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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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.

Executive Summary

KEY FINDINGS

We identified 48 studies on the use of low-dose radiation therapy (RT; <60 Gy) for the treatment of 9 prioritized benign diseases: heterotopic ossification, keloids, plantar fasciitis, pterygium, osteoarthritis, Dupuytren's contracture, Ledderhose disease, Peyronie's disease, and hidradenitis suppurativa.

Heterotopic Ossification (10 Randomized Controlled Trials [RCTs])

- RT may reduce the occurrence of heterotopic ossification. There was no significant difference in function (all with low confidence). Studies provided insufficient evidence (no conclusion) for radiologic failure, side effects, and patient satisfaction, experience of care, or quality of life.

Keloids (4 RCTs and 2 Nonrandomized Comparative Studies [NRCS])

- There was no significant difference in pain after RT (low confidence). Studies provided insufficient evidence (no conclusions) for recurrence of keloids, cosmetic outcomes, skin condition, or side effects and complications. No study reported data on patient satisfaction, experience, or quality of life.

Plantar Fasciitis (5 RCTs)

- RT may improve function. There was no significant difference in plantar fasciitis thickness, a composite measure of pain and function, and side effects (all with low confidence). Studies provided insufficient evidence (no conclusion) for pain or use of secondary treatment. No study reported data on patient satisfaction, experience, or quality of life.

Pterygium (Brachytherapy – 2 RCTs, 2 NRCS, and 1 Single Group Study)

- Studies provided insufficient evidence (no conclusion) for the recurrence of pterygium, symptomatic improvement, cosmetic results, or side effects. No study reported data on patient satisfaction, experience, or quality of life.

Pterygium (Non-Brachytherapy – 1 Single Group Study), Osteoarthritis (2 RCTs, 3 Single Group Studies, and 1 Systematic Review of Single Group Studies), Peyronie's Disease (5 Single Group Studies), Dupuytren's Contracture (5 Single Group Studies), Ledderhose Disease (1 RCT and 3 Single Group Studies), and Hidradenitis Suppurativa (1 Single Group Study)

- Mostly single group studies found disease-related symptoms improved after RT. Side effects were sparsely reported but included skin reactions. Some studies found patients were satisfied with treatment (certainty of evidence not assessed for these diseases and outcomes).

INTRODUCTION

RT targets inflammatory parameters, impedes cell growth, and is frequently used to treat cancer. Low-dose RT has been proposed as a treatment for benign inflammatory and degenerative musculoskeletal diseases, typically when conventional therapy fails. This includes the use of RT for the treatment (or prevention) of heterotopic ossification, keloids after surgical resection, osteoarthritis, and plantar fasciitis.

Benign inflammatory and degenerative musculoskeletal diseases can cause physical limitations and decreased quality of life. 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. RT is commonly used for the treatment of benign diseases in Germany. Outside of Germany, RT is rarely used to treat benign conditions. The Veterans Affairs (VA) Evidence Synthesis Program (ESP) was asked by the Veterans Health Administration (VHA) National Radiation Oncology Program for an evidence review on radiation treatment for benign conditions. In collaboration with VA partners, we developed the following Key Question (KQ): *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?*

METHODS

We searched for peer-reviewed articles in Medline (via PubMed), Embase, and ClinicalTrials.gov from inception to April 1, 2023. One included study was identified by the peer reviewers and was published in May 2023. Eligible studies evaluated the effect of low-dose RT for the 9 prioritized benign diseases (heterotopic ossification, keloids, plantar fasciitis, pterygium treated with and without brachytherapy, osteoarthritis, Dupuytren's contracture, Ledderhose disease, Peyronie's disease, and hidradenitis suppurativa). We excluded studies where participants were <18 years of age, where the majority of patients received re-irradiation of the same anatomic site, where brachytherapy (except for pterygium) was used, and where the majority of patients were treated before 1980. We followed a best evidence approach and prioritized comparative studies (*ie,* RT vs no RT) within each condition of interest. RCTs were given priority over NRCS. Single group studies were included when there were fewer than 5 comparative studies within a disease. When only single group studies were available, we reviewed those studies with the largest sample sizes (up to 5 studies per disease based on study budget). Prioritized outcomes included disease-related symptoms, side effects, and patient satisfaction, experience, and quality of life. Where there were at least 3 studies reporting results from sufficiently similar analyses (based on population, interventions, comparators, and outcomes), we conducted meta-analyses using random-effects models. When there were at least 3 comparative studies per disease, we used GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology to determine certainty of evidence. The review protocol was registered in PROSPERO (CRD42023447241).

RESULTS

Forty-eight studies reported on the effectiveness of low-dose RT for the treatment of heterotopic ossification ($N = 10$), keloids ($N = 6$), plantar fasciitis ($N = 5$), pterygium treated with brachytherapy ($N = 5$) and without brachytherapy ($N = 1$), Peyronie's disease ($N = 5$), Dupuytren's contracture ($N = 5$), Ledderhose disease ($N = 4$), hidradenitis suppurativa ($N = 1$), and osteoarthritis. For osteoarthritis, we included 1 systematic review of 7 single group studies and 5 studies identified from the updated search. Across all 48 studies, there was 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 (range = 17 to 2,164), and follow-up (range = 1 to 144 months). ES Table shows summary results by disease.

ES Table. Summary of Findings by Disease

Disease; Patients; Design (Studies)	Disease-Related Outcomes	Side Effects	Patient Satisfaction, Experience, QoL
Heterotopic ossification 1,530; RCT (10)	Low evidence for a difference in heterotopic ossification at follow-up (pooled OR = 0.47, 95% CI [0.19, 1.17]). No difference in function (low confidence). Insufficient evidence (no conclusion) for radiologic failure.	Insufficient evidence (no conclusion)	Insufficient evidence (no conclusion)
Keloids 599; RCT (4), NRCS (2)	Insufficient evidence (no conclusion) for a difference in keloid recurrence at follow-up (pooled OR = 1.32, 95% CI [0.40, 4.33]). No difference in pain (low confidence). Insufficient evidence (no conclusion) for cosmetic outcomes and skin conditions.	Insufficient evidence (no conclusion)	No evidence
Plantar fasciitis 1,153; RCT (2), NRCS (1), single group (2)	Function may improve after RT compared to alterative treatment (low confidence). No difference in plantar fasciitis thickness and a composite measure of pain and function (low confidence). Insufficient evidence (no conclusion) for pain, remission, or use of secondary treatment.	No difference (low confidence)	Insufficient evidence (no conclusion)
Pterygium (brachytherapy) 1,492; RCT (2), NRCS (2), single group (1)	Insufficient evidence (no conclusion) for recurrence of pterygium (pooled OR = 0.75, 95% CI [0.30, 1.92]), symptom improvement, cosmetic results.	Insufficient evidence (no conclusion)	No evidence
Pterygium (non-brachytherapy)[a] 65; single group (1)	Reduction in recurrence.	No evidence	No evidence
Osteoarthritis[a] 3662; RCT (2), single group (3), systematic review (1)	No difference in pain, function, stiffness, patient global assessment, composite measure of pain and function, and mental or physical health.	No difference	No difference
Peyronie's disease[a] 415; single group (5)	Symptoms improved after RT.	No long-term side effect; 39% reported erythema	Some satisfaction with sex life after RT. No evidence on patient satisfaction, experience or QoL.
Dupuytren's contracture[a] 653; single group (5)	Symptoms improved after RT.	Skin complications	Most patients were satisfied with RT. No evidence on QoL.
Ledderhose disease[a] 200; RCT (1) and single group (3)	Reduced pain and improved walking performance.	Skin complications and soft tissue fibrosis (mild)	Improved QoL. Most patients were satisfied with RT.
Hidradenitis suppurativa[a] 231; single group (1)	Symptoms improved after RT.	No evidence	No evidence

Notes. [a] Certainty of evidence not assessed.

Abbreviations. QoL=quality of life; RT=radiation therapy.

Heterotopic Ossification

Ten RCTs conducted between 1988 and 2008 (that analyzed 1530 participants) compared low-dose RT to surgery with or without non-steroidal anti-inflammatory drugs (NSAIDs). Three studies were conducted in US, 6 in Germany, and 1 in the Netherlands. Total radiation dose ranged from 5 to 12 Gy. Nine RCTs had medium risk of bias for poor reporting (unclear method of randomization, not reporting allocation concealment, and not reporting blinding). 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).

In summary (ES Table), there was a clinical, but not statistically significant, reduction in the occurrence of heterotopic ossification after RT compared to surgery with or without NSAIDs (9 studies). There was no significant difference in function between RT and surgery with or without NSAIDs (3 studies). Studies provided insufficient evidence for radiologic failure, pain, side effects, and patient satisfaction, experience of care, or quality of life (imprecise and inconsistent estimates and methodological limitations).

Keloids

Six comparative studies (4 RCTs and 2 NRCS) conducted between 1991 and 2021 (that analyzed 599 participants) compared low-dose RT to surgery, surgery with 5-fluorouracil or a topical steroid, or a topical steroid alone. Two studies were conducted in the US, 2 in China, 1 in Nigeria, and 1 in Pakistan. Total radiation dose ranged from 7 to 32 Gy. Three RCTs had medium risk of bias (not blinding participants/personnel and not clearly reporting whether outcomes assessors were independent), 1 RCT had high risk (only reporting outcomes for 52% of treated patients), and 2 NRCS reported unadjusted crude analyses (*ie,* high risk of bias).

In summary (ES Table), studies provided insufficient evidence that RT affects the recurrence rate of keloids compared to alternative treatments (6 studies). There was no difference in pain after RT compared to alternative treatments (1 study). Studies provided insufficient evidence for cosmetic outcomes, skin conditions, or side effects and complications. No study reported quality of life, patient satisfaction, or experience of care outcomes.

Plantar Fasciitis

Five studies (2 RCTs, 1 NRCS, and 2 single group) conducted between 2007 and 2020 (that analyzed 1,153 participants) reported on the use of low-dose RT. The RCTs and NRCS compared RT to platelet-rich plasma therapy, palpation-guided steroid injection, or extracorporeal shock wave therapy. Two studies were conducted in Turkey, 1 in India, and 2 in Germany. Total radiation dose was either 3 or 6 Gy. Two RCTs had medium risk of bias (outcome assessor was not blinded or unclear whether outcome assessor was blinded). The NRCS reported unadjusted crude analyses (*ie,* high risk of bias). Single group studies are unable to estimate the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), function may improve for patients who receive RT (2 studies). There was no significant difference in plantar fasciitis thickness (2 studies), a composite measure of pain and function (1 study), and side effects (4 studies). Studies provided insufficient evidence for effect of RT on pain or use of secondary treatment. No study reported quality of life, patient satisfaction, or experience of care outcomes.

Pterygium (Brachytherapy)

Five studies (2 RCTs, 2 NRCS, and 1 single group) conducted between 1989 and 2009 (that analyzed 1,492 participants) evaluated the use of brachytherapy for the primary treatment or prevention of recurrence of pterygium after excision compared to excision alone, excision with fluorouracil, or excision with mitomycin C. One study was conducted in Brazil, 1 in Israel, 1 in Nigeria, 1 in Turkey, 1 in Japan, and 1 in Germany. 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. Both RCTs had no methodological concerns. One NRCS only conducted crude analyses (*ie*, high risk of bias) and 1 NRCS only matched for age and sex (*ie,* medium risk of bias). The single group study was unable to estimate the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), studies provided insufficient evidence for the effect of RT on recurrence of pterygium, symptomatic improvement, cosmetic results, or side effects. No study reported quality of life, patient satisfaction, or experience of care outcomes.

Pterygium (Non-Brachytherapy)

One single group study conducted between 1987 and 2000 (that analyzed 65 participants) evaluated the use of RT (5 to 30 Gy) for the primary treatment or prevention of recurrence of pterygium after excision. The study authors are from Germany, but the specific location of the study was unclear. The single group study had minimal methodological limitations, but the design was unable to estimate the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), 23.5% of lesions recurred after RT (1 study). No long-term side effects were reported. The study did not report symptoms, cosmetic outcomes, and patient satisfaction, experience, or quality of life. Certainty of evidence was not assessed for these outcomes.

Osteoarthritis

Six studies (2 RCTs, 3 single group, and 1 systematic review of 7 single group studies) conducted between 2004 and 2020 (that analyzed 3,574 participants) reported on low-dose RT for the treatment of osteoarthritis. Three studies were conducted in Germany and 2 in the Netherlands. Total radiation dose ranged from 0.5 to 6 Gy. The RCTs had no methodological weaknesses. The single group studies had minimal methodological limitations, but the study design was unable to estimate the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), 4 single group studies but not 2 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 (2 RCTs). Single group studies, but not the 2 RCTs, reported improvements after RT on a version of the Short Form Health Survey. Certainty of evidence was not assessed for these outcomes.

Peyronie's Disease

Five single group studies conducted between 1982 and 2008 (that analyzed 415 participants) reported on the use of RT for the prevention or primary treatment of Peyronie's disease. Four studies were conducted in Germany and 1 in the Netherlands. Total radiation dose ranged from 12 to 40 Gy. The single group design was unable to determine the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), single group studies reported improvements or stabilization after RT in deviation/curvature (4 studies), foci quality (1 study), and an undefined measure of symptoms (3 studies), and a reduction in pain (4 studies) and number and size of foci (1 study). Between 36% and 51% of patients were satisfied with their sex life after RT (2 studies). Five studies reported different side effects that ranged from 0% (long-term) to 39% (erythema). Certainty of evidence was not assessed for these outcomes.

Dupuytren's Contracture

Five single group studies conducted between 1982 and 2013 (that analyzed 653 participants) reported on the use of RT for the primary treatment of Dupuytren's contracture. Four studies were conducted in Germany and 1 in Poland. Total radiation dose ranged from 21 to 32 Gy. The single group design was unable to determine the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), disease stage (3 studies) and nodules and symptoms (4 studies) either stabilized or regressed in most patients after RT. Skin-related complications were the most commonly reported side effect (5 studies). Most patients were satisfied with treatment (2 studies). No study reported quality of life or experience of care outcomes. Certainty of evidence was not assessed for these outcomes.

Ledderhose Disease

Four studies (1 RCT and 3 single group) conducted between 1996 and 2023 (that analyzed 200 participants) reported on the use of RT for treatment of Ledderhose disease. Two studies were conducted in Germany and 2 in the Netherlands. Total radiation dose ranged from 24 to 32 Gy. The RCT had no methodological concerns (*ie,* low risk of bias). The single group design was unable to determine the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), pain (4 studies), gait or walking speed (3 studies) and quality of life (1 study) improved after RT. Lesions and symptoms stabilized or improved and nodes and strands decreased or remained stable after RT (2 studies). Skin reactions were the most commonly reported side effect (13% to 25%; 4 studies). Most patients were satisfied with their treatment at follow-up (3 studies). Certainty of evidence was not assessed for these outcomes.

Hidradenitis Suppurativa

One single group study conducted between 1979 and 1997 (that analyzed 231 participants) reported on the use of RT for treatment of hidradenitis suppurativa. The study was conducted in Germany. The total radiation dose ranged from 3 to 20 Gy. The single group study was unable able to determine the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), after RT 78% of patients had a resolution or improvement of symptoms and 39% of patients had resolution of all symptoms. Side effects and patient satisfaction, experience, or quality of life were not reported. Certainty of evidence was not assessed for these outcomes.

DISCUSSION

RT, which is typically used to treat cancer, can also been used to treat benign inflammatory and degenerative musculoskeletal disorders. We identified few comparative studies that evaluated the effect of RT for the treatment of the 9 prioritized diseases. Furthermore, we were only able to evaluate

the certainty of evidence for 4 of the 9 diseases. The effect of RT on clinical outcomes is mixed. RT shows promise for the treatment or prevention of heterotopic ossification and function for people with plantar fasciitis. Low-dose RT may be safe. Local skin reactions were the most commonly reported side effect, but studies did not consistently report adverse events and it was not always clear whether an adverse event was due to RT, co-occurring intervention (*eg,* surgery), or a natural feature of the lesion. Patients and providers are concerned about the risk of radiation-induced malignancies. No study reported cases of radiation-induced malignancies, but studies were not powered (sample sizes were too small) or designed (follow-up time was too short) to detect this rare outcome. Single group studies predominantly informed the synthesis of the majority of diseases. Findings (especially causal inference) from single group studies need to be interpreted with caution because it is challenging to differentiate treatment effect from symptom resolution that could have occurred naturally over the study observation period.

The evidence base on RT for the 9 prioritized diseases has several important limitations. Few comparative studies evaluate the effect of RT. RCTs had independent outcome assessors but did not blind participants or personnel. Three RCTs evaluating RT employed sham RT as a comparison group, which could serve as a model for future studies. There was heterogeneity among studies both within and across diseases. This included variation in radiation dosing, administration of radiation (*ie,* before or after surgery), comparator group (when included), and timing of follow-up assessments. These differences make it challenging to determine the effect of radiation on outcomes. In addition, there was inconsistent reporting of disease characteristics, disease-related outcomes, and side effects. Finally, few studies reported patient quality of life, satisfaction, or experience.

None of the articles focused on a Veteran or military population. Nevertheless, the clinical findings likely translate to the VA population, as the underlying biology of these conditions do not differ by patient population. Patient satisfaction, experience of care, and quality of life are more sensitive to health system features. Only a few studies reported these outcomes (mostly positive findings), but it remains unknown how Veterans would rate their experience. Veterans may or may not receive radiation from 1 of the 41 VHA-operated radiation oncology centers. The location of care (and burden associated with receiving care) could meaningfully impact satisfaction, experience, and quality-related outcomes. RT is typically used after conventional therapy fails and requires a referral from the primary treating provider. For RT to become part of standard care (inside and outside the VA) requires educating referring providers on the benefits and harms of RT. To increase uptake of RT, VA can take the lead on developing a benign disease care pathway. One of the biggest concerns for patients and providers when considering RT is the risk of radiation-induced malignancies. As noted above, few studies reported on this outcome and no study was adequately designed to detect radiation-induced malignancies. There is an opportunity for VA to help fill this gap. VA administrative data combined with efforts from the VA National Radiation Oncology Program (VA-NROP) could be used to develop a registry to monitor radiation-induced malignancies.

Research Gaps/Future Research

There is a need for well-designed, adequately powered comparative studies. RCTs should consider employing sham radiation as the comparison group or other conservative modalities such as steroid injections. Most observational studies used data from medical records, but they did not account for confounding between groups. Future observational studies, including studies of electronic health records, should at minimum conduct causally explicit analyses to counter confounding bias. There is also a need to better understand patient quality of life, experience, and satisfaction, including

treatment-related burden. Finally, and as noted above, there is a need for a registry to collect data on radiation-induced secondary malignancies.

Limitations

This evidence review has several limitations. We employed a best-evidence approach due to the number of prioritized diseases and published studies. Our review included the strongest available evidence (*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. There was large variation in studies, and we were unable to investigate potential sources of heterogeneity of treatment effects. Sometimes it was unclear whether an adverse event was a negative consequence of the treatment. We sought to make minimal inference about adverse events and tried to stay true to how data were reported in the literature.

CONCLUSIONS

RT has been explored as a treatment (typically after conventional therapy fails) for a variety of benign diseases. There were few comparative studies on the use of RT for the treatment of the prioritized benign diseases. 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 after RT compared to alternative treatments. We have low confidence in these conclusions due to methodological limitations of the studies, imprecision, and inconsistency. One RCT found pain, walking speed, step rate, and quality of life improved in people with Ledderhose disease after RT compared to sham RT (certainty of evidence was not evaluated). There was either insufficient (due to no comparative design, methodological limitations, inconsistent estimates) or no evidence for the effect RT on most other 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. Despite the gaps in the evidence, we found no indication that RT should not be used after conventional therapy fails for the 9 prioritized diseases. We assess that there is equipoise about the clinical utility of RT in patients failing conventional therapies. Future research should conduct comparative studies (RCTs or NRCS that control for confounders) for the use of RT for benign conditions.

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

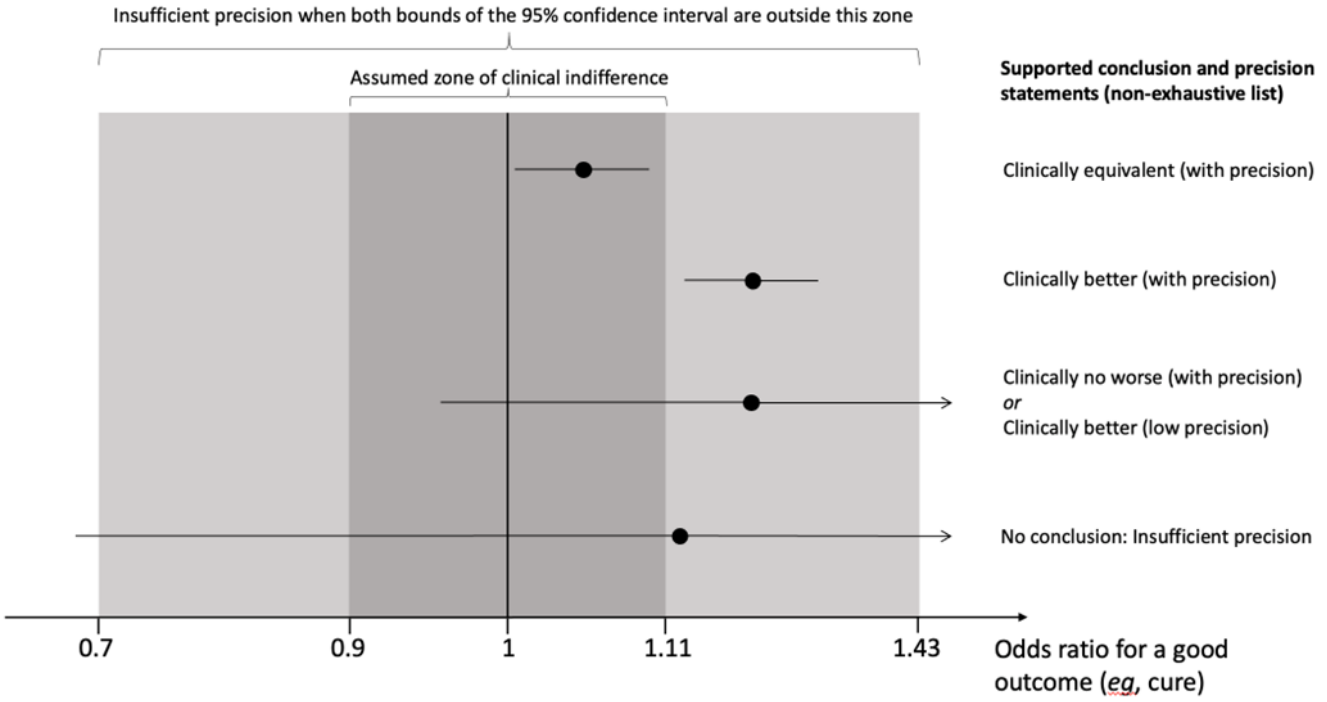
net mean differences (*ie,* difference-in-differences or between-intervention comparisons of within-intervention changes from baseline to follow-up) or mean differences (MD) between interventions for outcomes evaluated only post-intervention. Adjusted analyses were preferentially extracted over unadjusted (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.

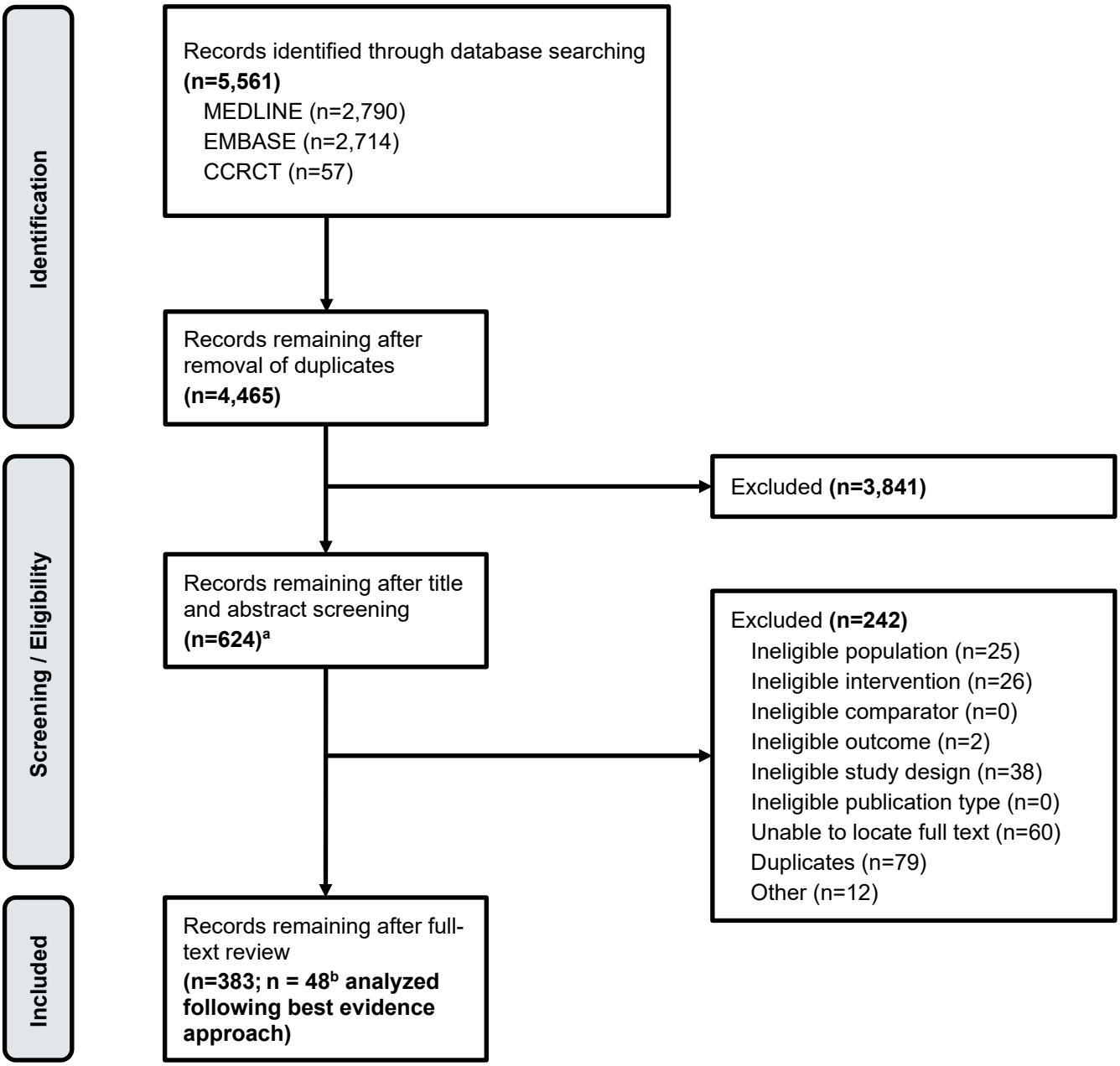
Figure 1. Precision of Statistical Estimates and Range of Clinically Important Effects



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.”

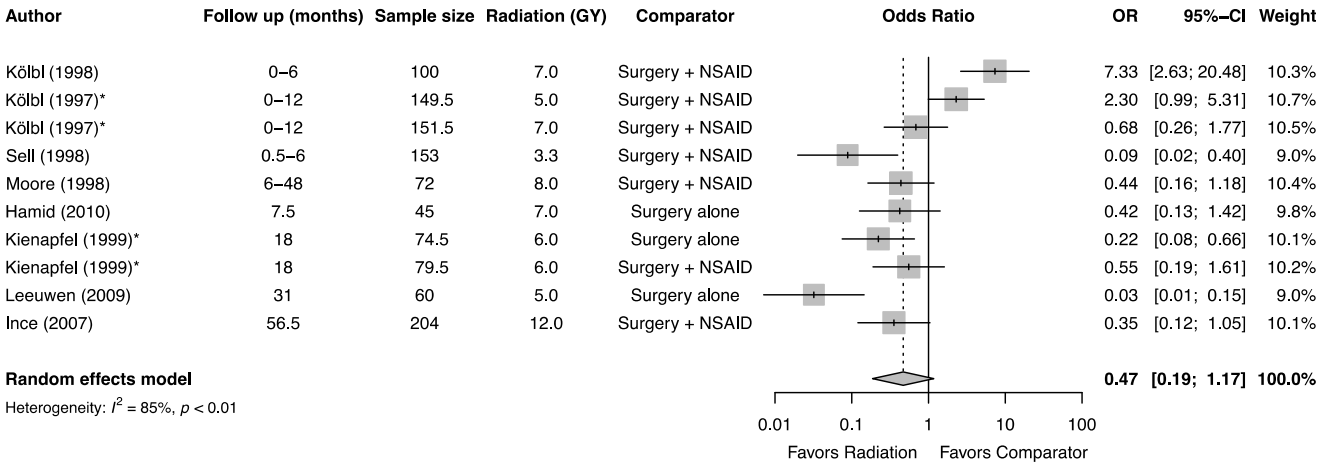
Abbreviations. CI=confidence interval; Gy=gray; mo=months; NA=not applicable; OR=odds ratio; RCT=randomized controlled trial.

