Radiation Therapy for Benign Conditions

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PREFACE

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

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

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Operational Partners

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

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Technical Expert Panel

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

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Disclosures

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

Main Report

Evidence Synthesis Program

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ABBREVIATIONS TABLE

Abbreviation	Definition
5-FU	5-fluorouracil
AOFAS	American Orthopedic Foot and Ankle Score
AUSCAN	Australian/Canadian Hand Osteoarthritis Index
CI	Confidence interval
ESP	Evidence Synthesis Program
ESWT	Extracorporeal shock wave therapy
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Gy	Gray
KQ	Key question
MD	Mean differences
MeSH	Medical Subject Headings
NMD	Net mean differences
NRCS	Nonrandomized comparative study
NRS	Numeric rating scale
NS	Not significant
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratios
OSAS	Observer Scar Assessment Scale
POSAS	Patient and Observer Scar Assessment Scale
PRP	Rich plasma therapy
PSAS	Patient Scar Assessment Scale
RCT	Randomized controlled trial
RD	Risk differences
REML	Restricted maximum-likelihood estimation
ROBINS-I	Risk Of Bias In Non-randomized Studies – of Interventions
RT	Radiation treatment
SF-SACRAH	Short Form Score for the Assessment and Quantification of Chronic Rheumatic affections of the hands
SF12	12 item Short Forms
SF36	Short Form Health Survey
SRDR+	Systematic Review Data Repository-Plus
TEP	Technical Expert Panel
VA	Veterans Affairs
VA-NROP	VA National Radiation Oncology Program
VAS	Visual analog scale
VHA	Veterans Health Administration
VSS	Vancouver Scar Scale
WOMAC	Western Ontario and McMaster University Osteoarthritis Index Scale

BACKGROUND

Radiation therapy (RT) is a standard part of care for many types of cancer.[1,2] Radiation can shrink tumor size or inhibit tumor growth by causing cancer cell death or senescence through its effect on DNA damage.[3-5] While RT is most frequently utilized for cancer treatment, low-dose RT has also been explored as a treatment for a variety of noncancerous inflammatory and degenerative musculoskeletal, orthopedic, and soft tissue diseases, typically after conventional medical treatments fail.[6-10] This includes the use of prophylactic RT for the prevention of heterotopic ossification after hip replacement[7] and keloids after surgical resection,[9] as well as the treatment of painful inflammatory diseases such as osteoarthritis and plantar fasciitis.[11,12]

RT is commonly used for benign inflammatory and degenerative musculoskeletal diseases in Germany, where an estimated 10-30% of RT is applied to people with noncancer conditions.[13-16] However, outside of Germany, RT is rarely used to treat benign conditions. The German Society of Radiation Oncology (DEGRO) S2e Consensus Guideline Radiation Therapy of Benign Diseases states that low-dose RT (between 3 and 6 Gy) for degenerative musculoskeletal disease is a reasonable approach when simple and non-invasive methods have failed.[17]

Benign inflammatory and degenerative musculoskeletal diseases can cause physical limitations, depression and anxiety, financial burden, and decreased quality of life.[18-22] Veterans are at increased risk for some benign inflammatory and degenerative musculoskeletal, orthopedic, and soft tissue conditions due to the physical demands and injuries related to military service. For example, between 60-95% of Veterans experience heterotopic ossification following combat-related injuries.[23-27] Similarly, a population-based study using Behavioral Risk Factor Surveillance System data found that arthritis was more prevalent in Veterans compared to non-Veterans (31.5% vs 22.1%).[28] Another study reported that overuse injuries, such as plantar fasciitis, are common among US military personnel.[29] Importantly, minority and woman Veterans are more likely to experience some inflammatory and degenerative musculoskeletal conditions. One study using data from the Defense Medical Epidemiology Database found that women and Black service members were significantly more likely than men and White service members to have plantar fasciitis (adjusted incidence rate ratio 1.95, 95% CI [1.94, 1.99] and 1.12, 95% CI [1.09, 1.12], respectively).[30]

Low-dose RT may be an effective treatment option for Veterans with a number of benign conditions resistant to conventional treatments. However, studies on the use of RT for benign conditions common in the Veteran population offer conflicting results about its effectiveness and potential adverse consequences. To inform guidance on the use of RT for benign conditions among Veterans, the Veterans Health Administration (VHA) National Radiation Oncology Program requested the following systematic review on the benefits and harms of low-dose RT for the treatment or prevention of benign hyperproliferative and degenerative skin/epithelial and musculoskeletal disorders.

METHODS

TOPIC DEVELOPMENT

We worked with representatives from VHA National Radiation Oncology Program and our Technical Expert Panel (TEP) to refine the review scope and develop the key question (KQ). We focused on studies that reported on low-dose RT (<60 Gy) for the prevention or management of heterotopic ossification, keloid scars, plantar fasciitis, pterygium, osteoarthritis, Peyronie's disease, Dupuytren's contracture, Ledderhose disease, or hidradenitis suppurativa. These 9 conditions were selected because RT has been postulated to be an effective treatment for them, they are known to impact the Veteran population, and they could be addressed jointly given available resources. We excluded studies that did not use external radiation for all diseases except for pterygium, for which we also included radiation with brachytherapy. We evaluated the effect of RT on disease-related symptoms (*eg,* function for people with heterotopic ossification), side effects, and patient-centered outcomes (*eg,* quality of life, satisfaction, and experience).

KEY QUESTIONS AND PROTOCOL

The following key question was the focus of this review:

Key Question	What are the benefits and harms of low-dose radiation therapy for the treatment or prevention of benign hyperproliferative and degenerative skin/epithelial, and musculoskeletal disorders such as keloid scars, hidradenitis suppurativa, Dupuytren's contracture, Ledderhose disease, Peyronie's disease, plantar fasciitis, heterotopic ossification, pterygium, or osteoarthritis in adults?

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (CRD42023447241). A draft version of this report was reviewed by external peer reviewers; their comments and author responses are located in Appendix M.

SEARCHING AND STUDY SELECTION

We searched Medline (via PubMed), Embase, and ClinicalTrials.gov from inception to April 1, 2023. We used Medical Subject Headings (MeSH) and free text terms relevant to the conditions (*eg, pterygium* and *keloid*) and radiation therapy (*eg, radiation*, *radiotherapy*, and *electron beam*). We ensured that known relevant publications were captured by our searches. Additional citations were sought from hand-searching reference lists of relevant systematic reviews and consultation with content experts. We identified a high quality published systematic review on the use of RT for osteoarthritis with search dates from inception to April 20, 2015; we relied on this review to identify eligible studies within its search period and updated its search to identify studies published later than April 2015. See Appendix A for complete search strategies.

Citations were uploaded into EndNote and duplicates were removed. We screened citations in Abstrackr (http://abstrackr.cebm.brown.edu),[31] which has machine learning algorithms to prioritize relevant citations. To ensure a common understanding of the eligibility criteria, we ran pilot rounds of 500 citations at a time, where all team members screened the same citations, until we achieved acceptable agreement. Subsequently, we screened citations in duplicate with conflicts adjudicated during team meetings or by a third senior researcher. Based on empirical evidence, we stopped screening when all remaining unscreened abstracts had a prediction score of <0.40 (on a 0–1 scale), and subsequently 400 abstracts in a row were rejected.[31] Accepted abstracts underwent full-text review

using an evidence mapping process independently by 1 researcher with confirmation of excluded articles by a second researcher. When necessary, the reviewers consulted a third senior researcher. A list of studies excluded at full-text review, with rejection reasons, is provided in Appendix B-1.

Study eligibility criteria are shown in Table 1. In brief, eligible study participants were ≥18 years of age treated with low-dose RT (<60 Gy) for a benign condition of interest (*eg,* heterotopic ossification). We included all types of ionizing radiation (*eg,* photons, electrons, hadrons) delivered externally via photon or heavier particle beams. Studies not using external ionizing radiation (*eg*, studies using brachytherapy) were generally excluded. The exception was brachytherapy for the management of pterygium, which was included because it is the main mode of radiation dose delivery in the treatment of pterygium. We excluded studies where the majority of patients received re-irradiation of the same anatomic site. Due to the changes in radiation treatment over time, we excluded studies that treated patients before 1980. For studies that included a portion of patients treated before this date, exclusion applied if the majority of patients would have been treated before 1980, assuming equal number of patients per year. We followed a best evidence approach and prioritized comparative studies (*ie,* using RT vs not using RT) within each condition of interest.[32] Randomized controlled trials (RCTs) were given priority over nonrandomized comparative studies (NRCS) and other comparative observational studies, whether prospective or retrospective, and regardless of whether they were adjusted for potential confounders. We only included single group studies when there were fewer than 5 comparative studies within a disease. In diseases with only single group studies, we reviewed those studies with the largest sample sizes (on average no more than 5 per condition, based on project budget). Appendix B-2 presents eligible studies that were not extracted following the best evidence approach.

Table 1. Inclusion and Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Population	Adults ≥18 years of age with heterotopic ossification, keloid scars, plantar fasciitis, pterygium, osteoarthritis, Peyronie's disease, Dupuytren's contracture, Ledderhose disease, or hidradenitis suppurativa	Cancer Nonmalignant tumors in head, neck, or brain. Central nervous system conditions Neurofibromatosis I and II Pre-cancerous conditions of the skin (*eg,* Bowen's disease) Patients receiving re-irradiation of same anatomic location Not alive
Intervention	Photon, electron (beta particle), alpha particle therapy, or other hadrons (positively charged particles) for treatment, recurrence, or prevention Only include brachytherapy for pterygium <60 Gy	Non-ionizing radiation and re-irradiation
Comparator	Sham radiation therapy Alternative treatments that do not include radiation No treatment	Alternative dose of RT
Outcomes	Disease-related symptoms (*eg,* pain, stiffness, ambulatory status,	

	Inclusion Criteria	Exclusion Criteria
	appearance of tissue, recurrence of lesion, control of symptoms, and physical function) Local (short-term) side effects (*eg,* skin irritation, discoloration, scarring, edema, fatigue, nausea, alopecia, anemia, atrophy) Patient satisfaction/experience or quality of life Burden related to accessing treatment (*eg,* wait time, distance traveled, travel cost)	
Timing	Any	
Setting	Any	
Study Design	Best evidence approach prioritizing comparative studies RCT Nonrandomized comparative study, prospective or retrospective Single group study[a]	Does not report patient level data Sample size ≤10 (among those receiving eligible treatment) Published before 1980 Reviews, editorials, opinion

Notes. [a] A study that evaluates distinct interventions that all include radiation therapy and does not inform on the treatment effect of using versus not using radiation therapy.

Abbreviations. Gy=gray; RCT=randomized controlled study; RT=radiation treatment.

DATA ABSTRACTION AND ASSESSMENT

We created a data extraction form in the Systematic Review Data Repository-Plus (SRDR+) online system (https://srdrplus.ahrq.gov). We extracted the following data from eligible studies: study design, setting, baseline population characteristics, total RT dose, duration of follow-up, disease-related symptoms, side effects, and patient-reported outcomes (*eg,* quality of life and satisfaction). All data extraction was first completed by 1 reviewer and then checked by a second reviewer. Disagreements were resolved by consensus or discussion with a third reviewer.

Study risk of bias was independently assessed by 1 reviewer and confirmed by a second using questions derived from the Cochrane Risk of Bias and the ROBINS-I (Risk Of Bias In Non-randomized Studies – of Interventions) tools (Appendix C).[33,34] In addition, we used AMSTAR-2 to evaluate the quality of the osteoarthritis systematic review. For all study designs, we also evaluated whether the article was free of discrepancies, and reporting of patient eligibility criteria, protocols, setting, and outcome assessments was sufficiently clear. For RCTs, we evaluated the method of randomization, allocation concealment, and whether intention-to-treat analysis was used. For NRCS, we evaluated whether patients in the treated and comparison groups were similar and what strategies were used to deal with confounders. Single group studies do not directly inform on the treatment effect of using versus not using RT. Therefore, these studies had high risk of bias to determine the effect of RT on outcomes.

SYNTHESIS AND CERTAINTY OF EVIDENCE

We compared results in study groups using odds ratios (OR) for dichotomous outcomes. When a study had 0 events in one group, we calculated risk differences (RD). We compared continuous data using

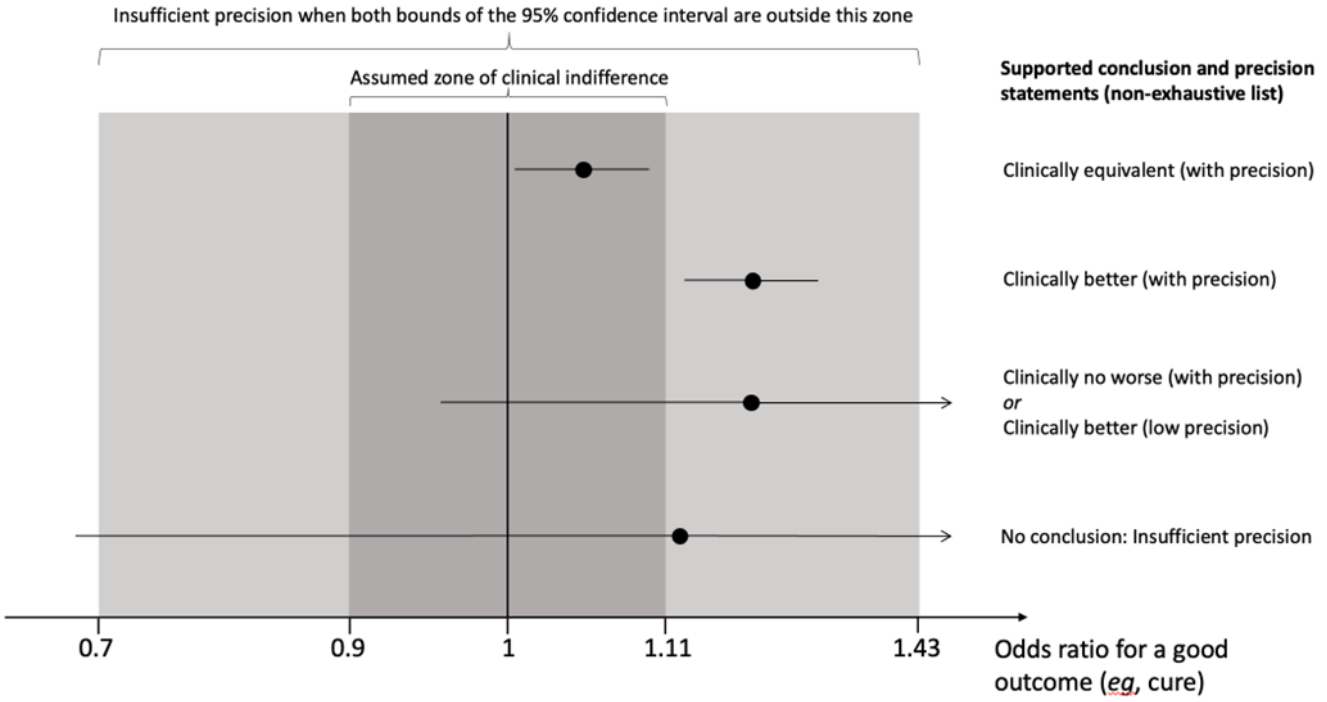
net mean differences (*ie,* difference-in-differences or between-intervention comparisons of within-intervention changes from baseline to follow-up) or mean differences (MD) between interventions for outcomes evaluated only post-intervention. Adjusted analyses were preferentially extracted over unadjusted (crude) comparisons. Where there were at least 3 studies reporting results from similar analyses (based on population, interventions, comparators, and outcomes), we conducted random effects meta-analyses using the restricted maximum-likelihood (REML) estimator for the variance of the random effects, as implemented in the "meta" package for R version 4.3.0 (2023-04-21). Statistical heterogeneity was estimated using the I^2 statistic, which estimates the percentage of heterogeneity ascribed to statistical heterogeneity (not ascribed to chance). In some cases, a 3-arm trial (*eg,* comparing an RT arm vs 2 non-RT interventions) contributed 2 comparisons in a meta-analysis. These comparisons have 1 arm in common (the RT arm in the example), which induces correlation in the estimates of the treatment effect. Such RCTs were represented in a meta-analysis as 2 independent trials in which the RT arm had half the sample size but the same proportion of events (for categorical outcomes) or the same mean outcome (for continuous outcomes). Using this heuristic, results from a meta-analysis of independent trials are numerically similar to those from an analysis that explicitly models the correlation in the estimated treatment effects for the RT versus non-RT comparisons from this trial. This heuristic is mentioned in textbooks, including the Cochrane Handbook.

When there were at least 3 comparative studies per disease, we assessed the certainty of evidence following the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.[35] We compiled key study findings in evidence profiles, which provide the basis for determination of certainty of evidence and summarize conclusions for outcomes. Within each outcome, we considered the study design, the number of studies and participants, methodological limitations, directness of the evidence, precision of the findings, consistency across studies, and other issues.

