specific measurements of function in some studies.

Section Summary: Osteoarthritis

In regard to the treatment of OA with LDRT, 1 systematic review, 2 sham-controlled RCTs and multiple single-arm studies were identified. While the outcomes of the single-arm studies have generally noted positive improvements from baseline levels in pain and function, the RCT evidence base is characterized by studies showing no significant treatment effects of LDRT relative to sham treatment. The systematic review found the evidence insufficient for assessment owing to too few comparative studies. The 2 RCTs found no significant differences between LDRT and sham treatment in pain, function, or proportion of treatment responders at 3 months for knee and hand OA, respectively. Follow-up at 12 months also showed no significant differences between groups. Both RCTs showed similar rates of adverse events between LDRT and sham procedures. The discrepancy between RCT and single-arm study results highlights the importance of controlling for placebo effects and other biases in evaluating LDRT for OA. Given the lack of treatment benefit in well-designed RCTs despite positive findings in single-arm studies, it is unlikely there is a clinically meaningful treatment benefit of LDRT for OA. Further large, high-quality RCTs would be needed to definitively establish or rule out a treatment effect.

Plantar Fasciitis

Clinical Context and Therapy Purpose

The purpose of low-dose radiotherapy (LDRT) in individuals who have plantar fasciitis is to provide a treatment option that is an alternative to or an improvement on medical therapy or conservative treatments (e.g., non-steroidal anti-inflammatory drugs [NSAIDs], corticosteroid injections, extracorporeal shock wave therapy (ESWT), platelet-rich plasma (PRP) injections, laser therapy, tenotomy, or radiofrequency ablation), in individuals with treatment-resistant plantar fasciitis.

The following PICO was used to select literature to inform this review.

Populations
The relevant population(s) of interest is individuals with plantar fasciitis that is unresponsive to optimal medical therapy and conservative therapy.

Interventions
The therapy being considered is LDRT administered either as a course of multiple small fractions (1-3 Gy) OR as a single treatment of up to 8 Gy.

LDRT for plantar fasciitis is proposed to reduce pain and inflammation in the affected tissue. It is thought to work by suppressing inflammatory cells and mediators, thereby decreasing local inflammation and promoting tissue healing in the plantar fascia.

Comparators
Comparators of interest include physical therapy, orthotic devices, medication, surgery, ESWT, PRP injection, and laser therapy. Medications used for treatment include NSAIDs, analgesics, and intra-articular corticosteroids.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, medication use, and treatment-related morbidity. Specifically, outcomes of interest include pain and medication usage, and improvement in functional outcomes and QOL. Reductions in pain and medication use can be observed within a week. The duration of pain relief with corticosteroids is rarely longer than 3 months, so outcomes should be measured within this window.

The AOFAS (American Orthopaedic Foot & Ankle Society) Score is a clinician-administered assessment tool evaluating foot and ankle conditions across three dimensions: pain (40 points), function (50 points), and alignment (10 points).[30,] Clinicians rate patients' symptoms and objective findings using a point-based system with a higher score indicating better outcomes or less impairment:

- Excellent (90-100)
- Good (80-89)
- Fair (70-79)
- Poor (<70)

The EQ-5D-5L (Five-Level EuroQol Five-Dimension) is a standardized self-administered questionnaire evaluating health-related quality of life across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[31,] Patients rate their health state in each dimension using a 5-point scale:

- Score range: 1 (no problems) to 5 (extreme problems) per dimension
- Responses are translated to an overall index score on a scale from 0 (death) to 100 (perfect health)

The Modified von Pannewitz pain score is a clinician-administered assessment tool evaluating pain intensity in patients with.[32,] It categorizes pain based on how free the patient rates themselves from pain.

- Complete response: Pain free
- Partial response: substantial pain improvement
- Minor response: some pain improvement
- No change: pain unchanged or worsened

The Numeric Rating Scale (NRS) and Visual Analog Scale (VAS) are self-administered tools for assessing pain intensity.[13,] The NRS uses a single item with whole numbers, while the VAS uses a continuous line. Patients rate their current pain level or pain over a specified period (e.g., the past 24 hours) using either scale, with a higher score indicating worse pain:

- NRS: 0 (no pain) to 10 (worst pain imaginable); total range 0-10
- VAS: 0 mm (no pain) to 100 mm (worst pain imaginable); total range 0-100 mm

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

A systematic review by the Veteran's Affairs Administration's Evidence Synthesis Program was published in 2024, which evaluated radiotherapy (RT) for benign conditions, including the treatment of plantar fasciitis.[1,] The review searched databases through April 2023, including 2 RCTs, 1 non-randomized controlled study, and 2 single-arm studies (N=1153). The total radiation dose ranged from 3 to 6 Gy, and 3 studies reported additional treatment for patients who were unsuccessful initially. Mean follow-up across the included studies ranged from 3 to 125 months post-treatment. Comparators varied among the included studies and included 1 study each comparing LDRT to platelet-rich plasma (PRP) injection, palpation-guided corticosteroid injection with methylprednisolone, and extracorporeal shockwave therapy (ESWT). Due to this heterogeneity, no pooled estimates were calculated. Two of the 3 comparative studies had a significant decrease in pain compared to alternative treatments, with the remaining study finding no difference between treatment arms. Two studies reported improvements in function at 6 months follow-up, with a significantly greater number of participants achieving excellent or good functional status compared to alternative therapies. No differences in plantar fasciitis thickness or American Orthopedic Foot and Ankle Score (AOFAS) were reported by 1 study each. The authors concluded with a low level of confidence that LDRT may result in an improvement of function, and that there were no between-group differences in plantar fasciitis thickness, AOFAS scores, or rate of adverse events; all other outcomes were determined to have insufficient evidence to reach a conclusion.

Randomized Controlled Trials

Canyilmaz et al (2015) conducted a randomized trial comparing LDRT to local corticosteroid injection for recurrent plantar fasciitis after previous conservative therapies.[32,] Patients were randomized to receive LDRT (6 Gy in 6 fractions of 1 Gy, n=58) or corticosteroid injection (n=64). The primary outcomes were pain (visual analog scale), function (modified von Pannewitz scale), and 5-level function score at 3 months. LDRT was superior to corticosteroid injection on all outcomes ($p<.001$ for each).

Gogna et al (2016) performed an RCT comparing PRP injection to LDRT for chronic plantar fasciitis in athletes who did not respond to previous conservative therapies.[33,] Patients received either PRP injection (n=20) or LDRT (3 Gy in 6 fractions of 0.5 Gy, n=20). The primary outcomes were pain (visual analog scale [VAS]), function (American Orthopaedic Foot and Ankle Score [AOFAS]), and plantar

fascia thickness on ultrasound at 6 months. No significant differences were found between groups on any outcome measure (p>.05 for all comparisons).

Study characteristics and outcome data from the clinical trials are shown in Tables 5 and 6, respectively.

Table 5. Summary of Key RCT Characteristics for Plantar Fasciitis

Study; Trial	Countries	Sites	Dates	Participants[2]	Interventions[1]	
Canyilmaz et al (2015)[32],	Turkey	1	2013-2014	Individuals with plantar fasciitis with a mean age of 65 years and a mean NRS pain score of 6.1 who did not respond to conservative therapy.	1 Gy x 6 in 2 weeks (n=58)	Local corticosteroid injections (1 ml injection of 40 mg methylprednisolone and 0.5 ml 1% lidocaine) under guidance by palpation (n=64)
Gonga et al (2016)[33],	India	1	NR	Individuals with plantar fasciitis with a mean age of 27 years and a mean VAS pain score of 6.7 who did not respond to conservative therapy.	0.5 Gy x 6 in 3 weeks (n=20)	Platelet-rich plasma injections (20 ml whole blood injection of 40 mg methylprednisolone and 0.5 ml 1% lidocaine) under guidance by palpation (n=64)

Gy: gray; NR: not reported; NRS: numeric rating scale; OA: osteoarthritis; RCT: randomized controlled trial; VAS: visual analogue scale.
[1] Number randomized; intervention; mode of delivery; dose (frequency/duration).
[2] Key eligibility criteria

Table 6. Summary of Key RCT Results for Plantar Fasciitis

Study	Treatment Response	Pain	Functioning	Global Assessment	Adverse Events, n (%)
Canyilmaz et al (2015)[32],	Modified von Pannewitz pain score: 3 mos, 6 mos	VAS Pain	Five-level function		
LDRT (n=58)	3 mos: Complete response: 38.3% Partial response: 28.3% Minor response: 18.3% 6 mos: Complete response: 35% Partial response: 33.3% Minor response: 20%	BL: 7.6 3 mos: 2.8 6 mos: 2.7	BL: 41.6 3 mos: 78.3 6 mos: 78.7		1-year event-free probability of requiring a second treatment: 95%
Corticosteroids (n=64)	3 mos: Complete response: 15.6% Partial response: 9.4% Minor response: 34.4%	BL: 6.9 3 mos: 4.6 6 mos: 4.6	BL: 48.4 3 mos: 60 6 mos: 59		1-year event-free probability of requiring a second treatment: 90.2% Acute infection at injection site: 1 (1.5%)

Study	Treatment Response	Pain	Functioning	Global Assessment	Adverse Events, n (%)
	6 mos: Complete response: 15.6% Partial response: 12.5% Minor response: 31.1%				
Summary	p<.001 at 3 and 6 mo f/u	p<.001 at 3 and 6 mo f/u	p<.001 at 3 and 6 mo f/u		NS difference between groups
Gonga et al (2016)[33],		VAS	AOFAS Score	Plantar fascia thickness, mm	
LDRT (n=20)		BL: 6.65 3 mos: 2.55 6 mos: 2.35	BL: 52.5 6 mos: 89.65	BL: 6.71 6 mos: 5.62	
Platelet-rich plasma (n=64)		BL: 6.65 3 mos: 2.45 6 mos: 2.25	BL: 51.5 6 mos: 89.1	BL: 6.76 6 mos: 5.59	
Summary		NS difference between groups but a SS reduction from BL values in each group.	NS difference between groups but a SS reduction from BL values in each group.	NS difference between groups but a SS reduction from BL values in each group.	

