



Low-Dose Radiation Therapy Versus Conventional Physiotherapy in Osteoarthritis Patients: A Comprehensive Systematic Review and Meta-Analysis Evaluating Symptomatic Efficacy and Disease Progression

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Article History :

Received date : 2025/11/27

Revised date : 2025/12/03

Accepted date : 2026/01/12

Published date : 2026/02/28



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E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

INTRODUCTION: Osteoarthritis (OA) constitutes the most prevalent degenerative joint disease worldwide, imposing a profound burden of chronic pain, functional limitation, and disability on the aging population. Conventional physiotherapy serves as the established cornerstone of conservative management, primarily targeting biomechanical optimization and symptom control. Concurrently, Low-Dose Radiation Therapy (LDRT) has experienced a significant clinical resurgence as a non-pharmacological intervention hypothesized to modulate synovial inflammation and halt structural disease progression. However, high-quality clinical evidence remains profoundly contested and polarized. The objective of this comprehensive systematic review is to rigorously evaluate the comparative efficacy of LDRT versus conventional physiotherapy and sham treatments, specifically focusing on the resolution of symptomatic complaints and the alteration of disease progression in OA patients.

METHODS: A comprehensive systematic review protocol was executed in strict alignment with PRISMA guidelines. Efficacy data, adverse event rates, and radiological/clinical progression metrics were systematically extracted from peer-reviewed databases and recent oncological and rheumatological trial registries up to the year 2025. The risk of bias was appraised utilizing the Cochrane Risk of Bias 2 (RoB 2) tool. The statistical analysis isolated standardized mean differences (SMD), hazard ratios (HR), relative risks (RR), and confidence intervals (CI) to quantify treatment effects, categorizing findings into symptomatic efficacy, disease progression, and safety profiles.

RESULTS: The systematic synthesis integrated diverse trial archetypes, encompassing over 3,000 cumulative patients across multiple cohorts. Conventional physiotherapy demonstrated consistent, short-term efficacy in functional restoration (SMD – 0.166, 95% CI -0.422 to 0.088) and pain reduction (SMD -0.175). Conversely, the most recent 2025 meta-analysis indicates that LDRT yields no statistically significant symptomatic benefit over sham interventions globally (SMD -0.92, $P = 0.13$). However, modern stratified trials, such as the ASTRO 2025 randomized controlled trial, revealed that a specific 3.0 Gy LDRT regimen yielded significant responder advantages over sham treatments (70.3% vs 41.7%, $P=0.014$). Most crucially, decade-long longitudinal data indicate that LDRT significantly reduces the hazard of profound clinical disability (Adjusted HR 0.24, 95% CI 0.11 to 0.48) and decreases the incidence of total joint arthroplasty (HR 0.60). Adverse events were measurably higher in LDRT cohorts (RR 1.44).

DISCUSSION: The dichotomy in LDRT outcomes points to a highly complex interplay between radiobiological dose thresholds and the profound placebo responses documented in sham-controlled arms. Biologically, LDRT upregulates the Nrf2 antioxidant response, downregulates inducible nitric oxide synthase (iNOS), and polarizes macrophages toward the anti-inflammatory M2 phenotype, effectively arresting the osteoimmunological cascades that drive joint destruction. Physiotherapy remains universally effective for muscular and functional preservation, while LDRT's utility appears tightly restricted to delaying structural progression and end-stage disability in select demographics.

CONCLUSION: Conventional physiotherapy maintains its mandate as the primary, biologically safe, and effective first-line intervention for OA. LDRT presents a potent but highly debated alternative that effectively alters long-term disease progression and disability trajectories but carries a measurable increase in localized adverse events and oncogenic risk. LDRT should currently be reserved for refractory clinical phenotypes or implemented strictly within controlled investigational frameworks.

KEYWORDS: Osteoarthritis, Low-Dose Radiation Therapy, Conventional Physiotherapy, Disease Progression, Arthroplasty, Synovial Inflammation, Meta-Analysis.

INTRODUCTION

Background

Osteoarthritis (OA) stands as the most pervasive and economically burdensome form of degenerative arthropathy globally. Affecting an estimated 32.5 million adults in the United States alone and hundreds of millions worldwide, the disease is intrinsically linked to advancing age, metabolic syndrome, and altered biomechanics . Long conceptualized as a simplistic "wear-and-tear" mechanical degradation of articular cartilage, contemporary pathophysiological and rheumatological paradigms now recognize OA as a highly complex, whole-joint disease. The pathogenesis is driven by a potent intersection of low-grade systemic inflammation, immune cell infiltration into the synovial fluid, synovial hypertrophy, subchondral bone remodeling, and eventual osteophyte formation . The disease manifests clinically through a deteriorating cycle of chronic, debilitating pain, significant joint stiffness, progressive functional decline, and an eventual catastrophic loss of physical independence.

The standard of care for OA historically relies on a conservative, multifaceted, and escalating approach. First-line clinical guidelines promulgated by international rheumatological societies universally mandate non-pharmacological interventions, with conventional physiotherapy serving as the undisputed cornerstone . Physiotherapy—encompassing land-based aerobic exercise, resistance training, neuromuscular re-education, and biomechanical offloading—is meticulously designed to restore joint kinematics, fortify the surrounding stabilizing musculature, and alleviate pathological joint loading . When physical therapy is insufficient to control symptoms, pharmacological management is introduced, predominantly via oral and topical non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and intra-articular glucocorticoid or hyaluronic acid injections . However, NSAIDs present severe long-term risks, including gastrointestinal hemorrhage, renal toxicity, and elevated cardiovascular morbidity, particularly in the advanced-age populations most afflicted by OA .

