Radiation Therapy 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.*
11. Malaker A, Ellis F, Paine CH. Keloid scars: a new method of treatment combining surgery with interstitial radiotherapy. *Clin Radiol*. Apr 1976;27(2):179-83. doi:10.1016/s0009-9260(76)80141-9. *Date of publication <= 1980.*
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.*
19. Reid R, Cooke H. Postoperative ionizing radiation in the management of heterotopic bone formation in the temporomandibular joint. *J Oral Maxillofac Surg*. Aug 1999;57(8):900-5; discussion 905-6. doi:10.1016/s0278-2391(99)90003-4. *Not disease of interest.*
20. Zalewska J, Węgierska M, Barczyńska T, Waszczak M, Żuchowski P, Jeka S. Efficacy of radiation synovectomy (radiosynovectomy or radiosynoviorthesis) with yttrium-90 in exudative inflammation of synovial membrane of knee joints in patients with rheumatic diseases - preliminary report. *Reumatologia*. 2016;54(1):3-9. doi:10.5114/reum.2016.58754. *Not disease of interest.*
21. Barragán VV, García AIA, García JF, Marín MJ, Vivas J, Rijo GJ. Perioperative interstitial high-dose-rate brachytherapy for keloids scar. *J Contemp Brachytherapy*. Feb 2022;14(1):29-34. doi:10.5114/jcb.2022.113547. *Not intervention of interest.*
22. Basdew H, Mehilal R, Al-Mamgani A, et al. Adjunctive treatment of keloids: comparison of photodynamic therapy with brachytherapy. *European journal of plastic surgery*. 2013;36:289-294. *Not intervention of interest.*
23. Beyer DC. Pterygia: single-fraction postoperative beta irradiation. *Radiology*. Feb 1991;178(2):569-71. doi:10.1148/radiology.178.2.1987626. *Not intervention of interest.*
24. Bijlard E, Timman R, Verduijn GM, Niessen FB, Hovius SER, Mureau MAM. Intralesional cryotherapy versus excision with corticosteroid injections or brachytherapy for keloid treatment: Randomised controlled trials. *J Plast Reconstr Aesthet Surg*. Jun 2018;71(6):847-856. doi:10.1016/j.bjps.2018.01.033. *Not intervention of interest.*
25. Daurade M, Breton P, Rouard N, Lorchel F, Ibrahim B, Sigaux N. Efficacy of surgical excision and brachytherapy in the treatment of keloids: a retrospective cohort study. *Adv Skin Wound Care*. Nov 2020;33(11):1-6. doi:10.1097/01.ASW.0000717228.02752.4e. *Not intervention of interest.*
26. Ehlich H, Kresnik E, Klett R, Freudenberg LS, Kampen WU. Intra-articular treatment of digital osteoarthritis by radiosynoviorthesis-clinical outcome in long-term follow-up. *Clin Nucl Med*. Nov 1 2022;47(11):943-947. doi:10.1097/rlu.0000000000004322. *Not intervention of interest.*
27. Fuenmayor P, Quiñonez H, Salas R, Pujadas Z. Outcomes of surgical excision and high-dose-rate brachytherapy for earlobe keloids. *World J Plast Surg*. Jan 2021;10(1):78-84. doi:10.29252/wjps.10.1.78. *Not intervention of interest.*

28. Jiang P, Baumann R, Dunst J, et al. Perioperative interstitial high-dose-rate brachytherapy for the treatment of recurrent keloids: feasibility and early results. *Int J Radiat Oncol Biol Phys*. Mar 1 2016;94(3):532-6. doi:10.1016/j.ijrobp.2015.11.008. *Not intervention of interest.*
29. Jürgenliemk-Schulz IM, Hartman LJ, Roesink JM, et al. Prevention of pterygium recurrence by postoperative single-dose beta-irradiation: a prospective randomized clinical double-blind trial. *Int J Radiat Oncol Biol Phys*. Jul 15 2004;59(4):1138-47. doi:10.1016/j.ijrobp.2003.12.021. *Not intervention of interest.*
30. Liepe K, Baehr M. Radiosynovectomy is effective in thumb basal joint arthritis. *Ann Nucl Med*. Nov 2021;35(11):1232-1239. doi:10.1007/s12149-021-01665-w. *Not intervention of interest.*
31. Maalej M, Frikha H, Bouaouina N, et al. [[Intraoperative brachytherapy in the management of keloids. Apropos of 114 cases]]. *Cancer Radiother*. Jul-Aug 2000;4(4):274-8. Place de la curiethérapie dans le traitement des chéloïdes. A propos de 114 cas. doi:10.1016/s1278-3218(00)80005-0. *Not intervention of interest.*
32. Manjunath KN, Venkatesh MS, Alva R, et al. Efficacy of surgical excision and adjuvant high-dose rate brachytherapy in treatment of keloid: our experience. *J Cutan Aesthet Surg*. Jul-Sep 2021;14(3):337-343. doi:10.4103/jcas.Jcas_120_16. *Not intervention of interest.*
33. Mourits MP, Wyrdeman HK, Jurgenliemk-Schulz IM, Bidlot E. Favorable long-term results of primary pterygium removal by bare sclera extirpation followed by a single 90Strontium application. *Eur J Ophthalmol*. May-Jun 2008;18(3):327-31. doi:10.1177/112067210801800301. *Not intervention of interest.*
34. Ozen S, Doganci EB, Ozyuvali A, Yalcin AP. Effectiveness of continuous versus pulsed short-wave diathermy in the management of knee osteoarthritis: A randomized pilot study. *Caspian J Intern Med*. Fall 2019;10(4):431-438. doi:10.22088/cjim.10.4.431. *Not intervention of interest.*
35. Piccolo D, Crisman G, Bovani B, et al. Combined laser treatment for ear keloids: case series: comparison between two mini-invasive protocols: comparison between two mini-invasive protocols. *J Cosmet Dermatol*. Jan 2022;21(1):296-306. doi:10.1111/jocd.14590. *Not intervention of interest.*
36. Reeboonlap N, Satitsmithpong N, Phisitkul P, Charakorn K. Outcome of plantar fasciitis treatment using monochrome infrared irradiation. *J Med Assoc Thai*. Oct 2012;95 Suppl 10:S147-50. *Not intervention of interest.*
37. Rio E, Bardet E, Peuvrel P, Pannier M, Dreno B. Perioperative interstitial brachytherapy for recurrent keloid scars. *Plast Reconstr Surg*. Jul 2009;124(1):180e-181e. doi:10.1097/PRS.0b013e3181a83b7e. *Not intervention of interest.*
38. Robert Y, Pauli L, Gysin P, Gloor B, Hendrickson P. Protracted ruthenium treatment of recurrent pterygium. *Graefes Arch Clin Exp Ophthalmol*. 1992;230(3):233-6. doi:10.1007/bf00176295. *Not intervention of interest.*
39. Shamim SA, Arora G, Jha P, et al. Comparison of Lutetium-177 tin colloid and Rhenium-188 tin colloid radiosynovectomy in chronic knee arthritis. *Nucl Med Commun*. Aug 2020;41(8):721-726. doi:10.1097/mnm.0000000000001210. *Not intervention of interest.*
40. Szerb I, Gál T, Kiss D, Nagy V, Hangody L. Efficacy assessment of radiosynoviorthesis on the progression of radiological osteoarthritic features of hip and ankle joint in patients with osteoarthritis and rheumatoid arthritis. *Nuklearmedizin*. Jun 2020;59(3):269-275.
41. Bewertung der Wirksamkeit der Radiosynoviorthese auf das Fortschreiten der radiologischen Arthrosezeichen von Hüfte und Sprunggelenk bei Patienten mit Arthrose und rheumatoider Arthritis. doi:10.1055/a-1108-1187. *Not intervention of interest.*
42. van Leeuwen MCE, Stokmans SC, Bulstra AJ, Meijer OWM, van Leeuwen PAM, Niessen FB. High-dose-rate brachytherapy for the treatment of recalcitrant keloids: a unique, effective

treatment protocol. *Plast Reconstr Surg*. Sep 2014;134(3):527-534. doi:10.1097/prs.0000000000000415. *Not intervention of interest.*

43. Yossi S, Krhili S, Mesgouez-Nebout N, et al. Adjuvant treatment of keloid scars: electrons or brachytherapy? *Cancer Radiotherapie: Journal de la Societe Francaise de Radiotherapie Oncologique*. 2013;17(1):21-25. *Not intervention of interest.*
44. Donaubauer AJ, Zhou JG, Ott OJ, et al. Low dose radiation therapy, particularly with 0.5 Gy, improves pain in degenerative joint disease of the fingers: results of a retrospective analysis. *Int J Mol Sci*. Aug 14 2020;21(16)doi:10.3390/ijms21165854. *Not population of interest.*
45. Hess CB, Stein-Wexler R, Qi L, Davids JR, Fragoso RC. Outcomes of preoperative versus postoperative radiation for heterotopic ossification prevention in children with neuromuscular hip dysplasia undergoing proximal femoral resection. *J Pediatr Orthop*. Feb 2019;39(2):e102-e107. doi:10.1097/bpo.0000000000001018. *Not population of interest.*
46. Rösler H, Zapf S, Kuffner H, Wissen-Siegert I, Kutzner J. Radiotherapy in scar-induced keloid. *Fortschritte der Medizin*. 1993;111(4):46-49. *Not population of interest.*
47. de Farias CC, Sterlenich T, de Sousa LB, Vieira LA, Gomes J. Randomized trial comparing multilayer amniotic membrane transplantation with scleral and corneal grafts for the treatment of scleral thinning after pterygium surgery associated with beta therapy. *Cornea*. Nov 2014;33(11):1197-204. doi:10.1097/ico.0000000000000207. *Not reporting quality of interest.*
48. Furtado F, Hochman B, Farber PL, Muller MC, Hayashi LF, Ferreira LM. Psychological stress as a risk factor for postoperative keloid recurrence. *J Psychosom Res*. Apr 2012;72(4):282-7. doi:10.1016/j.jpsychores.2011.12.010. *Not reporting quality of interest.*
49. Handel M, Brettschneider J, Köck FX, Anders S, Perlick L, Sell S. [Risk factors associated with heterotopic ossifications in primary total hip arthroplasty]. *Z Orthop Ihre Grenzgeb*. Sep-Oct 2004;142(5):564-70. Risikofaktoren für heterotope Ossifikationen in der primären Hüftgelenkstotalendoprothetik. doi:10.1055/s-2004-832310. *Not reporting quality of interest.*
50. Kutzner J, Schneider L, Seegenschmiedt MH. [Radiotherapy of keloids. Patterns of care study -- results]. *Strahlenther Onkol*. Jan 2003;179(1):54-8. Strahlentherapie des Keloids in Deutschland Patterns-of-Care-Studie -- Ergebnisse einer Umfrage. doi:10.1007/s00066-003-1023-2. *Not reporting quality of interest.*
51. Mavrogenis AF, Guerra G, Staals EL, Bianchi G, Ruggieri P. A classification method for neurogenic heterotopic ossification of the hip. *J Orthop Traumatol*. Jun 2012;13(2):69-78. doi:10.1007/s10195-012-0193-z. *Not reporting quality of interest.*
52. Qi Z, Liang W, Wang Y, et al. "X"-shaped incision and keloid skin-flap resurfacing: a new surgical method for auricle keloid excision and reconstruction. *Dermatol Surg*. Aug 2012;38(8):1378-82. doi:10.1111/j.1524-4725.2012.02455.x. *Not reporting quality of interest.*
53. Sheybani A, TenNapel MJ, Lack WD, et al. Risk of radiation-induced malignancy with heterotopic ossification prophylaxis: a case-control analysis. *Int J Radiat Oncol Biol Phys*. Jul 1 2014;89(3):584-9. doi:10.1016/j.ijrobp.2014.03.008. *Not reporting quality of interest.*
54. (S002) A 15-Year review of radiation therapy for keloids at two institutions. *Oncology (Williston Park)*. Apr 2016;30 Suppl. *Other.*
55. Cadosch D, Bauer S, Gautschi OP, Filgueira L, Zellweger R. [Surgical arthrolysis in patients with high-grade heterotopic ossification after hip joint endoprosthesis]. *Unfallchirurg*. Jul 2008;111(7):535-8. Operative Arthrolyse bei schwergradiger heterotoper Ossifikation nach Hüftgelenksendoprothese. doi:10.1007/s00113-008-1462-4. *Other.*
56. Chen HC, Ou SY, Lai YL. Combined surgery and irradiation for treatment of hypertrophic scars and keloids. *Zhonghua Yi Xue Za Zhi (Taipei)*. Apr 1991;47(4):249-54. *Other.*
57. Monselise M, Schwartz M, Politi F, Barishak YR. Pterygium and beta irradiation. *Acta Ophthalmol (Copenh)*. Apr 1984;62(2):315-9. doi:10.1111/j.1755-3768.1984.tb08408.x. *Other.*

58. Bijlard E, Timman R, Verduijn GM, et al. Intralesional cryotherapy versus excision and corticosteroids or brachytherapy for keloid treatment: study protocol for a randomised controlled trial. *Trials*. Dec 19 2013;14:439. doi:10.1186/1745-6215-14-439. *Protocol.*
59. Holtmann H, Niewald M, Prokein B, Graeber S, Ruebe C. Randomized multicenter follow-up trial on the effect of radiotherapy for plantar fasciitis (painful heels spur) depending on dose and fractionation - a study protocol. *Radiat Oncol*. Jan 20 2015;10:23. doi:10.1186/s13014-015-0327-6. *Protocol.*
60. Kim BH, Shin K, Kim MJ, et al. Low-dose radiation therapy for patients with knee osteoarthritis (LORD-KNEA): a protocol for a sham-controlled randomised trial. *BMJ Open*. Feb 10 2023;13(2):e069691. doi:10.1136/bmjopen-2022-069691. *Protocol.*
61. Niewald M, Seegenschmiedt MH, Micke O, Gräber S. Randomized multicenter trial on the effect of radiotherapy for plantar Fasciitis (painful heel spur) using very low doses--a study protocol. *Radiat Oncol*. Sep 18 2008;3:27. doi:10.1186/1748-717x-3-27. *Protocol.*
62. Hautmann MG, Neumaier U, Kölbl O. Re-irradiation for painful heel spur syndrome. Retrospective analysis of 101 heels. *Strahlenther Onkol*. Mar 2014;190(3):298-303. doi:10.1007/s00066-013-0462-7. *Re-irradiation.*
63. Hautmann MG, Rechner P, Hipp M, et al. Re-irradiation for osteoarthritis-retrospective analysis of 217 joints. *Strahlenther Onkol*. Dec 2019;195(12):1060-1067. Rebestrahlung bei Arthrose – retrospektive Analyse von 217 Gelenken. doi:10.1007/s00066-019-01500-2. *Re-irradiation.*
64. Emad M, Omidvari S, Dastgheib L, Mortazavi A, Ghaem H. Surgical excision and immediate postoperative radiotherapy versus cryotherapy and intralesional steroids in the management of keloids: a prospective clinical trial. *Med Princ Pract*. 2010;19(5):402-5. doi:10.1159/000316381. *Sample size <=10.*
65. Jackson I, Bhageshpur R, DiNick V, Khan A, Bhaloo S. Investigation of recurrence rates among earlobe keloids utilizing various postoperative therapeutic modalities. *European Journal of Plastic Surgery*. 2001;24(2):88-95. *Sample size <=10.*
66. Moriarty AP, Crawford GJ, McAllister IL, Constable IJ. Severe corneoscleral infection. A complication of beta irradiation scleral necrosis following pterygium excision. *Arch Ophthalmol*. Jul 1993;111(7):947-51. doi:10.1001/archopht.1993.01090070065021. *Sample size <=10.*
67. Rubenstein JH, Salenius SA, Blitzer PH, Katin MJ, Dosoretz DE. Prevention of heterotopic bone formation with low dose radiation therapy. *J Fla Med Assoc*. Dec 1992;79(12):828-32. *Sample size <=10.*
68. Salazar D, Golz A, Israel H, Marra G. Heterotopic ossification of the elbow treated with surgical resection: risk factors, bony ankylosis, and complications. *Clin Orthop Relat Res*. Jul 2014;472(7):2269-75. doi:10.1007/s11999-014-3591-0. *Sample size <=10.*
69. Widmann RF, Do TT, Doyle SM, Burke SW, Root L. Resection arthroplasty of the hip for patients with cerebral palsy: an outcome study. *J Pediatr Orthop*. Nov-Dec 1999;19(6):805-10. *Sample size <=10.*
70. Ball C, Izadi D, Verjee LS, Chan J, Nanchahal J. Systematic review of non-surgical treatments for early dupuytren's disease. *BMC Musculoskelet Disord*. Aug 15 2016;17(1):345. doi:10.1186/s12891-016-1200-y. *Systematic review.*
71. Blokhuis TJ, Frölke JP. Is radiation superior to indomethacin to prevent heterotopic ossification in acetabular fractures?: a systematic review. *Clin Orthop Relat Res*. Feb 2009;467(2):526-30. doi:10.1007/s11999-008-0532-9. *Systematic review.*