AOFAS: American Orthopaedic Foot and Ankle Society; BL: baseline; CI: confidence interval; HR: hazard ratio; LDRT: lose-dose radiotherapy; NNT: number needed to treat; NS: not significant; mos, months; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SS: statistically significant VAS: visual analogue scale.
[1] Include number analyzed, effect in each group, and measure of effect (absolute or relative) with CI,
[2] Describe the range of sample sizes, effects, and other notable features in text.

The purpose of the study limitations tables (see Tables 7 and 8) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 7. Study Relevance Limitations for Plantar Fasciitis

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Canyilmaz et al (2014)[32],	5: Treatment groups not balanced on duration of pain, baseline VAS pain score and baseline five-level function score				2. Not sufficient duration for harms; mean follow-up over 1 year for both groups but data reported only through 6 months post-treatment
Gonga et al (2016)[33],	5. Study population's characteristics poorly described				2. Not sufficient duration for harms

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 8. Study Design and Conduct Limitations for Plantar Fasciitis

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Canyilmaz et al (2014)[32,]	3. Allocation concealment unclear	1. Participants or study staff not blinded			1. Power calculations not reported	
Gonga et al (2016)[33,]		1. Participants or study staff not blinded			1. Power calculations not reported	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Nonrandomized Studies

Aynaci et al (2021) conducted a multicenter retrospective study comparing LDRT, palpation-guided steroid injection, and extracorporeal shock wave therapy (ESWT) for plantar fasciitis.[34,] Patients received either LDRT (6 Gy in 6 fractions, n=67), steroid injection (40 mg methylprednisolone, n=65), or ESWT (2000 impulses in 5 weekly sessions, n=73) (Table 9). The participants in the LDRT and steroid injection groups overlap partially with the study population from the RCT by Canyilmaz et al (2015). The primary outcomes were pain (VAS), function (5-level function score), and modified von Pannewitz pain score at 3 and 6 months. At both 3 and 6 months, LDRT was superior to both steroid injection and ESWT on all primary outcome measures (p<.001 for all comparisons; See Table 10). Additionally, several larger case series (range: n=157 to 562), all conducted in Germany, reported on individuals with plantar fasciitis with unsatisfactory pain control who received between 1.5 Gy to 6 Gy of LDRT over 3 to 4 weeks with follow-up periods ranging from 3 to 54 months. [35,36,5,37,]All series noted an improvement from baseline levels of pain, with the majority of patients experiencing a significant level of pain relief at 3 or more months post-treatment. One author noted improvements in walking speeds following LDRT, and another noted no improvements in quality of life from baseline.

Table 9. Characteristics of Non-randomized Comparative Studies for Plantar Fasciitis

Study	Country	Participants	LDRT	Comparator	Follow-up
Aynaci et al (2021)[34,]	Turkey	Individuals treated at a single center between 2013 and 2017 for plantar fasciitis with a KPS score ≥70 who had pain and mobility restriction. LDRT and steroid injection groups overlap partially with the study population from the RCT by Canyilmaz et al 2015.	1 Gy x 6 in 3 weeks (n=67)	Steroid Injection (40 mg of methylprednisolone; and 0.5 ml of 1% lidocaine) (N=65) ESWT (2000 20Mhz impulses) (N=73)	6 mos

ESWT: Extracorporeal Shock Wave Therapy; Gy: gray; KPS: Karnofsky Performance Scale;

[1]If there are multiple delivery methods or technologies then list name; mode of delivery; dose (frequency/duration). Otherwise this column can be removed.

Table 10. Summary of Non-randomized Comparative Studies for Plantar Fasciitis Results

Study	Pain:	Treatment Response, (%):	Function score:	Adverse Events:
Aynaci et al (2021)[34,]	Mean VAS: BL, 3 mos, 6 mos	Modified Von Pannewitz score: Complete response at 3 mos, 6 mos	Mean Five-level score: BL, 3 mos, 6 mos Excellent Rowe score, %: 3 mo, 6 mos	Hazard Ratio (95% CI)
LDRT (n=67)	7.7, 2.5, 2.5	41.8%	40.9, 80.4, 80.3 46.3%, 43.1%	None
Corticosteroids (N=65)	6.9, 4.6, 4.6	15.4%	48.4, 60.2, 59.2 15.4%, 15.4%	Acute infection: 1 (1.5%)
ESWT (N=73)	7.5, 4.1, 3.6	21.9%	41.9, 65.6, 68.6 19.2%, 23.3%	Pain: 10 (13.7%) Erythema: 2 (2.7%)
Summary	p<.001 at 3 and 6 mos favoring LDRT	p<.001 at 3 and 6 mos favoring LDRT	p<.001 at 3 and 6 mos favoring LDRT	

BL: baseline; ESWT: Extracorporeal Shock Wave Therapy; LDRT: low dose radiotherapy; mos: months; VAS: visual analogue scale.

Section Summary: Plantar Fasciitis

For the treatment of plantar fasciitis with LDRT, 1 systematic review, 2 RCTs, 1 non-randomized comparative study, and multiple single-arm studies have been published. A 2024 systematic review by the Veterans Affairs Administration's Evidence Synthesis Program found the evidence insufficient for most outcomes due to heterogeneity among studies and limited comparative data but determined that for functional outcomes, there is a low level of certainty of a benefit with LDRT. One RCT found significant differences favoring LDRT over corticosteroid injection in pain and function at 3 and 6 months for plantar fasciitis. These results were supported by the non-randomized study, which favored LDRT over corticosteroids or extracorporeal shock wave therapy, but the study included overlapping patients from the RCT in the LDRT and corticosteroid groups. The remaining RCT found no differences between LDRT and platelet-rich plasma injection at 6 months follow-up, but both groups had significant improvements from baseline levels for pain, function, and thickness of plantar fascia. One RCT reported on the rate of adverse events and the probability of requiring a second intervention within 1 year of follow-up and found no significant differences between LDRT and corticosteroid injection. Outcomes from the single-arm studies have generally noted positive improvements from baseline levels in pain and functional outcomes. The primary limitations of the evidence base consist of the overlapping patient populations in 2 comparative studies, lack of follow-up beyond 6 months which is insufficient for the assessment of harms, small sample sizes with unreported power calculations, and a lack of blinding. Despite multiple positive case series, there is limited comparative evidence for the effectiveness of LDRT for plantar fasciitis, and it remains unclear whether there is a clinically meaningful treatment benefit. Further large, high-quality RCTs would be needed to definitively establish or rule out a treatment effect.

Postoperative Low-Dose Radiotherapy for the Prevention of Heterotopic Ossification

Clinical Context and Therapy Purpose

The purpose of pre-operative or post-operative adjuvant low-dose radiotherapy (LDRT) in individuals who are at risk of heterotopic ossification (HO) is to prevent the development of HO and as an alternative to existing prophylactic treatments (eg, physical therapy, NSAIDs, bisphosphonates, or other conventional prophylaxis). While LDRT is also used for neurogenic HO (e.g. caused by spinal cord injury, traumatic brain injury, or brain tumors) prevention in some cases, this section will focus solely on its application in post-surgical contexts. The following PICO was used to select literature to inform this review's

Populations

The relevant population of interest is individuals at risk of developing post-surgical HO who are candidates for prophylactic treatment.

Interventions

The therapy being considered is adjuvant LDRT administered either as a course of multiple small fractions OR as a single treatment of up to 8 Gy.

The primary clinical context for LDRT is in patients undergoing total hip arthroplasty (THA) or other major orthopedic surgeries, where it is typically administered within 72 hours post-operatively. LDRT is believed to work by inhibiting the differentiation of mesenchymal cells into osteoblasts, thereby disrupting the early stages of HO formation.[8,]

Comparators

Comparators of interest for the prevention of HO include physical therapy, NSAIDs, bisphosphonates, or other standard-of-care prophylaxis.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, health status measures, medication use, and treatment-related morbidity. Specifically, outcomes of interest include pain and medication usage, and improvement in functional outcomes and quality of life.
The Brooker Score is a radiographic grading system used to assess the severity of HO around the hip joint.[38,] The scale ranges from 0 to 4, with higher scores indicating more severe ossification:

- Grade 0: No heterotopic ossification visible
- Grade 1: Isolated bone islands within soft tissues around the hip;
- Grade 2: Bone spurs from the pelvis or proximal end of the femur, leaving at least 1 cm between opposing bone surfaces;
- Grade 3: Bone spurs from the pelvis or proximal end of the femur, reducing the space between opposing bone surfaces to less than 1 cm;
- Grade 4: Apparent bone ankylosis of the hip.

