

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

Expert Panel for Radiotherapy for the Treatment of Peyronie's Disease (Induratio Penis Plastica):

Diane C. Ling, MD¹; Sevan Helo, MD²; Suzanne Russo MD³; Leo Doumanian, MD⁴; Andrea M. Harrow, MLIS⁵; Samuel Jean-Baptiste, MD, MS⁶; Austin N. Kirschner, MD, PhD⁷; Bobby Koneru, MD⁸; Christien Kluwe, MD⁹; Neil Newman, MD, MS¹⁰; Kevin Pearlstein, MD¹¹; Yasamin Sharifzadeh, MD¹²; Rahul Tendulkar, MD¹³; Austin Dove, MD¹⁴

¹Principal Author, Department of Radiation Oncology, Keck School of Medicine, University of Southern California, Los Angeles, CA

²Department of Urology – Men's Health, Mayo Clinic, Rochester, MN

³Department of Radiation Oncology, MetroHealth, Case Western Reserve University School of Medicine, Cleveland OH

⁴Division of Urology, Keck School of Medicine, University of Southern California, Los Angeles, CA

⁵USC Libraries, Keck School of Medicine, University of Southern California, Los Angeles, CA

⁶Department of Radiation Oncology, University of Florida, Jacksonville FL

⁷Department of Radiation Oncology, Vanderbilt University Medical Center, Nashville TN

⁸Department of Radiation Oncology, Cardinal Bernadin Cancer Center, Loyola University Stritch School of Medicine, Maywood, IL

⁹Department of Radiation Oncology, University of Texas Health Science Center at San Antonio, San Antonio, TX

¹⁰Department of Radiation Oncology, University of Miami, Miami, FL

¹¹Department of Radiation Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC

¹²Department of Radiation Oncology, Mayo Clinic, Rochester, MN

¹³Department of Radiation Oncology, Cleveland Clinic Foundation, Cleveland, OH

¹⁴Department of Radiation Oncology, Tennessee Oncology, Chattanooga, TN

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INTRODUCTION

Peyronie's Disease (PD), or Induratio Penis Plastica, is a condition characterized by the development of benign fibrous plaques within the tunica albuginea of the penis. PD affects an estimated 1-13% of men in the United States depending on the population studied and diagnostic criteria used, with the most common age at presentation in the mid-50s, although it can occur at any age.¹⁻³ Risk factors include penile trauma during sexual or nonsexual activities, family history of PD, diabetes mellitus, hypertension, and hyperlipidemia.^{4,5} Dupuytren's contracture and other fibrotic conditions share pathophysiologic features with PD and are frequently comorbid, while broader associations with autoimmune diseases have been suggested in some studies but not confirmed in large-scale analyses.^{6,7}

Symptoms can develop either suddenly or gradually and may include:

- Palpable plaque or induration of the penile shaft
- Penile curvature during erections, often resulting in difficulty with sexual intercourse
- Firm indentation or narrowing of the penis, sometimes resulting in an "hourglass" deformity
- Shortening of the penis
- Erectile dysfunction, which commonly coexists with PD and may predate or follow the onset of other symptoms

Pathophysiology

PD is associated with recurrent microvascular injury during sexual activity or physical injury, triggering an inflammatory cascade involving fibrin deposition, macrophage recruitment, cytokine overexpression, and aberrant wound healing of the tunica albuginea, resulting in fibrous plaque formation, most commonly located dorsally.⁸⁻¹¹ PD typically develops in two phases¹²:

1. Acute/Inflammatory Phase (typically lasting up to 6-18 months): Microvascular trauma to the tunica albuginea initiates extravascular protein deposition, fibrin accumulation, and recruitment of inflammatory cells, triggering aberrant wound healing and remodeling of the extracellular matrix. These processes alter the composition and organization of tunical collagen, reducing tissue elasticity. Persistent inflammation and fibrosis ultimately lead to plaque formation, resulting in penile deformity, curvature that may progress over time, and penile pain.
2. Chronic/Fibrotic Phase (typically beginning after 12-18 months): The penile curvature stabilizes and pain usually resolves. Erectile dysfunction may develop or worsen.