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]

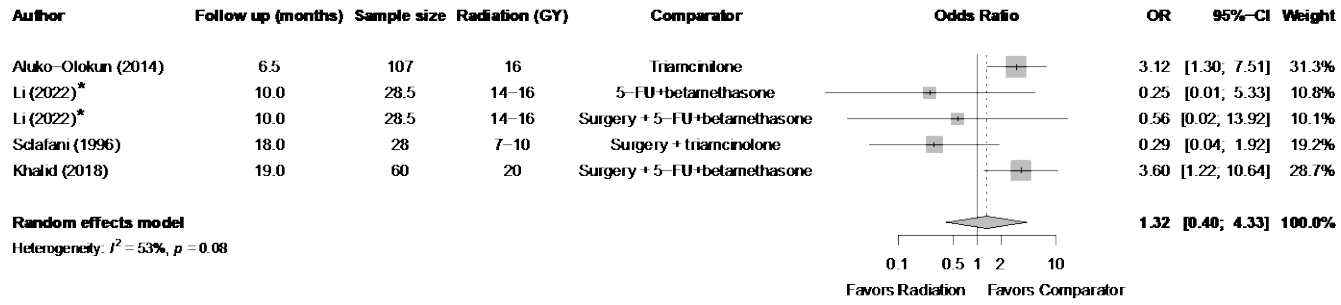
Abbreviations. Gy=gray; mo=months; N/A=non applicable; NRCS=non-randomized controlled trial; RCT=randomized controlled trial.

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

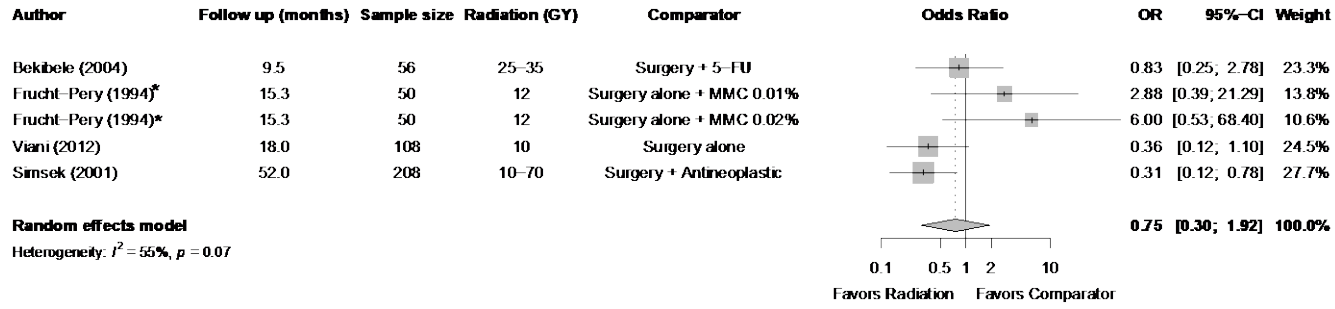
Notes. [a] Two of the 5 studies were high risk of bias; [b] Gy (10-70), comparators, and follow-up time points varied; [c] Confidence intervals from 1 study were wide (0.50, 16.48 and 0.65, 55.66)[2]; [d] One study reported lower recurrence in the RT arm, and 3 found no difference between RT and comparison 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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Appendix

APPENDIX A. SEARCH STRATEGIES

MEDLINE

((Keloid[MeSH Terms] OR "Pterygium"[Mesh] OR Pterygium* OR Keloid OR "Hidradenitis Suppurativa"[MeSH Terms] OR Suppurativ* Hidradenit* OR Acne Inversa* OR "Dupuytren Contracture"[MeSH Terms] OR (Dupuytren* AND (Disease* OR contracture)) OR Palmar Fibromatosis OR Ledderhos* Disease OR "Fibromatosis, Plantar"[Mesh] OR Plantar Fibromatosis OR "Penile Induration"[MeSH Terms] OR (Peni* AND (Fibromatosis OR Induration)) OR Fibrous Caverniti* OR Peyronie* Disease OR "Fasciitis, Plantar"[Mesh] OR Plantar Fasciitis OR Policeman* Heel OR Heel Spur Syndrome OR "Ossification, Heterotopic"[Mesh] OR heterotopic ossification)) AND ((Radiotherapy[MeSH Terms] OR Radiation[MeSH Terms] OR Targeted Radio* OR Radiatio* Therap* OR Radiatio* Treatment* OR radiotherap* OR electron beam))) NOT (("address"[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case reports"[pt] OR "comment"[pt] OR "congress"[pt] OR "dictionary"[pt] OR "directory"[pt] OR "festschrift"[pt] OR "government publication"[pt] OR "historical article"[pt] OR "interview"[pt] OR "lecture"[pt] OR "legal case"[pt] OR "legislation"[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR "comment"[ti] OR "Editorial" [Publication Type] OR "ephemera"[pt] OR "in vitro techniques"[mh] OR "introductory journal article"[pt] OR (("Animals"[Mesh] OR rats[tw] OR rat[tw] OR cow[tw] OR cows[tw] OR chicken*[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep[tw] OR ovine[tw] OR murinae[tw] OR cats[tw] OR cat[tw] OR dog[tw] OR dogs[tw] OR rodent[tw]) NOT "Humans"[Mesh]))

Search Strategy for Osteoarthritis

((((Osteoarthritis[MeSH Terms] OR Osteoarthrit* OR Osteoarthros* OR Degenerative Arthriti* OR Arthros*)) AND ((Radiotherapy[MeSH Terms] OR Radiation[MeSH Terms] OR Targeted Radio* OR Radiatio* Therap* OR Radiatio* Treatment* OR radiotherap* OR electron beam))) NOT (("address"[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case reports"[pt] OR "comment"[pt] OR "congress"[pt] OR "dictionary"[pt] OR "directory"[pt] OR "festschrift"[pt] OR "government publication"[pt] OR "historical article"[pt] OR "interview"[pt] OR "lecture"[pt] OR "legal case"[pt] OR "legislation"[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR "comment"[ti] OR "Editorial" [Publication Type] OR "ephemera"[pt] OR "in vitro techniques"[mh] OR "introductory journal article"[pt] OR (("Animals"[Mesh] OR rats[tw] OR rat[tw] OR cow[tw] OR cows[tw] OR chicken*[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep[tw] OR ovine[tw] OR murinae[tw] OR cats[tw] OR cat[tw] OR dog[tw] OR dogs[tw] OR rodent[tw]) NOT "Humans"[Mesh]))) AND (("2015/04/19"[Date - Publication] : "3000"[Date - Publication]))

EMBASE

No.	Query	Results
#34	#25 AND #32 AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [18-04-2015]/sd NOT [02-04-2023]/sd	911
#33	#25 AND #32	1,941
#32	#28 AND #29 OR #30 OR 31	257,976

#31	arthros*	84,930
#30	Degenerative AND arthriti*	8,691
#29	osteoarthros*	4,804
#28	'osteoarthritis'	184,633
#27	#18 AND #25 AND ([article]/lim OR [article in press]/lim) AND [humans]/lim	1,803
#26	#18 AND #25	3,491
#25	#19 OR #20 OR #21 OR #22 OR #23 OR #24	1,643,322
#24	'electron beam'	17,384
#23	radiatio* AND therap*	506,879
#22	radiatio* AND treatment*	457,873
#21	targeted AND radio*	71,082
#20	'radiation'	1,244,297
#19	'radiotherapy'	738,219
#18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	46,860
#17	'heterotopic ossification'	10,560
#16	heel AND spur AND syndrome	120
#15	'policeman heel'	42
#14	'plantar fasciitis'	2,780
#13	'peyronie disease'	4,914
#12	fibrous AND 'cavernitis'	1
#11	penile AND fibromatosis	35
#10	penile AND induration	444
#9	'plantar fibromatosis'	309
#8	ledderhose AND disease	179
#7	palmar AND fibromatosis	191
#6	dupuytren AND disease	5,227
#5	'dupuytren contracture'	4,088
#4	acne AND inversa	728
#3	hidradenitis AND suppurativa OR 'suppurative hidradenitis'	7,325
#2	'pterygium'	5,770
#1	'keloid'/exp OR 'keloid'	8,590

CLINICALTRIALS.GOV

Condition: (Keloid OR Pterygium OR Suppurativ* Hidradenit* OR Acne Inversa* OR Dupuytren* OR Palmar Fibromatosis OR Ledderhos* Disease OR Plantar Fibromatosis OR (Peni* AND (Fibromatosis OR Induration)) OR Fibrous Caverniti* OR Peyronie* Disease OR Plantar Fasc*) AND

Other terms: (radiation or radiotherapy)

APPENDIX B. EXCLUDED STUDIES

APPENDIX B-1. EXCLUDED STUDIES

1. Alaniz-Camino F. The use of postoperative beta radiation in the treatment of pterygia. *Ophthalmic Surg*. Dec 1982;13(12):1022-5. *At least 80% of participants treated before 1980.*
2. Bittard H, Schraub S, Bittard M. [Treatment of Peyronie's disease by a combination of radiotherapy and surgery. Apropos of 51 cases]. *Ann Urol (Paris)*. 1988;22(1):67-9. Traitement de la maladie de la peyronie par association radiochirurgicale. A propos de cinquante et un cas. *At least 80% of participants treated before 1980.*
3. Boer J. Long-Term Follow-Up after Radiotherapy of Hidradenitis Suppurativa. *Dermatology*. 2022;238(2):244-250. doi:10.1159/000517252. *At least 80% of participants treated before 1980.*
4. Campbell OR, Amendola BE, Brady LW. Recurrent pterygia: results of postoperative treatment with Sr-90 applicators. *Radiology*. Feb 1990;174(2):565-6. doi:10.1148/radiology.174.2.2296667. *At least 80% of participants treated before 1980.*
5. Hayasaka S, Noda S, Yamamoto Y, Setogawa T. Postoperative instillation of low-dose mitomycin C in the treatment of primary pterygium. *Am J Ophthalmol*. Dec 15 1988;106(6):715-8. doi:10.1016/0002-9394(88)90706-4. *At least 80% of participants treated before 1980.*
6. Miszczyk L, Jochymek B, Wozniak G. Retrospective evaluation of radiotherapy in plantar fasciitis. *Br J Radiol*. Oct 2007;80(958):829-34. doi:10.1259/bjr/79800547. *At least 80% of participants treated before 1980.*
7. Viljoen IM, Goedhals L, Doman MJ. Peyronie's disease--a perspective on the disease and the long-term results of radiotherapy. *S Afr Med J*. Jan 1993;83(1):19-20. *At least 80% of participants treated before 1980.*
8. Wilder RB, Buatti JM, Kittelson JM, et al. Pterygium treated with excision and postoperative beta irradiation. *Int J Radiat Oncol Biol Phys*. 1992;23(3):533-7. doi:10.1016/0360-3016(92)90008-6. *At least 80% of participants treated before 1980.*
9. Darzi MA, Chowdri NA, Kaul SK, Khan M. Evaluation of various methods of treating keloids and hypertrophic scars: a 10-year follow-up study. *Br J Plast Surg*. Jul 1992;45(5):374-9. doi:10.1016/0007-1226(92)90008-l. *Date of publication <= 1980.*
10. Ernst H, Besserer A, Flemming I. [Irradiation prophylaxis of keloids and cicatricial hypertrophies (author's transl)]. *Strahlentherapie*. Sep 1979;155(9):614-7. Strahlenprophylaxe von Keloiden und Narbenhypertrophien. *Date of publication <= 1980.*
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12. Narakula GK, Shenoy RK. A prospective clinical review of "multi model" approach for treating ear keloids. *Indian J Plast Surg*. Jan 2008;41(1):2-7. doi:10.4103/0970-0358.41103. *No eligible outcome reported.*
13. Tsuge T, Aoki M, Akaishi S, Dohi T, Yamamoto H, Ogawa R. Geometric modeling and a retrospective cohort study on the usefulness of fascial tensile reductions in severe keloid surgery. *Surgery*. Feb 2020;167(2):504-509. doi:10.1016/j.surg.2019.07.028. *No eligible outcome reported.*
14. Hermann RM, Trillmann A, Becker JN, Kaltenborn A, Nitsche M, Ruettermann M. Prospective evaluation of low-dose external beam radiotherapy (LD-EBRT) for painful trapeziometacarpal

osteoarthritis (rhizarthrosis) on pain, function, and quality of life to calculate the required number of patients for a prospective randomized study. *Med Sci (Basel)*. Oct 27 2021;9(4)doi:10.3390/medsci9040066. *Not disease of interest.*

15. Juniku N, Micke O, Seegenschmiedt MH, Muecke R. Radiotherapy for painful benign skeletal disorders: results of a retrospective clinical quality assessment. *Strahlenther Onkol*. Dec 2019;195(12):1068-1073. Radiotherapie bei schmerzhaften benignen muskuloskeletalen Erkrankungen : Ergebnisse einer retrospektiven klinischen Qualitätskontrolle. doi:10.1007/s00066-019-01514-w. *Not disease of interest.*
16. Kishkovskiĭ AN, Dudarev AL. [Radiotherapy in the prevention of postoperative and traumatic complications]. *Med Radiol (Mosk)*. May 1983;28(5):18-24. Luchevaia terapiia v preduprezhdenii posleoperatsionnykh i ranevykh oslozheniĭ. *Not disease of interest.*
17. Lo TC, Seckel BR, Salzman FA, Wright KA. Single-dose electron beam irradiation in treatment and prevention of keloids and hypertrophic scars. *Radiother Oncol*. Nov 1990;19(3):267-72. doi:10.1016/0167-8140(90)90153-n. *Not disease of interest.*
18. Ott OJ, Jeremias C, Gaipl US, Frey B, Schmidt M, Fietkau R. Radiotherapy for calcaneodynia. Results of a single center prospective randomized dose optimization trial. *Strahlenther Onkol*. Apr 2013;189(4):329-34. doi:10.1007/s00066-012-0256-3. *Not disease of interest.*
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treatment protocol. *Plast Reconstr Surg*. Sep 2014;134(3):527-534. doi:10.1097/prs.0000000000000415. *Not intervention of interest.*

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APPENDIX B-2. NOT EXTRACTED PER BEST EVIDENCE APPROACH

Dupuytren Contracture/Disease: 5 Exclusions

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Hetertopic Ossification: 129 Exclusions (2 Duplicates)

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Osteoarthritis: 15 Exclusions

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APPENDIX C. CRITERIA USED IN QUALITY ASSESSMENTS

APPENDIX C-1. COCHRANE RISK OF BIAS AND THE ROBINS-I FOR PRIMARY STUDIES

Question	Yes	No	Unclear
Clarity			
1. Clear reporting with no discrepancies (Y/N)			
2. Were eligibility criteria clear? (Y/N)			
3. Were interventions adequately described? (Y/N)			
4. Were the outcomes fully defined? (Y/N)			
Bias Assessment			
5. Random sequence generation: Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.			
6. Allocation concealment: Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.			
7. Blinding of participants and personnel: Performance bias due to knowledge of the allocated interventions by participants during the study.			
8. Blinding of outcome assessor (detection bias): Detection bias due to knowledge of the allocated interventions by outcome assessors.			
9. Incomplete outcome data (attrition bias): Attrition bias due to amount, nature or handling of incomplete outcome data.			
10. Selective Reporting (reporting bias): Reporting bias due to selective outcome reporting.			
11. Intention-to-treat-analysis: Bias due to incomplete reporting and analysis according to group allocation.			
12. If observational study, comparator group was sufficiently similar (and selected patients were all included or a random sample were included).			
13. If observational study, Adjustment for confounders. a. Crude analysis (unadjusted comparison between ADP and no ADP) [High RoB] b. Regression adjustment or patient-matching (accounting for at least age, sex, and symptom duration OR a risk score) [Low RoB] c. Regression adjustment or patient-matching (not accounting at least one of for age, sex, symptom duration, or risk score) [Moderate RoB] d. Propensity score analysis (or equivalent) [Low RoB]			

APPENDIX C-2. AMSTAR2

Question	Rating		
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	No	
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Partial Yes	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	No	
4. Did the review authors use a comprehensive literature search strategy?	Yes	Partial Yes	No
5. Did the review authors perform study selection in duplicate?	Yes	No	
6. Did the review authors perform data extraction in duplicate?	Yes	No	
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	Partial Yes	No
8. Did the review authors describe the included studies in adequate detail?	Yes	Partial Yes	No
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Partial Yes	No
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	No	
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	No	No meta-analysis conducted
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	No	No meta-analysis conducted
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	No	
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	No	
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	No	No meta-analysis conducted
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No	

Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

APPENDIX D. HETEROTOPIC OSSIFICATION

APPENDIX D-1. HETEROTOPIC OSSIFICATION DESIGN DETAILS

Author, Year, PMID, Protocol Number, Country	Study Design	Study Dates	Study Location Details (Hospital Type, Centers)	Intent of RT	Inclusion Criteria	Exclusion Criteria
Bremen-Kühne, 1997, 9446435, Germany	RCT	1992 - 1994	Other/unclear, Single center	Prevention of emergence	Patients at risk for HO after hip joint replacement surgery with cementless, ceramic-coated prostheses. Age 40 years or older.	Patients with contraindications for NSAIDs or radiation (including hematologic disease, ulcers, asthma and allergies, cardiac disease, neoplasms)
Burd, 2003, 12892193, USA	RCT	1992 - 2001	Teaching hospital, Single center	Prevention of emergence	Patients at risk for HO for using a posterior or extensile surgical approach or anterior surgical approach and appeared to be limited to with concomitant fractures of the femur, tibia, humerus, and/or forearm.	NR
Hamid, 2010, 20810853, USA	RCT	2005 - 2008	Other/unclear, Multicenter	Prevention of emergence	NR	Having associated injury of head, burns of >20% of the body surface area or involving the operative site, or a spinal cord injury affecting the upper extremity's function. Open fractures that could not be closed within 72 hours of the initial surgery.
Ince, 2007, 17415004, Germany	RCT and historical control	1988	Teaching hospital, Single center	Prevention of emergence	Availability of at least 4 consecutive pelvic radiographs.	NR
Kienapfel, 1999, 10447627, Germany	RCT	1992 - 1993	Teaching hospital, Single center	Prevention of emergence	Primary osteoarthritis, rheumatoid arthritis, secondary osteoarthritis due to congenital hip dysplasia or avascular necrosis of the femoral head and femoral neck fractures.	Idiopathic skeletal hyperostosis, ankylosing spondylitis, Paget's disease, acetabular or femoral stem fractures and total hip revision procedures.
Kölbl, 1997, 9392532, Germany	RCT and historical control	1993 - 1994	Other/unclear, NR/unclear	Prevention of emergence	NR	NR

Author, Year, PMID, Protocol Number, Country	Study Design	Study Dates	Study Location Details (Hospital Type, Centers)	Intent of RT	Inclusion Criteria	Exclusion Criteria
Kölbl, 1998, 9788422, Germany	RCT and historical control	1995 - 1996	Other/unclear, NR/unclear	Prevention of emergence	Total hip replacement operated because of degenerative diseases, and the risk for development of HO was low or medium.	Patients with known gastric ulcer.
Leeuwen, 1998, 9602765, Netherlands	RCT	1989 - 1992	NR/ynclear, Other/unclear	Prevention of emergence	Patients who did not use NSAIDs and were considered to be at risk for the development of ectopic bone.	NR
Moore, 1998, 9546456, USA	RCT	1993 - 1996	Teaching hospital, Single center	Prevention of emergence	Patients who required either a Kocher-Langenbeck, a combined anterior and posterior approach, or an extended iliofemoral approach for the fixation of an acetabular fracture.	Those with a history of allergy to indomethacin, an active peptic ulcer or who could not be transported for radiation.
Sell, 1998, 9880175, Germany	RCT	1992 - 1993	Teaching hospital, Single center	Primary treatment/ prevention of recurrence Prevention of emergence	NR	Any other prophylactic procedure for periarticular ossifications was excluded. Participants younger than 45 years of age and those with a previous irradiation of the extremity. Severe gastrointestinal problems (*eg*, gastrointestinal bleeding, severe ulcer) in the past were a contraindication for NSAID.

Abbreviations. HO=heterotopic ossification; NR=not reported; NSAIDs=non-steroid anti-inflammatory; PMID=PubMed ID; RCT=randomized controlled trial; RT=radiation therapy.

APPENDIX D-2. HETEROTOPIC OSSIFICATION BASELINE DATA

Author, Year, PMID	N Patients	Intervention	Age	% Male	% White	Location	HO History	Other
Bremen-Kühne, 1997, 9446435, Germany[a]	Surgery →RT = 35 (19 assessed)	THA followed by 6 Gy within 4 days	NR	38 (56)	NR	Hip	NR	
	Surgery →Indomethacin = 33 (31 assessed)	THA followed by 100 mg once, then 25 mg 3 times daily, for 10 days						
Burd, 2003, 12892193, USA	Surgery →RT = 74	ORIF followed by 8 Gy 72 hours.	38.6[b]	NR	NR	Humerus forearm Femur tibia/fibula	NR	Acetabular fracture, N (%) = 112 (100)
	Surgery →Indomethacin = 38	ORIF followed by 2 5mg 3 times daily, for 6 weeks.						
Hamid, 2010, 20810853, USA	Surgery →RT = 21	Fracture fixation followed by 7 Gy 72 hours.	44.3 (16.4)[b,c]	24 (55.6)[c]	NR	Elbow, humerus	NR	Open fracture (N=45), N (%) = 24 (53.3)[c] Fracture type (N=45), N (%) Patrial articular arcature = 16 (35.6)[c] Complete articular involvement = 29 (64.4)[c] *All patients sustained [an intraarticular distal humeral fracture or a fracture-dislocation of the elbow with proximal radial and/or ulnar fracture]*
	Surgery = 24	Fracture fixation with no prophylaxis.						
	Surgery →RT = 106	THA followed by 4 doses of 3 Gy at 2-day intervals beginning no later than the fifth	63.9 (11.3)[b,c]		NR	Hip	NR	Initial diagnosis (N=286), N (%)[c,d]

Author, Year, PMID	N Patients	Intervention	Age	% Male	% White	Location	HO History	Other
Ince, 2007, 17415004, Germany		postoperative da, total dose of 12Gy		146 (51.0) [c]				Osteoarthritis = 246 (86.0) Avascular osteonecrosis= 22 (7.7) Fracture= 6 (2.1) Developmental dysplasia of the hip= 13 (4.5)
	Surgery →Indomethacin = 98	THA followed by 2x50 mg per day with mucoprotection for 14 days beginning on the first postoperative day.						
	Surgery →Analgesia (historical control) = 82	THA followed by paracetamol, metamizole, and opioids.						
Kienapfel, 1999, 10447627, Germany	Surgery →RT = 49	THA followed by a single dose of 6 Gy 48-96 hours post-surgery.	64.7 (33-86)[c]	57 (37.0)[c]	NR	Hip	NR	
	Surgery →Indomethacin = 55	THA followed 50 mg twice a day for 42 days, post-surgery. All patients with a history of peptic ulcer, gastroduodenal haemorrhage or gastritis and those who developed dyspepsia during indomethacin medication were additionally medicated with the H2-receptor antagonist cimetidine 200 mg						
	Surgery = 50	Surgery with no prophylaxis.						
Kölbl, 1997, 9392532, Germany	Surgery →RT-5Gy = 93	THR followed by a single dose of 5 Gy within 4 days.	65.9[b]	142 (35.4) [c]	NR	Hip	Previous Brooker score 1-4, N (%)= 77 (19.2) [c]	*Most patients were operated because of degenerative diseases.*
	Surgery →RT-7Gy = 95	THR followed by a single dose of 7 Gy within 4 days.						
	Surgery → Indomethacin = 113	THR followed 2x50 mg for 7 days.						
	Surgery (historical control) = 100	THR with no prophylaxis.						
Kölbl, 1998, 9788422, Germany	RT →Surgery = 46	7 Gy 16-20 hours pre-surgery followed by THR.	65.0[b,c]	81 (40.5)[c]	NR	Hip	Previous Brooker score 1-4, N (%)= 27 (13.5)[c]	*Most patients were operated because of degenerative diseases*
	Surgery →Voltaren = 54	THR followed by 2x75 mg for 14 days with medicamentous protection of gastric mucosa, started at the first postoperative day						

Author, Year, PMID	N Patients	Intervention	Age	% Male	% White	Location	HO History	Other
	Surgery (historical control) = 100	THR with no prophylaxis.						
Leeuwen, 2009, 9602765, Netherlands	RT →Surgery = 41	5 Gy 24 hours pre-surgery followed by THA.	65.5 (24-80)[c,e]	17 (29.8)[c]	NR	Hip	NR	
	Surgery = 16	THA with no prophylaxis.						
Moore, 1998, 9546456, USA	Surgery →RT = 33	Acetabular fracture fixation followed by single dose of 8 Gy within48 hours post-surgery	45.0 (18-87)[c,e]	52 (69.3)	NR	Hip	NR	
	Surgery →Indomethacin = 39	Acetabular fracture fixation; 25 mg 24 hours pre-surgery and 25 mg daily, for 6 weeks post-surgery.						
Sell, 1998, 9880175, Germany	Surgery →RT = 76	THR followed by 3.3 Gy per fraction, total dose of 9.9 Gy completed within 8 days post-surgery.	60.8 (36-82)[c,e]	89 (58.2)[c]	NR	Hip	Brooker 1, n=1 Contralaterally Brooker 1, n=2 Brooker 2, n=1	
	Surgery →diclofenac= 77	THR followed by 3x50 mg. over a period of 3 weeks.						

Notes. [a] This study only reported per protocol data; [b] Mean (SD); [c] Values calculated by the research team based on data provided in the article; [d] Numbers are estimated based on data provided in the study; [e] Mean (range).

Abbreviations. Gy=gray; HO=heterotopic ossification; mg=milligrams; NR=not reported; NSAIDs=non-steroidal anti-inflammatory; ORIF=open reduction and internal fixation; PMID=PubMed ID; RT=radiation therapy; THA=total hip arthroplasty; THR=total hip replacement.

APPENDIX D-3. HETEROTOPIC OSSIFICATION QUALITY RATING

Author, Year, PMID, Design	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessor	Incomplete outcome data	Selective reporting	Intention-to-treat analysis	Clear reporting	Clear eligibility criteria	Interventions adequately described	Outcomes fully defined	Representativeness of the cohort	Comparator representativeness	Adjustment for confounders	Other bias	Overall RoB
Bremen-Kühne, 1997, 9446435 RCT	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	No (Low concern)	No (Low concern)	No (High concern)[a]	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	Yes (High concern)[b]	High (RCT)
Burd, 2003, 1289219, RCT	Unclear	Unclear	Yes (Low concern)	Yes (Low concern)	No (Low concern)	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	No (Low concern)	Medium (RCT)
Hamid, 2010, 2081085, RCT	Yes (Low concern)	Yes (Low concern)	Unclear	Yes (Low concern)	No (Low concern)	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	No (Low concern)	Medium (RCT)
Ince, 2007, 17415004, RCT	Yes (Low concern)	Unclear	Yes (Low concern)	Yes (Low concern)	No (Low concern)	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	No (Low concern)	Medium (RCT)
Kienapfel, 1999, 10447627, RCT	Unclear	Unclear	Unclear	Unclear	No (Low concern)	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	No (Low concern)	Medium (RCT)
Kölbl, 1997, 9392532, RCT	Unclear	Unclear	Unclear	Unclear	Unclear	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	No (Low concern)	Medium (RCT)
Kölbl, 1998, 9788422, RCT	Yes (Low concern)	Yes (Low concern)	Unclear	Unclear	No (Low concern)	No (Low concern)	Yes (Low concern)	Yes (Low concern	Yes (Low concern	Yes (Low concern	Yes (Low concern	NA	NA	NA	No (Low concern)	Medium (RCT)
Leeuwen, 1998, 9602765, RCT	Yes (Low concern)	Yes (Low concern)	Unclear	Unclear	No (Low concern)	No (Low concern)	Yes (Low concern)	Yes (Low concern	Yes (Low concern	Yes (Low concern	Yes (Low concern	NA	NA	NA	Yes (High concern)[c]	Medium (RCT)
Moore, 1998, 9546456, RCT	Yes (Low concern)	Unclear	No (High concern)	Yes (Low concern)	No (Low concern)	No (Low concern)	Unclear	Yes (Low concern	Yes (Low concern	Yes (Low concern	Yes (Low concern	NA	NA	NA	No (Low concern)	Medium (RCT)
Sell, 1998, 9880175, RCT	Yes (Low concern)	Unclear	No (High concern)	Unclear	No (Low concern)	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	No (Low concern)	Medium (RCT)

Notes. [a] No intention to treat results; [b] Only 19 out of 35 patients in the RT arm versus 31 out of 33 patients in the indomethacin arm were analyzed; [c] Unclear why patients were randomized unevenly to different treatment arms.

Abbreviations. NA=not applicable; RCT=randomized controlled trial.