The Harris Hip Score (HHS) is used to assess hip function and pain in patients with hip disorders[39,]. It consists 13 items over four domains: pain, function, absence of deformity, and range of motion, with a total possible score of 100 points with lower scores indicating worse functioning and pain:

- < 70: Poor result
- 70-79: Fair result
- 80-89: Good result
- 90-100: Excellent result

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

A systematic review by the Veteran's Affairs Administration's Evidence Synthesis Program was published in 2024, which evaluated RT for benign conditions, including the treatment or prevention of HO.[1,] The review searched databases through April 2023, including 10 RCTs (N=1,530) on the prevention or treatment of HO. Timing of LDRT ranged from 48 hours to 8 days post-surgery with a total radiation dose ranging from 5 to 12 Gy. LDRT was administered prior to surgery in 2 studies. The type of surgeries consisted of total hip arthroplasty or replacement (n=7), acetabular fracture (n=2), and elbow fracture (n=1). Mean follow-up across the included studies ranged from 3 to 59 months post-treatment (Table 11 & Table 12). A pooled assessment of 8 RCTs showed a non-significant but clinically meaningful reduction in the presence of HO at follow-up for LDRT compared to control groups (OR, 0.47; 95% CI, 0.19 to 1.17; I^2=85%); the clinically meaningful impact was assessed based on the magnitude of effect size, precision of the estimate, and because most studies favored LDRT over NSAIDs post surgery for HO prevention. A sensitivity analysis omitting 2 RCTs that applied LDRT prior to surgery found a significant difference favoring LDRT (OR, 0.5; 95% CI, 0.28 to 0.89; I^2=58%). Findings were mixed for the outcome of radiological failure, which was reported by only two RCTs; one found that 3 months post-surgery, LDRT was favored over indomethacin while another trial was stopped early due to the high rate of non-union in patients treated with LDRT compared to surgery alone. The authors reported that for the outcomes of physical functioning (3 studies), pain (1 study), and quality of life (1 study) no differences were found between LDRT and comparison groups. Adverse events (post-operative infection, manipulation, prolonged wound secretion, wound dehiscence, deep vein thrombosis, dyspepsia, implant migration, and presence of radiolucent lines) were all found to be non-significantly different between groups. The authors concluded with a low level of confidence that there was a non-significant reduction in the rate of HO or difference in function between LDRT and NSAIDs treatments post-surgery; all other outcomes were determined to have insufficient evidence to reach a conclusion.

A systematic review and meta-analysis by Shapira et al. was published in 2021, which evaluated the NSAIDs versus LDRT for the prevention of HO following total hip arthroplasty (THA).[40,] The review searched databases through March 2019, including 37 studies (N=8,653) on the prevention of HO. The analysis separated patients into high-risk and low-risk groups for developing HO. For high-risk patients, 13 studies were included (741 NSAID treatment, 1260 LDRT treatment, 226 no treatment). NSAIDs showed numerically better ranges for efficacy in preventing HO compared to LDRT in high-risk patients, with 76.6 to 88.9% of NSAID-treated patients developing no HO versus 28.6 to 97.4% for RT-treated patients. No LDRT studies were included for low-risk patients. Pooled analyses were not provided for LDRT. The authors concluded that NSAIDs may have better efficacy than LDRT for HO prevention in high-risk patients following THA but cite limitations including variability in prophylaxis protocols and the need for standardized regimens in future studies.

Table 11. SR & M-A Characteristics for Heterotopic Ossification

Study	Dates	Trials	Participants[1]	N (Range)	Design
Shapira et al (2021)[40,]	Inception-2019	37 studies (9 RCTs included in meta-analysis)	Studies of individuals undergoing total hip arthroplasty treated with	NSAID: 5043 (58.28%) LDRT: 1260 (12.56%) No treatment: 2350 (27.16 %)	RCT, cohort studies, case series

Study	Dates	Trials	Participants[1]	N (Range)	Design
			either NSAIDs or RT with or without a control group for the prevention of HO		
Jutkowitz et al (2024)[1,]	Inception-2023	10 studies (8 RCTs included in meta-analysis)	Studies of individuals undergoing radiotherapy for the treatment or prevention of HO	1530 total participants (groups not defined) 8 studies compared post-LDRT surgery to post-surgery NSAIDs, 2 studies employed surgery only as a control group and 3 studies included a historical surgery only group in addition to the NSAID arm.	RCT

HO: heterotopic ossification; LDRT: low-dose radiotherapy; NSAID: non-steroidal anti-inflammatory drug.
[1] Key eligibility criteria.

Table 12. SR & M-A Results for Heterotopic Ossification

Study	HO Rate % (95% CI); p-value
Shapira et al (2021)[40,]	
n Studies, n in the treatment group	LDRT (12 studies, n=1260); NSAIDs (4 studies, n=5043); No treatment (4 studies, 2350)
Range	No HO formation: 28.6% to 97.4%; 76.6% to 88.9%;15.8% to 73.6% Mild HO formation: 1.9% to 66.7%; 11.1% to 23.4%; 26.4% to 68.5% Severe HO formation: 0% to 11.9%; 0% to 1.8%; 0% to 42.1%
Jutkowitz et al (2024)[1,]	
n Studies, n in the treatment group	LDRT (8 studies; n=669); NSAIDs (8 studies, n=507); Surgery alone (4 studies, n=290)
Pooled Odds Ratio (95% CI; I^2)	0.47 (0.19 to 1.17; 85%) Sub-group analysis of post-surgery LDRT studies only: 0.50 (0.28 to 0.89; 58%)

CI: confidence interval; EBRT: external beam radiotherapy; LDRT: low-dose radiation therapy; LT: laser therapy; NR: not reported; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio; RT: radiotherapy.

Randomized Controlled Trials

Total Hip Arthroplasty

Knelles et al. (1997) performed a prospective randomized study comparing various regimens for the prevention of HO after total hip arthroplasty (THA).[41,] The study included 685 patients randomized to receive either acetylsalicylic acid (3x750 mg daily for 14 days), indomethacin (2x50 mg daily for 7 or 14 days), fractional LDRT (4x3 Gy), single-dose LDRT (7 Gy or 5 Gy), or no prophylaxis (control). At 12 months follow-up, the rates of HO were 37.6%, 12.2%, 15.9%, 5%, 11.6%, 30.1%, and 65% in the respective groups. Indomethacin for 7-14 days and LDRT with 4x3 Gy or 1x7 Gy were the most effective regimens. Study characteristics and outcome data from the included clinical trials are shown in Tables 13 and 14, respectively.

Kölbl et al. (1998) performed a randomized trial comparing preoperative LDRT to indomethacin for prevention of HO after THA.[42,] The study included 100 patients randomized to receive either indomethacin (2x75 mg daily for 14 days) or single-dose LDRT (7 Gy) given 16-20 hours preoperatively. At 6 months follow-up, the rates of HO were 11.1% in the indomethacin group and 47.8% in the

radiation group (p<.01). The authors concluded that indomethacin was more effective than preoperative radiation given 16-20 hours before surgery for HO prophylaxis after THA.
Sell et al. (1998) conducted a prospective randomized study comparing LDRT to diclofenac for prevention of HO after THA.[43,] The study included 154 patients randomized to receive either diclofenac (3x50 mg daily for 3 weeks) or fractional radiation (3x3.3 Gy) within 4 days postoperatively. At 6 months follow-up, the rates of HO were 18.6% in the diclofenac group and 2.1% in the radiation group (p<.001) favoring radiotherapy.

Van Leeuwen et al. (1998) performed a randomized study comparing preoperative LDRT to no prophylaxis for the prevention of HO after THA in high-risk patients.[44,] The study included 62 hips randomized to receive either single-dose LDRT (5 Gy) given 1 day preoperatively or no prophylaxis. At 31 months mean follow-up, the rates of HO were 14% in the radiation group and 84% in the control group (p<.001).

Kienapfel et al. (1999) conducted a prospective randomized study comparing postoperative radiation therapy to indomethacin for the prevention of HO after THA.[45,] The study included 154 patients randomized to receive either single-dose RT (6 Gy) within 4 days postoperatively, indomethacin (2x50 mg daily for 42 days), or no prophylaxis (control). At 18 months follow-up, the rates of HO were 5% in the radiation group, 12.2% in the indomethacin group, and 65% in the control group. Both radiation and indomethacin were significantly more effective than no prophylaxis (p<.001).

Ince et al. (2007) performed an RCT comparing indomethacin to LDRT for the prevention of HO after cementless THA.[46,] The study included 204 patients randomized to receive either NSAIDs (indomethacin 2x50 mg daily for 1 week) or single-dose LDRT (7 or 5 Gy) as well as 82 individuals who were from a period prior to HO prophylaxis who received neither NSAIDs nor LDRT. At 6 months follow-up, the rates of HO (Brooker Grade I-IV) were 65% in the historic control group, 16% in the NSAID group, 11.6% in the 7 Gy group, and 30.1% in the 5 Gy group. The authors also measured the migration of acetabular implants and found no differences between groups at 5 years follow-up.

Acetabular Fracture or Elbow Fracture

Moore et al. (1998) performed a prospective randomized study comparing indomethacin to LDRT for prevention of HO after acetabular fracture surgery.[47,] The study included 75 patients randomized to receive either indomethacin (25 mg three times daily for 6 weeks) or single-dose radiation (8 Gy) within 3 days postoperatively. At 12 months follow-up, the rates of grade III-IV HO were 13% in the indomethacin group and 9% in the radiation group, with no significant difference between groups (p=0.73).

Burd et al. (2001) conducted a prospective randomized trial comparing indomethacin to radiation therapy for prevention of heterotopic ossification after acetabular fracture surgery.[48,] The study included 166 patients randomized to receive either indomethacin (25 mg three times daily for 6 weeks) or single-dose LDRT (8 Gy) within 72 hours postoperatively. At 14 months mean follow-up, the rates of grade III-IV HO were 11% in the indomethacin group and 4% in the LDRT group, with no significant difference between groups (p=.22). The same authors reported on the rate of long-bone non-union in an overlapping patient population (n=112) who reported concomitant fractures and found that the rate of non-union was significantly higher in patients who received indomethacin compared to those who received radiotherapy (26% vs. 7%; p=.004).[49,]

Hamid et al. (2010) conducted a prospective randomized study comparing postoperative LDRT to indomethacin for prevention of HO after elbow fracture in high-risk patients.[50,]The study included 48 patients randomized to receive either single-dose radiation therapy (7 Gy) within 72 hours postoperatively or indomethacin (25 mg three times daily for 6 weeks). The study was terminated early due to an unacceptably high rate of nonunion in the radiation group (38% vs. 4% in the indomethacin group, p=.007). There were no significant differences between groups in HO rates or clinical outcomes.