The precision of effect estimates were used to assess the clinical significance of treatment effects. First, when an estimate's 95% confidence interval (CI) included large effects in both directions—for an OR, a CI with a lower bound <0.7 and a higher bound >1.4—we judged the estimate to be too imprecise to draw conclusions for the magnitude or even the direction of the true treatment effect. This scenario is illustrated in the bottom row of Figure 1. In other cases, we considered where the effect estimate and its CI fell relative to a narrow range around the null effect (*ie*, no difference between treatments), which we refer to as the zone of clinical indifference. For an OR, this range was between 0.9 and 1.1.

As illustrated in the first row of Figure 1, when an effect estimate and its CI were fully within the range of clinical indifference, RT was considered clinically equivalent to the treatment provided in the comparison condition (*ie*, no better or worse). In contrast, when the effect estimate and its CI were fully outside of the range and in the direction of benefit of RT (second row of Figure 1), RT was considered clinically superior to the comparison treatment. The final scenario was when an effect estimate was fully outside of the zone of clinical indifference and in the direction of benefit of RT, but was accompanied by a CI whose upper or lower bound fell within the zone of clinical indifference (third row of Figure 1). In this case, the true effect of RT could either be equivalent to the comparison treatment (if the true difference between treatments was in fact trivial) or superior to the comparison treatment (if the effect had been estimated with greater precision). An extension of the latter case was when the lower bound of the CI encompassed the null effect (1 for an OR), again as shown in the third row of Figure 1. Here, the effect of RT would be statistically nonsignificant but potentially clinically significant. The above scenarios are not exhaustive, but correspond to results encountered in this report.

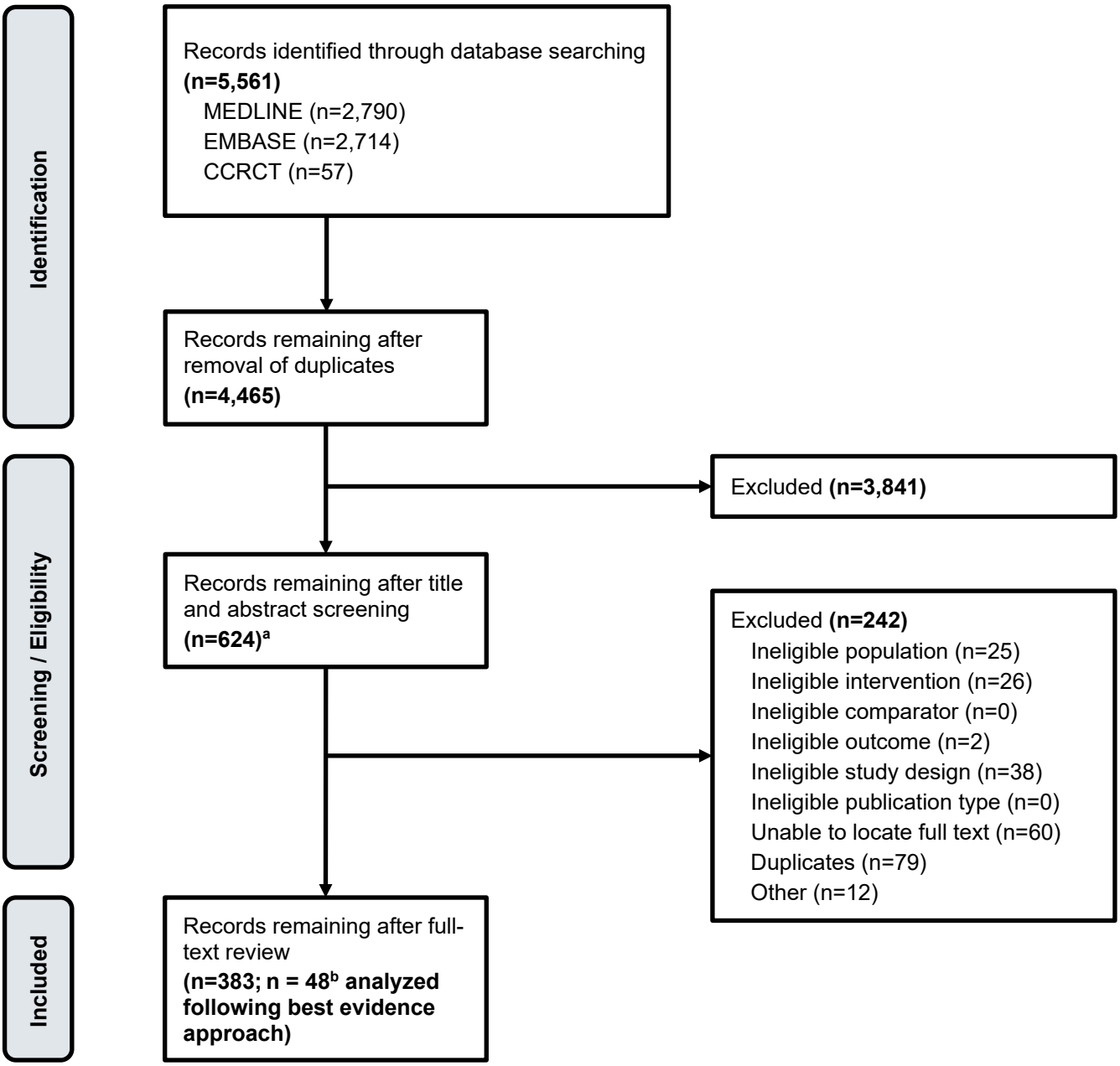
Figure 1. Precision of Statistical Estimates and Range of Clinically Important Effects



RESULTS

LITERATURE FLOW DIAGRAM

The literature flow diagram summarizes the results of the study selection process. A full list of excluded studies is provided in Appendix B.



Notes. [a]One additional record was recommended by a peer reviewer. [b]Five studies in Dupuytren's contracture, 1 in hidratenitis suppurativa, 6 in keloids, 4 in Ledderhose disease, 5 in Peyronie's disease, 5 in plantar fasciitis, 6 in pterygium, 10 in heterotopic ossification, and 5 studies and 1 systematic review in osteoarthritis.

LITERATURE OVERVIEW

Of 5,561 unique records screened, 624 studies underwent full-text review and 382 remained after full-text review. One included study that was published in May 2023 was identified by the peer reviewers. Upon reviewing these, 335 studies did not meet the best available evidence criteria (Appendix B-2) and 48 records were eligible (Figure 1).[12,36-82] The synthesized studies reported on RT for the treatment of heterotopic ossification (*N* = 10),[36-45] keloids (*N* = 6),[46-51] plantar fasciitis (*N* = 5),[12,52-55] pterygium treated with brachytherapy (*N* = 5)[56-60] and without brachytherapy (*N* = 1)[61], Peyronie's disease (*N* = 5),[68-72] Dupuytren's contracture (*N* = 5),[73-77] Ledderhose disease (*N* = 4),[78-81] and hidradenitis suppurativa (*N* = 1),[82] and osteoarthritis. For osteoarthritis, we included 1 systematic review[62] of 7 single group studies and 5 studies identified from the updated search.[63,64,65-67]

Table 2 shows the study design and summary characteristics of the eligible studies. Twenty-one studies were RCTs,[12,36-45,48-52,56,57,63,64,78] 5 were NRCS,[46,47,53,58,59] 21 were single group,[16,54,55,60,61,65-77,79,80,82] and 1 was a systematic review.[62] The effect of RT on prioritized outcomes was based on comparative studies available for heterotopic ossification (10 RCTs)[36-45] and keloids (4 RCTs and 2 NRCS).[46-51] A combination of comparative and single group studies were considered for plantar fasciitis (2 RCTs, 1 NRCS, and 2 single group),[12,52-55] and pterygium treated with brachytherapy (2 RCTs, 2 NRCS, and 1 single group)[56-60] osteoarthritis (2 RCTs, 3 single group and 1 systematic review of 7 single group studies), and Ledderhose disease (1 RCT and 3 single group).[62-67,79-81] Only single group studies were considered for pterygium treated with brachytherapy,[61] Dupuytren's contracture,[73-77] and hidradenitis suppurativa.[82]

Across the 48 studies, there was wide variation in the total dose of RT (in 47 studies range = 0.5 to 40 Gy and in 1 study <5% of patients received up to 70 Gy), sample size in the studies (range = 17 to 2,164), and follow-up (range = 1 to 144 months). Most of the studies were conducted in Germany (*N* = 23), followed by the Netherlands (*N* = 7), US (*N* = 5), Turkey (*N* = 3), Nigeria (*N* = 2), China (*N* = 2), Brazil (*N* = 1), Israel (*N* = 1), Japan (*N* = 1), Pakistan (*N* = 1), Poland (*N* = 1), and India (*N* = 1). Detailed descriptions of the literature by disease are provided in each section below.

Table 2. Summary Characteristics of Eligible Studies

Characteristics	Heterotopic Ossification (*N* = 10)	Keloids (*N* = 6)	Plantar Fasciitis (*N* = 5)	Pterygium (*N* = 6)[a]	Osteoarthritis (*N* = 6)	Peyronie's Disease (*N* = 5)	Dupuytren's Disease (*N* = 5)	Ledderhose Disease (*N* = 4)	Hidradenitis Suppurativa (*N* = 1)
Design									
RCT (*N* = *21*)	10	4	2	2	2	-	-	1	-
NRCS (*N* = *5*)	-	2	1	2	-	-	-	-	-
Single group (*N* = 21)	-	-	2	2	3	5	5	3	1
Systematic review (*N* = 1)	-	-	-	-	1 (7 single group studies)	-	-	-	-
Intervention and Study Features									
Total Gy range	5 to 12	7 to 32	3 to 6	10 to 70[b]	0.5 to 6	12 to 40	21 to 32	24 to 32	3 to 20
Total sample size (range)	1530 (16 to 113)	599 (17 to 95)	1153 (20 to 666)	1557 (24 to 1,080)	3574 (27 to 2,164)[c]	415 (58 to 106)	653 (96 to 206)	200 (24 to 84)	231
Follow-up months range	3 to 59	6.5 to 15	3 to 125	3 to 144	up to 6	8 to 140	3 to 48	6 to 132	1 to 1.5
Risk of Bias									
Low (*N* = 5)	-	-	-	2	2	-	-	1	-
Moderate (*N* = 15)	8	3	2	1	1[c]	-	-	-	-
High (*N* = 28)	2	3	3	3	3	5	5	3	1
Countries									
US (*N* = 5)	3	2	-	-	-	-	-	-	-
China (*N* = *2*)	-	2	-	-	-	-	-	-	-
Nigeria (*N* = 2)	-	1	-	1	-	-	-	-	-
Pakistan (*N* = *1*)	-	1	-	-	-	-	-	-	-
Germany (*N* = *23*)	6	-	2	1	3	4	4	2	1
Poland (*N* = 1)	-	-	-	-	-	-	1	-	-
Netherlands (*N* = *7*)	1	-	-	-	3	1	-	2	-
Turkey (*N* = 3)	-	-	2	1	-	-	-	-	-

Characteristics	Heterotopic Ossification (*N* = 10)	Keloids (*N* = 6)	Plantar Fasciitis (*N* = 5)	Pterygium (*N* = 6)[a]	Osteoarthritis (*N* = 6)	Peyronie's Disease (*N* = 5)	Dupuytren's Disease (*N* = 5)	Ledderhose Disease (*N* = 4)	Hidradenitis Suppurativa (*N* = 1)
India (*N* = 1)	-	-	1	-	-	-	-	-	-
Brazil (*N* = 1)	-	-	-	1	-	-	-	-	-
Israel (*N* = 1)	-	-	-	1	-	-	-	-	-
Japan (*N* = 1)	-	-	-	1	-	-	-	-	-
Outcomes									
Disease-related symptoms	10	6	5	6	6	5	5	4	1
Side effects	7	3	4	5	4	4	5	4	-
Patient satisfaction/ experience/ quality of life	1	-	-	-	3	2	2	23	-
Other	-	2[d]	-	2[d]	-	-	-	-	-

Notes. [a] One study is external beam radiation (*ie,* without brachytherapy).

[b] One study had <5% of patients receive between 51 and 70 Gy.

[c] Includes a systematic review of studies from inception to 2015. We updated the search to include studies from 2015 to April 1, 2023.

[d] Cosmetic outcomes.

EFFECT OF RADIATION THERAPY FOR HETEROTOPIC OSSIFICATION

Ten RCTs[36-45] evaluated the effect of RT for either the prevention or treatment of heterotopic ossification. Three of these studies also compared patients who received RT to a historical comparison group.[39,41,42] The studies were conducted between 1988 and 2008 with follow-up ranging on average from 3 to 59 months post treatment. Three studies were conducted in US, 6 in Germany, and 1 in the Netherlands (Appendix D-1). Importantly, 1 RCT (Hamid et al) was terminated early due to a high nonunion rate among patients who received RT.[38]

A total of 1530 participants were analyzed, and 566 were treated with RT following fracture fixation, total hip arthroplasty (THA), or total hip replacement (THR) surgery (Appendix D-2). Only 3 studies reported data on the proportion of patients who had previous lesions (<1% in 1 study and 14% to 19% in 2 studies). The mean age of participants ranged from 38.6 to 65.9 years, with the frequency of male participants ranging from 29.8% to 69.3%. No study reported information on race/ethnicity of participants.

Most ($N = 8$) studies employed RT post-surgery.[36-41,44,45] The timing of RT ranged from 48 hours to 8 days post-surgery, and the total radiation dose ranged from 5 to 12 Gy. Eight studies compared RT to surgery followed by non-steroidal anti-inflammatory drugs (NSAIDs),[36,37,39-42,44,45] and 3 of these studies also included an additional surgery-only control group,[40-42] of which 2 were historical groups.[41,42] Finally, 2 studies used surgery alone as the sole comparison.[38,43]

Nine RCTs did not clearly report their methods and had medium risk of bias (Appendix D-3). This included not reporting the method of randomization ($N = 3$),[37,40,41] not reporting whether there was allocation concealment ($N = 6$),[37,39-41,44,45] and not reporting whether participants, personnel, or outcome assessors were blinded ($N = 5$).[38,40-43] These are indicators for risk of confounding bias and reduce confidence in the causal attribution of the observed differences. One RCT reported results from a per protocol analysis and excluded a large number of patients from the RT arm raising concerns of selection bias (*ie*, high risk of bias).[36]

In summary (Table 3), RT resulted in a non-significant reduction in the occurrence of heterotopic ossification compared with surgery with or without NSAIDs (low confidence). Based on the magnitude and precision of the pooled effect estimate, and because most study results favored RT, we judged the effect of RT to be clinically significant despite the statistical non-significance of the pooled effect estimate. There was no significant difference in function between RT and surgery with or without NSAIDs (low confidence). Studies provided insufficient evidence (no conclusion) for radiologic failure, pain, side effects, and patient satisfaction, experience of care, or quality of life. Appendix D-4 presents detailed outcome data.

Table 3. Summary of Findings for Radiation Therapy for the Treatment of Heterotopic Ossification

Outcome	Studies (Patients); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Overall Confidence	Summary of Findings
Heterotopic ossification at follow-up[36,38-45]	9 (1418); RCT	Serious[a]	Indirect[b]	Not precise[c]	Inconsistent[d]		Low	Low evidence for a difference (pooled OR = 0.47, 95%CI [0.19, 1.17]
Radiologic failure (nonunion)[19,38]	2 (157); RCT	Serious[a]	Direct	Not precise[e]	Inconsistent[f]		Insufficient	No conclusion
Function[38-40]	3 (485); RCT	Serious[g]	Indirect[h]	Precise	Consistent		Low	No difference
Pain[36]	1 (68); RCT	Very serious[i]	NA	NA	NA		Insufficient	No conclusion
Side effects[38-40,42,43,45]	6 (895); RCT	Serious[a]	Indirect[j]	Not precise[k]	Inconsistent[g]		Insufficient	No conclusion
Patient satisfaction, experience, quality of life[36]	1 (50); RCT	Very serious[i]	Indirect[l]	Precise	NA		Insufficient	No conclusion

Notes. [a] RCTs had medium risk of bias because they did not clearly report the method of randomization, whether there was allocation concealment or whether participants, personnel, or outcome assessors were blinded; [b] Large variation in Gy (range = 5 to 12) and comparison groups varied, timing of RT was inconsistent, and follow-up data provided at different time points (range = 3 to approximately 31 months); [c] Wide confidence intervals; [d] High heterogeneity based on I^2; direction of results not consistent across all comparators; [e] One study had a wide confidence; [f] Direction of findings across studies is not consistent; [g] RCTs had medium risk of bias due to unclear reporting of key methodological details including random sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessors; [h] Gy (range = 6 to 12), comparison groups, timing (range = 7.5 mo to 24 mo), and assessment type varied across studies; [i] Per protocol analysis; [j] Gy (range = 5 to 12), comparison groups, timing (range = 3 to approximately 31 months), and side effects reported varied across studies; [k] The studies report wide range for estimates; [l] Self-assessment of outcome as “good” or “very good.”

