American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Use of Radiotherapy for Treatment of Osteoarthritis

Expert Panel for Use of Radiotherapy in the Treatment of Arthritis:
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Conflict of Interest Disclosure Statement

All panelists were required to declare all conflicts of interest for the previous 36 months prior to initiating work on this document. These complete disclosure forms are retained by the American Radium Society™ in perpetuity. The ARS Appropriate Use Criteria Steering Committee reviewed the disclosures with the chair and co-chair of this document and approved participation of the panelists prior to starting development of this work. Disclosures potentially relevant to the content of this guideline are provided:

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Introduction/Background

Introduction

Osteoarthritis (OA) is a progressive disease associated with joint stiffness, pain, and loss of mobility and is the 7th leading cause of disability worldwide, especially in patients over the age of 70.[1]. Risk factors include older age, higher body mass index, family history of OA, female sex, anatomic abnormalities, and previous joint injury.[2] OA is estimated to affect 7.6% of the global population, equivalent to 595 million individuals.[1] Prevalence of OA has increased by 132.2% over the past 30 years and is projected to rise by 60 to 100% by 2050.[1] Early-onset OA (EO-OA; occurring before age 55) rates have doubled between 1990 and 2019 accounting for much of the increase.[1] It is estimated that by the year 2040, over 10% of all adults will experience arthritis-related activity limitations, which may also increase the risk of developing other associated comorbid illnesses such as heart disease and depression.[3] The increase in OA has a profound impact on economic expenses, both directly due to cost of medical care, and indirectly due to productivity losses. One study estimated that OA resulted in global economic expenses exceeding 106.87 billion US dollars in 2019.[4]

Historically OA was considered a degenerative process, and is now recognized to be a complex process with inflammatory components. Proinflammatory mechanisms drive the recruitment of proteases, which lead to degradation of extracellular matrix and damage to bone, cartilage, menisci, ligaments, and synovium.[5] This damage is then exacerbated by biomechanical factors including excessive joint loading. Treatment of osteoarthritis varies with severity of disease. For mild cases, non-pharmacologic approaches such as education, exercise, weight loss, and braces are used. When non-pharmacologic approaches are insufficient, including non-steroidal anti-inflammatory (NSAIDS) and cyclooxygenase-2 (COX-2) inhibition agents are used, but are associated with risks such as gastrointestinal bleeding, acute and chronic renal failure and cardiovascular complications.[6,7] Intra-articular therapies including glucocorticoid or hyaluronic acid are more commonly used for patients with more severe OA.[8] Typically, multiple treatment strategies are used simultaneously. Surgical interventions, such as genicular artery ablation, radiofrequency ablation, arthroscopic surgery, and joint replacement are typically reserved for patient with OA that does not respond to other treatments. These costly therapies continue to contribute to the rising global expenses of OA. Hence incorporating additional therapies that improves outcomes for early-stage OA patient would be beneficial to patients and health care systems.

Biologic Rationale:

Low dose (LD) radiation therapy (RT) is a non-invasive treatment first reported in 1898 by Sokolaw who reported complete pain relief in 4 patients with OA.[9] Subsequent early studies using variable dose and fractionation schedules confirmed the benefit of RT in approximately two-thirds of patients with OA.[10] LDRT modulates immune response in degenerative joints by acting as an anti-inflammatory and subsequently, a pain-relieving modality. Low doses of RT have demonstrated anti-inflammatory effects by modulating inflammatory pathways, including the activity of endothelial cells, leukocytes, and macrophages, which secrete proinflammatory cytokines (such as TNF-α and IL-1β), reactive oxygen species, and nitric oxide.[11] LDRT reduces pro-inflammatory mediators (such as IL-1 and TNF) while increasing anti-inflammatory cytokines (such as TGF-1β1).[11] Activation of Nrf2 is induced by LDRT and appears to be a mediator of the antioxidant and anti-inflammatory responses by decreasing reactive oxygen species and increasing anti-oxidant enzymes (such as HO-1 and NQO1).[12] Activated Nrf 2 also inhibits the NF-κB pathway which also drives inflammation. Lastly, Nrf2 activation drives macrophage activation to the M2 anti-inflammatory state.[12] Low doses of RT have been shown to reduce nitric oxide production via modulation of macrophages through inhibition of nitrous oxide synthase[11-13] and polarizing macrophages toward M2 phenotype, reducing pro-inflammatory cytokine production.[12,14] It should be noted that higher doses of RT can polarize macrophages toward a proinflammatory M1 phenotype[14], illustrating the importance of dose fractionation in the treatment of OA. In addition, LDRT induces apoptosis in activated lymphocytes and synoviocytes resulting in reduced inflammation in the synovium. Low doses 0.3 and 1 Gray [Gy]) of RT have been shown to increase apoptosis and reduce adhesion and migration of leukocytes[11,14], as well as reduced leukocyte proinflammatory cytokine production.[14-16] In summary, LDRT reduces chronic inflammation by reducing proinflammatory cytokines and immune cell activation that contributes to OA pain and joint degradation, modulates macrophages to a less inflammatory phenotype resulting in reduced release of synovial inflammatory mediators, and stimulates anti-oxidant responses to mitigate joint damage. The end result is inhibition cytokines associated with pain and symptomatic relief. These effects are observed with very low RT doses which aims to minimize risk of secondary malignancies (as compared to higher RT doses used in cancer therapy. Preclinical studies using animal models demonstrate

that single doses of 0.5 to 1.5 Gy and total doses of 2.5 to 7.5 Gy result in anti-inflammatory efficacy.[17-19] A prospective study (IMMO-LDRT01 trial NCT02653079) investigated the effects of LDRT on peripheral blood immune status demonstrating that during and following 6 RT fractions of 0.5 Gy per fraction. Although there was no change in the total number of leukocytes, a slight reduction of B cells and an increase of eosinophils, basophils and plasmacytoid dendritic cells was observed. Furthermore, activated immune cells were decreased following LDRT, including a decrease in monocytic lineage cells which correlated to improvement in clinical symptoms in an interim analysis.[20,21] Additional studies continue to evaluate the exact mechanism of LDRT on inflammation.

Until recently, RT was rarely used to treat OA outside of Europe. In 1995 the Deutsche Gesellschaft für Radioonkologie (DEGRO), the German Society for Radiation Oncology, formed a task group to investigate the role of LDRT in the treatment of benign diseases (GCG-BD) which concluded that LDRT using modern techniques is effective in the treatment of OA and provides symptomatic pain relief in 60% to 90% of irradiated OA patients with almost no acute side effects.[22] There has been a renewed and growing interest in the use of LDRT as a cost-effective treatment for OA resulting in publication of many retrospective and prospective studies outlining the clinical benefit of this treatment. Recently, the DEGRO guidelines were updated in 2022.[23] These publications continue to evaluate criticisms regarding use of LDRT for the treatment of OA, which include risk of secondary malignancy[24] and the potential impact on future surgery, although there are no data that demonstrates negative impact on subsequent surgical procedures or any published case reports of secondary malignancy from LDRT treatment.[23]

Although use of LDRT has been long known to be effective in the treatment of OA, is not universally included in OA guidelines. This publication is anticipated to be of high interest not only to specialists including rheumatologists, orthopedic surgeons, and radiation oncologists, but also to the general practitioner, with the potential to help millions of patients given the expanding population with OA and the resurgence in interest in LDRT for treatment of OA.

This systematic review and guidelines summarize the current evidence for the appropriate use of Radiotherapy in the Treatment of OA and is intended to guide treatment decision making when considering LDRT for the treatment of OA. Herein, we review and outline studies with the highest quality of evidence published using modern RT techniques and discuss current treatment recommendations. The Population, Intervention, Comparator, and Outcome (PICO) questions included: (1) What is the role of LDRT for treatment of OA? (including patient selection), (2) What are the risks of LDRT for treatment of OA?, and (3) What is the optimal RT technique for treatment of OA? (including dose fractionation, life-time dose limit, modality and treatment volumes for different OA locations).

Methodology

This ARS AUC multi-specialty-led committee is comprised of radiation oncology, rheumatology, and orthopedic surgery specialists. Using the Population, Intervention, Comparator, Outcome, Timing and Study Design (PICOTS) framework, the evidence regarding treatment outcomes was assessed using Cochrane and PRISMA 2020 methodology.[25,26] Eligible studies included prospective studies, phase II-III trials, and retrospective analyses including $\geq$ 50 patients published between 1/1/2010 – 5/10/2025 in the Embase, Medline and PubMed databases. **Appendix A** contains the database search strategy. The lead authors independently screened the comprehensive list of articles, and one assessed the full text articles to determine the final studies included in the Summary of the Literature Review which advised our recommendations (**Appendix B**). Discrepancies between the reviewers were resolved by consensus. Of the 548 articles identified using the search strategy, 44 were selected for inclusion that met all inclusion criteria. Eight additional studies were included through backward citation searching that significantly contributed to the literature were identified from the reference list of articles found from the search strategy. An additional 31 studies referenced outside the "Summary of Literature Review" are included to provide context, but unless they are also cited within the "Summary of Literature Review" they were not used by the committee to guide recommendations. In total, 83 references were selected for inclusion (**Appendix C**). Study type and quality for these references were assessed via American Radium Society™ (ARS) Appropriate Use Criteria (AUC) methodology (**Appendix C**). The systematic review PRISMA 2020 checklist confirms the completion of essential elements (**Appendix D**). This projects follows the ACcurate COnsensus Reporting Document (ACCORD) consensus methodology using well-established RAND-UCLA consensus methodology (modified Delphi) to rate the appropriateness of the treatment options[27], with a total of 2 rounds of voting employed by the group. Categories included (1) usually not appropriate (U, score

1-3); (2) may be appropriate (M, score 4-6); and (3) usually appropriate (A, score 7-9). The project proposal as well as this executive summary were reviewed and approved by the ARS AUC steering committee, which includes a librarian with expertise in systematic reviews. For further details on ARS AUC methodology guidelines. See https://www.americanradiumsociety.org/page/aucmethodology.

Patient Advocate Statement:
"As a patient, I am all too familiar with OA as a significant contributor to disability characterized by pain, functional impairment, and a diminished capacity to engage in occupational, familial, social, and community activities. While its causes encompass various factors, some of which can be prevented or mitigated, OA frequently leads to a marked decline in quality of life, with limited therapeutic options available beyond NSAIDs or surgical intervention. As a patient advocate, I have been involved identifying gaps in patient-oriented measurement of the impact of arthritis and areas of need in the development of arthritis intervention. Advancing effective treatment options is not only important to the health and well-being of millions of OA patients, but also to improve the ability of these individuals as functioning members of society. I am hopeful that evidence-based guidelines such as these, will introduce more effective treatment options available to patients, and provide the necessary evidence for health care insurers to accept these therapies as cost-effective standards of care. The application of LDRT as a pain management strategy introduces a promising avenue for individuals who derive minimal benefit from conventional treatments and are deemed unsuitable for surgery. This approach may serve as a valuable addition to the limited repertoire of solutions for managing OA-related pain."

Summary of Literature Review

Topic 1/ What is the role of LDRT for treatment of OA?

Subtopic 1/ What are the clinical benefits associated with the use of LDRT for treatment of OA?

Well-established treatments for OA in the US include, lifestyle management (weight loss, exercise, bracing, physical therapy), pharmacologic treatment (NSAIDs and COX-2 inhibitors), intra-articular injections, and surgical management. The choice of therapy depends on the severity and response to prior therapies. Typically, multiple treatment strategies are used simultaneously. In general, the response rate for a newly diagnosed OA patient to multimodality lifestyle management is less than 50%[28]. Of the patients who require pharmacologic management, approximately 25% of patients will not respond to pharmacologic management or lose responsiveness over time[29]. Furthermore, many will need to discontinue treatment due to adverse effects, including acute and/or chronic renal failure[7], gastrointestinal toxicity[7] which is associated with a 4-fold risk of gastrointestinal bleed[30], and cardiovascular toxicity[6,7]. For example, there is an excess risk of non-fatal (7 in 1000) and fatal (2 in 1000) cardiovascular events in older patients who routinely take NSAIDs[6]. Patients who receive intra-articular therapy have inconsistent responses, often require multiple injections, and may become refractory, warranting consideration of alternative therapies. Interventional procedures for OA (including genicular artery ablation, radiofrequency ablation, arthroscopic surgery and joint replacement) are associated with risks of bleeding, infection, and iatrogenic procedural complication, and may require repeated treatment or revisions over time, contributing to financial toxicity. Incorporation of LDRT can provide additional therapy options that can potentially improve outcomes and lower costs of treatment for OA.

In the modern treatment era of LDRT for OA, multiple studies have been published demonstrating clinical benefits including pain reduction, increased joint mobility, and improved quality of life. While various factors including severity of disease, chronicity of diagnosis, and other co-morbidities can affect response rates, large retrospective and prospective studies have shown overall treatment response rates of 60-90%[29,31-38]. In one of the largest retrospective studies published, Mücke et al. published a large cohort study of almost 5,000 treated patients with knee OA from 230 institutions in Germany showing a 60% pain reduction at 3 months following treatment with no acute side effects reported[37]. Multiple other large retrospective studies have been published confirming both effectiveness and safety of treatment[31,32,34].