APPENDIX D-4. HETEROTOPIC OSSIFICATION RESULTS SUMMARY

Author, Year, PMID	Comparison	Heterotopic Ossification at Follow-Up	Function and Pain	Side Effects	Patient Satisfaction/Experience/ QoL
Bremen-Kühne, 1997, 9446435, Germany	Surgery → RT vs Surgery → Indomethacin Follow-up (mo) = 6-12	HO grade I or II Brooker classification (N = 19 vs 31), N(%)[a,b] 6 months 9 (47.4) vs 10 (32.3) OR = 1.89 (0.58, 6.11)[b] 12 months 9 (47.4) vs 10 (32.3) OR = 1.89 (0.58, 6.11)[b] HO grade III Brooker classification (N = 19 vs 31), [12 months], N (%)[a,b] 0 (0) vs 1 (3.2) RD = -0.32 (-0.094, 0.030)[b] No grade IV in per protocol analysis	Merle d'Aubigne (pain Score) was assessed but no comparisons extractable[a]	NR	Self-assessment of outcome as "good" or "very good" (N = 19 vs 31), N(%)[a,b] Discharge 17 (89.5) vs 28 (90.3) OR = 0.91 (0.14, 6.02)[b] 12 months 15 (80.0) vs 27 (87.1) OR = 0.56 (0.12, 2.55)[b]
Burd, 2003, 12892193, USA	Surgery → RT vs Surgery → Indomethacin Follow-up (mo), Mean = 5.3	Radiologic failure (fracture nonunion) (N= 74 vs 38 patients), [mean 5.3 mo], N (%)[b] 5 (6.8) vs 11 (28.9) OR = 0.18 (0.06, 0.56)[b]			NR
Hamid, 2010, 20810853, USA	Surgery → RT vs Surgery Follow-up (mo), Mean = 7.5	Incidence of HO (N= 21 vs 24), [mean 7.5 mo], N (%)[b] 7 (33.0) vs 13 (54.0) OR = 0.42 (0.13, 1.42)[b]	MEPS (points out of scale of 100)[c] , [mean 7.5mo] 69 vs 66, p = 0.6 Mean elbow flexion, [mean 7.5 mo] 116° vs 113°, p = 0.53	Post-operative infection (N=21 vs 24), [mean 7.5 mo], N (%)[b] 2 (9.5) vs 2 (8.3) OR = 1.16 (0.15, 9.03)[b]	NR

Author, Year, PMID	Comparison	Heterotopic Ossification at Follow-Up	Function and Pain	Side Effects	Patient Satisfaction/Experience/ QoL
		Grade III-IV HO (Brooker classification) (N= 21 vs 24), [mean 7.5 mo], N (%))[b] 2 (9.5) vs 4 (16.7) OR = 0.53 (0.09, 3.22)[b] Radiologic failure (fracture nonunion) (N= 21 vs 24), [mean 7.5 mo], N (%)[b] 8 (38.1) vs 1 (4.2) OR = 14.15 (1.59, 126.13)[b] Return to operating room for heterotopic ossification excision (N = 21 vs 24), N (%)[b] 0 (0) vs 3 (12) RD = -0.125 (-0.257, 0.007)[b]	Mean elbow extension, [mean 7.5 mo] 29° vs 22°, p = 0.18 Mean pronation, [mean 7.5 mo] 71° vs 69°, p = 0.8 Mean supination, [mean 7.5 mo] 70° vs 64°, p = 0.54	Manipulation (not defined) (N= 21 vs 24), [mean 7.5 mo], N (%)[b] 0 (0) vs 3 (12) RD = -0.125 (-0.257, 0.007)[b]	
Ince, 2007, 17415004, Germany	Surgery → RT vs Surgery → Indomethacin Follow-up (mo), Mean = 56.5[b]	Incidence of HO (Brooker Classification), (N=106 vs 98), [2y], N (%)[b] HO grade 1 5 (5.0) vs 9 (8.9) OR = 0.49 (0.16, 1.52)[b] HO grade 2 0 (0.0) vs 2 (2.2) RD = -0.020 (-0.048, 0.008)[b] HO grade 3 0 (0.0) vs 1 (1.1) RD = -0.010 (-0.030, 0.010)[b] HO grade 4 Zero events in both arms HO grade 1-4	Harris Hip Score [5y], Mean (SD) 86.2 (12.5) vs 87.1 (10.8) MD -0.90 (-4.14, 2.34)[b]	Number of Implants that migrated greater than 1 mm, N (%)[b] 2 year follow-up (N=106 vs 98) 7 (6.6) vs 8 (8.1) OR = 0.08 (0.28, 2.28)[b] 5 year follow-up (N=46 vs 49), 3 (6.5) vs 4 (8.2) OR = 0.78 (0.17, 3.71)[b] Radiolucent lines greater than 1 mm (5 years), N 0 vs 4	

Author, Year, PMID	Comparison	Heterotopic Ossification at Follow-Up	Function and Pain	Side Effects	Patient Satisfaction/Experience/ QoL
		5 (5.0) vs 12 (12.2) OR = 0.35 (0.12, 1.05)[b]		*No patient underwent hip revision surgery* *No acetabular component was considered loose*	
	Surgery → RT vs Surgery → Non-NSAID Analgesia (historical control) Follow-up (mo), Mean = 59.0[b]	Incidence of HO (Brooker Classification), (N=106 vs 82), [2y], N (%)[b] HO grade 1 5 (5.0) vs 21 (26.0) OR = 0.14 (0.05, 0.40)[b] HO grade 2 0 (0.0) vs 3 (15.0) RD = -0.037 (-0.077, 0.004)[b] HO grade 3 0 (0.0) vs 16 (19.0) RD = -0.195 (-0.281, -0.109)[b] HO grade 4 0 (0.0) vs 4 (5.0) RD = -0.049 (-0.095, -0.002)[b] HO grade 1-4 5 (5.0) vs 53 (65.0) OR = 0.03 (0.01, 0.07)[b]	Harris Hip Score [5y], mean (SD) 86.2 (12.5) vs 87.0 (10.0) MD = -0.80 (-4.13, 2.53)[b]	Number of implants that migrated greater than 1 mm, N(%)[b] 2 year follow-up (N= 106 vs 82) 7 (6.6) vs 4 (4.9) OR = 1.38 (0.39, 4.88)[b] 5 year follow-up (N= 46 vs 61) 3 (6.5) vs 5 (8.2) OR = 0.78 (0.18, 3.45)[b] Radiolucent lines greater than 1 mm (5 y), N 0 vs 7 *No patient underwent hip revision surgery* *No acetabular component was considered loose*	
Kienapfel, 1999, 10447627, Germany	Surgery → RT vs Surgery Follow-up (mo) = 18	Incidence of HO (Brooker Classification), (N= 49 vs 50), [18mo], N (%)[b] HO grade 1 10 (20.4) vs 8 (16.0) OR = 1.35 (0.48, 3.76)[b] HO grade 2 2 (4.1) vs 9 (18.0)	Harris Hip Score [18 mo], Mean (range) 86.4 (67-100) vs 81.7 (47-97), p-value = NS PAHHS [18 mo], Mean (range) 68.8 (53-80) vs 64.7 (36-77), p-value = NS	Prolonged (>5 days) wound secretion, [18 mo], N (%)[b] 6 (12.2) vs 1 (2.0) OR = 6.84 (0.79, 59.07)[b] Wound dehiscence, [18mo], N (%)[b] 1 (2.0) vs 1 (2.0) OR = 1.02 (0.06, 16.79)[b]	NR

Author, Year, PMID	Comparison	Heterotopic Ossification at Follow-Up	Function and Pain	Side Effects	Patient Satisfaction/Experience/ QoL
		OR = 0.19 (0.04, 0.95)[b] HO grade 3 0 (0.0) vs 11 (22.0) RD = -0.220 (-0.335, -0.105)[b] HO grade 4 0 (0.0) vs 2 (4.0) RD = -0.040 (-0.094, 0.014)[b] HO grade 1-4 12 (24.5) vs 30 (60.0) OR = 0.22 (0.09, 0.51)[b]	IAHHS [18 mo], Mean (range) 17.5 (12-20) vs 16.9 (10-20), p-value = NS	Deep vein thrombosis [18mo], N (%)[b] 3 (6.1) vs 3 (6.0) OR = 1.02 (0.20, 5.33)[b] Dyspepsia [18mo], N (%)[b] 4 (8.2) vs 5 (10.0) OR = 0.80 (0.20, 3.17)[b] *At the time of the last follow-up, none of the arthroplasties had failed, and no revision surgery had been necessary.*	
	Surgery → RT vs Surgery → Indomethacin Follow-up (mo) = 18	Incidence of HO (Brooker Classification), (N=49 vs 55), [18 mo], N (%)[b] HO grade 1 10 (20.4) vs 17 (30.9) OR = 0.57 (0.23, 1.41)[b] HO grade 2 2 (4.1) vs 3 (5.5) OR = 0.74 (0.12, 4.61)[b] HO grade 3 and 4 Zero events in both arms HO grade 1-4 12 (24.5) vs 20 (36.4) OR = 0.57 (0.24, 1.33)[b]	Harris Hip Score, Mean (range) 86.4 (67-100) vs 85.0 (63-100), p-value = NS PAHHS, Mean (range) 68.8 (53-80) vs 67.6 (47-80), p-value = NS IAHHS, Mean (range) 17.5 (12-20) vs 17.1 (12-20), p-value = NS	Prolonged (>5 days) wound secretion [18mo], N (%)[b] 6 (12.2) vs 0 (0.0) RD = 0.122 (0.031, 0.214)[b] Wound dehiscence [18mo], N (%)[b] 1 (2.0) vs 2 (4.0) OR = 0.55 (0.05, 6.28)[b] Deep vein thrombosis [18mo], N (%)[b] 3 (6.1) vs 4 (8.0) OR = 0.83 (0.18, 3.91)[b] Dyspepsia [18mo], N (%)[b] 4 (8.2) vs 15 (30.0) OR = 0.24 (0.07, 0.77)[b] *At the time of the last follow-up, none of the arthroplasties*	NR

Author, Year, PMID	Comparison	Heterotopic Ossification at Follow-Up	Function and Pain	Side Effects	Patient Satisfaction/Experience/ QoL
				had failed, and no revision surgery had been necessary.	
Kölbl, 1997, 9392532, Germany	Surgery → RT-5 vs Surgery → Indomethacin Follow-up (mo) = 0-12	Incidence of HO (Brooker Classification), (N= 93 vs 113), [3-12 mo], N (%)[b] HO grade 1 23 (24.7) vs 9 (8.0) OR = 3.80 (1.66, 8.69)[b] HO grade 2 4 (4.3) vs 7 (6.2) OR = 0.68 (0.19, 2.40)[b] HO grade 3 1 (1.1) vs 2 (1.7) OR = 0.60 (0.05, 6.76)[b] HO grade 4 Zero events in both arms. HO grade 1-4 28 (30.1) vs 18 (15.9) OR = 2.27 (1.16, 4.45)[b]		NR	NR
	Surgery → RT-5 vs Surgery (historical control) Follow-up = Immediately after, 3, and 12 mo post-therapy	Incidence of HO (Brooker Classification), (N= 93 vs 100), [3-12 mo], N (%)[b] HO grade 1 23 (24.7) vs 26 (26.0) OR = 0.94 (0.49, 1.79)[b] HO grade 2 4 (4.3) vs 15 (15.0) OR = 0.25 (0.08, 0.80)[b] HO grade 3 1 (1.1) vs 19 (19.0)			

Author, Year, PMID	Comparison	Heterotopic Ossification at Follow-Up	Function and Pain	Side Effects	Patient Satisfaction/Experience/ QoL
		OR = 0.05 (0.01, 0.35)[b] HO grade 4 0 (0.0) vs 5 (5.0) RD = -0.050 (-0.093, -0.007)[b] HO grade 1-4 28 (30.1) vs 65 (65.0) OR = 0.23 (0.13, 0.42)[b]			
	Surgery → RT-7 vs Surgery → Indomethacin Follow-up = Immediately after, 3, and 12 mo post-therapy	Incidence of HO (Brooker Classification), (N=95 vs 113), [3-12 mo], N (%)[b] HO grade 1 11 (11.6) vs 9 (8.0) OR = 1.51 (0.60, 3.82)[b] HO grade 2 0 (0.0) vs 7 (6.2) RD = -0.062 (-0.106, -0.018)[b] HO grade 3 0 (0.0) vs 2 (1.7) RD = -0.018 (-0.042, 0.007)[b] HO grade 4 Zero events in both arms. HO grade 1-4 11 (11.6) vs 18 (15.9) OR = 0.69 (0.31, 1.55)[b]			
	Surgery → RT-7 vs Surgery (historical control)	Incidence of HO (Brooker Classification), (N=95 vs 100), [3-12 mo], N (%)[b] HO grade 1 11 (11.6) vs 26 (26.0)			

Author, Year, PMID	Comparison	Heterotopic Ossification at Follow-Up	Function and Pain	Side Effects	Patient Satisfaction/Experience/ QoL
	Follow-up= Immediately after, 3, and 12 mo post-therapy	OR = 0.37 (0.17, 0.81)[b] HO grade 2 0 (0.0) vs 15 (15.0) RD = -0.150 (-0.220, -0.080)[b] HO grade 3 0 (0.0) vs 19 (19.0) RD = -0.190 (-0.267, -0.113)[b] HO grade 4 0 (0.0) vs 5 (5.0) RD = -0.050 (-0.093, -0.007)[b] HO grade 1-4 11 (11.6) vs 65 (65.0) OR = 0.07 (0.03, 0.15)[b]			
Kölbl, 1998, 9788422, Germany	RT → Surgery vs Surgery → Voltaren Follow-up= Immediately after, 3, and 6 mo post-therapy	Incidence of HO (Brooker Classification), (N=46 vs 54), [3-6 mo], N (%) HO grade 1 17 (36.9) vs 5 (9.3) OR = 5.74 (1.92, 17.22) HO grade 2 4 (8.7) vs 1 (1.8) OR = 0.42 (0.12, 1.44) HO grade 3 1 (2.2) vs 0 (0.0) RD = 0.022 (-0.020, 0.064) HO grade 4 Zero events in both arms.		Gastrointestinal side effects (not specified) leading to termination of therapy, N (%) 0 (0) vs 3 (5.6) RD = -0.056 (-0.117, 0.006)	NR

Author, Year, PMID	Comparison	Heterotopic Ossification at Follow-Up	Function and Pain	Side Effects	Patient Satisfaction/Experience/ QoL
		HO grade 1-4 22 (47.8) vs 6 (11.1) OR = 7.33 (2.63, 20.48)			
	RT → Surgery vs Surgery (historical control) Follow-up = Immediately after, 3, and 6 mo post-therapy	Incidence of HO (Brooker Classification), (N=46 vs 100), [3-6 mo], N (%)[b] HO grade 1 17 (36.9) vs 26 (26.0) OR = 1.67 (0.79, 3.52)[b] HO grade 2 4 (8.7) vs 15 (15.0) OR = 0.54 (0.17, 1.73)[b] HO grade 3 1 (2.2) vs 19 (19.0) OR = 0.09 (0.01, 0.73)[b] HO grade 4 0 (0.0) vs 5 (5.0) RD = -0.050 (-0.093, -0.007)[b] HO grade 1-4 22 (47.8) vs 65 (65.0) OR = 0.49 (0.24, 1.00)			
Leeuwen, 2009, 9602765, Netherlands	RT → Surgery vs Surgery Follow-up (mo), Mean (range)= 31 (19-62)	Prevalence of HO (Brooker Classification), (N=43 vs 19), [mean ≈31mo], N (%)[b] HO grade 1 5 (11.6) vs 4 (21.1) OR = 0.49 (0.12, 2.09)[b] HO grade 2 0 (0.0) vs 4 (21.1) RD = -0.211 (-0.394, -0.027)[b]		*One patient in the radiation group had a superficial wound infection.* No other side effects reported.	

Author, Year, PMID	Comparison	Heterotopic Ossification at Follow-Up	Function and Pain	Side Effects	Patient Satisfaction/Experience/ QoL
		HO grade 3 1 (2.3) vs 5 (26.3) OR = 0.07 (0.01, 0.62)[b] HO grade 4 0 (0.0) vs 3 (15.8) RD = -0.158 (-0.322, 0.006)[b] HO grade 1-4 6 (14.0) vs 16 (84.2) OR = 0.03 (0.01, 0.14)[b]			
Moore, 1998, 9546456, USA	Surgery → RT vs Surgery → Indomethacin Follow-up (mo), Mean (range) = 11.9[b] (6-48)	Incidence of HO (Brooker Classification) (N= 34 vs 41), [6-48mo], N (%)[b] HO grade 1 4 (12.1) vs 5 (12.8) OR = 0.94 (0.23, 3.82)[b] HO grade 2 2 (6.1) vs 6 (15.4) OR = 0.35 (0.07, 1.89)[b] HO grade 3 3 (9.1) vs 5 (12.8) OR = 0.68 (0.15, 3.09)[b] HO grade 4 0 (0.0) vs 2 (5.1) RD = -0.049 (-0.115, 0.017)[b] HO grade 1-4 9 (27.3) vs 18 (46.2) OR = 0.44 (0.16, 1.18)[b]		NR	NR

Author, Year, PMID	Comparison	Heterotopic Ossification at Follow-Up	Function and Pain	Side Effects	Patient Satisfaction/Experience/ QoL
Sell, 1998, 9880175, Germany	Surgery → RT vs Surgery → diclofenac Follow-up (mo) = 0.5, 3, and 6	Incidence of HO (Brooker Classification), (N=76 vs 77), [6mo], N (%)[b] HO grade 1 2 (2.6) vs 16 (20.8) OR = 0.10 (0.02, 0.47)[b] HO grade 2 0 (0.0) vs 2 (2.6) RD = -0.026 (-0.062, 0.010)[b] HO grade 3 and 4 Zero events in both arms HO grade 1-4 (Brooker Classification) [6mo] 2 (2.6) vs 18 (23.4) OR = 0.09 (0.02, 0.40)[b]		Reddening of wound [time not specified], N (%)[b] 3 (3.9) vs 1 (1.3) OR = 3.12 (0.32, 30.72)[b] Hematoma formation [time not specified], N (%)[b] 6 (7.9) vs 7 (9.1) OR = 0.86 (0.27, 2.68)[b] Staphylococcus epidermidis infection necessitating fistula revision [time not specified], N (%)[b] 1 (1.3) vs 0 (0) RD = 0.013 (-0.012, 0.039)[b] Wound dehiscence [time not specified], N (%)[b] 9 (11.8) vs 5 (6.5) OR = 1.93 (0.62, 6.06)[b] Gastrointestinal side effects (not specified) after the first week that caused discontinuation of treatment, N (%)[b] 0 (0) vs 11 (14.3) RD = -0.143 (-0.221, -0.065)[b] *There was no evidence of loosening of the prosthesis in any patient.* *There was no evidence that radiation had caused any*	NR

Author, Year, PMID	Comparison	Heterotopic Ossification at Follow-Up	Function and Pain	Side Effects	Patient Satisfaction/Experience/ QoL
				negative side effects in the region of the femoral component or the acetabulum.	

Notes. [a] Per protocol analysis; [b] Values calculated by the research team based on data provided in the article; [c] Mayo Elbow Performance Score (MEPS). This outcome tool is based on a 100-point scale, which measures pain (45 points), stability (10 points), function (25 points), and motion (20 points).

Abbreviation. HO=heterotopic ossification; IAHHS=investigator-assessed Harris Hip Score; MD=mean difference; MEPS=Mayo Elbow Performance Score; mm=millimeter; NR=not reported; mo=months; NSAID=non-steroidal anti-inflammatory; OR=odds ratio; PAHHS=patient-assessed Harris Hip Score; PMID=PubMed ID; QoL=quality of life; RT=radiation therapy; SD=standard deviation; unadOR=unadjusted odds ratio; unadRD=unadjusted risk difference; y=years.

APPENDIX E. KELOIDS

APPENDIX E-1. KELOIDS DESIGN DETAILS

Author, Year, PMID, Protocol Number, Country	Study Design	Study Dates	Study Location Details (Hospital Type, Centers)	Intent of RT	Inclusion Criteria	Exclusion Criteria
Akinbiyi, 2021, 32878694, USA	NRCS	2008 - 2017	Single center, teaching hospital	Primary treatment/prevention of recurrence	Adults with ICD-10 codes corresponding to keloid who were treated by physicians in the plastic surgery or dermatology departments.	<1 year follow-up and those treated with other oral or topical agents (for medical management group)
Aluko-Olokun, 2014, Nigeria	RCT	2005 - 2006	Single center other/unclear	Primary treatment/prevention of recurrence	NR	Infected or ulcerated lesions, chronic inflammatory conditions (*eg*, tuberculosis and other chronic granulomatous conditions), children under 6 years of age, pregnancy, immunosuppressive state, high blood pressure, glaucoma, epilepsy, Myasthenia gravis, cancer, and non-consenting patients
Khalid, 2018, 29534885, Pakistan	RCT	2014 - 2015	Teaching hospital, single center	Primary treatment/prevention of recurrence	12-65y	Treatment in the last 6 months, history of renal or liver disease, and being pregnant or lactating
Li, 2022, 36582847, China	RCT	2021 - 2021	Teaching hospital, single center	Primary treatment/prevention of recurrence	Age 18–70, did not experience any keloid treatment within 3 months, lesions without progression within 3 months, and assessed by the VSS with a score more than 4 and less than 13.	Pregnancy and lactation, systemic disease or tumor, infection of lesions, allergic to corticosteroids or 5-FU
Qiao, 2017, 29798227, China	NRCS	2007 - 2016	Teaching hospital/other/unclear, single center	Primary treatment/prevention of recurrence	Patients with ear scars admitted to Shanxi Provincial People's Hospital	NR

Author, Year, PMID, Protocol Number, Country	Study Design	Study Dates	Study Location Details (Hospital Type, Centers)	Intent of RT	Inclusion Criteria	Exclusion Criteria
Sclafani, 1996, 8646474, USA	RCT	1991 - 1996	Teaching hospital, single center	Primary treatment/prevention of recurrence	Keloid patients seen from Oct 1991-Dec 1992 at the New York Eye & Ear Infirmary with ear keloid.	Patients who had previously received radiation therapy to the head and neck region.

Abbreviations. NRCS=non-randomized study; NR=not reported; RCT=randomized controlled trial; VSS=Vancouver Scar Scale; PMID=PubMed ID; RT=radiation therapy; ICD=International Classification of Diseases; 5-FU=5-fluoracil.

APPENDIX E-2. KELOIDS BASELINE DATA

Author, Year, PMID	N Patients	Intervention	N Lesions	Age	N (%) Male	N (%) White	Keloid Characteristics				
							Location	Etiology	Lesion Age (Years)	Size	Other
Akinbiyi, 2021, 32878694	Surgical excision → RT = 95	3-8 Gy per fraction, total dose of 9-32 Gy, 24-48 hours post-excision involving 3-4 sessions on consecutive days	NR	37.2 (19.9)[a,b]	64[a] (33.9)	30[a] (15.9)	Head, Neck, Back, Upper Torso Lower Torso, Upper extremity, Lower extremity	NR	NR	Size of keloid (cm), median (IQR) surgical excision +RT (median, IQR) = 13.8 (6.7, 40.0) Surgical excision (median, IQR) = 6.1 (2.7, 15.0)	Recurrent keloids (at baseline), N (%) = 82 (43.3)[a] History of keloids, N (%) = 115 (60.8)[a]
	Surgical excision = 94	Keloid local excision with or without prior or concurrent corticosteroid therapy, but without radiation therapy									

Author, Year, PMID	N Patients	Intervention	N Lesions	Age	N (%) Male	N (%) White	Keloid Characteristics				
							Location	Etiology	Lesion Age (Years)	Size	Other
Aluko-Olokun, 2014	Surgical excision → RT = 53	One fraction pre-excision, 4 Gy pre-excision, 4 Gy per fraction, total dose of 16 Gy, 3 days post-excision	NR	27.1[a,b]	59[a] (55.1)	NR	Pinna, Cheek, Forehead, Submandibular, Lip	NR	NR	Pretreatment height (mm), mean = 7.5[a]	
	Triamcinolone = 54	Intralesional injections of 10 mg/cm of lesion for a maximum of 6 months									
Khalid, 2018, 29534885	Surgical excision → RT = 30	10 Gy in 2 fractions, total dose of 20 Gy, starting within 24 hours post-excision	60	31.8 (6.6)[a,b]	16 (26.7)[a,b]	NR	Ear 60(100): Lobule only = 38(63.3)[a]; Lobule and helix = 12 (20)[a]	Related to ear piercing, N (%) = 42 (70)[a]	4.7[a]	Size of scar: 5-FU+TAC= 2.3+ 0.98 cm RT = 2.5+ 1.10cm	Previous treatments Either (excision or intralesional injections), N (%) = 22 (36.67)[a]
	Surgical excision → 5-FU + triamcinolone acetonide = 30	Intralesional injections of 150 mg in a monthly interval or until cure									
Li, 2022, 36582847	Surgical excision → RT = 17	3.5-4 Gy per fraction starting within 24 hours of surgery and on the second, third- and fourth-days post-excision, total dose of 14-16 Gy	NR	32.2 (18.3)[a,b]	18 (32.8)[a]	NR	Head and face, trunk, limbs	Acne, folliculitis, surgery, injury, spontaneous	6.3 (5.8)[a,b]	NR	Previous therapy, N (%) = 30 (54.5)[a] Family history, N (%) = 49 (89.1)[a]
	Surgical excision → 5-FU + betamethasone = 18	Injections of 2 mL 5-FU, 1 mL betamethasone, and 1 mL lidocaine immediately after excision and every 4 weeks post-excision, total of 4 injections									
	5-FU + betamethasone = 20	Intralesional injections of 2 mL 5-FU, 1 mL betamethasone, and 1 mL lidocaine every 4 weeks, total of 4 injections									

Author, Year, PMID	N Patients	Intervention	N Lesions	Age	N (%) Male	N (%) White	Keloid Characteristics				
							Location	Etiology	Lesion Age (Years)	Size	Other
Qiao, 2017, 29798227	Surgical excision = 40	Keloid local excision	NR	NR	25.1	NR	Earlobe, helix, and the whole pinna	Ear piercing, trauma, ear surgery	1-15[c]	NR	
	Surgical excision → diprosone = 40	Corticosteroid injection locally during excision									
	Surgical excision → RT = 40	5Gy per fraction, total dose of 15Gy, post-excision									
	Surgical excision → RT + diprosone = 40	Corticosteroid injection locally during excision. 5 Gy per fraction, total dose of 15 Gy, post-excision.									
Sclafani, 1996, 8646474	Surgical excision → RT = 16	7-10 Gy per fraction and a single dose, 3 hours post-excision. Patients were instructed to apply Bacitracin ointment to the wound three times daily for 10 days. Patients were advised not to have their ears repierced.	28	28.4[a,b]	4 (14.3)[a]	1 (3.6)[a]	Ear Lobule only = 25 (89.3)[a]; Lobule and helix = 3 (10.7)[a]	Piercing	1.6[a,b]	NR	Previous steroid or surgery, N (%): 19 (67.9)[a]
	Surgical excision → Triamcinolone acetate = 12	Intralesional injections of 0.4 cc immediately after wound closure and on days 7, 21, and 35 post-excision. Patients were instructed to apply Bacitracin ointment to the wound three times daily for 10 days. Patients were advised not to have their ears repierced.									

Notes. [a] Values calculated by the research team based on data provided in the article; [b] Mean (SD); [c] Range.

Abbreviations. 5-FU=5-fluorouracil; cc=cubic centimeter; cm=centimeters; Gy=gray; IQR=interquartile range; mg=milligrams; mL=milliliter; NR=not reported; PMID=PubMed ID; RT=radiation therapy.

APPENDIX E-3. KELOIDS QUALITY RATING

Author, Year, PMID, Design	Random sequence generation	Allocation concealment	Blinding of participants or study personnel	Blinding of outcome assessor	Incomplete outcome data	Selective reporting	Intention-to-treat analysis	Clear reporting	Clear eligibility criteria	Interventions adequately described	Outcomes fully defined	Representativeness of the cohort	Comparator representativeness	Adjustment for confounders	Other bias	Overall RoB
Akinbiyi, 2021, 3287869, NRCS	NA	NA	NA	Unclear	No (Low concern)	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Unclear	Yes (Low concern)	No (High concern)[a]	No (Low concern)	High (NRCS)
Aluko-Olokun, 2014, RCT	No (Low concern)	No (High concern)	No (High concern)	Unclear	No (Low concern)	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	No (Low concern)	Medium (RCT)
Khalid, 2018, 2953488, RCT	No (Low concern)	Yes (Low concern)	No (High concern)	Unclear	No (Low concern)	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	No (Low concern)	Medium (RCT)
Li, 2022, 3658284, RCT	No (Low concern)	No (High concern	No (High concern)	Unclear	No (Low concern)	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	No (Low concern)	Medium (RCT)
Qiao, 2017, 2979822, NRCS	NA	NA	NA	Unclear	No (Low concern)	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	No (High concern)[a]	No (Low concern)	High (NRCS)
Sclafani, 1996, 8646474, RCT	Unclear	Unclear	No (High concern)	Unclear	Yes (High concern)[b]	No (Low concern)	No (High concern)[b]	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	No (Low concern)	High (RCT)

Notes. [a] Crude analysis; [b] 48% of patients were lost to follow-up and analysis included only those with complete follow-up.
Abbreviations. NA=not applicable; NRCS=non-randomized controlled study; RCT=randomized controlled trial.