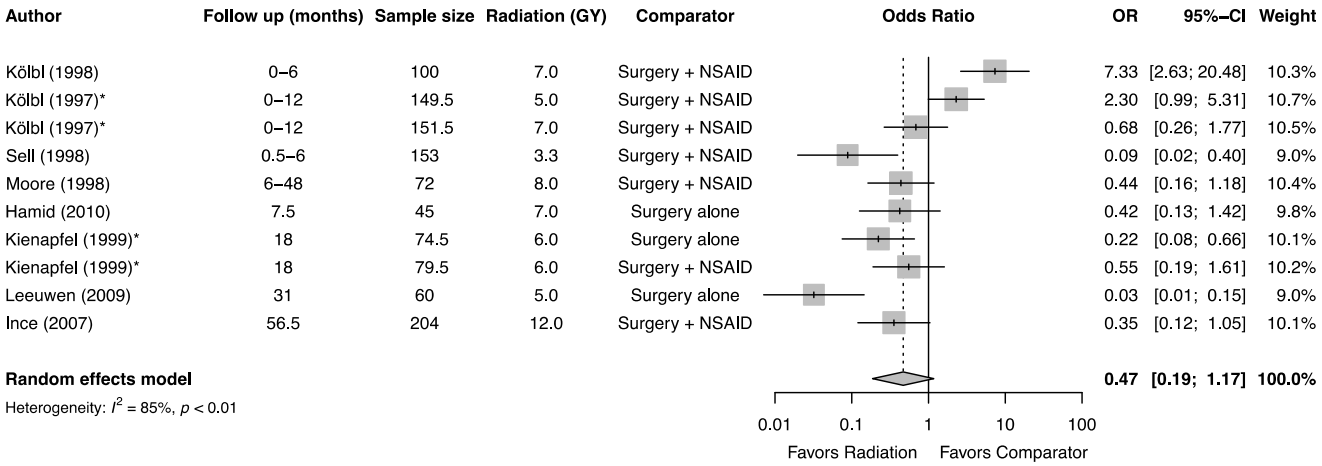
Abbreviations. CI=confidence interval; Gy=gray; mo=months; NA=not applicable; OR=odds ratio; RCT=randomized controlled trial.

HETEROTOPIC OSSIFICATION AT FOLLOW-UP

Nine RCTs reported the presence of heterotopic ossification at follow-up using the Brooker classification method.[36,38-45] Bremen-Kühne et al only presented a per protocol analysis with a large number of patients excluded from the analysis (*ie,* significant concern of selection bias) and was excluded from the meta-analysis. In pooled data from 8 RCTs, there was a non-significant but clinically meaningful reduction in the presence of heterotopic ossification at follow-up between people who received RT compared to a comparison group (pooled OR = 0.47, 95% CI [0.19, 1.17]; Figure 2).[38-45] We judged the difference to be clinically meaningful based on the magnitude of the effect size, precision of the pooled effect estimate and because most study results favored RT. Meta-analysis revealed statistical heterogeneity in ORs across studies. In a post hoc sensitivity analysis, we excluded Leeuwen et al and Kolbl (1998) et al. These were the only studies to apply RT prior to surgery, and both studies also reported outlier effect sizes. Excluding these studies resulted in a statistically and clinically significant reduction in the presence of heterotopic ossification at follow-up for patients randomized to RT compared to a comparison group (OR = 0.50, 95% CI [0.28, 0.89]; I^2 = 58%).

Three studies that compared RT to historical comparison groups reported effects in the same direction as the comparisons between the randomized arms.[39,41,42] Effect sizes were larger and more precise when comparing RT to a historical comparison than when RT was compared to a randomized control group. Specifically, Kolbl (1997) et al found a significant reduction in the occurrence of heterotopic ossification after RT (7 Gy or 5 Gy) compared to a historical comparison group that received surgery (OR = 0.23, 95% CI [0.13, 0.42] and 0.07, 95% CI [0.03, 0.15]). Ince et al found a significant reduction in the occurrence of heterotopic ossification after RT (12 Gy) compared to a historical comparison group that received surgery (OR = 0.03, 95% CI [0.01, 0.07]). Finally, Kolbl (1998) et al found a significant reduction in the occurrence heterotopic ossification after RT (7 Gy) compared to a historical comparison group that received surgery (OR = 0.49, 95% CI [0.24, 1.00]).

Figure 2. Heterotopic Ossification at Follow-Up: Radiation Therapy versus Comparison Group



Notes. *Kienapfel (1999) is a 3-arm RCT comparing an RT arm with 2 non-RT control arms. Each comparison is included in the meta-analysis as 2 independent trials in which each RT arm has half the patients. Kolbl (1997) is a 3-arm RCT that compared RT (5 GY) and RT (7 GY) with a common comparison group. Each comparison is included in the meta-analysis as 2 independent trials in which each comparison arm has half the patients.
Abbreviations. CI=confidence interval; Gy=gray; NSAID-non-steroidal anti-inflammatory; OR=odds ratio.

In another *post hoc* analysis, we evaluated the presence of heterotopic ossification grade III and IV events (the most severe categories) in the 8 RCTs. Most studies reported 0 events in both the RT and comparison arms. There was no significant or clinically meaningful difference in the presence of heterotopic ossification grade III or IV at follow-up between RT and the comparison group (pooled RD = 0, 95% CI [-0.1, 0.01]; I^2 = 69%).

Radiologic Failure

Two RCTs reported conflicting findings on the proportion of patients who had radiologic failure (*ie,* fracture nonunion) at follow-up.[37,38] One study reported significantly fewer patients had radiologic failure 3 months after RT (8 Gy) following surgery compared to surgery followed by indomethacin (6.8% vs 28.9%, OR = 0.18, 95% CI [0.06; 0.56]).[37] Conversely, a second RCT found a significantly greater proportion of patients had radiologic failure 6 months after RT (7 Gy) following surgery compared to surgery alone (38.1% vs 4.2%, OR = 14.15, 95% CI [1.59; 126.13]).[38] This study was terminated early due to the high nonunion rate among patients who received RT.

Physical Function

Three RCTs found no significant difference in physical function for RT relative to a comparison group.[38-40] One RCT found no significant difference in the Harris Hip score at 5 years follow-up between patients randomized to RT (12 Gy) after surgery compared to surgery + NSAID (MD = -0.90, 95% CI [-4.14, 2.34]). The same study found no significant difference between RT (12 Gy) after surgery and historical controls treated with non-NSAIDs post-surgery (MD = -0.80, 95% CI [-4.13; 2.53]).[39] Another RCT found no significant difference in the total Harris Hip score at 18 months after RT (6 Gy) following surgery compared to both surgery alone and indomethacin (mean 86.4 vs 81.7 vs 85, p = NS).[40] The same study reported no significant difference on subjective patient-assessed component and investigator-assessed component of the Harris Hip Score between groups.[40] A third RCT comparing RT (7 Gy) to surgery alone found no significant difference between arms at follow-up (mean 7.5 months) in the Mayo Elbow Performance Score (69 vs 66, p = 0.6), mean elbow flexion (116 vs 113, p = 0.53) and extension (29 vs 22, p = 0.18), and mean pronation (71 vs 69, p = 0.8) and supination (70 vs 64, p = 0.54).[38]

Pain

One RCT[36] reported pain scores for the treatment group following per protocol analysis and no comparative data were extractable.

Side Effects

RT With Surgery Compared to Surgery Alone or Surgery With Non-NSAID Analgesics

There were no significant differences in side effects among 3 studies that compared patients who received RT following surgery to surgery alone or with non-NSAID analgesics.[38-40] This included no significant difference in postoperative infection, manipulation, prolonged wound secretion, wound dehiscence, deep vein thrombosis, dyspepsia, number of implants that migrated greater than 1 mm, and radiolucent lines greater than 1 mm (OR range = 0.78 to 6.84, all nonsignificant with wide confidence intervals).[38-40]

One RCT (6 Gy) found no arthroplasties had failed in the RT group or in either comparison group.[40] Another RCT noted no patient underwent hip surgery revision and that no acetabular component was

considered loose after RT (12 Gy) or surgery followed by indomethacin (Ince). A RCT found that 1 patient had a superficial wound infection in the RT (5 Gy) group and there were no sides effects in the surgery-alone group.[43]

RT With Surgery Compared to Surgery With NSAIDs

Three studies reported side effects for patients who received RT following surgery compared to surgery plus NSAIDs.[39,40,45] One RCT reported significantly lower rates of dyspepsia among patients who received RT (6 Gy) compared to NSAID (OR = 0.24 [0.07, 0.77]).[40] Another RCT reported significantly lower rates of gastrointestinal side effects in the RT (9.9 Gy) compared to NSAID group (RD = -0.14, 95% CI [-0.22, -0.07]).[45] In contrast, 1 RCT found no significant difference in gastrointestinal side effects between RT (7 Gy) before surgery compared to surgery plus NSAIDs (RD = -0.06, 95% CI [-0.12, 0.01]).[42] No study reported significant difference in RT and NSAID arms in the number of implants that migrated greater than 1 mm, wound dehiscence, deep vein thrombosis, reddening of the wound, hematoma formation, or staphylococcus epidermidis infection necessitating fistula revision (OR range = 0.55 to 3.12 and RD range = 0.12 to 0.01, all nonsignificant with wide confidence intervals).[39,40,45] Finally, 1 RCT reported that loosening of the prosthesis was not observed in any patient and that there was no sign of any negative side effects from RT (3.3 Gy).[45]

Patient Satisfaction, Experience, Quality of Life

One RCT found no significant difference in the proportion of patients who rated their treatment outcomes as good or very good at 12 month follow-up between RT (6 Gy) after surgery compared to indomethacin after surgery (80.0% vs 87.1%, p = NS).[36]

No study reported data on patient experience and quality of life including burden accessing treatment.

EFFECT OF RADIATION THERAPY FOR KELOIDS

Six comparative studies (4 RCTs and 2 NRCS)[46-51] evaluated RT for the treatment or prevention of keloids. The studies were conducted between 1991 and 2021 with follow-up ranging on average from 6.5 to 15 months after treatment. One study[50] reported recurrence outcomes between 8 and 12 months and reported all other outcomes at 4 months post-treatment. Two studies were conducted in US, 2 in China, 1 in Nigeria, and 1 in Pakistan (Appendix E-1).

Overall, 599 participants were analyzed, and 291 were treated with RT following surgical excision of keloids. The mean age of participants ranged from 28.4 to 37.2 years, with the frequency of male participants ranging from 14.3% to 55.1%. Two studies reported ethnicity data (3.6% and 15.9% were White).[46,51] In 3 studies, piercing was the most common cause of keloids, [47,49,51] 1 study reported spontaneous etiology of keloids,[50] and 2 studies did not report data on the etiology.[46,48] In 3 studies, the mean age of the lesions was from 1.6 to 6.3 years,[49-51] and 1 study reported a range of 1 to 15 years.[47] Lesion size or height were reported in 3 studies (range = 2.3 cm to 13.8 cm)[46,48,49] (Appendix E-2). In 4 studies, between 37% and 67% patients had received previous treatment for keloids or had a history of keloids.[46,49-51]

RT was administered from 3 hours to 4 days post-excision, with total doses ranging from 7 to 32 Gy. Treatment in the comparison group included surgical excision, triamcinolone alone or with surgical excision, excision and 5-fluorouracil (5-FU) with or without betamethasone or triamcinolone, and diprosone after surgical excision. One NRCS compared RT to surgery alone and medical management.

We excluded data on the medical management arm because the study did not report recurrence (primary outcome) for the comparison of interest.[46]

Three RCTs had some methodological concerns due to not blinding participants/personnel and not clearly reporting whether outcomes assessors were independent (*ie,* medium risk of bias; Appendix E-3).[48-51] Lack of blinding may result in measurement errors, if outcome assessors have preconceptions about the anticipated response with each treatment, and in differential fidelity to the protocol by arm, if patients in 1 arm are engaged differently in each intervention arm (*eg,* not asking people who did not receive RT about side effects that are most commonly associated with radiation). One RCT was high risk of bias due to the above concerns and only reporting outcomes for 52% of treated patients.[51] Two NRCS reported unadjusted crude analyses, which is an indicator of confounding bias (*ie,* high risk of bias).[46,47]

In summary (Table 4), there was no difference in pain after RT compared to alternative treatments (low confidence). Studies provided insufficient evidence (no conclusions) for keloid recurrence, cosmetic outcomes, skin conditions, or side effects and complications. No study reported quality of life, patient satisfaction, or experience of care outcomes. Appendix E-4 presents detailed outcome data.

Table 4. Summary of Findings for Radiation Therapy for the Treatment of Keloids

Outcome	Studies (Patients); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Overall Confidence	Summary of Findings
Recurrence, persistence, or effectiveness[46-51]	6 (599); RCT, NRCS	Serious[a]	Indirect[b]	Not precise[c]	Inconsistent[d]		Insufficient	No conclusion (pooled OR = 1.32, 95% CI [0.40, 4.33])
Cosmetic outcomes and skin conditions[48,50]	2 (162); RCT	Serious[e]	Indirect[f]	Not precise[g]	Inconsistent[h]		Insufficient	No conclusion
Pain[50]	1 (55); RCT	Serious	Direct	Precise	NA		Low	No difference
Side effects and complications[46,48-50]	3 (411); RCT, NRCS	Serious[i]	Indirect[j]	Not precise[k]	Inconsistent[h]		Insufficient	No conclusion
Patient satisfaction, experience, quality of life	NA	NA	NA	NA	NA		NA	No evidence

Notes. [a] Three RCTs had medium risk of bias (not blinding participants/personnel) and unclear whether outcome assessor was independent; One RCT was high risk of bias due to above concerns and only reporting outcomes for 52% of randomized patients. Two NRCS only conducted crude analyses; [b] Gy varied (7 to 32) and large variation in follow-up time (6 mo to 15 mo); [c] Two studies included small samples[4,6] and 2 had wide ranges for estimates[3,5]; [d] Direction of findings across studies varied; [e] Two RCTs had medium risk of bias (not blinding participants/personnel) and unclear whether outcome assessor was independent; [f] Comparators differed between studies; [g] The studies reported wide range for estimates and different cosmetic outcomes and skin conditions; [h] Direction of findings across studies varied; [i] Three RCTs had medium risk of bias (not blinding participants/personnel) and unclear whether outcome assessor was independent and 1 NRCS only conducted crude analyses; [j] Gy varied (16 to 32) and comparators differed; [k] Confidence interval for 1 study was wide[1] and number of events was rare in 1 study.[3]

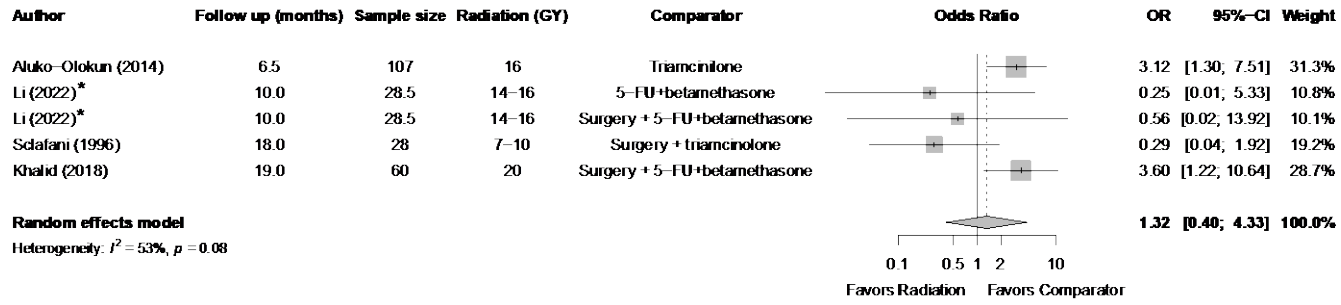
Abbreviations. Gy=gray; mo=months; N/A=non applicable; NRCS=non-randomized controlled trial; RCT=randomized controlled trial.

Recurrence or Effectiveness

Six studies (4 RCTs and 2 NRCS)[46-51] reported either keloid recurrence or treatment effectiveness. Qiao et al[47] (an NRCS) reported efficacy following the Darzi criterion and was excluded from meta-analyses since the other studies reported recurrence. In unadjusted analyses, the NRCS found that fewer patients had an "effective" outcome at 18 (median) months in the RT group (15 Gy) compared to excision alone (unadjusted odds ratio [unadOR] = 0.23, 95% CI [0.08, 0.65]). The same study reported no significant difference in effectiveness between RT (15 Gy) following surgery compared to surgery and corticoid steroids (OR = 0.85, 95% CI [0.28, 2.61]). The same study also found a large, but non-significant and imprecisely estimated difference between surgery with RT (15 Gy) and corticoid steroids (OR = 8.27, 95% CI [0.97, 70.74]).[47] This is an implausibly high estimate and suggests that the populations in these arms are not truly comparable. A second NRCS (Akinbiyi et al) was excluded from meta-analysis because it compared RT (9-32 Gy) alone (not as an adjuvant strategy) to surgery and only reported unadjusted outcomes (unadOR = 0.97, 95% CI [0.54, 1.75]).