In addition to retrospective data, several prospective studies have also been published showing similar response rates, strengthening the evidence for use of LDRT for OA[20,21,35,36,39-43]. A prospective randomized trial published by Makarova randomized 283 patients to pharmacologic treatments (oral glucosamine and chondroitin) or pharmacologic treatment with the addition of LDRT demonstrated a statistically significant improvement in quality of life measures at 3 years

follow up, including pain and joint function, emotional, social, mental health, and vitality, associated with use of LDRT compared to pharmacologic management alone[39]. It should be noted that although these pharmacologic treatments are standard of care in Russia, they are not regulated nor generally recommended in the US. Nine-year follow up data showed a 67% risk reduction for knee arthroplasty and 50% reduction in disability enrollment in patients treated with LDRT compared to pharmacologic management alone[35]. This trial also included MRI data demonstrating improved cartilage thickness, less bone marrow edema, and decreased osteophyte formation in patients treated with LDRT versus pharmacologic management alone[44].

In 2025, Fazilat-Panah et al. published a double-blind sham -controlled randomized trial which reported statistically significant improvement in pain score and decreased analgesic consumption in patients treated with LDRT, making it the first study of its design to show a benefit of LDRT over sham RT[36].

The ArthroRad trial randomized 133 patients with hand or knee OA to either 3 Gy in 6 fractions twice weekly versus 0.3 Gy in 6 fractions twice weekly[45]. At both 3 month and 12 month follow up pain improvement was seen in over 60% of patients in both arms. Lastly, an interim analysis of the IMMO_LDRT01 nonrandomized prospective trial evaluated pain response and peripheral blood modulation after LDRT in 125 OA patients and showed decreased pain and down-regulation of specific inflammatory markers in peripheral blood[20,21]. Despite the above evidence showing efficacy of LDRT, two small double blind randomized sham-controlled trial from the Netherlands were published that questioned the benefit of LDRT over placebo[46-48]. In both studies, patients were randomized to either 6 Gy in 6 fractions of LDRT or sham RT. At follow up of 3 months and 12 months, no statistically significant difference in pain outcomes were noted. Despite some aspects of these studies being well-designed, criticisms of these trials include small sample size (25 patients per arm powered for a large expected benefit), no re-irradiation offered for non-responders, and patient selection biases including chronicity and severity of disease[49].

Limited data exist to suggest particular joints sites have higher response rates compared to other locations[50]. Hand and knee joints have higher levels of evidence. For hand OA, Hermann et al. published results from a prospective series demonstrating improvement in function and pain on the mean Visual Analogue Scale (VAS) pain score following LDRT for trapeziometacarpal (TMC) arthrosis[51]. Alvarez et al. published a non-randomized prospective trial of 100 patients with hand OA (57 patients suffering from proximal/distal interphalangeal joint pain, 40 patients with thumb OA, 2 patients with radiocarpal joint pain, and 1 patient with metacarpophalangeal joint pain) treated with LDRT[41]. Prior to LDRT, mean VAS pain score was 8 with improvement after treatment at 3, 6, and 12 months of mean VAS 4, 3, and 3.5 respectively. Additionally, 70% of patients also reported functional improvement with no reported acute or late toxicity[41]. Rogers et al. published a prospective nonrandomized study of 99 OA patients (including 59 patients with interphalangeal OA) treated with LDRT showing not only pain relief but also improvement in grip strength using an isometric dynamometer[40]. Retrospective data[52] for hand OA treated with LDRT support these findings including a study published by Donaubauer et al.[29] including almost 500 patients treated reporting 70% pain improvement at 3 months following treatment..

For knee OA, both prospective and retrospective data support the benefits of LDRT. As previously discussed, Makarova et al. randomized 300 patients to standard arm of pharmacologic agents or an experimental arm with the addition of LDRT with statistically lower pain scores and improved QOL measured 3 years post treatment, reduced risk of disability enrollment of 50%, 67% reduction in knee arthroplasty rates, and decreased progression of OA via MRI findings demonstrated in patients with knee OA treated with LDRT[35]. In the large retrospective study published by Mücke et al. including nearly 5,000 patients with knee OA, pain reduction was observed in 60% of patients at 3 months[37]. Several other retrospective studies on knee specific treatment have also demonstrated similar clinical improvements[31-34,50,53,54].

In addition to knee and hand OA, other joint sites have been treated with LDRT with success. A retrospective study by Weissmann et al. demonstrated a with 3-month pain response rate of 84% in 196 foot and ankle OA patients[55]. Hautmann et al. published data of 66 patients with ankle and tarsal joint OA with median pain score reduced from 7 pretreatment to 4 at 12 month follow up[53]. Several other larger retrospective studies including foot and ankle joints show good response rates similar to other joints included[33,34,53,54 32]. Data for hip OA is limited to large retrospective data

with limited site-specific studies[32-34,53,54]. With regard to LDRT for spine OA, limited or no data is available and caution is recommended.

In summary, data for the use of LDRT including both prospective and retrospective publications support its use for LDRT in selected patients. Prospective clinical studies examining changes of serum inflammatory factors and miR-145 expression before and after treatment provides further supporting evidence for the use of LDRT for anti-inflammatory effects in the treatment of OA[56].

Table 1. summarizes studies using modern techniques using LDRT for treatment of OA.

Subtopic 2/ What is the appropriate patient selection criteria for use of LDRT for treatment of OA?

Patients should discuss all treatment options with their primary care physicians, rheumatologist, sports medicine physician, or orthopedic surgeon as appropriate. Shared decision-making should occur between the patient and their provider(s) prior to referral for evaluation for LDRT.

Multiple factors should be considered when evaluating appropriate patients for LDRT including age, joint location, and severity of disease. While LDRT has been associated with limited acute and late toxicities, concerns of ionizing RT exposure and risk of secondary malignancy should be considered when selecting patients. Given the latent risk of secondary malignancy development, in general patients under the age of 40 should not be considered appropriate for LDRT. In younger female patients, shoulder RT can lead to higher RT exposure to breast tissue, although retrospective data in this population suggests no higher risk of breast cancer than control populations[57]. In addition to age, location of treatment in relation to radiosensitive organs should be considered. While distal joints have limited RT exposure to radiosensitive organs, approximately 1-2% of total body bone marrow is located in the femoral and humeral heads and may be exposed to RT during LDRT for hips and shoulders.

With further consideration of patient selection, Hautmann et al. has demonstrated no difference in the efficacy of LDRT for treatment of OA developing in the primary[58] and post-traumatic setting.[38] When considering therapies for OA, the Kellgren-Lawrence (KL) grading system[59], which uses diagnostic X-rays to assess the severity of the condition, is commonly used. OA severity scores range from Grade 0: No radiographic features of OA, Grade 1: Possible joint space narrowing and/or osteophyte formation; Grade 2: Definite osteophyte formation and possible joint space narrowing, Grade 3: Moderate multiple osteophytes, definite joint space narrowing, some sclerosis, and possibly bone deformity, to Grade 4: Large osteophytes, marked joint space narrowing, severe sclerosis, and definite bony deformity. Choice of therapy should be influenced by grade of severity. Generally, LDRT has been reserved in patients who exhibit KL grade 1-3. For patients with advanced OA with KL grade 4 radiographic findings, response rates are expected to be lower however limited data exist to support the expected difference. LDRT is appropriate in selected KL stage 0-2 symptomatic patients as an adjunctive therapy to lifestyle management and pharmacologic agents, and has been shown to preserve cartilage thickness on serial MRI scans compared with pharmacologic management alone[35,39]. While historically LDRT has been limited to more advanced disease and in patients who have failed other previous pharmacologic or lifestyle management, LDRT appears to be appropriate in selected KL stage 0-2 symptomatic patients as an adjunctive therapy to lifestyle management and pharmacologic agents.

Topic 2/ What are the risks of LDRT for treatment of OA?

Subtopic 1/ What are the secondary malignant risks associated with LDRT for treatment of OA?

The potential risk of secondary malignancy following LDRT for OA is controversial. One hypothesis is that the risk of secondary malignancy following exposure to ionizing RT is a stochastic effect with no threshold dose and the risk increases proportionally with RT dose.[24] An alternative hypothesis is that RT-induced secondary malignancy is unlikely below a certain threshold dose. Multiple studies have tried to estimate the risk of second malignancy from LDRT[60-62] however, these estimations are based on extrapolation of data from atomic bomb survivors, or patients who developed RT-induced malignancies using older RT techniques and higher doses. The estimated risk of secondary malignancy

associated with the use of LDRT for treatment of OA should consider age, gender, volume of tissue, total RT dose, and anatomic location of treatment.[63] The risk of RT-induced malignancy is generally higher in younger individuals compared to older individuals due to factors like increased cell proliferation and a longer latent period for cancer development. Secondary malignancies due to RT exposure in middle age do not occur as often as in younger individuals and decrease with increasing age.[64] One study investigated fatal secondary malignancies following LDRT used to treat benign conditions and concluded that the estimated lifetime risk for an RT-induced fatal malignancy for a patient receiving 6 Gy LDRT for knee OA was 2 in 1000 (age 25), 0.7 in 1000 (age 50), and 0.3 in 1000 patients (age 70), respectively, when assuming an estimated effective dose of 13 mSv (similar to the effective dose received from an abdominopelvic computed tomography scan).[63,65,66] Joints in locations in close proximity to organs with higher susceptibility for carcinogenesis may be associated with a higher risk of secondary malignancy. For example, a retrospective study investigating breast cancer after LDRT for shoulder RT (delivered using ^{60}Co at a median age of 55 years) demonstrated that 7 patients (4.4%) developed breast cancer after a median of 21 years. Of important note, that according to incidence statistics 5.9% breast cancer would be expected in a control study population and the study concluded that exposure to LDRT for shoulder OA did not increase this risk.[57] Of important note, despite thousands of patients treated with LDRT for OA, no association of LDRT with secondary malignancy has ever been published but it should be recognized that lack of follow up and long-term reporting does not imply absence of the outcome. Nonetheless, the rate of secondary malignancy following LDRT using doses appropriate to treat OA is believed to be extremely low.

Subtopic 2/ What are the non-malignant risks associated with LDRT for treatment of OA?

When considering treatment options for OA, potential risks and benefits of all possible therapies must be considered. Minimal risks are associated with lifestyle management[67], whereas for pharmacologic agents, NSAIDs have shown to increase risks of gastrointestinal bleeds, cardiovascular events, and renal failure[7]. In older patients, 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[6], and a 4-fold increased risk of gastrointestinal bleed[30]. Intra-articular injections have risks of infection, bleeding, and thinning cartilage particularly with steroid injections[68]. Interventional surgical procedures include risks of infection, bleeding, blood clots, nerve damage, and arthrofibrosis[69]. While RT at higher doses have been used in other settings are associated with risks such as slow bone healing or non-union, bursitis, and wound complications, there have been no reports of these side effects associated with LDRT for treatment of OA. Mild (grade 1 - 2) erythema of the skin in the RT field has been reported as a rare side effect of LDRT[34,65,70-73], with one study reporting 2 cases of grade 1 skin toxicity in 230 patients receiving 3 Gy and 6 Gy LDRT for OA.[71] There have been no reports of grade 3-4 skin toxicity[71].

No data have been published to suggest higher risk of disease progression after LDRT. In fact, data have been published to show that LDRT might reduce risk of OA progression[39]. Preclinical studies have demonstrated decreased osteoclast and increased osteoblast activity after LDRT[74] as well as induction of a highly integrated multi-pathway process resulting in the formation of an anti-inflammatory phenotype which can both prevent the occurrence of arthritic changes and/or reverse such effects[75].

Additionally, no data have been published to show LDRT increases surgical risks or prohibit patients from undergoing surgical interventions after LDRT. Lastly, LDRT can be used concurrently with lifestyle management and pharmacologic interventions without known contraindications.

Topic 3/ What is the optimal RT technique for treatment of OA?

Subtopic 1/ What RT modality(ies) is/are appropriate for LDRT treatment of OA?

In the modern era of LDRT, multiple RT modalities have been used successfully to treat OA. Use of both orthovoltage and linear accelerator (LINAC)-based photon therapy for treatment of OA have been published with similar clinical results suggesting equipoise in treatment selection[34,70,76]. Other modalities for such as IMRT and proton therapy have limited clinical data and may be more complex techniques than necessary. When considering between LINAC and orthovoltage treatment, the main issue is thickness of tissue. Generally, a LINAC should be used for treatment of large joints, such as hip OA, whilst other joints can generally be treated with either LINAC or orthovoltage, depending on the

BMI and body habitus of the patient. A recent publication described the design of a dedicated Co-60 LDRT machine using Monte Carlo simulations to determine machine geometries with goal of providing a cost-effective treatment options with simple installation and management[77].