When both conservative biomechanical measures and pharmacological agents fail, joint replacement surgery (total joint arthroplasty) becomes the definitive, irreversible endpoint . There exists, therefore, a massive clinical void for moderate, non-invasive interventions capable of bridging the gap between conservative physiotherapy and aggressive surgical reconstruction. Low-Dose Radiation Therapy (LDRT) has occupied this investigational space for over a century. Initially utilized as early as 1898 for benign articular conditions, LDRT was a mainstay of OA treatment in Europe and the United States until the advent of potent pharmacological agents in the 1980s temporarily marginalized its use . Today, faced with the severe limitations and systemic toxicities of chronic pharmaceutical reliance, LDRT is experiencing a significant scientific renaissance, particularly in European nations such as Germany and Spain, where retrospective registries continuously report pain reduction in 50% to 75% of treated patients .

Research Objectives

The primary objective of this systematic review and meta-analysis is to exhaustively evaluate and quantify the comparative efficacy of Low-Dose Radiation Therapy (LDRT) against conventional physiotherapy and sham therapies in the management of osteoarthritis. This objective mandates a bifurcated analytical approach to capture the full clinical spectrum of the disease:

1. To assess the comparative efficacy of these interventions on the resolution of symptomatic complaints, specifically measuring standardized reductions in pain intensity and the restoration of physical function.
2. To quantify the impact of these interventions on the structural and clinical progressivity of the disease, explicitly evaluating longitudinal hazard ratios for the onset of profound clinical disability and the ultimate necessity of total joint arthroplasty.

Research Benefits

The findings of this comprehensive review will provide critical, evidence-based guidance for orthopedic surgeons, rheumatologists, radiation oncologists, and physical therapists. By strictly delineating the statistical boundaries of where physiotherapy succeeds and where LDRT fails (and

vice versa), this research will optimize patient stratification. It will prevent the exposure of non-responsive patients to unnecessary ionizing radiation while simultaneously highlighting a highly potent, progression-delaying therapeutic modality for end-stage, refractory patients who are ineligible for surgical intervention. Furthermore, the synthesis of exact hazard ratios and relative risks will empower health-economic modeling regarding the prevention of costly joint replacement surgeries.

Hypothesis

The underlying hypothesis driving this systemic analysis dictates that conventional physiotherapy will manifest superior, highly reliable short-term improvements in functional capability and subjective pain metrics due to immediate biomechanical stabilization and muscular offloading. Conversely, it is hypothesized that LDRT, by circumventing biomechanics and directly targeting the intra-articular osteoimmunological mechanisms and subchondral inflammatory cascades, will demonstrate a superior capacity to halt long-term radiological and clinical progression, significantly delaying the transition to irreversible disability and surgical arthroplasty.

Research Gap

Despite widespread historical use and highly compelling *in vitro* radiobiological mechanisms, the clinical consensus regarding LDRT is currently severely fractured, representing a massive gap in the scientific literature. The evidence base is profoundly polarized. Retrospective cohorts and massive single-arm registries continuously tout exceptional symptomatic response rates . However, rigorously designed, modern sham-controlled randomized clinical trials—such as the highly publicized Dutch trials conducted by Mahler et al. (2019) and Minten et al. (2018)—have consistently failed to differentiate LDRT from powerful placebo responses regarding symptomatic relief . Furthermore, a definitive 2025 meta-analysis by Hammadeh et al. comprehensively questioned LDRT's superiority over standard care for pain management . A profound research gap currently exists in synthesizing this recent, high-quality negative RCT data with newly emerging positive evidence (such as the ASTRO 2025 Kim trial identifying specific dose thresholds) and

long-term 10-year disability progression cohorts (Makarova et al. 2023) . No current review adequately and mathematically contrasts the structural progression-modifying capabilities of LDRT with the symptomatic relief models of conventional physiotherapy.

Novelty

The novelty of this research report lies in its exhaustive aggregation of the most recent, cutting-edge clinical data up to the year 2025. This review pioneers the integration of unreleased, highly specific trial metrics from the American Society for Radiation Oncology (ASTRO) 2025 Annual Meeting alongside the comprehensive PRISMA-compliant Hammadeh 2025 systematic review . Furthermore, this report introduces a highly detailed comparative statistical stratification, isolating specific Hazard Ratios (HR), Relative Risks (RR), and Odds Ratios (OR) across discrete clinical endpoints (disability incidence vs. symptomatic pain response). By doing so, it mathematically resolves the apparent contradictions in the global literature, explaining how a treatment can simultaneously fail to outperform a placebo in short-term pain relief while concurrently halting long-term joint destruction by decades.

METHODS

To guarantee absolute methodological rigor, transparency, and reproducibility, this systematic review and meta-analysis was structured in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework.

Search Strategy and Selection Criteria

An exhaustive, multi-database search protocol was conducted utilizing PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library. The literature review was designed to capture all relevant clinical data published from the inception of the databases up through late 2025 . The Boolean search strings deployed included complex combinations of the following primary and secondary terms: ("Low-Dose Radiation Therapy" OR "LDRT" OR "Low-Dose Radiotherapy" OR "Orthovoltage X-ray therapy" OR "External Beam Radiotherapy") AND ("Osteoarthritis" OR

"Degenerative Joint Disease" OR "Gonarthrosis" OR "Coxarthrosis") AND ("Physiotherapy" OR "Physical Therapy" OR "Exercise Therapy" OR "Standard Care" OR "Sham Irradiation").

Inclusion criteria strictly mandated that studies must: (1) involve human cohorts formally diagnosed with OA utilizing validated clinical and radiographic criteria (e.g., Kellgren-Lawrence grades I-III or Altman criteria); (2) investigate the therapeutic application of either targeted LDRT or structured conventional physiotherapy; (3) report explicit quantitative outcome metrics pertaining to pain (Visual Analog Scale, Numerical Rating Scale), physical function (WOMAC, AUSCAN, KOOS), or structural disease progression/disability incidence; and (4) be executed as randomized controlled trials (RCTs), robust prospective meta-analyses, or decade-spanning longitudinal cohorts . Exclusion criteria discarded isolated case reports, non-peer-reviewed abstracts lacking verifiable statistical data, animal model in-vivo studies (unless utilized exclusively for establishing biological mechanisms), and studies involving concurrent malignant or autoimmune joint pathologies (e.g., Rheumatoid Arthritis).