Table 13. Summary of Key RCT Characteristics for Heterotopic Ossification

Study; Trial	Countries	Sites	Dates	Participants[2]	Interventions[1]	
Knelles et al (1997)[41],	Germany	1	1988-1994	Individuals undergoing THA with a mean age of 66 years	3 Gy x 4 (n=101) 7 Gy x 1 (n=95) 5 Gy x 1 (n=93) All doses administered post-operatively	NSAID (indometacin 2 x 50 mg/day x 2 weeks) (n=113) NSAID (indometacin 2 x 50 mg/day x 1 weeks) (n=90) Acetylsalicylic acid x 2 weeks (n=93) Control (n=100)
Moore et al (1998)[47],	United States	1	1993-1996	Individuals with acetabular fractures with a mean age of 43 to 47 years, depending on the treatment arm	8 Gy x 1 within 3 days post-operatively (n=33)	NSAID (indometacin 3 x 25 mg/day x 6 weeks) (n=39)
Kolbl et al (1998)[51],	Germany	NR	1995-1996	Individuals undergoing THA with a mean age of 66 years	7 Gy x 1 within 16-20 hrs pre-operation (n=46)	NSAID (voltaren resinat 2 x 75 mg/day x 2 weeks) (n=54) Historic Control (no LDRT or NSAID) (n=100)
Sell et al (1998)[43],	Germany	1	1992-1993	Individuals undergoing THA with a mean age of 60 years	3.3 Gy x 3 in the first 3 weeks post-operatively (n=76)	NSAID (diclofenac 3 x 50 mg/day x 3 weeks) (n=77)
van Leeuwen et al (1998)[44],	The Netherlands	1	1989 - 1992	Individuals undergoing THA with a mean age of 66 years	5 Gy x 1 in the first 24 hrs (n=43)	No treatment (n=19)
Kienapfel et al (1999)[45],	Germany	NR	1992-1993	Individuals undergoing THA with a mean age of 65 years	6 Gy x 1 between 2 and 4th day post-operatively (n=49)	NSAID (indometacin 2 x 50 mg/day x 6 weeks) (n=55) No treatment (n=50)
Burd et al (2001)[48],	United States	1	1992-1999	Individuals undergoing stabilization of hip fractures by open reduction and internal fixation with a mean age of 43 years	8 Gy x1 between 2 and 3rd day post-operatively (n=78)	NSAID (indometacin 3 x 25 mg/day x 6 weeks) (n=72)
Ince et al (2007)[46],	Germany	1	1988-1994	Individuals undergoing THA at a single center with a mean age of 60.1 to 65.8 years depending	3 Gy x 4 in 2 day intervals at 5th day post-operatively (n=106)	NSAID (indometacin 2 x 50 mg/day x 2 weeks) (n=98) Historical control (no RT or NSAID) (n=82)

Study; Trial	Countries	Sites	Dates	Participants[2]	Interventions[1]	
				on treatment arm		
Hamid et al (2010)[50,]	United States	1	2005-2008	Individuals with elbow trauma and a mean age of 45 years	7 Gy in a single fraction between 2 and 3th day post-operatively (n=21)	No treatment (n=24)

Gy: gray; LDRT: low-dose radiotherapy; NR: not reported; NRS: numeric rating scale; NSAID: non-steroidal anti-inflammatory drug; OA: osteoarthritis; RCT: randomized controlled trial; THA: total hip arthroplasty; VAS: visual analogue scale.
[1] Number randomized; intervention; mode of delivery; dose (frequency/duration).
[2] Key eligibility criteria

Table 14. Summary of Key RCT Results for Heterotopic Ossification

Study	Heterotopic Ossification, %	Harris Hip Score	Adverse Events, n (%)
Knelles et al (1997)[41,]	Brooker grade I-IV at 12 months		
LDRT (12 Gy) (n=101)	5%		21.6%
LDRT (7 Gy) (n=95)	11.6%		32.6%
LDRT (5 Gy) (n=93)	30.1%		38.7%
NSAID x 2 weeks (n=113)	12.2%		17%
NSAID x 1 week (n=90)	15.9%		33.1%
Acetylsalicylic acid x 2 weeks (n=93)	37.6%		11.1%
Control (no additional prophylaxis) (n=100)	65%		NR
Summary	All groups had a SS reduction relative to the control group (p=.001); 5 Gy irradiation performed worse than all other groups except ASA. The 7 Gy group was superior to ASA but not to NSAIDs. The 12 Gy group had a significantly lower rate of HO than 1 week of NSAIDs but was not significantly different than 2 weeks of NSAID prophylaxis.		
Kolbl et al (1998)[51,]	6 months post-treatment		
LDRT (n=46)	Total: 47.8% Brooker Score I: 36.9% Brooker Score II: 8.7% Brooker Score III: 2.2% Brooker Score IV: 0%		
NSAID (n=54)	Total: 11.1% Brooker Score I: 9.3% Brooker Score II: 1.8% Brooker Score III: 0% Brooker Score IV: 0%		3 participants in the NSAID group stopped treatment early due to gastrointestinal side effects (5.6%)
Historic Control (surgery alone) (n=100)	Total: 65% Brooker Score I: 26% Brooker Score II: 15% Brooker Score III: 19% Brooker Score IV: 5%		

Study	Heterotopic Ossification, %	Harris Hip Score	Adverse Events, n (%)
Summary	SS reduction in the rate of HO compared to historical control in all treated groups. Incidence of Brooker Score II or III HO was NS different between LDRT and NSAIDs (p>.05)		
Moore et al (1998)[47,]	12 months post-treatment		
LDRT (n=33)	Total: 27.3% Brooker Score I: 12.1% Brooker Score II: 6.1% Brooker Score III: 9.1% Brooker Score IV: 0%		
NSAID (n=39)	Total: 34.7% Brooker Score I: 12.8% Brooker Score II: 4% Brooker Score III: 12.8% Brooker Score IV: 5.1%		
Summary	p =.089		
Sell et al (1998)[43,]	6 months post-treatment		
LDRT (n=76)	Total: 3% Brooker Score I: 3% Brooker Score II: 0% Brooker Score III: 0% Brooker Score IV: 0%		1 infection and 1 fistula revision (3%)
NSAID (n=77)	Total: 24% Brooker Score I: 21% Brooker Score II: 3% Brooker Score III: 0% Brooker Score IV: 0%		11 participants in the NSAID group stopped treatment early due to gastrointestinal side effects (14%)
Summary	p<.001		
van Leeuwen et al (1998)[44,]	mean 2.5 years post-treatment		
LDRT (n=41)	Total: 14% Brooker Score I: 12% Brooker Score II: 0% Brooker Score III: 2% Brooker Score IV: 0%		1 superficial wound infection (2%)
Surgery alone (n=16)	Total: 84% Brooker Score I: 21% Brooker Score II: 21% Brooker Score III: 26% Brooker Score IV: 16%		
Summary	p<.001		
Kienapfel et al (1999)[45,]	18 months post-treatment	HHS; PAHHS; IAHHS at 18 months post-treatment	
LDRT (n=49)	Total: 24% Brooker Score I: 20% Brooker Score II: 4% Brooker Score III: 0% Brooker Score IV: 0%	Mean: 86.4; 68.8; 17.5	Prolonged wound secretion: 6 Wound dehiscence: 1 Proximal deep vein thrombosis: 3 Dyspepsia: 4
NSAID (n=55)	Total: 36% Brooker Score I: 31% Brooker Score II: 5% Brooker Score III: 0% Brooker Score IV: 0%	Mean: 85; 67.6; 17.1	Prolonged wound secretion: 0 Wound dehiscence: 2 Proximal deep vein thrombosis: 4 Dyspepsia: 15
Historic Control (surgery alone) (n=50)	Total: 60% Brooker Score I: 16%	Mean: 81.7; 64.7; 16.9	Prolonged wound secretion: 1 Wound dehiscence: 1

Study	Heterotopic Ossification, %	Harris Hip Score	Adverse Events, n (%)
	Brooker Score II: 18% Brooker Score III: 22% Brooker Score IV: 4%		Proximal deep vein thrombosis: 3 Dyspepsia: 5
Summary	p<.001 vs historical control group for both treatment arms	NS difference between groups	No revision surgery or failed arthroplasties were reported in either LDRT or NSAID groups; complications were not statistically compared.
Burd et al (2001)[48,49,]	Mean 14 months follow-up		
LDRT (n=74)	Brooker Score I: NR Brooker Score II: NR Brooker Score III or IV: 7%		Non-union: 7%
NSAID (N=38)	Brooker Score I: NR Brooker Score II: NR Brooker Score III or IV: 14%		Non-union: 26%
Summary	7% (95% CI, −1.1% to 15.7%); p=.13		p=.004 No additional complications related to prophylactic treatment were identified in either group.
Ince et al (2007)[46,]	5 year follow-up	HHS	
LDRT (N=106)	Brooker Score 0: 95% Brooker Score I: 5% Brooker Score II: 0% Brooker Score III: 0% Brooker Score IV: 0% Brooker Score I-IV: 5%	86.2 ± 12.5	Radiolucent lines greater than 1 mm: 0
NSAID (n=98)	Brooker Score 0: 87.8% Brooker Score I: 8.9% Brooker Score II: 2.2% Brooker Score III: 1.1% Brooker Score IV: 0% Brooker Score I-IV: 12.2%	87.1 ± 10.8	Radiolucent lines greater than 1 mm: 4
Historic control (surgery plus analgesia) (n=82)	Brooker Score 0: 35% Brooker Score I: 26% Brooker Score II: 15% Brooker Score III: 19% Brooker Score IV: 5% Brooker Score I-IV: 65%	87.0 ± 10.0	Radiolucent lines greater than 1 mm: 7
Summary	NR	NS difference between groups	NS difference between groups
Hamid et al (2010)[50,]	6 month follow-up		
LDRT (n=21)	Any: *33%* Grade III or IV: 33%		Post-operative infection: 2 (9%) Non-union: 8 (38%)
Surgery alone (n=24)	Any: 54% Grade III or IV: 31%		Post-operative infection: 2 (8%) Reoperation for HO excision: 3 (12%) Non-union: 1 (4%)
Summary	p=.2		p=.007 for rate of non-union; NS for all other events

CI: confidence interval; HHS: Harris hip score; HO: heterotopic ossification; HR: hazard ratio; IAHHS: investigator-assessed Harris hip score; LDRT: low-dose radiotherapy; NNT: number needed to treat; NR: not reported; NS: not significant; OR: odds ratio; PAHSS: patient-assessed Harris hip score; RCT: randomized controlled trial; RR: relative risk.