In pooled data from 4 studies, there was no significant difference in keloid recurrence following RT relative to a comparison group (pooled OR = 1.32, 95% CI [0.40, 4.33]; Figure 3).[47-49,51] The lower bound of the CI could not exclude clinically important protective effects. There was variation in follow-up (6.5 to 19 months) and RT dose (7 to 20 Gy) between the studies. Two RCTs found clinically large increases in keloid recurrence after RT. In 1 RCT, a significantly higher proportion of patients experienced keloid recurrence or persistence between 14 and 26 weeks following RT (16 Gy) after surgery versus triamcinolone alone (OR = 3.12, 95% CI [1.30, 7.51]).[48] A second RCT also reported a significantly higher proportion of patients experienced recurrence at 6 month follow-up for those who received RT (20 Gy) following excision compared to 5-FU with triamcinolone acetonide (OR = 3.60 , 95% CI [1.22, 10.64]).[49] The remaining studies either reported no difference or a large reduction in keloid recurrence; however, the point estimates were accompanied by large confidence intervals. A post hoc sensitivity analysis including Akinbiyi et al (an NRCS that reported unadjusted outcomes and compared RT to surgery) did not alter the conclusion (pooled OR = 1.31, 95% CI [0.55, 3.10]).[46]

Figure 3. Keloid Recurrence at Follow-Up: Radiation Therapy versus Comparison Group



Notes. Li (2022) is a 3-arm RCT that compared RT with 2 non-RT control arms. Each comparison is included in the meta-analysis as 2 independent trials in each of which the RT arm has half the patients.
Abbreviations. 5-FU=5-fluorouracil; CI=confidence interval; Gy=gray; OR=odds ratio.

Cosmetic Outcomes and Skin Condition

Hyperpigmentation or Hypopigmentation

Two RCTs reported the occurrence of hyperpigmentation or hypopigmentation.[48,50] One RCT reported no significant difference in the proportion of patients who had hyperpigmentation at 14-26 weeks after RT (16 Gy) post-excision compared to triamcinolone alone (OR = 0.73, 95% CI [0.24, 2.28]). The same study reported significantly fewer rates of hypopigmentation among patients who received RT post-excision compared to triamcinolone alone (RD = -0.46, 95% CI [-0.60, -0.33]).[48] A second RCT also reported no significant difference in the rate of hyperpigmentation at 4 month follow-up between RT (14-16 Gy) post-excision and 5-FU and betamethasone alone (OR = 0.73, 95% CI [0.24, 2.28]), or 5-FU and betamethasone after surgical excision (OR = 3.33, 95% CI [0.55, 20.22]).[50] In the same study, there were no cases of hypopigmentation in the RT post-excision group or 5-FU and betamethasone alone and no significant differences in hypopigmentation between the RT arm and patients treated with 5-FU and betamethasone after surgical excision (RD = -0.06, 95% CI [-0.16, 0.05]).[50]

Telangiectasia

Two studies reported the presence of telangiectasia after treatment.[48,50] One RCT reported significantly lower rates of telangiectasia among patients who received RT (16 Gy) following excision compared to triamcinolone alone (RD = -0.15, 95% CI [-0.24, -0.05]).[48] Another RCT found no significant differences in telangiectasia between RT (14-16 Gy) after excision compared to 5-FU + betamethasone alone (OR= 5.58. 95% CI [0.58, 58.43]) or excision followed by 5-FU + betamethasone (OR= 2.46, 95% CI [0.39, 15.63]).[50]

Pruritis

Two RCTs reported outcomes of pruritis.[48,50] One RCT reported a significantly greater proportion patients experienced pruritus at follow-up (between 14 and 26 months) in the RT (16 Gy) group following surgery compared to triamcinolone alone (RD = 0.57, 95% CI [0.43, 0.70]). [48] A second RCT reported no significant difference in the proportion of patients who experienced pruritis on the Patient and Observer Scar Assessment Scale- Patient Scale between RT (14-16 Gy) and those receiving 5-FU + betamethasone (MD = 0.22, 95% CI [-1.07, 1.51]) as well as those receiving surgical excision follow by 5-FU + betamethasone (MD = 0.2, 95% CI [-1.25, 1.65]).[50]

Appearance

One RCT reported appearance on the Vancouver Scar Scale (VSS), Patient and Observer Scar Assessment Scale (POSAS), including the patient (PSAS) and the observer (OSAS) scale.[50] These scales evaluate scars from both the patient and observer perspective. The study reported a significant improvement in scar appearance on the VSS for patients treated with RT (14-16 Gy) after excision compared to 5-FU with betamethasone alone (MD= -1.86, 95% CI [-2.75, -0.98]). There was no significant difference in scar appearance between RT (14-16 Gy) and patients treated with surgical excision followed by 5-FU with betamethasone (MD= -0.32, 95% CI [-1.56, 0.92]). The same study reported a significantly lower overall PSAS score for patients who received RT (14-16 Gy) following surgery compared to 5-FU and betamethasone alone (MD = -11.75, 95% CI, [-15.9, -17.59], but there was no significant difference between RT and 5-FU and betamethasone after surgery (MD = -3.87, 95% CI [-8.19, 0.45]. The study also reported a lower score on the OSAS for patients who received RT (14-16 Gy) following surgery compared to 5-FU and betamethasone alone (MD = -4.82 95% CI,

[-8.22, -1.42]), but no significant difference between RT and 5-FU and betamethasone after surgery (MD = 0.03, 95% CI [-4.19, 4.25]).

Other Skin-Related Outcomes

Two RCTs also reported other skin-related outcomes.[48,50] One RCT reported that a significantly greater proportion of patients experienced tenderness at follow-up (between 14 and 26 months) in the RT (16 Gy) group following surgery compared to triamcinolone alone (RD = 0.15, 95% CI [0.06, 0.25]).[48] The same study also reported significantly lower rates of skin atrophy and ulceration among patients randomized to RT (16 Gy) following surgery (RD = -0.15, 95% CI [(-0.24, -0.05] and RD =-0.26, 95% CI [-0.38, -0.14]).[48] A second RCT reported no significant difference in the occurrence of scabs at 4 months for patients randomized to RT (14-16 Gy) following surgery compared to 5-FU and betamethasone alone or compared to surgical excision followed by 5-FU and betamethasone (OR = 0.35, [0.03, 3.77]) and OR = 0.31, 95% CI [0.03, 3.34]).[50]

Pain

One RCT reported no significant difference in pain as measured by the PSAS at follow-up (4 months) between patients who received RT (14-16 Gy) following surgery compared to 5-FU and betamethasone alone and 5-FU and betamethasone after surgery (MD = 0.00, 95% CI [-1.04, 1.04] and MD = 0.4, 95% CI [-0.46, 1.26]).[50]

Side Effects and Complications

Four studies reported data on treatment-related side effects or complications.[46,48-50] One NRCS reported significantly more complications (undefined) at follow-up (median 15.4 months) among patients who received RT (9-32 Gy) following surgical excision compared to surgery alone (17.9% vs 6.3%, unadOR = 3.88, 95% CI [1.37, 11.00]).[46] One RCT reported no significant difference in the rate of complications (undefined) between 14 and 26 week follow-up among patients randomized to RT (16 Gy) following surgery compared to triamcinolone alone (OR = 1.13, 95% CI [0.52, 2.42]).[48] A second RCT reported 2 patients in the 5-FU + triamcinolone acetonide arm developed epidermolysis and later wound dehiscence compared to 0 patients in the RT (20 Gy) after surgery arm (RD = -0.07, 95% CI [-0.16, 0.02]). The same study reported 3 patients experienced skin redness after RT (20 Gy) which resolved within a few weeks after conservative treatment compared to 0 cases among patients who received excision followed by 5-FU with triamcinolone acetonide (unadjusted RD = 0.10, 95% CI [-0.01, 0.21].[49] A third RCT reported that no patients experienced systemic side effects or malignant transformation in any arm.[50]

Patient Satisfaction, Experience, Quality of Life

No study reported on patient quality of life, satisfaction, or experience of care outcomes.

EFFECT OF RADIATION THERAPY FOR PLANTAR FASCIITIS

Five studies (2 RCTs, 1 NRCS, and 2 single group)[12,52-55] reported on the use of RT for the prevention or primary treatment of plantar fasciitis. Four studies were conducted between 2007 and 2020,[12,53-55] and 1 RCT published in 2016 did not report the dates of the study.[52] Follow-up time for the studies ranged from 3 to 125 months post RT. Two studies were conducted in Turkey, 1 in India, and 2 in Germany (Appendix F-1).

Together, these studies included 1,153 unique patients with plantar fasciitis. Of these patients, 346 (30%) were male, and the average age in 4 studies ranged from 27.6 to 56.9 years.[12,52-54] The fifth study reported a median age of 53 years.[55] None of the studies reported information about race/ethnicity or etiology of disease. One study reported on size of the lesion.[55] Two studies reported that the majority of lesions were on the plantar side of the foot (49.3% and 66.9%) and 1 study noted 70% of patients were treated on a single foot.[12,53,54] All 5 studies reported that most or all of patients had received previous treatment, though only 2 studies detailed the specific treatments received by patients (*eg,* ice/heat, extracorporeal shock wave, oral medication, injection, insole support, or prior radiation therapy).[12,55] The 5 studies also reported that most patients had experienced pain for at least 6 months before receiving RT (Appendix F-2).

One RCT compared RT (3 Gy) to platelet-rich plasma therapy (PRP),[52] and the other RCT compared RT (6 Gy) to palpation guided steroid injection (PGSI, 40 mg methylprednisolone mixed with 0.5 ml of 1% lidocaine).[12] The NRCS included a substantial portion of the same patients in Canyilmaz et al's RCT (RT vs PGSI).[12,53] Specifically, the NRCS compared RT (6 Gy) to PGSI and extracorporeal shock wave therapy (ESWT). We used the RCT to compare RT to PGSI and the NRCS to compare RT to ESWT.[53] Two single group studies applied RT (3 or 6 Gy).[54,55]

One RCT did not have an independent outcome assessor [52] and in the other RCT[12] it was unclear whether the outcome assessor was blinded. Lack of blinding increases the risk of measurement bias, especially if the outcome assessors have preconceptions about the anticipated results with each treatment (Appendix F-4). Therefore, the 2 RCTs had some methodological concerns (*ie*, medium risk of bias). The NRCS conducted crude unadjusted analyses for most outcomes, raising concerns of confounding bias, and the pain-related outcome was unclearly defined (*ie,* high risk of bias).[53] In 1 of the single group studies, 30% of patients were excluded due to missing data from 3-month outcomes.[54] In the other single group study, the outcomes were based on patient self-report of subjective measures, and therefore the assessment was not blinded.[55] The single group studies had no other concerns, but the study design is unable to estimate the effect of RT on outcomes (*ie,* high risk of bias).

In summary (Table 5), function may improve for patients who receive RT (low confidence). There is no significant difference in plantar fasciitis thickness, a composite measure of pain and function, and side effects (low confidence). Studies provided insufficient evidence (no conclusion) for effect of RT on pain or use of secondary treatment. Studies did not report patient satisfaction or quality of life. Appendix F-4 presents detailed outcome data.

Table 5. Summary of Findings for Radiation Therapy for the Treatment of Plantar Fasciitis

Outcome	Studies (Patients); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Overall Confidence	Summary of Findings
Pain[12,52-55]	4 (903); RCT, NCRS,[a] single group	Serious[b]	Indirect[c]	Not precise[d]	Inconsistent[e]		Insufficient	No conclusion
Function[12,53]	2 (197); RCT, NCRS[a]	Serious[f]	Direct	Not precise[g]	Consistent		Low	May improve function
Thickness[52]	1 (40); RCT	Serious[h]	Direct	Precise	Consistent	Small study	Low	No difference in thickness
Remission[55]	1 (250); single group	Serious[i]	Direct	Precise	Consistent		Insufficient	No conclusion
Composite Measures[52]	1 (40); RCT	Serious[h]	Indirect[i]	Precise	Consistent	Small study	Low	No difference in a composite of pain and function
Second treatment/ time to second treatment[12,53,54]	3 (863); RCT, NCRS,[a] single group	Serious[j]	Indirect[k]	Not precise[l]	Inconsistent[m]		Insufficient	No conclusion
Side effects[12,52-54]	4 (903); RCT, NCRS,[a] single group	Serious[b]	Direct	Not precise[n]	Consistent		Low	No difference in side effects
Patient satisfaction, experience, quality of life	NA	NA	NA	NA	NA		NA	No evidence

Notes. [a] Patients from NRCS and 1 RCT overlap; [b] Two RCTs were medium risk of bias; the NRCS and single group study were high risk of bias; [c] Gy varied (3.0-6.0) and follow-up data provided at different time points; [d] Three of the 4 studies estimated wide confidence intervals; [e] 1 RCT found no significant difference on the VAS, a second RCT found significantly lower pain scores on the VAS and more patients had a complete or partial response on the von Pannewtiz score; [f] One RCT had moderate concern for bias due to lack of blinding of participants, study personnel, and outcome assessor and had lack of clear reporting; 1 NRCS did not fully define outcomes and did not adjust for confounders in the analysis; [g] Studies included small samples and wide range for some estimates; [h] Study had moderate concern for bias due to lack of blinding of participants or study personnel and lack of clear reporting; [i] Study design is unable to estimate the effect of RT on outcomes and composite measure of outcomes; [j] Two studies had moderate risk of bias, and 1 study had no comparison group; [k] Second treatment used as a surrogate measure of effectiveness of treatment; [l] Two studies reporting on time to second treatment had wide range estimates, and 1 study reporting on proportion of heels receiving addition RT reported that the number of additional radiation treatments ranged from 1-3; [m] Treatment type (RT vs other treatment) was not significant in 1 RCT in a multivariate analysis for required second treatment, but an NRCS using the same sample with added data reported to be a significant factor in requiring a second treatment; [n] Small number of events.

Abbreviations. NA=not applicable; NCRS=nonrandomized comparative study; RCT=randomized controlled trial.

Pain

Two of 3 comparative studies reported decreases in pain on a visual analog scale (VAS) for patients who received RT compared to an alternative treatment.[12,53] One RCT found no significant change in a 10-point VAS pain score from baseline to 6 months for those who received RT (3 Gy) compared to PRP (difference in mean change = 0.25, 95% CI [-0.24, 0.74]),[52] although the study noted that more patients had increased pain 1-2 weeks after receiving RT (3 Gy) compared to PRP (5 vs 0 patients).[52] Another RCT found significantly lower pain scores on a 10-point VAS at 6 months for patients randomized to RT (6 Gy) compared to PGSI (mean [range] = 2.7 [0-10] vs 4.6 [0-10], $p < 0.001$).[12] However, in a multivariate analysis, RT was not a significant prognostic factor for pain relief during follow-up (time not specified; HR = 1.89, 95% CI [0.88, 4.04]). Adding to the data from this RCT, an NRCS reported significantly lower pain scores on the 10-point VAS at 6 months between patients who received RT (6 Gy), PGSI, and ESWT (mean [range] = 2.5 [0-10] vs 4.6 [0-10] vs 3.6 [0-10], overall $p < 0.001$).[53] A large single group study ($N = 666$) found that 31% of patients achieved a 75-100% pain reduction (defined as a change in pain on 0-100% VAS) on the last day of RT (3 or 6 Gy). The same study found that 65% achieved pain reduction 36 months after RT (3 or 6 Gy).[54] The same study also reported a 45.9% (95% CI [39.4, 52.4]) probability of insufficient pain control at 10 years.