72. Bueno TSP, Godoy GP, Furukava RB, et al. Heterotopic ossification in acetabular fractures: systematic review and meta-analysis of prophylaxis. *Acta Ortop Bras*. Nov-Dec 2021;29(6):331-340. doi:10.1590/1413-785220212906244689. *Systematic review.*
73. Cheraghi N, Cognetta A, Jr., Goldberg D. Radiation therapy for the adjunctive treatment of surgically excised keloids: A review. *J Clin Aesthet Dermatol*. Aug 2017;10(8):12-15. *Systematic review.*
74. Ellis MM, Jones LR, Siddiqui F, Sunkara PR, Ozog DM. The efficacy of surgical excision plus adjuvant multimodal therapies in the treatment of keloids: a systematic review and meta-analysis. *Dermatol Surg*. Aug 2020;46(8):1054-1059. doi:10.1097/dss.0000000000002362. *Systematic review.*
75. Gold MH, Nestor MS, Berman B, Goldberg D. Assessing keloid recurrence following surgical excision and radiation. *Burns Trauma*. 2020;8:tkaa031. doi:10.1093/burnst/tkaa031. *Systematic review.*
76. Henstenburg JM, Sherman M, Ilyas AM. Comparing options for heterotopic ossification prophylaxis following elbow trauma: a systematic review and meta-analysis. *J Hand Microsurg*. Jul 2021;13(3):189-195. doi:10.1055/s-0040-1721880. *Systematic review.*
77. Hsieh CL, Chi KY, Lin WY, Lee LT. Timing of adjuvant radiotherapy after keloid excision: a systematic review and meta-analysis. *Dermatol Surg*. Nov 1 2021;47(11):1438-1443. doi:10.1097/dss.0000000000003165. *Systematic review.*
78. Hu ZH, Chen W, Sun JN, et al. Radiotherapy for the prophylaxis of heterotopic ossification after total hip arthroplasty: a systematic review and meta-analysis of randomized controlled trails. *Med Dosim*. Spring 2021;46(1):65-73. doi:10.1016/j.meddos.2020.07.010. *Systematic review.*
79. Hwang NH, Chang JH, Lee NK, Yang KS. Effect of the biologically effective dose of electron beam radiation therapy on recurrence rate after keloid excision: A meta-analysis. *Radiother Oncol*. Aug 2022;173:146-153. doi:10.1016/j.radonc.2022.06.003. *Systematic review.*
80. Kadhum M, Smock E, Khan A, Fleming A. Radiotherapy in Dupuytren's disease: a systematic review of the evidence. *J Hand Surg Eur Vol*. Sep 2017;42(7):689-692. doi:10.1177/1753193417695996. *Systematic review.*
81. Kal HB, Veen RE. Biologically effective doses of postoperative radiotherapy in the prevention of keloids. Dose-effect relationship. *Strahlenther Onkol*. Nov 2005;181(11):717-23. doi:10.1007/s00066-005-1407-6. *Systematic review.*
82. Kal HB, Veen RE, Jürgenliemk-Schulz IM. Dose-effect relationships for recurrence of keloid and pterygium after surgery and radiotherapy. *Int J Radiat Oncol Biol Phys*. May 1 2009;74(1):245-51. doi:10.1016/j.ijrobp.2008.12.066. *Systematic review.*
83. Mankowski P, Kanevsky J, Tomlinson J, Dyachenko A, Luc M. Optimizing radiotherapy for keloids: a meta-analysis systematic review comparing recurrence rates between different radiation modalities. *Ann Plast Surg*. Apr 2017;78(4):403-411. doi:10.1097/sap.0000000000000989. *Systematic review.*
84. Mathew KK, Marchand KB, Tarazi JM, et al. Heterotopic ossification prophylaxis following operative fixation of acetabular fractures: a systematic review. *Surgical Technology International*. 2022;40. *Systematic review.*
85. Milakovic M, Popovic M, Raman S, Tsao M, Lam H, Chow E. Radiotherapy for the prophylaxis of heterotopic ossification: a systematic review and meta-analysis of randomized controlled trials. *Radiother Oncol*. Jul 2015;116(1):4-9. doi:10.1016/j.radonc.2015.05.022. *Systematic review.*

86. Miles OJ, Zhou J, Paleri S, Fua T, Ramakrishnan A. Chest keloids: effect of surgical excision and adjuvant radiotherapy on recurrence, a systematic review and meta-analysis. *ANZ J Surg*. Jun 2021;91(6):1104-1109. doi:10.1111/ans.16561. *Systematic review.*
87. Minten MJ, Mahler E, den Broeder AA, Leer JW, van den Ende CH. The efficacy and safety of low-dose radiotherapy on pain and functioning in patients with osteoarthritis: a systematic review. *Rheumatol Int*. Jan 2016;36(1):133-42. doi:10.1007/s00296-015-3337-7. *Systematic review.*
88. Pakos EE, Ioannidis JP. Radiotherapy vs. nonsteroidal anti-inflammatory drugs for the prevention of heterotopic ossification after major hip procedures: a meta-analysis of randomized trials. *Int J Radiat Oncol Biol Phys*. Nov 1 2004;60(3):888-95. doi:10.1016/j.ijrobp.2003.11.015. *Systematic review.*
89. Ploumis A, Belbasis L, Ntzani E, Tsekeris P, Xenakis T. Radiotherapy for prevention of heterotopic ossification of the elbow: a systematic review of the literature. *J Shoulder Elbow Surg*. Nov 2013;22(11):1580-8. doi:10.1016/j.jse.2013.07.045. *Systematic review.*
90. Popovic M, Agarwal A, Zhang L, et al. Radiotherapy for the prophylaxis of heterotopic ossification: a systematic review and meta-analysis of published data. *Radiother Oncol*. Oct 2014;113(1):10-7. doi:10.1016/j.radonc.2014.08.025. *Systematic review.*
91. Shapira J, Yelton MJ, Chen JW, et al. Efficacy of NSAIDs versus radiotherapy for heterotopic ossification prophylaxis following total hip arthroplasty in high-risk patients: a systematic review and meta-analysis. *Hip Int*. Sep 2022;32(5):576-590. doi:10.1177/1120700021991115. *Systematic review.*
92. Shin JY, Lee JW, Roh SG, Lee NH, Yang KM. A comparison of the effectiveness of triamcinolone and radiation therapy for ear keloids after surgical excision: a systematic review and meta-analysis. *Plast Reconstr Surg*. Jun 2016;137(6):1718-1725. doi:10.1097/prs.0000000000002165. *Systematic review.*
93. Sigaux N, Jacquemart M, Cousin AS, Lorchel F, Breton P. Association of surgical excision and brachytherapy for the management of keloids. *J Stomatol Oral Maxillofac Surg*. Jun 2017;118(3):161-166. doi:10.1016/j.jormas.2017.04.002. *Systematic review.*
94. Siotos C, Uzosike AC, Hong H, et al. Keloid excision and adjuvant treatments: a network meta-analysis. *Ann Plast Surg*. Aug 2019;83(2):154-162. doi:10.1097/sap.0000000000001951. *Systematic review.*
95. Tchero H, Herlin C, Bekara F, Fluieraru S, Teot L. Hidradenitis suppurativa: a systematic review and meta-analysis of therapeutic interventions. *Indian J Dermatol Venereol Leprol*. May-Jun 2019;85(3):248-257. doi:10.4103/ijdvl.IJDVL_69_18. *Systematic review.*
96. Thompson AM, Seivright J, Atluri S, et al. Radiotherapy for hidradenitis suppurativa: a systematic review. *Dermatology*. 2021;237(3):357-364. doi:10.1159/000514027. *Systematic review.*
97. van Leeuwen MC, Stokmans SC, Bulstra AE, et al. Surgical excision with adjuvant irradiation for treatment of keloid scars: a systematic review. *Plast Reconstr Surg Glob Open*. Jul 2015;3(7):e440. doi:10.1097/gox.0000000000000357. *Systematic review.*
98. Vavken P, Castellani L, Sculco TP. Prophylaxis of heterotopic ossification of the hip: systematic review and meta-analysis. *Clin Orthop Relat Res*. Dec 2009;467(12):3283-9. doi:10.1007/s11999-009-0924-5. *Systematic review.*
99. Walter WL. Another look at pterygium surgery with postoperative beta radiation. *Ophthalmic Plast Reconstr Surg*. Dec 1994;10(4):247-52. doi:10.1097/00002341-199412000-00004. *Systematic review.*

100. Xu J, Yang E, Yu NZ, Long X. Radiation therapy in keloids treatment: history, strategy, effectiveness, and complication. *Chin Med J (Engl)*. Jul 20 2017;130(14):1715-1721. doi:10.4103/0366-6999.209896. *Systematic review.*
101. Zeng W, Liu Z, Dai H, et al. Anti-fibrotic, anti-VEGF or radiotherapy treatments as adjuvants for pterygium excision: a systematic review and network meta-analysis. *BMC Ophthalmol*. Nov 25 2017;17(1):211. doi:10.1186/s12886-017-0601-5. *Systematic review.*

APPENDIX B-2. NOT EXTRACTED PER BEST EVIDENCE APPROACH

Dupuytren Contracture/Disease: 5 Exclusions

1. Keilholz L, Seegenschmiedt MH, Born AD, Sauer R. [Radiotherapy in the early stage of Dupuytren's disease. The indications, technic and long-term results]. *Strahlenther Onkol*. Jan 1997;173(1):27-35. Radiotherapie im frühen Stadium des Morbus Dupuytren. Indikation, Technik und Langzeitergebnisse. doi:10.1007/bf03039191
2. Schuster J, Saraiya S, Tennyson N, Nedelka M, Mukhopadhyay N, Weiss E. Patient-reported outcomes after electron radiation treatment for early-stage palmar and plantar fibromatosis. *Pract Radiat Oncol*. Nov-Dec 2015;5(6):e651-8. doi:10.1016/j.prro.2015.06.010
3. Seegenschmiedt MH, Olschewski T, Guntrum F. [Optimization of radiotherapy in Dupuytren's disease. Initial results of a controlled trial]. *Strahlenther Onkol*. Feb 2001;177(2):74-81. Optimierung der Radiotherapie bei Morbus Dupuytren. Erste Ergebnisse einer kontrollierten Studie. doi:10.1007/pl00002386
4. Seegenschmiedt MH, Olschewski T, Guntrum F. Radiotherapy optimization in early-stage Dupuytren's contracture: first results of a randomized clinical study. *Int J Radiat Oncol Biol Phys*. Mar 1 2001;49(3):785-98. doi:10.1016/s0360-3016(00)00745-8
5. Weinzierl G, Flügel M, Geldmacher J. [Lack of effectiveness of alternative non-surgical treatment procedures of Dupuytren contracture]. *Chirurg*. Jun 1993;64(6):492-4. Fehlen der Effektivität der alternativ nichtchirurgischen Behandlungsverfahren bei Morbus Dupuytren.

