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CRITICAL REVIEW

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

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

Introduction

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

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Epidemiology

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

Presentation and pathophysiology

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

Risk factors

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

Current treatment

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

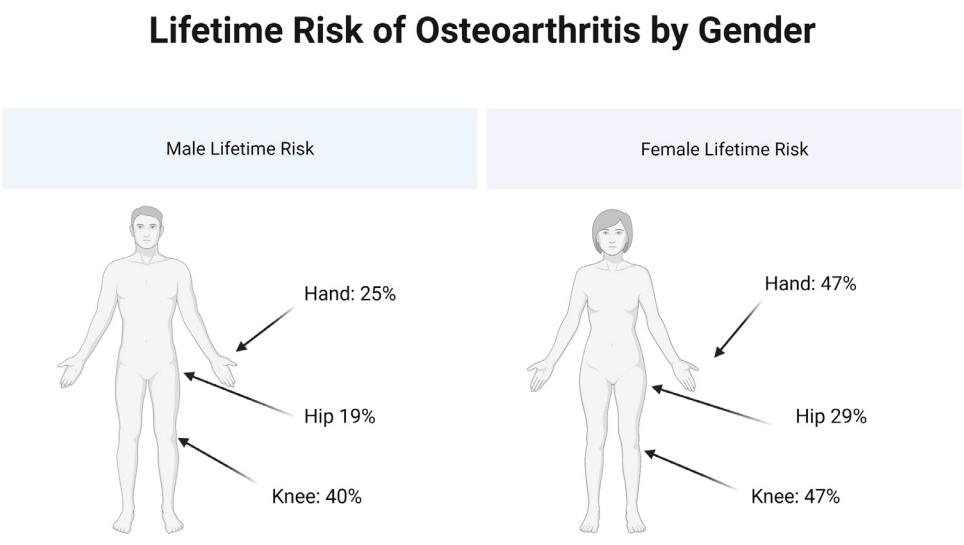

Fig. 1. Lifetime risk of osteoarthritis by sex and affected site.

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

Burden on health care system and patients

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

Overview of LDRT

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

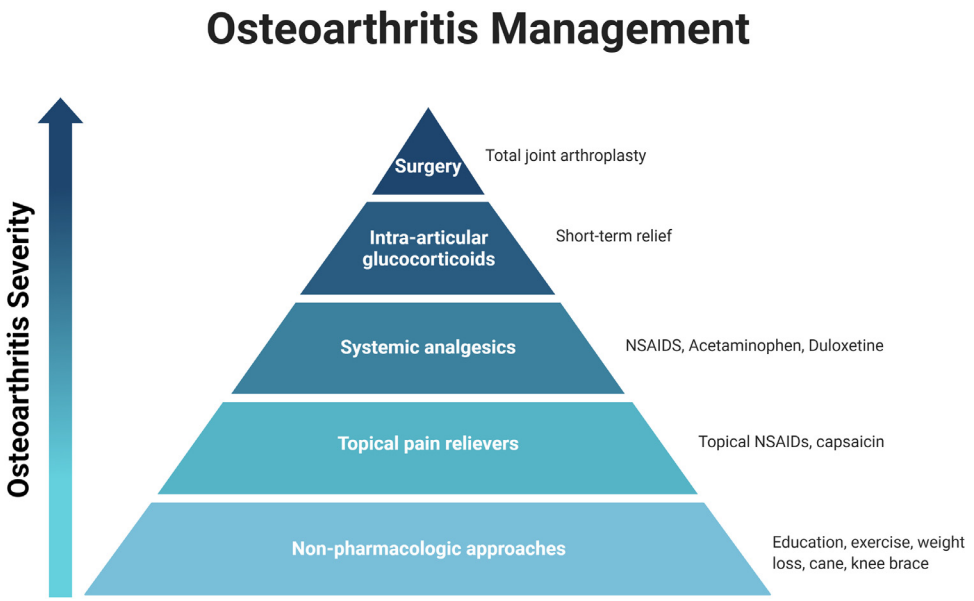

Fig. 2. Traditional management algorithm for osteoarthritis. Conservative management is first line, with progressively stronger (and potentially more toxic) pharmacologic management for persistent inflammation and pain. Surgery is reserved for patients who fail conservative and pharmacologic measures.