One RCT and 1 NRCS adding to the RCT also measured pain using the modified von Pannewtiz pain score.[12,53] The RCT reported more patients had a complete or partial pain response on the von Pannewtiz pain score at 6 months among people randomized to RT (6 Gy) compared to PGSI (35% and 33.3% vs 15.6% and 12.5%, $p < 0.001$ for difference across all pain categories).[12] The NRCS, which added ESWT arm to the trial, reported that at 6 months more patients in the RT (6 Gy) arm had a complete (40%) or partial response (32.3%) compared to the PGSI arm (15.4% and 13.8%) and ESWT arm (21.9% and 31.5%; $p = 0.001$ for difference across all pain categories).[53] The NRCS also reported that pain control (scale and timeframe unspecified) was achieved by more patients who received RT (6 Gy) compared to PGSI and ESWT (80.6% vs 72.3 vs 63%, p = NR).[53]

Function

One RCT and 1 NRCS that included patients from the RCT reported significant improvements on a function score (excellent, good, moderate, and poor) for patients who received RT compared to a comparison group.[12,53] The RCT reported significantly higher function scores at 6 months for patients randomized to RT (6 Gy) compared to PGSI (mean [range] = 78.7 [33-100] vs 59 [0-100], $p < 0.001$). This translated to more patients achieving an excellent or good functional score at 6 months in the RT (6 Gy) group compared to the PGSI group (38.3% and 38.3% vs 15.6% and 21.9%; overall across five-levels $p < 0.001$). [12] The NRCS reported similar results, with significantly higher scores at 6 months for those who received RT (6 Gy) compared to PGSI and ESWT (mean [range] = 80.3 [35-100] vs 59.2 [1-100] vs 68.6 [30-100], $p < 0.001$). These numbers translated to more patients achieving an excellent or good functional score at 6 months in the RT group (6 Gy) compared to PGSI and ESWT groups (43.1% and 35.4% vs 15.4% and 23.1% vs 23.3% and 12.3%, $p < 0.001$ overall across 5-level measure).[53]

Plantar Fasciitis Thickness

One RCT found no significant difference in plantar fasciitis thickness from baseline to 6 months for patients randomized to RT (3 Gy) compared to PRP (difference in mean change = 0.09, 95% CI [-0.11, -0.29]).[52] The study reported a significant decrease from baseline to 6 months within the RT group (6.71 vs 5.62, $p < 0.001$) and PRP group (6.77 vs 5.59, $p < 0.001$).

Remission

One single group study reported that 38% of patients achieved complete remission (not defined) and 32% achieved partial remission after RT (3 or 6 Gy).[55] A higher proportion of patients achieved complete remission in the 6 Gy RT group compared to 3 Gy RT (40% vs 27%), but the 6 Gy group had a greater portion of patients who experienced no change compared to the 3 Gy group (20% vs 16%).

Composite Measure

One RCT comparing RT (3 Gy) to PRP reported results on the American Orthopedic Foot and Ankle Score (AOFAS).[52] There was no significant difference in change in AOFAS from baseline to 6 months for patients randomized to RT (3 Gy) and PRP (difference in mean change = -0.45, 95% CI [-4.40, 3.50]). Both the RT and PRP groups had significant within-group increases in AOFAS scores from baseline to 6 months (52.5 vs 89.65 and 51.5 vs 89.1, $p < 0.001$ for both within-group change).[52]

Second Treatment

Three studies reported information on receipt of additional treatment for patients whose initial treatment was unsuccessful. [12,53,54] One RCT and 1 NRCS that included patients from the RCT reported on the time to a second treatment. In the RCT, a second treatment of RT (6 Gy), PGSI, or other treatment (not specified) was offered to those whose initial treatment results were unfavorable. The study reported no significant difference in the 1-year probability of patients not requiring a second treatment between people randomized to RT (6 Gy) and PGSI (95% vs 90.2%). The same study reported a significantly longer time between first and second treatment for patients randomized to RT (6 Gy) compared to PGSI (mean time 9 vs 6.4 months, $p = 0.045$). [12] The NRCS reported time to second treatment but did not report the type of secondary treatment offered. The NRCS reported no overall difference in months to secondary treatment for patients who received RT (6 Gy), PGSI, or ESWT (9 vs 6.4 vs 7.8, $p = 0.07$).[53] A single group study (6 Gy) reported the proportion of patients who opted to receive additional doses of RT in order to achieve stronger pain reduction.[54] Of the 864 heels included in this study, 292 (33.8%) received at least 1 additional radiation treatment of the same dose. Of note, 48 heels (5.6%) received 2 additional radiation treatments, and 6 (0.7%) received 3 additional radiation treatments after initial RT.

Side Effects

Three studies reported different side effects.[12,53,54] Another RCT reported that 1 patient developed an acute infection at the injection site in the PGSI group, and no acute side effects and long-term toxicity events in the RT (6 Gy) arm during follow-up (median 12.5 months).[12] An NRCS reported that 10 patients in the ESWT group had arm pain during treatment, and 2 patients in the ESWT group experienced reddening of the skin.[53] The single arm study qualitatively reported that, aside from an initial increase in pain during and shortly after RT, toxicity from RT was not observed in any patients.[54]

Patient Satisfaction, Experience, and Quality of Life

No study reported patient reported satisfaction, experience, or quality of life.

EFFECT OF RADIATION THERAPY (BRACHYTHERAPY) FOR PTERYGIUM

Five studies (2 RCTs, 2 NRCS, and 1 single group)[56-60] evaluated the use of brachytherapy for the primary treatment or prevention of recurrence of pterygium after excision. Three of the 5 studies were conducted between 1989 and 2009, and 2 studies did not report study dates. Follow-up time for the studies ranged from 3 to 144 months post-RT. One study was conducted in Brazil, 1 in Israel, 1 in Nigeria, 1 in Turkey, 1 in Japan, and 1 in Germany (Appendix G-1).

These five studies included 1492 patients and 1702 eyes.[56-60] The mean age of participants ranged from 40.2 to 59.0 years, with the frequency of male participants ranging from 43.5% to 65.3%. One study reported lesion dimension (mean 2.65 mm)[56] and 3 reported at least 98% of lesions being on the nasal side.[56,57,60] Only 1 study reported grade of pterygium (scale not specified), where 48.5%, 42.6%, and 9.3% of patients were classified as grade I, II, and III, respectively. [56] In 4 studies, total radiation dose ranged from 10 to 35 Gy. In 1 study, total radiation ranged from 10 to 70 Gy, but we included this study since <4% of patients received >60 Gy (Appendix G-2).

In both RCTs, it was not possible to blind participants, but both RCTs had blinded outcome assessors and no other major methodological limitations (*ie,* low risk of bias; Appendix G-3).[56,57] One NRCS had high risk of bias because they conducted crude unadjusted analyses (confounding bias)[59] and 1 NRCS only matched for age and sex (*ie,* medium risk of bias).[58] The 1 single group study is unable to estimate the effect of RT on outcomes (*ie,* high risk of bias).[60]

In summary (Table 6), studies provided insufficient evidence (no conclusion) for the effect of RT on the recurrence of pterygium, symptomatic improvement, cosmetic results, or side effects. Studies did not report data on patient satisfaction, experience, or quality of life. Appendix G-4 presents detailed outcome data.

Table 6. Summary of Findings for Radiation Therapy (Brachytherapy) for the Treatment of Pterygium

Outcome	Studies (Patients); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Overall Confidence	Summary of Findings
Recurrence[56-59]	5 (1492); RCT, NRCS, single group	Serious[a]	Indirect[b]	Imprecise[c]	Inconsistent[d]		Insufficient	No conclusion
Symptom improvement[56,58]	2 (144); RCT, NRCS	Serious[e]	Indirect[f]	Imprecise[g]	Inconsistent[h]		Insufficient	No conclusion
Cosmetic results[56,58]	2 (144); RCT, NRCS	Serious[e]	Indirect[i]	Precise	Consistent		Insufficient	No conclusion
Side effects[57-60]	4 (1396); RCT, NRCS, single group	Serious[j]	Indirect[k]	Imprecise[l]	Inconsistent[m]		Insufficient	No conclusion
Patient satisfaction, experience, quality of life	NA	NA	NA	NA	NA		NA	No evidence

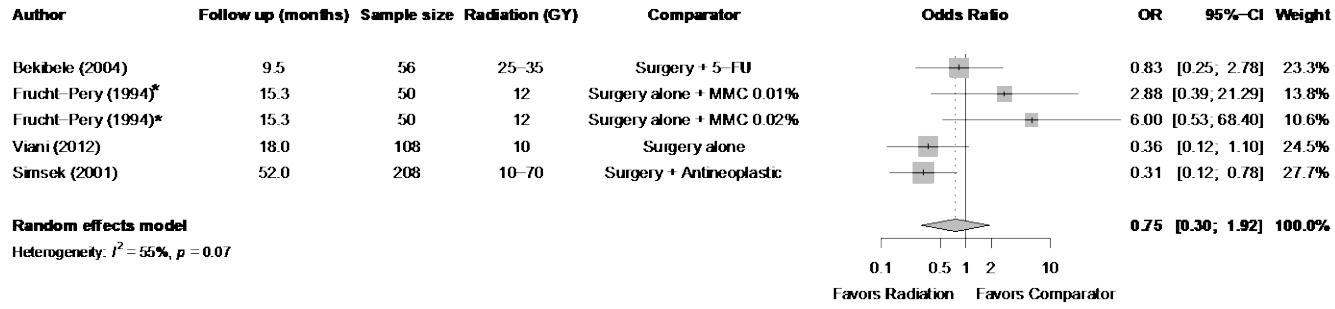
Notes. [a] Two of the 5 studies were high risk of bias; [b] Gy (10-70), comparators, and follow-up time points varied; [c] Confidence intervals from 1 study were wide (0.50, 16.48 and 0.65, 55.66)[2]; [d] One study reported lower recurrence in the RT arm, and 3 found no difference between RT and comparison groups; [e] One of the 2 studies was rated as medium risk of bias; [f] Gy (10-35) comparators, and follow-up time points varied, and different measures of symptom improvement were used; [g] Small number of events in 1 study[3]; [h] One study favored RT, 1 study had mixed results; [i] Gy (10-35) and comparators varied; follow-up data provided at different time points, different measure of cosmesis; [j] Two of the 4 studies were high risk of bias; [k] Gy (10-70) comparators, and follow-up time points varied, and different side effects were examined; [l] All studies had small numbers of events for at least on individual side effect; [m] Individual side effects were higher in the RT arm in some studies and lower in others.

Abbreviations. NA=not applicable; NRCS=nonrandomized comparative study; RCT=randomized controlled trial.

Recurrence

Four studies (3 RCTs and 1 NRCS) reported a non-significant decrease in pterygium recurrence after brachytherapy compared to the alternative treatment (pooled OR = 0.75, 95% CI [0.30, 1.92] Figure 4).[56-59] The pooled OR strongly favored RT, but the CI was wide (*ie*, low precision). One RCT found no significant difference in recurrence 18 months after patients received either excision plus brachytherapy (10 Gy) or excision alone (OR = 0.36, 95% CI [0.12, 1.10]).[56] In this same study, 6 patients in the surgery plus brachytherapy arm and 7 in the excision only arm received salvage surgery due to pterygium relapse. In an unadjusted analysis, 1 NRCS found no significant difference in recurrence between excision plus brachytherapy (25-35 Gy) to excision plus 5-FU (OR = 0.83, 95% CI [0.25, 2.78]).[58] Conversely, 1 NRCS, also in an unadjusted analysis, reported significantly fewer episodes of recurrence among patients who received excision plus brachytherapy (10-70 Gy) compared to Mitomycin-C 0.02% eyedrops (OR = 0.31. 95% CI [0.12, 0.78]).[59] A single arm study (excluded from meta-analysis) reported 7.7% of patients experienced recurrence after (mean 45 months) excision plus brachytherapy (30-35 Gy).[60]

Figure 4. Pterygium Recurrence at Follow-Up: Radiation Therapy (Brachytherapy) versus Comparison Group



Notes. * Frucht-Pery (1994) is a 3-arm trial that compared an RT arm with 2 non-RT control arms. Each comparison is included in the meta-analysis as 2 independent trials, in each of which the RT arm has half the patients.

Abbreviations. 5-FU=5-fluorouracil; CI=confidence interval; Gy=gray; OR=odds ratio.

Symptom Improvement

Two studies reported data on pterygium-related symptoms following RT.[56,58] One RCT reported that symptoms (undefined) improved 18 months after brachytherapy (10 Gy) following excision compared to excision alone.[56] This study reported that 72% of patients who were treated with brachytherapy (10 Gy) after excision reported symptom improvement, 20% reported partial improvement, and 8% reported no improvement compared to 50%, 28%, and 22%, respectively, in the excision-only arm (p = 0.001). An NRCS reported no change in visual acuity for patients in the brachytherapy (25-30 Gy) followed by excision.[58] Improvements in visual acuity were reported for patients who received excision plus 5-FU (9 eyes improved 2 or more Snellen lines and 2 eyes reduced 1-2 lines; p = NR).

Cosmetic

Two studies reported cosmetic outcomes.[56,58] One RCT reported significantly more patients had "excellent" or "good" cosmetic outcomes following brachytherapy (10 Gy) after excision compared to excision alone (94% vs 85%, p = 0.03).[56] An NRCS found no significant difference in the proportion

of patients who had cosmetically unacceptable outcomes between brachytherapy (25-35 Gy) after excision compared to surgery with 5-FU (OR = 0.55, 95% CI [0.09, 3.58]).[58]

Complications/Side Effects

Four studies reported data on complications.[57-60] One RCT compared brachytherapy (12 Gy) after excision to excision plus 0.01% or 0.02% mitomycin C. The study reported that during the 3-week post-operative period, all patients experienced ocular pain, photophobia, or lacrimation.[57] This study also reported that 1 patient in the 0.02% mitomycin C arm experienced a delay in conjunctival healing for 8 weeks after surgery, but noted that the patient had recurrent pterygium at baseline. One patient in this study also developed calcified degeneration of the conjunctiva in the operated area in the 0.02% mitomycin C arm, but the authors reported that this patient had 5 previous surgeries and previous brachytherapy. [57] One NRCS found no difference in cornea necrosis, conjunctivitis, and sclera granuloma side effects between brachytherapy (25-35 Gy) after excision and excision plus 5-FU.[58] The same study found fewer rates of corneal opacity in participants treated with brachytherapy after excision compared to excision plus 5-FU (OR = 0.06; 95% CI [0.01, 0.48]).[58] Another NRCS noted that "almost all" patients who received brachytherapy (10-70 Gy) after excision reported pain, photophobia, tearing, and foreign body sensation during the week following treatment. Similarly, "almost all" patients who received mitomycin C 0.02% complained of burning and foreign body sensation, tearing, and photophobia during treatment.[59] This study reported a wide variety of complications experienced by both arms, with more complications occurring in the mitomycin C arm compared to the brachytherapy arm ($p < 0.001$).[59] In 1 single arm study, moderate conjunctivitis (0.2%), local pain (4.9%), visual disturbance (5.7%), and photophobia/increase in tear flow (5.6%) were reported as potential side effects/complications for patients who receive brachytherapy (30-35 Gy) after excision.[60] The authors reported that there were no severe late complications in the treated patients.

Patient Satisfaction/Experience/Quality of Life

No study reported data on patient satisfaction, experience, or quality of life.

EFFECT OF RADIATION THERAPY (NON-BRACHYTHERAPY) FOR PTERYGIUM

One single group study reported on the use of external ionizing radiation (5-30 Gy) for the primary treatment or prevention of recurrence of pterygium after excision (Appendix G-1).[61] The study was conducted between 1987 and 2000 (Appendix G-2). The authors are from Germany, but the specific location of the study was unclear. The study included 65 patients. Until 1995, 34 cases were treated with RT (5-30 Gy total dose) postoperatively and patients were followed for an average of 52 months. Starting in 1995, 47 cases were treated with RT (17-27 Gy total dose) both pre- and postoperatively, and patients were followed on average for 31 months. Collectively, the majority of the patients were male (74%) and the mean age of patients was 53.7 years.[61] Although the single group study had minimal methodological limitations, the study design is unable to estimate the effect of RT on outcomes (*ie,* high risk of bias; Appendix G-3).

In summary, 23.5% of lesions recurred after (mean 36 months) RT (5-30 Gy).[61] Recurrence was more common among patients who received RT only postoperatively compared to pre- and postoperatively (44% vs 8.5%). Conjunctivitis and superficial keratitis were reported in the first few days (numbers not reported) after RT, and there were no reported cases of scleral necrosis or thinning, symblepharon, radiation-induced cataract, or glaucoma.[61] Symptoms, cosmetic outcomes, and patient satisfaction, experience, or quality of life were not reported. Certainty of evidence was not assessed for these outcomes.

EFFECT OF RADIATION THERAPY FOR OSTEOARTHRITIS

Previous Review

A previous systematic review (search dates: inception to April 20, 2015) examining low-dose RT for osteoarthritis included 7 single group studies with a total of 2,164 osteoarthritis patients (Appendix H-1).[62] The majority of patients were between the ages of 50-70 and most were female (range = 47%-72%; Appendix H-2). In the 7 studies, RT dose ranged from 0.5-12.0 Gy. The review outcomes of interest included pain, function, and side effects of treatment. Most outcomes were evaluated using non-validated measures. The review authors concluded the 7 studies had weak methodological quality due to concerns related to confounding and not blinding outcome assessors or data collectors. The review was of moderate quality, did not provide a clear explanation for the selection of study design, and did not explain whether data extraction was performed in duplicate (*ie,* moderate quality; Appendix H-3). The results of Minten et al's systematic review are narratively incorporated into the findings below.

Newly Identified Studies

Our updated search identified 2 RCTs[63,64] and 3 single group studies[65-67] (1 of the single group studies was an RCT analyzed as 2 single groups) on the use of RT for the prevention or primary treatment of OA. The RCT that we analyzed as a single group compared 2 different doses of RT,[67] which is not a comparison of interest. The 2 RCTs were conducted by the same research group.[63,64] The 5 studies were conducted between 2004 and 2020. One study did not report study dates but was approved by an ethics committee in 2017 and results were published in 2022.[67] The 5 studies reported follow-up data immediately following RT to 6 months post-RT. Four of these studies were conducted in Germany and 1 in the Netherlands (Appendix H-1).