Hetertopic Ossification: 129 Exclusions (2 Duplicates)

1. Alberti W, Quack G, Krischke W, Lommatzsch A, Huyer C, Krahl H. [Prevention of heterotopic ossification by radiotherapy following total hip prosthesis]. *Dtsch Med Wochenschr*. Jul 14 1995;120(28-29):983-9. Verhinderung ektoper Ossifikationen nach Totalendoprothese des Hüftgelenks durch Strahlentherapie. doi:10.1055/s-2008-1055435
2. Alberti W, Quack G, Krischke W, Lommatzsch A, Huyer C, Krahl H. [Prevention of heterotopic ossification by radiotherapy following total hip prosthesis]. *Dtsch Med Wochenschr*. Jul 14 1995;120(28-29):983-9. Verhinderung ektoper Ossifikationen nach Totalendoprothese des Hüftgelenks durch Strahlentherapie. doi:10.1055/s-2008-1055435
3. Anglen JO, Moore KD. Prevention of heterotopic bone formation after acetabular fracture fixation by single-dose radiation therapy: a preliminary report. J Orthop Trauma. 1996;10(4):258-63. doi:10.1097/00005131-199605000-00006
4. Anthony P, Keys H, Evarts CM, Rubin P, Lush C. Prevention of heterotopic bone formation with early post operative irradiation in high risk patients undergoing total hip arthroplasty: comparison of 10.00 Gy vs 20.00 Gy schedules. *Int J Radiat Oncol Biol Phys*. Mar 1987;13(3):365-9. doi:10.1016/0360-3016(87)90010-1
5. Archdeacon MT, d'Heurle A, Nemeth N, Budde B. Is preoperative radiation therapy as effective as postoperative radiation therapy for heterotopic ossification prevention in acetabular fractures? *Clin Orthop Relat Res*. Nov 2014;472(11):3389-94. doi:10.1007/s11999-014-3670-2
6. Ashton LA, Bruce W, Goldberg J, Walsh W. Prevention of heterotopic bone formation in high risk patients post-total hip arthroplasty. *J Orthop Surg (Hong Kong)*. Dec 2000;8(2):53-57. doi:10.1177/230949900000800210
7. Balboni TA, Gaccione P, Gobezie R, Mamon HJ. Shielding of the hip prosthesis during radiation therapy for heterotopic ossification is associated with increased failure of prophylaxis. *Int J Radiat Oncol Biol Phys*. Apr 1 2007;67(5):1499-505. doi:10.1016/j.ijrobp.2006.11.007

8. Blount LH, Thomas BJ, Tran L, Selch MT, Sylvester JE, Parker RG. Postoperative irradiation for the prevention of heterotopic bone: analysis of different dose schedules and shielding considerations. *Int J Radiat Oncol Biol Phys*. Sep 1990;19(3):577-81. doi:10.1016/0360-3016(90)90483-z
9. Boffeli TJ, Pfannenstein RR, Thompson JC. Radiation therapy for recurrent heterotopic ossification prophylaxis after partial metatarsal amputation. *J Foot Ankle Surg*. May-Jun 2015;54(3):345-9. doi:10.1053/j.jfas.2014.07.010
10. Boissonneault A, Harkin E, Slobogean G, et al. Is external beam radiation therapy really associated with low rates of heterotopic ossification after acetabular surgery? *J Orthop Trauma*. Aug 1 2023;37(8):382-385. doi:10.1097/bot.0000000000002598
11. Braun W. [Irradiation for the prevention of heterotopic ossification following surgery of the hip and knee joint. Report of initial experiences]. *Chirurg*. Nov 1989;60(11):795-800. Die Bestrahlung zur Prophylaxe heterotoper Ossifikationen nach Eingriffen am Hüft- und Ellbogengelenk. Bericht über erste Erfahrungen.
12. Braun K. [Preoperative radiation for prevention of heterotopic ossifications after hip endoprosthesis replacement]. Z Orthop Ihre Grenzgeb. Mar-Apr 1999;137(2):Oa22-3. Präoperative Radiatio zur Prophylaxe heterotoper Ossifikationen nach endoprothetischem Hüftgelenkersatz.
13. Brückl R, Frey M. [Prevention of para-articular ossifications by radiotherapy after cementless total hip endoprosthesis implantation]. *Z Orthop Ihre Grenzgeb*. Sep-Oct 1997;135(5):430-3. Prophylaxe paraartikulärer Ossifikationen durch Strahlentherapie nach zementloser Hüft-TEP-Implantation. doi:10.1055/s-2008-1039412
14. Burd TA, Lowry KJ, Anglen JO. Indomethacin compared with localized irradiation for the prevention of heterotopic ossification following surgical treatment of acetabular fractures. J Bone Joint Surg Am. Dec 2001;83(12):1783-8. doi:10.2106/00004623-200112000-00003
15. Burnet NG, Nasr P, Yip G, et al. Prophylactic radiotherapy against heterotopic ossification following internal fixation of acetabular fractures: a comparative estimate of risk. *Br J Radiol*. Oct 2014;87(1042):20140398. doi:10.1259/bjr.20140398
16. Cadieux CL, DesRosiers C, McMullen K. Risks of secondary malignancies with heterotopic bone radiation therapy for patients younger than 40 years. *Med Dosim*. Autumn 2016;41(3):212-5. doi:10.1016/j.meddos.2016.02.001
17. Chao ST, Lee SY, Borden LS, Joyce MJ, Krebs VE, Suh JH. External beam radiation helps prevent heterotopic bone formation in patients with a history of heterotopic ossification. *J Arthroplasty*. Aug 2006;21(5):731-6. doi:10.1016/j.arth.2005.08.014
18. Childs III HA, Cole T, Falkenberg E, et al. A prospective evaluation of the timing of postoperative radiotherapy for preventing heterotopic ossification following traumatic acetabular fractures. *International Journal of Radiation Oncology* Biology* Physics*. 2000;47(5):1347-1352.
19. Cichos KH, Spitler CA, Quade JH, Almaguer A, McGwin G, Jr., Ghanem ES. Do Indomethacin or Radiation for Heterotopic Ossification Prophylaxis Increase the Rates of Infection or Wound Complications After Acetabular Fracture Surgery? J Orthop Trauma. Sep 2020;34(9):455-461. doi:10.1097/bot.0000000000001775
20. Cipriano C, Pill SG, Rosenstock J, Keenan MA. Radiation therapy for preventing recurrence of neurogenic heterotopic ossification. Orthopedics. Sep 2009;32(9)doi:10.3928/01477447-20090728-33
21. Citak M, Backhaus M, Kälicke T, et al. [Treatment of heterotopic ossification after spinal cord injury - clinical outcome after single-dose radiation therapy]. *Z Orthop Unfall*. Jan

2011;149(1):90-3. Therapie der heterotopen Ossifikation bei frischem Rückenmarkstrauma - Klinisches Outcome nach einmaliger Radiatio. doi:10.1055/s-0030-1250688
22. Citak M, Grasmücke D, Cruciger O, et al. Heterotopic ossification of the shoulder joint following spinal cord injury: an analysis of 21 cases after single-dose radiation therapy. *Spinal Cord*. Apr 2016;54(4):303-5. doi:10.1038/sc.2015.182
23. Citak M, Grasmücke D, Suero EM, et al. The roles of serum alkaline and bone alkaline phosphatase levels in predicting heterotopic ossification following spinal cord injury. *Spinal Cord*. May 2016;54(5):368-70. doi:10.1038/sc.2015.211
24. Cornes PG, Shahidi M, Glees JP. Heterotopic bone formation: irradiation of high risk patients. *Br J Radiol*. May 2002;75(893):448-52. doi:10.1259/bjr.75.893.750448
25. d'Heurle A, Archdeacon MT, Hiratzka S, Casstevens C, Finnan R, McCoy B. Do surrogates of injury severity influence the occurrence of heterotopic ossification in fractures of the acetabulum? J Orthop Trauma. Apr 2016;30(4):213-6. doi:10.1097/bot.0000000000000490
26. D'Lima DD, Venn-Watson EJ, Tripuraneni P, Colwell CW. Indomethacin versus radiation therapy for heterotopic ossification after hip arthroplasty. Orthopedics. Dec 2001;24(12):1139-43. doi:10.3928/0147-7447-20011201-11
27. Daugherty LC, Bell JR, Fisher BJ, et al. Radiation prophylaxis as primary prevention of heterotopic ossification of the knee: classification of disease and indications for treatment. *Journal of Radiation Oncology*. 2013;2:87-94.
28. Davis JA, Roper B, Munz JW, et al. Does postoperative radiation decrease heterotopic ossification after the Kocher-Langenbeck Approach for acetabular fracture? *Clin Orthop Relat Res*. Jun 2016;474(6):1430-5. doi:10.1007/s11999-015-4609-y
29. DeFlitch CJ, Stryker JA. Postoperative hip irradiation in prevention of heterotopic ossification: causes of treatment failure. *Radiology*. Jul 1993;188(1):265-70. doi:10.1148/radiology.188.1.8511309
30. Ebinger T, Roesch M, Kiefer H, Kinzl L, Schulte M. Influence of etiology in heterotopic bone formation of the hip. *J Trauma*. Jun 2000;48(6):1058-62. doi:10.1097/00005373-200006000-00010
31. Effenberger H, Ramsauer T, Kranzinger M, Grethen C, Dorn U. [Prophylaxis of heterotopic ossification in hip revisions with 7 Gy single-dose radiation]. *Z Orthop Ihre Grenzgeb*. May-Jun 2002;140(3):317-22. Ossifikationsprophylaxe bei Hüft-Wechseloperationen mit 7-Gy-Einzelbestrahlung. doi:10.1055/s-2002-32472
32. Eulert J, Knelles D, Barthel T. [Heterotopic ossifications]. Unfallchirurg. Aug 1997;100(8):667-74. Heterotope Ossifikationen. doi:10.1007/s001130050173
33. Fingeroth RJ, Ahmed AQ. Single dose 6 Gy prophylaxis for heterotopic ossification after total hip arthroplasty. Clin Orthop Relat Res. Aug 1995;(317):131-40.
34. Freije SL, Kushdilian MV, Burney HN, Zang Y, Saito NG. A retrospective analysis of 287 patients undergoing prophylactic radiation therapy for the prevention of heterotopic ossification. *Adv Radiat Oncol*. May-Jun 2021;6(3):100625. doi:10.1016/j.adro.2020.11.010
35. Gehl HB, Karstens JH, Casser HR, Savvidis E, Ammon J. [The prevention of ectopic ossification in total hip endoprostheses. Studies on field volume, total dosage and timing of postoperative radiotherapy]. Rontgenpraxis. Apr 1991;44(4):117-21. Prophylaxe ektoper Ossifikationen bei Hüftgelenktotalendoprothesen. Untersuchungen über Zielvolumen, Gesamtdosis und Zeitpunkt der postoperativen Radiotherapie.
36. Geller JS, Allegra PR, Seldon CS, et al. Prophylactic radiotherapy for prevention of heterotopic ossification after periacetabular fractures: A review of efficacy and associated conditions. *J Surg Orthop Adv*. Summer 2022;31(2):113-118.

37. Georhakopoulos I, Kouloulias V, Kougiountzopoulou A, et al. Radiation therapy for the prevention of heterotopic ossification: Efficacy and toxicity of single fraction radiotherapy. *Orthop Rev (Pavia)*. Aug 6 2020;12(2):8577. doi:10.4081/or.2020.8577
38. Goldmann AR, Seegenschmiedt M, Andreas P, Hohmann D, Sauer R, Beck H. [Radiation therapy in the prevention of periarticular, heterotopic ossification following implantation of a total hip endoprosthesis]. *Z Orthop Ihre Grenzgeb*. Mar-Apr 1993;131(2):151-5. Strahlentherapie zur Prophylaxe von periartikulären, heterotopen Ossifikationen nach Implantation von Hüfttotalendoprothesen. doi:10.1055/s-2008-1040220
39. Gregoritch SJ, Chadha M, Pelligrini VD, Rubin P, Kantorowitz DA. Randomized trial comparing preoperative versus postoperative irradiation for prevention of heterotopic ossification following prosthetic total hip replacement: preliminary results. *Int J Radiat Oncol Biol Phys*. Aug 30 1994;30(1):55-62. doi:10.1016/0360-3016(94)90519-3
40. Haas ML, Kennedy AS, Copeland CC, Ames JW, Scarboro M, Slawson RG. Utility of radiation in the prevention of heterotopic ossification following repair of traumatic acetabular fracture. *Int J Radiat Oncol Biol Phys*. Sep 1 1999;45(2):461-6. doi:10.1016/s0360-3016(99)00191-1
41. Han CD, Choi CH, Suh CO. Prevention of heterotopic bone formation after total hip arthroplasty using 600 rad in single dose in high risk patient. *Yonsei Med J*. Apr 1997;38(2):96-100. doi:10.3349/ymj.1997.38.2.96
42. Hanna M, Farid YR, Finn HA. Low-dose preoperative unshielded radiation is effective in heterotopic ossification prophylaxis and does not affect porous fixation in total hip arthroplasty at 2 years minimum follow-up: A radiographic study. *J Am Acad Orthop Surg*. Mar 1 2022;30(5):223-228. doi:10.5435/jaaos-d-21-00113
43. Hashem R, Tanzer M, Rene N, Evans M, Souhami L. Postoperative radiation therapy after hip replacement in high-risk patients for development of heterotopic bone formation. *Cancer Radiother*. Jul 2011;15(4):261-4. doi:10.1016/j.canrad.2010.10.003
44. Healy WL, Lo TC, Covall DJ, Pfeifer BA, Wasilewski SA. Single-dose radiation therapy for prevention of heterotopic ossification after total hip arthroplasty. *J Arthroplasty*. Dec 1990;5(4):369-75. doi:10.1016/s0883-5403(08)80097-6
45. Healy WL, Lo TC, DeSimone AA, Rask B, Pfeifer BA. Single-dose irradiation for the prevention of heterotopic ossification after total hip arthroplasty. A comparison of doses of five hundred and fifty and seven hundred centigray. *J Bone Joint Surg Am*. Apr 1995;77(4):590-5. doi:10.2106/00004623-199504000-00013
46. Hedley AK, Mead LP, Hendren DH. The prevention of heterotopic bone formation following total hip arthroplasty using 600 rad in a single dose. *J Arthroplasty*. Dec 1989;4(4):319-25. doi:10.1016/s0883-5403(89)80033-6
47. Heyd R, Buhleier T, Zamboglou N. Radiation therapy for prevention of heterotopic ossification about the elbow. *Strahlenther Onkol*. Aug 2009;185(8):506-11. doi:10.1007/s00066-009-1968-x
48. Heyd R, Schopohl B, Kirchner J, Böttcher HD. [Preoperative radiotherapy for prevention of heterotopic ossifications after hip endoprosthesis]. *Aktuelle Radiol*. Sep 1997;7(5):270-3. Präoperative Radiotherapie (RT) zur Prophylaxe heterotoper Ossifikationen (HO) nach Hüftendoprothese.
49. Heyd R, Strassmann G, Kirchner J, Schopohl B, Böttcher HD. [Postoperative radiotherapy in the prevention of heterotopic ossification after endoprosthetic hip joint replacement]. *Strahlenther Onkol*. Oct 1996;172(10):543-52. Postoperative Strahlentherapie zur Prävention heterotoper Ossifikationen nach endoprothetischem Huftgelenkersatz.

