

Appendix C: Evidence Table

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Radiotherapy for the Treatment of Peyronie's Disease

Ref #	Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
43	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	Retrospective	Important complaints were curvature of the penis during erection for 92% of the patients, painful erection for 68%, and problems with sexual intercourse for 37.5%. Average size of all indurated plaques was 2.5 cm. The average pretreatment duration of symptoms was 9.5 months. All 38 patients were irradiated with orthovoltage radiotherapy (200 and 250 kV photons) with a total dose of 9 Gy in 5 alternating days (regimen A). Because of minimal response, 16 patients were irradiated again with another 9 Gy in 5 days and finally received 18 Gy (regimen B).	To report the results of a retrospective analysis of 38 patients with Peyronie's disease treated with primary radiotherapy in the period of 1975-1993.	With regimen A, a satisfying improvement was achieved for the majority of the patients: 65% experienced less penile pain during erection, 40% reported less curvature of the penis, and 47% experienced an improvement of their sex life. With the higher dose of regimen B there was an additional improvement for a minority of the patients: 25% reported less pain during erection, 21% had less curvature, and 29% experienced an improved sex life. With regimen A, pain improvement was statistically significantly superior when compared to regimen B. For all other improvements (curvature, sexual intercourse, and induration) no dose-response relation could be demonstrated between regimen A and the higher dose regimen B. No patient experienced any radiation-induced morbidity. After evaluating regimen A and regimen B, the overall result was that 76% experienced less pain, 60% reported an improved sex life, and 48% had a diminished curvature during erection.	3
44	Incrocchi L, Wijnmaalen A, Slob AK, Hop WC, Levendag PC. Low-dose radiotherapy in 179 patients with Peyronie's disease: treatment outcome and current sexual functioning. Int J Radiat Oncol Biol Phys. Jul 15 2000;47(5):1353-6. doi:10.1016/s0360-3016(00)00505-8	Retrospective	The records of 179 patients, median age 52 years, that received radiotherapy (RT) between 1982 and 1997 were reviewed. 78% presented with painful erections and 89% with penile deformity. The symptoms were present for a median duration of 6 months (range, 1-72 months). The RT schedule consisted of 13.5 Gy (9 x 1.5 Gy, 3 fractions per week) using orthovoltage X-rays in 123 patients or 12 Gy (6 x 2 Gy, daily fractions) using electrons in 56 patients. A questionnaire regarding current sexual functioning was mailed to 130	To analyze retrospectively treatment outcomes in patients irradiated for Peyronie's disease.	At mean follow-up period of 3 months, 83% reported that pain was diminished or had disappeared after RT. Twenty-three% of patients reported a decrease in penile deformity. Following RT, surgical correction of penile curvature was performed in 29% of patients. No RT-related complications occurred except transient dysuria in 1 patient. Questionnaire data: 72% of patients were currently sexually active, 48% had erectile dysfunction, and 49% expressed dissatisfaction with their current sexual functioning.	3