APPENDIX E-4. KELOIDS RESULTS SUMMARY

Author, Year, PMID	Comparison	Recurrence, Persistence, Effectiveness, or Pain	Side Effects	Cosmetic Outcomes and Skin Condition	Patient Satisfaction/Experience/ QoL
Akinbiyi, 2021, 32878694	Surgical excision → RT vs Surgical excision Follow-up (mo), Median (IQR) = 15.4 months (IQR: 5.6-30.7)	**Recurrence (undefined) (N=94 vs 95), [Median 15.4 mo], N (%)**[a] 35 (37.9) vs 36 (37.2) *U*nadOR = (95% CI) = 1.03 (0.57, 1.85)[a]	**Complication (undefined)) (N=94 vs 95), [Median 15.4 mo], N (%)**[a] 17 (17.9) vs 6 (6.3) *U*nadOR = (95% CI) = 3.88 (1.37, 11.00)[a]	NR[b]	NR
Aluko-Olokun, 2014	Surgical excision → RT vs Triamcinolone Follow-up (wk) = 26	**Recurrence or persistence (flattened lesion swells above invades normal skin) (N= 53 vs 54), [14-26 weeks], N (%)** 22 (41.5) vs 10 (18.5) OR = (95% CI) = 3.12 (1.30, 7.51)[a]	**Complications (undefined) (N=53 vs 54), [14-26 weeks], N (%)** 31 (58.5) vs 30 (55.6) OR = (95% CI) = 1.13 (0.52, 2.42)[a]	**Cosmetic Outcomes and Skin conditions (Complications) (N=53 vs 54), [14-26 weeks], N (%)**[a] Hyperpigmentation 6 (11.3) vs 8 (14.8) OR = (95% CI) = 0.73 (0.24, 2.28)[a] Hypopigmentation 0 (0.0) vs 25 (46.3) RD = (95% CI) = -0.463 (-0.596, -0.330)[a] Skin atrophy 0 (0.0) vs 8 (14.8) RD = (95% CI) = (95% CI) = -0.148 (-0.243, -0.053)[a] Pruritus 30 (56.6) vs 0 (0.0) RD = (95% CI) = *0.566* (0.431, 0.699)[a] Tenderness 8 (15.1) vs 0 (0.0) RD = (95% CI) = *0.151* (0.055, 0.247)[a] Ulceration 0 (0.0) vs 14 (25.9)	NR

Author, Year, PMID	Comparison	Recurrence, Persistence, Effectiveness, or Pain	Side Effects	Cosmetic Outcomes and Skin Condition	Patient Satisfaction/Experience/ QoL
				RD = (95% CI) = -0.259 (-0.376,-0.142)[a] Telangiectasia 0 (0.0) vs 8 (14.8) RD = (95% CI) = -0.148 (-0.243, -0.053)[a]	
Khalid, 2018, 29534885	Surgical excision → RT vs Surgical excision → 5-FU + TAC Follow-up (mo), Median= 19 vs 20	**Recurrence (undefined) (N=30 vs 30), [6 mo], N (%)** 17 (56.7) vs 8 (26.7)[a] OR = (95% CI)= 3.60 (1.22, 10.64)[a]	**Epidermolysis and later wound dehiscence (N=30 vs 30), N (%)** 0 (0) vs 2 (6.67) RD = (95% CI)= *-0.067 (-0.156, 0.023)* **Skin redness (N=30 vs 30), N (%)** 3 (10) vs 0 (0) RD = (95% CI)= *0.100 (-0.007, 0.207)*[a]	NR	NR
Li, 2022, 36582847	Surgical excision → RT vs 5-FU + betamethasone Follow-up (mo), Median= 10 vs 9	**Recurrence (pruritus or pain increased, keloid appearing again and exceeding the original range) (N=17 vs 20), [8-12 mo], N (%)** 1 (5.9) vs 4 (20.0) OR = (95% CI)= 0.25 (0.03, 2.49)[a] **Pain (POSAS-PSAS) (N=17 vs 20), [4 mo], Mean (SD)** 1.7 (1.6) vs 1.7 (1.5) MD = 0.00 (-1.04, 1.04)[a]	*There was none of the malignant transformation or systemic side effects.*	**Cosmetic Outcomes and Skin conditions (Adverse side effects) (N=17 vs 20), [4 mo] , N (%)**[a] Hyperpigmentation 5 (29.4) vs 1 (5.0) OR = (95% CI) = 7.92 (0.82, 76.28)[a] Hypopigmentation 0 (0.0) vs 0 (0.0) Scab 1 (5.9) vs 3 (15.0) OR = (95% CI) = 0.35 (0.03, 3.77)[a] Telangiectasia 4 (23.5) vs 1 (5.0) OR = (95% CI) = 5.58 (0.58, 58.43)[a]	

Author, Year, PMID	Comparison	Recurrence, Persistence, Effectiveness, or Pain	Side Effects	Cosmetic Outcomes and Skin Condition	Patient Satisfaction/Experience/ QoL
				Appearance (VSS), Mean (SD) 4.24 (1.48) vs 6.10 (1.17) MD = -1.86 (-2.75, -0.98)[a] Pruritus (POSAS-PSAS), Mean (SD) 2.3 (2.4) vs 2.08 (1.39) MD = (95%CI) = 0.22 (-1.07, 1.51)[a] **POSAS-OSAS (N=17 vs 20), [4 mo], Mean (SD)** 18.53 (6.15) vs 23.35 (3.95) MD = -4.82 (-8.22, -1.42)[a] **POSAS-PSAS (N= 17 vs 20), [4 mo], Mean (SD)** 16.83 (4.45) vs 28.8 (7.38) MD = -11.75 (-15.9, -17.59)[a]	
	Surgical excision → RT vs Surgical excision → 5-FU + betamethasone Follow-up (mo), Median= 10 vs 9	**Recurrence (pruritus or pain increased, keloid appearing again and exceeding the original range) (N=17 vs 18), [8-12 mo], N (%)** 1 (5.9) vs 2 (11.1) OR = (95% CI) = 0.50 (0.04, 6.08)[a] **Pain (POSAS-PSAS) (N=17 vs 18), [4 mo], Mean (SD)** 1.7±1.6 vs 1.3±0.8 MD = 0.4 (-0.46, 1.26)[a]	*There was none of the malignant transformation or systemic side effects*.	**Cosmetic Outcomes and Skin conditions (Adverse side effects) (N=17 vs 18), [4 mo] , N (%)[a]** Hyperpigmentation 5 (29.4) vs 2 (11.1) OR = (95% CI) = 3.33 (0.55, 20.22)[a] Hypopigmentation 0 (0.0) vs 1 (5.6) RD = (95% CI) = -0.056 (-0.161, 0.050)[a] Scab 1 (5.9) vs 3 (16.7) OR = (95% CI) = 0.31 (0.03, 3.34)[a] Telangiectasia	

Author, Year, PMID	Comparison	Recurrence, Persistence, Effectiveness, or Pain	Side Effects	Cosmetic Outcomes and Skin Condition	Patient Satisfaction/Experience/ QoL
				4 (23.5) vs 2 (11.1) OR = (95% CI) = 2.46 (0.39, 15.63)[a] Appearance (VSS), Mean (SD) 4.24 (1.48) vs 4.56 (2.06), MD = -0.32 (-1.56, 0.92)[a] Pruritus (PSAS), Mean (SD) 2.3 (2.4) vs 2.1 (1.8) MD = (95%CI) = 0.2 (-1.25, 1.65)[a] **POSAS-OSAS (N=17 vs 18), [4 mo], Mean (SD)** 18.53 (6.15) vs 18.5 (6.12), MD = 0.03 (-4.19, 4.25) **POSAS-PSAS (N=17 vs 18), [4 mo], Mean (SD)** 16.83 (4.45) vs 20.7 (7.6) MD = -3.87 (-8.19, 0.45)[a]	
Qiao, 2017, 29798227	Surgical excision → RT vs Surgical excision Follow-up (mo) = 12	**Ineffectiveness (Dariz Criteria) (N=40 vs 40), N (%)** 7 (17.5) vs 19 (47.5)[a] UnadOR = (95% CI) = 0.23 (0.08, 0.65)[a]	NR	NR	-
	Surgical excision → RT vs Surgical excision → corticoid Follow-up (mo) = 12	**Ineffectiveness (Dariz Criteria) (N=40 vs 40), N (%)** 7 (17.5) vs 8 (20.0)[a] UnadOR = (95% CI) = 0.85 (0.28, 2.61)[a]	NR	NR	
	Surgical excision → RT vs Surgical excision → RT + corticoid	**Ineffectiveness (Dariz Criteria) (N=40 vs 40), N (%)** 7 (17.5) vs 1 (2.5)[a] UnadOR = (95% CI) = 8.27 (0.97, 70.74)[a]	NR	NR	

Author, Year, PMID	Comparison	Recurrence, Persistence, Effectiveness, or Pain	Side Effects	Cosmetic Outcomes and Skin Condition	Patient Satisfaction/Experience/ QoL
	Follow-up (mo) = 12				
Sclafani, 1996, 8646474	Surgical excision → RT vs Surgical excision → Triamcinolone Follow-up (mo), Median = 18	**Recurrence (Any visible or palpable nodularity to the scar) (N=16 vs 12), [Median 18 mo], N (%)** 2 (12.5) vs 4 (33.0) OR = (95% CI) = 0.29 (0.04, 1.92)[a]	NR	NR	-

Notes. [a] Values calculated by the research team based on data provided in the article; [b] Data were only available for the medical management arm so were not extracted.

Abbreviations. 5-FU=5-fluorouracil; CI=confidence interval; Gy=gray; IQR=interquartile range; mo=months; NR=not reported; POSAS=Patient and Observer Assessment Scale; PSAS=patient assessment scale; QoL=quality of life; RT=radiation therapy; SD=standard deviation; TAC=triamcinolone acetonide; OSAS=observer assessment scale; UnadMD=unadjusted mean difference; UnadOR=unadjusted odds ratio; UnadRD=unadjusted risk difference; VSS=Vancouver Scar Scale.

APPENDIX F. PLANTAR FASCIITIS

APPENDIX F-1. PLANTAR FASCIITIS DESIGN DETAILS

Author, Year, PMID, Protocol Number, Country	Study Design	Study Dates	Study Location Details (Hospital Type, Centers)	Intent of RT	Inclusion Criteria	Exclusion Criteria
Gogna, 2016, 27521483 India	RCT	NR	Teaching hospital	Primary treatment/ prevention of recurrence	Patients who were diagnosed with plantar fasciitis and failed conservative treatment (activity modification, ice packs, NSAIDs, orthotics, and plantar fascia and tendoachilles stretching) for 6 months were identified and included in the study.	Patients with diabetes mellitus, gout, generalized inflammatory arthritis (Rheumatoid arthritis, Ankylosing spondylitis, Psoriatic arthritis), malignancy, pregnancy, bleeding diathesis, radiculopathy, and those who had received local steroid injections within the last 6 months
Canyilmaz, 2015, 25936814 Turkey	RCT	2013-2014	Teaching hospital	Primary treatment/ prevention of recurrence	Patients were included if they met the following criteria: (1) symptoms and clinical diagnosis of a painful heel spur; (2) duration of symptoms longer than 6 months; (3) radiologically proven heel spur; (4) Karnofsky performance status 70; and (5) age 40 years	Patients who had previous radiation therapy, trauma to the foot, severe psychiatric disorders, rheumatic and/or vascular diseases, or were pregnant or breastfeeding
Aynaci, 2021 Turkey	NRCS	2013-2017	Teaching hospital	Primary treatment/ prevention of recurrence	Confirmed diagnosis of PF with Karnofsky performance status ≥70, presenting with pain and/or mobility restrictions	Trauma to the foot, severe psychiatric disorders, rheumatic and/or vascular diseases, and pregnancy or breastfeeding
Rudat 2021, 33502569 Germany	Single group	2009-2020	Other/unclear	Primary treatment/ prevention of recurrence	Patients treated with LD-EBRT for painful plantar heel spurs during the study dates	Patients with a previous LD-EBRT for painful PCS
Hermann 2013 24120823 Germany	Single group	2007-2009	Other/unclear	Primary treatment/ prevention of recurrence	Localized plantar heel pain, irrespective of its radiologic evidence, not undergone surgery or radiation therapy within the previous 3 years	NR

Abbreviations. LD-EBRT=low-dose external beam radiotherapy; NSAID=non-steroidal anti-inflammatory; NRCS=nonrandomized comparative study; NR=not reported; RCT=randomized controlled trial; RT=radiation therapy; mo=month; PMID=PubMed ID; PCS=plantar calcaneal spurs.

APPENDIX F-2. PLANTAR FASCIITIS BASELINE DATA

Author, Year, PMID	N Patients	Intervention	N Lesions	Age Mean(SD)	N (%) Male	N (%) White	Lesion Characteristics				
							Location	Lesion Age	Size (mm)	Previous Treatment	Other
Gogna, 2016, 27521483	RT = 20	Total of 3.0 Gy radiation applied as 0.5 Gy twice weekly	NR	27.58 (NR)[a]	16 (65)[a]	NR	Foot	>6 mo	NR	All failed conservative treatment for 6 mo	All sports persons
	Plasma = 20	Platelet Rich Plasma									
Canyilmaz, 2015, 25936814	RT = 60	6 fraction of 1 Gy 3x per week for 2 weeks for a total dose of 6 Gy using a 6 mv photon beam of a linear accelerator	NR	Mean (range) = 53.65 (40-74)[a,b]	27 (21.8)[a]	NR	Plantar = 83 (66.9)[a] Dorsal = 20 (16.1)[a] Both = 21 (16.9)[a]	Pain duration (mo), Mean (SD): 16.3 (6-48)[a] Duration of pain (mo), N (%)[a] ≤6 = 34 (27.4) >6 = 90 (72.6)	NR	Previous treatment, N (%)[a] Ice/heat= 13 (10.5) Extracorporeal shock wave = 26 (21.0) Oral medication = 17 (13.7) Injection = 38 (30.7) Insole support t = 21 (16.9) Ultrasound application = 9 (7.3) *All had recurrent symptoms after previous conservative treatments.*	
	Palpation-guided steroid injection = 64	40 mg methylprednisolone mixed with 0.5ml of 1% lidocaine									
Aynaci[c], 2021	Extracorporeal shock-wave therapy = 73	2000 (11 times per sec) shockwave impulses (20 MHz) at 3 bar air pressure were delivered using a 16-mm head, carried out in 5 sessions with weekly intervals.	NR	Mean (range) = 50.4 (26-78)[b]	15 (20.5)[c]	NR	Plantar = 36 (49.3) Dorsal = 2 (2,7) Both = 3 (4.1) Achillodynia = 12 (16.4) Calcaneodynia = 20 (27.4)	Duration of pain (mo), Mean (range) = 16,4 (1-96) Duration of pain (mo), N (%) ≤6 = 21 (29.2) >6 = 52 (70.8)	NR	*All patients had received various treatments previously.*	

Author, Year, PMID	N Patients	Intervention	N Lesions	Age Mean(SD)	N (%) Male	N (%) White	Lesion Characteristics				
							Location	Lesion Age	Size (mm)	Previous Treatment	Other
Rudat 2021, 33502569	RT = 666	LD-EBRT: 0.5 Gy 3 times a week to a total of 3.0 Gy or 1 Gy 3 times a week to a total of 6.0 Gy	864	56.9 (20-95)	217 (32.6)	NR	Treatment, N (%) Bilateral (concomitantly) = 123 (18.5) Right and left heel sequentially 79 (11.9) Right heel = 223 (33.5) Left heel = 241 (36.2)	History of pain before RT (heels) (mo), N (%) <6 = 285 (40.7) 6–12 = 242 (34.5) >12 = 174 (24.8%)	NR	*Most patients received multiple conservative treatments before referral to [radiotherapy].*	Re-irradiation 3 mo after previous RT treatment Re-RT1 = 238 Re-RT2 = 48 Re-RT3 = 6
Hermann-2013-24120823	250	44 heels: single dose of 0.5 Gy (total dose, 3 Gy). 241 patients: 1 Gy 2 times per week (total dose, 6 Gy All: 6 MVX photons	285	Median (range) = 53 (23-86)	71 (28.4)	NR	NR	Onset of pain: <6mo = 75 (26) 6-12 mo = 74 (26) >12 mo = 120 (42) Not known = 16 (6)	Mean length of heel spur (mm)= 6.5 mm (range 0.6-25)	Prior radiation therapy >3 years = 16 (8) Insole support = 156 (75) Local injections = 84 (41) Extracorporeal shock waves = 44 (21) Systemic NSAIDs =133 (64)	Comorbidities: Foot deformities = 127 (45) Endoprosthesis = 16 (6) Diabetes = 9 (3)

Notes. [a] Values calculated by the research team based on data provided in the article; [b] Mean (range); [c] Only includes data from the ESWT arm.

Abbreviations. Gy=gray; mo=month; LD-EBRT=low-dose external beam radiotherapy; MHz=megahertz; ml=milliliters; mm=millimeter; mv=megavolt; MVX=megavoltage x-rays; NR=not reported; NSAIDs=nonsteroidal anti-inflammatory drugs; PMID=PubMed ID; RT=radiation therapy; SD=standard deviation.

APPENDIX F-3. PLANTAR FASCIITIS QUALITY RATING

Author, Year, PMID, Design	Random sequence generation	Allocation concealment	Blinding of participants and study personnel	Blinding of outcome assessor	Incomplete outcome data	Selective reporting	Intention-to-treat analysis	Clear reporting	Clear eligibility criteria	Interventions adequately described	Outcomes fully defined	Representa-tiveness of the cohort	Comparator representative-ness	Adjustment for confounders	Other bias	Overall RoB
Gogna, 2016, 27521483, RCT	Yes (Low concern)	Unclear	No (High concern)	Unclear	No (Low Concern)	No (Low Concern)	Yes (Low Concern)	No (High concern) [a]	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	No (Low Concern)	**Medium (RCT)**
Canyilmaz, 2015, 25936814, RCT	Yes (Low concern)	Unclear	No (High concern)	No (High concern)	No (Low Concern)	No (Low Concern)	Yes (Low Concern)	No (High concern) [b]	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	No (Low Concern)	**Medium (RCT)**
Aynaci, 2021 Turkey, NRCS	NA	NA	NA	Unclear	No (Low Concern)	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	No (High concern) [c]	Unclear	Yes (Low concern)	No (High concern) [d]	No (Low Concern)	**High (NRCS)**
Rudat 2021, 33502569, Single group	NA	NA	NA	Unclear	No (Low Concern)	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	Yes (High Concern) [e]	**High (Single Group)[f]**
Hermann-2013-24120823	NA	NA	NA	No (High concern)	No (Low Concern)	NA	NA	No (Low concern)	No (Low concern)	No (Low concern)	No (Low concern)	No (Low concern)	NA	NA	No (Low Concern)	**High (Single Group)[f]**

Notes. [a] Dates of study not reported and lack of clarity surrounding comparisons reported in results; [b] Unclear whether follow-up measures were reported as mean or medians difference; [c] Unclear about which pain measures were reported; [d] Crude analysis; [e] 30% of patients lost to follow-up at 3 months; [f] The study design is unable to estimate the effect of RT on outcomes.

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

APPENDIX F-4. PLANTAR FASCIITIS RESULTS SUMMARY

Author, Year, PMID	Comparator	Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
Gogna, 2016, 27521483	RT 3.0 Gy vs PRP or Baseline vs follow-up Follow-up, mo = 3 and 6	Pain (VAS), (N = 20 vs 20), Mean (SD) Baseline = 6.5 (0.889) vs 6.65 (0.819) 3mo = 2.55 (NR) vs 2.45 (NR) 6mo = 2.35 (0.745) vs 2.25 (0.639) Pain (VAS), (N = 20 vs 20), p-value (between group) 3mo = 0.6093 6mo = 0.6510 Mean decrease in Pain (VAS), Baseline vs 6mo 4.15 vs 4.40 Net change (between-group) = 0.25 (-0.238, 0.738), p = 0.315[a] Difference in Pain (VAS), p-value (within-group) PRP Baseline vs PRP 3mo = <0.0001 PRP 3mo vs PRP 6mo = <0.1625 RT Baseline vs RT 3mo = 0.0001 RT 3mo vs RT 6mo = NR Difference in Pain (VAS), Baseline vs 6mo (within-group) PRP Net change = -4.4 (-4.725, -4.075), p<0.001 [a] RT Net change = -4.15 (-4.512, -3.788), p<0.001 [a] Plantar fasciitis thickness (mm), (N = 20 vs 20), Mean (SD) [a] Baseline = 6.71 (0.290) vs 6.765 (0.308) 6mo = 5.62 (0.353) vs 5.585 (0.315) Net change = 0.09 (-0.108, -0.288) p = 0.372 Difference in Planta fasciitis thickness (mm), (N = 20 vs 20), p-value (between group) Baseline to 3mo = NS	Initial worsening of pain in the 1 to 2-week period post-radiation followed by progressive improvement, N 5 vs 0	

Author, Year, PMID	Comparator	Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
		Difference in Planta fasciitis thickness (mm), p-value (within group) PRP Baseline vs PRP 6mo = <0.0001 RT Baseline vs RT 6mo = <0.0001 American Orthopedic Foot and Ankle Score, (N = 20 vs 20), mean (SD) [a] Baseline = 52.5 (7.674) vs 51.5 (8.751) 6mo = 89.65 (3.528) vs 89.1 (3.626) Net Change = -0.45 (-4.397, 3.497) p = 0.823 Difference in American Orthopedic Foot and Ankle Score, PRP (N = 20 vs 20), p-value (between group) Baseline to 3mo = 0.6290 Baseline to 6mo = NS Difference in American Orthopedic Foot and Ankle Score, p-value (within group) PRP Baseline vs PRP 6mo = <0.0001 RT Baseline vs RT 6mo = <0.0001		
Canyilmaz, 2015, 25936814	RT 6 Gy vs PGSI Follow-up, Median (range), mo = 12.5 (6.5-18.5)	Pain (VAS), (N = 60 vs 64) Baseline: Mean = 7.6 vs 6.9 Min = 4 vs 4 Max = 10 vs 10 Median = 8 vs 7 p = 0.009 3 mo follow-up: Mean = 2.8 vs 4.6 Min = 0 vs 0 Max = 9 vs 10 Median = 2 vs 5 p<0.001 6 mo follow-up: Mean = 2.7 vs 4.6	Acute infection at injection site PGSI group = 1 *Acute side effects or long-term toxicity did not occur in the radiation therapy arm.*	

Author, Year, PMID	Comparator	Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
		Min = 0 vs 0 Max = 10 vs 10 Median = 2 vs 5 p<0.001 Modified von Pannewitz pain score, (N = 60 vs 64), N (%) Response at 3 mo follow-up: Complete = 23 (38.3) vs 10 (15.6) Partial = 17 (28.3) vs 6 (9.4) Minor = 11 (18.3) vs 22 (34.4) No change = 8 (13.3) vs 20 (31.3) Increased pain = 1 (1.7) vs 6 (9.4) p<0.001 Response at 6mo follow-up: Complete = 21 (35) vs 10 (15.6) Partial = 20 (33.3) vs 8 (12.5) Minor = 12 (20) vs 20 (31.3) No change = 6 (10) vs 20 (31.3) Increased pain = 1 (1.7) vs 6 (9.4) p<0.001 Five-level function score, (N = 60 vs 64) Baseline: Mean = 41.6 vs 48.4 Min = 20 vs 30 Max = 70 vs 85 Median = 40 vs 50 p<0.001 3mo follow-up: Mean = 78.3 vs 60 Min = 30 vs 6 Max = 100 vs 100 Median = 85 vs 57.5 p<0.001 3mo, N (%):[b] Excellent = 24 (40) vs 10 (15.6) Good = 24 (40) vs 12 (18.8)		

Author, Year, PMID	Comparator	Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
		Moderate = 12 (20) vs 32 (50) Poor = - vs 10 (15.6) 6mo follow-up: Mean = 78.7 vs 59 Min = 35 vs 0 Max = 100 vs 100 Median = 80 vs 60 p<0.001 6mo, N (%):[b] Excellent = 23 (38.3) vs 10 (15.6) Good = 23 (38.3) vs 14 (21.9) Moderate = 13 (21.7) vs 29 (45.3) Poor = 1 (1.7) vs 11 (17.2) Pain relief, RT vs PGSI (Time not specified)[c] HR (95%CI) = 1.89 (0.88, 4.04), p = 0.102 Time interval required for second treatment (mo), RT vs PGSI: Mean = 9 vs 6.4 Min = 4 vs 3.1 Max = 15.2 vs 14.1 p = 0.045 1-year probability of patients not requiring a second treatment: 95% vs 90.2%		
Aynaci, 2021	RT 6 Gy vs PGSI vs ESWT Follow-up, Median (range), mo = 15.5 (6.5-37.4)	Pain (VAS), (N = 67 vs 65 vs 73) Baseline: Mean = 7.7 vs 6.9 vs 7.5 Min = 4 vs 4 vs 4 Max = 10 vs 10 vs 9 Median = 8 vs 7 vs 8 Overall p = 0.004 RT vs ESWT p = 0.347	Arm pain during treatment ESWT = 10 Reddening of the skin (time not specified) ESWT = 2	

Author, Year, PMID	Comparator	Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
		3mo follow-up: Mean = 2.5 vs 4.6 vs 4.1 Min = 0 vs 0 vs 0 Max = 9 vs 10 vs 9 Median = 2 vs 5 vs 4 Overall = p<0.001 RT vs ESWT = (p<0.001) 6mo follow-up: Mean = 2.5 vs 4.6 vs 3.6 Min = 0 vs 0 vs 0 Max = 10 vs 10 vs 10 Median = 2 vs 5 vs 3 Overall p<0.001 Pain control (free of pain, considerable, and some improvement) (not specified) (time not specified), % 80.6 vs 72.3 vs 63 Modified von Pannewitz pain score, (N = 67 vs 65 vs 73), N (%) Response at 3 mo follow-up: Complete = 28 (41.8) vs 10 (15.4) vs 11 (15.1) Partial = 20 (29.9) vs 7 (10.8) vs 20 (27.4) Minor = 10 (14.9) vs 22 (33.8) vs 27 (37) No change = 8 (11.9) vs 20 (30.8) vs 15 (20.5) Increased pain = 1 (1.5) vs 6 (9.2) vs – Overall p<0.001 Response at 6 mo follow-up: Complete = 26 (40) vs 10 (15.4) vs 16 (21.9) Partial = 21 (32.3) vs 9 (13.8) vs 23 (31.5) Minor = 11 (16.9) vs 20 (30.8) vs 20 (27.4) No change = 6 (9.2) vs 20 (30.8) vs 14 (19.2) Increased pain = 1 (1.5) vs 6 (9.2) vs – Overall p<0.001		

Author, Year, PMID	Comparator	Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
		Five-level function score, (N = 67 vs 65 vs 73) Baseline: Mean = 40.9 vs 48.4 vs 41.9 Min = 20 vs 30 vs 20 Max = 70 vs 85 vs 80 Median = 40 vs 50 vs 45 Overall p<0.001 3mo follow-up: Mean = 80.4 vs 60.2 vs 65.6 Min = 30 vs 6 vs 30 Max = 100 vs 100 vs 100 Median = 85 vs 60 vs 65 Overall p<0.001 3mo, N (%):[d] Excellent = 31 (46.3) vs 10 (15.6) vs 14 (19.2) Good = 24 (35.8) vs 13 (20) vs 6 (8.2) Moderate = 12 (17.9) vs 32 (49.2) vs 49 (67.1) Poor = - vs 10 (15.6) vs 4 (5.5) 6mo follow-up: Mean = 80.3 vs 59.2 vs 68.6 Min = 35 vs 0 vs 30 Max = 100 vs 100 vs 100 Median = 85 vs 60 vs 65 Overall = p<0.001 6mo, N (%):[d] Excellent = 28 (43.1) vs 10 (15.4) vs 17 (23.3) Good = 23 (35.4) vs 15 (23.1) vs 9 (12.3) Moderate = 13 (20) vs 29 (44.6) vs 44 (60.3) Poor = 1 (1.5) vs 11 (16.9) vs 3 (4.1) Time interval required for second treatment (mo), (N = 67 vs 65 vs 73), Mean (range) 9 (4,14.1) vs 6.4 (2.1, NR) vs 7.8 (3.1,13.9) Overall p = 0.069		

Author, Year, PMID	Comparator	Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
		Required second treatment, PGSI vs RT (time unclear)[c] HR (95%CI) = 0.41 (0.2, 0.86), p = 0.018		
Rudat 2021, 33502569	RT 3.0-6.0 Gy Baseline vs follow-up Follow-up, Median (range), mo = 16 (3-125)	Patients who achieved pain reduction of 75%-100% (VAS) (N =864 heels), N (%)[a] Last day of RT = 268 (31) 3mo after RT = 553 (64) 12mo after RT = 588 (68) 24mo after RT = 605 (70) 36mo after RT = 536 (62) >36mo after RT = 562 (65) Probability of insufficient pain control (pain reduction of less than 75%) at 10 years: 45.9% (39.4, 52.4%) Opted for re-irradiation for stronger pain reduction 3m post-RT, N (%) (864 heels) No Re-RT = 572 (66.2) Re-RT 1 = 238 (27.5) Re-RT 2 = 48 (5.6) Re-RT 3 = 6 (0.7)	*Apart from the initial increase in pain during and shortly after [RT], toxicity clearly attributable to acute or late radiation reactions was not observed in any patient.*	

Author, Year, PMID	Comparator	Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
Hermann-2013-24120823	RT 3 or 6 Gy Baseline vs follow-up Follow-up, Mean (range), mo = 11 (1-57)	Symptom remission (not defined) (N =285 heels), N (%) Complete remission = 107 (38) Partial remission = 91 (32) No change = 54 (19) Unknown = 33 (11) Symptom remission (not defined) by total Gy (N = 285 heels), N (%) 3 Gy (N =44) Complete remission = 12 (27) Partial remission = 18 (41) No change = 7 (16) Not known = 7 (16) 6 Gy (N =241) Complete remission = 95 (40) Partial remission = 73 (30) No change = 47 (20) Not known = 26 (10)	NR	NR

Notes. [a] Values calculated by the research team based on data provided in the article; [b] Excellent = 90-100 points; Good = 70-85 points; Fair = 40-69 points; and Poor = 0-39 points; [c] Model adjusted for age, sex, BMI, and duration of pain; [d] Excellent = 90-100 points; Good = 70-89 points; Fair = 40-69 points; Poor = 0-39 points.

Abbreviations. CI=confidence interval; ESWT=extracorporeal shock-wave therapy; Gy=gray; y=years; HR=hazard ratio; Max=maximum; Min=minimum; mm=millimeters; mo=month; NR=not reported; NS=not significant per article text; PGSI=palpation guided steroid injection; PMID=PubMed ID; PRP=plasma rich protein; QoL=quality of life; RT=radiation therapy; SD=standard deviation; VAS=Visual Analog Scale.