50. Heyd R, Tselis N, Ackermann H, Röddiger SJ, Zamboglou N. [Functional outcome after megavoltage irradiation for heel spurs]. *Strahlenther Onkol*. Dec 2006;182(12):733-9. Funktionelle Ergebnisse nach Megavoltbestrahlung beim Fersensporn. doi:10.1007/s00066-006-1569-x
51. Honore T, Bonan I, Salga M, et al. Effectiveness of radiotherapy to prevent recurrence of heterotopic ossification in patients with spinal cord injury and traumatic head injury: A retrospective case-controlled study. J Rehabil Med. May 31 2020;52(5):jrm00066. doi:10.2340/16501977-2692
52. Jasty M, Schutzer S, Tepper J, Willett C, Stracher MA, Harris WH. Radiation-blocking shields to localize periarticular radiation precisely for prevention of heterotopic bone formation around uncemented total hip arthroplasties. *Clin Orthop Relat Res*. Aug 1990;(257):138-45.
53. Jensen AW, Viozzi CF, Foote RL. Long-term results of radiation prophylaxis for heterotopic ossification in the temporomandibular joint. *J Oral Maxillofac Surg*. May 2010;68(5):1100-5. doi:10.1016/j.joms.2009.12.018
54. Jiang J, Fang T, Chen L, Chen Y, Sun B. [Efficacy and prognostic factors of preoperative radiation therapy of elbow arthrolysis]. *Zhonghua Yi Xue Za Zhi*. Apr 8 2014;94(13):1003-5.
55. Kandaz M, Aynaci Ö, Canyılmaz E, Aynacı O, Yoney A. Radiotherapy results for heterotopic ossification prophylaxis: single center experience from eastern Black Sea Region of Turkey. *UHOD-ULUSLARARASI HEMATOLOJI-ONKOLOJI DERGISI*. 2019;29(2)
56. Kennedy WF, Gruen TA, Chessin H, Gasparini G, Thompson W. Radiation therapy to prevent heterotopic ossification after cementless total hip arthroplasty. Clin Orthop Relat Res. Jan 1991;(262):185-91.
57. Kersh R, Constable W, Spaulding C, Eisert D, Selby J, Cook D. Low-dose radiotherapy for control of heterotopic bone formation. *Appl Radiol*. 1989;10:31-34.
58. Kitchen J, Hartley B, Seligson D. Heterotopic ossification prophylaxis after acetabular fracture fixation using a posterior approach: a retrospective study at a level 1 trauma center. *Current Orthopaedic Practice*. 2022:10.1097.
59. Knelles D, Barthel T, Karrer A, Kraus U, Eulert J, Kölbl O. Prevention of heterotopic ossification after total hip replacement. A prospective, randomised study using acetylsalicylic acid, indomethacin and fractional or single-dose irradiation. *J Bone Joint Surg Br*. Jul 1997;79(4):596-602. doi:10.1302/0301-620x.79b4.6829
60. Koelbl O, Seufert J, Pohl F, et al. Preoperative irradiation for prevention of heterotopic ossification following prosthetic total hip replacement results of a prospective study in 462 hips. *Strahlenther Onkol*. Nov 2003;179(11):767-73. doi:10.1007/s00066-003-1088-y
61. Kölbl O, Flentje M, Eulert J, Barthel T, Knelles D, Kraus U. [Prospective study on the prevention of heterotopic ossification after total hip replacement. Non-steroidal anti-inflammatory agents versus radiation therapy]. *Strahlenther Onkol*. Dec 1997;173(12):677-82. Prospektive Studie zur Vermeidung heterotoper Ossifikationen nach Hüftgelenksersatz. Nichtsteroidales Antirheumatikum versus Strahlentherapie. doi:10.1007/bf03038450
62. Konski A, Pellegrini V, Poulter C, et al. Randomized trial comparing single dose versus fractionated irradiation for prevention of heterotopic bone: a preliminary report. *Int J Radiat Oncol Biol Phys*. May 1990;18(5):1139-42. doi:10.1016/0360-3016(90)90450-x
63. Krauss H, Maier D, Bühren V, Högel F. Development of heterotopic ossifications, blood markers and outcome after radiation therapy in spinal cord injured patients. *Spinal Cord*. May 2015;53(5):345-8. doi:10.1038/sc.2014.186
64. Kruser TJ, Kozak KR, Cannon DM, Platta CS, Heiner JP, Illgen RL, 2nd. Low rates of heterotopic ossification after resurfacing hip arthroplasty with use of prophylactic radiotherapy in select patients. J Arthroplasty. Aug 2012;27(7):1349-53. doi:10.1016/j.arth.2011.11.017

65. Le Duff MJ, Takamura KB, Amstutz HC. Incidence of heterotopic ossification and effects of various prophylactic methods after hip resurfacing. Bull NYU Hosp Jt Dis. 2011;69 Suppl 1:S36-41.
66. Linclau L, Dokter G, Debois JM, Gutwirth P. Radiation therapy to prevent heterotopic ossification in cementless total hip arthroplasty. Acta Orthop Belg. 1994;60(2):220-4.
67. Linclau L, Dokter G, Debois JM, Gutwirth P. The influence of radiation therapy on the Harris hip score in cementless total hip arthroplasty. Acta Orthop Belg. 1995;61(1):48-52.
68. Liu JZ, Frisch NB, Barden RM, Rosenberg AG, Silverton CD, Galante JO. Heterotopic ossification prophylaxis after total hip arthroplasty: randomized trial of 400 vs 700 cGy. *J Arthroplasty*. Apr 2017;32(4):1328-1334. doi:10.1016/j.arth.2016.10.030
69. Liu XH, Jiang XY, Gong MQ, Zha YJ. [Effect of radiotherapy and indomethacin together in the prevention of recurrence of ectopic ossification around the elbow after resection]. *Beijing Da Xue Xue Bao Yi Xue Ban*. Apr 18 2016;48(2):230-3.
70. Lo TC, Healy WL, Covall DJ, et al. Heterotopic bone formation after hip surgery: prevention with single-dose postoperative hip irradiation. *Radiology*. Sep 1988;168(3):851-4. doi:10.1148/radiology.168.3.3136510
71. Lonardi F, Gioga G, Coeli M, et al. Preoperative, single-fraction irradiation for prophylaxis of heterotopic ossification after total hip arthroplasty. *Int Orthop*. 2001;25(6):371-4. doi:10.1007/s002640100281
72. Macheras GA, Lepetsos P, Leonidou A, Anastasopoulos PP, Galanakos SP, Tsiridis E. Results from the surgical resection of severe heterotopic ossification of the hip: a case series of 26 patients. *Eur J Orthop Surg Traumatol*. Dec 2017;27(8):1097-1102. doi:10.1007/s00590-017-1980-2
73. MacLennan I, Keys HM, Evarts CM, Rubin P. Usefulness of postoperative hip irradiation in the prevention of heterotopic bone formation in a high risk group of patients. *Int J Radiat Oncol Biol Phys*. Jan 1984;10(1):49-53. doi:10.1016/0360-3016(84)90411-5
74. Maier D. [Heterotopic ossification spinal cord injury. Management through early diagnosis and therapy]. *Orthopade*. Feb 2005;34(2):120, 122-7. Heterotope Ossifikationen bei Querschnittlähmung. Management zur Frühdiagnose und Therapie. doi:10.1007/s00132-004-0754-9
75. Maloney WJ, Jasty M, Willett C, Mulroy RD, Jr., Harris WH. Prophylaxis for heterotopic bone formation after total hip arthroplasty using low-dose radiation in high-risk patients. *Clin Orthop Relat Res*. Jul 1992;(280):230-4.
76. Martini F, Sell S, Reize P, Jani R, Kusswetter W. Perioperative side-effects of preventative measures against heterotopic-oddification diclofenac versus irradiation. *Aktuelle Rheumatologie*. 1995;20(2):61-65.
77. Mishra MV, Austin L, Parvizi J, Ramsey M, Showalter TN. Safety and efficacy of radiation therapy as secondary prophylaxis for heterotopic ossification of non-hip joints. *J Med Imaging Radiat Oncol*. Jun 2011;55(3):333-6. doi:10.1111/j.1754-9485.2011.02275.x
78. Miszczyk L, Spindel J, Maciejewski B, et al. [Radiotherapy as prevention of heterotopic ossification--preliminary results]. *Przegl Lek*. 2004;61(2):61-4. Zastosowanie radioterapii jako metody zapobiegajacej kostnieniu pozakostnemu--doniesienie wstepne.
79. Moed BR, Letournel E. Low-dose irradiation and indomethacin prevent heterotopic ossification after acetabular fracture surgery. *J Bone Joint Surg Br*. Nov 1994;76(6):895-900.
80. Mohamed R, Iqbal A, Elawadi AA. Fifteen years' experience of radiation therapy for resected advanced heterotopic ossification following motor vehicle accidents: outcome and side effects. *J Egypt Natl Canc Inst*. Nov 21 2022;34(1):48. doi:10.1186/s43046-022-00149-w

81. Mourad WF, Packianathan S, Ma JK, et al. Computerized tomography-based radiotherapy improves heterotopic ossification outcomes. *Bone*. Nov 2013;57(1):132-6. doi:10.1016/j.bone.2013.08.001
82. Mourad WF, Packianathan S, Shourbaji RA, et al. The impact of body mass index on heterotopic ossification. *Int J Radiat Oncol Biol Phys*. Apr 1 2012;82(5):e831-6. doi:10.1016/j.ijrobp.2011.11.033
83. Mourad WF, Packianathan S, Shourbaji RA, et al. A prolonged time interval between trauma and prophylactic radiation therapy significantly increases the risk of heterotopic ossification. *Int J Radiat Oncol Biol Phys*. Mar 1 2012;82(3):e339-44. doi:10.1016/j.ijrobp.2011.06.1981
84. Mourad WF, Packianathan S, Shourbaji RA, et al. The influence of pregnancy on heterotopic ossification post-displaced acetabular fractures surgical repair. *J Orthop Res*. Jun 2013;31(6):944-8. doi:10.1002/jor.22309
85. Mourad WF, Packianathan S, Shourbaji RA, et al. The impact of class III (morbid) obesity on heterotopic ossification outcomes. *Pract Radiat Oncol*. Jul-Sep 2012;2(3):e1-e6. doi:10.1016/j.prro.2011.11.003
86. Müseler AC, Grasmücke D, Jansen O, et al. In-hospital outcomes following single-dose radiation therapy in the treatment of heterotopic ossification of the hip following spinal cord injury-an analysis of 444 cases. *Spinal Cord*. Mar 2017;55(3):244-246. doi:10.1038/sc.2016.112
87. Nasr E, Nehme R, Ghanem I, Azoury F, Nasr DN, Dagher F. [Role of radiotherapy in heterotopic ossification]. *Cancer Radiother*. Jan 2009;13(1):42-6. Rôle de la radiothérapie dans l'ossification hétérotopique. doi:10.1016/j.canrad.2008.06.003
88. Padgett DE, Holley KG, Cummings M, et al. The efficacy of 500 CentiGray radiation in the prevention of heterotopic ossification after total hip arthroplasty: a prospective, randomized, pilot study. *J Arthroplasty*. Sep 2003;18(6):677-86. doi:10.1016/s0883-5403(03)00265-1
89. Pakos EE, Pitouli EJ, Tsekeris PG, Papathanasopoulou V, Stafilas K, Xenakis TH. Prevention of heterotopic ossification in high-risk patients with total hip arthroplasty: the experience of a combined therapeutic protocol. *Int Orthop*. Apr 2006;30(2):79-83. doi:10.1007/s00264-005-0054-y
90. Pakos EE, Tsekeris PG, Paschos NK, Pitouli EJ, Motsis EK, Xenakis TA. The role of radiation dose in a combined therapeutic protocol for the prevention of heterotopic ossification after total hip replacement. *J buon*. Jan-Mar 2010;15(1):74-8.
91. Pakos EE, Papadopoulos DV, Gelalis ID, et al. Is prophylaxis for heterotopic ossification with radiation therapy after THR associated with early loosening or carcinogenesis? Hip Int. Sep 2020;30(5):559-563. doi:10.1177/1120700019842724
92. Pakos EE, Stafilas KS, Politis AN, Tsekeris PG, Mitsionis G, Xenakis TA. Heterotopic ossification after total hip arthroplasty (THA) in congenital hip disease: comparison of two different prophylactic protocols. Clin Transl Oncol. Feb 2009;11(2):103-8. doi:10.1007/s12094-009-0322-1
93. Pakos EE, Stafilas KS, Tsekeris PG, Politis AN, Mitsionis G, Xenakis TA. Combined radiotherapy and indomethacin for the prevention of heterotopic ossification after total hip arthroplasty. Strahlenther Onkol. Aug 2009;185(8):500-5. doi:10.1007/s00066-009-1954-3
94. Parkinson JR, Evarts CM, Hubbard LF. Radiation therapy in the prevention of heterotopic ossification after total hip arthroplasty. *Hip*. 1982:211-27.
95. Pellegrini VD, Jr., Gregoritch SJ. Preoperative irradiation for prevention of heterotopic ossification following total hip arthroplasty. *J Bone Joint Surg Am*. Jun 1996;78(6):870-81. doi:10.2106/00004623-199606000-00010

96. Piatek S, Westphal T, Arbter D, Winckler S. [Value of a combined ossification prophylaxis with indomethacin and radiotherapy for acetabular fractures]. *Unfallchirurg*. Jul 2006;109(7):556-62. Wertigkeit einer kombinierten Ossifikationsprophylaxe mit Indometacin und Bestrahlung bei Azetabulumfrakturen. doi:10.1007/s00113-006-1083-8
97. Pohl F, Seufert J, Tauscher A, et al. The influence of heterotopic ossification on functional status of hip joint following total hip arthroplasty. *Strahlenther Onkol*. Aug 2005;181(8):529-33. doi:10.1007/s00066-005-1352-4
98. Rashid RH, Qadir I, Ahmed W, Umer M. Prophylaxis against heterotopic ossification after elbow and acetabular fractures - Do we really need it. *J Pak Med Assoc*. Nov 2015;65(11 Suppl 3):S87-90.
99. Robinson CG, Polster JM, Reddy CA, et al. Postoperative single-fraction radiation for prevention of heterotopic ossification of the elbow. *Int J Radiat Oncol Biol Phys*. Aug 1 2010;77(5):1493-9. doi:10.1016/j.ijrobp.2009.06.072
100. Rudicel S. [Para-articular (ectopic or heterotopic) ossification following total hip prosthesis]. *Orthopade*. Feb 1985;14(1):54-7. Paraartikuläre (ektopische oder heterotope) Ossifikationen nach Hüfttotalprothese. Ruo Redda MG, De Colle C, Bianco L, et al. Heterotopic ossifications: role of radiotherapy as prophylactic treatment. *Radiol Med*. Jun 2018;123(6):463-468. doi:10.1007/s11547-018-0853-z
101. Sarafis KA, Karatzas GD, Yotis CL. Ankylosed hips caused by heterotopic ossification after traumatic brain injury: a difficult problem. *J Trauma*. Jan 1999;46(1):104-9. doi:10.1097/00005373-199901000-00017
102. Sauer R, Seegenschmiedt MH, Goldmann A, Beck H, Andreas P. [Prevention of periarticular ossification following endoprosthetic hip replacement using postoperative irradiation]. Strahlenther Onkol. Feb 1992;168(2):89-99. Prophylaxe periartikulärer Verknöcherungen nach endoprothetischem Hüftgelenksersatz durch postoperative Bestrahlung.
103. Sautter-Bihl ML, Hültenschmidt B, Liebermeister E, Nanassy A. Fractionated and single-dose radiotherapy for heterotopic bone formation in patients with spinal cord injury. A phase-I/II study. *Strahlenther Onkol*. Apr 2001;177(4):200-5. doi:10.1007/pl00002399
104. Sautter-Bihl ML, Liebermeister E, Heinze HG, Nanassy A, Stoltze D. [The radiotherapy of heterotopic ossifications in paraplegics. The preliminary results]. *Strahlenther Onkol*. Aug 1995;171(8):454-9. Strahlentherapie heterotoper Ossifikationen bei Querschnittsgelähmten. Präliminäre Ergebnisse.
105. Sautter-Bihl ML, Liebermeister E, Nanassy A. Radiotherapy as a local treatment option for heterotopic ossifications in patients with spinal cord injury. *Spinal Cord*. Jan 2000;38(1):33-6. doi:10.1038/sj.sc.3100847
106. Schai P, Brunner R, Morscher E, Schubert KH. Prevention of heterotopic ossification in hip arthroplasties by means of an early single-dose radiotherapy (6 Gy). *Arch Orthop Trauma* Surg. 1995;114(3):153-8. doi:10.1007/bf00443389
107. Schai P, Brunner R, Morscher E, Schubert KH. Prevention of heterotopic ossification in hip arthroplasties by means of an early single-dose radiotherapy (6 Gy). *Arch Orthop Trauma Surg*. 1995;114(3):153-8. doi:10.1007/bf00443389
108. Seegenschmiedt MH, Goldmann AR, Wölfel R, Hohmann D, Beck H, Sauer R. Prevention of heterotopic ossification (HO) after total hip replacement: randomized high versus low dose radiotherapy. *Radiother Oncol*. Mar 1993;26(3):271-4. doi:10.1016/0167-8140(93)90270-i
109. Seegenschmiedt MH, Keilholz L, Martus P, et al. Prevention of heterotopic ossification about the hip: final results of two randomized trials in 410 patients using either preoperative or postoperative radiation therapy. *Int J Radiat Oncol Biol Phys*. Aug 1 1997;39(1):161-71. doi:10.1016/s0360-3016(97)00285-x