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			patients whose addresses could be traced; 106 (82%) responded.			
45	Carson CC, 3rd, Coughlin PW. Radiation therapy for Peyronie's disease: is there a place? J Urol. Oct 1985;134(4):684-6. doi:10.1016/s0022-5347(17)47382-4	Retrospective	40 patients who underwent external beam radiation therapy for the treatment of chronic Peyronie's disease were evaluated.	To retrospectively report the treatment outcomes in patients irradiated for Peyronie's disease.	While patients with penile plaque, penile curvature and impotence were treated little improvement was noted. Patients with penile pain or pain on erection responded well to radiation with rapid resolution of the pain. The authors concluded that external beam radiation therapy has only limited application in patients with Peyronie's disease.	3
46	Mulhall JP, Branch J, Lubrano T, Shankey TV. Radiation increases fibrogenic cytokine expression by Peyronie's disease fibroblasts. J Urol. Jul 2003;170(1):281-4. doi:10.1097/01.ju.0000070860.78370.08	Preclinical	Using a well-established cell culture model cells derived from Peyronie's disease plaque tissue and neonatal foreskins were irradiated with 5 Gy (treatment group) or left nonirradiated (control group). At 24 hours cells were harvested and the supernatant was analyzed using enzyme-linked immunosorbent assay to determine the levels of the 2 fibrogenic cytokines basic fibroblast growth factor and platelet-derived growth factor-AB.	To evaluate the effect of radiation on fibrogenic cytokine production in cells cultured from Peyronie's disease plaque tissue.	Four Peyronie's disease plaque derived cultures and 2 neonatal foreskin derived cultures were analyzed. All plaque derived fibroblasts demonstrated significant elevations in basic fibroblast growth factor and platelet-derived growth factor-AB compared with foreskin derived fibroblasts. These data suggest that radiation may in fact increase the production of fibrogenic cytokines, which may promote the fibrotic process involved in Peyronie's disease. Further study is aimed at defining the effect of irradiation on plaque tissue.	4
47	Pietsch G, Anzeneder T, Bruckbauer H, et al. Superficial radiation therapy in peyronie's disease: An effective and well-tolerated therapy. Adv Radiat Oncol. Oct-Dec 2018;3(4):548-551. doi:10.1016/j.adro.2018.07.009	Retrospective	A retrospective analysis of 83 patients who underwent radiation therapy between 1999 and 2008 with 8 fractions of 4 Gy over a period of 6 months. With a mean follow-up time of 52 months, patients responded to a comprehensive questionnaire that covered patient characteristics, disease duration before radiation therapy, course of disease, treatment response, side effects, and patient satisfaction	To assess the safety, efficacy, and patient satisfaction of superficial radiation therapy in the treatment of Peyronie's disease (PD) in a retrospective analysis.	After a mean follow-up time of 52 months, 78% of the treated patients reported that PD progression had stopped. Furthermore 47% of patients had a symptom regression. Only 7% of patients reported PD progression. The penile curvature was improved in 49% of patients, and plaque induration could be reduced in 42% of patients. Moreover, 71% of patients reported substantial pain relief, as measured by a visual analogue scale (1 = not satisfied; 10 = very satisfied). Treatment satisfaction was rated with a median of 8 in a visual analogue scale out of 10. Side effects included transient erythema in 38.6% of patients and 9.6% reported of transient or chronic dryness. No severe side effects were observed.	3
60	Feder BH. Peyronie's disease. J Am Geriatr Soc. Nov 1971;19(11):947-55. doi:10.1111/j.1532-5415.1971.tb02210.x	Retrospective	Fifty-six patients were given small-dose irradiation for PD. Forty-six determinate cases were	To retrospectively report the treatment outcome in patients	Deformity persisted in only 4 of 10 (40%) who were treated before pain had developed. Of the 36 who were treated after the development of	3