Together, the newly identified studies included 1,410 patients with osteoarthritis (Appendix H-2). One RCT included patients with osteoarthritis of the knee, and the other included patients with osteoarthritis of the hand. One of the single group studies focused on patients with osteoarthritis of the foot and ankle,[66] and the other 2 single group studies included patients with osteoarthritis of the hand, knee, shoulder, hip, foot, and other non-specified sites.[65,67] The mean age of patients across the studies ranged from 65-76 years old. Four of the 5 studies included information about the proportion of male patients in the study samples (range = 21.4%-49.1%).[63-66] No studies reported information on etiology. Four studies reported duration of osteoarthritis symptoms prior to RT.[63,64,67] One study reported that 56% of patients experienced symptoms for ≤5 years prior to RT,[63] another study reported that 61% of patients experienced symptoms for ≥5 years,[64] and 2 studies reported mean duration of pain prior to RT (56.2 and 49.6 months).[67] All studies reported that at least some patients received treatment for osteoarthritis prior to RT (*eg,* analgesics and oral medications, ice/heat, ultrasound, and intraarticular corticosteroid injections) (ALL). Two RCTs compared RT (6 Gy) to sham RT.[63,64] In the 3 single arm studies, the total RT dose ranged from 0.3 to 6 Gy.[65-67]

The 2 RCTs had low risk of bias (*ie,* no major methodological weaknesses; Appendix H-4).[63,64] Both RCTs stratified allocation of participants by pain intensity and later adjusted for this in their analyses. Although the single group studies had minimal methodological limitations, the study design is unable to estimate the effect of RT on outcomes (*ie,* high risk of bias).[65-67]

In summary, single group studies but not RCTs reported improvements in pain, function, a composite measure, and somatic measure. Side effects including fatigue, local reactions, skin reactions, and nail

reactions were comparable between RT and sham RT. Single group studies, but not RCTs, reported improvements after RT on a version of the Short Form Health Survey. Certainty of evidence was not assessed for these outcomes (see Methods). Appendix H-5 presents detailed outcome data.

Pain

From the previous systematic review, 3 single group studies used the von Pannewtiz score to assess pain, and 4 single group studies used other non-validated pain scores.[62] Across the studies, a short-term (≤3 month) decrease in pain was reported in 13-90% of patients, and a long-term (>3 months) decrease in pain was reported in 44-87% of patients. The review noted that none of the included studies were of sufficient quality and concluded there was insufficient evidence for the effect of RT on pain.

All 5 of the newly identified studies reported pain outcomes.[63,64,65-67] Assessments used across studies included the Western Ontario and McMaster University Osteoarthritis Index Scale (WOMAC) pain scale, the Australian/Canadian Hand Osteoarthritis Index (AUSCAN) pain scale, von Pannewtiz score, a visual analog scale (VAS) or numeric rating scale (NRS) for pain, or an undefined pain scale.

Two RCTs found no significant difference in pain scores between RT and sham RT.[63,64] One RCT found no significant difference in change in WOMAC scores from baseline to 12 months follow-up between RT (6 Gy) and sham RT in patients with osteoarthritis of the knee (mean difference= -1.9, 95% CI [-9.9, 6.0]).[63] Another RCT found no significant difference in the change in AUSCAN score from baseline to 12 months follow-up between RT (6 Gy) and sham RT in patients with osteoarthritis of the hand (mean difference = 3.3, 95% CI [-4.6, 11.2]).[64] Both RCTs also found no significant difference in NRS pain score from baseline to 3 months follow-up between RT and sham RT (difference in mean change $\beta = 0.1$, 95% CI [-0.9, 1.2] and $\beta = -0.1$, 95% CI [-1.2, 1.0]).[63,64]

One single arm study found a significant decrease in NRS pain score from baseline to immediately following RT(3-6 Gy; $p < 0.001$) and 8 weeks after RT ($p < 0.001$).[65] One single arm study found that 60% of patients had complete or partial pain response on the von Pannewtiz score immediately following RT (3-6 Gy), and 65.6% of patients achieved a complete or partial pain response 8 weeks after RT.[65] One study reporting on 3 Gy and 0.3 Gy reported pain using a VAS.[67] There was a significant decrease in pain scores from baseline to 3 month follow-up for both 3 Gy and 0.3 Gy (mean difference in change score = -18.9, 95% CI [-23.98, -13.82] and -15.8, 95% CI [-20.57, -11.04], respectively). In both studies, patients reported that pain improved or markedly improved in 59% of joints.[67] In another single arm study, 75.5% of patients exceeded the clinical benchmark of 20% for subjective improvement in pain 6 months after RT (3-6 Gy) and only 2 (1%) of patients had worsening pain. However, the scale used to assess pain was not defined.[66]

Function

In the previous review, 3 studies reported function outcomes after RT using several site-specific measures (Harrison hip score [hip], Constant score [shoulder], Japanese knee score [knee], Tegner-Lysholm score [knee], Insall-Knee score [knee], and an investigator-developed score [thumb]).[62] In one single group study (2.5-6.0 Gy) included in the prior review, the long-term effect on mobility was reported as satisfying, good, or very good in 74% of shoulder osteoarthritis patients and 62% of knee osteoarthritis patients. Another single group study found that function scores after RT (6 or 12 Gy) improved in 55-71% of patients depending on osteoarthritis site. A third single group study (0.5-10 Gy) reported improvement in ability to move in 39.8% of patients, and 56.5% of patients reported this

as stable. Overall, the review concluded that there was insufficient evidence on the relationship between RT and function.[62]

From the newly identified studies, 2 RCTs and a single arm study examined the use of RT on function in osteoarthritis patients.[63,64,67] Both RCTs found no significant difference in function scores at follow-up between RT (6 Gy) and sham RT. One RCT in patients with osteoarthritis of the knee found no significant difference in change in WOMAC function scores 12 months after RT(6 Gy) compared to sham RT (mean difference = -1.0, 95% CI [9.0, 6.6]).[63] The other RCT in patients with osteoarthritis of the hand also found no significant difference in AUSCAN functioning from baseline to 12-month follow-up between RT (6 Gy) and sham RT (mean difference = -1.2, 95% CI [-8.3, 5.8]).[64] As single study evaluating 2 does of RT (3 Gy and RT 0.3 Gy) found significant improvements in the Knee Injury and Osteoarthritis Outcome Score from baseline to 3 month after RT (MD = -5.5, 95% CI [-7.54, -3.46] and MD = -4.9, 95% CI [-6.98, -2.83]).[67]

Stiffness

The previous review did not report stiffness outcomes. Two newly identified RCTs examined changes in stiffness between RT (6 Gy) and sham RT. These studies found no significant differences in change in stiffness from baseline to 3-month follow-up between groups (WOMAC difference in mean change $\beta = 2$, 95% CI [-8, 13] and AUSCAN index difference in mean change $\beta = 6.0$, 95% CI [-4.5, 17]).[63,64]

Patient Global Assessment

The previous review did not report global assessment outcomes. Two RCTs reported change in the patient global assessment (PGA) from baseline to 3-month follow-up (0 = best outcome and 10 = worst outcome). Both RCTs found no significant change in PGA scores from baseline to 12 month follow-up between the RT (6 Gy) and sham RT groups (mean difference = 0.0, 95% CI [-1.2, 1.2]) [63] and mean difference = -0.1, 95% CI [-1.2, 1.1]).[64]

Composite Measures

The previous review did not report composite measures. Four studies (2 RCTs and a single group) reported various composite measures.[63,64,67] Two RCTs used the OMERACT-OARSI criteria (composite of pain and function) to assess the proportion of patients who responded to RT at 12 months post-RT. Both RCTs found no significant difference in the proportion of responders between patients who received RT (6 Gy) compared to sham RT at 12-month follow-up (OR= 1.41, 95% CI [0.45, 4.48] [63] and OR = 1.23, 95% CI [0.37, 4.12]).[64] A single study used the Short Form Score for the Assessment and Quantification of Chronic Rheumatic affections of the hands (SF-SACRAH) to examine the effect of a total dose of 3.0 Gy and 0.3 Gy on osteoarthritis from baseline to 3-months post-RT. In both groups, there was a significant improvement in SF-SACRAH score from baseline to follow-up (MD = -5.7, 95% CI [-8.09, -3.31] and MD = -4.4, 95% CI [-6.64, -2.17]).[67]

Side Effects

The previous review noted that 4 included studies reported data on side effects.[62] The previous review found that 2 studies reported 0 short-term side effects, and 4 studies reported potential long-term side effects but specific results were not discussed by the studies. The review authors concluded that there is insufficient evidence of the safety of RT for osteoarthritis.[62]

From the newly identified studies, 2 RCTs and a single arm study provided information about side effects.[63,64,67] In 1 RCT in patients with knee osteoarthritis, 1 patient reported severe knee pain during and after sham treatment and 1 patient reported cold sensation in the lower leg after sham treatment. The same study reported 1 patient had severe back pain after a fall at home in the RT (6 Gy) group, leading to discontinuation of treatment.[63] The RCT also reported 2 patients were diagnosed with colon carcinoma in the sham group, but the authors noted that they did not expect these to be related to treatment.[63] Fatigue was reported in both RT and sham groups (6 [22%] vs 3 [11%]) and local reactions (not specified) were reported to be comparable between groups.[63] At 12 months post treatment, there were minimal differences in skin or nail reactions, fatigue, other or any reactions, or serious adverse events between the RT and sham arms, though there were 3 reported serious adverse events in the sham arm compared to none in the RT arm. In another RCT, RT (6 Gy) versus sham RT in patients with osteoarthritis of the hand, skin reactions (46.4% vs 39.3%), nail reactions (28.6% vs 10.7%), fatigue (25% vs 21.4%), and other reactions (not defined, 32.1% vs 21.4%) were reported at the 3-month follow-up.[64] Serious adverse events (not defined) were reported in 2 patients in the RT (6 Gy) arm verses none in the sham arm, and 1 patient withdrawal was reported due to an adverse event (nail discoloration) in the RT arm. At 12 months follow-up, there was a higher proportion of patients who experienced nail reactions in the RT arm compared to the sham group, and there were 2 serious adverse events reported in the RT arm compared to 0 in the sham arm. [64]Two single arm studies reported no acute side effects.[67]

Patient Satisfaction, Experience, and Quality of Life

Four studies (2 RCTs and 1 single arm study) reported measures of patient satisfaction or quality of life.[63,64,67] Both RCTs found no significant difference in change in the Short Form Health Survey (SF36) mental component from baseline to 3-month follow-up between RT (6 Gy) and sham RT (difference in mean change $\beta = 5$, 95% CI [0, 10] and 0.6, 95% CI [-3.9, 5.0]). Both RCTs also found no significant difference in change in the SF36 physical component (difference in mean change = -2, 95% CI [-6, 2] and -1.1, 95% CI [-4.6, 2.4], respectively).[63,64] A single arm study examined the change in the 12 item Short Form's (SF12) somatic and psychic scales based on both patients' and doctors' judgments for patients administered either 3.0 Gy and 0.3 Gy. [67] The study found significant improvements from baseline to 3 months post- RT (3 Gy) on the somatic scale based on both doctors' (MD = 5.7, 95% CI [2.83, 8.57]) and patients' (MD = 5.1, 95% CI [2.66, 7.54]) judgments. However, there was no significant change in psychiatric scores from baseline to 3-month follow-up based on the doctor's (MD = 1.2, 95% CI [-0.36, 2.76]) or patients' (MD = 0.1, 95% CI [-1.55, 1.75]) judgments.[67] The same study found significant improvements from baseline to 3 months after RT (0.3 Gy) on the doctor's and patients' judgments on the somatic scale (MD = 3.1, 95% CI [0.44, 5.76] and MD = 2.8, 95% CI [2.65, 2.95], respectively) but not on the psychic scale (MD = 0.18, 95% CI [-1.69, 2.05] and MD = 0.03, 95 % CI [-1.89, 1.95]).[67]

EFFECT OF RADIATION THERAPY FOR PEYRONIE'S DISEASE

Five single group studies reported on the use of RT for the prevention or primary treatment of Peyronie's disease (Appendix I-1).[68-72] Three of the 5 studies reported data before and after patients received RT for select outcomes with the remaining outcomes reported only at follow-up. The studies were conducted between 1982 and 2008, but 1 study published in 2003 did not report specific dates. Three studies explicitly reported follow-up time (range = 8 to 1,400 months). In 1 study,[68] the time to follow-up was unclear because patients were given RT between 1982 and 1997 and a follow-up questionnaire was conducted in 1998. Four studies were conducted in Germany and 1 in the Netherlands.

Together, these studies included a total of 357 patients with Peyronie's disease (Appendix I-2). In 4 studies, the mean age of patients ranged from 54-59 years old,[68-71] and 1 study did not report mean age but noted the majority of patients (44.8%) were 49 to 59 years old.[72] All patients were males. No study reported information on race/ethnicity. One study reported information on the etiology of the disease, with 19% of patients experiencing trauma to the penis.[68] In 3 studies, the mean durations of symptoms before RT were between 11 and 18 months but the range was wide (1 to 204 months). One study reported that 31.0% of patients had symptoms <6 months, 25.8% had symptoms for >6 months, and in 43.1% of patients the duration of symptoms was unknown.[71] Two studies described the majority of patients as having progressive or rapid/very rapid disease progression prior to RT (59 [85.5%] and 83 [68.8%]).[69,70] Two studies reported information on size of foci[72] and 1 study reported the quality of foci, with 28 [31%] classified as fibrous, 27 [30%] classified as cartilaginous, and 34 [39%] classified as calcified.[69] Three studies reported data on previous treatment, which included vitamin E, corticosteroids, oral medication, potassium para-aminobenzoate, hyaluronate, and surgery, or no treatment.[68,69,71] Five studies reported the proportion of patients with Dupuytren's disease (range = 11% to 36%),[68-72] and 2 studies reported the proportion of patients with Ledderhose disease (17.9% and 4.5%) and keloids (7.1%).[70,72] Radiation doses ranged from 12-40 Gy.

The single group studies had methodological concerns (*ie*, high risk of bias) including incomplete outcome data (low response rate to surveys and loss to follow-up),[68,69] conducting unadjusted analyses for pre-post outcomes,[68-70] unclear reporting on blinding of outcome assessors,[68-70,72] unclear representativeness of the cohort and unclear follow-up duration (Appendix I-3).[68]

In summary, single group studies reported improvements after RT in deviation/curvature, foci quality, and an undefined measure of symptoms, and a reduction in pain, number, and size of foci. Between 36% and 51% of patients were satisfied with their sex life after RT. Studies reported different side effects that ranged from 0% (long-term side effect) to 39% (erythema). Certainty of evidence was not assessed for these outcomes. Appendix I-4 presents detailed outcome data.

Pain

Four single group studies reported reductions in pain after RT.[68,72,69,71] One study reported that among the 44% of patients who had pain before RT, 69% had diminished pain after RT (12 or 13.5 Gy).[70] In this study, the time to follow-up was unclear.[68] The second single group study reported a significant reduction in the proportion of patients reporting pain 1400 days after RT (30-40 Gy) compared to before RT (RD = -0.43, 95% CI [-0.56, -0.31]).[69] In this study (N = 92), 52% had pain before RT (30-40 Gy), 30% had pain 80 days after RT, 27% had pain 460 days after RT, 20% had pain 1100 days after RT, and 10% had pain 1400 days after RT. Of note, 40% of patients were lost to follow-up by 1400 days. The third single group study (24-30 Gy) reported that 65% of patients had an improvement

in pain (among those with pain at baseline) after RT.[71] The fourth study reported that among 25 patients with pain before RT, 17 patients (68%) had complete regression of pain after (6 months to 5 years) RT (32 Gy) and another 4 (17%) reported a stark improvement in pain.[72]

Deviation/Curvature

Four studies reported penile deviation or curvature after RT.[68,72,69,71] One study found that of the 97% of patients who had reported penile curvature at baseline, 29% reported a decrease in curvature after (unclear follow-up time) RT (12 or 13.5 Gy).[68] This study also found that 24% of patients underwent surgery to correct persisting penile curvature after RT (12 or 13.5 Gy). Another study reported that for the individual best result of any patient across all time points (80 to 1,400 days), deviation improved in 47% of patients, did not change in 52% of patients, and progressed in 2% of patients after RT (30-40 Gy). [69] A third study reported that of 54 patients who experienced penile deviation on erection at baseline, 24.1% had improvement in deviation after RT. [71] The fourth study reported that 12.1% of patients had complete improvement in deviation, and 27.6% of patients had at least some improvement after RT (32 Gy).[72]

Changes in Foci

One study reported no change in the number, size, and quality of foci between 80-1,400 days following RT (30-40 Gy).[69] Following RT, 32% of patients had a reduction in the number of foci, 68% had no change in the number of foci, and 0 patients had progression in the number of foci.[69] Based on individual best results at any time during follow-up, foci size was reduced in 49% of patients, foci size did not change in 51% of patients, and foci size progressed in 0% of patients.[69] Quality of foci (undefined) improved in 51% of patients, did not change in 48%, and progressed in 1% of patients.