Patient Evaluation

PD is primarily a clinical diagnosis established by a urologist based on a focused history and physical examination. Evaluation includes assessment of symptom duration, penile pain, erectile function, and the degree of bother, along with palpation of the penile plaque. Penile deformity should be assessed in the erect state, with measurement of the direction and degree of curvature to guide treatment planning.¹³ Routine imaging is not required for diagnosis, although penile ultrasound may be useful in selected patients to further characterize plaque features or evaluate associated erectile dysfunction.¹⁴

Treatment Options

Treatment is not indicated for all patients with PD. Observation is appropriate for patients with minimal deformity, preserved sexual function, and little or no bother. Spontaneous resolution of curvature is uncommon, reported in approximately 3–12% of untreated patients, while the majority experience stable or worsening deformity.^{15,16} For those patients with bothersome curvature, penile deformity that interferes with sexual function, persistent symptoms, or significant psychosocial distress, treatment is directed at improving penile deformity, restoring sexual function, and enhancing quality of life. Treatment options include observation, oral therapies, intralesional injections, penile traction devices, extracorporeal shock wave therapy (ESWT), radiotherapy, and surgery.

Nonsurgical treatments are typically used when PD is in the acute phase.¹⁷

- **Oral medicines** including Vitamin E¹², colchicine^{18,19}, potassium para-aminobenzoate, and pentoxifylline²⁰ have been investigated in the treatment of PD, but no oral agent has demonstrated strong, consistent efficacy in placebo-controlled trials.¹⁷ Nonsteroidal anti-inflammatory drugs (NSAIDs) are often recommended for pain management.
- **Intralesional injections** deliver therapeutic agents directly into the PD plaque within the tunica albuginea, enabling targeted drug action at the site of fibrosis. Theoretical advantages over oral medications include targeted delivery of agents whose mechanisms of action require direct interaction with the plaque extracellular matrix, bypassing the limitations of systemic bioavailability and poor penetration of the relatively avascular tunica albuginea. Side effects vary by agent and may include penile hematoma, penile swelling, penile pain, corporal rupture, flu-like symptoms, dizziness, and nausea.
 - **Intralesional collagenase of *Clostridium histolyticum* (CCH)** injections (Xiaflex) are currently the only FDA-approved treatment for PD in patients with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy. In vitro studies suggest that CCH disrupts type I and III collagen, which are the most abundant types found in PD plaques. Additional proposed mechanisms include induction of fibroblast apoptosis and decreased expression of TGF- β and fibronectin, based on preclinical data. The primary demonstrated clinical benefit of CCH is reduction of penile curvature.^{17,21-25}
 - **Intralesional interferon** has been investigated as a treatment for PD. *In vitro*, interferons alter the metabolic activity of myofibroblasts, decrease fibroblast and collagen proliferation, and increase collagenase production — mechanisms that may counteract the fibrotic process underlying PD plaque formation.²⁶ Two early randomized controlled trials (RCT) produced conflicting results: a placebo-controlled RCT demonstrated statistically significant improvements in curvature reduction, plaque size, and pain resolution in patients with stable PD, while a second RCT in patients with early-stage disease (<6 months) showed no significant improvement in any parameter.^{27,28} Larger retrospective series have confirmed curvature improvement, but have not consistently demonstrated an improvement in penile hemodynamics.^{29,30}
 - **Intralesional verapamil** is a calcium channel blocker that inhibits the synthesis and secretion of extracellular matrix molecules including collagen, glycosaminoglycans, and fibronectin, while also increasing collagenase activity and modifying transforming growth factor-beta (TGF- β) activity. These properties may slow, prevent, or reverse plaque formation by stimulating the remodeling and degradation of extracellular matrix. The clinical evidence for intralesional verapamil remains weak and conflicting. The literature is challenging to interpret given varied patient inclusion criteria (including focus on patients in the active disease stage with dynamic and evolving symptoms), varied treatment protocols, and conflicting findings.^{31,32} Further studies are warranted to determine which patients may benefit from intralesional verapamil. Potential adverse events specific to intralesional verapamil include dizziness and nausea.
- Penile traction therapy (PTT) has been studied in both the acute and stable/chronic phases of PD. The proposed mechanism involves mechanotransduction — continuous traction increases the activity of degradative enzymes, decreases smooth muscle actin, and increases matrix metalloproteinase activity within treated tissue, ultimately leading to collagen degradation and scar remodeling with re-orientation of collagen fibrils in the direction of applied force.³³ Evidence supports a reduction in penile curvature, improved penile length, and lower risk of surgical intervention.^{34,35}
- ESWT has been investigated as a treatment for PD but has not demonstrated efficacy for reducing penile curvature or plaque size in randomized controlled trials.³⁶ The one area where ESWT has shown potential benefit is pain reduction.³⁷ However, penile pain commonly resolves over time regardless of treatment, limiting the overall clinical utility of ESWT in PD management.^{38,39}