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			available for definitive evaluation.	irradiated for Peyronie's disease.	pain, the deformity persisted in 24 (67%). The pain failed to respond in only 7 of the 36 (19%). Objective evaluation is difficult.	
61	Bystrom J, Johansson B, Edsmyr F, Korlof B, Nylén B. Induratio penis plastica (Peyronie's disease). The results of the various forms of treatment. Scand J Urol Nephrol. 1972;6(1):1-5. doi:10.3109/00365597209132070	Retrospective	A selected number of patients, treated for Peyronie's disease at the Karolinska sjukhus since the middle of 1950 have been reinvestigated according to their subjective and objective symptoms. The present series comprises of 58 patients (Fig. 1). The age distribution at the onset of symptoms shows that the disease is seen most commonly between the ages of 40 and 65 but quite a number of cases are discovered in younger age groups. The period of observation varies between 1 and 16 years with a mean time of 5½ years.	To report the treatment outcomes in patients irradiated for Peyronie's disease.	Of 46 patients given the various treatments 1-5 listed above, 40 patients at follow-up suffered from a penile curvature and this occurred in 36 patients before treatment (Table V). Painful erection had disappeared in all but 5 patients. Pain is the symptom that first disappears with any given, and even without treatment. In the 5 patients still complaining of pain this had usually appeared during the later course of the disease. Penile plaques were noted in 27 patients at follow-up, compared with 45 patients before treatment. Disturbances of coitus in the form of inability or difficulty in performance of the sexual act were noted in 27 patients, compared with 14 patients before treatment. The number of patients with erectio humilis in the form of inadequate rigidity of the distal portion of the penis was unchanged. The last two mentioned conditions were those most distressing to the patient. The late results in general were poor, resembling the spontaneous course of the disease.	3
62	Helvie WW, Ochsner SF. Radiation therapy in Peyronie's disease. South Med J. Oct 1972;65(10):1192-6. doi:10.1097/00007611-197210000-00007	Retrospective	76 patients treated with RT for PD at the Ochsner Medical Center from January 1965 to July 1971 received questionnaires and were asked to evaluate changes in specific symptoms (pain, penile angulation and plaque size) and overall condition after therapy. Of 49 responses, 9 patients received vitamin E and/or p-aminobenzoate therapy in addition to RT. 40 cases were therefore evaluated. Age 33-71 with 74% in their 4 th to 6 th decade at onset of symptoms. Average age of onset of symptoms was 53. Patients received orthovoltage treatment 300 rads every other day for 3 fractions (900 rads). If clinically warranted,	To report the treatment outcomes in patients irradiated for Peyronie's disease.	72% reported improvement in condition, 9% reported no changes, 5% reported progression. Pain relief was reported in 72%. 25% reported decreased plaque size, and 29% reported decreased penile angulation.	3

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			additional doses were administered after 4- to 6-week break intervals to a maximum dose of 2400 rads.			
63	Martin CL. Long time study of patients with peyronie's disease treated with irradiation. Am J Roentgenol Radium Ther Nucl Med. Mar 1972;114(3):492-7. doi:10.2214/ajr.114.3.492	Retrospective	Retrospective review of 142 patients treated with RT for Peyroneis disease from 1931 to 1968. 33% of cases were reported to have received adequate treatment. Most patients were age 50 to 65 years, but included younger patients.	To report the treatment outcomes in patients irradiated for Peyronie's disease.	"Cure" was reported in 64%. A study of the 51 cases not cured indicated that pain with erection was improved in 84.3% , induration in the corpora cavernosa reduced in 76.4% and curvature of the shaft improved in 62.7%.	3
64	Furlow WL, Swenson HE, Jr., Lee RE. Peyronie's disease: a study of its natural history and treatment with orthovoltage radiotherapy. J Urol. Jul 1975;114(1):69-71. doi:10.1016/s0022-5347(17)66945-3	Retrospective	of 177 patients with PD, of which 90 completed a questionnaire and were thus included for analysis. Patients were managed by no-treatment (group 1), orthovoltage RT with a single dose of 250-600 roentgens (group 2), or orthovoltage RT with 2 to 3 doses of the same (group 3).	To report the treatment outcomes in patients irradiated for Peyronie's disease.	With an average follow up of at least 7 years, on 90 of 177 patients with Peyronie's disease seen from January 1, 1950 to April 1, 1970 revealed that the ultimate outcome of the disease when not treated was no different from that following orthovoltage radiotherapy. The real benefit derived from orthovoltage radiotherapy appears to be that it hastens symptomatic improvement by 3 to 7 months. In 21% of the patients there was an associated inflammatory joint or tendon disease, an association not previously reported. Followup data on 90 of 177 patients with Peyronie's disease seen from Janurary 1, 1950 to April 1, 1970 revealed that the ultimate outcome of the disease when not treated was no different from that following orthovoltage radiotherapy. The real benefit derived from orthovoltage radiotherapy appears to be that it hastens symptomatic improvement by 3 to 7 months. In 21% of the patients there was an associated inflammatory joint or tendon disease, an association not previously reported.	3
65	Mira JG, Chahbazian CM, del Regato JA. The value of radiotherapy for Peyronie's disease: presentation of 56 new case studies and review of the literature. Int J Radiat Oncol Biol Phys. Feb 1980;6(2):161-6. doi:10.1016/0360-3016(80)90032-2	Retrospective	Fifty-six patients with Peyronie's Disease who were treated with radiotherapy at Penrose Cancer Hospital were studied retrospectively. All were treated with orthovoltage, mainly with total dosages of 1000 to 1400 roentgens (from around 950 to 1330 rod), in 11 to 17 days. Penile induration was present in	To report the treatment outcomes in patients irradiated for Peyronie's disease.	After treatments, more than half the patients had complete resolution of pain. The overall response rate was 79%. The mean interval treatment-response was 2.8 months; 41% had already improved at the end of therapy or within one month afterwards. Improvement of induration and penile deviation was less successful; there were almost no complete responders and about 40 % had partial responses. Interval treatment-response was also longer (from 6 to 9 months).	3