Subtopic 2/ What are necessary components of RT simulation for LDRT treatment of OA?
The approach for appropriate simulation and immobilizations of patients being treated with LDRT should be similar to those used for RT treatments for malignant indications. Patient positioning should focus on maximal exposure for targets with minimal exposure of normal tissues. Immobilization devices including Vac lock bags and thermoplastic devices should be considered. Cross sectional imaging with CT simulation is encouraged for 3D based planning and target delineation. Specific considerations for each disease locations are discussed in **Subtopic 6**.

Subtopic 3/ What are considerations for RT treatment planning and appropriate treatment volumes for LDRT treatment of OA?
Treatment with three-dimensional (3D)-based planning should highly be considered. While RT doses in the treatment of OA are significantly lower than for malignant conditions, an emphasis on ALARA principles particularly in limiting dose to normal tissues should be applied. Additionally, applying modern technology with improved dose calculation algorithms and 3D planning can ensure appropriate dose to intended targets while minimizing dose to organs at risk.

Multiple treatment approaches for target delineation and treatment field design have been described in the literature[78-80]. While recommendations for each joint are described in Subtopic 6., it is important to acknowledge that treatment design should be an individualized approach for each patient based on clinical history, examination, and prior treatments. In general, volumes should encompass not only the joint space and underlying bony changes, but also the surrounding joint capsule and tendon insertions. Data have been published for carpometacarpal OA that larger more comprehensive field sizes appear to have better response rates than limited fields, which probably reflects OA changes that were not covered with the smaller fields.[52] While data is lacking in other sites, surrounding tissues that are affected by the inflammatory process of OA should be included in the RT treatment volumes. **Appendix E.** provides examples of RT field designs for treatment of OA involving different joints.

Subtopic 4/ What are considered optimal RT dose/fractionation treatment regimens for LDRT treatment of OA?
Various dose fractionations have been used in both prospective and retrospective studies in the treatment of OA with LDRT within the modern era. Preclinical data demonstrate that single doses of 0.5 to 1 Gy and total doses of 2.5 to 7.5 Gy result in anti-inflammatory efficacy.[17-19] Currently, the two most commonly used dose fractionations are 0.5 Gy or 1 Gy per fraction for total of 6 fractions (total dose 3 to 6 Gy) every other day or twice weekly. While not specifically for OA, the prospective randomized Erlanger Dose Optimization Trial randomized patients with the inflammatory musculoskeletal condition of painful elbow to either 0.5 Gy or 1 Gy for total of 6 fractions[72]. With median follow up of 35 months, the authors concluded equipoise between the two doses and favored 0.5 Gy per fraction based on ALARA principles. Many have adopted 0.5 Gy for treatment of OA extrapolating from this trial. More recently published data suggests superiority of 0.5 Gy per fraction leading to increased adoption of this dose fractionation[29]. In addition, a retrospective study by Donaubauer et al. found that pain relief with 0.5 Gy per fraction was superior to that with 1 Gy per fraction in patients treated with LDRT for hand OA.[29] While 0.5 Gy per fraction is commonly selected, other data have been published showing efficacy for alternative schemes. In the recently published ArthroRad trial, even lower doses of RT with 0.05 Gy in single fractions for total of 0.3 Gy showed similar clinical response to 3 Gy in 6 fractions[81]. Additionally, the prospective randomized Russian trial used 0.45 Gy per fraction delivered on alternate days for a total of 10 fractions.[35]

In patients who undergo a first course of RT with limited or no treatment response, a second course of treatment should be considered at 8 to 12 weeks either with same dose and fractionation scheme or a modified dose and fractionation

scheme, depending on the initial dose-fractionation applied. Currently, various dose fractionation schemes are appropriate and can be utilized while future anticipated clinical trials on dose fractionation schemes are awaited.

Subtopic 5/ What is considered the life-time dose limit for retreatment for LDRT treatment of OA?

There is no well-defined life-time dose limit for the retreatment of OA with LDRT. When considering re-irradiation, each case should be evaluated on an individualized basis including various factors such as prior treatment response, time from last treatment, joint treated, expected patient prognosis, and other treatment options available. For patients who undergo initial treatment with minimal or no treatment response at 6 to 12 weeks, consideration of a second phase of treatment is recommended and should be considered as standard of care. Multiple studies have shown both the safety and effectiveness of re-irradiation with a second course of LDRT with data suggesting total response rates of greater than 80%[33,34,41,82]. For patients who have recurrent symptoms after two courses of LDRT, a third course of LDRT can be considered. Ideally, this would be reserved for patients with limited alternative treatment options, for patients who reported initial response to prior therapy, and in patients with initial durable response of at least 1 year. Patients who undergo a third course should be appropriately consented that additional LDRT generally is thought to be less effective than initial treatment, particularly in patients who did not have initial robust response[33]. For re-irradiation, discussion regarding increased risk of ionizing RT exposure should be discussed including risk of secondary malignancy. Additional courses of LDRT can be considered in unique situations, particularly in patients with limited alternative treatment options.

Subtopic 6/ What are considerations for various OA treatment locations?

When considering treatment of small joints, Orthovoltage or LINAC-based treatment is generally appropriate. CT simulation and 3D planning is encouraged. Appropriate beam energy should be selected based on tissue separation and beam arrangement. When considering treatment of large joints, LINAC-based treatment with at least 6MV is generally appropriate. While RT doses for treatment of OA are significantly lower than for malignant conditions, limiting dose to normal tissues and organs at risk should be prioritized.

For hand OA, several different approaches for immobilization can be considered including either prone position with arms above head with thermoplastic immobilization of hands or standing position with hands immobilized on treatment table. Lead nail shielding or collimation with multi-leaf collimators (MLCs) to block nails in hand or foot RT is advised, particularly for re-irradiation. For elbow LDRT, placing the arm in akimbo position with immobilization can limit RT of normal tissues. Thermoplastic head and shoulder immobilization should be used for shoulder treatments with appropriate collimation and use of MLCs to avoid lung and breast exposure. For hip treatment, immobilization with vac lock bag and gonadal shielding are recommended. Immobilization of the knee with physical separation of non-treated knee is recommended. Various approaches for foot and ankle treatment include prone position with foot plantarflexion or supine with plantarflexion with thermoplastic immobilization.

Discussion

The level of evidence to support the use of LDRT for OA is limited. Further high-level evidence including prospective, randomized, sham-controlled trials adequately powered to detect statistical significance for clearly defined and optimally evaluated endpoints is certainly warranted. Although there are a number of prospective nonrandomized[20,40-43,51] and retrospective studies[29,31-34,37,38,42,50,52-55,76,82] that describe pain reduction following treatment of OA with LDRT, we acknowledge limitations of the supporting evidence which is heterogeneous with the majority of these studies being retrospective and non-randomized. Retrospective studies are confounded by selection biases, referral biases, and differences in prior therapies. There are 8 randomized trials included as evidence[35,36,39,44-47,81], with an additional trial[48] combining results of 2 of the trials with longer follow up. Evaluation of the evidence base including these randomized studies is limited by variable dose/fractionation regimens, variable evaluation and follow up durations, and inconsistent endpoints. We also recognize that clinical trials evaluating the benefit of LDRT for OA have the potential for a large placebo effect, therefore setting up a high-quality placebo-controlled trial is necessary to evaluate efficacy. Only 2 studies included in this review were high-quality sham-controlled[46,47], but included only a small number of patients (55 knee[46] and 56 hand[47])

with short-term follow up. Although these trials did not demonstrate a difference in pain reduction during early follow up at 3 to 6 months, Van den Ende et al.[48] combined these studies to include 111 patients and provided longer follow up at 12 months which demonstrated a greater proportion of patients treated with LDRT experiencing pain reduction compared to sham (Knee: LDRT 52%, sham 44%; hand: LDRT 31%, sham 27%). Criticisms of these trials include small sample size which included 25 patients per arm powered for a large expected benefit, no re-irradiation offered for non-responders, and patient selection biases including chronicity and severity of disease[49]. A third double-blind sham-controlled study (30 patients per arm) by Fazilat-Panah et al.[36] included in the evidence demonstrated a statistically significant improvement in pain score and decreased analgesic consumption in patients with knee OA treated with LDRT compared to sham RT but has been criticized for unclear description of the actual improvement in the treatment arms, with no quantitative data on treatment effect.

Future Directions:

Multiple ongoing trials comparing LDRT to placebo as well as comparing different dose fractionation schemes are actively recruiting. In South Korea, LoRD-KneA is a prospective multicentered sham-controlled randomized trial accruing target of 114 patients randomized to either sham RT, 0.3 Gy in 6 fractions, or 3 Gy in 6 fractions[83] (NCT05562271). Similarly, ROGOCO is a trial for patients with either knee or hip (large joint) OA randomized to 3 Gy in 6 fractions, or 6 Gy in 6 fractions with target accrual of 338 patients (NCT04424628). In Germany, the IMMO-LDRT2 trial is a prospective, placebo-controlled, double-blind randomized trial of 3 Gy in 6 fractions compared to sham RT investigating outcomes of both visual analog scale and peripheral blood immunologic changes (NCT05887284). In the United States, Radio-KO is a single center, single-blinded, sham-controlled randomized controlled trial at Mayo Clinic investigating efficacy of 3 Gy in 6 fractions versus sham RT (NCT06887829).

Summary of Recommendations

1. The panel recommends strongly that LDRT may be appropriate for the typical case with OA of the hand when refractory or unable to tolerate other therapies [**Variant 1**.].
2. The panel recommends strongly that LDRT may be appropriate for the typical case with OA of the elbow when refractory or unable to tolerate other therapies [**Variant 2**].
3. The panel recommends that LDRT may be appropriate for the typical case with OA of the shoulder when refractory or unable to tolerate other therapies [**Variant 3**].
4. The panel recommends strongly that LDRT may be appropriate for the typical case with OA of the hip when refractory or unable to tolerate other therapies [**Variant 4**].
5. The panel recommends strongly that LDRT is usually appropriate for the typical case with OA of the knee when refractory or unable to tolerate other therapies [**Variant 5**].
6. The panel recommends strongly that LDRT may be appropriate for the typical case with OA of the foot/ankle when refractory or unable to tolerate other therapies [**Variant 6**].
7. The panel recommends strongly that LDRT is usually not appropriate for the typical case with OA of the spine [Variant 7].
8. The panel recommends strongly that LDRT re-irradiation may be appropriate for the typical case with OA of that has responded to a prior course of LDRT [**Variant 8**].
9. LDRT for OA should be based on joint decision making after comprehensive discussion of potential risks, benefits, and alternative treatment between the physician and patient.
10. Further high-level evidence including prospective, randomized, sham-controlled trials adequately powered to detect statistical significance for clearly defined and optimally evaluated endpoints investigating LDRT for OA is warranted.

Variant Cases and Treatment Algorithm

Variant cases were developed as examples for these guidelines to illustrate practical applications of consensus recommendations. A **treatment algorithm** (Figure 1.) is also provided to assist with treatment decisions when LDRT for treatment of OA. **Appendix E**. provides examples of RT field designs for treatment of OA involving different joints.

Summary of Evidence

This section summarizes the references on the evidence table.

Of the 83 references cited in the American Radium Society® Appropriate Use Criteria for Use of for Treatment of Osteoarthritis, 44 were identified through the search strategy, with 8 additional studies included through backward citation searching, identified by examining the reference lists of articles directly found through the search strategy. No studies were identified by forward citation. 31 additional studies referenced outside the "Summary of Literature Review" are included to provide context, but unless they are also cited within the "Summary of Literature Review" they were not used by the committee to guide recommendations. In sum, the authors added 38 citations from bibliographies, websites, or books not found in the literature search.

Of the 52 references used as evidence, 52 are categorized as therapeutic references including 10 well-designed studies (Phase II randomized and Phase III), 15 moderately well- designed studies that account for most common biases (matched cohort and Phase II studies), 18 studies with design limitations (retrospective reviews), 8 supplemental studies (not useful as primary evidence), and 1 reference that is a meta-analysis study.

Supporting Documents

For additional information on the ARS Appropriate Use Criteria methodology and other supporting documents go to http://www.americanradiumsociety.org/page/aucmethodology.

The American Radium Society™ Appropriate Use Criteria and its expert panels have developed criteria for determining appropriate procedures for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide treating and referring physicians in making decisions regarding diagnosis and treatment of cancers and related or associated conditions. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate diagnostic procedures or treatments. Only those examinations or treatments generally used for evaluation of the patient's condition are ranked. Other procedures necessary to evaluate or treat other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate procedures or treatments. Procedures, techniques, or other interventions classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment, applications, and treatment protocols should be encouraged. The ultimate decision regarding the appropriate use of any specific examination or treatment must be made by the referring physician and oncologist in light of all the circumstances presented in an individual examination.