Symptoms (Undefined/Other)

Three single group studies reported on symptoms after RT.[72,69,70] One study reported patient symptoms (undefined) following (mean 52 months) RT (32 Gy). The single group study found that 47% of patients had improvement in symptoms, 90.4% of patients experienced no recurrence of symptoms after RT, and in 78.3% of patients, reported progression of Peyronie's disease was stopped.[70] Another study found of 10.3% patients experienced complete resolution of all symptoms by 2 years after RT (24-30 Gy). The same study found 17.2% of patients had at least a 50% decrease in induration and symptoms at 2 years after RT.[71] Finally, the same study reported that 27.6% of those who experienced induration at baseline had improvement in symptoms after RT.[71] A third single group study found symptoms (undefined) declined in 10.7% of patients after RT (32 Gy).[72] The same study found that 43.3% of patients had a significant improvement in symptoms, and 14.9% had a moderate to mild improvement in symptoms.[72] This same study also reported that disease progression (undefined) was stopped in 86.6% of patients after RT. Finally, the study found that 32.9% of patients had complete improvement in penile induration after RT. The same study reported 15.7% of patients had some improvement in induration, and 10% of patients reported that the induration was softer. [72]

Sexual Function

Three single group studies reported either objective or subjective measures of sexual function.[68,69,70] One study found that among patients with erectile disfunction at baseline, 13% had an improvement in erectile disfunction after (follow-up time unclear) RT (12 or 13.5 Gy).[68] In this study, 12% of patients were receiving erectile disfunction treatment, including intracavernosal injections, use of a vacuum device, or other unspecified treatment at follow-up. Another study reported no significant change in the

proportion of patients with erectile disfunction 1,400 days after RT (30-40Gy) compared to before (RD = -0.05, 95% CI, [-0.12, 0.02]).[69] Of note, this study reported that 2% ($N = 2$) patients received oral medication for erectile disfunction after RT.[69] One study conducted a survey of patients' sexual function after (unclear follow-up time) RT (12 or 13.5 Gy).[68] This study reported a significant decrease in the proportion of patients who were sexually active after compared to before RT (72% vs 92%, $p = 0.002$).[68] There was an increase in the proportion of patients taking medication (antihypertensive or antidepressant agents) known to possibly affect sexual functioning after RT compared to before (56 [53%] and 31 [29%]). After RT, spontaneous erections occurred at least once per day in 16% of patients, once a week in 27% of patients, 2-6 times a week in 21% of patients, and never in 36% of patients.[68] After RT, 51% and 61% of patients reported sometimes or always having difficulty getting and maintaining an erection. After RT, 46% of patients in the study reported their spontaneous erections during the past 4 weeks to be rigid or very rigid, and another 44% reported the rigidity as half. Additionally, 46% of patients reported their erections during sexual intercourse to be rigid or very rigid after RT, and another 50% reported the rigidity as half.[68] The same study reported that 62% of patients had no decrease in sexual interest, 33% had no decrease in sexual activity, and 51% had no decrease in sexual pleasure after RT.

Two studies reported sexual satisfaction after RT.[68,70] In 1 study with an unclear time to follow-up, 26% of patients reported being very satisfied with their current (past 4 weeks) sexual life after RT (12 or 13.5 Gy), while 25% reported being somewhat satisfied, and 49% reported being not satisfied. [68] In a second study, 36% of patients felt RT (32 Gy) had a positive impact on their sexual life while 53% felt it did not. The same study also evaluated subjective satisfaction on a 10-point visual analogue scale at follow-up (mean = 52 months; mean = 6.2 [3.1]). [70]

Side Effects

Five single group studies reported side effects.[68-72] One study reported a variety of side effects after (mean 52 months) RT (32 Gy).[70] This included telangiectasias (12%), skin atrophy (9.6%), paresthesia (6%), erythema (38.6%), and dry skin (9.6%). Another study reported acute dermatitis (28%) and mild urethritis (4%) after (1,400 months) RT (30-40 Gy).[69] The same study reported no long-term side effects (not defined) or indications of malignancy during follow-up (1,400 months). Another single group study reported 11% of patients experienced discomfort during RT (12 or 13.5 Gy).[68] This study did not report any other side effects. One study stated that no patients experienced telangiectasias, ulcers, or atrophy after RT (24-30 Gy).[71] Finally, 1 study reported that patients experienced discrete telangiectasias and minimal hyperpigmentation (9%), and minor redness (3%) in the radiation field after (6 month-5 years) RT (32 Gy).[72]

EFFECT OF RADIATION THERAPY FOR DUPUYTREN'S CONTRACTURE

Five single group studies reported on the use of RT for the primary treatment and/or prevention of Dupuytren's contracture.[73-77] The studies were conducted between 1982 and 2013. The longest study was 24 years and the shortest study was 5 years, and the studies reported outcomes between 3 months and 10 years post-RT. Four studies were conducted in Germany and 1 in Poland (Appendix J-1).

Overall, 653 participants were enrolled, and 1,003 hands were treated with RT (Appendix J-2). The mean age of participants was 54.0 and 61.0 in 2 studies,[74,75] 2 studies reported a median age of 62.9 years and 53.5 years,[76,77] and 1 study did not report age.[73] The frequency of male participants ranged from 59.7% to 68.8%. No studies reported information on race/ethnicity. Stage of disease was reported in 2 studies[74,77] and disease activity was reported by only 1 study.[76] One study reported duration of clinical symptoms before RT, with a mean length of time of 8 (4) years.[74] Comorbidities were reported in 4 studies including Ledderhose disease (6% to 11.5%), Peyronie's disease (1% to 6.3%), diabetes (8.7% to 16.8%), keloids (3.4%), knuckle pads (2.4% and 8.7%), liver disease or cirrhosis (2% for both), among others.[73,74,76,77] No study reported data on the proportion of patients with a history of Dupuytren's, but 3 studies noted patients had received previous treatments (*eg,* surgery and steroid injections).[73,75,76] Four studies reported 28.6% to 63.6% of patients had a family history of Dupuytren's disease.[73,74,76,77] Total radiation doses ranged from 21 to 32 Gy.

In all 5 single group studies, it was unclear whether outcome assessors were blinded (Appendix J-3),[73-77] and the representativeness of the cohorts was unclear in 2 studies.[75,77] There were no other major methodological concerns (*eg,* outcomes fully defined); however, the single group study design is unable to determine the effect of RT on outcomes (*ie,* high risk of bias).

In summary, single group studies reported disease stage, nodules, and symptoms either stabilized or regressed in most patients after RT. Skin-related complications were the most commonly reported side effect. Most patients were satisfied with treatment at follow-up and the studies did not report on quality of life. Certainty of evidence was not assessed for these outcomes. Appendix J-4 presents detailed outcome data.

Disease Stage and Progression

Three studies reported change in Dupuytren's disease stage following Tubiana et al's staging methodology, which is based on flexion deficits of the joints.[77,73,74] One single group study found that disease stabilized or regressed in 69% of patients 13 years (median) after RT (30 Gy).[73] The same study found that the number of nodules and cords stabilized or regressed in 58% of patients after RT (30 Gy). A second single group study found 94% of hands had a stable or improved stage after (mean 6 years) after RT (30 Gy).[74] The same study found 17% of nodules and cords remained unchanged over the follow-up period, while 72% of patients experienced a reduction in size and improvement in consistency of nodules and cords and 11% experienced progression. A third study found 10% of patients experienced regression in the course of disease after (median 10 years) RT (30 Gy). The same study found disease stabilized in 49% of patients.[77] At the same time, 41% of patients in the study experienced in-field or out-field progression of disease after RT, and 22% experienced recurrence in the irradiated area.

Two single group studies did not report the method of staging disease.[75,76] One of these studies found that disease stabilized or regressed in 93% of patients 4.8 months (mean) after RT (21 Gy).[75] The other single group study reported 80% of patients had no further disease progression (including patients with

regression) 40 months (median) after RT (32 Gy), and that there was 21.6% subjective reduction of nodes and cords.[76]

Symptoms

Three single group studies reported data on disease symptoms.[73,74,76] In 2 of 3 single group studies, symptoms either stabilized or regressed in the majority of patients (45% in 1 study and 80% and 96% in 2 studies).[76,73] One single group study reported 45% of patients experienced symptom regression (undefined) 40 months (median) after RT (32 Gy).[76] In another study, 66% of patients reported dysesthesia, burning/itching, and/or pressure/tension prior to RT (30 Gy). At follow-up (median 13 years), 16% of patients with symptoms had complete relief, 18% had good relief, 32% had minor relief, 14% had no change, and 20% had a progression in symptoms.[73] Another study reported that 4% of patients had complete relief of symptoms 3 months after RT (30 Gy), while 29% had a major reduction in symptom complaints and 45% had a moderate reduction.[74] However, 18% of patients had no changes in complaints of symptoms and 4% of patients reported worst symptoms.

Side Effects

Five single group studies reported treatment related side effects after RT (range = 21 to 32 Gy).[73-77] One study evaluated toxicity using the Radiation Therapy Oncology Group EORTC criteria and in 3 studies the method to evaluate side effects was unclear. Four studies reported dry skin (2.5% to 64%) and skin atrophy (3.0% to 13%).[73,74,76,77]Three studies reported between 2% and 20.4% of patients developed erythema.[73,75,76] Another study reported erythema in conjunction with other symptoms, including radiodermatitis (14%).[74] One study reported a small proportion of patients experienced superficial epidermal exfoliation (2.5%),[75] and another study reported side effects of telangiectasia (3%), sensory affect (2%), lack of sweating (4%), and desquamation (2 to 3.8%). One study reported that most patients complained of itching and burning sensations during RT.[74] Two studies reported that no grade 3 or 4 reactions were observed,[73,74] and 1 study reported that no induction of cancer was detected as of the last follow-up.[73] Finally, 1 study reported most patients did not have side effects (63%).[77]

Patient Satisfaction, Experience, and Quality of Life

Two studies reported patient satisfaction at follow-up.[74,76] One study reported average patient satisfaction with RT (32 Gy) on the visual analogue scale (1 = not satisfied, 10 = very satisfied) at median follow-up of 40 months (mean [SD] VAS = 7.9 [2.7]).[76] Another study reported that 87% of patients were satisfied with their long-term outcomes after RT (30 Gy), though it was not clear when this outcome was assessed.[74]

EFFECT OF RADIATION THERAPY FOR LEDDERHOSE DISEASE

One RCT and 3 single group studies reported on the use of RT for the prevention or primary treatment of Ledderhose disease (Appendix K-1).[78-81] The studies were conducted between 1996 and 2023 with follow-up data reported from 6 to 132 months post-treatment. Two studies were conducted in Germany and 2 in the Netherlands.

Together, these studies included 200 patients with Ledderhose disease and a total of 171 feet (37 right, 46 left, and 44 bilateral; Appendix K-2). Of these patients, 110 (55%) were male, the average age was between 52 and 55 in 3 studies,[78,79,80] and the median age was 56 years in the third study.[81] None of the studies reported on the etiology of disease, and 1 study reported information about lesion size and strand length at baseline.[81] One study reported lesions were on average 14 years old, and 2 studies did not report legion age.[80] Two studies reported patients had received other treatments for Ledderhose prior to RT including decompressive insoles, NSAIDs, and surgery.[79,80] Both studies reported co-occurring related diseases, with male patients having Peyronie's disease (4% and 14%)[79,81] and 53.5% of patients in both studies having Dupuytren's disease. In 3 studies, the radiation was 30 Gy[78,79,81] and in the other study radiation varied between 24-32 Gy.[80]

The RCT had no methodological concerns (*ie,* low risk of bias). The 3 single group studies had methodological concerns (*ie*, high risk of bias) due to self-reporting of outcomes, unclear reporting of some outcome measures, and insufficient data to determine the representativeness of the cohorts (Appendix K-3).[79-81] In addition, the single group design is unable to estimate the effect of RT on outcomes.

In summary, 1 RCT and 3 single group studies reported pain and walking improved after RT. The RCT reported quality of life improved after RT. Lesions and symptoms stabilized and nodes and strands decreased after RT. Side effects included skin irritation (13% to 20%) and erythema (3% to 25%). Most patients were satisfied with their treatment at follow-up. Certainty of evidence was not assessed for these outcomes. Appendix K-4 presents detailed outcome data.

Pain

One RCT and 3 single group studies include pain as an outcome.[78-81] The RCT reported a significant reduction in pain as measured by the Numeric Rating Scale 18 months after RT (30 Gy) compared to sham RT (mean difference = -1.3, 95% CI [-2.2, -0.4]).[78] The same study reported that a greater proportion of patients who received RT compared to sham RT had complete or partial pain response (77% vs 54%, $p = 0.002$).[78] One single group study reported a significant reduction in an investigator-developed pain measure from baseline to 49 months (median) after RT (30 Gy; change score = -4, 95% CI [-4.56, -3.44]).[79] The same study found that after RT, patients had no pain in 41.2% of feet, a partial reduction in pain in 37.3% of feet, no change in pain in 21.5% of feet, and 0 patients experienced an increase in pain after RT.[79] The study also reported the mean Brief Pain Inventory pain score at follow-up (1.3 [SD = 1.8]). Finally, at follow-up, 69% of patients reported a permanent positive effect of RT on pain.[79] In another single group study, 68.4% (of 19 patients who had pain prior to RT) experienced pain remission 22.5 months (median) after RT (24-32 Gy). Slight pain persisted for 21% of patients and moderate pain persisted for 16% of patients at follow-up.[80] A third study reported that pain completely resolved in 56% patients after RT (30 Gy), and pain remained stable in 44% of patients.[81]

Progression and Remission of Lesion

One single group study reported complete remission of lesions in 33.3% of patients, partial remission in 54.4%, and stable in 12.1% of patients 22.5 months (median) after RT (24-32 Gy).[80] In this study, no patients experienced progression in the size or number of lesions or symptoms at follow-up. Another single group study reported that no patient experienced progression or needed surgery at follow-up (median 42 months) after RT (30 Gy).[81] In the same study, 1 or more symptoms decreased for 80% of patients after RT. The number of nodes and strands decreased after treatment by an average of 1.5 cm (number before vs after RT: 63 vs 46 after 20 vs 11, p = NR, respectively). Further, reduction in swelling or pressure was achieved in 50% of patients who had experienced these symptoms prior to RT.

Gait

One RCT and 1 single group study reported walking outcomes. The RCT found no significant between-group difference in walking speed or step rate at 18 month follow-up after RT (30 Gy) compared to sham RT (mean difference = 0.07 m/sec, 95% CI [-0.07, 0.21] and -0.13 steps/sec, 95% CI [-0.24, 0.02], respectively).[78] However, the same study found a higher mean walking speed and step rate over time for patients who received RT compared to sham RT (p = 0.02 for both). One single group study found that 73.3% (of 15 patients who had difficulty walking prior to treatment) had improvement in their gait 22.5 months (median) after RT (24-32 Gy).[80] Among this group, 60% of patients achieved gait normalization. Another study reported a reduction in the number of patients with gait disturbance 42 months (median) after RT (30 Gy; number before vs after RT: 8 vs 3, p = NR).[81]

Side Effects

The RCT found no significant difference in adverse events between people who received RT or sham RT.[78] In the RCT, the most frequently reported adverse events in the RT and sham RT arms included erythema (33% vs 18%, p = 0.14), skin dryness (30% vs 15%, p = 0.12), burning sensation (18% vs 18%, p = 0.96), and pain (25% vs 21%, p = 0.64). One single group study reported long-term side effects of dryness of the skin (15%) and erythema (3%) after (unclear time point) RT (24-32 Gy).[79] Another single group study also reported erythema (25%) and soft tissue fibrosis and dryness of the skin (12.5%) after (time point unclear) RT (30 Gy).[80] A third study reported some patients experienced skin redness (20%) after (median 42 months) RT (30 Gy).[81]

Patient Satisfaction, Experience, and Quality of Life

Three single group studies assessed patient satisfaction at follow-up.[79,80,81] One study found that 78% of patients were satisfied with their treatment (investigator-developed measure) at 49 months (median) after RT (30 Gy).[79] A second study found that 91.6% of patients had an improvement in subjective satisfaction with functional status on the linear analog scale from baseline to 22.4 months (median) after RT (24-32 Gy).[80] Finally, a third study found that 24% of patients reported a 75-100% improvement on a VAS.[81]

One RCT and 1 single group study assessed quality of life. The RCT found the EQ-5D-5L and EQ visual analogue scale significantly improved 18 months after RT compared to sham RT ($p < 0.001$ and p = 0.04). A single group study reported that the mean (SD) EQ-5D-5L score at 49 months (median) after RT (24-32 Gy) from the societal and patient perspectives were 0.85 (0.18) and 82.3 (14.5), respectively.[79] These values were comparable to the Dutch general population in the same age category

of 0.85 (0.183) and 80.6 (NR), respectively. The same study reported that 57% of patients considered RT to not be burdensome.[79]

EFFECT OF RADIATION THERAPY FOR HIDRADENITIS SUPPURATIVA

One single group study reported on the use of RT for treatment of hidradenitis suppurativa.[82] This study was conducted in Germany between 1979-1997 and had a follow-up time of 1 to 1.5 months (Appendix L-1).