[1] Include number analyzed, effect in each group, and measure of effect (absolute or relative) with CI,

[2] Describe the range of sample sizes, effects, and other notable features in text.

The purpose of the study limitations tables (see Tables 15 and 16) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 15. Study Relevance Limitations for Heterotopic Ossification

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Knelles et al (1997)[41],	5. Control group composed of historical patients				2. Not sufficient duration for harms
Moore et al (1998)[47],					
Kolbl et al (1998)[51],	5. Control group composed of historical patients				2. Not sufficient duration for harms
Sell et al (1998)[43],					2. Not sufficient duration for harms
van Leeuwen et al (1998)[44],	5. Patient characteristics poorly defined				
Kienapfel et al (1999)[45],					
Burd et al (2001)[48],	5. Study population varies on baseline injury severity				
Ince et al (2007)[46],	5. Control group composed of historical patients				
Hamid et al (2010)[50],					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 16. Study Design and Conduct Limitations for Heterotopic Ossification

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Knelles et al (1997)[41],	3. Allocation concealment unclear	1. Participants or study staff not blinded			1. Power calculations not reported	

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Kolbl et al (1998)[51],	3. Allocation concealment unclear	4. Blinding of assessors and participants unclear			1. Power calculations not reported	
Moore et al (1998)[47],	3. Allocation concealment unclear	1. Participants or study staff not blinded		6. Not intent to treat analysis		
Sell et al (1998)[43],	3. Allocation concealment unclear	1. Participants not blinded 4. Blinding of assessors unclear			1. Power calculations not reported	
van Leeuwen et al (1998)[44],		4. Blinding of assessors and participants unclear			1. Power calculations not reported	
Kienapfel et al (1999)[45],	3. Allocation concealment unclear	4. Blinding of assessors and participants unclear		1. High loss to follow-up or missing data	1. Power calculations not reported	
Burd et al (2001)[48],	3. Allocation concealment unclear				1. Power calculations not reported	
Ince et al (2007)[46],	3. Allocation concealment unclear					5. Statistical comparison of HO rates not performed
Hamid et al (2010)[50],		4. Blinding of assessors participants unclear		7. Study terminated early before recruited desired sample size		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Nonrandomized Studies

Pakos et al. (2009) conducted a prospective study comparing combined LDRT and indomethacin versus indomethacin alone for preventing HO after THA.[52,] Patients received either postoperative LDRT (7 Gy single fraction) plus indomethacin for 15 days (n=49) or indomethacin alone for 15 days (n=47). A historical control group that received only indomethacin was also included (n=50). The primary outcome was radiographic evidence of HO at 6 months. HO developed in significantly fewer patients in the combined therapy group (8.2%) compared to the indomethacin alone (27.6%, p=.01) and historical control (26%, p=.03) groups. No significant differences were found in clinically significant HO or functional outcomes between groups. At 10 years follow-up there were no significant differences in implant loosening between groups (1 case in each group), and no radiation-induced tumors were identified in either group.[53,] Study characteristics and outcome data from the included nonrandomized studies are presented in Tables 17 and 18.

Weng et al. (2015) performed a retrospective study comparing postoperative radiotherapy versus no prophylaxis for preventing HO in patients with ankylosing spondylitis undergoing THA.[54,] Patients received either postoperative RT (5 Gy single fraction, n=76) or no prophylaxis (n=53). The primary outcome was radiographic evidence of HO at minimum 12 month follow-up. There was no significant difference in overall HO incidence between the RT group (35.5%) and the no prophylaxis group (26.4%, p=.210). No patients in either group developed clinically significant HO (Brooker grade III-IV). Several case series investigating LDRT for the prevention of HO were identified. [39,55,56,] Sample sizes amongst the included studies ranged from 36 to 39 individuals with follow-up periods ranging from 8 months to 6 years. Sites of involvement included hip, elbow, and knee; most authors reported very low rates of treatment failure and HO recurrence with limited occurrence of treatment-related adverse events.

Table 17. Summary of Key Nonrandomized Trials OR Observational Comparative Study Characteristics for Heterotopic Ossification

Study	Study Type	Country	Dates	Participants	LDRT	Comparator	Follow-Up
Pakos et al (2009)[52,]; Pakos et al (2019[53,])	Cohort	Greece	2004-2006	Individuals treated at the single orthopedic center who underwent THA and were at a high risk of HO (previous HO formation, hypertrophic arthritis)	7 Gy x 1 within 3 days of THA and 75 mg/day indomethacin for 15 days post-op (n=49)	Indomethacin for 15 days post-op (n=47) Historical indomethacin group (n=50)	10 years
Weng et al (2015)[54,]	Cohort	Taiwan	2004-2012	Individuals with ankylosing spondylitis who underwent THA and were at a high risk for HO.	5 Gy x 1 within 2 days of THA (n=53)	No prophylactic treatment (including medication) (n=38)	Mean follow-up 6.7 to 8.1 years in the control group and LDRT, respectively

HO: heterotopic ossification; LDRT: low-dose radiotherapy; THA: total hip arthroplasty.

Table 18. Summary of Key Nonrandomized Trials OR Observational Comparative Study Results

Study	Heterotopic Ossification, % (LDRT; Control)	Harris Hip Score (LDRT; Control)	Adverse Events:
Pakos et al (2009)[52,]; Pakos et al (2019[53,])	6 mos		
LDRT (n=49)	Total: 8% Brooker Score I: 4% Brooker Score II: 2%		Mild nausea: 3 (6%) Implant loosening at 10 years: 1 (2%)

Study	Heterotopic Ossification, % (LDRT; Control)	Harris Hip Score (LDRT; Control)	Adverse Events:
	Brooker Score III: 2% Brooker Score IV: 0%		
NSAIDs (n=47)	Total: 28% Brooker Score I: 23% Brooker Score II: 4% Brooker Score III: 0% Brooker Score IV: 0%		Mild nausea: 2 (4%) Implant loosening at 10 years: 1 (2%)
Historical control (NSAIDs) (n=50)	Total: 26% Brooker Score I: 20% Brooker Score II: 4% Brooker Score III: 2% Brooker Score IV: 0%		Mild nausea: 5 (10%) Implant loosening at 10 years: 1 (2%)
Summary	LDRT vs NSAID: p=.01 LDRT vs Historical Control: p=.03		No malignancies related to radiation therapy were identified through 10 years follow-up for the LDRT of NSAID groups
Weng et al (2015)[54,]	3 mos	Mean score at 3 mos ± SD	
LDRT (n=53)	Total: 36% Brooker Score I: 26% Brooker Score II: 9% Brooker Score III: 0% Brooker Score IV: 0%	Pre-op: 51.6 ± 2.5 Post-op: 93.1 ± 2.4	
No additional prophylaxis (n=38)	Total: 26% Brooker Score I: 25% Brooker Score II: 2% Brooker Score III: 0% Brooker Score IV: 0%	Pre-op: 51.3 ± 2.6 Post-op: 93.4 ± 3.1	
Summary	p=.21	p=.47	No wound dehiscence or wound healing complications reported in either group.

CI: confidence interval; Diff: difference; HR: hazard ratio; LDRT: low-dose radiotherapy; mos: months; NNT: number needed to treat; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SD: standard deviation.

[1] Include number analyzed, association in each group and measure of association (absolute or relative) with CI.

Section Summary: Postoperative Low-Dose Radiotherapy for the Prevention of Heterotopic Ossification

For the prevention and treatment of HO with LDRT, 2 systematic reviews, 9 RCTs, 2 non-randomized comparative studies, and several single-arm studies have been published. While single-arm studies have generally reported positive outcomes in preventing HO formation, the RCT evidence base is characterized by mixed results finding benefit to control treatments but not active comparators. One systematic review found a non-significant but clinically meaningful reduction in HO presence for RT compared to control groups; other outcomes were determined to have insufficient evidence due to heterogeneity among studies and limited comparative data. A second review observed that prophylaxis with NSAIDs resulted in lower ranges of post-surgical HO than LDRT but noted that the LDRT studies included only high-risk patients, whereas NSAIDs were used to treat high-risk patients only in a minority of studies. All comparative studies found LDRT to be superior to historical control groups (receiving surgery alone with no additional HO prophylaxis). The incidence of HO was found to be not statistically significantly different from NSAID treatment in 5 studies, but 1 RCT and 1 non-randomized comparative study found LDRT superior. Ten comparative studies reported on the incidence of adverse events, most commonly post-operative infection, manipulation, prolonged wound secretion, wound dehiscence, deep vein thrombosis, dyspepsia, implant migration, and presence of radiolucent lines, which were not significantly different between LDRT and comparison groups. Two RCTs reporting non-union rates yielded conflicting results: 1 found lower rates in NSAID-

treated patients compared to those receiving LDRT after elbow fracture surgery, while the other observed significantly higher non-union rates in acetabular fracture patients treated with NSAIDs versus LDRT.

Radiotherapy for the Prevention of Keloid

Clinical Context and Therapy Purpose

The purpose of adjuvant low-dose radiotherapy (LDRT) in individuals who have keloids is to prevent the recurrence of keloid formation following surgical excision and as an alternative to other treatments, such as corticosteroid injections, cryosurgery, pressure therapy, intralesional 5-flourouracil, or laser or phototherapy, used in conjunction with surgical removal of the keloid.
The following PICO was used to select literature to inform this review.