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Table 1. Select studies using modern techniques using LDRT for treatment of OA

Author (year)	Study Type (SQ) (sample size)	Joint Location(s)	Treatment Modality	Dose/ fractionation	Pain Scoring	Follow -up	Time to re-irradiation	Outcome
Makarova[34] (2023)	Prospective randomized (1) (292 patients)	Knee	Orthovoltage	4.5 Gy/10 Fx every other day	n/a	9 years	n/a	Knee arthroplasty rates: 4.1% LDRT arm, 7.5% control (NSAIDS, SYSADOA) p=0.340
Makarova[43] (2019)	Prospective randomized (1) (292 patients)	Knee	Orthovoltage	4.5 Gy/10 Fx every other day	n/a	3 years	n/a	LDRT versus control: cartilage thickness (8.6 vs 1.9; p=0.009), the extent of bone marrow edema (5.7 vs 0.6; p=0.024), articular surface thinning (1.6 vs 0.3; p=0.042; t=2.11, df=34), the presence of marginal osteophytes (4.4 vs 1.8; p=0.042) and synovitis (1.1 vs 0.5; p=0.022)
Makarova[38] (2021)	Prospective randomized (1) (283 patients)	Knee	Orthovoltage	4.5 Gy/10 Fx every other day	Short Form 36- Item Health Survey	3 years	n/a	Adding LDRT to the standard SYSADOA/NSAIDs treatment for knee OA of stages 0-2 statistically improved mental well-being of patients for at least 3 years.
Fazilat-Panah[35] (2025)	Prospective randomized (1) (60 patients)	Knee	Linac	3.0 Gy/6 Fx every day	VAS and Lysholm 100-point Scale	6 months	n/a	All variables including VAS pain score, Lysholm scale, PS and analgesic consumption were improved following radiation from first month to the end of assessments ($p < 0.01$).
Mahler[45] (2019)	Prospective randomized (1) (55 patients)	Knee	Linac	Standard dose: 6.0 Gy/6 Fx Experimental dose: sham radiation/6 Fx	OMERACT-OARSI	3 months	n/a	44% RR in treatment group at 3 months 43% RR in sham group at 3 months
Mucke[36] (2010)	Retrospective (3) (4,544 patients)	Knee	Linac/ Orthovoltage	Variety (median total dose 6 Gy (range 3-12 Gy), median single dose 1 Gy (0.25-3 Gy)	?	1 year	30%, n/a	60% reported pain reduction at 3 months 40% reported pain reduction at 12 months
Keller[30] (2013)	Retrospective (3) (1,037 patients)	Knee	Linac/ Orthovoltage	Delivered once weekly in 611/1659 series (36.8%), twice weekly in 1045/1659 series (63.0%), or daily in 3/1659 series (0.2%). The single (total) doses ranged between 0.5 and 1.5 Gy (0.5 and 10 Gy)	VPS	2 months	n/a	79.3% VPS 0-2 at 2 months
Niewald[44] (2022) Niewald[80] (2024)	Prospective randomized (1) (151 patients)	Hand/Knee	Linac	Standard dose: 3.0 Gy/6 Fx twice weekly Experimental dose: 0.3 Gy/6 Fx twice weekly	VAS, KOOS-PS, SF-SACRAH sum score, and SF-12	12 months	n/a	59% RR at 3 months (no significant difference)
Van den Ende[47] (2019)	Prospective randomized (1) (111 patients)	Hand/Knee	Linac	Standard dose: 6.0 Gy/6 Fx Experimental dose: sham radiation/6 Fx	OMERACT-OARSI	12 months	n/a	6 months knee: LDRT 41% RR, Sham 35% 12-month Knee: LDRT 52%, Sham 44% 6 months hand: LDRT 28% RR, Sham 31% 12-month knee: LDRT 31%, Sham 27%
Alvarez[40] (2022)	Prospective nonrandomized (2) (100 patients)	Hand	Linac	3 – 6 Gy/6 Fx (0.5-1 Gy/Fx) every other day	VAS, VPS	12 months	63%, 12 weeks	Mean VAS pretreatment: 8 Mean VAS post-treatment: 5 Mean VAS 3 months: 4 Mean VAS 6 months: 6

								Mean VAS 12 months: 3.5
Rogers[39] (2020)	Prospective nonrandomized (2) (99 patients)	Hand	Orthovoltage	4.0 Gy/ 8 Fx (0.5 Gy/Fx) twice weekly	VAS	12 months	81.8%, 8 weeks	Median VAS pretreatment: 5 Median VAS 12 months: 2 Improvement in handgrip strength (median change = 2.5 kg, p = 0.004)
Hermann[50] (2021)	Prospective nonrandomized (2) (25 patients)	Hand	Linac	3 Gy/6 Fx twice weekly	VAS, VPS, PRWE	12 months	32%, 12 weeks	Median VAS pretreatment: 7 Median VAS 3 months: 3 (p = 0.046) Median VAS 12 months: 2 (p = 0.013) PRWE Baseline: 0.5 PRWE 3 months: 0.36 (p = 0.05) PRWE 12 months: 0.27 (p = 0.0009)
Donaubauer[28] (2020)	Retrospective (3) (483 patients)	Hand	Orthovoltage	3 – 6 Gy/6 Fx (0.5-1 Gy/Fx) every other day	n/a	6 months	12 weeks	70% reported pain reduction
Kaltenborn[51] (2016)	Retrospective (3) (84 patients)	Hand	Linac	6 Gy/6 Fx twice weekly	n/a	12 months	n/a	70% reported pain reduction 3 months: 60% 12 months: 70%
Weissmann[54] (2021)	Retrospective (3) (196 patients)	Ankle/Foot	Orthovoltage	3 – 6 Gy/6 Fx (0.5-1 Gy/Fx) every other day	Patient reported pain reduction as % improvement, response defined as at least 20% improvement	6 months	84%, 12 weeks	75% RR by 6 months 37% reported 80%-100% pain reduction

Hautmann[37] (2020)	Retrospective (2) (66 joints)	Ankle/Foot	Linac	3 – 6 Gy/6 Fx (0.5-1 Gy/Fx) every other day	NRS	24 months	40.9%, 12 weeks	Median NRS pretreatment: 7 Median NRS 6 weeks: 5 Median NRS 12 weeks: 5 Median NRS 12 months: 4
Donaubauer[19] (2021)	Prospective nonrandomized (2) (125 patients)	Large and small joints	Orthovoltage	3 Gy/6 Fx twice weekly	VAS	6 months	61.6%, 12 weeks	Median VAS pretreatment: 6.5 Median VAS 6 months: 3.8
Koc[42] (2019)	Prospective nonrandomized (2) (12 patients)	Large Joints	Linac	6 Gy/6 Fx every other day	NRS	1 year	n/a	50% reported pain reduction at 6 weeks 25% reported pain reduction at 1 year
Ruhle[31] (2021)	Retrospective (3) (970 patients)	Large and small joints	Linac	6 Gy/ 6 Fx-77.3% 3 Gy/ 6 Fx-21.7% 2-3 times weekly	NRS, VPS	8 weeks	32.4%, 8 weeks	End RT: 60% VPS 0-2 (1.5% with CR) 8 weeks: 65.5% VPS 0-2 (6.9% with CR)
Micke[33] (2018)	Retrospective (3) (703 patients)	Large and small joints	Linac/ Orthovoltage	3-6 Gy/6 Fx (0.5-1 Gy/Fx) every other day	VAS, VPS	33 months	n/a	37.6% RR at end of RT 58.4% RR at 33 months
Juniku[32] (2019)	Retrospective (3) (598 patients)	Large and small joints	Linac	3 – 5 Gy 0.5 Gy/Fx	VAS	38 months	43.3%, not reported	Median VAS pretreatment: 7 Median VAS postreatment: 5 Median VAS 38 months: 4
Hautmann[52] (2020)	Retrospective (3) (295 joints)	Large and small joints	Linac	Various: 6 Gy/6 Fx, 5 Gy/5 Fx, 1 Gy/1 Fx, 3 Gy/6 Fx, 5 Gy/10 Fx, 1.5 Gy/3 Fx)	NRS	24 months	22.4%, 12 weeks	Median NRS pretreatment: 7 Median NRS 6 weeks: 4 Median NRS 12 months: 3 Median NRS 24 months: 3
Hautmann[81] (2019)	Retrospective (3) (217 joints)	Large and small joints	Linac	3.0 Gy/6 Fx or 1.5 Gy/3Fx 2-3 times weekly	NRS	24 months	100%, 12 weeks	Median NRS pretreatment: 6 Median NRS 6 weeks: 4 Median NRS 12 weeks: 3 Median NRS 6 months: 3 Median NRS 12 months: 3 Median NRS 24 months: 3
Micke[53] (2017)	Retrospective (3) (166 patients)	Large and small joints	Linac/ Orthovoltage	3-6 Gy/6 Fx (0.5-1 Gy/Fx) every other day	VAS, VPS	29 months	8.4%, 12 weeks	37.3% RR at end of RT 49.6% RR at 29 months
Alvarez[41] (2020)	Prospective nonrandomized (2) (108 patients)	Large and small joints	Linac	6 Gy/6 Fx every other day	VAS, Analgesic intake	8 months	52%, 8 weeks	91% reported pain reduction 46% less analgesic medications needed Median VAS pretreatment: 7 Median VAS at follow up: 3 ($p<0.0001$)
Abdelmaqsoud[75] (2023)	Retrospective (3) (91 patients)	Large and small joints	Orthovoltage	6 Gy/12 Fx every other day	NRS	6 months	n/a	65% reported pain reduction at 6 months
Koneru[49] (2025)	Retrospective (3) (69 patients)	Large and small joints	Linac	3 Gy/6 Fx twice weekly	VAS, VPS	10 weeks	33%	Median VAS pretreatment: 6.3 Median VAS postreatment: 4.0 Median VAS 10 weeks: 4.0

Abbreviations: LDRT, low-dose radiotherapy; OA, osteoarthritis; SQ, study quality; Gy, Gray; Fx, fraction; NSAIDS, non-steroidal anti-inflammatory drugs; SYSADOA, symptomatic slow-acting drugs for osteoarthritis; VAS, Visual Analog Scale; VPS, Von Pannwitz Score; OMERACT-OARSI, Outcome Measures in Rheumatology–Osteoarthritis Research Society International; RR, response rate; KOOS-PS, Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form; SF-SACRAH; Short Form Score for the Assessment and Quantification of Chronic Rheumatic Affections of the Hands in Daily Clinical Routines; PRWE, Patient-Rated Wrist Evaluation; NRS, Numerical Rating Scale

Study Quality Category Definitions

Category 1 The study is well-designed and accounts for common biases.

Category 2 The study is moderately well-designed and accounts for most common biases.

Category 3 There are important study design limitations.

Variant 1: Bilateral thumbs (metacarpophalangeal (MCP) and carpometacarpal (CMC) joints)

54 year-old right-handed female (BMI = 23) who texts frequently notes progressive pain and stiffness in bilateral proximal thumbs which is now interfering with her duties as a data entry specialist. Imaging identifies KL grade 2 OA on the right and KL grade 1 OA on the left MCP/CMC joints. She has persistent pain despite > 6 months of conservative* and pharmacologic** treatments. She has been evaluated by an orthopedic surgeon and is deemed fit for intraarticular*** and surgical options****.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment Options														
LDRT	M	0	0	0	0	1	10	2	0	0	6		M	↑
if LDRT, Treatment Volume														
• Superior border is halfway between MCP and interphalangeal (IP) joint, inferior border is 2cm margin on CMC joint, lateral and medial border is 1cm on MCP joint. A typical field size is 8cm x 4cm	A	0	0	0	1	0	0	5	7	0	8		EO/EC	-
if LDRT, LDRT Dose														
• **3.0 Gy/0.5 Gy Fx 2-3 times weekly**	A	0	0	0	0	0	1	0	12	0	8		M	↑
• **6.0 Gy/1.0 Gy Fx 2-3 times weekly**	A	0	0	0	0	1	1	11	0	0	7		M	↑

*Conservative measures including nonpharmacologic approaches such as weight loss, exercise, bracing, physical therapy
**Pharmacologic management including NSAIDS and targeted agents
***Intraarticular corticosteroids
****Carpometacarpal arthroplasty

Variant Discussion:
In patients with symptomatic carpometacarpal OA who have failed conservative management (defined as rehabilitation and lifestyle management), treatment approach is primarily dictated on patients' preference to undergo more aggressive interventional procedures versus trial of additional less invasive approaches. With early radiographic evidence of OA, initially attempting less aggressive interventions are likely more appropriate with surgical interventional reserved for progression of symptoms or functionality.

LDRT would be an appropriate tool to consider. For patient selection, studies are lacking to inform whether patients of erosive hand OA or the presence of synovitis would be more or less responsive to LDRT. For dose considerations, 0.5 or 1 Gy per fraction would both be considered acceptable and field size depends on involved joints, but in general should include the whole involved joint capsule(s). When considering LDRT, appropriate counseling of risk of ionizing radiation exposure and joint specific consideration for nail bed shielding should be considered as appropriate. If the distal interphalangeal joint (DIP) joint is involved nail bed shielding would result in inadequate coverage of the target joint.