110. Seegenschmiedt MH, Makoski HB, Micke O. Radiation prophylaxis for heterotopic ossification about the hip joint--a multicenter study. *Int J Radiat Oncol Biol Phys*. Nov 1 2001;51(3):756-65. doi:10.1016/s0360-3016(01)01640-6
111. Seegenschmiedt MH, Martus P, Goldmann AR, Wölfel R, Keilholz L, Sauer R. [Pre- and postoperative radiotherapy to prevent heterotopic ossification of the hip joint]. *Strahlenther Onkol*. May 1994;170(5):281-91. Prä- und postoperative Radiotherapie zur Prophylaxe von heterotopen Ossifikationen am Hüftgelenk.
112. Seegenschmiedt MH, Martus P, Goldmann AR, Wölfel R, Keilholz L, Sauer R. Preoperative versus postoperative radiotherapy for prevention of heterotopic ossification (HO): first results of a randomized trial in high-risk patients. *Int J Radiat Oncol Biol Phys*. Aug 30 1994;30(1):63-73. doi:10.1016/0360-3016(94)90520-7
113. Sell S, Jany R, Kremling E, Esenwein S, Gaissmaier C, Küsswetter W. [Prevention of heterotopic ossification following cementless hip replacement using 5 x 2 Gy fractionated irradiation. A prospective study]. *Z Orthop Ihre Grenzgeb*. Jul-Aug 1996;134(4):375-80. Prävention heterotoper Ossifikationen nach zementfreiem Hüftgelenksersatz durch fraktionierte Radiatio mit 5 x 2 Gy. Eine prospektive Studie. doi:10.1055/s-2008-1039778
114. Slawson RG, Poka A, Bathon H, Salazar OM, Bromback RJ, Burgess AR. The role of post-operative radiation in the prevention of heterotopic ossification in patients with post-traumatic acetabular fracture. *Int J Radiat Oncol Biol Phys*. Sep 1989;17(3):669-72. doi:10.1016/0360-3016(89)90122-3
115. Spry NA, Dally MJ, Benjamin B, Chapman P, Morum P, Christie DR. Heterotopic bone formation affecting the hip joint is preventable in high risk patients by post-operative radiation. *Australas Radiol*. Nov 1995;39(4):379-83. doi:10.1111/j.1440-1673.1995.tb00316.x\
116. Starr AJ, Watson JT, Reinert CM, et al. Complications following the "T extensile" approach: a modified extensile approach for acetabular fracture surgery-report of forty-three patients. J Orthop Trauma. Sep 2002;16(8):535-42. doi:10.1097/00005131-200209000-00001
117. Stein DA, Patel R, Egol KA, Kaplan FT, Tejwani NC, Koval KJ. Prevention of heterotopic ossification at the elbow following trauma using radiation therapy. *Bull Hosp Jt Dis*. 2003;61(3-4):151-4.
118. Strauss JB, Wysocki RW, Shah A, et al. Radiation therapy for heterotopic ossification prophylaxis afer high-risk elbow surgery. *Am J Orthop (Belle Mead NJ)*. Aug 2011;40(8):400-5.
119. Sylvester JE, Blount LH, Selch MT. Technical considerations in the use of prophylactic radiation therapy to prevent heterotopic bone formation. *Semin Arthroplasty*. Jul 1992;3(3):167-71.
120. Sylvester JE, Greenberg P, Selch MT, Thomas BJ, Amstutz H. The use of postoperative irradiation for the prevention of heterotopic bone formation after total hip replacement. *Int J Radiat Oncol Biol Phys*. Mar 1988;14(3):471-6. doi:10.1016/0360-3016(88)90262-3
121. Tabaie SA, Dombrowski J, Moed BR. Does prophylactic irradiation port size affect the extent of heterotopic ossification after acetabular fracture surgery? A pilot study. *Current Orthopaedic Practice*. 2014;25(6):592-596.
122. Wahl B, Grasshoff H, Meinecke I, Neumann HW. [Clinical and radiological results of surgical removal of periarticular ossifications after hip prosthesis implantation]. *Unfallchirurg*. Jun 2002;105(6):523-6. Klinische und radiologische Ergebnisse der operativen Entfernung von periartikulären Ossifikationen nach Hüftendoprothese. doi:10.1007/s00113-001-0381-4
123. Warren SB, Brooker AF, Jr. Excision of heterotopic bone followed by irradiation after total hip arthroplasty. *J Bone Joint Surg Am*. Feb 1992;74(2):201-10.

124. Weng HK, Wu PK, Chen CF, et al. Total hip arthroplasty for patients who have ankylosing spondylitis: Is postoperative irradiation required for prophylaxis of heterotopic ossification? *J Arthroplasty*. Oct 2015;30(10):1752-6. doi:10.1016/j.arth.2015.04.022
125. Wey J, DiPasquale D, Levitt L, Quitkin H. Operative treatment of acetabular fractures through the extensile Henry approach. *J Trauma*. Feb 1999;46(2):255-60. doi:10.1097/00005373-199902000-00010
126. Wingo T, Shankar DS, Essilfie AA, Youm T. Endoscopic Excision of Hip Heterotopic Ossification, Plus Indomethacin and Radiation, Is Effective in Treating and Preventing Recurrence. *Arthrosc Sports Med Rehabil*. Feb 2023;5(1):e165-e169. doi:10.1016/j.asmr.2022.11.008
127. Wölfel R, Seegenschmiedt MH, Günther K, Sauer R, Beck H, Hohmann D. [Prevention of para-articular ossifications after endoprosthetic hip joint replacement by postoperative irradiation]. *Chirurg*. Nov 1994;65(11):1015-22. Prophylaxe paraarticulärer Ossifikationen nach endoprothetischem Hüftgelenkersatz durch postoperative Bestrahlung.
128. Wu FF, Gao HL, Huang S, et al. [NSAIDs combined with radiotherapy to prevent heterotopic ossification after total hip arthroplasty]. *Zhongguo Gu Shang*. Jun 25 2018;31(6):538-542. doi:10.3969/j.issn.1003-0034.2018.06.011
129. Wu XB, Yang MH, Zhu SW, et al. Surgical resection of severe heterotopic ossification after open reduction and internal fixation of acetabular fractures: a case series of 18 patients. *Injury*. Oct 2014;45(10):1604-10. doi:10.1016/j.injury.2014.05.018

Keloids: 138 Exclusions

1. Abdus-Salam AA, Orekoya AA, Jimoh MA, Olabumuyi AA. Radiotherapy treatment of keloids in Ibadan. *J West Afr Coll Surg*. Oct-Dec 2016;6(4):104-116.
2. Ahmad M, Ahmad H, Khattak MR, et al. Postoperative single versus multiple fractions high-dose rate iridium-192 surface mould brachytherapy for keloid treatment: a comparative study. Journal of Radiotherapy in Practice. 2018;17(1):60-65.
3. Akita S, Akino K, Yakabe A, et al. Combined surgical excision and radiation therapy for keloid treatment. *J Craniofac Surg*. Sep 2007;18(5):1164-9. doi:10.1097/scs.0b013e3180de62a1
4. Anderson EM, David J, Phillips T, et al. Interstitial high-dose-rate brachytherapy in the treatment of keloids: Moving toward a volumetric approach. Brachytherapy. Jan-Feb 2021;20(1):185-188. doi:10.1016/j.brachy.2020.07.008
5. Arima J, Dohi T, Kuribayashi S, Akaishi S, Ogawa R. Z-plasty and postoperative radiotherapy for anterior chest wall keloids: An analysis of 141 patients. *Plast Reconstr Surg Glob Open*. Mar 2019;7(3):e2177. doi:10.1097/gox.0000000000002177
6. Arnault JP, Peiffert D, Latarche C, Chassagne JF, Barbaud A, Schmutz JL. Keloids treated with postoperative Iridium 192* brachytherapy: a retrospective study. J Eur Acad Dermatol Venereol. Jul 2009;23(7):807-13. doi:10.1111/j.1468-3083.2009.03190.x
7. Arneja JS, Singh GB, Dolynchuk KN, Murray KA, Rozzelle AA, Jones KD. Treatment of recurrent earlobe keloids with surgery and high-dose-rate brachytherapy. *Plast Reconstr Surg*. Jan 2008;121(1):95-99. doi:10.1097/01.prs.0000293755.64918.22
8. Bautista Hernandez Y, Villavicencio Queijero MA, Quezada Bautista AA, Vazquez Tinajero A. Surface brachytherapy in the treatment of keloid scars in Mexico. Rep Pract Oncol Radiother. Jan-Feb 2020;25(1):133-138. doi:10.1016/j.rpor.2019.11.002
9. Bennett KG, Kung TA, Hayman JA, Brown DL. Treatment of keloids with excision and adjuvant radiation: A single center experience and review of the literature. *Ann Plast Surg*. Feb 2017;78(2):157-161. doi:10.1097/sap.0000000000000903

10. Berman B, Nestor MS, Gold MH, Goldberg DJ, Weiss ET, Raymond I. A retrospective registry study evaluating the long-term efficacy and safety of superficial radiation therapy following excision of keloid scars. *J Clin Aesthet Dermatol*. Oct 2020;13(10):12-16.
11. Bertiere MN, Jousset C, Marin JL, Baux S. [Value of interstitial irradiation of keloid scars by Iridium 192. Apropos of 46 cases]. *Ann Chir Plast Esthet*. 1990;35(1):27-30. Intérêt de l'irradiation interstitielle des cicatrices chéloïdes par Iridium 192. A propos de 46 cas.
12. Bhusari P, Shukla J, Kumar M, et al. Noninvasive treatment of keloid using customized Re-188 skin patch. *Dermatol Ther*. Sep 2017;30(5)doi:10.1111/dth.12515
13. Bijlard E, Verduijn GM, Harmeling JX, et al. Optimal high-dose-rate brachytherapy fractionation scheme after keloid excision: A retrospective multicenter comparison of recurrence rates and complications. Int J Radiat Oncol Biol Phys. Mar 1 2018;100(3):679-686. doi:10.1016/j.ijrobp.2017.10.044
14. Bischof M, Krempien R, Debus J, Treiber M. Postoperative electron beam radiotherapy for keloids: objective findings and patient satisfaction in self-assessment. *Int J Dermatol*. Sep 2007;46(9):971-5. doi:10.1111/j.1365-4632.2007.03326.x
15. Caccialanza M, Dal Pozzo V, Piccinno R, Beretta M, Gnecchi L. Postoperative radiotherapy of earlobe keloids. *Giornale italiano di dermatologia e venereologia*. 1998;133(6):399-404.
16. Caccialanza M, Piccinno R, Schiera A. Postoperative radiotherapy of keloids: a twenty-year experience. *Eur J Dermatol*. Jan-Feb 2002;12(1):58-62.
17. Capel AV, Palop JV, Olivé AP, Fernández AS-R. Adjuvance in refractory keloids using electron beams with a spoiler: Recent results. *Reports of Practical Oncology and Radiotherapy*. 2015;20(1):43-49.
18. Carvajal CC, Ibarra CM, Arbulo DL, Russo MN, Solé CP. Postoperative radiotherapy in the management of keloids. *Ecancermedicalscience*. 2016;10:690. doi:10.3332/ecancer.2016.690
19. Chaudhry MR, Akhtar S, Duvalsaint F, Garner L, Lucente FE. Ear lobe keloids, surgical excision followed by radiation therapy: a 10-year experience. *Ear Nose Throat J*. Oct 1994;73(10):779-81.
20. Chen F, Kuo YR, Huang CJ, Tang JY, Chiang CH, Huang MY. Lesion site is the key prognostic factor for keloid patients receiving surgery with adjuvant radiotherapy. *Ann Plast Surg*. Dec 1 2022;89(6):626-630. doi:10.1097/sap.0000000000003315
21. Clavere P, Bedane C, Bonnetblanc JM, Bonnafoux-Clavere A, Rousseau J. Postoperative interstitial radiotherapy of keloids by iridium 192: a retrospective study of 46 treated scars. *Dermatology*. 1997;195(4):349-52. doi:10.1159/000245986
22. De Cicco L, Vischioni B, Vavassori A, et al. Postoperative management of keloids: low-dose-rate and high-dose-rate brachytherapy. Brachytherapy. Sep-Oct 2014;13(5):508-13. doi:10.1016/j.brachy.2014.01.005
23. De Lorenzi F, Tielemans HJ, van der Hulst RR, et al. Is the treatment of keloid scars still a challenge in 2006? Ann Plast Surg. Feb 2007;58(2):186-92. doi:10.1097/01.sap.0000237761.52586.f9
24. Deng K, Xiao H, Liu X, Ogawa R, Xu X, Liu Y. Strontium-90 brachytherapy following intralesional triamcinolone and 5-fluorouracil injections for keloid treatment: A randomized controlled trial. PLoS One. 2021;16(3):e0248799. doi:10.1371/journal.pone.0248799
25. Dohi T, Kuribayashi S, Aoki M, Tosa M, Akaishi S, Ogawa R. Combination therapy composed of surgery, postoperative radiotherapy, and wound self-management for umbilical keloids. *Plast Reconstr Surg Glob Open*. Oct 2020;8(10):e3181. doi:10.1097/gox.0000000000003181
26. Dohi T, Kuribayashi S, Tosa M, Aoki M, Akaishi S, Ogawa R. Z-plasty and postoperative radiotherapy for upper-arm keloids: An analysis of 38 patients. *Plast Reconstr Surg Glob Open*. Nov 2019;7(11):e2496. doi:10.1097/gox.0000000000002496