Surgical Treatment represents the most rapid and reliable approach to correct penile curvature in PD. Surgery is not recommended until the disease has entered the stable (chronic) phase, typically defined as stable curvature for at least 3 to 6 months, with most surgical studies requiring PD symptoms for at least 12 months. Indications for surgery include penile deformity that prevents satisfactory sexual intercourse despite conservative therapies and/or concurrent erectile dysfunction unresponsive to medical management.¹³

The choice of surgical technique is guided by the degree and complexity of curvature, the presence or absence of erectile dysfunction, and patient goals. While surgical outcomes are generally favorable, potential risks include penile shortening, changes in penile sensation, and erectile dysfunction in a minority of patients, with risk profiles varying by procedure type.

- **Penile or tunical plication** shortens the convex side of the tunica albuginea to straighten the penis and is the most common procedure, with curvature correction rates of $\geq 90\%$ in most studies. Penile shortening is the most commonly reported side effect of plication, with perceived shortening reported in up to 78% of patients, though objective length loss is typically modest (mean ~ 0.4 cm). Penile sensory changes occur in approximately 9% of patients but typically resolve within one year. De novo erectile dysfunction rates vary by technique but are generally low.¹³
- **Plaque incision or partial excision with grafting** addresses the concave (plaque) side and is typically offered for more severe or complex curvatures ($>60^\circ$), with curvature correction rates generally $>80\%$. This technique lengthens the concave (plaque) side of the tunica albuginea and is typically offered for patients with curvatures $>60^\circ$ and/or complex deformities (hourglass or hinge effect), where plication would result in unacceptable penile shortening. Curvature correction rates generally exceed 80% across studies. Unlike plication, this approach may result in a small gain in stretched penile length, though perceived shortening is still reported in approximately 29% of patients.^{40,41} Penile sensation changes occur in up to 21% of patients early postoperatively but typically resolve, with only 3% persisting beyond 12 months.⁴² New-onset erectile dysfunction has been reported in up to 22% of previously potent men, with cardiovascular and metabolic comorbidities being significant predictors rather than surgical factors such as graft size or deformity complexity.⁴² As with plication, the most appropriate candidates are patients with adequate preoperative erectile function.¹³
- **Penile prosthesis implantation** is reserved for patients with concurrent refractory erectile dysfunction and is the mainstay of surgical treatment for PD in men with drug-refractory erectile dysfunction. Prosthesis placement addresses both erectile dysfunction and penile deformity, with curvature improvement reported at $>80\%$ across studies. In patient with mild curvature, prosthesis placement alone may achieve adequate straightening. Those with more severe curvature may require manual modeling, penile plication, or plaque incision with grafting to achieve optimal curvature correction.¹³