LDRT is typically used before surgery. Other treatment options can be considered and would be sequential pending outcome of initial therapy. No data have been published to suggest LDRT would increase risks of future surgical procedures.

(See **Appendix E.** Example 1. of LDRT radiation field for thumb OA)

Variant 2: Unilateral elbow (humeroulnar joint)

61 year-old right-handed male (BMI = 24) has progressive, constant pain in his right elbow following a motorcycle accident which limits his range of motion. Imaging identifies KL grade 2 OA in the right humeroulnar joint. He has progressive pain and limitations despite > 1 year of conservative measures*, pharmacologic treatments**, and intraarticular injections***. He has been evaluated by an orthopedic surgeon and is deemed fit for surgical options****.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment Options														
LDRT	M	0	0	0	2	6	5	0	0	0	5		M	↑
if LDRT, Treatment Volume														
• A 2:1 ratio of superior to inferior coverage relative to the humeroulnar joint space is used. Superior border is approximately 6cm from joint, Inferior border approximately 3cm from joint, lateral and medial border 2cm from joint.	A	0	0	0	1	0	0	6	6	0	7		EO/EC	↑
if LDRT, LDRT Dose														
• **3.0 Gy/0.5 Gy Fx 2-3 times weekly**	A	0	0	0	1	0	0	2	10	0	8		M	↑
• **6.0 Gy/1.0 Gy Fx 2-3 times weekly**	A	0	0	0	0	0	0	10	0	0	7		M	↑

*Conservative measures including nonpharmacologic approaches such as weight loss, exercise, bracing, physical therapy
**Pharmacologic management including NSAIDS and targeted agents
***Intraarticular therapies including corticosteroids or hyaluronic acid
****Surgical approaches including arthroscopic surgery and joint replacement

Variant Discussion:

In patients who have failure conservative management (defined as rehabilitation and lifestyle management), and intra-articular injections, limited non-surgical options remain available. LDRT would be a reasonable option prior to undergoing surgical intervention and provides the opportunity to avoid surgical risks.

LDRT is typically used before surgery. Other treatment options can be considered and would be sequential pending outcome of initial therapy. No data have been published to suggest LDRT would increase risks of future surgical procedures.

(See **Appendix E.** Example 2. of LDRT radiation field for elbow OA)

Variant 3: Unilateral shoulder (glenohumeral joint)

32 year-old right-handed female (BMI = 30) who works as a housekeeper reports progressive, constant pain in her right shoulder which limits her range of motion and ability to perform her job functions for approximately 1 year. Imaging identifies KL grade 1 OA in the glenohumeral joint. MRI shows no evidence of rotator cuff pathology. She has progressive pain and limitations despite 1 year of conservative measures*, pharmacologic treatments**, and intraarticular injections***. She has been evaluated by an orthopedic surgeon and is deemed fit for surgical options****.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment Options														
LDRT	M	1	0	0	10	0	1	0	0	0	4		M	-
if LDRT, Treatment Volume														
• Superior border is set at the superior aspect of the clavicle and includes the lateral 1/3 of the clavicle, inferior border is 1-2cm below inferior aspect of tubercle of humerus, lateral border is 2cm from humeral head, and medial border is placed to ensure coverage of coracoid process with shielding of breast tissue and chest wall.	A	0	0	0	1	0	0	5	5	1	8		EO/EC	↑
if LDRT, LDRT Dose														
• **3.0 Gy/0.5 Gy Fx 2-3 times weekly**	A	0	0	0	0	1	0	1	10	0	8		M	↑
• **6.0 Gy/1.0 Gy Fx 2-3 times weekly**	A	0	0	0	1	0	2	8	1	0	7		M	-

*Conservative measures including nonpharmacologic approaches such as weight loss, exercise, bracing, physical therapy
**Pharmacologic management including NSAIDS and targeted agents
***Intraarticular therapies including corticosteroids or hyaluronic acid
****Surgical approaches include joint replacement

Variant Discussion:
In general, early intervention of OA is associated with improved treatment response long-term.

LDRT should be used with caution in patients under the age of 40 except in unique, rare situations in which prognosis is limited primarily due to the concerns of secondary malignancy risk with ionizing radiation exposure. One additional consideration regarding secondary malignancy risk is anatomic location of treatment. LDRT for the shoulder should be approached with thoughtful consideration given the predicted higher effective dose (dose used to estimate secondary malignancy risk) due to the higher tissue weighting factor assigned for breast, bone marrow (humeral head), and lung. Consideration of surgical or conservative treatment options are appropriate.

(See **Appendix E.** Example 3. of LDRT radiation field for shoulder OA)

Variant 4: Elderly female with hip OA (acetabulofemoral joint) and limited treatment options

92 year-old female (BMI = 25) with constant pain in her left hip which limits ambulation. She has been treated over the last decade and is now refractory to conservative measures*, pharmacologic treatments**, and intraarticular injections***. She has been deemed unfit for surgical options**** by her orthopedic surgeon. Current imaging identifies KL grade 4 OA in the left acetabulofemoral joint.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment Options														
LDRT	M	0	0	0	0	0	8	1	1	0	6		M	↑
if LDRT, Treatment Volume														
• Superior border is at the anterior superior iliac spine (ASIS), inferior 1–2 cm below the lesser trochanter, lateral is at the greater trochanter and medial at the lateral edge of the obturator foramen. The pelvis blocked as needed to spare healthy tissue. Typical ratio of 1:2 to ensure coverage of the acetabulofemoral joint while minimizing exposure to surrounding structures.	A	0	0	0	1	0	0	5	3	1	7		EO/EC	↑
if LDRT, LDRT Dose														
• **3.0 Gy/0.5 Gy Fx 2-3 times weekly**	A	0	0	0	0	1	0	1	7	1	8		M	↑
• **6.0 Gy/1.0 Gy Fx 2-3 times weekly**	A	0	0	0	1	0	1	7	1	0	7		M	-

*Conservative measures including nonpharmacologic approaches such as weight loss, exercise, bracing, physical therapy
**Pharmacologic management including NSAIDS and targeted agents
***Intraarticular therapies include corticosteroid
****Surgical approaches include joint replacement

Variant Discussion:
In patients with KL grade 4 OA who have been refractory to conservative (defined as rehabilitation and lifestyle management), pharmacologic, and intraarticular injections who are not candidates for hip arthroplasty, LDRT may be considered. LDRT results in lower rates of treatment response (estimated to be 40-50%) in patients with KL grade 4 OA.

LDRT is a relatively low-risk treatment option. Alternative treatments include escalation of pharmacologic therapy with well documented risks. A consideration in this case is that a 92 year has a greater risk associated with pharmacologic therapy compared to a younger patient.

(See **Appendix E.** Example 4. of LDRT radiation field for hip OA)

Variant 5: Bilateral knees (tibiofemoral joint)

72 year-old female (BMI = 33) with constant pain and stiffness of bilateral knees, worse with physical activity and limiting ambulation. Imaging identifies KL grade 3 OA in bilateral tibiofemoral joints with joint space narrowing and moderate multiple osteophytes. She has progressive pain and limitations despite > 1 year of conservative measures*, pharmacologic treatment**, and intraarticular injections***. She is not a candidate for surgical options**** due to risks associated with comorbid severe cardiac disease.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment Options														
LDRT	A	0	0	0	0	0	1	3	4	2	8		S	↑
if LDRT, Treatment Volume														
• A 2:1 ratio of superior to inferior coverage relative to the tibiofemoral joint space is used to ensure complete joint capsule coverage while treating tendon insertions and surrounding structures. Superior border is approximately 10cm from joint, Inferior border approximately 5cm joint, and medial and lateral border 3cm from joint.	A	0	0	0	1	0	0	2	6	1	8		EO/EC	↑
if LDRT, LDRT Dose														
• **3.0 Gy/0.5 Gy Fx 2-3 times weekly**	A	0	0	0	0	1	0	1	7	1	8		M	↑
• **6.0 Gy/1.0 Gy Fx 2-3 times weekly**	A	0	0	0	1	0	1	7	1	0	7		M	↑

*Conservative measures including nonpharmacologic approaches such as weight loss, exercise, bracing, physical therapy
**Pharmacologic management including NSAIDS and targeted agents
***Intraarticular therapies including corticosteroids or hyaluronic acid
****Surgical approaches including genicular artery ablation, radiofrequency ablation, arthroscopic surgery and joint replacement

Variant Discussion:

In patients with advanced OA (KL grade 3) who have been refractory to conservative, pharmacologic, and intraarticular injections who are not candidates for knee arthroplasty, LDRT should be considered. KL grade 4 is typically not as responsive to LDRT. LDRT has been shown to be effective in providing pain relief, increased mobility, and improved quality of life in patients who respond to therapy. Alternative treatments include escalation of pharmacologic therapy with well documented risks.

In general, 70% of patients will require a second phase of LDRT, and 10% will require a third phase to achieve maximal symptom improvement.

(See **Appendix E.** Example 5. of LDRT radiation field for knee OA)

<u>Variant 6</u>: Bilateral foot and ankle (talocrural (TC) and subtalar (ST) joints)

70 year-old female (BMI = 32) with chronic OA of TC and ST joints develops progressive pain and stiffness of bilateral feet and ankles, which is limiting ambulation. Imaging identifies KL grade 3 OA in the right and KL grade 2 OA in the left TC and ST joints. She has persistent pain despite > 1 year of conservative measures*, pharmacologic treatment**, and intraarticular injections. She has been evaluated by an orthopedic surgeon and is deemed fit for surgical options****.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment Options														
LDRT	M	0	0	0	0	0	10	0	0	0	6		M	↑
if LDRT, Treatment Volume														
• Superior border is about 2cm proximal to TC joint, inferior border is placed with margin along tarsal bones, lateral and medial borders are with a margin to joint space with blocks to shield along the lateral edge of calcaneus.	A	0	0	0	1	0	0	5	3	1	7		EO/EC	↑
if LDRT, LDRT Dose														
• **3.0 Gy/0.5 Gy Fx 2-3 times weekly**	A	0	0	0	0	1	0	1	7	1	8		M	↑
• **6.0 Gy/1.0 Gy Fx 2-3 times weekly**	A	0	0	0	1	0	1	8	0	0	7		M	↑

*Conservative measures including nonpharmacologic approaches such as weight loss, exercise, bracing, physical therapy
**Pharmacologic management including NSAIDS and targeted agents
***Intraarticular therapies including corticosteroids or hyaluronic acid
****Surgical approaches include fusion and joint replacement

<u>Variant Discussion:</u>
In patients who have debilitating OA impeding ambulation, orthopedic evaluation with surgical intervention may be considered. LDRT for refractory OA can also be considered. LDRT may be effective in both post-traumatic and non post-traumatic OA.

Regarding multiple joints, radiation fields and volumes depend on the particular joints involved. Treating multiple joints simultaneously is a reasonable approach.

(See **Appendix E.** Example 6. of LDRT radiation field for foot/ankle OA)

Variant 7: Lumbar spine OA in a patient refusing surgery

62 year-old male (BMI = 31) progressive pain in the low back, worse with movement, and with periods severe flares which limits ability to function. He has been treated over the last year with conservative measures*, pharmacologic treatments**, and intraarticular injections***, and has been deemed fit for surgical options****, but is declining surgical intervention. He is now refractory to injections*** and pharmacologic management**.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment Options														
LDRT	U	0	4	4	2	0	0	0	0	0	3		L	↑

*Conservative measures including nonpharmacologic approaches such as weight loss, exercise, bracing, physical therapy
**Pharmacologic management including NSAIDS and targeted agents
***Injection therapies including corticosteroid facet injections, epidural injections, or nerve block
****Surgical approaches including radiofrequency ablation, discectomy, or fusion procedures

Variant Discussion:

The paucity of data and possible increased risks preclude recommendation for LDRT in spine OA, except in cases with exceptional circumstances. Historically, spinal disease such as ankylosing spondylitis was treated with radiation with success; however, after case reports of secondary malignancy from treatment in young patients were published, this treatment approached was abandoned. Given the increased volume of bone marrow as well as visceral organs irradiated, spinal treatment with LDRT is believed to carry a higher risk of secondary malignancy. For patients who do not have a limited life expectancy, LDRT for spine OA should be avoided.