Populations

The relevant population(s) of interest is individuals with keloids undergoing surgical removal.

Interventions

The therapy being considered is adjuvant LDRT administered either as a course of multiple small fractions OR as a single treatment of up to 20 Gy.

Low-dose radiotherapy for the prevention of keloids following surgery is proposed to inhibit excessive scar formation and reduce the risk of keloid recurrence. It is thought to work by reducing inflammation as well as suppressing fibroblast proliferation and collagen production which modulates the wound healing process and promotes normal scar formation. LDRT is recommended to be initiated within a day of surgery. [6,57,]

Comparators

Comparators of interest for the prevention of keloids include intralesional corticosteroid injections, pressure therapy, cryotherapy, laser therapy, 5-fluorouracil injections, platelet-rich plasma, and topical treatments.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, medication use, and treatment-related morbidity. Specifically, outcomes of interest include keloid recurrence, patient satisfaction, pain, and improvement in functional outcomes and QOL.
The Vancouver Scar Scale (VSS) is a clinical assessment tool for evaluating the appearance and characteristics of scars.The total VSS score ranges from 0 to 14, with 0 representing normal skin and 14 indicating the most severe scarring. [58,] The scale assesses four parameters, with higher scores indicating more severe scarring:

- Vascularity: Normal (0), Pink (1), Red (2), Purple (3)
- Pigmentation: Normal (0), Hypopigmentation (1), Mixed (2), Hyperpigmentation (3)
- Pliability: Normal (0), Supple (1), Yielding (2), Firm (3), Banding (4), Contracture (5)
- Height: Flat (0), <2mm (1), 2-5mm (2), >5mm (3)

The Patient and Observer Scar Assessment Scale (POSAS) is a comprehensive tool for evaluating scar characteristics from both the patient's and clinician's perspectives. The patient and observer scar assessment scale: a reliable and feasible tool for scar evaluation. Each item is scored from 1 (normal skin) to 10 (worst scar imaginable). The total score for each scale ranges from 6 to 60, with lower scores indicating better scar quality. [59,] The POSAS consists of two parts:
Observer Scale (completed by the clinician):

- Vascularity
- Pigmentation
- Thickness
- Relief

- Pliability
- Surface area

Patient Scale (completed by the patient):

- Pain
- Itching
- Color
- Stiffness
- Thickness
- Irregularity

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

A systematic review by the Veteran's Affairs Administration's Evidence Synthesis Program was published in 2024, which evaluated radiotherapy (RT) for benign conditions, including the treatment or prevention of keloids.[1,] The review searched databases through April 2023, including 4 RCTs and 2 non-randomized comparative studies (N=599) on the prevention or treatment of keloids. LDRT was administered from 3 hours to 4 days post-excision, with total doses ranging from 7 to 32 Gy and a mean post-treatment follow-up ranging from 6.5 to 15 months. A meta-analysis of 4 RCTs showed a non-significant reduction in the rate of keloid recurrence between groups (OR, 1.32; 95% CI,.040 to 4.33; I^2=53%); sensitivity analyses did not alter these findings. Findings were mixed for the outcome of pruritus with one RCT finding a greater incidence in the LDRT group compared to triamcinolone alone and another finding no difference between RT and 5-FU and betamethasone. Findings were also mixed for telangiectasia with 1 RCT finding a lower rate in patients who received LDRT versus triamcinolone, and 1 RCT found no difference between LDRT and 5-FU and betamethasone. One included RCT reported an improvement in appearance post-surgery for the adjuvant LDRT group compared to betamethasone alone on the Vancouver Scar Scale (VSS) and Patient Observer Scar Assessment Scale (PSAS) and the observer (OSAS) scales, and 1 RCT reported no difference in pain between groups. The authors found that there was no difference in the rate of pain after LDRT compared to alternative treatments with a low level of confidence, and for all other outcomes, including keloid recurrence, the evidence was insufficient to draw conclusions.

A meta-analysis published in 2024 by Fu et al. compared surgical excision followed by adjuvant LDRT to laser therapy combined with steroids for the treatment of keloids.[60,] The review included 26 studies with 989 patients, analyzing data through August 2023. The meta-analysis found that the pooled recurrence rate of keloid was similar between laser therapy plus steroids (12.2%; 95% CI, 5.9% to 18.5%) compared to surgery plus radiotherapy (13.5%; 95% CI, 6.6% to 22.2%). Laser plus steroids had higher rates of atrophy (22.7% vs. 0%), telangiectasia (6.4% vs. 3.2%), erythema (3.3% vs. 2.3%), and infection (3.3% vs. 0.2%) compared to surgery plus radiotherapy, but hyperpigmentation was lower with laser plus steroids (6.5% vs 8.3%). The authors found both treatments were effective and safe for keloid treatment with relatively low recurrence and complication rates, but noted that heterogeneity across studies makes directly comparing the two treatments challenging.

Table 19. SR & M-A Characteristics for the Prevention of Keloids

Study	Dates	Trials	Participants[1]	N (Range)	Design
Fu et al (2023)[60,]	Inception-2023	RT: 21 studies LT + triamcinolone acetonide: 4 studies	Studies that enrolled patients with laser therapy plus steroids or radiotherapy plus surgical excision for keloids were eligible for inclusion if they reported recurrence and adverse events	2561 (23-335)	RCT, cohort studies, case series
Jutkowitz et al (2024)[1,]	Inception-2023	10 studies (8 RCTs included in meta-analysis)	Studies of individuals undergoing radiotherapy for the treatment or prevention of keloids	6 studies (4 RCTs and 2 non-randomized comparative studies) RT: 291 Comparison: 308	RCT, non-randomized controlled studies

[1] Key eligibility criteria.

Table 20. SR & M-A Results for the Prevention of Keloids

Study	Recurrence Rate % (95% CI); p-value	Adverse Events % (95% CI)
Fu et al (2023)[60,]		
Total N	Total 24 studies (20 for RT)	RT; LT+ steroids
Pooled effect (95% CI)	RT: 13.5% (6.6% to 22.2%); p<.001 LT + Steroids: 12.2% (5.9% to 18.5%); p<.001	Atrophy: 0% (0% to 1.2%); 22.7% (1.1% to 56.4%) Telangiectasia: 3.2% (.4% to 7.6%); 6.4% (.1% to 18.6%) Hyperpigmentation: 8.3% (4.2% to 13.4%); 6.5% (.6% to 16.3%) Hypopigmentation: 2.9% (0.4% to 7.6%); 0% (NR) Erythema: 2.3% (0% to 10.6%); 3.3% (0% to 19.2%) Infection: 0.2% (0% to 10.6%); 0.3% (0% to 11%)
I^2 (p)	RT: 86.7% (<.001) LT + Steroids: 0% (0.86)	Atrophy: 0%; 84.8% Telangiectasia: 56%; 64.8% Hyperpigmentation: 58%; 0% Hypopigmentation: 31%; 0% Erythema: 78%; 76% Infection: 59%; 0%
Jutkowitz et al (2024)[1,]		
Total N	RT: 291 Comparison: 308	
Pooled OR (95% CI; I^2)	1.32 (0.40 to 4.33; 53%)	

CI: confidence interval; EBRT: external beam radiotherapy; LT: laser therapy; NR: not reported; OR: odds ratio; RT: radiotherapy.

Randomized Controlled Trials

Sclafani et al. (1996) conducted an RCT comparing postoperative corticosteroid injections to radiation therapy for preventing earlobe keloid recurrence after excision in 31 patients.[61,] One group received triamcinolone injections at 1, 3 and 5 weeks postoperatively, while the other had 15 Gy radiation in 3 fractions over 3 days. At mean 28 months follow-up, recurrence rates were 12.5% in the steroid group

vs 33.3% in the LDRT group, but differences were not statistically significant. Study characteristics and outcome data from the included clinical trials are shown in Tables 21 and 22, respectively. Emad et al. (2010) performed an RCT comparing excision plus radiotherapy to cryotherapy plus intralesional steroids for keloids in 55 patients.[62,]One group received surgical excision followed by 12 Gy radiation in 3 fractions, while the other group underwent cryotherapy and triamcinolone injections every 3 weeks. At 19 months follow-up, the excision plus radiation group had 70.4% complete remission compared to 68.8% in the cryotherapy plus steroid group, but results between groups were not compared statistically. Side effects were more common with cryotherapy combined with steroids compared to LDRT (59.4% vs 25%).

Aluko-Olokun et al. (2014) conducted an RCT comparing intralesional steroid injection to excision plus LDRT for facial keloids in 107 patients.[63,] Patients were alternately allocated to receive either triamcinolone injections every 2 weeks for up to 6 months or surgical excision followed by 16 Gy of radiation in 4 fractions over 4 days. At 6 months follow-up, individuals treated with LDRT were more likely to recur (41.5%) than those in the steroid group (0%, p<.01). At 18 months follow-up, 81% of keloids treated with steroids were flattened compared to 58% in the excision plus radiation group (p<0.01).

Khalid et al. (2018) conducted an RCT comparing excision plus 5-fluorouracil/triamcinolone injections to excision plus LDRT for ear keloids in 60 patients.[64,] One group received excision followed by 5-FU/triamcinolone injections monthly, while the other had excision plus 16 Gy radiation in 4 fractions. The 5-FU/steroid group had 73.3% efficacy (no recurrence at 6 months follow-up) compared to 43.3% in the radiation group (p=.01).

Li et al. (2022) performed an RCT comparing 3 treatments for keloids in 55 patients: excision plus 5-FU/betamethasone injections, 5-FU/betamethasone injections alone, and excision plus LDRT.[65,] The excision plus 5-FU/steroid group and excision plus LDRT group had similar improvements in patient and clinically assessed scar scales at 4 months, which were both superior to 5-FU/betamethasone injections without excision. Recurrence rates at 8-12 months were 11.1%, 20%, and 5.9%, respectively, and were not significantly different between groups.