Radiotherapy (RT) has been used as a non-surgical treatment for PD for over half a century, with early reports describing its application during the acute inflammatory phase to address penile pain and potentially slow disease progression.^{1,43,44}

Published studies have typically employed orthovoltage x-rays or electrons, with total doses usually ranging from 9–20 Gy delivered in fractionated regimens.^{43,44} Reported outcomes have varied across studies, with uncontrolled series suggesting pain relief in up to 76–83% of patients.⁴⁵ Because RT acts by inducing structural and fibrotic changes, there is ongoing debate over whether prolonged or higher doses could actually promote further long-term scarring and tissue damage in the penis.⁴⁶ It is not considered first line therapy for PD by urologic societies because of the potential risks of RT to erectile tissue¹³.

Biologic Rationale for RT

The specific molecular effects of RT on PD tissue remain incompletely understood. RT has been used in patients with PD to target the acute inflammatory phase of the disease to reduce pain and potentially slow disease progression, as

it is relatively ineffective at reversing established penile plaque or curvature.⁴⁷ RT in the 0.3 to 0.7 Gy range, lower than typical fractionation regimens historically used to treat PD, selectively inhibits the differentiation and hyperproliferation of fibroblasts and myofibroblasts⁴⁸ and suppresses the expression and release of pro-fibrotic and pro-inflammatory cytokines (such as G-CSF, PDGF-BB, and IL-8)⁴⁸⁻⁵¹ that would otherwise perpetuate tissue inflammation and scar. However, at very low levels (e.g., <0.1 Gy), RT may trigger adaptive stress responses, transiently activating signaling pathways like MAPK/ERK and PI3K/AKT, which can actually enhance proliferation or survival in certain healthy fibroblasts.^{52,53}

RT has been administered in patients with PD in fractionated doses of about 2 Gy, which are higher than the low-dose RT fractionations shown to suppress inflammation. *In vitro* data from Mulhall et al. demonstrated that RT of PD (5 Gy single fraction) plaque-derived fibroblasts actually increased the production of the fibrogenic cytokines β FGF and PDGF-AB, raising the concern that RT may paradoxically promote fibrosis in PD tissue.⁴⁶ RT has been shown to inhibit fibroblast proliferation through DNA damage and oxidative stress and induce cell cycle arrest placing the fibroblasts into senescence.^{54,55} Although not specifically demonstrated in PD, these damaged fibroblasts have been shown to alter function and adapt a senescence-associated secretory phenotype, causing them to release a heavy load of inflammatory cytokines (IL-6 and IL-8) and growth factors, which may result in a chronic inflammatory loop.^{54,56} This discordance between the proposed anti-fibrotic mechanism and the *in vitro* cytokine data underscores the need for further investigation into the biologic effects of RT on PD-specific tissue. Investigations should ideally evaluate the effect of various dose fractionation schemes on biologic effects and clinical efficacy.

This systematic review and guidelines examines the evidence for the appropriate use of RT for the treatment of PD (Induratio Penis Plastica). The Population, Intervention, Comparator, and Outcome (PICO) questions included (1) what is the role of RT in the treatment of PD?, (2) what are the risks associated with adjuvant RT?, and (3) what is the role of RT in comparison to other treatments?