Variant 8: Unilateral hip (relapse s/p LDRT, consideration of re-irradiation)

72 year-old female (BMI = 31) with constant pain in her left hip limits ambulation. She has been treated over the last decade with conservative measures*, pharmacologic treatments**, and intraarticular injections***, and has been deemed fit for surgical options**** by her orthopedic surgeon. Approximately 2 years ago she received LDRT to the left hip (0.5 Gy twice weekly; total 3 Gy, followed by second course of same dose fractionation 8 weeks later) which resulted in reduction in pain for approximately 1 year. She now complains of gradual worsening of left hip pain which limits ambulation and is refractory to intraarticular injections*** and pharmacologic management**. Current imaging identifies KL grade 3 OA in the left acetabulofemoral joint. She presents for consideration of re-irradiation.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment Options														
LDRT re-irradiation	M	0	0	0	0	3	6	1	0	0	6		M	↑
if LDRT, Treatment Volume														
• Superior border is at the anterior superior iliac spine (ASIS), inferior 1–2 cm below the lesser trochanter, lateral is at the greater trochanter and medial at the lateral edge of the obturator foramen. The pelvis blocked as needed to spare healthy tissue. Typical ratio of 1:2 to ensure coverage of the acetabulofemoral joint while minimizing exposure to surrounding structures.	A	0	0	0	1	0	0	5	5	0	7		EO/EC	↑
if LDRT, LDRT Dose														
• **3.0 Gy/0.5 Gy Fx 2-3 times weekly**	A	0	0	0	0	1	0	3	7	0	8		M	↑
• **6.0 Gy/1.0 Gy Fx 2-3 times weekly**	A	0	0	0	0	0	1	9	0	0	7		M	-

*Conservative measures including nonpharmacologic approaches such as weight loss, exercise, bracing, physical therapy
**Pharmacologic management including NSAIDS and targeted agents
***Intraarticular therapies including corticosteroids or hyaluronic acid
****Surgical approaches include joint replacement

Variant Discussion:

In the setting of relapsed pain limiting ambulation, discussion regarding benefits and risks of hip arthroplasty with orthopedic surgery is recommended. Reirradiation is also appropriate considering good results with prior LDRT. Since this patient has responded well to two courses of 3 Gy, it is reasonable to consider an additional 3 Gy.

Although there is a significant amount of marrow in the hip field, the risk of radiation-induced malignancy is small in a 72 year old. Joint specific consideration of gonadal shielding should be addressed. LDRT is typically used before surgery. Other treatment options can be considered and would be sequential pending outcome of initial therapy. No data have been published to suggest LDRT would increase risks of future surgical procedures.

(See **Appendix E.** Example 4 of LDRT radiation field for hip OA)

Please refer to the supporting documentation for a more complete discussion of the concepts and definitions below.

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate
Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.
SOE: S Strong; M Moderate; L Limited; EC Expert Consensus; EO Expert Opinion
SOR: ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak

Key:
BMI: Body mass index

KL grade: Kellgren-Lawrence grading system, which uses X-rays to assess the severity of the condition ranging from:
Grade 0: No radiographic features of OA.
Grade 1: Possible joint space narrowing and/or osteophyte formation.
Grade 2: Definite osteophyte formation and possible joint space narrowing.
Grade 3: Moderate multiple osteophytes, definite joint space narrowing, some sclerosis, and possibly bone deformity.
Grade 4: Large osteophytes, marked joint space narrowing, severe sclerosis, and definite bony deformity.

OA: osteoarthritis

LDRT: low-dose radiation therapy

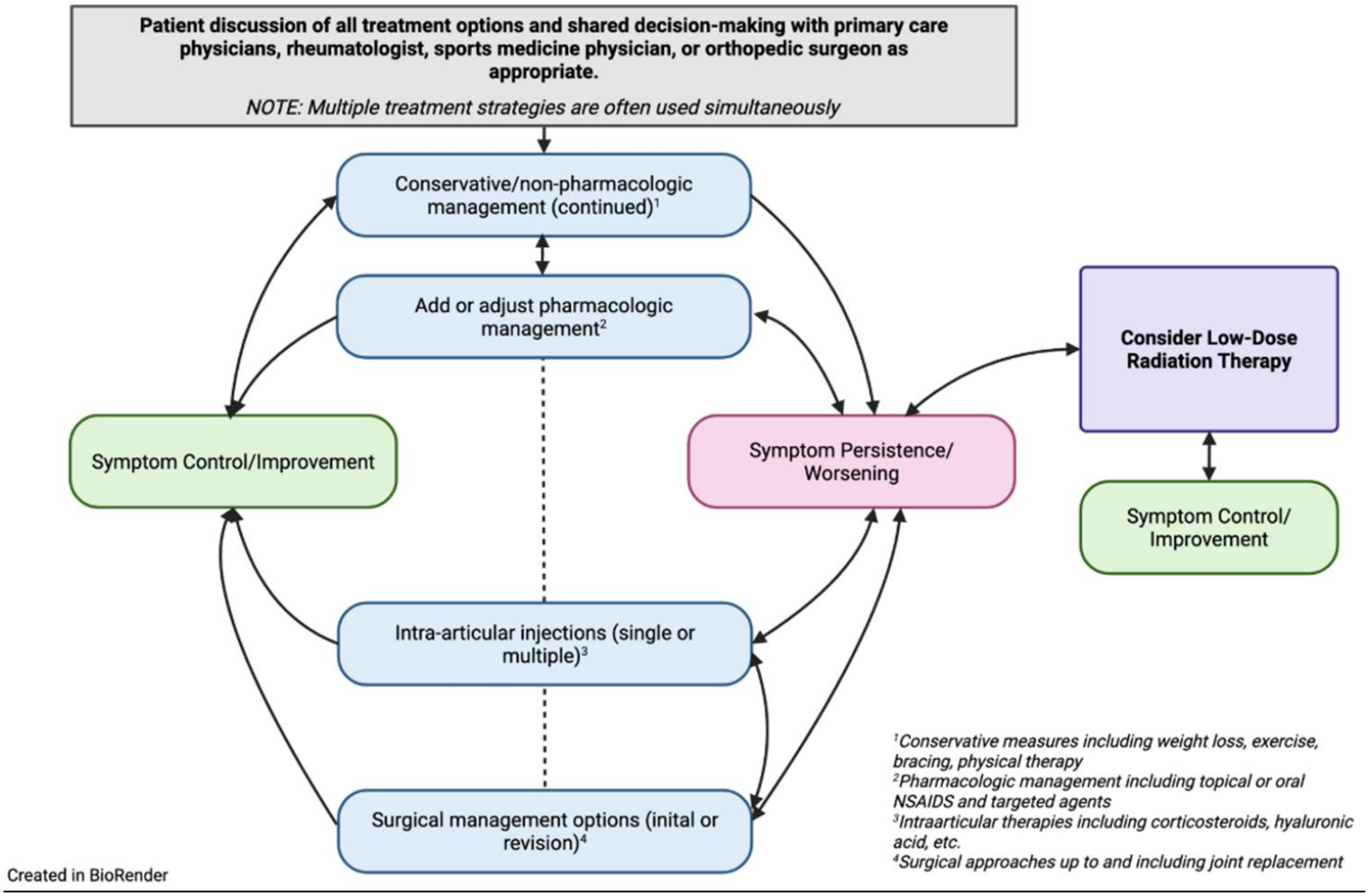
cm: centimeter

Gy: Gray

Fx: fraction

NSAIDS: non-steroidal anti-inflammatory drugs

FIGURE 1. ALGORITHM FOR CONSIDERATION OF LOW-DOSE RADIATION FOR TREATMENT OF SYMPTOMATIC OSTEOARTHRITIS



Appendix A: Search Strategy for ARS AUC for Radiotherapy for Treatment of Osteoarthritis

Search Dates 01 Jan 2010 through 10 May 2025

EMBASE AND MEDLINE

No.	Query	Results
#3	#2 AND (2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py OR 2022:py OR 2023:py OR 2024:py OR 2025:py)	89
#2	#1	232
#1	(radiotherap* OR radiat* OR irradiat*) AND ((((((osteoarthritides* OR 'arthritis,'/exp OR arthritis,) AND degenerative* OR arthritides,) AND degenerative* OR degenerative) AND arthritides* OR degenerative) AND arthritis* OR osteoarthritis* OR osteoarthrosis* OR 'osteoarthrosis'/exp OR osteoarthrosis) AND deformans* OR arthrosis* OR arthroses*)	232

PUBMED

(radiotherap* or radiat* or irradiat*) and (osteoarthritides* or arthritis, degenerative* or arthritides, degenerative* or degenerative arthritides* or degenerative arthritis* or osteoarthritis* or osteoarthrosis* or osteoarthrosis deformans* or arthrosis* or arthroses*)

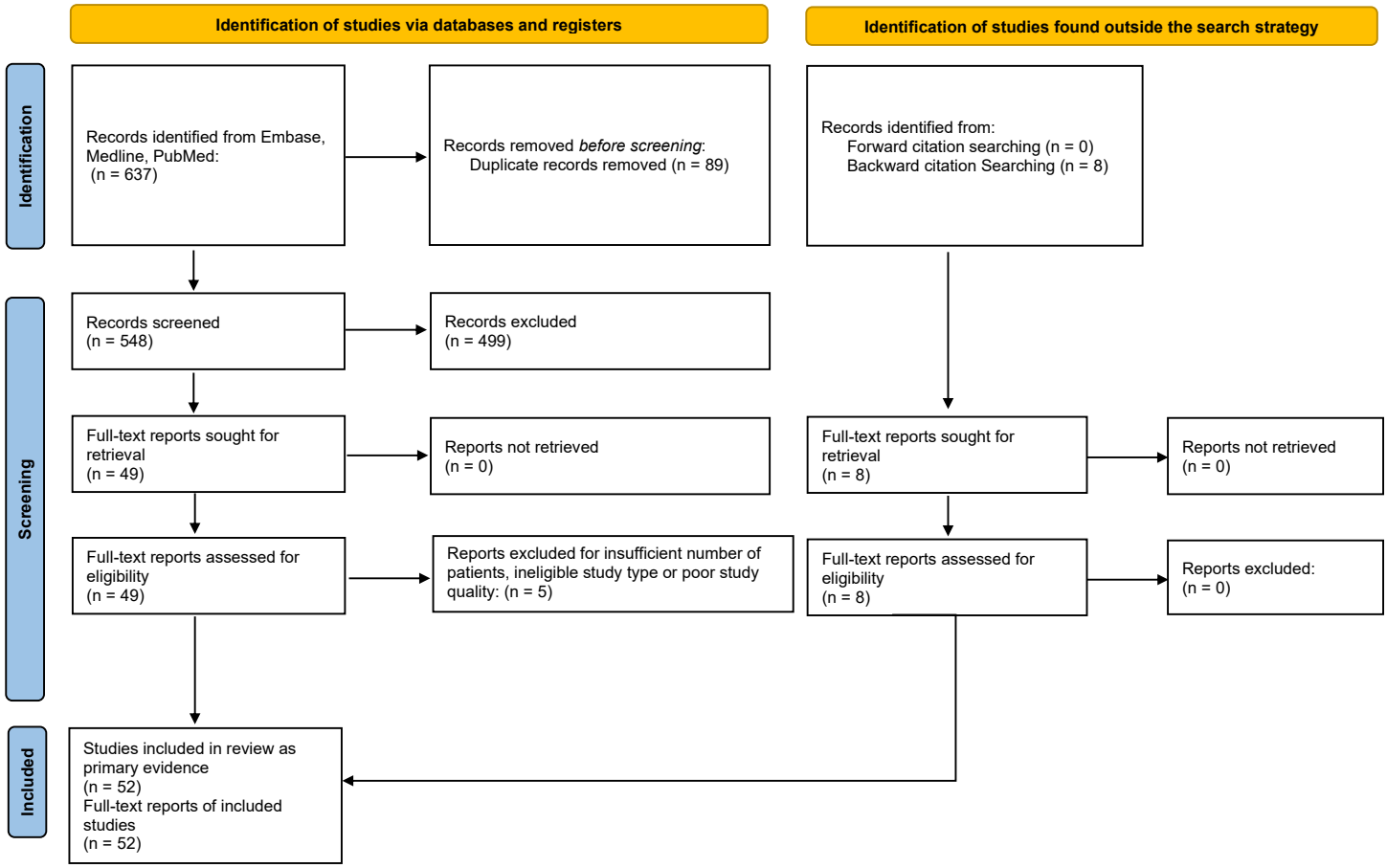
Filters: English, Humans, from 2010/1/1 - 2025/5/10

548 Results

TOTAL - 637

DUPLICATES REMOVED - 89

Appendix B: PRISMA 2020[24,25] Study Selection Flow Diagram for Use of Radiotherapy for Treatment of Osteoarthritis