APPENDIX G. PTERYGIUM

APPENDIX G-1. PTERYGIUM DESIGN DETAILS

Author, Year, PMID, Protocol Number, Country	Study Design	Study Dates	Study Location Details (Hospital Type, Centers)	Intent of RT	Inclusion Criteria	Exclusion Criteria
Pterygium Brachytherapy Only						
Viani, 2020, 22284040, Brazil	RCT	2008-2009	Teaching hospital, single center	Unclear	Fresh pterygium resected by a conjunctival autograft method and given b-radiotherapy within 3 days. Clinical diagnosis of pterygium after CAG surgery, without a previous surgery, or adjuvant treatments.	NR
Frucht, Pery, 1994, 8152772, Israel	RCT	1989-1992	Otherunclear, single center	Primary treatment/prevention of recurrence	18 or older, recurrent pterygium or primary fleshy, and growing pterygium which invaded more than 2 mm into the cornea.	Atrophic primary pterygium.
Bekibele, 2004, 15587769, Nigeria	NRCS	1999	Non-teaching hospital, single center	Primary treatment/prevention of recurrence	NR	NR
Simşek, 2001, 11456012, Turkey	NRCS	NR	Other/unclear, NR/unclear	Primary treatment/prevention of recurrence	18 or older, 2mm or more invasion of the cornea, primary or recurrent pterygium with active growth, symptomatic.	NR
Isohashi, 2006, 16896589, Japan	Single group	NR	Teaching hospital, single center	Primary treatment/prevention of recurrence	Complete surgical resection and received no other adjuvant	Not followed up for a period of at least 3 months and who had not received a total dose of at least 30 Gy.
Pterygium Not Brachytherapy						
Willner, 2001, 11544903, Germany	Single group	1987-2000	Other/unclear, NR/unclear	Primary treatment/prevention of recurrence	NR	NR

Abbreviations. CAG=conjunctival autograft; Gy=gray; mm=millimeters; NR=not reported; NRCS=nonrandomized controlled study; PMID=PubMed ID; RCT=randomized controlled trial; RT=radiation therapy.

APPENDIX G-2. PTERYGIUM BASELINE DATA

Author, Year, PMID	N Patients	Intervention	N Lesions	Follow-Up Treatment	Age	Male, N (%)	% White	Lesion Dimension (mm)	Lesion Location, N (%)	Other Information
Pterygium Brachytherapy Only										
Viani, 2012, 22284040	96	Conjunctival autografting followed by a total dose of 10Gy (SR90).	Surgery → RT = 54		53 (21-88)[a]	47 (43.5) (eyes)	NR	2.65[b,c]	Nasal = 107 (99.0%)[c] Temporal = 1(1.0%)[c]	Grade, N (%) (eyes):[c] I- 52 (48.1) II- 46 (42.6) III- 10 (9.3)
		Conjunctival autografting.	Surgery = 54							
Frucht-Pery, 1994, 8152772	Surgery → RT = 25	Surgical excision followed by a total dose of 12Gy (SR90).	Surgery → RT = 25	*Steroids treatment for 3 months and topical antibiotics until epithelization was complete*	40.2 (18-61) 0	49 (65.3)[c]	NR	NR	*All located nasally*	Recurrent Pterygium (at baseline):[c] 19 (25.3%)
	Surgery → mitomycin C 0.01% = 25	Surgical excision followed by mitomycin C (0.01%).	Surgery → mitomycin C 0.01% = 25							
	Surgery → mitomycin C 0.02% = 25	Surgical excision followed by mitomycin C (0.02%) .	Surgery → mitomycin C 0.02% = 25							
Bekibele, 2004, 15587769	Surgery → RT = 24	Surgical excision followed by 25-35 Gy (SR90).	Surgery → RT = 31		46.5[b]	24 (50.0)[c]	NR	NR	NR	
	Surgery → 5-FU = 24	Surgical excision followed by 25mg/ml of 5-FU soak for 5 min.	Surgery → 5-FU = 27							

Author, Year, PMID	N Patients	Intervention	N Lesions	Follow-Up Treatment	Age	Male, N (%)	% White	Lesion Dimension (mm)	Lesion Location, N (%)	Other Information
Simşek, 2001, 11456012	Surgery → RT = 130	Surgical excision followed by a total dose of 10-70Gy[d] (SR90).	Surgery → RT = 141	*Antibiotic drops were prescribed during the first postopera-tive week and steroid drops (1% predniso-lone acetate, qid) and artificial tear drops during the following month.*	42.6 (18-80)[a]	109 (56.5)[c]	NR	NR	NR	Recurrent Pterygium (at baseline) (Lesions), N (%): 91 (43.8)
	Surgery → Antineoplastic = 63	Surgical excision followed by mitomycin C (0.02%) eyedrops four times a day up to one week	Surgery → Antineoplastic = 67							
Isohashi, 2006, 16896589	Surgery → RT = 1080	Surgical excision followed by a total dose of 30-35Gy (SR90).	Surgery → RT = 1253		59 (16-90)[c]	556 (51.5)	NR	NR	Nasal = 1228 (98) Temporal = 25 (2)	Pterygium (at baseline) (lesions), N (%): Primary = 1,102 (87.9) Recurrent after surgery only =115 (9.2) Recurrent after surgery and RT 36 (2.9)
Pterygium Not Brachytherapy										
Willner, 2001, 11544903	N = 65 patients	7Gy immediately pre-excision and 5Gy within 24 hours post-excision and every other day for a total dose of 17-27Gy, or 5Gy post-excision for a total dose of 5-30Gy started within 0-15 days and completed within 13 days	RT → Surgery → RT = 47 pterygium or Surgery → RT = 34 pterygium		53.7 (eye)[b,c]	48 (73.8 (of patient s)[c]	North Europea n = 68 (84.0%) (of eyes) Mediterr anean = 13 (16.0%) (of eyes)	NR	Nasal =71 (87.7%) (of pterygium) Temporal = 10 (12.3%) (of eyes)	

Notes. [a] Mean (range); [b] Mean (SD); [c] Values calculated by the research team based on data provided in the article; [d] <5% of patients receive between 51 and 70 Gy.
Abbreviations. 5-FU=5-fluorouracil; Gy=gray; mg=milligram; ml=milliliter; NR=not reported; PMID=PubMED ID; RT=radiation therapy.

APPENDIX G-3. PTERYGIUM QUALITY RATING

Author, Year, PMID, Design	Random sequence	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessor	Incomplete outcome data	Selective reporting	Intention-to-treat analysis	Clear reporting	Clear eligibility criteria	Interventions adequately described	Outcomes fully defined	Representativeness of the cohort	Comparator representativeness	Adjustment for confounders	Other bias	Overall RoB
Pterygium - Brachytherapy Only																
Viani, 2020, 22284040, RCT	Un-clear	Yes (Low concern)	No (High concern)[a]	Yes (Low concern)	No (Low Concern)	No (Low concern)	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	No (Low concern)	Low (RCT)
Frucht, Pery, 1994, 8152772, RCT	Yes (Low con-cern)	Unclear	No (High concern) [a]	Yes (Low concern)	No (Low concern)	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	No (Low concern)	Low (RCT)
Bekibele, 2004, 15587769, NRCS	NA	NA	NA	Unclear	No (Low concern)	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)[b]	No (Low concern)	Medium (NRCS)
Simşek, 2001, 11456012, NRCS	NA	NA	NA	Unclear	No (Low concern)	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	No (High concern)[c]	No (Low concern)	High (NRCS)
Isohashi, 2006, 16896589, Single group	NA	NA	NA	Unclear	No (Low concern)	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	No (Low concern)	High (Single Group)[d]
Pterygium - Not Brachytherapy																
Willner, 2001, 11544903, Single group	NA	NA	NA	Unclear	No (Low concern)	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	No (Low concern)	High (Single Group)[d]

Notes. [a] Participants unable to be blinded to treatment; [b] Match for age and sex; [c] Crude analysis; [d] The study design is unable to estimate the effect of RT on outcomes.
Abbreviations. NA=not applicable; NRCS: nonrandomized controlled study; PMDI=PubMed ID; RCT=randomized controlled trial.

APPENDIX G-4. PTERYGIUM RESULTS SUMMARY

Author, Year, PMID	Comparison	Efficacy	Cosmetic	Patient Satisfaction/ Experience/QoL	Complication/ Side Effects
Pterygium - Brachytherapy Only					
Viani, 2012, 22284040	Surgery → RT(10Gy) vs Surgery Follow-up, Mean (range), mo = 18 (6-26)	Recurrence (N=54 vs 54 eyes), [Mean 18mo], N (%) 5 (9.3) vs 12 (22.2) OR (95% CI) = 0.36 (0.12, 1.10)[a] PT symptoms – improvement, [Mean 18mo], N (%)[a] Improvement = 39 (72) vs 27 (50) Partial = 11 (20) vs 15 (28) No improvement = 4 (8) vs 12 (22) p=0.001 Received salvage surgery (eyes), N (%)[a] Surgery + RT = 6 (11.1) Surgery alone = 7 (13.0) OR (95% CI) = 0.84 (0.26, 2.68)	Cosmetic results (not defined) [Mean 18mo], N (%)[a,b] Excellent/good = 51 (94.4) vs 46 (85.2) Not satisfactory = 3 (5.6) vs 8 (14.8) p=0.03	NR	NR
Frucht-Pery, 1994, 8152772	Surgery → RT(12Gy) vs Surgery → MMC 0.01% Follow-up, Mean (range), mo = 15.3 (7-27)	Recurrence (N=25 vs 25), [Mean 15.3 mo], N (%) 5 (20.0) vs 2 (8.0) OR (95% CI) = 2.88 (0.50, 16.48) [a]	NR	NR	*During the first three postoperative weeks, all patients had complaints of ocular pain, photophobia and lacrimation.* Delay in conjunctival healing for 8 weeks postop, N MMC 0.02% = 1 (patient had recurrent pterygium) Calcified degeneration of conjunctiva in the operated area, N MMC 0.02% = 1 (patient had 5 previous pterygium surgeries and previous RT)
	Surgery → RT(12Gy) vs Surgery → MMC 0.02% Follow-up, Mean (range), mo = 15.3 (7-27)	Recurrence (N=25 vs 25), [Mean 15.3mo], N (%) 5 (20.0) vs 1 (4.0) OR (95% CI) = 6.00 (0.65, 55.66) [a]			
Bekibele, 2004, 15587769	Surgery → RT (25-35 Gy) vs Surgery → 5-FU Follow-up, Mean (range), mo = 9.5 (2 wk- 2 y)[a]	Recurrence (N=31 vs 27 eyes), [4mo to 1y], N (%) 7 (22.5) vs 7 (25.9) unadOR (95% CI) = 0.83 (0.25, 2.78) [a]	Cosmetically unacceptable recurrence (N=31 vs 27 eyes), [4mo to 1y], N (%) 2 (6.5) vs 3 (11.1)	NR	Cornea opacity (N= 31 vs 27), [4mo to 1y], N (%) 1 (3.2) vs 10 (37.0) unadOR (95% CI) = 0.06 (0.01, 0.48) [a]

Author, Year, PMID	Comparison	Efficacy	Cosmetic	Patient Satisfaction/ Experience/QoL	Complication/ Side Effects
			unadOR (95% CI) = 0.55 (0.09, 3.58) [a]		
		Visual acuity changes (Snellen lines) (N=31 vs 27 eyes), N (%)[a] Improvement of 2+ lines = 0 (0.0) vs 9 (33.3) Reduction of 1 to 2 lines = 0 (0.0) vs 2 (7.5)			Conjunctivitis (N= 31 vs 27), [4mo to 1y], N (%) 3 (9.7) vs 3 (11) unadOR (95% CI) = 0.86 (0.16, 4.65) [a] Cornea necrosis (N= 31 vs 27), [4mo to 1y], N (%) 0 (0) vs 1 (3.7) RD (95% CI) = -0.04 (-0.11, 0.03)[a] Sclera granuloma(N= 31 vs 27), [4mo to 1y], N (%) 0 (0.0) vs 3 (11.1) RD (95% CI) = -0.11 (-0.23, 0.07)[a]
Simşek, 2001, 11456012	Surgery → RT(10-70Gy) vs Surgery → Antineoplastic Follow-up, Mean (range), mo = 52 (3- 144)[a]	Recurrence (N=141 vs 67 eyes), [2-12 mo], N (%) 9 (6.4) vs 12 (17.9) unadOR (95% CI) = 0.31 (0.12, 0.78)[a]	NR	NR	*Almost all patients complained about pain photophobia, tearing and foreign body sensation after Sr-90 treatment in the first postoperative week.* *Almost all patients treated with MMC complained of burning and foreign body sensation, tearing and photophobia during treatment.* Complications (N= 141 vs 67 eyes), N (%): Lense opacity = 4 (2.8) vs 0 (0.0) Scleral melting = 3 (2.1) vs 6 (9.0) Conjunctival scar formation = 3 (2.1) vs 0 (0.0) Granuloma formation = 1 (0.7) vs 0 (0.0) Iris prolapse = 1 (0.7) vs 0 (0.0)

Author, Year, PMID	Comparison	Efficacy	Cosmetic	Patient Satisfaction/ Experience/QoL	Complication/ Side Effects
					Punctate keratopathy = 0 (0.0) vs 4 (6.0) Purulent conjunctivitis = 0 (0.0) vs 2 (3.0) Corneal microabscess = 0 (0.0) vs 1 (1.5) Increased pigmentation = 0 (0.0) vs 1 (1.5) *More complications were seen in [the excision plus MMC arm]* = p<0.001
Isohashi, 2006, 16896589	Surgery → RT(30-35Gy) Follow-up, Median (range), mo = 45 (3-120)[a]	Recurrence (N= 1253), [Median 45mo], N (%) 97 (7.7)	NR	NR	Side effects (N=1253), [3mo], N (%) Moderate conjunctivitis = 2 (0.2) Local pain = 60 (4.9) Visual disturbance = 71 (5.7) Photophobia or an increase in tear flow = 58 (5.6) *No severe late complications, such as scleral ulcer, scleral necrosis and scleromalacia, were encountered.*
Pterygium - Not Brachytherapy					
Willner, 2001, 11544903	RT → Surgery → RT = 47 or Surgery → RT = 34 Follow-up, Mean, mo = 32	Recurrence (New pterygium at the same site diagnosed by an ophthalmologist) by treatment (Mean 32 months), N(%)[a] 4 (8.5) vs 15 (44.1) unadOR (95% CI) = 0.12 (0.03, 0.40)			*Only conjunctivitis and superficial keratitis was transiently observed within the first days following treatment.* *[At publication] no case of severe side effects like scleral necrosis or thinning, symblepharon, radiation-induced cataract or glaucoma were observed in both groups.*

Notes. [a] Values calculated by the research team based on data provided in the article; [b] Unit of analysis was unclear, which we inferred was eyes.

Abbreviations. CI=confidence interval; Gy=gray; MMC=mitomycin C; mo=months; PMID=PubMed ID; QoL=quality of life; RD=risk difference; RT=radiation therapy; unadOR=unadjusted odds ratio; wk=weeks, y=year.

APPENDIX H. OSTEOARTHRITIS

APPENDIX H-1. OSTEOARTHRITIS DESIGN DETAILS

Author, Year, PMID, Protocol Number, Country	Study Design	Study Dates	Study Location Details (Hospital Type, Centers)	Intent of RT	Inclusion Criteria	Exclusion Criteria
Minten, 2016, 26747050 Netherlands	Systematic review	1982-2013 (included studies)	NR	Treatment of OA	Studies aimed to treat OA, used an intervention of external beam radiotherapy, the effects of RT on pain or functioning were assessed, and study was a journal article.	No primary data presented, in a language other than English, German or Dutch, or published prior to 1980
Mahler, 2019 30366945 NTR4574 Netherlands[a]	RCT	2015-2017	Teaching hospital Other/unclear	Primary treatment/prevention of recurrence	Patients from rheumatology outpatient clinic who fulfilled the clinical ACR knee OA criteria, were >= 50 years old, had a numeric pain score of >=5/10 in the index knee, and had insufficient response to analgesics and exercise therapy	Treatment by a physical therapist in the last 6 months, NRS pain score >2/10 in the contralateral knee or hips, corticosteroids int eh previous 4 weeks, fibromyalgia, Kellgren & Lawrence score >3
Minten 2018 30231990 NTR4574 Netherlands[a]	RCT	2016-2017	Teaching hospital Other/unclear	Primary treatment/prevention of recurrence	ACR criteria hand OA, Age>=50, hand pain score >=5/10 on NRS for at least 15 days of the last 30 days despite analgesic use and occupational and/or physical therapy; ability to read, write, and communicate well in Dutch	Predominant pain in the metacarpophalangeal joins and or wrist; unilateral hand OA; treatment for hand OA by an occupational or physical therapist in the last 6 months; other rheumatic diseases with hand localization; previous or scheduled surgical treatment on hand joints; corticosteroid injections in the previous 4 weeks; fibromyalgia according to 2011 modified ACR criteria; presence of a pacemaker or implantable cardioverter-defibrillator; Kellgren & Lawrence score >3 in over 25% of the hand joints;
Niewald 2022 34724085 DKRS00011870 Germany	RCT (treated as two single arm studies)		Teaching hospital	Primary treatment/prevention of recurrence	Clinical diagnosis of OA of the knee and/or hand or finger joints, radiological proof of the diagnosis (plain radiographs), duration of anamnesis more than 3 months, favorable general health status.	Patients presenting with previous joint replacement; previous radiation therapy to the affected joint; previous trauma; rheumatic, arterial, or venous vessel diseases; manifest lymphatic edema; pregnancy or breastfeeding; or severe psychiatric disorders. Patients having undergone surgical interventions or

Author, Year, PMID, Protocol Number, Country	Study Design	Study Dates	Study Location Details (Hospital Type, Centers)	Intent of RT	Inclusion Criteria	Exclusion Criteria
						injections to the involved joint after radiotherapy were excluded as soon as this therapy became known.
Rühle 2021 34342662 Germany	Single group	2008-2020	Other/unclear	Primary treatment/prevention of recurrence	>= 65 years at the time of RT	
Weissmann 2022 35046940 Germany	Single group	2004-2019	Teaching hospital	Primary treatment/prevention of recurrence		

Notes. [a] Copublication: Van den Ende, C.H., Minten, M.J., Leseman-Hoogenboom, M.M., van den Hoogen, F.H., Den Broeder, A.A., Mahler, E.A. and Poortmans, P.M., 2020. Long-term efficacy of low-dose radiation therapy on symptoms in patients with knee and hand osteoarthritis: Follow-up results of two parallel randomized, sham-controlled trials. The Lancet Rheumatology, 2(1), pp.e42-e49.

Abbreviations. NR=not reported; OA=osteoarthritis; PMID=PubMed ID; RCT=randomized controlled trial; RT=radiation therapy.

APPENDIX H-2. OSTEOARTHRITIS BASELINE DATA

Author, Year, PMID	N Patients	Intervention	N Lesions	Age (Years), Mean (SD)	N (%) Male	N (%) White	Location	Lesion Age	Previous Treatment, N (%)	Other
Minten, 2016, 26747050	2164 (OA patients)	0.5-12 Gy	NR	Most between 50-70	28 (53%)	NR	Knee, Hip, Shoulder, Spine, Thumb	Duration of symptoms: <8 weeks- 15 years	NR	Varied
Mahler, 2019 30366945	RT = 27	Six fractions of 1 Gy delivered every other day over 2 weeks for a total dose of 6 Gy	NR	65 (9)	27 (49.1)[a]	NR	Knee	Duration of symptoms ≤5 years (N=54), N (%): 30 (55.5)[a]	Analgesic use in previous month: 35 (63.6)[a]	Kellgren and Lawrence >=2, N (%) = 32 (58.2)[a]
	Sham = 28	The radiation therapy device was not activated, and patients were exposed to recordings of the sound of the device								
Minten, 2018 30231990	RT = 28	Six fractions of 1 Gy, delivered every other day over 2 weeks, for a total dose of 6 Gy	NR	65 (7)	12 (21.4)[a]	NR	Hand	Duration of symptoms ≥ 5 years, N (%): 34 (60.7)[a]	Medication use, yes: 43 (76.8)[a]	RT arm Kellgren and Lawrence >=2 joint count, n (0-30), median (IQR): 10.5 (6.5- 13.5) Sham Arm Kellgren and Lawrence >=2 joint count, n (0-30), median (IQR): 6 (2-8.5)
	Sham = 28	Sham: Received six 0 Gy-fractions over the two-week period, during which an audio sound were played to mimic sounds of a linear accelerator during operation								
Niewald 2022 34724085	RT (Standard Dose) = NR[b]	Received 6 fractions of 0.5 Gy twice a week for a total dose of 3.0 Gy	110	68.2 (NR)	NR	NR	Location, N(%): Hand =77 (70); Knee =33 (30); Bilateral =39 (62); Unilateral =24 (38)	Duration of pain (months), M (SD) = 56.2 (52.3)	Previous treatment, N (%): Ice/heat =52 (47); Ultrasound =0; Microwaves =2 (2); Oral medication = 77 (70); Injections =34 (31); External splints =4 (4); Arthroscopy (multiple choices possible) =16 (15)	

Author, Year, PMID	N Patients	Intervention	N Lesions	Age (Years), Mean (SD)	N (%) Male	N (%) White	Location	Lesion Age	Previous Treatment, N (%)	Other
Niewald 2022 34724085	RT (Experimental Dose) = NR[b]	Received 6 fractions of 0.05 Gy twice a week for a total dose of 0.3 Gy	111	66.3 (NR)	NR	NR	Location, N(%): Hand = 81 (73); Knee = 30 (27); Bilateral = 45 (61); Unilateral = 29 (39)	Duration of pain (months), M(SD) = 49.6 (46)	Previous treatment, N(%): Ice/heat = 33 (30); Ultrasound = 0; Microwaves = 2 (2); Oral medication = 69 (62); Injections = 24 (22); External splints = 2 (2); Arthroscopy (multiple choices possible) = 12 (11)	
Rühle 2021 34342662	RT = 970	6 fractions of 0.5 or 1 Gy doses given two or three times a week (total dose of 3-6 Gy) via a linear accelerator either after computed tomography-based 3-dimensional treatment planning or after treatment simulation using 2-dimensional X-ray imaging.	1185	76 (65-98) Median (Range) Mean (SD) = 76 (5.5) [a]	327 (27.6)[a] of lesions	NR	Location, N (%): Hand = 363 (30.6); Shoulder = 147 (12.4); Hip =33 (2.8); Knee = 419 (35.4); Foot = 219 (18.5); Others =4 (0.3)	NR	NSAIDs = 733 (61.9); Intraarticular corticosteroid injection = 221 (18.6)	
Weissmann 2022 35046940	RT = 196	6 fractions of 0.5 or 1 Gy doses (total dose of 3-6 Gy) delivered over 3 weeks with an interfractional radiation-free interval of at least 2 days.	NR	65.9 (14.5)	47 (24) [a]	NR	Location, N (%): Foot and ankle; Right = 83 (42); Left = 73 (37); Both = 40 (20)	NR	*All patients had received several therapies before undergoing LDRT*	

Notes. [a] Values calculated by the research team based on data provided in the article; [b] Total patients for each arm not reported, but there were 133 total in both the standard and experimental dose arms.

Abbreviations. Gy=gray; IQR=interquartile range; LDRT=low-dose radiation therapy; NR=not reported; NSAIDs=non-steroidal anti-inflammatories; OA=osteoarthritis; PMID=PubMed ID; RT=radiation therapy; SD=standard deviation.

APPENDIX H-3. OSTEOARTHRITIS SYSTEMATIC REVIEW QUALITY RATING (AMSTAR-2)

Author, Year, PMID, Design	Did the research questions and inclusion criteria for the review include the components of PICO?	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Did the review authors explain their selection of the study designs for inclusion in the review?	Did the review authors use a comprehensive literature search strategy?	Did the review authors perform study selection in duplicate?	Did the review authors perform data extraction in duplicate?	Did the review authors provide a list of excluded studies and justify the exclusions?	Did the review authors describe the included studies in adequate detail?	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Did the review authors report on the sources of funding for the studies included in the review?	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Overall
Minten, 2016, 26747050SR	No (High concern)[a]	Partial Yes (Moderate concern)[b]	No (High concern)[c]	Partial Yes (Moderate concern)[d]	Yes (Low concern)	No (High concern)[e]	Partial Yes (Moderate concern)[f]	Partial Yes (Moderate concern)[g]	Yes (Low concern)	No (High concern)[h]	NA	NA	Yes (low concern)	No (High concern)[i]	NA	Yes (low concern)	Medium

Notes. [a] Population and outcomes not specified; [b] Indicated that PRISMA guidelines were followed but was not explicit about when review methods were established; [c] No statement about why they chose to include noncomparative studies, though this was likely due to literature availability; [d] Did not appear to review trial/study registries or grey literature; [e] No statement about extraction preformed in duplicate; [f] Provided justification for some of the excluded studies but did not provide a list of excluded studies; [g] Study settings were not described; [h] Did not report funding sources of the included studies; [I] No discussion of heterogeneity.

Abbreviations. NA=not applicable; PMID: PubMed ID; SR=systematic review.

APPENDIX H-4. OSTEOARTHRITIS QUALITY RATING

Author, Year, PMID, Design	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessor	Incomplete outcome data	Selective reporting	Intention-to-treat-analysis	Clear reporting	Clear eligibility criteria	Interventions adequately described	Outcomes fully defined	Representativeness of the cohort	Comparator representativeness	Adjustment for confounders	Other bias	Overall EOB
Mahler, 2019, 30366945, RCT	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	No (Low concern)	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	No (Low concern)	Low (RCT)
Minten, 2018, 30231990, RCT	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	No (Low concern)	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	No (Low concern)	Low (RCT)
Niewald 2022, 34724085, RCT – Single group	NA	NA	NA	Unclear	Yes (High concern)[a]	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	No (Low concern)	High (RCT-Assessed as single group)
Rühle 2021, 34342662, Single group	NA	NA	NA	Unclear	No (Low concern)	NA	NA	No (High concern)[b]	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	No (Low concern)	High (Single group)[c]
Weissmann 2022, 35046940, Single group	NA	NA	NA	Unclear	No (Low concern)	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	No (Low concern)	High (Single group)[c]

Notes. [a] Seven in standard group lost to follow-up; 1 in the experimental group lost to follow-up; [b] Results in figures are not all reported in the text; [c] The study design is unable to estimate the effect of RT on outcomes.

Abbreviations. NA=not applicable; RCT=randomized controlled trial.