METHODS

Using the Population, Intervention, Comparator, Outcome, Timing and Study Design (PICOTS) framework, the evidence regarding treatment outcomes was assessed using Cochrane and PRISMA 2020 methodology.^{57,58} Eligible studies included prospective studies, phase II-III trials, and retrospective analyses including ≥ 15 patients published between 1/1/1970 – 6/24/2026 in the Pubmed MEDLINE, Embase and Scopus databases. Appendix A contains the database search strategy designed by a librarian specializing in systematic reviews. The lead authors independently screened the comprehensive list of articles, and one assessed the full text articles to determine the final studies included as evidence in the Summary of the Literature Review which advised our recommendations (Appendix B). Discrepancies between the reviewers were resolved by consensus. Of the 90 articles identified using the search strategy, 19 were selected for inclusion (Appendix C). Study type and quality for these references were assessed via American Radium Society™ (ARS) Appropriate Use Criteria (AUC) methodology (Appendix C). The systematic review PRISMA 2020 checklist confirms the completion of essential elements (Appendix D). Well-established RAND-UCLA consensus methodology (modified Delphi) was used by the expert panel to rate the appropriateness of the treatment options⁵⁹, with a total of 1 rounds of voting employed by the group. Categories included (1) usually not appropriate (U, score 1-3); (2) may be appropriate (M, score 4-6); and (3) usually appropriate (A, score 7-9). The project was reviewed and approved by the ARS AUC steering committee, which includes a librarian with expertise in systematic reviews. For further details on ARS AUC methodology guidelines. See <https://www.americanradiumsociety.org/page/aucmethodology>.

RESULTS/SUMMARY OF LITERATURE REVIEW

Topic 1/ What is the role of RT in the treatment of Peyronie's Disease (Induratio Penis Plastica)?

The outcomes of RT for PD have been reported in retrospective and observational studies, with several studies reporting long term outcomes >5 years post-treatment. The symptom with the highest reported response rates

after RT is pain, with response rates ranging between 50-90%. Improvement of penile curvature has been reported in 20-75%, and improvement of plaques or induration in 20-50%.^{43-45,47,60-69} Conversely, curvature worsening has been reported in 7.5% to 20%^{45,64}, with one study showing that 18% of patients developed new PD lesions even after RT.⁶⁷ The rate of erectile dysfunction is inconsistently reported in the literature, with most studies making no mention of this outcome at all^{47,61,62,65}, though a few series reported an improvement in erectile dysfunction in 7-8%.^{44,67} Overall, all of the published studies have severe design and/or methodological limitations which limit the interpretation of efficacy.

Subtopic 1/ Orthovoltage RT

Feder reported outcomes for 46 patients treated with orthovoltage RT, with a total dose of 600-800 cGy delivered in 4 fractions.⁶⁰ Among 37 patients with pain at presentation, 56% had a “good” response to RT, 25% had a “fair” response, and 19% had no response, resulting in an overall pain response rate of 67%. A “good” or “fair” response in penile deformity occurred in 39%. There was no definition of what constituted a “good” or “fair” response and no mention of what time point these responses were achieved. Byström et al. reported on 58 patients given various forms of treatment for PD, including 19 patients who were treated with orthovoltage RT (140-170 kV), to a dose of 1200 rad given over 7 days.⁶¹ Four out of 19 patients were described as noting “improvement” post-RT although the authors do not describe what specific outcomes were improved, whereas the condition remained unchanged in 15 patients. An additional 7 patients in their series had no treatment, of which 6 experienced spontaneous symptom resolution. The authors concluded that the results of RT were hardly different from the spontaneous course of the disease.

Helvie et al. mailed questionnaires to 76 patients who had been treated for PD between 1965 to 1971 with orthovoltage x-rays (280 kvp) or superficial x-rays (50 kvp), 300 cGy on alternate days for a total dose of 900 to 2400 cGy.⁶² Of 40 responses received, for which the mean time since RT was 2.2 years, the authors reported that 72% had improvement in either pain, penile angulation, and/or plaque size; 23% had no change; and 5% reported progression. Of those who noted any improvement, 72% experienced relief of pain, 35% noted decrease in plaque size, and 29% noted decrease in penile angulation; rate of erectile dysfunction was not reported.

Martin et al. treated 142 patients with orthovoltage RT (100-260 kV), 2100 cGy delivered at 300 rad per session over 8 days, repeated for up to 3 total courses.⁶³ Of these, 77 patients were able to be reached by telephone or mail and were included for outcome reporting. Overall, 26 (33%) reported complete resolution of symptoms. Of the remaining 51 with persistent symptoms, 84% reported improvement in pain with erection, and 63% reported improvement in penile curvature. Again, no outcomes regarding erectile dysfunction were reported.