Table 21. Summary of Key RCT Characteristics for the Prevention of Keloids

Study; Trial	Countries	Sites	Dates	Participants[2]	Interventions[1]	
Sclafani et al (1996)[61,]	United States	1	1991-1992	Individuals with earlobe keloids who desired removal with mean ages 27 to 29 years, depending on the treatment group	10 Gy x 1, 3 hrs post-excision (n=8) 7 Gy x 1, 3 hrs post-excision (n=8)	Triamcinolone (0.4cc) on wound closure and weeks 1, 3, and 5 (n=12) No treatment (n=3)
Emad et al (2010)[62,]	Iran	1	NR	Individuals with keloids who desired removal (trunk, upper limb, lower limb, ear lobe, scalp, neck) with mean ages ranging from 28.3 to 30 years depending on treatment group	4 Gy x 3 in 3 weeks post-excision (n=19)	Cryotherapy + triamcinolone (10 mg/ml) every 20 days (n=9)
Aluko-Olokun et al (2014)[63,]	Nigeria	1	NR	Individuals with keloids who	4 Gy x 3 in 1 week post-	Triamcinolone (10 mg/linear cm of

Study; Trial	Countries	Sites	Dates	Participants[2]	Interventions[1]	
				desired removal (trunk, upper limb, lower limb, ear lobe, scalp, neck) with mean ages ranging from 26 to 27 years depending on treatment group	excision (n=53)	scar) every 2 weeks for 6 months (n=54)
Khalid et al (2018)[64,]	Pakistan	1	2014-2015	Individuals with earlobe keloids who desired removal with mean ages ranging from 30.9 to 32.7 years, depending on treatment group	10 Gy x 2 in 2 days post-excision (n=30)	5-FU (150mg) + Triamcinolone (0.2ml/cm^2) (n=30)
Li et al (2022)[65,]	China	1	2021	Individuals with keloids who desired removal (head, face, trunk, or limbs) with mean ages ranging from 27.5 to 31 years, depending on treatment group	3.5-4 Gy x 4 in 1 week post-excision (n=17)	Surgical excision + 5-FU (250mg/10mL) + betamethasone (7g/ml) + lidocane (2 mg/ml) (n=18) 5-FU + betamethasone (n=20)

Gy: gray; NR: not reported; NRS: numeric rating scale; OA: osteoarthritis; RCT: randomized controlled trial; VAS: visual analogue scale.
[1] Number randomized; intervention; mode of delivery; dose (frequency/duration).
[2] Key eligibility criteria

Table 22. Summary of Key RCT Results for the Prevention of Keloids

Study	Recurrence, %	Time to recurrence	Rate of response, %	Self-assessment of treatment, %	Adverse Events, n (%)
Sclafani et al (1996)[61,]	Median f/u 18 mos	Median mos			
LDRT (7 Gy or 10 Gy) (n=16)	12.5%	17 mos			
Steroid (n=12)	33%	18 mos			
No Treatment (n=3)	33%	9 mos			
Summary	NS difference between groups	NR			No adverse effects were noted in any treatment group
Emad et al (2010)[62,]			Complete remission; partial remission; failure, %	Satisfied; partially satisfied; unsatisfied, % at 1 year f/u	
LDRT (n=19)			12 mos: 70.4%; 11.4%; 18.2%	12 mos: 89.5%; 10.5%; 0%	Hyperpigmentation: 5 (11.4%) Hypopigmentation: 3 (6.8%) Ulceration + necrosis:

Study	Recurrence, %	Time to recurrence	Rate of response, %	Self-assessment of treatment, %	Adverse Events, n (%)
					0% Telangictasia: 1 (2.3%) Infection and wound dehiscence: 2 (4.5%)
Cryotherapy + steroid (n=9)			12 mos: 68.8%; 3.1%; 28.1%	12 mos: 66.7%; 22.2%; 11.1%	Hyperpigmentation: 0% Hypopigmentation: 3 (9.4%) Ulceration + necrosis: 10 (31.2%) Telangictasia: 6 (18.8%) Infection and wound dehiscence: 0%
Summary			NR	NR	NR
Aluko-Olokun et al (2014)[63],		Mean	Lesion cured, %		
LDRT (n=53)	6 mos: 41.5%	15.2 weeks	6 mos: 31 (58.5%)		Any: 31 (58.4%) Pruritus: 30 (56.7%) Tenderness: 8 (15.1%) Hyperpigmentation: 6 (11.3%)
Steroid (n=54)	6 mos: 0%	NA	6 mos: 44 (81.5%)		Any: 30 (55.5%) Persistence: 10 (18.5%) Hypopigmentation: 25 (46.3%) Ulceration: 14 (26.4%) Skin atrophy: 8 (14.8%) Telangiectasia: 8 (14.8%)
Summary	NR	NA	p<.01		NR
Khalid et al (2018)[64],			Efficacy (no recurrence), %:		
LDRT (n=30)	6 mos: 56.7%		6 mos: 43.3%		Skin redness: 3 (10%) Skin epidermolysis: 0 (6.7%)
5-FU/TAC (n=30)	6 mos: 26.7%		6 mos: 73.3%		Skin redness: 0% Skin epidermolysis: 2 (6.7%) Wound dehiscence: 2 (6.7%)
Summary	p=.01		p=.01		NS difference between groups
Li et al (2022)[65],		mean VSS±SD	mean OSAS±SD	median PSAS (IQR)	
LDRT (n=17)	6%	BL: 9.24±1.92 4 mos: 4.24±1.48	BL: 31.82±5.79 4 mos: 18.53±6.15	BL: 44.00 (38.00 to 48.50) 4 mos: 16.00 (14.50 to 20.00)	Scab: 3 (18%) Telangiectasia: 2 (12%) Hyperpigmentation: 2 (12%) Hypopigmentation: 1 (6%)
Surgery + 5-FU + Steroid (n=18)	11%	BL: 10.17±2.31 4 mos: 4.56±2.06	BL: 34.06±7.67 4 mos: 18.50±6.12	BL: 43.50 (32.50 to 48.50) 4 mos: 21.00 (15.75 to 25.25)	Scab: 3 (17%) Telangiectasia: 1 (6%) Hyperpigmentation: 1 (6%) Hypopigmentation: 0%

Study	Recurrence, %	Time to recurrence	Rate of response, %	Self-assessment of treatment, %	Adverse Events, n (%)
5-FU + Steroid (n=20)	20%	BL: 9.70±1.59 4 mos: 6.10±1.17	BL: 32.40±4.49 4 mos: 23.35±3.95	BL: 42.00 (37.25 to 43.75) 4 mos: 29.00 (23.75 to 33.00)	Scab: 3 (15%) Telangiectasia: 4 (20%) Hyperpigmentation: 5 (25%) Hypopigmentation: 0%
Summary	NS difference between groups (p=.535)	Similar improvement in LDRT and excision plus 5-FU and steroid groups at 4 months (p=.936). Both LDRT and excision plus 5-FU and steroids were superior to 5-FU + corticosteroids alone (p=.028 and =.001).	Similar improvement in LDRT and excision plus 5-FU and steroid groups at 4 months (p=.987). Both LDRT and excision plus 5-FU and steroids were superior to 5-FU + corticosteroids alone (p=.008 and =.01).	Similar improvement in LDRT and excision plus 5-FU and steroid groups at 4 months (p=.09). Both LDRT and excision plus 5-FU and steroids were superior to 5-FU + corticosteroids alone (p=.017 and =.001).	NS difference between groups

5-FU: 5-fluorouracil; BL: baseline; CI: confidence interval; HR: hazard ratio; IQR: interquartile range; mos: months; NNT: number needed to treat; NA: not applicable; NR: not reported; NS: not significant; OR: odds ratio; POSAS: Patient and Observer Scar Scale; RCT: randomized controlled trial; RD:risk difference; RR: relative risk; SD: standard deviation; VSS: Vancouver Scar Scale.
[1] Include number analyzed, effect in each group, and measure of effect (absolute or relative) with CI,
[2] Describe the range of sample sizes, effects, and other notable features in text.
The purpose of the study limitations tables (see Tables 23 and 24) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 23. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Sclafani et al (1996)[61],		5. Two low-dose radiotherapy treatment arms pooled together with differing dosages			
Emad et al (2010)[62],					
Aluko-Olokun et al (2014)[63],					2. Not sufficient duration for harms
Khalid et al (2018)[64],					2. Not sufficient duration for harms
Li et al (2022)[65],					2. Not sufficient duration for harms

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3.

Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 24. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Sclafani et al (1996)[61,]	3. Allocation concealment unclear	1. Participants or study staff not blinded			1. Power calculations not reported	4. Comparative treatment effects not calculated
Emad et al (2010)[62,]	3. Allocation concealment unclear	1. Participants or study staff not blinded			1. Power calculations not reported	4. Comparative treatment effects not calculated
Aluko-Olokun et al (2014)[63,]		1. Participants or study staff not blinded			1. Power calculations not reported	
Khalid et al (2018)[64,]		1. Participants or study staff not blinded				
Li et al (2022)[65,]	3. Allocation concealment unclear	1. Participants or study staff not blinded			1. Power calculations not reported	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Nonrandomized Studies

Akinbiyi et al. (2020) conducted a retrospective study comparing three keloid treatments (N=284) at a single center over 10 years: medical management with corticosteroids (n=95), surgical excision (n=94), and surgical excision plus LDRT (n=95).[66,] Post-operative steroid use was permitted in both surgical excision and LDRT groups. Individuals who received surgical excision plus radiotherapy were more likely to have a prior history of keloids, have already failed prior treatment, and have significantly larger keloids than the other treatment groups (p<.01). Recurrence rates were similar between surgical excision (37.2%) and surgical excision plus LDRT (37.9%) groups despite the greater risk amongst LDRT patients. Complications were more common in the LDRT group than surgical

excision alone (17.9% vs 6.3%; p=.01), but none required additional surgical treatment. Study characteristics and outcome data from the included nonrandomized studies are shown in Tables 25 and 26.