APPENDIX H-5. OSTEOARTHRITIS RESULTS SUMMARY

Author, Year, PMID	Comparator	Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
Minten, 2016, 26747050	All included studies were single group	*Insufficient evidence for a positive effect of [RT] on pain* *Insufficient evidence for a positive effect of [RT] on functioning*	*Insufficient evidence for the safety of [RT] as treatment for OA.*	NR
Mahler, 2019[a] 30366945	RT 6 Gy vs Sham Follow-up, mo= 1, 2, and 3	Pain (WOMAC), M (SD) Baseline (N = 27 vs 28): 59 (14) vs 61 (17) Absolute change at 3-month follow-up (N = 27 vs 28): 8 (3) vs 11 (14) β (95% CI) = -3 (-10,4)[b] Mean difference (95% CI) from baseline to 12 mo: -1.9 (-9.9, 6.0)[c] Pain (NRS)[d], M (SD) Baseline (N = 27 vs 28): 5.8 (1.6) vs 5.4 (1.6) Absolute change at 3-month follow-up (N = 27 vs 28): -1.1 (1.6) vs -1.3 (2.4) RT vs Sham, β (95% CI) = 0.1 (-0.9, 1.2)[b] Function (WOMAC), M (SD) Baseline (N = 27 vs 28): 60 (17) vs 62 (19) Absolute change at 3-month follow-up (N = 26 vs 28): 9.7 (8) vs 6.3 (14) β (95% CI) = 4 (-3, 10)[b] Mean difference (95% CI) from baseline to 12 mo: -1.0 (9.0, 6.6)[c]	Severe knee pain during and after treatment (N = 27 vs 28), N (%) 0 (0) vs 1 (4)[e] Cold sensation in lower leg (N = 27 vs 28), N (%) 0 (0) vs 1 (4)[e] Severe back pain after fall at home, leading to discontinuation of treatment (N = 27 vs 28), N (%) 1 (4) vs 0 (0) Colon carcinoma diagnosis, (N = 27 vs 28), N (%) 0 (0) vs 2 (7)[e] Fatigue (N = 27 vs 28), N (%) 6 (22) vs 3 (11) *Local reactions were comparable between groups* Side effects between baseline to 12 mo (N =27 vs 28), N (%) Skin reactions = 5 (19) vs 5 (18) Nail reactions = 4 (15) vs 3 (11) Fatigue = 6 (22) vs 4 (14) Other reactions = 3 (11) vs 4 (14) Any reactions = 10 (37) vs 10 (36) Serious adverse events = 0 (0) vs 3 (11)	SF36 Mental Component Scale; M (SD) Baseline (N = 25 vs 28): 53 (10) vs 52 (10) Absolute change at 3-mo follow-up (N = 25 vs 27): 0.9 (8.4) vs -4.2 (10) β (95% CI) = 5 (0,10)[b] SF36 Physical Component Scale, M (SD) Baseline (N = 27 vs 28): 39 (7) vs 39 (8) Absolute change at 3-month follow-up (N = 25 vs 27): 0.1 (7.0) vs 2.4 (6.9) β (95% CI) = -2 (-6, 2)[b]

Author, Year, PMID	Comparator	Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
		PGA of knee OA impact during the previous week, M (SD) Baseline (N = 27 vs 28): 5.6 (2.2) vs 4.6 (2.3) Absolute change at 3-month follow-up (N = 27 vs 28): -1.0 (2) vs -0.9 (3) β (95% CI) = 0 (-1, 1)[b] Mean difference (95% CI) from baseline to 12 mo: 0.0 (-1.2, 1.2)[c] Stiffness (WOMAC), M (SD) Baseline (N = 27 vs 28): 47 (13) vs 55 (20) Absolute change at 3-month follow-up (N = 27 vs 28): -11 (9) vs 9 (21) β (95% CI) = 2 (-8, 13)[b] Proportion OMERACT-OARSI responders, % (95% CI)[f] 1 month follow-up (N = 27 vs 28): 37 (19, 55) vs 21 (6, 37) Difference in proportion, % (95% CI) = 16 (-8, 39) OR =2.3 (0.7, 7.5)[b] 2 months follow-up (N = 27 vs 28): 33 (16, 51) vs 22 (9, 42) Difference in proportion, % (95% CI) = 11 (-13, 35) OR = 1.8 (0.5, 6.3)[b] 3 months follow-up (N = 27 vs 28): 44 (26, 63) vs 43 (25, 61)		

Author, Year, PMID	Comparator	Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
		Difference in proportion, % (95% CI) = 2 (-25, 28) p =0.9 OR = 1.1 (0.4, 3.2)[b] OR =1.3 (0.4, 4.2)[g] 12 months follow-up (N =25 vs 25), N (%): 13 (52) vs 11 (44) Difference in proportion, % (95% CI) = 8 (-29, 35) OR = 1.41 (0.45, 4.48)[b]		
Minten 2018 30231990[a]	RT 6 Gy vs Sham Follow-up, mo = 1, 2, and 3	Pain (AUSCAN) (N = 28 vs 28), M (SD) Baseline 54 (19) vs 56 (15) Absolute change, 3-month follow-up: -3.3 (12) vs -7.8 (16) β (95% CI) = 4.5 (-3.4,12)[b] MD (95% CI) from baseline to 12 mo: 3.3 (-4.6, 11.2)[c] Pain (NRS)[d] (N = 28 vs 28), M (SD) Baseline 6.1 (1.9) vs 6.3 (1.5) Absolute change, 3-month follow-up: -1.1 (1.6) vs -0.9 (2.3) β (95% CI) = -0.1 (-1.2, 1.0)[b] Function (AUSCAN) (N = 28 vs 28), M (SD) Baseline 55 (25) vs 59 (16) Absolute change, 3-month follow-up: -2.6 (12) vs -9.9 (17) β (95% CI) = 7.4 (-0.8, 16)[b]	Skin reaction (undefined) (N = 28 vs 28), 3-month follow-up, N (%) 13 (46.4) vs 11 (39.3)[e] Nail reaction (undefined) (N = 28 vs 28), 3-month follow-up, N (%) 8 (28.6) vs 3 (10.7)[e] Fatigue (undefined) (N = 28 vs 28), 3-month follow-up, N (%) 7 (25.0) vs 6 (21.4)[e] Other reactions (undefined) (N = 28 vs 28), 3-month follow-up, N (%) 9 (32.1) vs 6 (21.4)[e] Serious adverse events (undefined) (N = 28 vs 28), 3-month follow-up, N (%) 2 (7.1) vs 0 (0) Withdrawal due to AE (nail discoloration) (N = 28 vs 28), N (%) 1 (4) vs 0 (0) Side effects between baseline to 12 mo (N = 28 vs 28), N (%) Skin reactions = 14 (50) vs 12 (43) Nail reactions = 10 (36) vs 4 (14) Fatigue = 8 (29) vs 8 (29)	SF36 Mental Component Scale (N = 28 vs 28), M (SD) Baseline 55 (9) vs 50 (11) Absolute change, 3-month follow-up: 1.6 (6.9) vs 1.0 (8.9) β (95% CI) = 0.6 (-3.9, 5.0)[b] Between group difference at 3-month (95% CI) = 5.7 (0.6, 10.1) SF36 Physical Component Scale (N = 28 vs 28), M (SD) Baseline 38 (9) vs 36 (8) Absolute change, 3-month follow-up: 1.4 (6.8) vs 2.3 (6.0) β (95% CI) = -1.1 (-4.6, 2.4)[b]

Author, Year, PMID	Comparator	Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
		Mean difference (95% CI) from baseline to 12 mo: -1.2 (-8.3, 5.8)[c] PGA (N = 28 vs 28), M (SD) Baseline 5.3 (2.2) vs 5.9 (1.7) Absolute change, 3-month follow-up: -0.8 (2.3) vs -1.1 (2.3) β (95% CI) = 0.4 (-0.9, 1.6)[b] Mean difference (95% CI) from baseline to 12 mo: -0.1 (-1.2, 1.1)[c] Stiffness (AUSCAN) (N = 28 vs 28), M (SD) Baseline 56 (24) vs 62 (20) Absolute change, 3-month follow-up: -1.4 (17) vs -7.6 (21) β (95% CI) = 6.0 (-4.5, 17)[b] Proportion OMERACT-OARSI responders (N = 28 vs 28), N (%)[h] 1 month follow-up: 5 (18) vs 7 (25) Difference in proportion, % (95% CI) = -7 (-29, -14) OR (95% CI) = 0.65 (0.18, 2.35)[b] 2-month follow-up: 8 (29) vs 9 (32) Difference in proportion, % (95% CI) = -4 (-28, 20) OR (95% CI) = 0.82 (0.26, 2.60)[b] 3-month follow-up: 8 (29) vs 10 (36)	Other reactions = 9 (32) vs 6 (21) Any reactions = 21 (75) vs 18 (64) Serious adverse events = 2 (7) vs 0 (0)	

Author, Year, PMID	Comparator	Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
		Difference in proportion, % (95% CI) = -7 (-31,17) OR (95% CI) = 0.69 (0.22, 2.17)[b] 12 months follow-up (N =26 vs 26), N (%): 8 (31) vs 7 (26) Difference in proportion, % (95% CI) = 4 (-20, 29) OR = 1.23 (0.37, 4.12)[b]		
Niewald 2022 34724085	RT 3.0 Gy Baseline to 3 months post RT Follow-up, mo = 3	Pain (VAS)[j] Baseline: N = 110 joints M (SD) = 59.3 (16.7) Min = 10 Max = 90 Difference 3 months post RT: N = 110 joints MD (SD) = -18.9 (27.2) Min = -80 Max = 50 95% CI = -23.98, -13.82[e] Change in pain[j], N[e] (%): Markedly improved = 46 (42) Improved = 19 (17) Stable = 26 (24) Worse = 19 (17) Knee injury and OA outcome score sum score—physical function short form (KOOS-PS)[k] Baseline: N = 32 joints M (SD) = 20.5 (4.9) Min = 8 Max = 28 Difference 3 months post RT: N = 32 joints MD (SD) = -5.5 (5.9)	Acute side effects (undefined), N (%) = 0 (0)	Short form 12 (SF-12), somatic scale, doctor's judgement Baseline: N=68 joints M (SD) = 29.8 (10.5) Min = 14 Max = 52 Difference 3 months post RT: N=67 joints MD (SD) = 5.7 (12.0) Min = -25 Max = 36 95% CI = 2.83, 8.57[e] Short form 12 (SF-12), psychic scale, doctor's judgement Baseline: N = 68 joints M (SD) = 56.0 (5.8) Min = 32 Max = 72 Difference 3 months post RT: N = 67 joints MD (SD) = 1.2 (6.5) Min = -16 Max = 23 95% CI = -0.36, 2.76[e]

Author, Year, PMID	Comparator	Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
		Min = -19 Max = 7 95% CI = -7.54, -3.46 [e] Short form score for the assessment and quantification of chronic rheumatic affections of the hands (SF-SACRAH) Baseline: N =75 joints M (SD) = 21.3 (10.6) Min = 3 Max = 46 Difference 3 months post RT: N =74 joints MD (SD) = -5.7 (10.5) Min = -38 Max = 7 95% CI = -8.09, -3.31 [e]		Short form 12 (SF-12), somatic scale, patient's judgement Baseline: N=68 joints M (SD) = 30.3 (11.1) Min = 15 Max = 52 Difference 3 months post RT: N=67 joints MD (SD) = 5.1 (10.2) Min = -25 Max = 31 95% CI = 2.66, 7.54 [e] Short form 12 (SF-12), psychic scale, patient's judgement Baseline: N = 68 joints M (SD) = 57.8 (6.7) Min = 43 Max = 72 Difference 3 months post RT: N=67 joints MD (SD) = 0.1 (6.9) Min = -16 Max = 14 95% CI = -1.55, 1.75 [e]
Niewald 2022 34724085	RT 0.3 Gy Baseline vs 3 months post RT Follow-up, mo = 3	Pain (VAS)[i] Baseline: N=110 joints M (SD)= 57.1 (15.0) Min = 20 Max = 90 Difference 3 months post RT: N =110 joints MD (SD) = -15.8 (25.5) Min = -70	Acute side effects (undefined), N (%) = 0 (0)	Short form 12 (SF-12), somatic scale, doctor's judgement Baseline: N=60 joints M (SD) = 32.0 (9.6) Min = 17 Max = 52 Difference 3 months post RT: N=60 joints MD (SD) = 3.1 (10.5)

Author, Year, PMID	Comparator	Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
		Max = 60 95% CI = -20.57, -11.04 [e] Change in pain[j], %: Markedly improved = 44 (40) Improved = 21 (19) Stable = 23 (21) Worse = 22 (20) Knee injury and OA outcome score sum score—physical function short form (KOOS-PS)[k] Baseline: N = 29 joints M (SD) = 19.9 (4.6) Min = 8 Max = 27 Difference 3 months post RT: N = 29 joints MD (SD) = -4.9 (5.7) Min = -15 Max = 8 95% CI = -6.98, -2.83 [e] Short form score for the assessment and quantification of chronic rheumatic affections of the hands (SF-SACRAH) Baseline: N = 80 joints M (SD) = 20.7 (10.4) Min = 5 Max = 50 Difference 3 months post RT: N = 80 joints MD (SD) = -4.4 (10.2) Min = -32 Max = 26 95% CI = -6.64, -2.17 [e]		Min = -18 Max = 32 95% CI = 0.44, 5.76 [e] Short form 12 (SF-12), psychic scale, doctor's judgement Baseline: N=60 joints M (SD) = 57.4 (7.1) Min = 36 Max =73 Difference 3 months post RT: N=60 joints MD (SD) = 0.18 (7.4) Min = -18 Max = 20 95% CI = -1.69, 2.05 [e] Short form 12 (SF-12), somatic scale, patient's judgement Baseline: N=60 joints M (SD) = 33.2 (10.0) Min = 18 Max = 52 Difference 3 months post RT: N=60 joints MD (SD) = 2.8 (0.6) Min = -19 Max = 29 95% CI = 2.65, 2.95 [e] Short form 12 (SF-12), psychic scale, patient's judgement Baseline: N=60 joints M (SD) =56.7 (8.8)

Author, Year, PMID	Comparator	Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
				Min = 29 Max = 72 Difference 3 months post RT: N=60 joints MD (SD) = 0.03 (7.6) Min = -16 Max = 21 95% CI = -1.89, 1.95 [e]
Rühle 2021 34342662	RT 3-6 Gy Baseline vs follow-up Follow-up, weeks = 8	Pain (Pannewitz Score)[l] Immediately following RT (N=1185 lesions), N (%) Complete pain relief = 18 (1.5) Partial pain relief = 693 (58.5) Unaltered pain = 428 (36.2) Increases in pain = 46 (3.9) Complete or partial pain response (Pannewitz Score)[l] Immediately following treatment (N=1185 lesions), N (%) 711(60) Pain response (Pannewitz Score)[l] approximately 8 weeks after RT (N=590 patients), N (%) Complete or partial = 387 (65.6) Stable pain = 166 (28.1) Increased pain = 37 (6.3) Pain (NRS), M (SD) Baseline = 66.0 (11.1) Immediately following RT = 53.4 (18.0) Approximately 8 weeks after RT = 44.5 (23.7) Baseline vs Immediately following RT p<0.001 Baseline vs 8 weeks after RT p<0.001 Pain (NRS), MD (SD) of patients with information at all timepoints (N=590) Baseline vs Immediately following RT =		

Author, Year, PMID	Comparator	Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
		-12.3 (15.4) Baseline vs 8 weeks after RT = -21.0 (23.9)		
Weissmann 2022 35046940	RT 3-6 Gy Baseline vs best therapeutic response of the patients immediately following the last RT session, as well as 3 and 6 months after RT, if available. Follow-up, mo = Up to 6	Improvement in pain levels (undefined) (N=196), N (%) 0-20% = 46 (23.5) [e] 20-40% = 22 (11) 40-60% = 30 (15) 60-80% = 25 (12) 80-100% = 71 (37) Worsening of pain (N=196), N (%) 2 (1) Subjective improvement exceeding the clinical benchmark of 20% (N=196) N (%) 148 (75.5)		

Notes: [a] Copublication: Van den Ende, C.H., Minten, M.J., Leseman-Hoogenboom, M.M., van den Hoogen, F.H., Den Broeder, A.A., Mahler, E.A. and Poortmans, P.M., 2020. Long-term efficacy of low-dose radiation therapy on symptoms in patients with knee and hand osteoarthritis: Follow-up results of two parallel randomized, sham-controlled trials. The Lancet Rheumatology, 2(1), pp.e42-e49; [b] Adjusted for stratification of NRS pain <8 vs ≥8/10; [c] Adjusted for baseline values and stratification of pain, and pain medication; [d] Scale of 0-10 where 0 represents the best outcome; [e] Values calculated by the research team based on data provided in the article; [f] Responde r= Either relative improvement in pain or function ≥50% and an absolute improvement of ≥20/100 points or 2 of the following: pain, function or patient's global assessment (relative improvement ≥20% and ≥10/100 points absolute for pain and function or 1/10 points absolute for PGA); [g] Adjusted for age BMI, PGA; [h] Responder = Patients who improve in either pain or function with ≥50% (relative) and ≥20/100(absolute); or if improvement is ≥20% (relative) and ≥10/100 (absolute) for 2 of the following: pain, functioning, and PGA; [i] Linear scale, 0 = no pain, 100 = maximum imaginable pain; [j] Markedly improved = DeltaVAS ≥ 30 points, improved = 0<DeltaVAS<0; [k] 0= No functional impairment; 100 = Maximum impairment; [l] Complete response was considered a Pannewitz score = 0; Partial response was considered a Pannewitz score= 1-2; Unaltered response was considered a Pannewitz score = 3

Abbreviations. AE=adverse event; AOR=adjusted odds ratio; AUSCAN=Australian/Canadian Hand Osteoarthritis Index; BMI=body mass index; CI=confidence intervals; Gy=gray; KOOS-PS=Knee Injury and Osteoarthritis Outcome Score Sum Score- Physical Function Short From; M=mean; Max=maximum; MD=mean difference; Min=minimum; mo=months; NRS=numeric rating scale; OA=osteoarthritis; OMERACT-OARSI=Outcome Measures in Arthritis Clinical Trials - Osteoarthritis Research Society International; OR=odds ratio; PGA=Patient Global Assessment; QoL=quality of life; RT=radiation therapy; SD=standard deviation; SF-12=Short form 12; SF36=short form 36; SF-SACRAH=Short Form Score for the Assessment and Quantification of Chronic Rheumatic Affections of the Hand; VAS=visual analog scale; WOMAC=Western Ontario and McMaster University Osteoarthritis Index Scale.

APPENDIX I. PEYRONIE'S DISEASE

APPENDIX I-1. PEYRONIE'S DISEASE DESIGN DETAILS

Author, Year, PMID, Protocol Number, Country	Study Design	Study Dates	Study Location Details (Hospital Type, Centers)	Intent of RT	Inclusion Criteria	Exclusion Criteria
Incrocci, 2000, 11113753, Netherlands	Single group	1982-1997	Other/Unclear	Primary treatment / prevention of recurrence	Patients with PD treated with RT	NR
Niewald, 2006, 16169684, Germany	Single group	1983-2000	Teaching Hospital	Primary treatment / prevention of recurrence	Patients with PD who were irradiated and had at least one complete follow-up data set	NR
Pietsch, 2018, 30370354, Germany	Single group	1999-2008	Other/Unclear	Primary treatment / prevention of recurrence	Patients with PD treated with superficial x-ray therapy	NR
Pambor, 2003, 14605750, Germany	Single group	[NR 7 year span]	Teaching Hospital, Single center	Primary treatment / prevention of recurrence	Patients with PD treated with superficial beta radiation therapy	NR
Meineke, 2003, 12627261 Germany	Single group	1990-1995	Technical University of Munich (polyclinic)	Primary treatment / prevention of recurrence	Patients with induration penis plastica (IPP) or the so-called Morbus Pyronine	NR

Abbreviations. NR: not reported; PD=Peyronie's disease; PMID=PubMed ID; RT=Radiation therapy.

APPENDIX I-2. PEYRONIE'S DISEASE BASELINE DATA

Author, Year, PMID	N Patients	Intervention	N Lesions	Age Mean (Range)	N (%) Male	N (%) White	Location	Lesion Age	Etiology	Size (mm)	Previous Treatment	Other
Incrocci, 2000, 11113753	RT= 106	Patients treated with either 9 fractions of 1.5 Gy (three fractions weekly, total dose=13.5Gy) using orthovoltage x-ray (N=64) or 6 fractions of 2 Gy (daily, total dose=12 Gy) with electrons (N=42)	NR	59 (35-84)	106 (100)	NR	Penis	Duration of symptoms before RT (months): median=6; mean=11; SD=NR; range=1-72	Trauma to the penis = 19%	NR	Previously treated unsuccessfully = 22% *(Vitamin E = 5; Corticosteroids = 10; Verapamil = 1; Surgical correction of the penile deformity = 6; Not reported = 84)*	Dupuytren's disease=36% Patients taking medication known to possibly affect sexual functioning (antihypertensive or antidepressant agents) (N = 106), N (%)[a] At the time of RT = 31 (29) At follow-up = 56 (53)
Niewald, 2006, **16169684**	RT= 101	Daily reactions of 2Gy delivered to total doses: 30 Gy in 72 patients; 36 Gy in 25 patients; 32–34 Gy in 1 patient; 38–40 Gy in 3 patients Used Co-60 gamma rays or 4-MV, 6-MV photon beams of a linear accelerator, or a direct electron beam (5 MeV up to 8 MeV) depending on the location of the foci.	Number of foci (N=83), N(%): 1=54 (65); 2=25 (30); 3 or more=4 (5)	54 (32-73)	101 (100)	NR	Penis	Duration of symptoms before RT (months) (N = 80), Mean, (range) = 18 (1-204)	NR	Maximum diameter of foci (N-84), N (%): <5mm = 7 (8); 5-10mm = 36 (43); >10mm = 41 (49)	Pretreatment (N=94), N(%)[a]: Oral medication=24 (25.5); Injections into the foci=10 (10.6); Previous operation=2 (2.1); Previous local RT before=1(1.1) No pretreatment=57 (60.6)	Dupuytren's disease (N=88), N (%) = 15 (17.1) Symptoms progression before RT (N=69 patients), N(%) = 59 (85.5) Quality of foci (N=89), N(%): Fibrous = 28 (31); Cartilaginous=27 (30); Calcified=34 (39)
Pietsch, 2018, **30370354**	RT = 83	4 cycles of 50 kV photons at 25 mA with a 2 mm cellon filter and a 1 mm	NR	59 (8.3) (Mean, SD)	83 (100)	NR	Penis	Duration of symptoms before RT (months):	NR	NR	NR	Progression type of PD[b], N (%):

Author, Year, PMID	N Patients	Intervention	N Lesions	Age Mean (Range)	N (%) Male	N (%) White	Location	Lesion Age	Etiology	Size (mm)	Previous Treatment	Other
		aluminum filter administered with superficial x-rays followed by a single dose of 4Gy two days in a row, for a total dose of 32 Gy						Mean = 10.6 SD = 9.3 Median = 8				Very rapid = 24 (28.9); Rapid = 33 (39.7); Slow progression = 18 (21.7); Batch-wise progression = 1 (1.2); No answer = 7 (8.4) Cooccurring benign fibroproliferative disorders (N=83), N(%) = 28 (33.7%) Specific cooccurring disorder in those with cooccurring with benign fibroproliferative disorders (N=28), N (%): Dupuytren's disease = 22 (78.6) Plantar fibromatosis (Ledderhose Disease) = 5 (17.9) Knuckle pads = 4 (14.3) Keloids = 2 (7.1) Double affection in patients = 5 (17.9)

Author, Year, PMID	N Patients	Intervention	N Lesions	Age Mean (Range)	N (%) Male	N (%) White	Location	Lesion Age	Etiology	Size (mm)	Previous Treatment	Other
Pambor, 2003, 14605750	RT = 58	RT with beta radiation (6-8 MeV), 2 or 3 times a week 3Gy each time for a total of 24-30Gy	58	Median (IQR) 54 (34 - 67)	15 (100)	NR	Penis, dorsal	Duration of symptoms (months), N (%): <6 = 18 (31.0); >6 = 15 (25.9); Unclear = 25(43.1)]	NR	NR	15 patients (26%) have history of failed conservative treatment (potassium para-aminobenzoate, Vitamin E, and/or hyaluronate)	Dupuytren's disease, N (%) = 11 (19)
Meineke, 2003, 12627261	RT = 67	External beam: Total dose, 32 Gy, through10 fractions, 2-4 Gy per dose, 8-16 based on fraction dose over 420 days, using the Dermopan II (Siemens, Munich, Germany), 50 kV, 1.0 mm aluminum filter.	76	Age up to 29 yrs 2 (3.0) >29 to 39 yrs 4 (6.0) >39 to 49 yrs 10 (14.9) >49 to 59 yrs 30 (44.8) >59 to 69 yrs 16 (23.9) >69 to 79 yrs 5 (7.5)	67 (100)	NR	Sagittal plane (N = 76 lesions): Anterior third 19 (25) Middle third 31 (40.79) Posterior third 17 (22.37) Over the whole Length 2 (2.63) Frontal plane: Dorsal 39 (51.32) Left 18 (23.68) Right 9 (11.84) Caudal 2 (2.63)	NR	Comorbidities (N = 67 patients): Dupuytren's disease = 21 (31.34) Knuckle pads = 6 (9.0) Ledderhose disease = 3 (4.5) Diabetes mellitus = 7 (10.4)	Size (N = 67 lesions) ≤ 1 x1cm = 34 (44.74) Up to 2x 2 cm = 25 (32.89) Up to 2 x4 cm =5 (6.58) ≥ 2x 4cm = 2 (2.63) No informa-tion = 10 (13.16)	NR	NR

Notes. [a] Numbers estimated by research team based on percentages presented in the article; [b] Very rapid = Weeks until 6 months; Rapid = Over 6 months until a year; Slow progression = In years.

Abbreviations. cm=centimeter; Gy=gray; kV=kilovoltage; mA=milliamperes; MeV=megavoltage; mm=millimeter; NR=not reported; PD=Peyronie's disease; RT=radiation therapy; SD=standard deviation.

APPENDIX I-3. PEYRONIE'S DISEASE QUALITY RATING

Author, Year, PMID, Design	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessor	Incomplete outcome data	Selective reporting	Intention-to-treat-analysis	Clear reporting	Clear eligibility criteria	Interventions adequately described	Outcomes fully defined	Representativeness of the cohort	Comparator representativeness	Adjustment for confounders	Other bias	Overall RoB
Incrocci, 2000, 11113753, Single group	NA	NA	NA	Unclear	Yes (High concern)[a]	NA	NA	No (High concern)[b]	Yes (Low concern)	Yes (Low concern	Yes (Low concern	Yes (Low concern	NA	No (High concern)[c]	No (Low concern)	High (Single group)[d]
Niewald, 2006, 16169684, Single group	NA	NA	NA	Unclear	Yes (High concern)[e]	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern	Yes (Low concern	Yes (Low concern	NA	No (High concern)[c]	No (Low concern)	High (Single group)[d]
Pietsch, 2018, 30370354, Single group	NA	NA	NA	Unclear	No (Low concern)	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern	No (High concern)[f]	Yes (Low concern	NA	No (High concern)[c]	No (Low concern)	High (Single group)[d]
Pambor, 2003, 14605750	NA	NA	NA	Unclear	No (Low concern)	NA	NA	Yes (Low Concern)	Yes (Low concern)	Yes (Low concern)	No (High concern)[g]	Unclear	NA	No (High concern)[c]	No (Low concern)	High RoB (Single group)[d]
Meineke, 2003, 12627261	NA	NA	NA	Unclear	No (Low concern)	NA	MA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern	Unclear	NA	NA	No (Low concern)	High RoB (Single group)[d]

Notes. [a] 179 patients treated with RT but only 130 could be sent a questionnaire, and only 106 responded to the questionnaire; [b] Follow-up time unclear; [c] Crude analysis; [d] The study design is unable to estimate the effect of RT on outcomes; [e] 40% missing at last follow-up time point (1400 days); [f] Symptoms not clearly defined; [g] Methods for outcome assessment was not clear.

Abbreviations. NA=not applicable.

APPENDIX I-4. PEYRONIE'S DISEASE RESULTS SUMMARY

Author, Year, PMID	**Comparator**	**Efficacy** **Mean (SD) or N (%)**	**Side Effects** **N (%)**	**Patient Satisfaction/Experience/QoL** **Mean (SD) or N (%)**
Incrocci, 2000, 11113753	RT 12 or 13.5 Gy Baseline vs follow-up (RT between 1982-1997 and follow-up questionnaire conducted in 1998) Follow-up = unknown	Patients reporting diminished pain (not defined) at follow-up of the 47 (44%) who had reported pain before RT, N (%)[a] = 33 (69) Patients with pain before RT compared to patients with diminished pain after RT (N=106) RD (95% CI)[a] = -0.132 (-0.261, -0.003) p=0.045 Patients reporting decreased penile curvature (not defined) at follow-up of the 103 (97%) who had reported curvature before RT, N (%)[a] = 30 (29) RD (95% CI)[a] = 0.689 (0.587, 0.780) p<0.001 Patients reporting improved erectile disfunction (not defined) at follow-up of the 22 (21%) reporting erectile disfunction before RT, N (%)[a] = 3 (13) RD (95% CI)[a] = 0.179 (0.096, 0.263) p<0.001 Patients reporting being sexually active (not defined) (N=106), N (%)[a] Before RT = 98 (92) After RT = 76 (72) p = 0.002 RD (95% CI)[a] = 0.208 (0.108, 0.307)	Discomfort during RT (N=106), N (%)[a] = 12 (11)	Satisfaction with current (past 4 weeks) sexual life after RT (N=106), N (%)[a] Not satisfied = 52 (49) Somewhat satisfied = 27 (25) Very much satisfied = 28 (26)

Author, Year, PMID	**Comparator**	**Efficacy** **Mean (SD) or N (%)**	**Side Effects** **N (%)**	**Patient Satisfaction/Experience/QoL** **Mean (SD) or N (%)**
		Patients who reported no decrease in sexual interest after RT (N=106), N (%)[a] = 66 (62) Patients who reported no decrease in sexual activity after RT, N (%)[a] = 35 (33) Patients who reported no decrease in sexual pleasure after RT, N (%)[a] = 54 (51) Frequency of spontaneous erections in the past 4 weeks (N=91), N(%) Never = 33 (36) 1/wk = 25 (27) 2-6/wk = 19 (21) 1/day = 10 (11) ≥2/day = 4 (5) Patients reporting difficulty getting an erection in the past 4 weeks (N=67), N (%) No = 33 (49) Sometimes = 21 (31) Always = 13 (20) Patients reporting difficulty maintaining an erection in the past 4 weeks (N=67), N (%) No = 26 (39) Sometimes = 26 (39) Always = 15 (22) Rigidity of spontaneous erections in the past 4 weeks (N=59), N (%) Not at all = 1 (2) Somewhat = 5 (8) Half = 26 (44) Rigid = 20 (34) Very Rigid = 7 (12) Rigidity of erections during sexual activity in the past 4 weeks (N=68), N (%) Not at all = 3 (4)		

Author, Year, PMID	**Comparator**	**Efficacy** **Mean (SD) or N (%)**	**Side Effects** **N (%)**	**Patient Satisfaction/Experience/QoL** **Mean (SD) or N (%)**
		Somewhat = 0 (0) Half = 34 (50) Rigid = 18 (27) Very Rigid = 13 (19) Patients who underwent surgery to correct persisting penile curvature after RT, N(%)[a] = 25 (24) *At the time of the questionnaire (before Viagra was introduced in The Netherlands), only 13 patients were receiving ED treatment: 5 received intracavernosal injections, 3 used a vacuum device, and in 5 patients the treatment was not specified*		
Niewald, 2006, 16169684	RT 30-40 Gy Baseline vs follow-up (best result from any timepoint or at 80, 460, 1100, 1400 days) Follow-up= 80-1400 days	Pain (undefined), Numerator/Denominator (%): Before RT = 48/92 (52) 80 days = 26/87 (30) 460 days = 25/92 (27) 1100 days = 14/69 (20) 1400 days = 5/56 (10) Before RT vs 1400 days, RD (95% CI) = 0.43 (0.31, 0.56), p<0.001[a] Deviation (undefined), N (%) Individual best at any timepoint (N=101): Improvement = 47 (47) No Change = 52 (51) Progression = 2 (2) At 80 days (N=101): Improved = 23 (23) Stable = 71 (70) Worse = 7 (7) At 460 days (N=89): Improved = 23 (26)	Acute dermatitis (Grade 1 Common Toxicity Criteria) at the end of RT (N=101), N (%) = 28 (28) Mild urethritis (Grade 1 Common Toxicity Criteria) at the end of RT (N=101), N (%) = 4 (4) Long term side effects (note defined), N (%) = 0 (0) Indication of malignancy during follow-up (not defined), N (%) = 0 (0) Patients who received oral medication after RT (N=101), N (%) = 2 (2)	