Furlow et al. published a series of 177 patients with PD, of which 90 completed a questionnaire and were thus included for analysis.⁶⁴ 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). With an average follow up of at least 7 years, they found no benefit to orthovoltage RT, in comparison with the no-treatment group. There were similar rates of curvature improvement between RT (50% for those receiving one dose vs. 39% for those receiving 2 or 3 doses) and the no-treatment group (52%). The rate of plaque improvement was similar for the RT groups (55% and 44%) vs. the no-RT group (58%), and pain improvement rates were excellent in all groups (100% and 92% for the two RT groups, vs. 100% in the no-RT group). However, authors did note that improvement of painful intercourse or erections seemed to occur sooner with RT, with an average time to improvement of 16 months in the no-treatment group, compared to 9 months for those receiving RT.

Mira et al. reported results for 56 patients treated with orthovoltage RT.⁶⁵ Pain during intercourse was the symptom with the highest overall response rate at 79%, with a median treatment-response interval of 2.8

months. The overall response rates for curvature and induration were lower, at 38% and 44%, respectively. Erectile dysfunction rates were not reported. The authors found a statistically significant interaction between treatment response and duration of symptoms pre-treatment, with a 56% response rate among patients with pre-treatment symptom duration <5 months vs. 24% response rate for those with >5 months symptom duration.

Carson et al. reported that 78.5% of patients presenting with pain as the initial primary symptom experienced improvement in pain.⁴⁵ However, the improvement rate for plaques was 13.3%, and only 6.3% with penile curvature improved. None of the 3 patients who presented with impotence experienced any change in erectile function, nor did any patient report new onset of impotence after RT.

Viljoen et al. reported outcomes for 98 patients treated with orthovoltage RT, mostly to 25 Gy at 2.5 Gy per fraction.⁶⁷ Clinic-based follow-up at a median time of 33 months showed that 18% of patients actually had disease progression consisting of new lesions. Questionnaire-based follow-up obtained at a median time of 111 months post-treatment showed that pain improved in 84%, penile curvature improved in 38.6%, and erectile function improved in 7%.

Rodrigues et al. treated 38 patients with orthovoltage RT to 3 Gy x 3 fractions on alternating days (total dose 9 Gy; regimen A), with 16 patients undergoing a second course due to persistent symptoms (total dose 18 Gy; regimen B).⁴³ Among patients who received only one treatment course (regimen A), 66% experienced less pain during erection (complete response 12%, partial response 54%), and 40% had improvement in curvature. Response to induration was lower, with partial plaque regression achieved in 24% and complete regression in 8%. Median time to improvement was 8 weeks post-treatment. Among patients who received two treatment courses (regimen B), the results were less successful as only 25% had less pain with erection and 21% had decreased curvature, suggesting that this subset had disease more refractory to RT. Notably, 23% of all patients experienced no improvement in any symptom. Overall, 60% reported an improved sex life, although the rate of erectile dysfunction was not reported.

Pietsch et al. performed retrospective analysis of patients treated for PD with 4 Gy x 8 fractions (total 32 Gy) over 6 months.⁴⁷ A total of 234 patients were treated, of which 83 completed questionnaires at a median follow-up time of 52 months and were included for analysis. In total, 78% of patients reported that disease progression had stopped, with 47% reporting symptom regression and 7% reporting progression. Penile curvature was improved in 49%, and plaque induration was reduced in 42%. Pain relief, measured by visual analogue scale, was achieved in 71%. No mention is made of erectile function pre- or post-treatment.