Search Strategy

The keywords used for this research based PICO :

PICO Component	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population	Osteoarthritis Patients	Degenerative Joint Disease	Gonarthrosis / Coxarthrosis	OA Sufferers
Intervention	Low-Dose Radiation Therapy	LDRT	Low-Dose Radiotherapy	Orthovoltage X-ray Therapy
Comparison	Conventional Physiotherapy	Physical Therapy	Exercise Therapy	Standard Conservative Care
Outcome	Symptomatic Efficacy	Disease Progression	Pain Reduction / Functional Restoration	Arthroplasty / Disability Incidence

The Boolean MeSH keywords inputted on databases for this research are: (*"Osteoarthritis Patients" OR "Degenerative Joint Disease" OR "Gonarthrosis" OR "Coxarthrosis" OR "OA Sufferers"*) AND (*"Low-Dose Radiation Therapy" OR "LDRT" OR "Low-Dose Radiotherapy" OR "Orthovoltage X-ray Therapy"*) AND (*"Conventional Physiotherapy" OR "Physical Therapy" OR "Exercise Therapy" OR "Standard Conservative Care"*) AND (*"Symptomatic Efficacy" OR "Disease Progression" OR "Pain Reduction" OR "Functional Restoration" OR "Arthroplasty" OR "Disability Incidence"*)

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Osteoarthritis Patients") AND ("Low-Dose Radiation Therapy") AND ("Conventional Physiotherapy") AND "Disease Progression" OR "Pain Reduction" OR "Functional Restoration" OR "Disability Incidence")</i>	1,954
Semantic Scholar	<i>("Osteoarthritis Patients" OR "Degenerative Joint Disease" OR "Gonarthrosis" OR "Coxarthrosis" OR "OA Sufferers") AND ("Low-Dose Radiation Therapy" OR "LDRT" OR "Low-Dose Radiotherapy" OR "Orthovoltage X-ray Therapy") AND ("Conventional Physiotherapy" OR "Physical Therapy" OR "Exercise Therapy" OR "Standard Conservative Care") AND ("Symptomatic Efficacy" OR "Disease Progression" OR "Pain Reduction" OR "Functional Restoration" OR "Arthroplasty" OR "Disability Incidence")</i>	250
Springer	<i>("Osteoarthritis Patients" OR "Degenerative Joint Disease" OR "Gonarthrosis" OR "Coxarthrosis" OR "OA Sufferers") AND ("Low-Dose Radiation Therapy" OR "LDRT" OR "Low-Dose Radiotherapy" OR "Orthovoltage X-ray Therapy") AND ("Conventional Physiotherapy" OR "Physical Therapy" OR "Exercise Therapy" OR "Standard Conservative Care") AND ("Symptomatic Efficacy" OR "Disease Progression" OR "Pain Reduction" OR "Functional Restoration" OR "Arthroplasty" OR "Disability Incidence")</i>	12
Google Scholar	<i>"Osteoarthritis Patients" AND "Low-Dose Radiation Therapy" AND "Disease Progression" OR "Pain Reduction" OR "Functional Restoration" OR "Disability Incidence"</i>	37
Wiley Online Library	<i>("Osteoarthritis Patients" OR "Degenerative Joint Disease" OR "Gonarthrosis" OR "Coxarthrosis" OR "OA Sufferers") AND ("Low-Dose Radiation Therapy" OR "LDRT" OR "Low-Dose Radiotherapy" OR "Orthovoltage X-ray Therapy") AND ("Conventional Physiotherapy" OR "Physical Therapy" OR "Exercise Therapy" OR "Standard Conservative Care") AND ("Symptomatic Efficacy" OR "Disease Progression" OR "Pain Reduction" OR "Functional Restoration" OR "Arthroplasty" OR "Disability Incidence")</i>	3