27. Doornbos JF, Stoffel TJ, Hass AC, et al. The role of kilovoltage irradiation in the treatment of keloids. *Int J Radiat Oncol Biol Phys*. Apr 1990;18(4):833-9. doi:10.1016/0360-3016(90)90405-9
28. Duan Q, Liu J, Luo Z, Hu C. Postoperative brachytherapy and electron beam irradiation for keloids: A single institution retrospective analysis. Mol Clin Oncol. May 2015;3(3):550-554. doi:10.3892/mco.2015.498
29. Durosinmi-Etti FA, Olasinde TA, Solarin EO. A short course postoperative radiotherapy regime for keloid scars in Nigeria. *West Afr J Med*. Jan-Mar 1994;13(1):17-9.
30. Eaton DJ, Barber E, Ferguson L, Mark Simpson G, Collis CH. Radiotherapy treatment of keloid scars with a kilovoltage X-ray parallel pair. *Radiother Oncol*. Mar 2012;102(3):421-3. doi:10.1016/j.radonc.2011.08.002
31. Enhamre A, Hammar H. Treatment of keloids with excision and postoperative X-ray irradiation. *Dermatologica*. 1983;167(2):90-3. doi:10.1159/000249754
32. Escarmant P, Zimmermann S, Amar A, et al. The treatment of 783 keloid scars by iridium 192 interstitial irradiation after surgical excision. Int J Radiat Oncol Biol Phys. May 20 1993;26(2):245-51. doi:10.1016/0360-3016(93)90204-9
33. Fierro-Arias L, Peyro-Quiñones E, Peniche-Castellanos A, Ponce-Olivera RM. Superficial radiotherapy in Dermatology. Thirty-years experience in the Hospital General de Mexico Dr. Eduardo Liceaga. *Dermatología Revista Mexicana*. 2015;59(3):195-200.
34. Fraunholz IB, Gerstenhauer A, Böttcher HD. Results of postoperative (90)Sr radiotherapy of keloids in view of patients' subjective assessment. Strahlenther Onkol. Nov 2005;181(11):724-9. doi:10.1007/s00066-005-1411-x
35. Furtado F, Hochman B, Ferreira LM. Evaluating keloid recurrence after surgical excision with prospective longitudinal scar assessment scales. *J Plast Reconstr Aesthet Surg*. Jul 2012;65(7):e175-81. doi:10.1016/j.bjps.2012.02.005
36. Guix B, Henríquez I, Andrés A, Finestres F, Tello JI, Martínez A. Treatment of keloids by high-dose-rate brachytherapy: A seven-year study. Int J Radiat Oncol Biol Phys. May 1 2001;50(1):167-72. doi:10.1016/s0360-3016(00)01563-7
37. Ha B, Kim SJ, Lee YJ, Im S, Park TH. Early outcomes of complete excision followed by immediate postoperative single fractional 10 Gy for anterior chest keloids: A preliminary results. *Int Wound J*. May 2023;20(5):1418-1425. doi:10.1111/iwj.13996
38. Hafkamp CJH, Lapid O, Dávila Fajardo R, et al. Postoperative single-dose interstitial high-dose-rate brachytherapy in therapy-resistant keloids. Brachytherapy. Mar-Apr 2017;16(2):415-420. doi:10.1016/j.brachy.2016.12.009
39. Han CM, Shao HW, He XJ, Wang LC. [Postoperative electron beam irradiation therapy for keloid:a follow-up study of 48 patients]. *Zhonghua Wai Ke Za Zhi*. Mar 7 2004;42(5):288-90.
40. Handl-Zeller L, Hohenberg G. [Postoperative prevention of hypertrophic scars and keloids using radiotherapy]. *Hautarzt*. Mar 1990;41(3):146-8. Postoperative Prophylaxe hypertropher Narben und Keloide mittels Strahlentherapie.
41. Hao Y, Liang Z, Liu H, et al. A nomogram with the keloid activity assessment acale for predicting the recurrence of chest keloid after surgery and radiotherapy. *Aesthetic Plast Surg*. Apr 2023;47(2):872-879. doi:10.1007/s00266-022-03187-w
42. Heianna J, Iida N, Otsuka K, et al. Investigation of the optimal dose on postoperative radiotherapy for earlobe keloid. *The Journal of JASTRO*. 2004;16(1):47-51.
43. Hernandez YB, Gomez KV, Lopez AL. Treatment of benign tumours and related pathologies with radiotherapy: experience of the General Hospital of Mexico. Rep Pract Oncol Radiother. 2022;27(4):684-690. doi:10.5603/RPOR.a2022.0072

44. Hoang D, Reznik R, Orgel M, Li Q, Mirhadi A, Kulber DA. Surgical excision and adjuvant brachytherapy vs external beam radiation for the effective treatment of keloids: 10-Year Institutional Retrospective Analysis. *Aesthet Surg J*. Feb 2017;37(2):212-225. doi:10.1093/asj/sjw124
45. Hsueh WT, Hung KS, Chen YC, et al. Adjuvant radiotherapy after keloid excision: Preliminary experience in Taiwan. *Ann Plast Surg*. Jan 2019;82(1S Suppl 1):S39-s44. doi:10.1097/sap.0000000000001728
46. Hung YT, Lin SM, Tzeng IS, Ng CY. Optimizing surgical outcome of auricular keloid with a novel multimodal approach. *Sci Rep*. Mar 3 2022;12(1):3533. doi:10.1038/s41598-022-07255-8
47. Hwang NH, Lee NK, Chae JH, Park SH, Yoon ES. The efficacy of CT-based conformal electron beam radiation therapy after keloid excision. *Dermatol Surg*. Apr 1 2022;48(4):435-440. doi:10.1097/dss.0000000000003398
48. Jiang P, Geenen M, Siebert FA, et al. Efficacy and the toxicity of the interstitial high-dose-rate brachytherapy in the management of recurrent keloids: 5-year outcomes. Brachytherapy. May-Jun 2018;17(3):597-600. doi:10.1016/j.brachy.2017.12.002
49. Jones ME, Ganzer CA, Bennett D, Finizio A. Surgical excision of keloids followed by in-office superficial radiation therapy: Prospective study examining clinical outcomes. *Plast Reconstr Surg Glob Open*. May 2019;7(5):e2212. doi:10.1097/gox.0000000000002212
50. Jones ME, Hardy C, Ridgway J. Keloid management: A retrospective case review on a new approach using surgical excision, platelet-rich plasma, and in-office superficial photon x-ray radiation therapy. *Adv Skin Wound Care*. Jul 2016;29(7):303-7. doi:10.1097/01.Asw.0000482993.64811.74
51. Jones ME, McLane J, Adenegan R, Lee J, Ganzer CA. Advancing keloid treatment: A novel multimodal approach to ear keloids. *Dermatol Surg*. Sep 2017;43(9):1164-1169. doi:10.1097/dss.0000000000001145
52. Kärcher H, Hackl A. [Post-operative radiation in scar corrections in the head and neck region]. *Dtsch Z Mund Kiefer Gesichtschir*. Nov-Dec 1984;8(6):476-80. Die Nachbestrahlung bei Narbenkorrekturen im Kopf-halsbereich.
53. Kim J, Lee SH. Therapeutic results and safety of postoperative radiotherapy for keloid after repeated Cesarean section in immediate postpartum period. *Radiat Oncol J*. Jun 2012;30(2):49-52. doi:10.3857/roj.2012.30.2.49
54. Kim K, Son D, Kim J. Radiation therapy following total keloidectomy: A retrospective study over 11 Years. *Arch Plast Surg*. Sep 2015;42(5):588-95. doi:10.5999/aps.2015.42.5.588
55. Klumpar DI, Murray JC, Anscher M. Keloids treated with excision followed by radiation therapy. *J Am Acad Dermatol*. Aug 1994;31(2 Pt 1):225-31. doi:10.1016/s0190-9622(94)70152-0
56. Kovalic JJ, Perez CA. Radiation therapy following keloidectomy: a 20-year experience. *Int J* Radiat *Oncol Biol Phys*. Jul 1989;17(1):77-80. doi:10.1016/0360-3016(89)90373-8
57. Kuribayashi S, Miyashita T, Ozawa Y, et al. Post-keloidectomy irradiation using high-dose-rate superficial brachytherapy. J Radiat Res. 2011;52(3):365-8. doi:10.1269/jrr.10159
58. Latini C, Onesti M, Spalvieri C, Barile A, Scuderi N. Regressive vicariation of pathologic hypertrophical scars with antihomotoxic therapy. *Biologische Medizin*. 1999;28:11-15.
59. Lee SY, Park J. Postoperative electron beam radiotherapy for keloids: treatment outcome and factors associated with occurrence and recurrence. *Ann Dermatol*. Feb 2015;27(1):53-8. doi:10.5021/ad.2015.27.1.53
60. Levy DS, Salter MM, Roth RE. Postoperative irradiation in the prevention of keloids. *AJR Am J Roentgenol*. Sep 1976;127(3):509-10. doi:10.2214/ajr.127.3.509

61. Li L, Yuan C, Zhang X, Wang B, Yan Y. Superficial X-ray-induced hyperpigmentation in postoperative keloid radiotherapy: A study of 70 keloids to identify clinical features and risk factors. *J Cosmet Dermatol*. Sep 2021;20(9):2880-2886. doi:10.1111/jocd.14308
62. Li PC, Jia CY, Li YM, et al. [Clinical efficacy of keloids treated by surgical ablation and immediate postoperative adjuvant radiotherapy]. *Zhonghua Yi Xue Za Zhi*. Dec 6 2011;91(45):3223-4.
63. Li W, Wang Y, Wang X, Liu Z. A keloid edge precut, preradiotherapy method in large keloid skin graft treatment. *Dermatol Surg*. Jan 2014;40(1):52-7. doi:10.1111/dsu.12374
64. Liang C, Chuan C, Xiaoge L, Dongyun Y, Shirong L. Surgery and follow-up care for auricular keloid: a report of 156 cases. *Journal of Medical Colleges of PLA*. 2013;28(2):107-112.
65. Lin YF, Shueng PW, Roan TL, et al. Tomotherapy as an alternative irradiative treatment for complicated keloids. *J Clin Med*. Nov 20 2020;9(11)doi:10.3390/jcm9113732
66. Lindsey WH, Davis PT. Facial keloids. A 15-year experience. *Arch Otolaryngol Head Neck Surg*. Apr 1997;123(4):397-400. doi:10.1001/archotol.1997.01900040031005
67. Litoux P, Pannier M, Stalder JF. [Treatment of keloid]. *Ann Dermatol Venereol*. 1986;113(9):875-6. Traitement des chéloïdes.
68. Liu CL, Yuan ZY. Retrospective study of immediate postoperative electron radiotherapy for therapy-resistant earlobe keloids. *Arch Dermatol Res*. Aug 2019;311(6):469-475. doi:10.1007/s00403-019-01922-z
69. Liu S, Liang W, Song K, Wang Y. Keloid skin flap retention and resurfacing in facial keloid treatment. *Aesthetic Plast Surg*. Feb 2018;42(1):304-309. doi:10.1007/s00266-017-0949-1
70. Liu X, Wang H, Cen Y, Li Z. [Synthetic therapy for keloid in aural region]. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. Jan 2008;22(1):56-8.
71. Liu Y, Xiao H, Liu X, et al. [Effectiveness of internal mammary artery perforator propeller flap repair combined with radiotherapy for chest keloid in female patients]. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. Sep 15 2018;32(9):1196-1200. doi:10.7507/1002-1892.201803004
72. Long X, Wang XJ, Wang YB, Li WB, Sun XS. [An individualized approach combining local flaps with radiotherapy for the treatment of auricle keloid]. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao*. Apr 2013;35(2):213-6. doi:10.3881/j.issn.1000-503X.2013.02.015
73. Long X, Zhang M, Wang Y, Zhao R, Wang Y, Wang X. Algorithm of chest wall keloid treatment. *Medicine*. 2016;95(35)
74. Lyu A, Xu E, Wang Q. A retrospective analysis of surgical resection of large ear keloids. *Australas J Dermatol*. Feb 2019;60(1):29-32. doi:10.1111/ajd.12872
75. Ma QY, Yang YT, Chen ZA, et al. Laser combined with radiotherapy for keloid treatment: A novel and efficient comprehensive therapy with a lower recurrence rate. *Plast Reconstr Surg*. Dec 1 2023;152(6):1022e-1029e. doi:10.1097/prs.0000000000010376
76. Maarouf M, Schleicher U, Schmachtenberg A, Ammon J. Radiotherapy in the management of keloids. Clinical experience with electron beam irradiation and comparison with X-ray therapy. *Strahlenther Onkol*. Jun 2002;178(6):330-5. doi:10.1007/s00066-002-0935-6
77. Maemoto H, Iraha S, Arashiro K, Ishigami K, Ganaha F, Murayama S. Risk factors of recurrence after postoperative electron beam radiation therapy for keloid: Comparison of long-term local control rate. *Rep Pract Oncol Radiother*. Jul-Aug 2020;25(4):606-611. doi:10.1016/j.rpor.2020.05.001
78. Malaker K, Vijayraghavan K, Hodson I, Al Yafi T. Retrospective analysis of treatment of unresectable keloids with primary radiation over 25 years. *Clin Oncol (R Coll Radiol)*. Jun 2004;16(4):290-8. doi:10.1016/j.clon.2004.03.005
79. Malaker K, Zaidi M, Franka MR. Treatment of earlobe keloids using the cobalt 60 teletherapy unit. *Ann Plast Surg*. Jun 2004;52(6):602-4. doi:10.1097/01.sap.0000095408.74866.f1

80. Margiotta E, Ramras S, Shteynberg A. Recurrence of primary and secondary keloids in a select African American and Afro-Caribbean population. *Ann Plast Surg*. May 1 2022;88(3 Suppl 3):S194-s196. doi:10.1097/sap.0000000000003173
81. Masoodi Z, Ahmad I, Khurram MF, Haq A. Excision, skin grafting, corticosteroids, adjuvant radiotherapy, pressure therapy, and emancipation: the ESCAPE model for successful taming of giant auricular keloids. *Adv Skin Wound Care*. Sep 2014;27(9):404-12. doi:10.1097/01.ASW.0000451340.59196.9d
82. Meythiaz A, De Mey A, Lejour M. Treatment of keloids by excision and postoperative radiotherapy. *European Journal of Plastic Surgery*. 1992;15:13-16.
83. Mitsuhashi K, Miyashita T. [Treatment of so-called keloid with excision and postoperative electron irradiation]. *Nihon Ika Daigaku Zasshi*. Apr 1995;62(2):186-95. doi:10.1272/jnms1923.62.186
84. Mohamed R, Elawadi AA, Al-Gendi R, Al-Mohsen S, Wani S, Wafa A. The outcome of postoperative radiation therapy following plastic surgical resection of recurrent ear keloid: a single institution experience. *J Egypt Natl Canc Inst*. Jan 24 2022;34(1):4. doi:10.1186/s43046-022-00105-8
85. Mohammadi AA, Mohammadian Panah M, Pakyari MR, et al. Surgical excision followed by low dose rate radiotherapy in the management of resistant keloids. *World J Plast Surg*. Jun 2013;2(2):81-6.
86. Nang'ole FW, Anzala O, Ogeng'o J, Agak GW. Determinants of keloid recurrence: The Nairobi keloid recurrence scoring system; A cohort, prospective study. *International Journal of Surgery Open*. 2023;52:100596.
87. Narkwong L, Thirakhupt P. Postoperative radiotherapy with high dose rate iridium 192 mould for prevention of earlobe keloids. *J Med Assoc Thai*. Apr 2006;89(4):428-33.
88. Norris JE. Superficial x-ray therapy in keloid management: a retrospective study of 24 cases and literature review. *Plast Reconstr Surg*. May 1995;95(6):1051-5. doi:10.1097/00006534-199505000-00015
89. Ogawa R, Akaishi S, Dohi T, Kuribayashi S, Miyashita T, Hyakusoku H. Analysis of the surgical treatments of 63 keloids on the cartilaginous part of the auricle: effectiveness of the core excision method. *Plast Reconstr Surg*. Mar 2015;135(3):868-875. doi:10.1097/prs.0000000000000962
90. Ogawa R, Huang C, Akaishi S, et al. Analysis of surgical treatments for earlobe keloids: analysis of 174 lesions in 145 patients. *Plast Reconstr Surg*. Nov 2013;132(5):818e-825e. doi:10.1097/PRS.0b013e3182a4c35e
91. Ogawa R, Mitsuhashi K, Hyakusoku H, Miyashita T. Postoperative electron-beam irradiation therapy for keloids and hypertrophic scars: retrospective study of 147 cases followed for more than 18 months. *Plast Reconstr Surg*. Feb 2003;111(2):547-53; discussion 554-5. doi:10.1097/01.Prs.0000040466.55214.35
92. Ogawa R, Miyashita T, Hyakusoku H, Akaishi S, Kuribayashi S, Tateno A. Postoperative radiation protocol for keloids and hypertrophic scars: statistical analysis of 370 sites followed for over 18 months. *Ann Plast Surg*. Dec 2007;59(6):688-91. doi:10.1097/SAP.0b013e3180423b32
93. Park TH. Aesthetic reconstruction of auricular keloids with a novel hemi-keystone flap. *Aesthetic Plast Surg*. Dec 2022;46(6):2807-2813. doi:10.1007/s00266-022-02909-4
94. Pontoriero A, Potami A, Iatì G, et al. Post-operative radiotherapy of keloids. A 10-years experience of kilovoltage irradiation. 2015;