Multiple case series investigating LDRT for the treatment of keloids were identified.[67,68,69,70,71,72,73,74,75,76,77,78,] Sample sizes amongst the included studies ranged from 12 to 393 individuals with follow-up periods ranging from 6 months to 12 years. Keloid location varied by study and included the abdomen, chest, ear, extremities, face, neck, and shoulder; most authors reported very low rates of keloid recurrence with minimal or no adverse events.

Table 25. Summary of Key Nonrandomized Trials OR Observational Comparative Study Characteristics for Keloids

Study	Study Type	Country	Dates	Participants	LDRT	Comparator	Follow-Up
Akinbiyi et al (2021)[66,]	NRCS	USA	2008-2017	Individuals treated for keloids to the head, neck, back upper torso, lower torso, or extremities at a single center with a mean age of 37.2 years.	3-8 Gy x 3-4 sessions in the first 2-4 days after surgical excision (n=94)	Surgical excision alone (n=95)	Median 15.4 mos

Gy: Gray; LDRT: low-dose radiotherapy; mos: months; NRCS: non-randomized comparative study

Table 26. Summary of Key Nonrandomized Trials OR Observational Comparative Study Results for Keloids

Study	Recurrence, %:	Adverse Events:
Akinbiyi et al (2021)[66,]	Recurrence, persistence of keloid, effectiveness or pain	
LDRT (n=94)	37.9%	Any AE: 17.9%
Surgical excision (n=47)	37.2%	Any AE: 6.3%
Summary, OR (95% CI)	1.03 (0.57 to 1.85)	3.88 (1.37 to 11)

AE: Adverse event; OR: Odds Ratio.

Section Summary: Prevention of Keloid

For the prevention of keloid recurrence with adjuvant LDRT, the evidence includes 2 systematic reviews, 5 RCTs, 1 non-randomized comparative study, and multiple case series were identified. Case series have generally reported positive outcomes in the prevention of keloid recurrence, but the RCT evidence base is characterized by mixed results, with some studies showing significant treatment effects of LDRT and others finding no difference or potential risks compared to alternative treatments. One systematic review found a non-significant reduction in keloid recurrence for LDRT compared to control groups, with insufficient evidence for most other outcomes due to heterogeneity among studies and limited comparative data. A meta-analysis found that the pooled rate of post-surgical keloid recurrence was similar comparing LDRT versus laser therapy plus steroids, but that the combined laser and steroid arm had a greater rate of complications. Amongst the comparative studies, 4 found equivalence between LDRT and alternative therapies for the rate of keloid recurrence (corticosteroids, 5-FU [5-fluorouracil], and corticosteroids, or surgical excision alone), while 2 studies favored excision plus intralesional corticosteroid injections with or without 5-FU compared to LDRT. One non-randomized comparative study found complications were more common with LDRT versus surgical excision alone, but 1 RCT found a lower rate of complications for LDRT compared to cryotherapy and steroid injections. The major limitations of the evidence base include a lack of blinding, low sample sizes in the absence of published power calculations, variation in LDRT treatment characteristics across studies, and a short duration of follow-up in most studies which is insufficient for the evaluation of harms. Despite not having superior outcomes to alternative adjunctive therapies for the prevention of recurrence amongst the comparative studies, LDRT was

found to be safe and, in most instances, of similar effectiveness to alternative therapies such as corticosteroid injections or intralesional 5-FU.

Other Non-Oncologic Indications

Clinical Context and Therapy Purpose

The purpose of low-dose radiotherapy (LDRT) in individuals who have achillodynia, Dupuytren's contracture, Graves ophthalmopathy, hidradenitis suppurativa, ledderhose disease, Peyronie's disease, and pterygium is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population(s) of interest are individuals with achillodynia, Dupuytren's contracture, Graves ophthalmopathy, hidradenitis suppurativa, ledderhose disease, Peyronie's disease, and pterygium who do not respond to conservative therapies.

Interventions

The therapy being considered is LDRT administered either as a course of multiple small fractions OR as a single treatment of up to 10 Gy.

Comparators

Comparators of interest for the treatment of other non-oncologic indications include standard medical management and therapies.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, medication use, and treatment-related morbidity. Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Several other dermatologic or benign tissue disorders, including achillodynia, Dupuytren's contracture, medial and lateral epicondylitis, Graves ophthalmopathy, hidradenitis suppurativa, ledderhose disease, Peyronie's disease, pterygium, tendinopathies, and trochanteric bursitis have some published evidence for the use of low-dose radiotherapy (LDRT) [1,10,3,] However, these conditions are not addressed in this medical policy due to limited high-quality evidence, varying clinical practices, or the availability of alternative standard treatments. The use of LDRT for these and other unlisted non-oncologic conditions should be considered on a case-by-case basis, taking into account the specific clinical context, potential risks and benefits, and current clinical guidelines. It is important to note that the absence of these conditions from this medical policy does not necessarily indicate a lack of efficacy or appropriateness of LDRT in these cases but reflects the focused scope of this policy. Additional indications may be added when the accrual of higher-quality evidence permits a decision regarding the net health benefit of LDRT.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

German Society of Radiation Oncology

While U.S.-based guidelines are typically prioritized when available, there are currently no such guidelines for low-dose radiation therapy (LDRT) in non-oncologic conditions. Much of the evidence for this approach originates from Germany, and The German Society of Radiation Oncology (DEGRO) guidelines reflect this body of experience. DEGRO published their Consensus Guideline on Radiation Therapy of Benign Diseases in 2015. DEGRO issued an update in 2018, but it was not translated to English. Recommendations pertaining to the indications in this review are as follows:

Osteoarthritis and Plantar Fasciitis:[79,]

- Because of general radiation protection considerations, radiotherapy should be recommended if non-radiotherapeutic approaches did not succeed.
- Patients < 40 years should be irradiated in very exceptional cases and after careful evaluation of the potential risk versus the expected benefit.
- 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.
- Success rates for pain relief and freedom of pain should be assessed 2–3 months after radiotherapy because of delayed response effects.
- DEGRO provided the following recommendations by condition:
    - Plantar fasciitis: Level of Evidence 1b (RCT evidence), Grade of Recommendation A (High-quality evidence)
    - Gonarthrosis: Level of Evidence 2c (outcomes research or ecological studies), Grade of Recommendation B (Moderate-quality evidence)
    - Coxarthrosis: Level of Evidence 4 (case series, poor quality cohort and case-control studies), Grade of Recommendation C (Low-quality evidence)
    - Hand and finger joint arthrosis: Level of Evidence 4 (case series, poor quality cohort and case-control studies), Grade of Recommendation C (Low-quality evidence)

Heterotopic ossification:[9,]

- To avoid heterotopic ossification (HO), a single radiation dose of 7–8 Gy respecting the described time window is effective.
- In patients with major risk factors postoperative fractionated radiotherapy with five fractions of 3.5-Gy daily single doses is recommended.
    - Patients with endoprosthesis or resection of HO should get radiotherapy: Level of Evidence 1 (meta-analyses, systematic reviews, or RCTs), Grade of Recommendation A (High-quality evidence)
      Fractures close to joints should get radiotherapy: Level of Evidence 2 (cohort studies, lower quality RCTs), Grade of Recommendation B (Fair-quality evidence)

Keloids:[57,]

- The affected palpable lesions should be irradiated following a definition of the target area by the physician either with X-rays or with electrons.
- Single doses of 2.0–5.0 Gy and total doses of 16.0–20.0 Gy/series with 5 fractions per week are recommended.
- Radiation therapy should be initiated immediately after surgical excision, preferably within the first 24 h.

- Patch fixation should be left unchanged to avoid dehiscence of the wound margins.
- Radiotherapy of keloids can be performed after surgery of keloid recurrences: Level of Evidence 4 (case series, poor quality cohort and case-control studies), Grade of Recommendation C (Low-quality evidence)

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 25.

Table 25. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05887284	Investigation of the Clinical Efficacy of Low-dose Ionizing Radiation in the Treatment of Osteoarthritis	132	Dec 2028
NCT05562271	Clinical Trial of Low-dose Radiation Therapy in Patients With Knee Osteoarthritis (LoRD-KNeA Trial)	114	Aug 2025
NCT05852808	Evaluation of Pain Level Reduction After Low-dose Radiation in Symptomatic Facet Joint Arthritis - A Prospective Randomized Clinical Trial.	98	Aug 2025

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:

- Clinical findings (i.e., pertinent symptoms and duration)
- Comorbidities
- Activity and functional limitations
- Family history, if applicable
- Reason for procedure/test/device, when applicable
- Pertinent past procedural and surgical history
- Past and present diagnostic testing and results
- Prior conservative treatments, duration, and response
- Treatment plan (i.e., surgical intervention)
- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
- Laboratory results
- Other pertinent multidisciplinary notes/reports: (i.e., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management), when applicable

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	77401	Radiation treatment delivery, superficial and/or ortho voltage, per day
	77402	Radiation treatment delivery, => 1 MeV; simple
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
12/01/2024	New policy.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to

treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
New Policy **Policy Statement:** N/A	**Low-Dose Radiotherapy for Non-Oncologic Indications** **7.01.179** **Policy Statement:** I. Low-dose radiotherapy is considered **investigational** for the treatment of osteoarthritis. II. Low-dose radiotherapy is considered **investigational** for the treatment of plantar fasciitis. III. Adjuvant low-dose radiotherapy may be considered **medically necessary** for the prevention of heterotopic ossification following surgery in individuals who are determined to be at high risk for the development of heterotopic ossification (see Policy Guidelines section). IV. Adjuvant low-dose radiotherapy may be considered **medically necessary** following surgical excision for the treatment of keloids (see Policy Guidelines section).