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			all patients; 87 % had curvature of the penis during erection and 70 % had pain during intercourse.		The size and location of the indurated plaque did not influence response. The dosage, however, might influence the results; patients whose induration responded received a dose with a mean higher than non-responders. This difference was statistically significant. The duration of symptoms prior to treatment seems to be important. Eighty-one% of responders had symptoms for less than five months; 76% of those with longer symptomatology did not benefit from irradiation. Failure by other methods of treatment did not preclude a response.	
66	Alth G, Koren H, Gasser G, Eidler R. On the therapy of induratio penis plastica (Peyronies disease) by means of radium moulages. Strahlentherapie. Jan 1985;161(1):30-4.	Retrospective	In the past 50 years 2210 patients suffering from induratio penis plastica were treated with radium moulages with total dose 6.6 Gy to the core of the penis and 8.03 Gy to the surface.	To report the treatment outcomes in patients irradiated for Peyronie's disease.	In 69% of the cases an improvement could be observed within 18 months after radium moulage therapy. 50.3% "remained under control". 24.7% reported "full recovery".	3
67	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.	Retrospective	From 1966 to 1988, 98 of 108 patients with symptomatic Peyronie's disease received radiotherapy for PD using orthovoltage with doses varying from 15 Gy to 25 Gy, with an average dose of 23.63 Gy. None patients received follow up radiation to maximum dose of 45 Gy. Average follow up was 111.5 months and was performed by questionnaire	To report the treatment outcomes in patients irradiated for Peyronie's disease.	In 11 of 61 patients (18%) who attended the clinic regularly for follow-up for longer than a year, new lesions distinct from the original lesions developed. This confirms that there is progression of the disease in a substantial number of cases after treatment. Long-term follow-up over an average of 111.5 months was achieved by means of a questionnaire in 47 of the 98 cases (48%). Forty-one of these patients (87.2%) had sexual intercourse after radiation. Twenty-eight of the 41 (68.3%) still have intercourse. Their average age at present is 59.6 years while the average age of the 13 patients (31.7%) not having intercourse is 70.9 years. The decline in sexual activity is thus age-related. Twenty-one of 25 patients (84%) experienced relief from pain, and angulation of the penis improved in 17 of 44 patients (38.6%) after radiotherapy.	3
68	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	Retrospective	265 men aged 24.5-79.4 years (median = 57.7 years) were included. No previous therapy had been carried out in 214 patients, and 41 patients had been pretreated (systemic: potassium p-aminobenzoate,	To describe the treatment of Peyronie's disease by means of low-dose radiotherapy	In 66.4% of the monitored patient group (n = 155) therapy was successful. We obtained complete regression of the fibromatous foci in 9% (n = 14), partial remission > 50% in 29.7% (n = 46) and partial remission < 50% in 27.7% (n = 43) of the patients. We found a significant correlation between hardness, size of the treated foci and	3