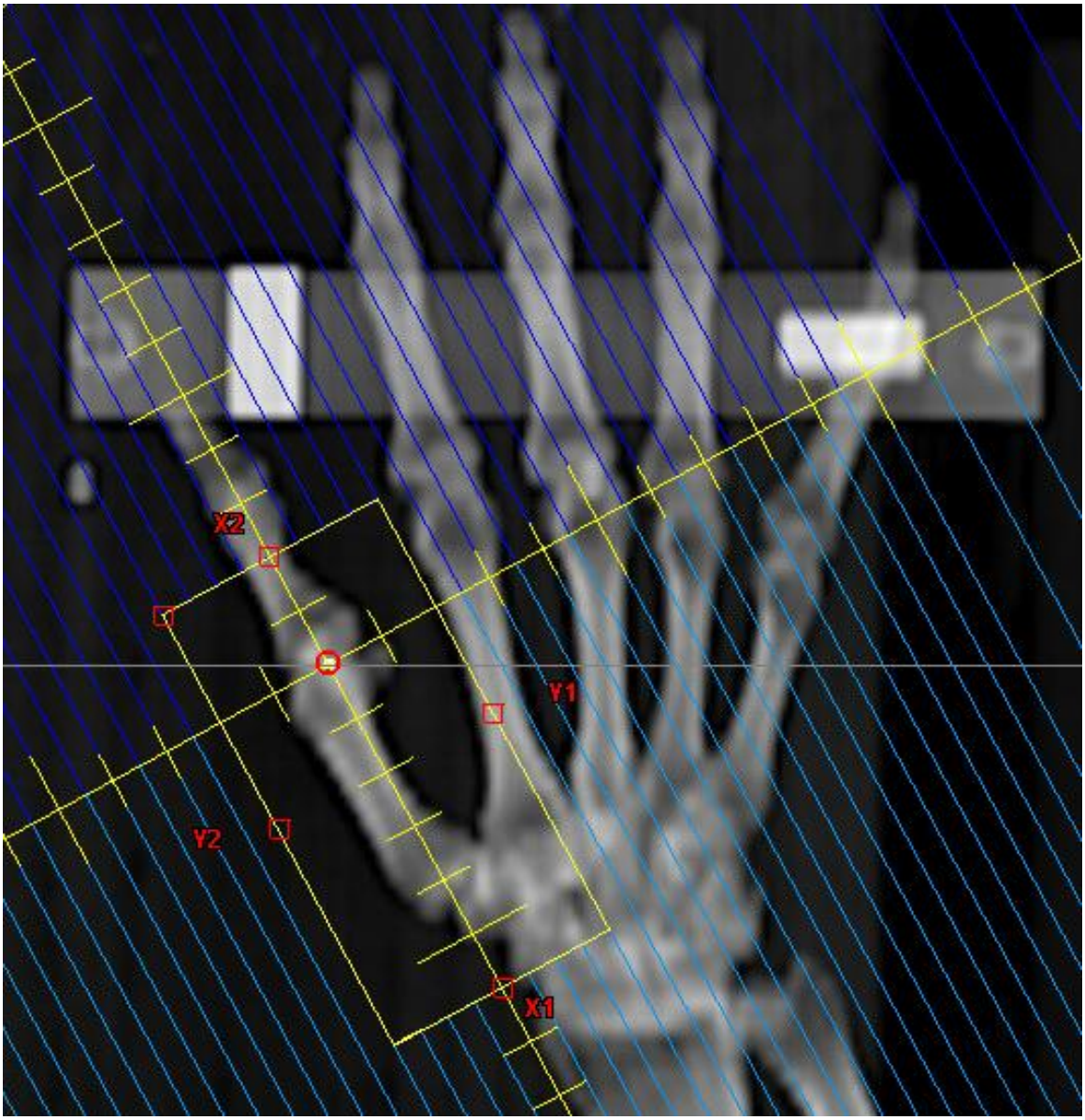
Appendix D: PRISMA 2020 Checklist for Use of Radiotherapy for Treatment of Osteoarthritis

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			INTRODUCTION/BACKGROUND
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	¶2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	¶2
METHODS			METHODOLOGY
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	¶1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	¶1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix A: Search Strategy
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	¶1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	¶1
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	¶1
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	¶1
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Appendix C: Evidence Table
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Variants 1-8 via Strength of Evidence (SOE)
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Appendix B: Flow Diagram
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Appendix B: Flow Diagram
Study characteristics	17	Cite each included study and present its characteristics.	Appendix C: Evidence Table
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appendix C: Evidence Table
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Variants 1-8 via Strength of Evidence (SOE) and Strength of Recommendation (SOR), & section "SUMMARY OF RECOMMENDATIONS"
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	SUMMARY OF LITERATURE REVIEW Topics 1 - 3
	23b	Discuss any limitations of the evidence included in the review.	N/A
	23c	Discuss any limitations of the review processes used.	N/A
	23d	Discuss implications of the results for practice, policy, and future research.	N/A
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Title Page
Competing interests	26	Declare any competing interests of review authors.	Title Page
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	https://www.americanradiumsociety.org/page/aucmethodology

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

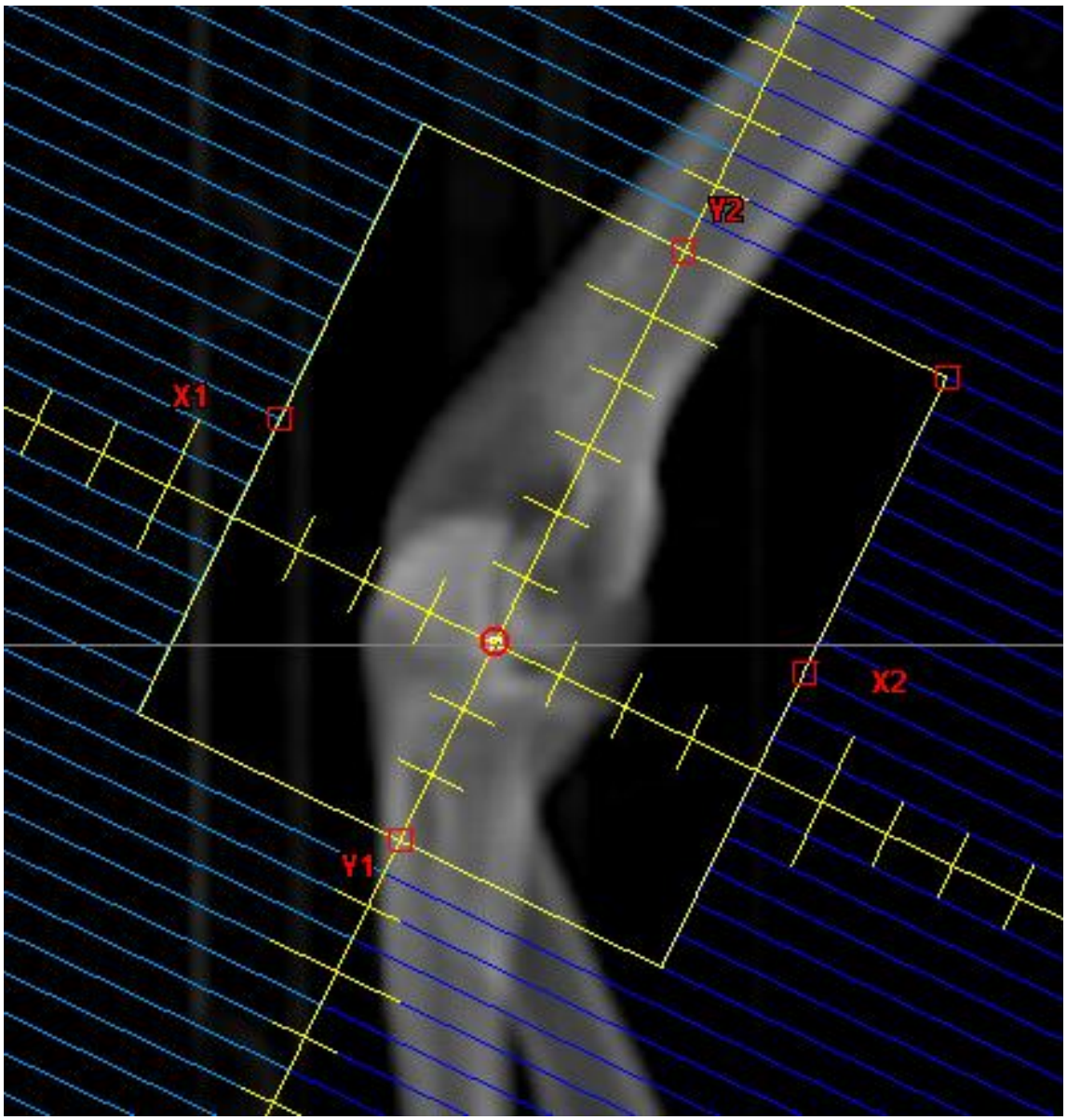
For more information, visit: {HYPERLINK "http://www.prisma-statement.org/"}

Appendix E: Examples Low-Dose Radiotherapy Field Design for Treatment of Osteoarthritis



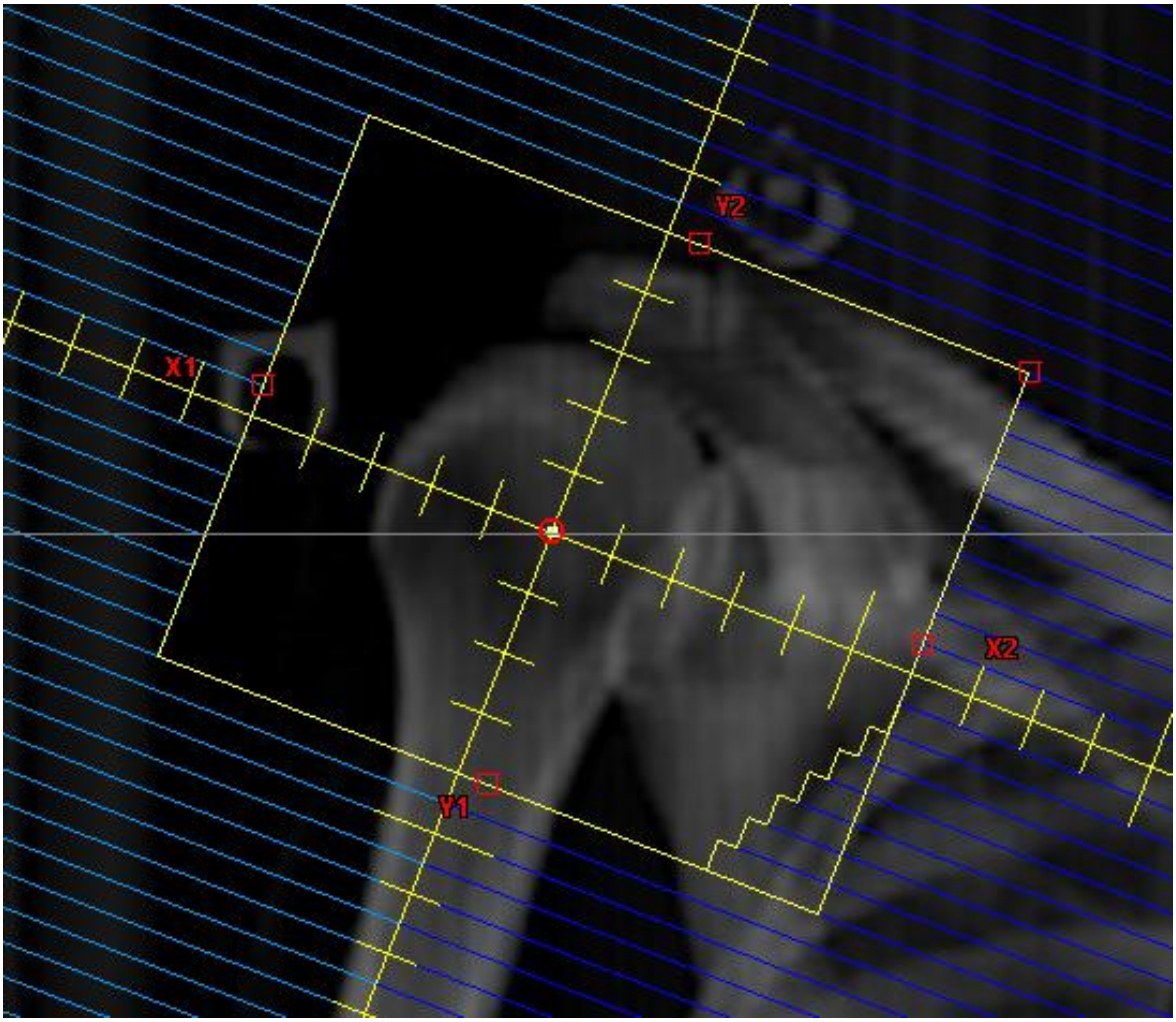
Example 1. of LDRT for thumb OA.

For OA involving the metacarpophalangeal (MCP) and carpometacarpal (CMC) joints, field design should be an individualized approach based on clinical history, examination, and prior treatments. Volumes should encompass not only the joint space and underlying bony changes, but also the surrounding joint capsule and tendon insertions as identified using 3D-based treatment planning from CT simulation. In general, the superior border is halfway between MCP and interphalangeal (IP) joint, inferior border is 2cm margin on CMC joint, lateral and medial border is 1cm on MCP joint. A typical field size is 8cm x 4cm.