Subtopic 2/Electron Therapy

In a series by Incrocci et al., 179 patients were irradiated for PD with either orthovoltage x-rays to 13.5 Gy at 1.5 Gy per fraction (n=123) or electrons to 12 Gy at 2 Gy per fraction once daily (n=56). Symptoms were present for a median duration of 6 months prior to RT. At a median follow-up of 3 months post-RT, 83% reported that pain was resolved or diminished, 23% had decrease in penile deformity, and erectile function was improved in 8%.⁴⁴ The authors mailed a questionnaire to patients at an average of 9 years post-treatment, which 106 patients completed.⁷⁰ Before RT, 92% of patients were sexually active, vs. 72% post-RT, with 49% reporting dissatisfaction with their current sexual life. However, this seemed to be related to patient age, with older patients reporting worse functioning, at a rate consistent with the general population. Niewald et al. reported on 101 patients treated with mostly 30-36 Gy at 2 Gy per fraction. For distal lesions, the penis was positioned in a slit tube fixed in an upright position with a clamp, and RT was delivered with opposing fields using Co-60 gamma rays or 4-6 MV photons. For patients with lesions near the abdominal wall, the penis was placed in a flat position and an en face 5-8 MeV electron beam was used.⁶⁹ The mean duration of symptoms before RT was 18 months, and the mean follow-up was 5 years. The best results ever at any time during follow-up were: penile deviation improved in 47%, reduction of number

of foci in 32%, less induration in 52%. Approximately 50% reported pain relief after RT. After RT, erectile dysfunction was reported in 6/71 (8%) patients. There was no difference in results between 30 or 36 Gy, and the authors noted that in 2001 they reduced their standard total dose to 20 Gy in 10 daily fractions.

Subtopic 3/ Iridium-192 Moulage

Koren et al. reported a series of 265 patients treated with Iridium-192 molds to a median dose of 9.45 Gy.⁶⁸ Therapy response was estimated by palpation and ultrasound. Follow up was performed on 155 patients from 2.5 to 72 months (median 12 months). Complete regression of the plaques was obtained in 9%, partial remission of >50% in 20%, partial remission between 25-50% in 38%, no remission/stable in 30%, while 3% had further disease progression. Of patients with pain as an initial presenting symptom, 61% had resolution of pain after 5-6 months. Regarding complications, pain during therapy occurred in 38 patients, and hematuria in 7 after removal of the moulage, which resolved spontaneously in a few days. One patient developed acute urinary retention requiring premature stopping of treatment.

Subtopic 4/ Appropriate Candidates for Consideration of RT

The use of RT for PD remains controversial. The 2015 guidelines from the American Urologic Society (AUA) recommend against use of RT for this disease, citing potential risks of RT (see **Topic 2.**) exposure in the setting of unproven benefit.¹³ Given significant shortcomings of the published studies, it is not possible to establish a patient population that would clearly be appropriate candidates for RT.

The overall body of evidence appears to suggest that RT may be associated with a reduction in penile pain, or at least shorter time to resolution of pain compared to the natural disease course. The presence of pain tends to correspond with the acute, or active phase of PD. Patients with shorter duration of symptoms and younger age also tended to respond better to RT^{44,45}, again consistent with potential efficacy in the acute phase. Accordingly, German guidelines published in 2015⁷¹ describe RT as clinically indicated for patients with early-stage disease presenting with soft, localized penile plaques (as opposed to calcified plaques). Some have suggested that the role of RT be restricted to patients with severe penile pain.⁴⁵ However, there is a lack of high-quality studies to support the routine use of RT. It should not be considered as first-line therapy to treat pain associated with acute-phase PD but may be considered in a patient with active-phase PD unresponsive to NSAIDs and ESWT, and who is not a candidate for intralesional collagenase clostridium histolyticum.

Patients with calcified plaques, associated with later stages of disease, have been reported to have lower response rates to RT than patients with non-calcified lesions.⁶⁸ Overall RT response rates for penile curvature or plaques appear to be lower than for pain, and do not appear to be any different from patients not receiving treatment.⁶⁴ Based on the literature, there is no clear role for RT for patients in the stable chronic phase, where predominant presenting complaints are often penile deviation or plaque formation without pain. There is no role of RT in the treatment of erectile dysfunction associated with PD.