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

Radiobiological mechanism

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

Risk of secondary malignancy

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

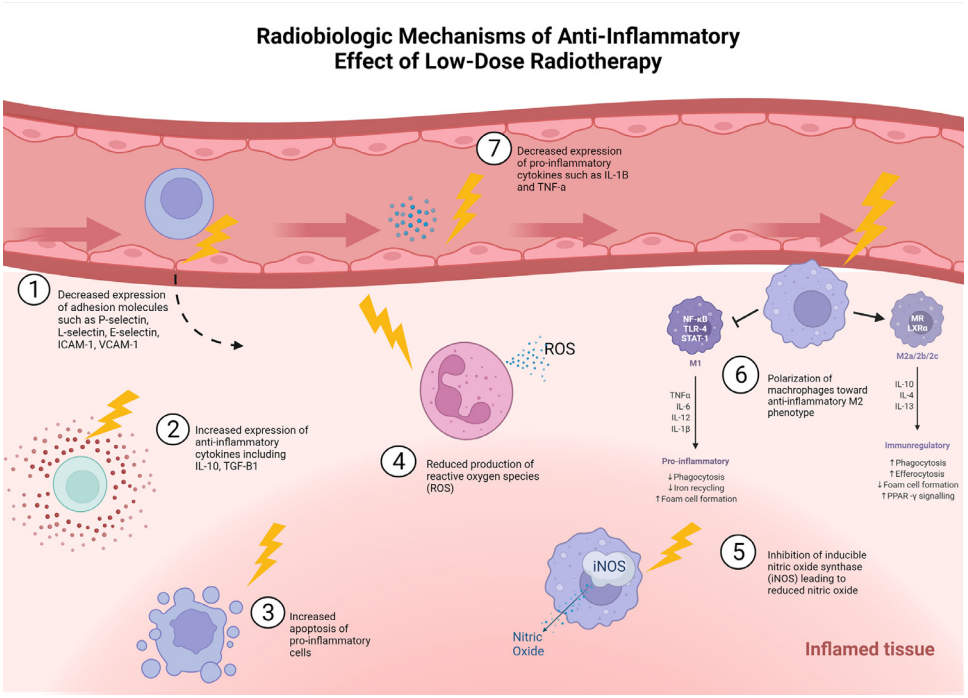

Fig. 3. Radiobiological mechanisms of anti-inflammatory effect of low-dose radiation therapy (LDRT). LDRT modulation of endothelial cells by reduced expression of adhesion molecules (1), resulting in a cascade of decreased cell migration and increased anti-inflammatory cytokines (2). Irradiated leukocytes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

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

Noncarcinogenic risks

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

History of LDRT

Beginnings

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

American experience

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

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

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

Modern Day LDRT

German pioneers

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

Recent literature for OA

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

Benefit of LDRT

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

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

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

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

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

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

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

(*Continued*)

Table 1 (*Continued*)

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

(*Continued*)

Table 1 (*Continued*)

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

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

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

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

Criticisms of LDRT

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

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

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

Future directions of LDRT for OA

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

Treatment Planning

Overview

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

Small joints

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

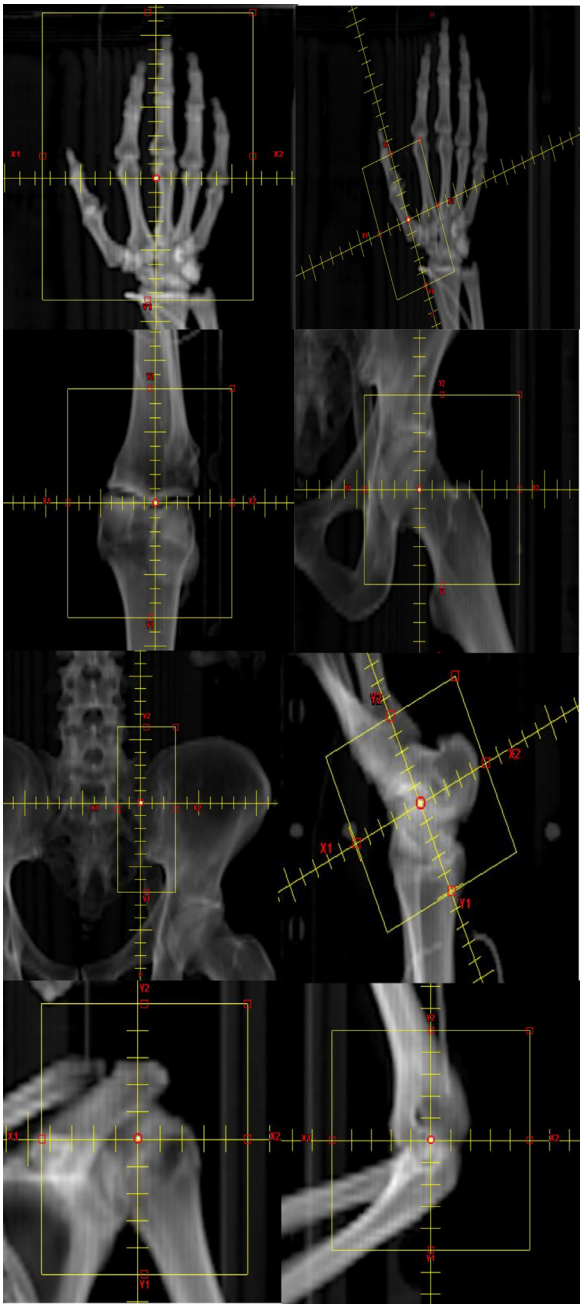

Fig. 4. Representative radiation fields for various sites of osteoarthritis (OA). Targets include third metacarpophalangeal (MCP) joint, first carpometacarpal joint, patellofemoral joint, acetabulofemoral joint, sacroiliac (SI) joint, glenohumeral joint, and humeroulnar joint. Center red circles represent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

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

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

Large joints

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

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

Treatment indications

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

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

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

(*Continued*)

Table 2 (*Continued*)

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

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

* Can consider orthovoltage.

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

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

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

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

Discussion

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

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

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

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

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

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

Conclusions

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

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