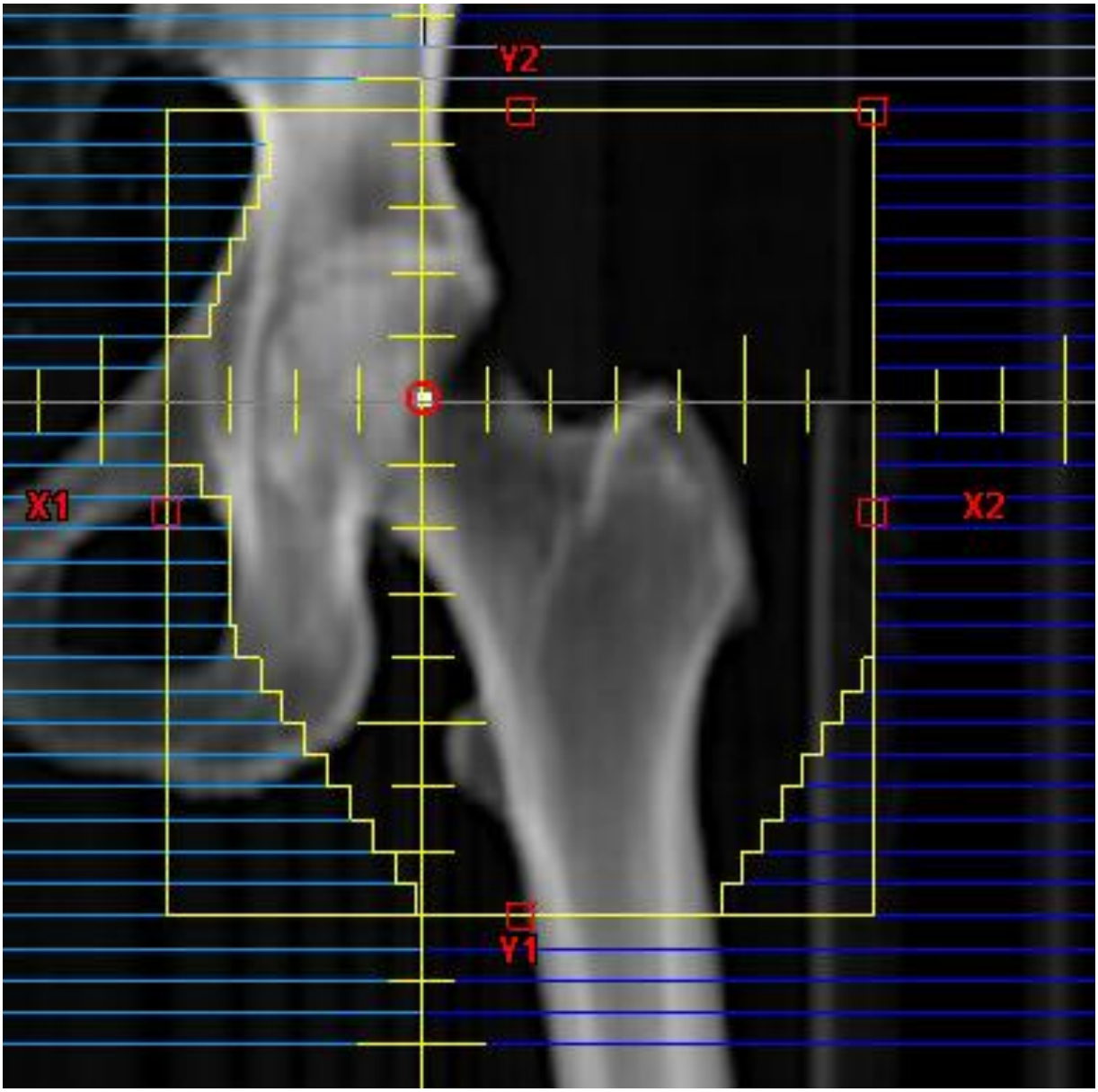
Example 2. of LDRT for elbow OA.

For OA involving the humeroulnar joint, field design should be an individualized approach based on clinical history, examination, and prior treatments. Volumes should encompass not only the joint space and underlying bony changes, but also the surrounding joint capsule and tendon insertions as identified using 3D-based treatment planning from CT simulation. In general, a 2:1 ratio of superior to inferior coverage relative to the joint space is used. Superior border is approximately 6cm from joint, Inferior border approximately 3cm from joint, lateral and medial border 2cm from joint.



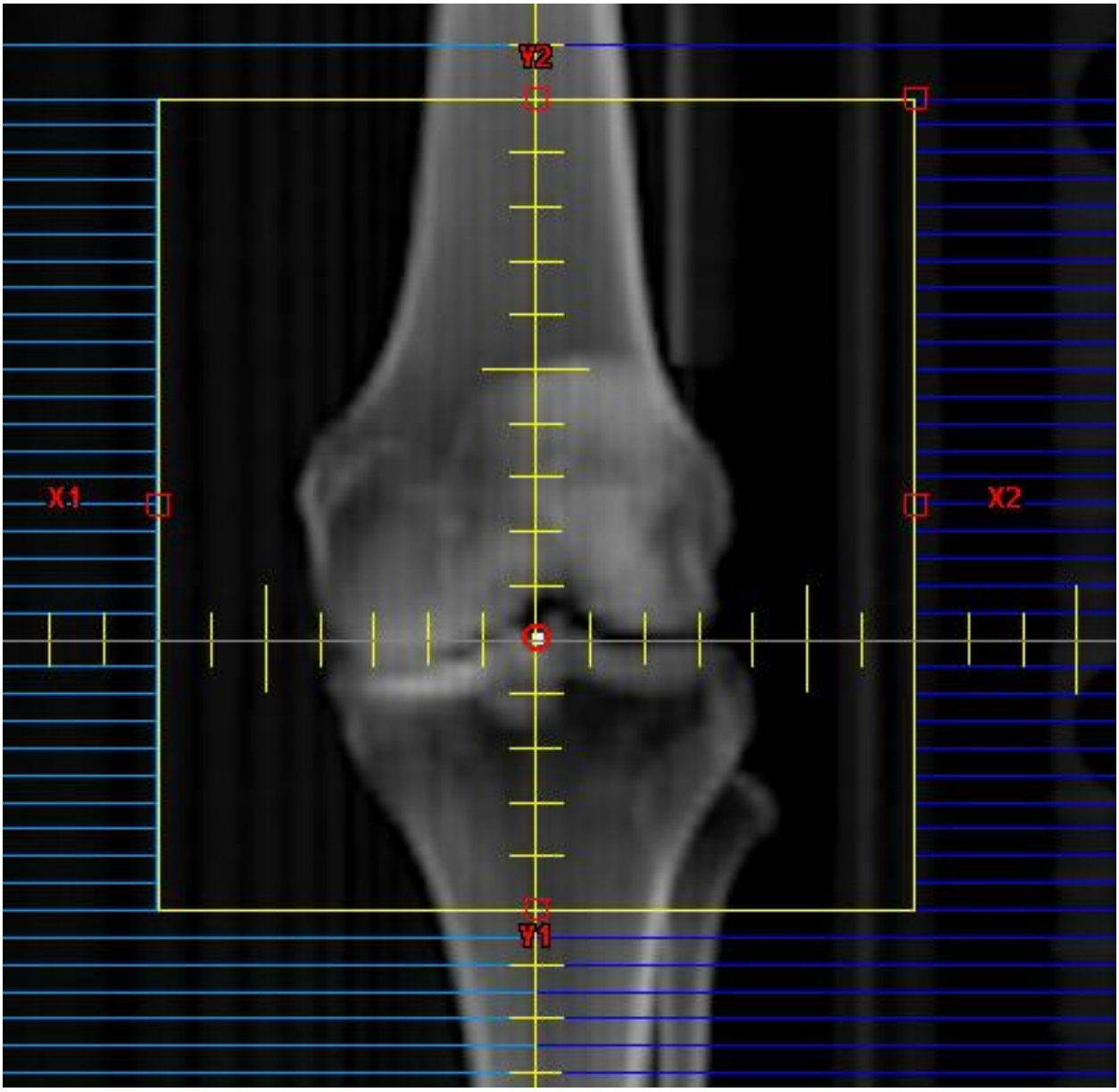
Example 3. of LDRT for shoulder OA.

For OA involving the glenohumeral joint, field design should be an individualized approach based on clinical history, examination, and prior treatments. Volumes should encompass not only the joint space and underlying bony changes, but also the surrounding joint capsule and tendon insertions as identified using 3D-based treatment planning from CT simulation. In general, the superior border is set at the superior aspect of the clavicle and includes the lateral 1/3 of the clavicle, inferior border is 1-2cm below inferior aspect of tubercle of humerus, lateral border is 2cm from humeral head, and medial border is placed to ensure coverage of coracoid process with appropriate shielding of breast tissue and chest wall.



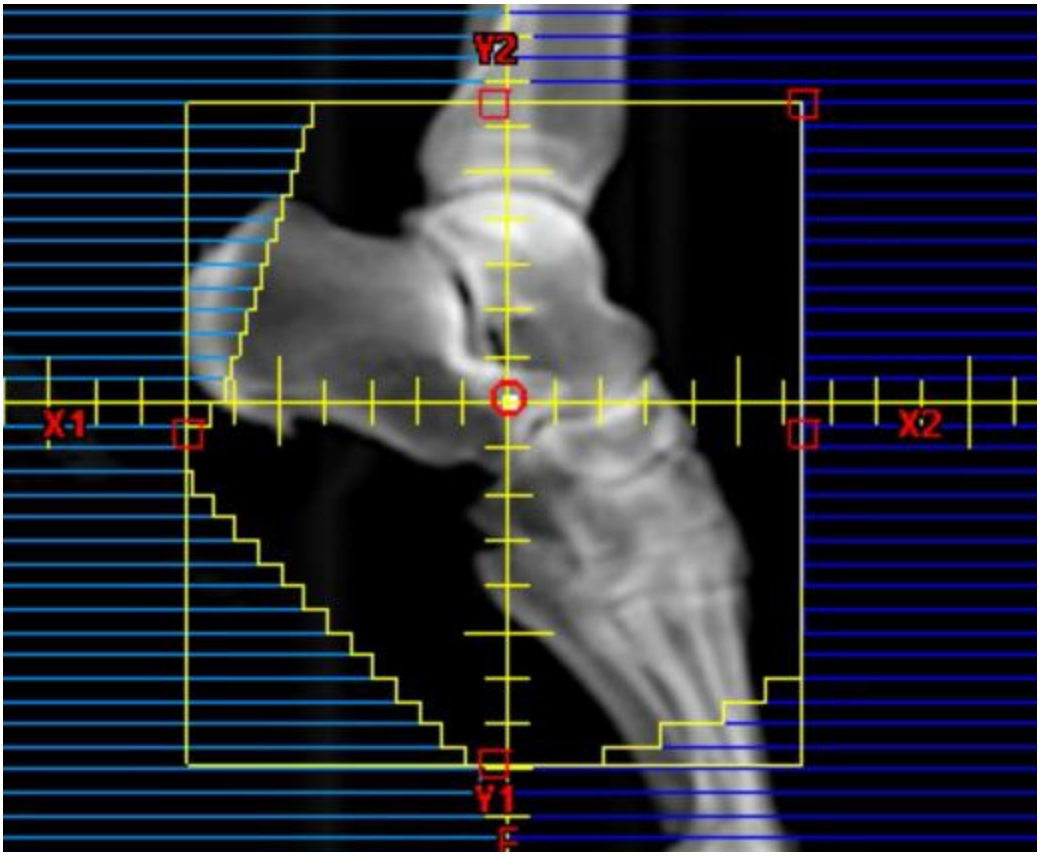
Example 4. of LDRT for hip OA.

For OA involving the acetabulofemoral joint, field design should be an individualized approach based on clinical history, examination, and prior treatments. Volumes should encompass not only the joint space and underlying bony changes, but also the surrounding joint capsule and tendon insertions as identified using 3D-based treatment planning from CT simulation. In general, the superior border is at the anterior superior iliac spine (ASIS), inferior 1–2 cm below the lesser trochanter, lateral is at the greater trochanter and medial at the lateral edge of the obturator foramen. The pelvis blocked as needed to spare healthy tissue. The field's proportions follow a ratio of 1:2, ensuring coverage of the hip joint while minimizing exposure to surrounding structures.



Example 5. of LDRT for knee OA.

For OA of the tibiofemoral joint, field design should be an individualized approach based on clinical history, examination, and prior treatments. Volumes should encompass not only the joint space and underlying bony changes, but also the surrounding joint capsule and tendon insertions as identified using 3D-based treatment planning from CT simulation. In general, a 2:1 ratio of superior to inferior coverage relative to the joint space is used to ensure complete joint capsule coverage while treating tendon insertions and surrounding structures. Superior border is approximately 10cm from joint, Inferior border approximately 5cm joint, and medial and lateral border 3cm from joint.



Example 6. of LDRT for foot/ankle OA.

For OA involving the talocrural (TC) and subtalar (ST) joint, field design should be an individualized approach based on clinical history, examination, and prior treatments. Volumes should encompass not only the joint space and underlying bony changes, but also the surrounding joint capsule and tendon insertions as identified using 3D-based treatment planning from CT simulation. In general, superior border is about 2cm proximal to TC joint, inferior border is placed with margin along tarsal bones, lateral and medial borders are with a margin to joint space with blocks to shield along the lateral edge of calcaneus.