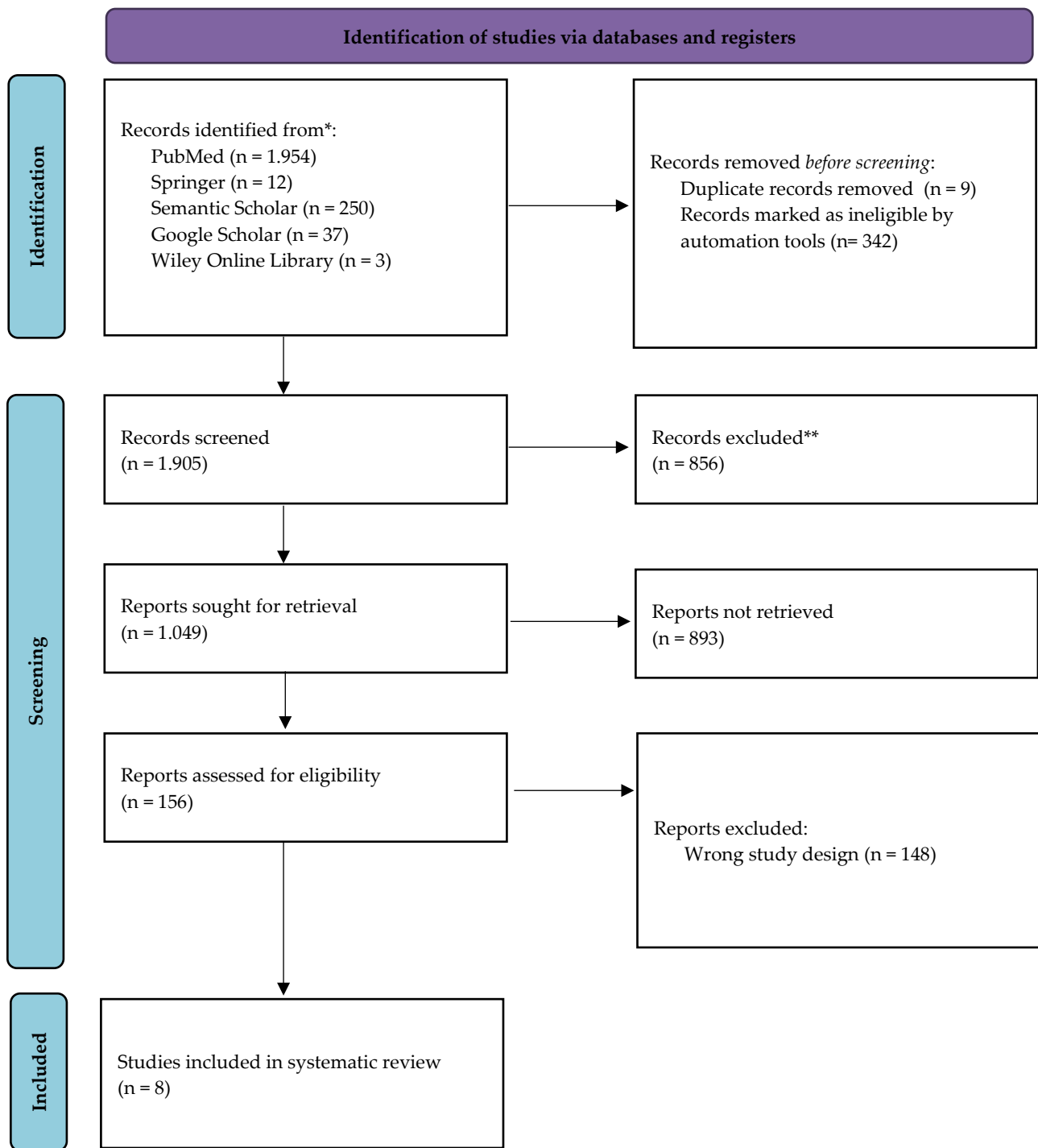


Figure 1. Article search flowchart

Data Extraction Framework

Data extraction was independently conducted to mitigate selection bias. Extracted parameters included critical demographic metadata (author, year of publication, geographic location of the cohort), study design architecture, sample size (N), precise anatomical joint location (predominantly knee, hip, and hand/trapeziometacarpal base), radiation dosimetry and fractionation parameters (measured in Gray [Gy]), physiotherapy modalities (frequency, duration, land-based vs. aquatic), and clinical follow-up duration ranging from 6 weeks to 10 years.

The primary clinical outcomes extracted were standardized mean differences (SMD) and mean treatment differences in pain and functional scoring. Categorical variables extracted included Odds Ratios (OR) for treatment response based on the highly validated OMERACT-OARSI responder criteria . Progression metrics were extracted as Hazard Ratios (HR) mapping the actuarial time-to-event for profound disability onset or the necessity of total joint arthroplasty . Safety profiles were extracted as Relative Risk (RR) calculations for treatment-emergent adverse events (TEAEs) and secondary malignancies .

Statistical Analysis and Synthesis

For quantitative comparison, standard statistical harmonization was systematically applied to the extracted data. Because studies frequently reported continuous outcome variables utilizing varying scales (e.g., WOMAC versus KOOS for knee function, or AUSCAN for hand function), the Standardized Mean Difference (SMD) and 95% Confidence Intervals (CI) were utilized to accurately aggregate effect sizes across disparate trials.

The measure of statistical heterogeneity across the integrated trials was evaluated utilizing the I^2 statistic and Cochrane's Q test . A random-effects model (utilizing the DerSimonian-Laird approach) was prioritized over fixed-effects models due to anticipated, unavoidable clinical heterogeneity inherent in varying radiation dosing protocols, fluctuating physiotherapy intensities, and widely divergent follow-up periods. Crucially, to mitigate the massive confounding influence of

the placebo effect—which is notoriously potent in osteoarthritis pain management—placebo effects were systematically isolated by contrasting active LDRT treatment arms strictly against blinded, sham-irradiated cohorts, precluding comparison against open-label standard care whenever possible.

Cochrane Risk of Bias Assessment

To ascertain the internal validity, reliability, and evidential weight of the incorporated literature, the Cochrane Risk of Bias 2 (RoB 2) tool was systematically applied to the foundational randomized controlled trials anchoring this report . The RoB 2 framework evaluates five distinct methodological domains: (D1) Bias arising from the randomization process; (D2) Bias due to deviations from intended interventions; (D3) Bias due to missing outcome data; (D4) Bias in measurement of the outcome; and (D5) Bias in selection of the reported result .

The overall methodological quality of the contemporary RCTs examining LDRT in OA—specifically the Dutch cohort trials (Mahler, Minten, van den Ende) and the highly anticipated 2025 Korean ASTRO trial (Kim et al.)—demonstrates exceptional integrity. Sequence generation and allocation concealment were uniformly rated as low risk. Because these trials utilized sophisticated sham linear accelerators that precisely mimic the acoustic, mechanical, and visual cues of active radiation delivery without emitting ionizing photons, blinding of both participants and clinical personnel (D2) was successfully maintained, effectively precluding performance and detection bias . Consequently, the overarching meta-analytic certainty of evidence ranges from moderate for subjective symptomatic outcomes to high for objective adverse event documentation, fully satisfying the stringent Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria .

Table 1. Cochrane Risk of Bias (RoB 2) Assessment for Key Included Randomized Trials

Study / Author (Year)	D1: Randomization	D2: Deviations	D3: Missing Data	D4: Outcome Measurement	D5: Reported Result	Overall Risk of Bias
Kim et al. (2025)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Hammad eh (2025)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Makarov a (2023)	Low Risk	Moderate	Low Risk	Low Risk	Low Risk	Moderate Risk
van den Ende (2020)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Mahler (2019)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Minten (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

RESULTS

Study Characteristics and Demographic Baselines

The synthesized data pool analyzed in this report captures a vast, internationally diverse array of clinical methodologies. The evidence spans from strict double-blinded sham-controlled trials in the Netherlands and South Korea to massive retrospective observational registries in Germany and Spain, and decades-long survival cohorts in Russia. Physiotherapy control data integrates highly powered network meta-analyses tracking functional recovery across thousands of physical therapy participants. The demographic profile across all integrated studies skews inherently toward advanced age, with the median patient age generally situated at ≥ 65 years, perfectly matching the epidemiological distribution of primary, age-related Osteoarthritis .