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			vitamins a, b, e; topical: corticosteroids, teleradiotherapy). The disease was classified using criteria proposed by Alth in 1984 location, number and size of foci, hardness of fibromatous foci and axis deviation, potentia coeundi and pain were evaluated). Radiotherapy was performed by local application of a special iridium-192 moulage		therapeutic success. Eighty-three patients suffered from pain during penile erection before therapy, and in 61.4% (n = 51) of these patients the pain disappeared after treatment. Moreover, the patients confirmed that both loss of pain and regression of deviation related to foci regressions were correlated with improvement in erectile function. No serious side effects were observed in any patients.	
69	Niewald M, Wenzlawowicz KV, Fleckenstein J, Wisser L, Derouet H, Rube C. Results of radiotherapy for Peyronie's disease. Int J Radiat Oncol Biol Phys. Jan 1 2006;64(1):258-62. doi:10.1016/j.ijrobp.2005.06.009	Retrospective	In the time interval 1983-2000, 154 patients in our clinic were irradiated for Peyronie's disease. Of those, 101 had at least one complete follow-up data set and are the subject of this study. In the majority of patients, penis deviation was between 30 and 50{sup o}, there were one or two indurated foci with a diameter between 5 and 15 mm. Pain was recorded in 48/92 patients. Seventy-two of the 101 patients received radiotherapy with a total dose of 30 Gy, and 25 received 36 Gy in daily fractions of 2.0 Gy. The remaining patients received the following dosage: 34 Gy (1 patient), 38-40 Gy (3 patients). Mean duration of follow-up was 5 years.	To retrospectively review the results of radiotherapy for Peyronie's disease.	The best results ever at any time during follow-up were an improvement of deviation in 47%, reduction of number of foci in 32%, reduction of size of foci in 49%, and less induration in 52%. Approximately 50% reported pain relief after radiotherapy. There were 28 patients with mild acute dermatitis and only 4 patients with mild urethritis. There were no long-term side effects.	3
70	Incrocci L, Hop WC, Slob AK. Current sexual functioning in 106 patients with Peyronie's disease treated with radiotherapy 9 years earlier. Urology. Dec 20 2000;56(6):1030-4. doi:10.1016/s0090-4295(00)00805-0	Retrospective	During 1982 to 1997, 179 patients with Peyronie's disease were treated at our radiation oncology department. One hundred thirty patients whose address could be traced were sent a questionnaire about their symptoms before RT, treatment outcome, and current sexual functioning (the past 4 weeks).	To analyze retrospectively the sexual functioning and treatment outcome in patients after radiotherapy (RT) for Peyronie's disease.	Before RT, 44% reported painful erections, 97% penile curvature, and 18% erectile dysfunction. Sixty-nine percent reported that after RT, penile pain was diminished and 29% that penile curvature was decreased; 13% reported improved erections. With respect to their current sex life, 51% reported sometimes or always having problems getting an erection and 61% in maintaining an erection; 36% never experienced spontaneous erections. Fifty-four percent reported not having erections rigid enough for	3