Author, Year, PMID	**Comparator**	**Efficacy** **Mean (SD) or N (%)**	**Side Effects** **N (%)**	**Patient Satisfaction/Experience/QoL** **Mean (SD) or N (%)**
		Stable = 55 (62) Worse = 11 (12) At 1100 days (N=68): Improved = 17 (25) Stable = 46 (68) Worse = 5 (7) At 1400 days (N=47): Improved = 15 (32) Stable = 29 (62) Worse = 3 (6) Number of foci (undefined), N (%) Individual best at any timepoint (N=101): Improvement = 32 (32) No Change = 69 (68) Progression = 0 (0) At 80 days (N=101): Improved = 16 (16) Stable = 79 (78) Worse = 6 (6) At 460 days (N=87): Improved = 16 (18) Stable = 66 (76) Worse = 5 (6) At 1100 days (N=62): Improved = 9 (15) Stable = 52 (84) Worse = 1 (1) At 1400 days (N=36): Improved = 5 (14) Stable = 30 (83) Worse = 1 (3) Size of foci (undefined), N (%)		

Author, Year, PMID	**Comparator**	**Efficacy** **Mean (SD) or N (%)**	**Side Effects** **N (%)**	**Patient Satisfaction/Experience/QoL** **Mean (SD) or N (%)**
		Individual best at any timepoint (N=101): Improvement = 49 (49) No Change = 52 (51) Progression = 0 (0) At 80 days (N =101): Improved = 23 (23) Stable = 71 (70) Worse = 7 (7) At 460 days (N=93): Improved = 28 (30) Stable = 57 (61) Worse = 8 (9) At 1100 days (N=69): Improved = 16 (23) Stable = 47 (68) Worse = 6 (9) At 1400 days (N=48): Improved = 13 (27) Stable = 32 (67) Worse = 3 (6) Quality of foci (undefined), N (%) Individual best at any timepoint (N=101): Improvement = 52 (51) No Change = 48 (48) Progression = 1 (1) At 80 days (N=101): Improved = 32 (32) Stable = 65 (64) Worse = 4 (4) At 460 days (N=84): Improved = 22 (26) Stable = 54 (64) Worse = 8 (10)		

Author, Year, PMID	**Comparator**	**Efficacy** **Mean (SD) or N (%)**	**Side Effects** **N (%)**	**Patient Satisfaction/Experience/QoL** **Mean (SD) or N (%)**
		At 1100 days (N=63): Improved = 18 (29) Stable = 42 (67) Worse = 3 (4) At 1400 days (N=36): Improved = 8 (22) Stable = 26 (72) Worse = 2 (6) Erectile dysfunction, Numerator/Denominator (%): Before RT = 1/72 (1) 80 days = 6/85 (7) 460 days = 4/84 (5) 1100 days = 6/71 (8) 1400 days = 3/47 (6) Before RT vs 1400 days, RD (95% CI) = -0.05 (-0.12, 0.02), p=0.191[a]		
Pietsch, 2018, 30370354	RT 32 Gy Baseline to follow-up Follow-up (mo): Mean = 52 SD = 23 Media = 49 Range = 8-98	Regression of symptoms (undefined) (N=83), N (%): Yes = 39 (47) No = 39 (47) Unclear = 5 (6) Recurrence of symptoms (undefined (N = 83), N (%): Yes = 1 (1.2) No = 75 (90.4) Unclear = 7 (8.4) Stopped PD progression (undefined) (N=83), N (%): Yes = 65 (78.3) No = 12 (14.5) Unclear = 6 (7.2)	Side effects (N = 83), N (%): Telangiectasias = 10 (12) Atrophic skin = 8 (9.6) Paresthesia = 5 (6) Erythema = 32 (38.6) Dry skin = 8 (9.6)	Subjective satisfaction using visual analog scale[b] in 80/83 patients: Mean (SD) = 6.2 (3.1) Median = 7 Positive impact on sexual life (N=83), N (%): Yes = 30 (36.2) No = 44 (53) Unclear = 9 (10.8)
Pambor, 2003,	RT 24 to 30 Gy	Complete resolution of all symptoms (cure) (N = 58), N(%) By 6 weeks = 1 (1.7)	No patient had telangiectasias, ulcers, or atrophy after treatment	ND

Author, Year, PMID	**Comparator**	**Efficacy** **Mean (SD) or N (%)**	**Side Effects** **N (%)**	**Patient Satisfaction/Experience/QoL** **Mean (SD) or N (%)**
14605750	Follow- up = 6 weeks- 2 years	By 3 months = 2 (3.4) By ½ year = 3 (5.2) By 1 year = 5 (8.6) By 2 years = 6 (10.3) 50% Regression (Significant decrease in induration and symptoms) (N = 58), N (%) By 6 weeks = 1 (1.7) By 3 months = 3 (5.2) By ½ year = 5 (8.6) By 1 year = 8 (13.8%) By 2 years = 10 (17.2%) Improvement in penile induration after therapy vs before therapy among those with symptoms/signs at baseline (N = 58), N (%) = 16 (27.6) Improvement in Penile deviation on erection after therapy vs before therapy among those with symptoms/signs at baseline (N = 54), N (%): 13 (24.1) Improvement in pain on erection after therapy vs before therapy among those with symptoms/signs at baseline (N = 20), N (%): 13 (65)		
Meineke, 2003, 12627261	RT = Up to 32 (Gy) Follow-up = 6mo-5yrs	Progression (N = 67) [6mo-5y], N (%) Could be stopped by therapy = 58 (86.6) Could not be stopped by therapy = 5 (7.5) No longer progressing (not fully defined) = 4 (6.0) Symptom Improvement (N=67) [6mo-5y], N (%) Reduction of all symptoms = 7 (10.7) Significant improvement of symptoms = 29 (43.3) Moderate to mild improvement of symptoms = 10 (14.9) Stable symptoms = 16 (23.9) Deterioration = 5 (7.5)	Discrete telangiectasias and minimal hyperpigmentation (N=67) [6mo-5y], N (%) 6 (9) (a patient with a second cycle of radiation) Minor redness in radiation field (N=67) [6mo-5y], N (%) 2 (3)	

Author, Year, PMID	**Comparator**	**Efficacy** **Mean (SD) or N (%)**	**Side Effects** **N (%)**	**Patient Satisfaction/Experience/QoL** **Mean (SD) or N (%)**
		Change in pain (of those reporting pain before RT) (N = 25) [6mo-5y], N (%) Complete regression = 17 (68.0) Stark Improvement = 4 (17.0) Medium/low improvement = 0 (0.0) Same = 2 (8.0) Increase = 2 (8.0) Induration changes (N = 70) [6mo-5y], N (%) Complete improvement = 23 (32.9) Some Regression (including strong, medium, little) = 11 (15.7) Softer = 7 (10) Same = 23 (32.9) Worse = 6 (8.9) Deviation changes (N = 58) [6mo-5y], N (%) Complete improvement = 7 (12.1) Some Improvement (including, strong, medium and little) = 16 (27.6) Same = 30 (51.7) Worse = 5 (8.7) Onset of improvement (Pain improvement), N (%) After the 1st radiation (N=21) = 3 (14.3) After several radiation treatments (N=21) = 8 (38.1) Onset of improvement (induration) (N=39) = NR After several radiation treatments (N=39) = 12 (30.8) Onset of improvement (Deviation) (N=20), N (%) After the 1st radiation = NR		

Author, Year, PMID	**Comparator**	**Efficacy** **Mean (SD) or N (%)**	**Side Effects** **N (%)**	**Patient Satisfaction/Experience/QoL** **Mean (SD) or N (%)**
		After several radiation treatments = 4 (20) Onset of improvement (Pain) In relation to therapy time, N (%) Toward the end of therapy (N=21) = 4 (19) ≤ 3 months after the end of therapy (N=20) = 3 (14.3) > 3 months after the end of therapy (N=20) = 3 (14.3) Onset of improvement (Induration) In relation to therapy time (N=39), N (%) Toward the end of therapy = 11 (28.2) ≤ 3 months after the end of therapy = 11(28.2) > 3 months after the end of therapy = 5 (12.8) Onset of improvement (Deviation) In relation to therapy time (N=20), N (%) Toward the end of therapy = 8 (40) ≤ 3 months after the end of therapy = 6 (30) > 3 months after the end of therapy = 2(10)		

Notes. [a] Numbers estimated by research team based on percentages presented in the article; [b] 1=not satisfied, 10=very satisfied.

Abbreviations. CI=confidence interval; Gy=gray; mo=months; PD=Peyronie's disease; PMID=PubMed ID; QoL=quality of life; RD=risk difference; RT=radiation therapy; SD=standard deviation; wk=week; y=years.

APPENDIX J. DUPUYTREN'S CONTRACTURE

APPENDIX J-1. DUPUYTREN'S CONTRACTURE DESIGN DETAILS

Author, Year, PMID, Protocol Number, Country	Study Design	Study Dates	Study Location Details (Hospital Type, Centers)	Intent of RT	Inclusion Criteria	Exclusion Criteria
Betz, 2010, 20127225, Germany	Single group	1982-2006	Teaching Hospital, Single center	Primary treatment / prevention of recurrence	Patients with clinically evident and progressive early-stage Dupuytren's contracture.	NR
Keilholz, 1996, 8960518, Germany	Single group	1982-1993	Other/Unclear, NR / Unclear	Primary treatment / prevention of recurrence	Patients with clinically evident Dupuytren's contracture.	NR
Latusek, 2017, Poland	Single group	NR	Other/Unclear, Single center	Primary treatment / prevention of recurrence	NR	NR
Zirbs, 2015, 25201324, Germany	Single group	2009-2013	Teaching Hospital, Single center	Primary treatment / prevention of recurrence	Patients with Dupuytren's contracture treated between 1999 and 2008.	NR
Adamietz, 2001, 11757183	Single group	1982-1994	Single Center	Primary treatment	Patient with Morbus Dupuytren	NR

Abbreviations. NR=not reported; PMID=PubMed ID; RT=radiation therapy.

APPENDIX J-2. DUPUYTREN'S CONTRACTURE BASELINE DATA

Author, Year, PMID	N Patients	Intervention Characteristics	N Hands	Age	N (%) Male	N (%) White	Previous Treatment	Comorbidities	Other
Betz, 2010, 20127225, Germany	RT = 135	Two separate courses of five daily fractions of 3Gy each to a total dose of 30Gy with 6 weeks between courses.	RT = 208	NR	127 (61.1) (hands)[a]	NR	Patients who had received previous treatment (N = 135), N(%) 9 (6.7) Surgery and corticoid therapy.	Comorbidities (N = 208 hands), N (%)[a] Ledderhose = 24 (11.5) Peyronies = 11 (5.3) Knuckle pads = 5 (2.4) Diabetes = 35 (16.8) Alcoholism = 9 (4.3)	Family history, N (%) = 78 (37.5%)[a]
Keilholz, 1996, 8960518, Germany	RT = 96	Two courses of five fractions of 3Gy per fraction to a total dose of 30Gy with 6 weeks between courses	RT = 142	54.0 (14.0)[b]	66 (68.8)[a]	NR	NR	Comorbidities (N = 96), N (%)[a] Epilepsy = 2 (2.1) Diabetes = 11 (11.5) Alcoholism = 17 (17.7)	Family history (patients, N (%) = 33 (34.4)[a] Stage, N (%)[d] N = 82 (58) N/I = 17 (12) I = 30 (21) II = 12 (8) III = 1 (1) Duration of clinical symptoms before RT (years), mean = 8 +/- 4
Latusek, 2017, Poland	RT = 117	Up to 21 Gy administered in 7 fractional doses.	RT = 180[a]	61[b] 62 (30-82)[c]	78 (66.7)[a]	NR	Patients who had received previous treatment (N = 117), N (%) 19 (16%)[a] Laser therapy, surgical treatment, ultrasound, steroid	NR	History of smoking, N (%) = 68 (58)[a] Smoked during treatment, N (%) = 23 (20)[a]
Zirbs, 2015, 25201324, Germany	RT = 206	Four courses of 2 fraction of 4Gy per fraction to a total dose of 32Gy, with 8 weeks between courses.	RT = 297	62.9[c]	123 (59.7)	NR	Patients who had received previous treatment (N = 206), N (%) 37 (18%) Surgery, needle fasciotomy, local steroid injection, vitamins,	Comorbidities (N = 206), N(%) Ledderhose = 18 (8.7) Induration penis plastica = 13 (6.3) Knuckle pads = 18 (8.7) Keloids = 7 (3.4) Cardiovascular disease = 21 (10.2)	Patients reporting a positive family history of Dupuytren's, (N = 206), N (%) = 59 (28.6) Disease Activity (not defined) (N =206), N (%) Slow progressive activity = 122 (59.2)

Author, Year, PMID	N Patients	Intervention Characteristics	N Hands	Age	N (%) Male	N (%) White	Previous Treatment	Comorbidities	Other
							shock-wave therapy, magnetic field therapy, massage, NSAID.	Diabetes = 18 (8.7) Liver disease = 4 (1.9) Epilepsy =1 (0.5)	Slow progression in batches = 23 (11.2) Rapid progression = 25 (12.1) Very rapid progression =14 (6.8)
Adamietz-2001-11757183	99	External beam: Total dose, 30 Gy, through10 fractions, 3 Gy per dose, 5 fractions per week, with 6-8 weeks interval using orthovoltage device (Stabiliplan, Siemens, Erlangen, 120-kv photon/20 mAs/4-mm aluminum filter)	176	Median (range) 53.5 (18-70)	66 (66.7)	NR	NR	Concomitant diseases 25 (25) Ledderhose disease 6 (6) Induratio penis plastica 1 (1) Diabetes mellitus 10 (10) Liver cirrhosis 2 (2) Condition after accident/hand injury 12 (12)	Family History 63 (63.6) Stages (N = 176 hands) 0: n = 5 (2.8) N: n = 76 (43.2) N/I: n = 15 (8.5) I: n = 65 (36.9) II: n = 12 (6.8) III: n = 3 (1.7)

Notes. [a] Values calculated by the research team based on data provided in the article; [b] Mean (SD); [c] Median; [d] N= nodes without flexion deformity; N/I= nodes with flexion deformity 1-5 degrees; I= nodes with flexion deformity 6-45 degrees; II= nodes with flexion deformity 46-90 degrees; III= nodes with flexion >90 degrees.

Abbreviations. Gy=gray; kV=kilovoltage; mA=milliamperes; mm=millimeter; NR=not reported; NSAID=non-steroidal anti-inflammatory drugs; RT=radiation therapy.

APPENDIX J-3. DUPUYTREN'S CONTRACTURE QUALITY RATING

Author, Year, PMID, Design	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessor	Incomplete outcome data	Selective reporting	Intention-to-treat analysis	Clear reporting	Clear eligibility criteria	Interventions adequately described	Outcomes fully defined	Representativeness of the cohort	Comparator representa-tiveness	Adjustment for confounders	Other bias	Overall RoB
Betz, 2010, 20127225, Single group	NA	NA	NA	Unclear	No (Low concern)	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	No (Low concern)	High (Single group)[a]
Keilholz, 1996, 8960518, Single group	NA	NA	NA	Unclear	No (Low concern)	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	No (Low concern)	High (Single group) [a]
Latusek, 2017, Single group	NA	NA	NA	Unclear	No (Low concern)	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Unclear	NA	NA	No (Low concern)	High (Single group) [a]
Zirbs, 2015, 25201324, Single group	NA	NA	NA	Unclear	No (Low concern)	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	No (Low concern)	High (Single group) [a]
Adamietz-2001-11757183 Single group	NA	NA	NA	Unclear	No (Low concern)	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern	Unclear	NA	NA	No (Low Concern)	High RoB (Single Group) [a]

Notes. [a] The study design is unable to estimate the effect of RT on outcomes.
Abbreviations. NA=not applicable.

APPENDIX J-4. DUPUYTREN'S CONTRACTURE RESULTS SUMMARY

Author, Year, PMID	Treatment	Stage and Regression	Symptoms	QoL and Patient Satisfaction/ Experience of Care	Side Effects
Betz, 2010, 20127225	Baseline vs follow-up Follow-up, Median (range), y = 13 (NR)	Changes in stage, (N = 208), [median 13 y], N (%)[a,b] Regression = 20 (9.6) Progression = 65 (31.3) Stable = 123 (59.1) Changes in stage by duration of disease (N = 208), [median 13 y], %[a] Regression 1-12 mo = 24 13-24 mo = 11 25-36 mo = 3 37-48 mo = 3 > 48 mo = 3 Progression 1-12 mo = 2 13-24 mo = 19 25-36 mo = 41 37-48 mo = 43 > 48 mo = 55 Stable 1-12 mo = 74 13-24 mo = 70 25-36 mo = 56 37-48 mo = 53 > 48 mo = 41 Changes in stage by pre-RT stage, (N=208), [median 13 y], N (%)[a] Regression N = 7 (6) N/I = 10 (30) I = 3 (6)	Symptom relief (not defined) [median 13 y], N (%)[b] Composite (Dysesthesia, Burning/itching, Pressure/tension) (N=87), No Change = 12 (14) Minor relief = 28 (32) Good relief = 16 (18) Complete relief = 14 (16) Progression = 17 (20) Dysesthesia (N=8) No Change = 2 (25) Minor relief = 3 (37.5) Good relief = 1 (12.5) Complete relief = 0 (0) Progression = 2 (25) Pressure/tension (N=45) No Change = 6 (13.3) Minor relief = 13 (28.9) Good relief = 10 (22.2) Complete relief = 8 (17.8) Progression = 8 (17.8) Burning/itching (N=34) No Change = 4 (11.8) Minor relief = 12 (35.3) Good relief = 5 (14.7) Complete relief = 6 (17.6) Progression = 7 (20.6)	NR	Radiation Therapy Oncology Group/ EORTC criteria. Skin atrophy with occasional telangiectasia [median 13 y], N (%) = 14 (7) Dry skin and increased desquamation [median 13 y], N (%) = 47 (23) Erythema up to 1 y [median 13 y], N (%) = 5 (2) *Chronic grade 3 or 4 reactions were not observed. No induction of cancer could be detected at last follow-up*

Author, Year, PMID	Treatment	Stage and Regression	Symptoms	QoL and Patient Satisfaction/ Experience of Care	Side Effects
		II, III and IV Zero cases Progression in-field N = 9 (8) N/I = 8 (24) I = 12 (24) II, III and IV Zero cases Progression out-field N = 0 (0) N/I = 2 (6) I = 4 (8) II, III and IV Zero cases Progression in+out N = 6 (5) N/I = 0 (0) I = 15 (30) II = 6 (86) III = 2 (100) IV = 1 (100) Stable N 93 (81) N/I 13 (40) I 16 (32) II 1 (14) III and IV Zero cases Change in numbers of nodules and cords (N = 208), [median 13 y], N (%)[c] Regression = 50 (24) Progression in-field = 33 (16) Progression out-field = 21 (10) Progression in+out = 34 (16) Stable = 70 (34)			

Author, Year, PMID	Treatment	Stage and Regression	Symptoms	QoL and Patient Satisfaction/ Experience of Care	Side Effects
		Change in numbers of nodules and cords By pre-RT stage (N=208), [median 13 y], N (%)[a,c] Regression N = 42 (37) N/I = 6 (18) I = 2 (4) II, III and IV Zero cases Progression in-field N = 17 (15) N/I = 5 (15) I = 11 (22) II, III and IV Zero cases Progression out-field N = 11 (10) N/I = 6 (18) I = 4 (8) II, III and IV Zero cases Progression in+out N = 9 (8) N/I = 0 (0) I = 15 (30) II = 7 (100) III = 2 (100) IV = 1 (100) Stable N 36 (31) N/I 16 (48) I 18 (36) II, III, and IV Zero cases			
Keilholz, 1996, 8960518	Baseline vs follow-up Follow-Up, Mean (range), y = 6 (1-12)	Change in stage (N = 142) [3 mo], N (%)[d] No progression = 130 (92) Improvement = 10 (7)	Changes in complaints of symptoms (not defined) (N = 142) [3 mo], N (%) Unchanged = 25 (18) Moderate reduction = 64 (45)	Satisfaction of long-term outcome (time not specified) (N = 96), N (%) = 83 (87)	Total hands that developed acute mild skin reactions (Grade 1), erythema, and dry desquamation [time not specified] (N = 142), N (%) = 61 (43.0)

Author, Year, PMID	Treatment	Stage and Regression	Symptoms	QoL and Patient Satisfaction/ Experience of Care	Side Effects
		Decrease in functional status = 2 (1) Changes to size and consistency of palpable nodules and cords (N = 142) [3 mo], N (%)[e] Stable = 33 (23) Moderate reduction =52 (37) Good reduction = 40 (28) Excellent reduction = 15 (11) Progression = 2 (1) Change in stage (N = 142) [mean follow-up of 6 +/- 2 y], N (%)[d] Stable or improved = 133 (94) Progressions (in the RT field) = 9 (6) Changes to size and consistency of palpable nodules and cords (N = 142) [mean follow-up of 6 +/- 2 y] N (%) Stable = 24 (17%) Reduction of size and softer consistency = 102 (72%) Progression = 16 (11%) Change of palpable nodules and cords according to baseline stage [3 mo], N (%)[b,e] Stage N (N=82) Stable = 17 (20.7) Moderate = 35 (42.7) Good = 23 (28.1) Excellent = 7 (8.5) Progression = 0 (0.0) Stage N/I (N=17)	Major reduction = 41 (29) Complete relief = 6 (4) Worse symptoms = 6 (4)		Radiodermatitis with pronounced erythema and moderate edema (Grade 2) [time not specified] (N = 142), N (%) = 14 (10.0) Mild skin atrophy accompanied by slight fibrosis or occasional telangiectasia within the irradiated area [mean follow-up of 6 +/- 2 y], N (%) = 19 (13.0) Dry skin and desquamation within the irradiated area [mean follow-up of 6 +/- 2 y], N (%) = 91 (64.0) *Grade 3/4 toxicities were not observed.* *Chronic Grade 3 or 4 reactions were not observed* *During RT, most patients complained of itching and burning sensations.*

Author, Year, PMID	Treatment	Stage and Regression	Symptoms	QoL and Patient Satisfaction/ Experience of Care	Side Effects
		Stable = 2 (11.8) Moderate = 6 (35.3) Good = 7 (41.1) Excellent = 2 (11.8) Progression = 0 (0) Stage I (N=30) Stable = 6 (20.0) Moderate = 6 (20.0) Good = 10 (33.3) Excellent = 6 (20.0) Progression = 2 (6.7) Stage II/III (N=13) Stable = 8 (61.5) Moderate = 5 (38.5) Zero events on good and excellent.			
Latusek, 2017	Baseline vs follow-up Follow-up, Mean, mo = 4.4[b]	Change on condition after RT[f] Immediately following RT Improvement = 35% Stable = 58% Deterioration = 7% At follow-up [mean 4.8mo] Improvement = 57.5% Stable = 35% Deterioration = 7.5%	NR	NR	Erythema [4.8mo] 7.5% Superficial epidermal exfoliation [4.8mo] 2.5% Palmar dryness [4.8mo] 2.5%
Zirbs, 2015, 25201324	Baseline vs follow-up Follow-up, Median (range), mo = 40 (6-115)	No further disease progression (including patients with regression) (not defined) (N = 206), [Median 40 mo], N (%) = 165 (80.0) Subjective therapeutic effect (reduction, not defined) (N = 426 nodes and cords), [Median 40 mo], N (%) = 92 (21.6)	Regression of symptoms (not defined) (N = 206), [Median 40 mo], N (%) = 93 (45.0)	Patient's satisfaction (VAS 0-10) (N =198) [Median 40 mo], Mean (SD) = 7.9 (2.7)	Side effects (N =206), [Time not specified], N (%) Erythema = 42 (20.4) Missing data = 27 (13.1) Dry skin = 82 (39.8) Missing data = 15 (7.3) Desquamation = 8 (3.8) Chronic Side-Effects (N=206), [>4 week], N (%) Desquamation = 8 (3.8) Skin atrophy = 7 (3.0)

Author, Year, PMID	Treatment	Stage and Regression	Symptoms	QoL and Patient Satisfaction/ Experience of Care	Side Effects
					Lack of sweating = 8 (4.0) Telangiectasia = 6 (3.0) Sensory affection = 4 (2.0) Desquamation = 5 (2) Dry skin = 41 (20)
Adamietz-2001-11757183	Baseline vs follow-up Follow-up, Median (range), yrs = 10 (7–18)	Regression (N = 176 hands) [10 yrs], N (%) 18 (10%) Regression by lesion stage at baseline (Tubiana et al. classification) [10 yrs], N (%) 0 (N = 5) = 0 (0) N (N = 76) = 12 (16) N/I (N = 15) = 2 (13) I (N = 65) = 4 (6) II (N = 12) = 0 (0.0) III (N = 3) = 0 (0.0) Stable (N = 176 hands) [10 yrs], N (%) 86 (49) Stability by lesion stage at baseline (Tubiana et al. classification) [10 yrs], N (%) 0 (N = 5) = 5 (100) N (N = 76) = 52 (68) N/I (N = 15) = 8 (54) I (N = 65) = 19 (29) II (N = 12) = 2 (17) III (N = 3) = 0 (0.0) Progression in the field (N = 176 hands) [10 yrs], N (%) 38 (22) Progression in the field by lesion stage at baseline (Tubiana et al. classification) [10 yrs], N (%)	NR	NR	Skin atrophy (occasionally associated with telangiectasia) (N = 176 hands) [10 yrs], N (%) 15 (8.5) Anhidrosis with severe scaling (N = 176 hands) [10 yrs], N (%) 44 (25) Side effects by LENT-SOMA score (min: 0.7, max: 3.5) (N = 176 hands) [10 yrs], N (%) Score 0.07 = 111 (63) Score 0.14 = 32 (18) Score 0.21 = 11(6) Score 0.28 = 4 (2.27) No late side effect (N = 176 hands) [10 yrs], N (%) 111 (63)

Author, Year, PMID	Treatment	Stage and Regression	Symptoms	QoL and Patient Satisfaction/ Experience of Care	Side Effects
		0 (N = 5) = 0 (0.0) N (N = 76) = 6 (8) N/I (N = 15) = 2 (13) I (N = 65) = 19 (29) II (N = 12) = 8 (66) III (N = 3) = 3 (100) Progression outside the field (N = 176 hands) [10 yrs], N (%) 34 (19) Progression outside the field by lesion stage at baseline (Tubiana et al. classification) [10 yrs], N (%) 0 (N = 5) = 0 (0.0) N (N = 76) = 6 (8) N/I (N = 15) = 3 (20) I (N = 65) = 23 (36) II (N = 12) = 2 (17) III (N = 3) = 0 (0.0) Recurrence in the former radiation field (N = 176 hands) [10 yrs], N (%) 38 (22)		

Notes. [a] Staging followed Tubiana et al, which classification is based on the total flexion deformity/extension deficit of the involved the medial phalangeal and the proximal interphalangeal finger joints. Stage I = nodules, cords, skin retraction/fixation, no extension deficit/flexion deformity; Stage N/I = flexion deformity between 1 and 5 degrees; Stage I = 6-45 degrees; Stage II = 46-90 degrees; Stage III = 91-135 degrees; Stage IV = >135 degrees; [b] Values calculated by the research team based on data provided in the article; [C] Regression = Decrease in nodules/cord; Progression = Increase in nodules/cords; Stable = No change in nodules/cords; [d] Staging according to Tubiana et al. which classification is based on the total flexion deformity/extension deficit of the involved the medial phalangeal and the proximal interphalangeal finger joints. Stage 0 = no (apparent) lesion; Stage N = nodule without flexion deformity; Stage N/I = flexion deformity between 1 and 5 degrees; Stage I = 6-45 degrees; Stage II = 46-90 degrees; Stage III = 91-135 degrees; Stage IV = >135 degrees; [e] Stable = No change in of the flexion deformity; Moderate = 25-50% reduction of module or cord with some softening; Good = 51-75% reduction of module or cord with major softening; Excellent = >75% reduction of module or cord or complete resolution; Progression = progression of deformity or enlargement of area; [f] Improvement was defined as a decrease in the size of nodules, reduction of contracture, or the improvement of manual function.

Abbreviations. EORTC=European Organization for Research and Treatment of Cancer mo=months; NR=not reported; QoL=quality of life; RT=radiation therapy; VAS=visual analogue scale; y=years.

APPENDIX K. LEDDERHOSE DISEASE

APPENDIX K-1. LEDDERHOSE DISEASE DESIGN DETAILS

Author, Year, PMID, Protocol Number, Country	Study Design	Study Dates	Study Location Details (Hospital Type, Centers)	Intent of RT	Inclusion Criteria	Exclusion Criteria
De Hann, 2023, 37211283, Netherlands	RCT	2018-2019	Multicenter	Primary treatment / prevention of recurrence	Adult patients (18 or over) with a WHO performance score 0-2, Pain score related to Ledderhose disease>= 2, good understanding of the Dutch language, ability and willingness to attend follow-up visits, and complete several questionnaires in Dutch.	Patients with previous RT treatment and/or surgery for Ledderhose disease in the affected foot, any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol or follow-up schedule, unable to lie in a prone position for at least 15 minutes, pregnancy at entry or planning to become pregnant within 6 months.
de Hann 2022, 35101465 NCT04229147 Netherlands	Single Group	2008-2017	Teaching Hospital	Primary treatment / prevention of recurrence	Patients with Ledderhose who were treated with RT from 2008-2017 with a minimum of 2 years follow-up	NR
Heyd 2010, 20082184 Germany	Single Group	2003-2008	Other/Unclear	Primary treatment / prevention of recurrence	NR	Patients receiving a deviating RT protocol or with incomplete follow-up
Seegenschmiedt, 2003, 14652674	Sigle group	1996-2002	Single clinic	Primary treatment/prevention of recurrence	Patients with ML (Morbus Ledderhose)	Patients with minor symptoms or very small nodes were not treated

Abbreviations. NR=not reported; PMID=PubMed ID; RT=radiation therapy.