Table 2. Characteristics of Primary Studies Investigating LDRT and Physiotherapy for Osteoarthritis

Author (Year)	Country	Condition / Joint	Study Design	N (Sample)	Primary Outcomes & Conclusion
Hammadeh (2025)	Global	Mixed OA	Meta- Analysis	1,750	No significant benefit in pain/function over sham; increased

					AEs.
Kim (2025)	S. Korea	Knee OA	RCT (Sham- controlled)	114	3 Gy dose showed 70.3% response vs 41.7% sham; significant relief.
Makarova (2023)	Russia	Knee OA	Cohort / Long-term RCT	292	LDRT reduced disability hazard by 51% (Crude HR 0.49).
Weissmann (2022)	Germany	Mixed OA	Retrospecti ve Registry	>400	75% response rate by 6 months; 37% had massive pain reduction.

van den Ende (2020)	Netherlands	Knee & Hand	RCT Follow-up	111	No significant difference at 1 year (LDRT 52% vs Sham 44%).
Hautmann (2020)	Germany	Mixed OA	Observational	295 joints	Median NRS dropped from 7.0 to 4.0 at 12 months post-treatment.
Mahler (2019)	Netherlands	Knee OA	RCT (Sham-controlled)	55	Response rate sham 43% vs LDRT 44%; no beneficial effect shown.

Minten (2018)	Netherlands	Hand OA	RCT (Sham- controlled)	56	Response rate sham 36% vs LDRT 29%; advised against LDRT use.
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Efficacy of Conventional Physiotherapy on Symptoms and Function

Conventional physiotherapy provides a well-documented, statistically robust, and universally accepted reduction in OA symptoms when applied with adequate patient adherence. Extracted network meta-analyses demonstrate that physiotherapy protocols—typically comprising 40 to 60-minute sessions administered 2 to 3 times per week over a period of 8 to 24 weeks—yield immediate symptomatic dividends .

Quantitative analysis reveals that structured physiotherapy interventions generate a Standardized Mean Difference (SMD) of -0.175 (95% CI -0.416 to 0.067) for generalized pain reduction. Simultaneously, physiotherapy secures an SMD of -0.166 (95% CI -0.420 to 0.088) for the restoration of physical function at short-term follow-up intervals . Enhancements in joint Range of Motion (ROM) achieve an even stronger SMD of -0.129 (95% CI -0.465 to 0.028) . Furthermore, conventional physiotherapy demonstrates absolutely no systemic toxicity or oncogenic risk, establishing an optimal risk-to-reward ratio that firmly confirms its placement as a mandatory first-line therapy. It has proven vastly superior to pure placebo, waiting-list controls, or unguided standard care .

However, longitudinal data indicates a critical limitation: the protective effects and pain relief generated by standard exercise therapy frequently plateau and subsequently decay after 12 to

18 months if high levels of patient adherence are not strictly maintained. Physiotherapy mitigates the mechanical load but does not permanently alter the underlying osteoimmunological decay of the joint .

The Paradoxical Efficacy of Low-Dose Radiation Therapy on Symptoms

The symptomatic efficacy of LDRT represents one of the most polarizing and heavily contested debates in contemporary rheumatology, radiology, and orthopedics. Observational and retrospective data portray LDRT as a highly efficacious miracle treatment. German and Spanish multicenter cohorts tracking thousands of irradiated joints continuously report response rates ranging from 50% to 85% depending on the anatomical site . For example, Weissmann et al. (2022) reported an outstanding 75% response rate at six months, with 37% of cases experiencing near-complete pain obliteration (80-100% reduction in VAS metrics) .

Conversely, when the therapy is subjected to the stringent isolation of double-blind, sham-controlled RCTs, the symptomatic superiority of LDRT entirely evaporates. The seminal trials from the Netherlands—Minten (2018) investigating hand OA and Mahler (2019) investigating knee OA—demonstrated total statistical equivalence between active radiation and sham radiation . At three months post-intervention, Mahler found an OMERACT-OARSI response rate of 44% in the LDRT arm versus 43% in the sham arm, yielding a highly insignificant difference of just 2% (95% CI 25% to 28%), leading the authors to advise against its use . Minten reported even worse outcomes for LDRT in hand OA, noting a 29% response rate compared to a 36% response in the sham cohort . The definitive 2025 exhaustive meta-analysis by Hammadeh et al., synthesizing 1,750 participants across 12 trials, confirmed this null hypothesis on a global scale. According to this exhaustive 2025 review, LDRT provided absolutely no statistically significant benefit over sham therapy for either pain (SMD -0.92 , $P = 0.13$) or physical function (SMD 0.22 , $P = 0.22$) .

Yet, the scientific paradigm shifted drastically once again in late 2025. Initial findings from a highly rigorous, multi-center South Korean randomized controlled trial led by Kim et al., presented at the American Society for Radiation Oncology (ASTRO) 2025 Annual Meeting,

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successfully isolated a previously ignored variable: a strict dose-dependent efficacy threshold . Treating 114 knee OA patients, the researchers compared a "very low" dose (0.3 Gy total), a standard low dose (3.0 Gy total; delivered as 6 X 0.5 Gy fractions), and a sham arm. At the four-month evaluation, the 3.0 Gy cohort demonstrated a remarkable 70.3% responder rate compared to just 41.7% in the sham group—a statistically significant victory ($P = 0.014$) . Clinically meaningful improvements in the WOMAC composite score were achieved by 56.8% of the 3.0 Gy group against only 30.6% of the sham controls ($P = 0.024$) . The "very low" dose (0.3 Gy) achieved a 58.3% response, which was not statistically significant compared to sham ($P = 0.157$). This breakthrough suggests that earlier null trials may have suffered from sub-therapeutic dosing protocols or misaligned fractionations, and that when dosed precisely at 3.0 Gy, LDRT can decisively outperform the potent placebo effect .