This study included 231 patients (270 lesions) with hidradenitis suppurativa (Appendix L-2). Most patients were males (58%) and they were on average 40 years old (range = 20-79 years). Approximately 43% of lesions were on the right side of the body, 40% on the left, and 17% on both sides. Forty-one percent of lesions were less than a week old, 20% were 1-2 weeks old, and 18% were 2 weeks to a month old. Previous treatments included drainage (39%), antibiotics and ointment (17%), and only antibiotics (7%). Approximately 45% of patients received no previous treatment. Prior to RT, patients experienced multiple symptoms including pain (28%), induration (29%), and redness (6%). In terms of disease severity, 41% of patients had beginning stages of disease, 9% had course nodular with course granular swellings, 8% had an advanced form with gross nodular swelling of the glands and abscess formation, 40% had chronic recurrent hidradenitis with inflammation of the skin, and 2% had phlegmonous hidradenitis with spread of inflammation into the depth of the armpit. Total radiation doses ranged from 3-10 Gy.

The single group design is unable to determine the effect of RT on outcomes (*ie,* high risk of bias; Appendix L-3).

In summary, 78% of patients had a resolution or improvement of symptoms 1 to 1.5 months after RT (3-10 Gy). In addition, 39% of patients had resolution of all symptoms. Twenty-one percent of patients had a resolution via abscessation, and 1% had no improvement in symptoms. Side effects and patient satisfaction, experience, or quality of life were not reported. Appendix L-4 presents detailed outcome data.

DISCUSSION

Overall, we identified 48 studies (21 RCTs, 5 NRCS, 21 single group studies, and 1 systematic review) across 9 diseases of interest. All the studies reported data on disease related symptoms. Studies less frequently reported data on side effects or patient satisfaction, experience, or quality of life. Only 5 studies were conducted in the US, and none were conducted in the VA.

Heterotopic Ossification

- There was a clinical reduction in the occurrence of heterotopic ossification after RT and surgery without NSAIDs (low confidence). The difference was not statistically significant.
- There was no significant difference in function between RT and surgery with or without NSAIDs (low confidence).
- Studies provided insufficient evidence (no conclusion) for radiologic failure, side effects, and patient satisfaction, experience of care, or quality of life.

Keloids

- There was no significant difference in pain after RT (low confidence).
- Studies provided insufficient evidence (no conclusions) for keloid recurrence, cosmetic outcomes, skin conditions, or side effects and complications.
- Studies did not report patient satisfaction, experience, or quality of life.

Plantar Fasciitis

- Function may improve after RT compared to alternative treatments (low confidence).
- There was no significant difference in plantar fasciitis thickness, a composite measure of pain and function, and side effects (low confidence).
- Studies provided insufficient evidence (no conclusion) for pain or use of secondary treatment. Studies did not report patient satisfaction or quality of life.

Pterygium (Brachytherapy)

- Studies provided insufficient evidence (no conclusion) for the recurrence of pterygium, symptom improvement, cosmetic results, or side effects.
- Studies did not report patient satisfaction, experience, or quality of life.

Pterygium (Non-Brachytherapy; Certainty of Evidence Not Assessed)

- There was a reduction in recurrence after RT.
- Studies did not report side effects, patient satisfaction, experience, or quality of life.

Osteoarthritis (Certainty of Evidence Not Assessed)

- There was no significant change in pain, function, stiffness, patient global assessment, composite measure of pain and function, and mental or physical health in 2 RCTs. Single group studies found significant improvements in disease-related outcomes.
- Side effects (fatigue, local reactions, skin reactions, and nail reactions) were comparable between RT and sham RT.
- Short Form Health Survey scores increased after RT in single group studies, but not RCTs. Studies did not report patient satisfaction or experience.

Peyronie's Disease (Certainty of Evidence Not Assessed)

- Disease-related symptoms improved after RT including pain, deviation/curvature, erectile disfunction, and number, size, and quality of foci.
- Side effects ranged from 0% (long-term side effect) to 39% (erythema).
- Some patients were satisfied with their sex life after RT. Studies did not report patient experience or quality of life.

Dupuytren's Contracture (Certainty of Evidence Not Assessed)

- Disease stage, nodules, and symptoms either stabilized or regressed in most patients after RT.
- Skin-related complications were the most commonly reported side effect.
- Most patients were satisfied with RT. Studies did not report on quality of life.

Ledderhose Disease (Certainty of Evidence Not Assessed)

- Pain, walking speed, step rate, and quality of life improved after RT compared to sham RT.
- Lesions and symptoms stabilized and nodes and strands decreased after RT.
- Side effects ranged from 3% to 33% and included erythema, dryness, soft tissue fibrosis, and redness of the skin.
- Most patients were satisfied (overall or specific to function) with RT.

Hidradenitis Suppurativa (Certainty of Evidence Not Assessed)

- Clinical symptoms either resolved or improved after RT.
- Side effects and patient satisfaction, experience, or quality of life were not reported.

SUMMARY

Inflammatory, degenerative, and benign proliferative musculoskeletal conditions, such as heterotopic ossification, keloids, plantar fasciitis, and osteoarthritis can lead to pain, physical limitations, depression, anxiety, financial strain, and lower quality of life.[6-10] RT, typically employed to treat cancer, has also been used to treat these benign inflammatory and degenerative musculoskeletal conditions. Clinically, RT is hypothesized to reduce cell proliferation, which is the main pathology underlying many of these benign conditions.[43,62] Although in Germany an estimated 10-30% of RT is

applied to treat benign diseases, there are surprisingly few comparative studies on the effectiveness of RT for the 9 diseases prioritized in this review.[13-16]

The effect of RT on outcomes is mixed among the 4 diseases for which were able to evaluate certainty of evidence. RT reduced the occurrence of heterotopic ossification, and improved function for people with plantar fasciitis. The studies on heterotopic ossification at follow-up reported point estimates that strongly favored RT and were clinically meaningful, but the pooled effect estimate was accompanied by a very wide confidence interval and was not statistically significant. RT was not uniformly associated with clinical benefits within a disease. For example, there were clinically meaningful improvements in function after RT for patients with plantar fasciitis, but there was no significant difference in thickness, a composite measure that included function, and insufficient evidence for pain. Importantly, most studies found minimal evidence of adverse events, indicating that RT may be a safe treatment. However, these studies did not consistently report adverse events and at times it was unclear whether an adverse event was due to RT, co-occurring intervention (*eg,* surgery), or a natural feature of the lesion. While RT shows promise as a treatment modality for some of the prioritized diseases, findings are based on mostly small studies with heterogenous comparison groups, follow-up duration, and RT dosing.

Single group studies predominantly informed the synthesis of the diseases for which we were unable to evaluate certainty of evidence. Overall, these studies reported improvements in clinical outcomes after RT. However, these findings need to be interpreted with caution. The challenges of inferring causality from single group designs are exemplified by the literature on RT for osteoarthritis. Two RCTs found no clinical or statistically significant difference in outcomes between patients randomized to RT or sham RT. However, 3 single group studies found clinically and statistically significant improvements in outcomes after RT. When relying on single group studies, it is challenging to differentiate treatment effect from symptom resolution that could have occurred naturally over the study observation period.

RT for the 9 prioritized diseases is generally used after conventional therapy fails. The referral practice of the primary provider treating the disease is a key factor in determining whether a patient receives RT. Although we did not extract data on referral networks, no study explicitly described how patients were referred to RT. For RT to become part of the standard care for the 9 prioritized diseases will require educating referring providers on the benefits and harms of RT. One of the biggest concerns for patients and providers when considering RT is the risk of radiation-induced secondary malignancies.[83] This is especially a concern for younger patients.[10,84] Most of the benign conditions we reviewed present later in life. Secondary malignancy can take years (10+) to occur and may be less of a concern of older patients. Finally, there were limited data on patient satisfaction, experience, or quality of life in most included studies.

STRENGTHS AND LIMITATIONS OF THE EVIDENCE BASE

The evidence base on RT for the 9 prioritized diseases has several important limitations. First, only 6 of 9 diseases had any comparative data, and we were only able to evaluate certainty of evidence for 4 of 9 diseases. Further, only 1 disease category, heterotopic ossification, included evidence exclusively from RCTs. The lack of comparative data for much of the evidence base makes it challenging to determine the effect of RT compared to non-RT treatments. Most RCTs had independent outcome assessors but did not blind participants or personnel. Two RCTs evaluating RT for osteoarthritis and 1 for Ledderhose disease employed sham RT as a comparison group, which was a practical approach to ensure blinding of participants. Most of the NRCS reported unadjusted (*ie,* crude) results and did not

adjust for confounding. Most diseases included single group studies, and there were many more single group studies that were eligible for analysis but not included in our synthesis (Appendix B-2). Although the single group studies are unable to determine the effect of RT on outcomes, if sufficiently powered they could provide insight into some adverse events including radiation-induced secondary malignancies. Unfortunately, many of the single group studies had small sample sizes and relatively short follow-up.

Second, there was substantial methodological variation between studies, both within and across diseases. This included variation in inclusion and exclusion criteria. Some studies included patients with a history of the disease of interests, and others only included incident cases. Within each disease category there was often meaningful variation in total radiation dose. There was also variation in the timing of when radiation was administrated (*ie,* before or after surgery). Further, comparator groups (when included) varied and included sham radiation, other active treatments, or other adjuvant treatments. Finally, there was wide variation in follow-up assessment across studies (1 to 144 months). Together, the differences across studies (both within and between diseases) makes it difficult to determine the effect of radiation on outcomes.

Third, inconsistent reporting of sample characteristics and outcomes limited interpretation of findings. Studies inconsistently reported disease characteristics before RT (*eg*, lesion size or duration of symptoms) and often did not report data on race or ethnicity. Most studies reported disease-related outcomes, but studies often did not use the same definition or measure to assess the outcome. Sometimes the measure or definition of an outcome was not clearly reported. In addition, studies did not clearly report whether they examined incidence or recurrence of disease. This was exemplified in the heterotopic ossification literature. Studies did not systematically report side effects. In addition, it was often unclear whether reported side effects were a secondary unintended consequence of the RT, the co-occurring intervention (*eg,* surgery), or a disease-related outcome. Radiation-induced cancer is a major concern of clinicians and patients, and no study reported any cases of secondary cancer, but no study was powered to detect this outcome. Finally, few studies reported patient quality of life, satisfaction, or experience.

IMPLICATIONS FOR VA POLICY AND PRACTICE

None of the articles included in this review focused on a Veteran or military population. Many of the clinical diagnoses reviewed here likely translate to the VA population because the underlying biology and mechanisms of action of these conditions do not differ by patient population. Providers and Veterans are left with limited options when the prioritized conditions are resistant to conventional therapy. Although there are limitations to the evidence base, we found no indication that RT should not be used for the 9 prioritized diseases after conventional therapy fails. We therefore assess that there is equipoise about the clinical utility of RT in patients failing conventional therapies. This means that better-controlled comparative data are needed to determine the effect of RT on outcomes and whether low-dose RT provides value (*ie,* is cost effective from a VA or a health care sector perspective).

In the absence of ongoing RCTs, it may be practical to first accumulate observations within the VA setting by assembling a cohort of consecutive patients who meet criteria. As long as VA RT protocols are prospectively standardized, it should be possible to use the wealth of data in VA records to compare patients who were treated with RT with similar patients who did not receive RT using causally explicit analyses. A practical problem in such situations is to enroll enough people. There are opportunities for VA to learn from Germany, where 10-30% of RT is applied to treat benign

conditions. To increase the uptake of RT, the VA can take the lead in developing guidelines on the use of RT, educate specialists about RT, and develop a benign disease care pathway to RT.

Few studies reported data on patient satisfaction or experience with care. These measures are more sensitive to health system structure, and it is unknown how Veterans would rate their experience with RT for benign diseases. There are 41 VHA-operated radiation oncology centers across the nation. Although VHA radiation oncology centers are strategically located, some Veterans may live closer to community oncology centers.[85] Where Veterans receive care impacts their experience and quality of care, with a recent systematic review finding that care in the VA is either the same or better than the community.[86]

Furthermore, there are the limited data on radiation-induced secondary malignancies. VA has an opportunity to help fill these critical evidence gaps by drawing on past experiences in developing quality measures for cancer care. For example, the VA National Radiation Oncology Program (VA-NROP) invested in infrastructure to measure the quality and outcomes of cancer care.[87] This has included consensus quality measures and dosing constraints for breast cancer,[88] rectal cancer,[89] prostate cancer,[90] and head and neck cancer.[91] A similar effort could be undertaken to measure quality and outcomes for benign disease treated by RT. To fill gaps on the effect of RT on radiation-induced secondary malignancies, VA could build off its medical record to develop a registry that includes information on site of the radiation for the begin disease and site of any follow-up cancer.

RESEARCH GAPS/FUTURE RESEARCH

As noted above, many studies used a single group design. While a single group design can provide insight into changes that occur before and after treatment, it is challenging to disentangle the natural evolution of a disease from the effect of treatment. Thus, there is a need for well-designed, adequately powered comparative studies. Three RCTs employed sham radiation as the comparison group, which can serve as a useful model for future trials. Most observational studies used data from medical records, but they did not account for confounding between groups. Future NRCS should make use of an explicit causal inference framework and account for likely confounders of treatment effects by incorporating patient demographic, clinical, and prior treatment characteristics into analyses. There is also a need to better understand patient quality of life, experience, and satisfaction, including treatment-related burden, which should be collected with validated instruments. Although radiation-induced secondary malignancies are an extremely rare event, it is a concern of younger patients. To determine whether low-dose radiation causes cancer requires a large sample and long follow-up (20+ years). Administrative data, including the VA medical record, may provide a large sample size with sufficient follow-up, but these sources typically do not provide enough data on the anatomic site of radiation and cancer. Therefore, there is a need for the creation of a registry that follows patients after radiation. Finally, there is a need for the development of a benign disease care pathway so that referring providers are aware of RT as a treatment for when conventional therapy fails.

STRENGTHS AND LIMITATIONS OF THE REVIEW PROCESS

Our review represents the most up-to-date evaluation of evidence on the use of low-dose RT for the treatment of 9 benign diseases. A strength of our review was the focus on a large number of diseases that are candidates for RT when conventional therapy fails and meta-analyzing findings for 3 of these diseases. This evidence review has several limitations. We employed a best-evidence approach to assess the effect of RT due to the large number of prioritized diseases and large number of published studies. This method allowed the strongest available evidence to be included in the synthesis of the

literature (*ie,* comparative designs prioritized over single group studies). Nevertheless, we may have excluded studies with important data on the benefits and harms of RT for benign conditions. Furthermore, there was large variation in studies, and we were unable to investigate potential sources of heterogeneity of treatment effects (*eg,* effect of RT dose) because of small numbers of studies within a given disease. At times it was unclear whether an adverse event was actually a negative consequence of the treatment (*ie,* RT) or a feature of the lesions. We sought to limit inference about adverse events and therefore described these events as they were reported in the literature. Finally, several studies compared different radiation doses, which we treated as single group analyses because our key question was on the effect of RT relative to non-RT treatment.

CONCLUSIONS

RT has been explored as a secondary treatment option for a variety of benign inflammatory and degenerative musculoskeletal conditions. In comparative studies, we found that RT may reduce the occurrence of heterotopic ossification and improve function in plantar fasciitis. There was no significant difference in pain for people with keloids. We have low confidence in these findings due to methodological limitations and imprecise and inconsistent estimates. One RCT found pain, walking speed, step rate, and quality of life improved for people with Ledderhose disease after RT compared to sham RT (certainty of evidence was not evaluated). Aside from these, there was either insufficient (due to no comparative design, methodological limitations, inconsistent estimates) or no evidence for the effect of RT on disease-related outcomes, side effects, or patient satisfaction, experience, or quality of life for people with keloids, pterygium, osteoarthritis, Peyronie's disease, Dupuytren's contracture, and hidradenitis suppurativa. Although there are gaps in the evidence, we found no indication that RT should not be used after conventional therapy fails for the 9 prioritized diseases. We therefore assess that there is equipoise about the clinical utility of RT in patients failing conventional therapies. High-quality comparative studies (RCTs or NRCS that account for likely confounders) are needed to clarify whether RT is beneficial for benign conditions.

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