APPENDIX K-2. LEDDERHOSE DISEASE BASELINE DATA

Author, Year, PMID	N Patients	Intervention	N Lesions	Age (Years), Mean (SD)	N (%) Male	N (%) White	Location	Lesion Age	Size (mm)	Previous Treatment	Comorbidities
De Hann, 2023, 37211283	RT = 42	Five daily fractions of 3 Gy for 10 weeks for total dose of 30.	RT = 65	55.9 (9.4)	57 (67.9)	NR	Foot	NR	NR	NR	NR
	Sham = 42	The radiation therapy device was not activated, and patients were exposed to recordings of the sound of the device	RT = 65								
de Hann 2022, 35101465	RT = 67	Participants received two courses of 5 daily fractions of 3 Gy repeated after 10 weeks for a total dose of 30 Gy. Patients were irradiated using either orthovolt (N = 9 feet) or electrons (N = 3 feet).	102	55 (9.6) Mean (SD)	28 (41.8)	NR	Foot (20 left; 12 right; 35 bilateral)	NR	NR	Received surgery for the disease prior to RT, N (%) = 13 (19.4) Re-irradiated on new nodules outside the previously treated area, N (%) = 1 (1.5)	Cooccurring disease, N (%): Dupuytren's disease = 40 (60%) Peyronie's disease = 4 (6.0%) *50% of patients had a family history of Ledderhose, Dupuytren's, and/or Peyronie's disease*
Heyd 2010, 20082184	RT = 24	Participants received either five weekly fractions of 3.0 Gy repeated at 6 weeks for a total dose of 30.0 Gy (N=20) or two fractions of 4.0 Gy on consecutive	33	52 (28-83) Mean (Range)	12 (50)	NR	Foot (9 right, 6 left, 9 bilateral)	Persistence of complaints prior to RT was 2-60 months (Median= 9.5; Mean= 14.2)	NR	*The majority of patients were previously treated by prescription of decompressive insoles or oral administration of nonsteroidal anti-*	Concomitant Morbus Dupuytren, N (%)= 10 (41.7)

Author, Year, PMID	N Patients	Intervention	N Lesions	Age (Years), Mean (SD)	N (%) Male	N (%) White	Location	Lesion Age	Size (mm)	Previous Treatment	Comorbidities
		days, repeated every 4 weeks to a total dose of 24–32 Gy (N=4). Patients were irradiated using either orthovoltage X-ray (N=21) or electrons of a linear accelerator (N=3).								*inflammatory drugs.* *In addition, 2 patients underwent surgery and RT was prescribed for treatment of recurrent disease.*	
Seegenschmiedt, 2003, 14652674	RT = 25	External beam: Total dose, 30 Gy, through10 fractions, 3 Gy per dose, 5 fractions per week, with 8-12 weeks interval using orthovoltage device (Philips, Hamburg, Gulmay Medical, Bristol, UK) 150-kv photon/20 mA/4-mm aluminum filter)	36	Median (range) 56 (9-76)	13 (52)	NR	Right feet: 16 (44.4), Left feet: 20 (55.6)	NR	Nodes size: average 2.4 cm (range 0.5-6.5 cm) Strands length: average 2.5 cm (range 1-4 cm)	NR	Morbus Dupuytren 12 (48) typical knuckle pads: 2 (8) Induration penis plastica: 1 (4)

Abbreviations. Gy=gray; kV=kilovoltage; mA=milliamperes; NR=not reported; PMID=PubMed ID; RT=radiation therapy; SD=standard deviation.

APPENDIX K-3. LEDDERHOSE DISEASE QUALITY RATING

Author, Year, PMID, Design	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessor	Incomplete outcome data	Selective reporting	Intention-to-treat analysis	Clear reporting	Clear eligibility criteria	Interventions adequately described	Outcomes fully defined	Representativeness of the cohort	Comparator representative	Adjustment for confounders	Other bias	Overall RoB
De Hann, 2023, 37211283	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Unclear	No (Low concern)	No (Low concern)	No (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	NA	NA	NA	No (Low concern)	Low (RCT)
de Hann 2022, 35101465, Single group	NA	NA	NA	No (High concern) [a]	No (Low concern)	NA	MA	No (High concern) [b]	Yes (Low concern)	Yes (Low concern)	Yes (Low concern)	Unclear	NA	NA	No (Low concern)	High (Single group)[c]
Heyd 2010, 20082184, Single group	NA	NA	NA	Unclear	No (Low Concern)	NA	NA	Yes (Low concern	Yes (Low concern)	Yes (Low concern)	No (High concern) [d]	Yes (Low concern)	NA	NA	No (Low concern)	High (Single group)[c]
Seegen-schmiedt, 2003, 14652674	NA	NA	NA	No (High concern) [e]	No (Low Concern)	NA	NA	Yes (Low concern	Yes (Low concern)	Yes (Low concern)	No (High concern) [d]	Unclear			No (Low concern)	High (Single group)[c]

Notes. [a] Outcomes were self-reported; [b] Unclear which measure was used when reporting pain outcomes; [c] The study design is unable to estimate the effect of RT on outcomes [d] Unclear definition of outcomes; [e] Some outcomes were self-reported.

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

Appendix K-4. Ledderhose Disease Results Summary

Author, Year, PMID	Comparator	Symptoms/Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
De Hann, 2023, 37211283	RT vs Sham Follow-up, mo = 6, 12, and 18	Pain (NRS), M (SD) Baseline (N=42 vs 42) 5.8 (2.1) vs 5.6 (2.1) 6 mo follow-up (N=40 vs 40) 3.2 (2.6) vs 3.4 (2.5) Mean difference (95% CI): -0.2 (-1.1 to 0.7) 12 mo follow-up (N=40 vs 39) 2.5 (2.5) vs 3.6 (3.0) Mean difference (95% CI): -1.1 (-2.1 to -0.1) 18 mo follow-up (N=40 vs 39) 2.1 (2.3) vs 3.4 (2.8) Mean difference (95% CI): -1.3 (-2.2 to -0.4) RT pain response (%) 6 mo follow-up (N=40) Progressive pain 5% Stable pain 34% Partial pain response 48% Complete pain response 13% 12 mo follow-up (N=40 Progressive pain 2% Stable pain 24% Partial pain response 37% Complete pain response 37% 18 mo follow-up (N=40 Progressive pain 5% Stable pain 18% Partial pain response 38% Complete pain response 39%	Adverse side effects Erythema foot soles 13 (33) vs 7 (18) OR (95%CI) 2.20 (0.77; 6.30) Dryness skin foot 12 (30) vs 6 (15) OR (95%CI) 2.36 (0.78; 7.09) Increased pain 10 (25) vs 8 (21) OR (95%CI) 1.29 (0.45; 3.72) Burning sensation 7 (18) vs 7 (18) OR (95%CI) 0.97 (0.31; 3.08) Mental impact 5 (13) vs 2 (5) OR (95%CI) 2.64 (0.48; 14.52) Fatigue 5 (13) vs 4 (10) OR (95%CI) 1.25 (0.31; 5.05) Increased sensitivity 4 (10) vs 3 (8) OR (95%CI) 1.33 (0.28; 6.39) Edema feet 3 (8) vs 3 (8)	QoL (EQ D5), M (SD) Baseline (N=42 vs 42) 0.63 (NR) vs 0.71 (NR) 6 mo Follow-up (N=40 vs 40) 0.82 (NR) vs 0.77 (NR) 12 mo Follow-up (N=40 vs 39) 0.85 (NR) vs 0.77 (NR) 18 mo Follow-up (N=39 vs 40) 0.84 (NR) vs 0.76 (NR) Overall improvement more “pronounced” for patients who received RT (p <0.001) QoL (EQ VAS), M (SD) Baseline (N=42 vs 42) 71.9 (NR) vs 67.8 (NR) 6 mo Follow-up (N=40 vs 40) 74.8 (NR) vs 74.8 (NR) 12 mo Follow-up (N=40 vs 39) 76.8 (NR) vs 74.0 (NR) 18 mo Follow-up (N=40 vs 39) 78.8 (NR) vs 73.8 (NR) Overall improvement more “pronounced” for patients who received RT (p = 0.04)

Author, Year, PMID	Comparator	Symptoms/Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
		Sham RT pain response (%) 6 mo follow-up (N=40) Progressive pain 5% Stable pain 34% Partial pain response 48% Complete pain response 13% 12 mo follow-up (N=39 Progressive pain 14% Stable pain 30% Partial pain response 39% Complete pain response 17% 18 mo follow-up (N=39) Progressive pain 9% Stable pain 37% Partial pain response 39% Complete pain response 15% Overall pain response (4 categories) significantly different (p = 0.002) Walking speed m/sec, M (SD) Baseline (N=42 vs 42) 1.53 (0.27) vs 1.56 (0.31) 6 mo follow-up (N=40 vs 40) 1.61 (0.27) vs 1.59 (0.26) Mean difference (95% CI): 0.02 (-0.12 to 0.16) 12 mo follow-up (N=40 vs 39) 1.65 (0.23) vs 1.61 (0.26) Mean difference (95% CI): 0.04 (-0.09 to 0.17) 18 mo follow-up (N=40 vs 39) 1.65 (0.26) vs 1.58 (0.30) Mean difference (95% CI): 0.07 (-0.07 to 0.21)	OR (95%CI) 0.97 (0.18; 5.14) Tingling feeling 1 (3) vs 3 (8) OR (95%CI) 0.31 (0.03; 3.09) Telangiectasia 1 (3) vs 0 (0) Blisters 1 (3) vs 0 (0) Other 25 (63) vs 22 (56) OR (95%CI) 1.29 (0.52; 3.17) Serious adverse events 1 (2) vs 2 (5) OR (95%CI) 0.47 (0.04; 5.45)	

Author, Year, PMID	Comparator	Symptoms/Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
		Step rate (steps/sec), M (SD) Baseline (N=42 vs 42) 2.18 (0.26) vs 2.24 (0.58) 6 mo follow-up (N=40 vs 40) 2.25 (0.27) vs 2.15 (0.23) Mean difference (95% CI): 0.10 (-0.01 to 0.21) 12 mo follow-up (N=40 vs 39) 2.28 (0.28) vs 2.18 (0.21) Mean difference (95% CI): -0.01 to 0.21) 18 mo follow-up (N=40 vs 39) 2.12(0.22) vs 2.25 (0.26) Mean difference (95% CI): -0.13 (-0.24 to 0.02)		
de Hann 2022, 35101465	Baseline vs follow-up[a], Follow-up (mo), median (range) = 49 (24-132)	Pain (LedRad-LTE)[b] (N=102 feet), M (SD) Pre-RT = 5.7 (2.5) Follow-up = 1.7 (2.1) p<0.001 MD (CI) = -4 (-4.451, -3.549)[c] Pain interference (Brief Pain Inventory) (N=102 feet), at follow-up, Mean (SD)=1.3 (1.8) Response to pain at follow-up (N=102 feet) (LedRad-LTE), N (%)[d] Complete = 42 (41.2) Partial = 38 (37.3) No change = 22 (21.5) Progressive = 0 (0) Patient reporting a permanent positive effect of radiation therapy on pain (N=67 patients)[f]= 46 (69)	Long-term side effect, time not specified) (N=67 patients), N (%) Dryness = 10 (15) Erythema = 2 (3)	EURO-QOL-5D-5L- societal perspective at follow-up (N=64 patients), Mean (SD) Study sample [Mean (SD) 59.8 (9.7) years old] = 0.856 (0.130) Reference values of the Dutch general population (50-60 years old) = 0.857 (0.183) EURO-QOL-5D-5L- patient perspective at follow-up (N=64 patients), Mean (SD) Study sample [Mean (SD) 59.8 (9.7) years old] = 82.3 (14.5) Reference values of the Dutch general population (50-60 years old) = 80.6 (NR) Patient satisfaction with treatment (N=67 patients), N (%)[e,f]= 52 (78)

Author, Year, PMID	Comparator	Symptoms/Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
				Patients who considered treatment not burdensome (N=67 patients) m N (%)[f]= 38 (57)
Heyd 2010, 20082184	Baseline vs follow-up Follow-up (mo), median (range) = 22.5 (6-76)	Pain remission among those who experienced pain at baseline (N=19 patients), N (%)[g] = 13 (68.4) Persistent pain (undefined) among those who experienced pain at baseline (N=19 patients), N (%) Slight = 4 (21.1) Moderate = 3 (15.8) Lesion Remission (undefined) (N = 33 lesions), N (%): Complete = 11 (33.3) Partial[h] = 18 (54.4) Stable = 4 (12.1) Progression of size and number of the lesions or clinical symptoms at follow-up (N=24), N (%) = 0 (0) Gait abnormality improvement among those with gait abnormalities at baseline (N=15 patients), N (%)[i] = 11 (73.3) Gait normalization among those with gait abnormalities at baseline (N=15 patients), N (%)[i] = 9 (60.0)	Erythema or hyperpigmentation (time not specified) (N=24 patients), N (%) = 6 (25) Soft tissue fibrosis and an increased dryness of the skin (time not specified) (N=24 patients), N (%) = 3 (12.5)	Improvement in subjective satisfaction of functional status (N=24 patients), N (%)[j] = 22 (91.6)
Seegenschmiedt, 2003, 14652674	Follow-up (mo), Median = 42	Prevention of progression (N=36 lesions), N (%) = 36 (100) Decrease in one or more findings or symptoms (N = 25 patients), N (%) 20 (80) Physical function (Gait: Complete response) Patients N = 25, n/N (%) = 5/25 (20)	Skin redness (CTC concept) (N=25) [up to 3mo post RT] = 5 (20)	NR

Author, Year, PMID	Comparator	Symptoms/Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
		Number of patients with gait disturbance Before treatment = 8 After treatment = 3 Number of nodes Before treatment = 63 After treatment = 46 Average decrease in size of nodes (cm) (N =63), Mean (range) = 1.5 (1-3) Number of strands: Before treatment = 20 After treatment = 11 Average decrease length of strands (cm) (N =20), Mean (range) = 1.5 (1-2) Stable nodes (no node enlarged, or new nodes appeared) (N=25), N (%) 15 (60) Strands remained stable (N-25), N (%) = 15 (60) Disappearance of additional symptoms (swelling, pressure sensation) (N=12), N (%) 6 (50) Patients with remaining “tension sensation” (N=7), N (%) 6 (86) Patients reported improvement on VAS (N=25), N (%) Improved by 75-100% = 6 (24) Improved by 50-74% = 8 (32) Improved by 25-49% = 6 (24) No improvement/stable = 5 (20)		

Author, Year, PMID	Comparator	Symptoms/Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
		Pain response (N=16), N (%) Complete response = 9 (56) Remained the same = 7 (44)		

Notes. [a] Follow-up defined as time between last day of radiation and completion of questionnaire (months); [b] Investigator developed, non-validated custom-made questionnaire; [c] Numbers estimated by research team based on percentages presented in the article; [d] Complete pain response (absence of pain)=current pain score of 0 points with decrease of the initial pain score by at least two points; partial pain response=current pain score of at least 1 point with a decrease of the initial pain score by at least 2 points; no change=1 or zero point change in either direction from initial pain score; progressive=increase in initial pain score by at least 2 points; [e] Very satisfied to very unsatisfied; [f] Total N not specified but assumed to be full sample; [g] No, slight, moderate, severe; [h] Classified as partial due to a reduced number or size of cords; [i] No limitations, >1km, ≤1km, complete limitation; [j] Using linear analog scale.

Abbreviations. CI=confidence interval; CTC=common toxicity criteria; EURO-QOL-5D-5L=European Quality of Life-5 Dimensions – 5 levels scale; MD=mean difference; LedRad-LTE=Ledderhose disease – Long Term Effects of Radiotherapy Treatment; Mo=months; NRS=numeric rating scale;NR=not reported; QoL=quality of life; RT=radiation therapy; SD=standard deviation.

APPENDIX L. HIDRADENITIS SUPPURATIVA

APPENDIX L-1. HIDRADENITIS SUPPURATIVA DESIGN DETAILS

Author, Year, PMID, Protocol Number, Country	Study Design	Study Dates	Study Location Details (Hospital Type, Centers)	Intent of RT	Inclusion Criteria	Exclusion Criteria
Fröhlich 2000, 10897256 Germany	Single Group	1979-1997	2 hospitals (unclear level of care)	Primary treatment as first line or later line therapy	Patients with axillary hidradenitis suppurativa	NR

Abbreviations. NR=not reported; PMID: PubMed ID; RT=radiation therapy.

APPENDIX L-2. HIDRADENITIS SUPPURATIVA BASELINE DATA

Author, Year, PMID	N Patients	Treatment	N Lesions	Age	N (%) Male	N (%) White	Lesion Characteristics				
							Location	Lesion Age	Symptoms and Severity	Previous Treatment	Comorbidities
Froehlich 2000, 10897256	RT = 231	Linear accelerator X rays, 175KeV. Acute cases treated 0.5G, up to 5 days/week frequency for a total of 3 Gy Chronic cases treated with up to 1.5Gy per dose, up to 3 day per week frequency for a total dose of up to 8 Gy. Most patients (n=190) received 6 doses; 9 patients more than 8 and up to 10 Gy For 34 patients with persisting symptoms after 6 weeks, a second series was done (total dose 20 Gy in both series).	270	Median about 40y (range 20, 79)	58	NR	Axilla (right 43%, left 40%, both 17%)	Less than 1 week (n=95, 41%) 1 to 2 weeks (n=47, 20%) 2 weeks to 1 month (n=42, 18%)	Pain (n=65, 28%) Induration (n=67, 29%) Redness (n=13, 6%), Full manifestation (n=79, 34%) Severity* Beginning (n=95, 41%), Coarse nodular with coarse glandular swellings (n=21, 9%) Advanced form with gross nodular swelling of the glands and abscess formation (n=18, 8%), Chronic recurrent hidradenitis with inflammation of the skin (n=92, 40%). Phlegmonous hidradenitis with spread of the inflammation into the depth of the armpit (n=5, 2%).	None (n=105, 45%) Drainage (n=90, 39%) Antibiotics (n=16, 7%) Antibiotics and ointments (n=20, 17%)	NR

Notes. * Per Dornuf et al: Dornuf G. Schönwald H. Zur Röntgentherapie der sogenannten Schweißdrüsenabscesse. Strahlentherapie 1951:84:439- 48.
Abbreviations. Gy=gray; KeV=kilo-electrovolt; NR=not reported; RT=radiation therapy; SD=standard deviation.

APPENDIX L-3. HIDRADENITIS SUPPURATIVA QUALITY RATING

Author, Year, PMID, Design	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessor	Incomplete outcome data	Selective reporting	Intention-to-treat analysis	Clear reporting	Clear eligibility criteria	Interventions adequately described	Outcomes fully defined	Representativeness of the cohort	Comparator representativeness	Adjustment for confounders	Other bias	Overall RoB
Froehlich 2000, 10897256	NA	NA	NA	Unclear	No (Low concern)	NA	NA	Yes (Low concern)	Yes (Low concern)	Yes (Low concern	Yes (Low concern	Yes (Low concern	NA	NA	No (Low Concern)	High RoB (Single Group)[a]

Notes. [a] The study design is unable to estimate the effect of RT on outcomes.

Abbreviations. ITT=intention-to-treat; NA=not applicable; NRCS=nonrandomized comparative study; RCT=randomized controlled trial.

APPENDIX L-4. HIDRADENITIS SUPPURATIVA RESULTS SUMMARY

Author, Year, PMID	Comparator	Symptoms/Efficacy	Side Effects	Patient Satisfaction/Experience/QoL
Froehlich 2000, 10897256	None Follow-up 1 to 1.5 months.	Resolution of all symptoms: 89/231 (39%) Resolution or improvement in symptoms 181/231 (78%) Resolution via abscessation (with or without spontaneous drainage) 48/231 (21%) No improvement 2/231 (1%)	NR	NR

Abbreviations. CI=confidence interval; Mo=months; MD=mean difference; NR=not reported; PMID=PubMed ID; QoL=quality of life; RT=radiation therapy; SD=standard deviation.

APPENDIX M. PEER REVIEW DISPOSITION

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	Thank you.
2	2	Yes	Thank you.
3	3	Yes	Thank you.
4	4	Yes	Thank you.
Is there any indication of bias in our synthesis of the evidence?			
5	1	No	Thank you.
6	2	No	Thank you.
7	3	No	Thank you.
8	4	No	Thank you.
Are there any published or unpublished studies that we may have overlooked?			
9	1	No	Thank you.
10	2	No	Thank you.
11	3	No	Thank you.
12	4	Yes - Although published one month past literature search end date, phase III randomized LedRad-study provides significant impact to evidence of RT in Ledderhose disease and should be considered. PMID: 37211283	Thank you. We have incorporated this study in the report and updated the summary statement. Note that we do not evaluate certainty of evidence for Ledderhose disease because this disease had less than 3 comparative studies.
Additional suggestions or comments can be provided below.			
13	1	This review offers a lengthy, organized, and detailed summary of low-dose radiation therapy (RT) for benign conditions, with a specific focus on those affecting veterans. Conducted by the Veterans Affairs (VA) Evidence Synthesis Program, the systematic analysis outlines the purpose, background, methods, and initial results. In the introduction, the purpose is clearly stated, detailing the specific request from the Veterans Health Administration and explaining how the evidence review aims to inform guidance on RT for benign	Thank you.

Comment #	Reviewer #	Comment	Author Response
		conditions among veterans. The background section supports the rationale for the review, offering a comprehensive overview of RT's use for various benign conditions and justifying the exploration of low-dose RT as an alternative treatment, particularly for musculoskeletal conditions among veterans.	
14	1	The methods section is detailed and transparent, explaining topic development, key questions, and protocol registration, enhancing the review's credibility. Clear definitions of inclusion and exclusion criteria contribute to the transparency of the study selection process. The search strategy is well-described, indicating the databases searched and the time frame covered. The use of abstracts for citation screening and an explanation of the screening process add transparency to the study selection. The section on data abstraction and risk of bias assessment is thorough, outlining the process and tools used for evaluating study quality. The discussion of risk of bias assessment for different study designs adds depth to the evaluation. The synthesis section provides a comprehensive overview of included studies, employing meta-analysis and considering factors like statistical heterogeneity to strengthen the analysis.	Thank you.
15	1	Emphasizing the certainty of evidence for each conclusion would enhance readers' understanding of the findings' robustness and study limitations.	The methods describes our approach for assessing certainty of evidence. Specifically, we assessed certainty of evidence when there were at least 3 comparative studies per disease (*ie,* heterotopic ossification, keloids, plantar fasciitis, and pterygium with brachytherapy). The text and key findings note when certainty of evidence was not assessed.
16	1	The results discussion offers a comprehensive overview of studies on low-dose RT for various benign musculoskeletal conditions. While the conclusion is succinct and summarizes key findings, reinforcing the implications for clinical practice and policy would strengthen its impact.	Thank you.

Comment #	Reviewer #	Comment	Author Response
17	1	The discussion is well-structured, providing a comprehensive overview of studies examining the use of low-dose RT for various benign conditions. The text is skillfully organized with clear headings and subheadings, facilitating an easy understanding of the review's structure. The separation of purpose, background, methods, and results enhances readability. In conclusion, I find this manuscript to be well-organized, presenting information in a clear and structured manner. It comprehensively addresses various diseases, offering a thorough overview of studies conducted on each condition. The document outlines the review's methodologies, including search and eligibility criteria, and data analysis methods. Incorporating diverse study types such as RCTs, NRCS, single-group studies, and systematic reviews broadens the perspective on existing literature. The meticulous evaluation of each condition, along with a summary of findings, enhances the overall clarity of the review. Results are presented lucidly, with the inclusion of tables and figures for better comprehension. Furthermore, the incorporation of a sensitivity analysis and examination of historical comparison groups adds nuance to result interpretation. Emphasizing the necessity for high-quality comparative studies and highlighting the VA's potential leadership in developing RT guidelines for benign diseases is crucial.	Thank you.
18	1	Minor suggestions: Although the review acknowledges limitations, including potential biases, variability in RT doses, and limited availability of high-quality evidence, explicitly stating the certainty of evidence for each discussed condition would be beneficial. While some diseases mention certainty of evidence, others lack this clarification.	We evaluated certainty of evidence when there were at least 3 comparative studies per disease (*ie,* heterotopic ossification, keloids, plantar fasciitis, and pterygium with brachytherapy). The text and key findings note when certainty of evidence was not assessed.

Comment #	Reviewer #	Comment	Author Response
19	1	When discussing methodological concerns, specify what these concerns might mean for the reliability and validity of the study results.	Thank you. We revised the risk of bias descriptions to comment on the relevant concerns for reliability and validity of the study results.
20	1	Additionally, expanding the discussion section to elaborate further on the potential implications for VA policy and practice and provide more context on findings' implications, potential clinical applications, and future research areas focusing on conditions affecting veterans would be valuable. Suggest recommendations for how the VA can integrate low-dose RT into its care strategies for these conditions.	We expanded the discussion section to provide more context on the potential implications for VA policy and practice.
21	1	There are a few typos, some of which are listed below: P9, L41: “Clincally” P21, L37: “reccurece” P22, line 50, “scare” P25, L26: “inonsistent” P25, L37: “inconsistat” P25, L43: “consistant” P25, L56: “treatement” P30, L22: “reccurece” P45, L3: “condtions” Appendix D, table row= Ince, 2007: “osteoartritis” Appendix D2, table row=Kolbl 1998: “indomethacin” Appendix D2, table row=last: “contralateraly” Appendix E4, row=Qiao 2017: “Criterai” Appendix F2, bottom legend: “megaboltage” Appendix G2, row=Simsek 2001: “Pterigium” “Anteneoplastic” Appendix G4, row=Simsek, 2001: “Lense” Appendix J2, row=Adamietz 2001: “orthovoltae devide” Appendix K2, row=Seegenschmiedt 2003: “orthovoltae devide” Appendix J4, row= Adamietz 2001: “teleangiectasia” Appendix K4, bottom legend: “toxity”	Thank you. We revised the typos.
22	2	page iv, line 26; remove common between James and Rudolph page v, line 49; remove Radiation Oncology	Thank you. We have fixed these typos.

Comment #	Reviewer #	Comment	Author Response
		(redundant with Chief, Radiotherapy on line above) page vi, line 13, Dr. Wolfson's title is Professor page vi, line 14, Dr. Wolfson is in the "Department of Radiation Oncology, University of Miami" page viii, line 54 remove "and" before keloids page xiii, line 57 "can also be used to treat" page xiv, line 57 "radiation-induced secondary malignancies" page 3, line 34 "platelet-rich plasma therapy" page 4, line 49 "US military personnel." page 9 line 42 "range of clinically important effects" page 13, line 38; the numbers in the row do not add up to 26 page 13, line 44, the numbers in the row do not add up to 21 page 18, line 16 "In contrast, 1 RCT..." page 21, line 37 "Figure 4. Keloid recurrence at follow up:" page 24, line 52 "no significant difference in plantar fasciitis" page 26, line 12 "compared to PGSI" page 30, line 17 "brachytherapy (10-70 Gy)" page 39, line 29 "Tubiana et al's staging methodology" page 40, line 53 "co-occurring related diseases" page 42, line 50 "Side effects and patient" page 45, line 11 "improved function for people"	
23	2	page 19, lines 8-10, given that the focus is adjuvant RT for keloids, should the NCRS that compares RT to surgery be included?	Thank you. The primary meta-analysis of keloids now excludes the NRCS. In a post hos sensitivity analysis, we included the NRCS in the meta-analysis and note this did not alter our conclusions.
24	3	No comments.	Thank you.
25	4	Overall, excellent summation of the strength of literature for LDRT in various benign conditions. Provided excellent example for need for further high quality research of the use of LDRT for benign diseases. Below are a few suggestions:	Thank you.

Comment #	Reviewer #	Comment	Author Response
26	4	Page Xii Line 10- would be helpful to describe how brachytherapy was prescribed and what isotope used if available.	Appendix G-2 now reports the isotopes used in each study employing brachytherapy. During the development of our study protocol, we were guided by the Technical Expert Panel and partners to only report the total Gy.
27	4	Page Xiii Line 27- Randomized blind phase 3 study published in May 2023 shows significant benefit of RT versus sham providing high level evidence of efficacy. While outside literature search by 1 month, would be disservice to not include given level of evidence doi: 10.1016/j.radonc.2023.109718	Thank you. We have incorporated this study in the report and updated the summary statement. Note that we do not evaluate certainty of evidence for Ledderhose disease because there were less than 3 comparative studies.
28	4	Page XIV Line 51- In addition to sham, could consider comparison to other conservative modalities such as steroid injections, NSAIDs, etc.	Thank you. We incorporated this suggestion in the Discussion.
29	4	Page XV Line 30- Ledderhose conclusion should be re-evaluated in light of recent positive phase 3 data	We revised the summary statement for Ledderhose to reflect the findings from the RCT. "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."
30	4	Page 4 Line33- Estimated that over one-third all RT in Germany is for benign disease doi:10.1259/bjr.20150080	The study (Seegenschmiedt 2015) noted by the reviewer states: "Non-malignant indications for RT comprise about 10–30% of all treated patients in most academic, public and private RT facilities in Germany." We revised the introduction to note that 10-30% of RT in Germany is applied to people with noncancer conditions.
31	4	Page 26 Line 24- *von Pannewtiz score (VPS)	Thank you.
32	4	Page 33 Line 16-*von Pannewtiz score (VPS)	Thank you.

Comment #	Reviewer #	Comment	Author Response
33	4	Page 40 Line 36- Randomized blind phase 3 study published in May 2023 shows significant benefit of RT versus sham providing high level evidence of efficacy. While outside pubmed search by 1 month, would be disservice to not include given level of evidence doi: 10.1016/j.radonc.2023.109718	Thank you. We have incorporated this RCT in our reported and updated our conclusions accordingly.
34		Page 45 Line 3- Estimated that over one-third all RT in Germany is for benign disease doi:10.1259/bjr.20150080	Thank you. Please see our response to comment #29.