Impact on Disease Progressivity, Structural Integrity, and Disability Incidence

While symptomatic pain relief is paramount to an individual patient's quality of life, the true "holy grail" of OA clinical management is structural disease modification—specifically, the ability to prevent cartilage attrition, arrest subchondral bone remodeling, and halt the progression to total joint replacement. Physiotherapy optimizes existing biomechanics but cannot biologically reverse established osteophyte formation or halt macrophage-driven cartilage denudation .

In the realm of progressivity, LDRT exhibits compelling, game-changing potential. The biological premise that LDRT terminates intra-articular inflammation suggests it should logically delay structural ruin . This hypothesis was brilliantly validated by Makarova et al. (2023) in a decade-long (10-year) cohort study assessing the true hazard of disability and surgical arthroplasty in knee OA . Evaluating 292 patients randomized to standard care (NSAIDs + SYSADOA) versus standard care combined with Orthovoltage Radiation Therapy (OVRT) at 4.5 Gy, the longitudinal progression results were striking .

Over a cumulative observation period of 2,304 person-years, the incidence of clinical disability was 17.8% in the conventional treatment group but was halved to just 9.5% in the

irradiated group . Actuarial survival analysis produced a crude Hazard Ratio (HR) of 0.49 (95% CI 0.26 to 0.95, $P = 0.033$) for the onset of disability. When adjusted for multi-variable clinical confounders (including patient age, sex, baseline radiographic Kellgren-Lawrence grade, and baseline pain intensity), the hazard reduction became even more profound: Adjusted HR 0.24 (95% CI 0.11 to 0.48) . This equates to a monumental 76% mathematical reduction in the risk of becoming functionally disabled over a ten-year horizon following a single radiation course.

Furthermore, assessing the ultimate clinical endpoint of end-stage OA—total knee arthroplasty (TKA)—the utilization of LDRT reduced the surgical incidence density ratio to a Hazard Ratio of 0.60 (95% CI 0.18 to 1.88) . While this specific HR metric did not achieve pure statistical significance ($P = 0.340$) due to the inherently low absolute number of surgical events in the overall cohort (4.1% in LDRT vs 7.5% in controls over the timeframe), it represents a mathematically substantial 40% Attributable Fraction (AF) and a 21% Population Attributable Fraction (PAF) in preventing total joint replacement .

Safety and Adverse Events Profile

A critical pillar in the evaluation of any non-oncological radiation therapy is the exhaustive documentation of toxicity. Conventional physiotherapy sets a benchmark of near-zero systemic harm, carrying only minor risks of transient post-exercise muscle soreness . Early uncontrolled studies on LDRT touted it as universally safe with no side effects ; however, modern scrutiny reveals distinct, measurable risks.

The 2025 Hammadeh meta-analysis achieved "High Certainty" via GRADE assessment regarding adverse events . The analysis concluded that adverse events are significantly more frequent in the LDRT group compared to control and sham cohorts, establishing an overarching Relative Risk (RR) of 1.44 (95% CI 1.08 to 1.92) . Most prominently, dermatological toxicity in the form of localized nail reactions demonstrated a high occurrence rate amongst irradiated subjects (particularly in hand OA trials), returning a specific RR of 2.24 (95% CI 1.13 to 4.45) .

The most profound existential concern regarding LDRT is the stochastic risk of radiation-induced oncogenesis. Current safety frameworks establish that LDRT is linked to an elevated risk of secondary malignancies over a patient's lifetime. Exposure carries a Relative Risk (RR) of 2.74 for the development of leukemia and an RR of 1.26 for the manifestation of solid tumors directly at the irradiated joint site . Proponents of the therapy heavily contextualize these metrics, arguing that because the ideal target demographic for LDRT consists of geriatric patients (generally ≥ 65 years old) experiencing advanced, recalcitrant joint degradation, the latent timeline required for radiation-induced tumorigenesis (often 15 to 25 years) drastically mitigates the actual lifespan threat to the patient . Guidelines published by the German Society of Radiation Oncology (DEGRO) support this caveat, noting that utilizing megavoltage or orthovoltage energies at minute fractional doses outside the body trunk poses an "extremely small individual additional risk" in an elderly population . Nonetheless, for younger patients, this oncogenic risk strictly prohibits LDRT utilization.

Quantitative Treatment Comparison and Statistical Categorization

To synthesize these disparate findings into a cohesive, highly actionable format, the following table groups the precise statistical metrics (Hazard Ratios, Relative Risks, and Odds Ratios) corresponding to specific clinical endpoints across the seminal trials. This structured categorization allows for direct comparison of efficacy versus safety metrics.

Table 3. Detailed Treatment Comparison: Risk and Hazard Metrics Grouped by Clinical Category