95. Ragoowansi R, Cornes PG, Glees JP, Powell BW, Moss AL. Ear-lobe keloids: treatment by a protocol of surgical excision and immediate postoperative adjuvant radiotherapy. *Br J Plast Surg*. Sep 2001;54(6):504-8. doi:10.1054/bjps.2001.3656
96. Ragoowansi R, Cornes PG, Moss AL, Glees JP. Treatment of keloids by surgical excision and immediate postoperative single-fraction radiotherapy. *Plast Reconstr Surg*. May 2003;111(6):1853-9. doi:10.1097/01.Prs.0000056869.31142.De
97. Recalcati S, Caccialanza M, Piccinno R. Postoperative radiotherapy of auricular keloids: a 26-year experience. *J Dermatolog Treat*. Feb 2011;22(1):38-42. doi:10.3109/09546630903460278
98. Renz P, Hasan S, Gresswell S, Hajjar RT, Trombetta M, Fontanesi J. Dose effect in adjuvant radiation therapy for the treatment of resected keloids. *Int J Radiat Oncol Biol Phys*. Sep 1 2018;102(1):149-154. doi:10.1016/j.ijrobp.2018.05.027
99. Ribault L, Martin JP, Larroque G. [Keloid cicatrix of the face and neck. Apropos of 81 cases treated in Dakar]. *Ann Chir Plast Esthet*. Mar 1992;37(2):202-6. Les cicatrices chéloïdes cervico-faciales. A propos de 81 cas traités à Dakar.
100. Rishi KS, Sarkar N, Kesari P, et al. Single institution experience of postoperative electron beam radiation therapy in the treatment of keloids. *Adv Radiat Oncol*. Mar-Apr 2021;6(2):100596. doi:10.1016/j.adro.2020.10.009
101. Rong L, Wu X, Hou Y, Ma X, Ye M, Bai Y. [Long-term results of postoperative electronic irradiation for 53 patients with keloids]. *Zhonghua Zheng Xing Wai Ke Za Zhi*. Jul 2014;30(4):270-4.
102. Sakamoto T, Oya N, Shibuya K, Nagata Y, Hiraoka M. Dose-response relationship and dose optimization in radiotherapy of postoperative keloids. *Radiother Oncol*. May 2009;91(2):271-6. doi:10.1016/j.radonc.2008.12.018
103. Sällström KO, Larson O, Hedén P, Eriksson G, Glas JE, Ringborg U. Treatment of keloids with surgical excision and postoperative X-ray radiation. *Scand J Plast Reconstr Surg Hand Surg*. 1989;23(3):211-5. doi:10.3109/02844318909075120
104. Shen J, Lian X, Sun Y, et al. Hypofractionated electron-beam radiation therapy for keloids: retrospective study of 568 cases with 834 lesions. *J Radiat Res*. Sep 2015;56(5):811-7. doi:10.1093/jrr/rrv031
105. Ship AG, Weiss PR, Mincer FR, Wolkstein W. Sternal keloids: successful treatment employing surgery and adjunctive radiation. *Ann Plast Surg*. Dec 1993;31(6):481-7.
106. Son Y, Phillips EON, Price KM, et al. Treatment of keloids with a single dose of low-energy superficial X-ray radiation to prevent recurrence after surgical excision: An in vitro and in vivo study. *J Am Acad Dermatol*. Nov 2020;83(5):1304-1314. doi:10.1016/j.jaad.2020.06.023
107. Song C, Wu HG, Chang H, Kim IH, Ha SW. Adjuvant single-fraction radiotherapy is safe and effective for intractable keloids. *J Radiat Res*. Sep 2014;55(5):912-6. doi:10.1093/jrr/rru025
108. Song KX, Liu S, Zhang MZ, et al. Hyperbaric oxygen therapy improves the effect of keloid surgery and radiotherapy by reducing the recurrence rate. *J Zhejiang Univ Sci B*. Nov. 2018;19(11):853-862. doi:10.1631/jzus.B1800132
109. Song KX, Wang YB, Zhang MZ, Wang XJ. A parasternal intercostal perforator flap for esthetic reconstruction after complete chest keloid resection: A retrospective observational cohort study. *J Cosmet Dermatol*. Dec 2018;17(6):1205-1208. doi:10.1111/jocd.12782
110. Speranza G, Sultanem K, Muanza T. Descriptive study of patients receiving excision and radiotherapy for keloids. *Int J Radiat Oncol Biol Phys*. Aug 1 2008;71(5):1465-9. doi:10.1016/j.ijrobp.2007.12.015
111. Sruthi K, Chelakkot PG, Madhavan R, Nair RR, Dinesh M. Single-fraction radiation: A promising adjuvant therapy to prevent keloid recurrence. *J Cancer Res Ther*. Oct-Dec 2018;14(6):1251-1255. doi:10.4103/jcrt.JCRT_20_17

112. Stahl S, Barnea Y, Weiss J, et al. Treatment of earlobe keloids by extralesional excision combined with preoperative and postoperative "sandwich" radiotherapy. *Plast Reconstr Surg*. Jan 2010;125(1):135-141. doi:10.1097/PRS.0b013e3181c2a46e
113. Sun Q, Yu ET, Zhou Y, Tong S, Zhou KJ, Guo S. Individualized surgery combined with radiotherapy and triamcinolone acetonide injection for the treatment of auricular keloids. *BMC Surg*. May 22 2021;21(1):256. doi:10.1186/s12893-021-01253-9
114. Supe SS, Sharma AK, Deka A, Deka B. Can we use radiotherapy alone in the treatment of keloids? *Journal of the European Academy of Dermatology and Venereology*. 1995;5(2):150-152.
115. Supe SS, Supe SJ, Rao SM, Deka AC, Deka BC. Treatment of keloids by 90Sr-90Y beta-rays. Strahlenther Onkol. Jul 1991;167(7):397-402.
116. Ting W, Chong Y, Xu J, Huang J, Yu N, Liu Z. Treatment of keloids using plasma skin regeneration combined with radiation therapy under the evaluation of patient and observer scar assessment scale. *Clin Cosmet Investig Dermatol*. 2021;14:981-989. doi:10.2147/ccid.S321348
117. Tresoldi MM, Ivaldi GB, Porcu P, et al. Immediate postoperative treatment of keloids with intraoperative radiation therapy technology: A pilot study. *Plast Reconstr Surg Glob Open*. Sep 2021;9(9):e3738. doi:10.1097/gox.0000000000003738
118. van de Kar AL, Kreulen M, van Zuijlen PPM, Oldenburger F. The results of surgical excision and adjuvant irradiation for therapy-resistant keloids: a prospective clinical outcome study. *Plast Reconstr Surg*. Jun 2007;119(7):2248-2254. doi:10.1097/01.prs.0000260751.20217.28
119. Veen RE, Kal HB. Postoperative high-dose-rate brachytherapy in the prevention of keloids. Int J Radiat Oncol Biol Phys. Nov 15 2007;69(4):1205-8. doi:10.1016/j.ijrobp.2007.04.032
120. Viani GA, Stefano EJ, Afonso SL, De Fendi LI. Postoperative strontium-90 brachytherapy in the prevention of keloids: results and prognostic factors. Int J Radiat Oncol Biol Phys. Apr 1 2009;73(5):1510-6. doi:10.1016/j.ijrobp.2008.07.065
121. Wagner W, Schopohl B, Böttcher HD, Schnepper E. [Results of scar keloid prevention using contact irradiation with strontium 90]. *Rontgenpraxis*. Jul 1989;42(7):248-52. Ergebnisse der Narbenkeloidprophylaxe durch Kontaktbestrahlung mit Strontium 90.
122. Wagner W, Alfrink M, Micke O, Schäfer U, Schüller P, Willich N. Results of prophylactic irradiation in patients with resected keloids--a retrospective analysis. Acta Oncol. 2000;39(2):217-20. doi:10.1080/028418600430806
123. Wang J, Min P, Grassetti L, et al. Preliminary outcomes of Distal IMAP and SEAP Flaps for the treatment of unstable keloids subject to recurrent inflammation and infections in the lower sternal and upper abdominal areas. *J Reconstr Microsurg*. Nov 2015;31(9):621-30. doi:10.1055/s-0035-1556078
124. Wang LZ, Ding JP, Yang MY, Chen B. Forty-five cases of chest keloids treated with subcutaneous super-tension-reduction suture combined with postoperative electron-beam irradiation. *Dermatol Surg*. Dec 2014;40(12):1378-84. doi:10.1097/dss.0000000000000163
125. Wang QG, Li XM, Zhang M, et al. [Effect of two dose fractionations on postoperative radiotherapy of keloid: an analysis of 107 patients]. *Beijing Da Xue Xue Bao Yi Xue Ban*. Feb 18 2014;46(1):169-72.
126. Wang Y, Ma J, Zhang Z, Shen H. Combined surgical excision and electron external beam radiation improves the treatment of keloids: A descriptive study. *Dermatol Ther*. Jul 2020;33(4):e13494. doi:10.1111/dth.13494
127. Wen P, Wang T, Zhou Y, Yu Y, Wu C. A retrospective study of hypofractionated radiotherapy for keloids in 100 cases. *Sci Rep*. Feb 11 2021;11(1):3598. doi:10.1038/s41598-021-83255-4
128. Wong CM, Zhang J, Gui L, Zhou ZS. Individualized therapy for keloid in aural region. Chinese Journal of Clinical Rehabilitation.

129. Wu H, Dong G, Hu J, et al. Contour first-retrospective study of an algorithmic approach of auricular keloids. *J Cosmet Dermatol*. Apr 2023;22(4):1304-1311. doi:10.1111/jocd.15554
130. Yamawaki S, Naitoh M, Ishiko T, Muneuchi G, Suzuki S. Keloids can be forced into remission with surgical excision and radiation, followed by adjuvant therapy. *Ann Plast Surg*. Oct 2011;67(4):402-6. doi:10.1097/SAP.0b013e31820d684d
131. Yan D, Zhao B, Yang H, Zhu B, Wang J. A combination of nonoperative treatment modalities used for treatment of keloids. *Dermatol Ther*. Jan-Feb 2014;27(1):48-51. doi:10.1111/dth.12044
132. Yang X, Shao Y, Yu W, et al. A novel radiotherapy approach for keloids with intrabeam. *Biomed Res Int*. 2019;2019:4693528. doi:10.1155/2019/4693528
133. Yokokawa T, Shirai T, Kawasaki T, Furui S. Postoperative irradiation of earlobe. *Nippon Hoshasen Shuyo Gakkai-Shi*. 2006;18(3):141-145.
134. Zeng A, Song K, Zhang M, et al. The "Sandwich Therapy": A microsurgical integrated approach for presternal keloid treatment. *Ann Plast Surg*. Sep 2017;79(3):280-285. doi:10.1097/sap.0000000000000975
135. Zhang W, Liu Z, Zhu L, et al. Combining micro-plasma radio-frequency with hypofractionated electron-beam radiation as a novel treatment of keloids: A case series. *Medicine (Baltimore)*. Nov 2019;98(48):e18094. doi:10.1097/md.0000000000018094
136. Zhang YG, Cen Y, Liu XX, Yu R, Xu XW. Clinical improvement in the therapy of aural keloids. *Chin Med J (Engl)*. Dec 5 2009;122(23):2865-8.
137. Zhu Y, Zhang Q, Gong T, et al. Sports bras improve chest keloids but outcomes are dependent on breast size: A retrospective analysis. *Front Oncol*. 2022;12:871115. doi:10.3389/fonc.2022.871115
138. Zhuang By, Hu Fc, You Y, Zhang L. Observation of the clinical efficacy of isotope phosphorus-32 dressing combined with diprospan and mucopolysaccharide polysulphate cream in the treatment of keloids. *Journal of Cosmetic Dermatology*. 2022;21(12):7140-7146.