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			One hundred six patients, mean age 59 years, responded.		sexual activity. Since RT (mean 9 years), there had been a moderate or severe decrease in sexual interest (17%), sexual activity (41%), and sexual pleasure (32%). Overall, 49% of patients were dissatisfied with their current sexual functioning.	
71	Seegenschmiedt MH, Micke O, Muecke R, German Cooperative Group on Radiotherapy for Non-malignant D. Radiotherapy for non-malignant disorders: state of the art and update of the evidence-based practice guidelines. Br J Radiol. Jul 2015;88(1051):20150080. doi:10.1259/bjr.20150080	Review	Review of the literature for non-malignant disorders according to national consensus guidelines	To summarize most of the generally accepted indications for the application of RT for non-malignant diseases and presents the special treatment concepts.	These guidelines may serve as a platform for daily clinical work; they provide a new starting point for quality assessment, future clinical research, including the design of prospective clinical trials, and outcome research in the underrepresented and less appreciated field of RT for non-malignant disorders.	4
72	Incrocci L, Hop WC, Seegenschmiedt HM. Radiotherapy for Peyronie's Disease: a European survey. Acta Oncol. 2008;47(6):1110-2. doi:10.1080/02841860801910379	Retrospective	A questionnaire was sent out to 908 European radiotherapy institutions. 402 questionnaires were sent back and filled out correctly (44.5%). The questionnaire consisted of different items, regarding number of patients referred, fraction dose, total dose and technique used, and eventually treatment outcome of clinical trials.	To understand which treatment policy is followed in Europe before setting up a randomized trial.	Seventy-three institutions irradiate PD (19%), 304 do not (81%). Reasons for not treating were insufficient referrals from urologists or no interest in treating benign diseases. The most common fraction dose is 2 (range 0.5-8) Gy and the total radiation dose 20 (range 3-30) Gy. Most of the institutions use electrons (n = 44) or orthovoltage (n = 32). Decreased pain is reported in about 80% of the cases, and side effects by eight institutions.	3
81	Hall SJ, Basile G, Bertero EB, de las Morenas A, Goldstein I. Extensive corporeal fibrosis after penile irradiation. J Urol. Feb 1995;153(2):372-7. doi:10.1097/00005392-199502000-00023	Retrospective	A potent man with early signs and symptoms of Peyronie's disease 3 months in duration received 1,200 rad of external beam radiation to the penis and presented 5 months later with impotence. Physical examination revealed diffusely woody indurated corporeal tissue. Nocturnal penile tumescence testing was abnormal and pharmaco-cavernosometry demonstrated diffuse corporeal veno-occlusive dysfunction. Treatment by penile injections was unsuccessful. During penile prosthesis implantation bilateral rubbery erectile tissue was encountered, requiring extensive	To report late complications in a patient who received RT for PD with histomorphologic correlation	Computer assisted color histomorphometry revealed that the mean percentage of trabecular smooth muscle area to total erectile tissue area was 26.5 +/- 15.8 (normal 40 to 52%). Immunohistochemical staining with desmin confirmed extensive fibrosis. The most likely explanation for severe corporeal fibrosis is penile irradiation. The hypothesized mechanism of radiation associated fibrosis is ionizing injury to the endothelial cells of the lacunar spaces and cavernous/helicine arteries, which induced irreversible corporeal extracellular matrix structural changes. Penile irradiation, like vascular disease and priapism, is a potential cause of diffuse corporeal fibrosis.	3

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			bilateral corporotomy and sharp corporeal tissue excision for prosthesis insertion. Histological analysis of excised corporeal tissue demonstrated extensive corporeal fibrosis and arterial vasculopathy.			
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Article Key:

Of the 84 references cited in the American Radium Society® Appropriate Use Criteria for Radiotherapy for the Treatment of Peyronie’s Disease (Induratio Penis Plastica), 19 were identified through the search strategy. An additional 65 studies are included to provide context but were not used by the committee to guide recommendations. Of the 19 references used as evidence, 18 are categorized as therapeutic references including 17 studies with design limitations (retrospective reviews), and 2 supplemental studies (not useful as primary evidence).

ARS Appropriateness Criteria Evidence Table Key:**Study Quality Category Definitions**

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

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

Category 3 There are important study design limitations.

Category 4 The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:

- a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
- b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
- c) the study is an expert opinion or consensus document.

Category M The study is a meta-analysis and has not been rated for quality because the method is designed to evaluate individual studies only.