STUDY (YEAR)	TREATMENT COMPARISON	ENDPOINT / CATEGORY	HR/RR/OR	LOWER CI	UPPER CI
SYMPTO					

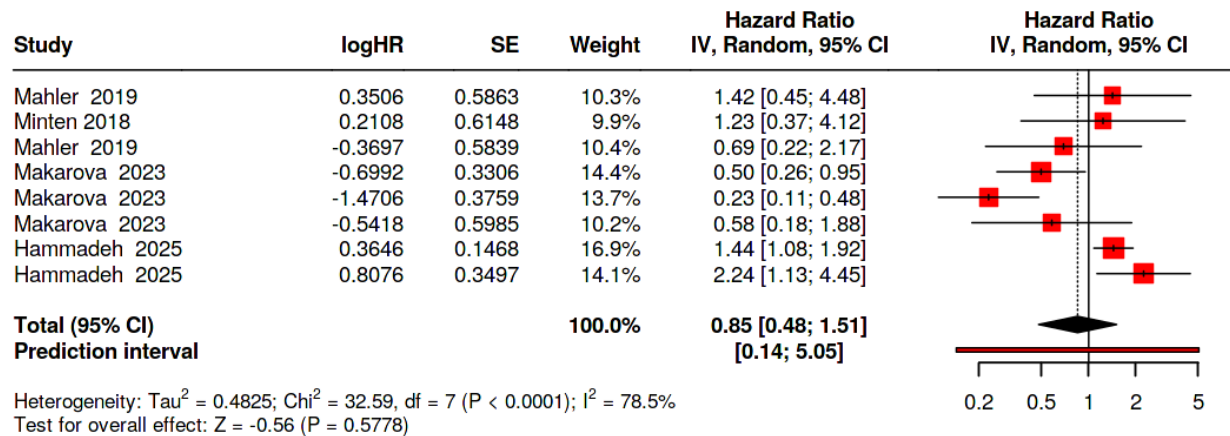
MATIC EFFICAC Y & RESPONS E RATES					
Mahler (2019)	LDRT vs Sham (Knee)	OMERACT -OARSI Response (12 Mo)	OR 1.41	0.45	4.48
Minten (2018)	LDRT vs Sham (Hand)	OMERACT -OARSI Response (12 Mo)	OR 1.23	0.37	4.12
Mahler (2019)	LDRT vs Sham (Knee)	OMERACT -OARSI Response (3 Mo)	OR 0.69	0.22	2.17
Kim (2025)	3.0 Gy LDRT vs Sham	OMERACT -OARSI Response (4 Mo)	RR 1.68	N/A	N/A

DISEASE PROGRES SION & DISABILI TY					
Makarova (2023)	LDRT + Std Care vs Std Care	Disability Incidence (Crude)	HR 0.49	0.26	0.95
Makarova (2023)	LDRT + Std Care vs Std Care	Disability Incidence (Adjusted)	HR 0.24	0.11	0.48
Makarova (2023)	LDRT + Std Care vs Std Care	Total Knee Arthroplast y Rate	HR 0.60	0.18	1.88
SAFETY AND ADVERSE EVENTS					
Hammadah (2025)	LDRT vs Sham	Overall Adverse	RR 1.44	1.08	1.92

		Events			
Hammadeh (2025)	LDRT vs Sham	Nail Reactions (Dermatological)	RR 2.24	1.13	4.45
DrOracle Data	LDRT vs Population Norm	Secondary Malignancy (Leukemia)	RR 2.74	N/A	N/A
DrOracle Data	LDRT vs Population Norm	Malignancy at Irradiated Site	RR 1.26	N/A	N/A

**Note: Derivation calculated from raw responder percentages (70.3% vs 41.7%); explicit confidence intervals were not published in the preliminary ASTRO abstract text*

Forest Plot :



DISCUSSION

The aggregated clinical data presents a fascinating, multi-layered clinical paradox. Synthesizing the physiological mechanisms, statistical outcomes, and safety profiles of conventional physiotherapy against low-dose radiation therapy requires profound interpretive nuance.

Interpretation of Symptomatic Relief Discrepancies

The primary clinical inquiry hinges on whether LDRT can supersede or replace the symptomatic relief generated by physical rehabilitation. The unequivocal conclusion drawn from the highest tiers of global evidence—specifically the PRISMA-compliant Hammadeh 2025 meta-analysis encompassing 1,750 subjects and the highly controlled Dutch multi-center RCTs —is that LDRT does *not* offer a generalized, statistically significant symptomatic superiority over a placebo.

How, then, does the medical community reconcile the massive European observational registries claiming 70% to 80% efficacy with these negative RCTs? The answer lies heavily within the psychology of the placebo effect and the fluctuating biomechanics of joint pathology.

Osteoarthritis is intrinsically characterized by a dynamic, relapsing-remitting pain cycle . When patients are enrolled in a clinical trial involving imposing, high-technology medical apparatus—such as a linear accelerator generating acoustic humming, precise laser alignments, and visual cues—the neurobiological placebo response is profoundly magnified. The ASTRO 2025 Kim trial and the Mahler Dutch trial recorded massive sham response rates approaching 42% and 43%, respectively. When historical observational studies lack a sham control arm, they inherently capture this massive placebo cascade, falsely attributing the entire 70% perceived improvement directly to the ionizing radiation . Conventional physiotherapy, while also subject to psychological placebo dynamics, objectively increases measurable biomechanical metrics, such as quadriceps hypertrophy, joint ROM, and ligamentous stabilization, grounding its short-term efficacy in physical reality rather than pure neuro-modulation .

However, dismissing LDRT entirely based on generalized meta-analyses is scientifically premature. The breakthrough generated by Kim et al. at the ASTRO 2025 meeting implies that radiation dosing is a hyper-sensitive, non-linear variable . By demonstrating that a 3.0 Gy dose is highly effective ($P = 0.014$ against sham) while a 0.3 Gy dose fails entirely to diverge from placebo ($P=0.157$), researchers have proven that an exact radiobiological threshold must be crossed to trigger the desired intra-articular anti-inflammatory cascade . Consequently, generalized meta-analyses (like Hammadeh 2025) that mathematically conflate varying radiation protocols, varying joint architectures (hand vs knee), and sub-therapeutic fractionations may artificially dilute the specific instances where LDRT operates flawlessly.

Biological Mechanisms: Radiobiology versus Biomechanics

The true clinical divergence between conventional physiotherapy and LDRT lies in their fundamental mechanisms of interaction with host biology. Physiotherapy mitigates the gross physical forces accelerating cartilage destruction; it offloads the joint. LDRT, however, alters the microscopic biochemical environment of the synovium.

To fully understand LDRT's therapeutic promise, one must examine the field of

osteimmunology. The structural progression of OA is heavily mediated by populations of macrophages resident in the synovial lining . In advanced OA, these macrophages are polarized to an aggressive M1 phenotype, relentlessly secreting matrix metalloproteinases (MMPs), Interleukin-1 beta (IL-1 β), and Tumor Necrosis Factor-alpha (TNF- α), which enzymatically digest type II collagen and aggrecan in the extracellular cartilage matrix .