Osteoarthritis: 15 Exclusions

1. Álvarez B, Montero A, Alonso R, et al. Low-dose radiation therapy for hand osteoarthritis: shaking hands again? *Clin Transl Oncol*. Mar 2022;24(3):532-539. doi:10.1007/s12094-021-02710-w
2. Álvarez B, Montero Á, Aramburu F, et al. Radiotherapy for ostheoarticular degenerative disorders: When nothing else works. *Osteoarthr Cartil Open*. Jan-Feb 2020;1(3-4):100016. doi:10.1016/j.ocarto.2019.100016
3. Hautmann MG, Hipp M, Neumaier U, et al. Radiotherapy for osteoarthritis of the ankle and tarsal joints-analysis of 66 joints. *Strahlenther Onkol*. Jun 2020;196(6):569-575. doi:10.1007/s00066-019-01551-5
4. Hautmann MG, Rechner P, Neumaier U, et al. Radiotherapy for osteoarthritis-an analysis of 295 joints treated with a linear accelerator. *Strahlenther Onkol*. Aug 2020;196(8):715-724. doi:10.1007/s00066-019-01563-1
5. 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

6. Kaltenborn A, Bulling E, Nitsche M, Carl UM, Hermann RM. The field size matters: low dose external beam radiotherapy for thumb carpometacarpal osteoarthritis : Importance of field size. *Strahlenther Onkol*. Aug 2016;192(8):582-8. Relevanz der Feldgröße in der Reizbestrahlung bei Rhizarthrose : Relevanz der Feldgröße. doi:10.1007/s00066-016-0995-7
7. Koc BB, Schotanus MGM, Borghans R, et al. Short-term pain reduction after low-dose radiotherapy in patients with severe osteoarthritis of the hip or knee joint: a cohort study and literature review. *Eur J Orthop Surg Traumatol*. May 2019;29(4):843-847. doi:10.1007/s00590-019-02377-8
8. Marigi EM, Johnson QJ, Dancy ME, et al. Shoulder arthroplasty after prior external beam radiation therapy: a matched cohort analysis. *J Shoulder Elbow Surg*. Mar 2023;32(3):e85-e93. doi:10.1016/j.jse.2022.08.014
9. Razumov AN, Puriga AO, Yurova OV. [The long-term results of the application of the combined rehabilitative treatment in the patients presenting with knee osteoarthrosis]. *Vopr Kurortol Fizioter Lech Fiz Kult*. Nov-Dec 2015;92(6):42-44. doi:10.17116/kurort2015642-44
10. Rogers S, Eberle B, Vogt DR, et al. Prospective evaluation of changes in pain levels, quality of life and functionality after low dose radiotherapy for epicondylitis, plantar fasciitis, and finger osteoarthritis. *Front Med (Lausanne)*. 2020;7:195. doi:10.3389/fmed.2020.00195
11. Sell S, Jany R, Kremling E, Esenwein S, Gaissmaier C, Küsswetter W. [Prevention of heterotopic ossification following cementless hip replacement using 5 x 2 Gy fractionated irradiation. A prospective study]. *Z Orthop Ihre Grenzgeb*. Jul-Aug 1996;134(4):375-80. Prävention heterotoper Ossifikationen nach zementfreiem Hüftgelenksersatz durch fraktionierte Radiatio mit 5 x 2 Gy. Eine prospektive Studie. doi:10.1055/s-2008-1039778
12. Szentesi M, Nagy Z, Géher P, Papp I, Kampen WU. A prospective observational study on the long-term results of (90)Yttrium citrate radiosynoviorthesis of synovitis in osteoarthritis of the knee joint. *Eur J Nucl Med Mol Imaging*. Jul 2019;46(8):1633-1641. doi:10.1007/s00259-019-04350-3
13. Szentesi M, Nagy Z, Géher P, Papp I, Kampen WU. [Long-term (10 year) results of Yttrium-90 radiosynoviorthesis in inflammed knee osteoarthritis: A prospective observational study]. Orv Hetil. Oct 25 2020;161(43):1831-1839. Yttrium-90 radiosynoviorthesis hosszú távú (10 éves) eredményei inflammált térdarthrosisban: Prospektív obszervációs vizsgálat. doi:10.1556/650.2020.31728
14. Usman Z, Maharaj SS, Kaka B. Effects of combination therapy and infrared radiation on pain, physical function, and quality of life in subjects with knee osteoarthritis: A randomized controlled study. *Hong Kong Physiother J*. Dec 2019;39(2):133-142. doi:10.1142/s1013702519500124
15. Van den Ende CH, Minten MJ, Leseman-Hoogenboom MM, et al. Long-term efficacy of low-dose radiation therapy on symptoms in patients with knee and hand osteoarthritis: Follow-up results of two parallel randomised, sham-controlled trials. *The Lancet Rheumatology*. 2020;2(1):e42-e49.

Peyronies Disease: 4 Exclusions

1. Kammerer R. [Radiotherapy of induratio penis plastica]. *Z Urol Nephrol*. May 1988;81(5):323-8. Strahlentherapie der Induratio penis plastica (IPP).
2. Koren H, Alth G, Schenk GM, Jindra RH. Induratio penis plastica: effectivity of low-dose radiotherapy at different clinical stages. *Urol Res*. 1996;24(4):245-8. doi:10.1007/bf00295900

3. Rodrigues CI, Njo KH, Karim AB. Results of radiotherapy and vitamin E in the treatment of Peyronie's disease. Int J Radiat Oncol Biol Phys. Feb 1 1995;31(3):571-6. doi:10.1016/0360-3016(94)00378-x
4. Weisser GW, Schmidt B, Hübener KH, Ahlemann LM, Kordonias D. [Radiation treatment of plastic induration of the penis]. Strahlenther Onkol. Jan 1987;163(1):23-8. Die Strahlenbehandlung der Induratio penis plastica.

Plantar Fasciitis: 11 Exclusions

1. Abdelmaqsoud A, Vorotniak N, Strauß D, Hentschel B. The analgesic effect of low-dose radiotherapy in treating benign musculoskeletal painful disorders using different energies: A retrospective cohort study. *Journal of Radiotherapy in Practice*. 2023;22:e78.
2. Badakhshi H, Buadch V. Low dose radiotherapy for plantar fasciitis. Treatment outcome of 171 patients. *Foot (Edinb)*. Dec 2014;24(4):172-5. doi:10.1016/j.foot.2014.07.005
3. Hajtmanová E, Kinclová I, Kostková L, Hajtman A, Péc M. [Low-dose radiotherapy in the treatment of plantar fasciitis]. *Klin Onkol*. 2010;23(2):104-10. Nizkodávková rádioterapia v liecbe plantárnej fasciitídy.
4. Heyd R, Tselis N, Ackermann H, Röddiger SJ, Zamboglou N. Radiation therapy for painful heel spurs: results of a prospective randomized study. *Strahlenther Onkol*. Jan 2007;183(1):3-9. doi:10.1007/s00066-007-1589-1
5. Kędzierawski P, Stando R, Macek P. Retrospective evaluation of the effectiveness of radiotherapy in patients with plantar fascitis (heel spurs). *Rep Pract Oncol Radiother*. May-Jun 2017;22(3):209-211. doi:10.1016/j.rpor.2016.11.001
6. Micke O, Seegenschmiedt MH. [Radiotherapy for painfull heel spurs]. *MMW Fortschr Med*. Apr 17 2008;150(16):32-4. Bestrahlung gegen den schmerzhaften Fersensporn.
7. Niewald M, Holtmann H, Prokein B, et al. Randomized multicenter follow-up trial on the effect of radiotherapy on painful heel spur (plantar fasciitis) comparing two fractionation schedules with uniform total dose: first results after three months' follow-up. *Radiat Oncol*. Aug 19 2015;10:174. doi:10.1186/s13014-015-0471-z
8. Niewald M, Seegenschmiedt MH, Micke O, et al. Randomized, multicenter trial on the effect of radiation therapy on plantar fasciitis (painful heel spur) comparing a standard dose with a very low dose: mature results after 12 months' follow-up. *Int J Radiat Oncol Biol Phys*. Nov 15 2012;84(4):e455-62. doi:10.1016/j.ijrobp.2012.06.022
9. Rogers S, Eberle B, Vogt DR, et al. Prospective evaluation of changes in pain levels, quality of life and functionality after low dose radiotherapy for epicondylitis, plantar fasciitis, and finger osteoarthritis. *Front Med (Lausanne)*. 2020;7:195. doi:10.3389/fmed.2020.00195
10. Schäfer U, Micke O, Glashörster M, Rübe C, Prott FJ, Willich N. [The radiotherapy treatment of painful calcaneal spurs]. *Strahlenther Onkol*. Apr 1995;171(4):202-6. Strahlentherapeutische Behandlung des schmerzhaften Fersenbeinsporns.
11. Surenkok S, Dirican B, Beyzadeoglu M, Oysul K. Heel spur radiotherapy and radiation carcinogenesis risk estimation. *Radiat Med*. Oct 2006;24(8):573-6. doi:10.1007/s11604-006-0075-5

Pterygium: 31 Exclusions

1. Al-Salem KM, Saif AT, Saif PS. Comparing adjuvant beta radiation, mitomycin C, and conjunctival autograft in primary pterygium treatment, a three-year follow-up study. The Open Ophthalmology Journal. 2020;14(1)

2. Amano S, Motoyama Y, Oshika T, Eguchi S, Eguchi K. Comparative study of intraoperative mitomycin C and beta irradiation in pterygium surgery. Br J Ophthalmol. Jun 2000;84(6):618-21. doi:10.1136/bjo.84.6.618
3. Aswad MI, Baum J. Optimal time for postoperative irradiation of pterygia. Ophthalmology. Nov 1987;94(11):1450-1. doi:10.1016/s0161-6420(87)33267-1
4. Chayakul V. Postoperative mitomycin-C eye drop and beta radiation in the treatment of pterygia. J Med Assoc Thai. Sep 1991;74(9):373-6.
5. Dash RG, Boparai MS. Pterygium--evaluation of management (primary & recurrent). Indian J Ophthalmol. Jan-Feb 1986;34(1):7-10.
6. de Keizer RJ, Swart-van den Berg M, Baartse WJ. Results of pterygium excision with Sr 90 irradiation, lamellar keratoplasty and conjunctival flaps. Doc Ophthalmol. Sep-Oct 1987;67(1-2):33-44. doi:10.1007/bf00142695
7. Dusenbery KE, Alul IH, Holland EJ, Khan FM, Levitt SH. Beta irradiation of recurrent ptergia: results and complications. *Int J Radiat Oncol Biol Phys*. 1992;24(2):315-20. doi:10.1016/0360-3016(92)90687-d
8. Fukushima S, Inoue T, Inoue T, Ozeki S. Postoperative irradiation of pterygium with 90Sr eye applicator. Int J Radiat Oncol Biol Phys. Feb 1 1999;43(3):597-600. doi:10.1016/s0360-3016(98)00431-3
9. Gulani A, Dastur YK. Simultaneous pterygium and cataract surgery. *J Postgrad Med*. Jan-Mar 1995;41(1):8-11.
10. Karabatsas CH, Marsh GW, Cook AM, Cook SD. Different therapeutic approaches and outcome in the treatment of pterygium. *Eur J Ophthalmol*. Jul-Sep 1998;8(3):148-52. doi:10.1177/112067219800800305
11. Lanchy P, Reguigui A, Urbajtel M, Hart M. [Beta therapy (strontium 90) associated with the removal of pterygium in order to avoid its recurrence]. Bull Soc Ophtalmol Fr. Jan 1989;89(1):153-5. La bétathérapie (Strontium 90) associée à l'exérèse du pterygion dans le but d'éviter sa récidive.
12. Monteiro-Grillo I, Gaspar L, Monteiro-Grillo M, Pires F, Ribeiro da Silva JM. Postoperative irradiation of primary or recurrent pterygium: results and sequelae. *Int J Radiat Oncol Biol Phys*. Oct 1 2000;48(3):865-9. doi:10.1016/s0360-3016(00)00701-x
13. Nakamatsu K, Nishimura Y, Kanamori S, et al. Randomized clinical trial of postoperative strontium-90 radiation therapy for pterygia: treatment using 30 Gy/3 fractions vs. 40 Gy/4 fractions. Strahlenther Onkol. Jul 2011;187(7):401-5. doi:10.1007/s00066-011-2212-z
14. Nishimura Y, Nakai A, Yoshimasu T, et al. Long-term results of fractionated strontium-90 radiation therapy for pterygia. *Int J Radiat Oncol Biol Phys*. Jan 1 2000;46(1):137-41. doi:10.1016/s0360-3016(99)00419-8
15. Ozarda AT. Evaluation of postexcisional strontium 90 beta ray therapy for pterygium. *South Med J*. Nov 1977;70(11):1304. doi:10.1097/00007611-197711000-00017
16. Pajic B, Greiner RH. Long term results of non-surgical, exclusive strontium-/yttrium-90 beta-irradiation of pterygia. *Radiother Oncol*. Jan 2005;74(1):25-9. doi:10.1016/j.radonc.2004.08.022
17. Pajic B, Pallas A, Aebersold D, Gruber G, Greiner RH. Prospective study on exclusive, nonsurgical strontium-/yttrium-90 irradiation of pterygia. Strahlenther Onkol. Aug 2004;180(8):510-6. doi:10.1007/s00066-004-1230-5
18. Pajic B, Pugnale-Verillotte N, Greiner RH, Pajic D, Eggspühler A. [Results of strontium-yttrium-90 for pterygia]. J Fr Ophtalmol. May 2002;25(5):473-9. Résultat de la thérapie au strontium-yttrium-90 des ptérygions.

19. Pajonk F, Flick H, Mittelviefhaus H, Slanina J. Postoperative pterygium prevention by radiotherapy with strontium-90 beta-rays. Front Radiat Ther Oncol. 1997;30:259-64. doi:10.1159/000425712
20. Paryani SB, Scott WP, Wells JW, Jr., et al. Management of pterygium with surgery and radiation therapy. The North Florida Pterygium Study Group. *Int J Radiat Oncol Biol Phys*. Jan 1 1994;28(1):101-3. doi:10.1016/0360-3016(94)90146-5
21. Qin XJ, Chen HM, Guo L, Guo YY. Low-dose strontium-90 irradiation is effective in preventing the recurrence of pterygia: a ten-year study. *PLoS One*. 2012;7(8):e43500. doi:10.1371/journal.pone.0043500
22. Rigendinger F, Aebersold DM, Cvejic Z, Pajic B. Changes of corneal biomechanical properties upon exclusive Ytt-/Sr-90 irradiation of pterygium. *Sensors (Basel)*. Feb 2 2021;21(3)doi:10.3390/s21030975
23. Schultze J, Hinrichs M, Kimmig B. The role of strontium-90 surface application in the prevention of recurrent pterygium. *Strahlentherapie und Onkologie*. 1996;172(8):417-421.
24. Schultze J, Hinrichs M, Kimmig B. Results of adjuvant radiation therapy after surgical excision of pterygium. Ger J Ophthalmol. Jul 1996;5(4):207-10.
25. Tarr KH, Constable IJ. Late complications of pterygium treatment. *Br J Ophthalmol*. Jul 1980;64(7):496-505. doi:10.1136/bjo.64.7.496
26. Vastardis I, Pajic B, Greiner RH, Pajic-Eggspuehler B, Aebersold DM. Prospective study of exclusive strontium-/yttrium-90 beta-irradiation of primary and recurrent pterygia with no prior surgical excision. Clinical outcome of long-term follow-up. *Strahlenther Onkol*. Dec 2009;185(12):808-14. doi:10.1007/s00066-009-2000-1
27. Viani GA, Stefano EJ, De Fendi LI, Fonseca EC. Long-term results and prognostic factors of fractionated strontium-90 eye applicator for pterygium. *Int J Radiat Oncol Biol Phys*. Nov 15 2008;72(4):1174-9. doi:10.1016/j.ijrobp.2008.02.075
28. Viani GA, De Fendi LI, Fonseca EC, Stefano EJ. Low or high fractionation dose β-radiotherapy for pterygium? A randomized clinical trial. Int J Radiat Oncol Biol Phys. Feb 1 2012;82(2):e181-5. doi:10.1016/j.ijrobp.2010.11.017
29. Yamada T, Mochizuki H, Ue T, Kiuchi Y, Takahashi Y, Oinaka M. Comparative study of different β-radiation doses for preventing pterygium recurrence. *Int J Radiat Oncol Biol Phys*. Dec 1 2011;81(5):1394-8. doi:10.1016/j.ijrobp.2010.07.1983
30. Yamamoto M, Hada Y, Akagi Y. Postoperative radiotherapy of pterygium with Strontium-90 plaque. The Journal of JASTRO. 2000;12(2):125-130.
31. Zhu X, Yu L. Care of patients with pterygium during postoperative 90Sr beta-ray therapy. *Zhonghua hu li za zhi= Chinese Journal of Nursing*. 1996;31(11):649-650.

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.