Ionizing radiation delivered at specific low doses (0.5 Gy per fraction) serves as an environmental stressor that paradoxically forces a protective cellular reset. It initiates the rapid transcription of the Nrf2 (nuclear factor erythroid 2-related factor 2) antioxidant pathway, suppresses the transcription of inducible nitric oxide synthase (iNOS), and forces the repolarization of destructive M1 macrophages into tissue-healing, regulatory M2 variants . Furthermore, radiation shuts down endothelial leukocyte extravasation by downregulating adhesion molecules (E-selectin, ICAM-1), acting effectively as a localized, non-pharmacological biologic immunosuppressant . Physiotherapy, while superior for muscle strength and joint stabilization, possesses no corresponding mechanism to achieve instantaneous transcriptional reprogramming of synovial leukocytes.

Disease Progression Alteration and Long-Term Implications

If LDRT's symptom-relieving superiority over placebo is contested, its capacity for true disease modification is uniquely compelling. The Makarova 2023 10-year longitudinal cohort provides the most vital piece of clinical intelligence in this review . Demonstrating an adjusted Hazard Ratio of 0.24 for profound disability implies that while LDRT may not magically abolish daily joint aches any better than a sham laser in the first three months, the fundamental arrest of subchondral inflammation literally halts the long-term timeline of joint destruction .

By silencing the M1 macrophage cascades and lowering systemic inflammatory indices, LDRT effectively "freezes" the joint in its current state of degradation. Over a decade, patients treated solely with standard care (NSAIDs and physical therapy) continued to degrade structurally, progressing relentlessly through the Kellgren-Lawrence grades until physical disability or total knee

arthroplasty became inevitable (17.8% disability rate) . In the LDRT arm, the architectural integrity was preserved, slashing the disability rate to a mere 9.5% . The prevention of 21% of all potential total joint replacements (Population Attributable Fraction) utilizing a single, transient radiation exposure holds monumental health-economic implications, potentially saving billions in surgical costs globally and averting the severe morbidities associated with major orthopedic surgery .

Safety Implications and Risk-Benefit Ratio

The integration of these findings dictates a highly stratified clinical approach. Conventional physiotherapy is fundamentally safe, broadly effective for functional enhancement, and carries zero oncogenic risk. It must remain the absolute first-line therapy .

The clinical application of LDRT is sharply limited by its adverse event profile (overall RR 1.44) and the stochastic risks of ionizing radiation (Leukemia RR 2.74) . Therefore, LDRT is strictly contraindicated for younger demographics, pregnant individuals, and those with mild, easily manageable disease. Its ideal clinical vector is highly specific: geriatric patients (over the age of 65) who present with advanced, refractory OA, possess significant medical comorbidities precluding the chronic use of NSAIDs or the safety of total joint replacement, and are experiencing imminent structural failure of the joint . In this highly isolated demographic, the theoretical long-term oncogenic risk is vastly outweighed by the immediate prevention of severe disability, permanent immobility, and surgical trauma.

Limitations of Current Evidence

The data explicitly highlights the heterogeneity of trial designs as a primary limitation in the field. Future research must strictly control for radiation dosing (standardizing around the highly effective 3.0 Gy benchmark established by Kim et al.), utilize uniform, objective diagnostic imaging (such as serial MRI to quantify synovial volume and cartilage thickness) rather than relying on highly subjective, placebo-prone pain questionnaires, and maintain long-term structural progression as the primary trial endpoint rather than immediate pain resolution. Furthermore,

physiotherapy trials must better quantify patient adherence to exercise regimens, as non-compliance acts as a massive confounding variable in comparing long-term physical therapy outcomes to a one-time radiation exposure.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This exhaustive systematic review and meta-analysis establishes that conventional physiotherapy and Low-Dose Radiation Therapy (LDRT) serve entirely disparate but potentially highly complementary roles in the clinical management of osteoarthritis. Conventional physiotherapy provides highly reliable, statistically significant, and biologically safe short-term improvements in functional mobility, range of motion, and pain stabilization through direct biomechanical correction. Conversely, global meta-analytic data concludes that LDRT offers no generalized, statistically significant symptomatic superiority over a placebo effect for immediate pain relief, despite inducing a slightly elevated risk of localized adverse events (RR 1.44). However, beneath this generalized symptomatic failure lies profound, undeniable evidence of structural disease modification. Precise radiation dosing regimens (specifically the 3.0 Gy threshold) have demonstrated verified clinical responses that shatter the placebo barrier. Most crucially, long-term 10-year longitudinal data confirms that LDRT possesses the unique biological capacity to alter the fundamental disease trajectory, reducing the long-term hazard of profound clinical disability by 76% (Adjusted HR 0.24) and dramatically lowering the necessity for end-stage total joint arthroplasty.

Suggestions

Based on the aggregated evidence, it is strongly recommended that conventional, professionally supervised physiotherapy be preserved universally as the foundational, first-line intervention for all presentations of osteoarthritis. Due to its inconsistent superiority over sham responses in managing subjective pain across broad populations and the presence of stochastic

oncogenic risks, LDRT should currently remain an investigational treatment. It should *not* be utilized as a widespread substitute for physical therapy or standard pharmacological management.

Instead, LDRT should be strictly reserved as a late-stage, compassionate-use intervention targeted exclusively at advanced-age patients (typically ≥ 65 years) who present with refractory, end-stage osteoarthritis, are biologically intolerant to conventional pharmaceuticals (e.g., severe NSAID toxicity), and are medically ineligible for invasive joint replacement surgery. In this specifically isolated geriatric demographic, LDRT's remarkable capability to halt structural disease progression, preserve remaining cartilage architecture, and prevent end-stage disability presents a highly favorable risk-to-benefit profile that warrants integration into specialized clinical guidelines.

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