Subtopic 5/ RT Technique

The following details for RT technique are not intended to promote use of RT for PD, but rather to provide details of appropriate RT planning and delivery that are described in the literature if one were to consider its use.

- **RT Modality:** RT for PD has been delivered mainly with orthovoltage x-rays or low-energy (4-12 MeV) electrons, with low-energy (4-6 MV) photons a less commonly used option.⁷² A 5-10 mm bolus may be used to achieve optimal dosimetry to the surface of plaques.^{69,72}
- **Dose-Fractionation:** Most published studies have utilized a range of 9 to 20 Gy total dose, delivered at 2-3 Gy per fraction. A 2008 survey of European institutions found that the most commonly used dose fractionation was 20 Gy in 10 fractions delivered 5 times a week.⁷²

- **Timing and Sequencing:** Some reports have suggested that treatment response rates are higher among patients with a shorter duration of symptoms prior to treatment.^{62,65} However, RT is not considered a first-line therapy for PD and if treatment is needed, other non-invasive therapies should be considered first.¹³
- **Simulation/Set-up:** One possible setup consists of supine positioning with the legs in a frog-leg position, with 2-5 mm thick lead shielding placed over at minimum the scrotum and testes, and ideally also the suprapubic region.^{60,70,72} An en-face AP beam is then used for treatment delivery. Alternatively, the penis may be placed in an upright position using a fixation technique, and treated with lateral opposing fields.⁶⁹
- **RT Field Design:** The RT field generally includes the entire penis, with the exception of the glans which is excluded to minimize toxicity.^{43,44}

Table 1 summarizes key studies Investigating use of RT in the treatment of Peyronie’s Disease (Induratio Penis Plastica)

Topic 2/ What are the risks associated with RT?

Subtopic 1/ Secondary Malignancy Risks

Age, total RT dose, and treatment field size should be considered in assessing potential risk for secondary malignancy. For older adults treated with low to intermediate dose RT for benign conditions, the risk of RT-induced cancer is likely very small and diminishes further with increasing age at treatment.⁷³ The risk of secondary malignancy may be higher for younger individuals, especially under the age of 50, due enhanced radiosensitivity and a longer potential latency period. Nevertheless, the absence of long-term prospective data and incomplete follow-up remain important limitations.

RT-induced malignancies are a known potential risk of x-ray exposure and can include soft tissue sarcomas (usually malignant fibrous histiocytoma or fibrosarcoma), skin cancer, leukemia, and others. The linear-no-threshold model is one approach to describe risk of RT-induced malignancy.^{74,75} Under the linear-no-threshold model, RT-induced malignancies are considered a stochastic effect, meaning these are random statistical occurrences, the probability of which is dose-dependent with no threshold. Alternatively, a competing hypothesis is that RT-induced malignancy is unlikely below a certain threshold dose, although such a dose has never been clearly identified.^{76,77}

Some have suggested that risks of RT-induced malignancy should be estimated on an organ-specific basis using epidemiologic data.⁷⁸ Using this approach, the risk of an in-field basal cell carcinoma has been estimated at <0.1% for a 100 cm² field of sun-exposed skin treated with 1 Gy, and would be an order of magnitude lower for skin fields not exposed to sunlight.⁷⁸ Post-RT sarcoma has been reported to occur after a median dose of about 50 Gy (range: 8 to 60 Gy) with a median latency period of 10 years (range: 2 years to 50 years).⁷⁹ This is much higher than the doses generally used to treat non-malignant conditions. In the Life Span Study cohort of atomic bomb survivors, 5 excess cases were documented after a mean total-body dose of 0.23 Gy, which is consistent with a lifetime risk of <0.1%.⁸⁰ Corrected for a RT field size of 100 cm², the risk of RT-induced sarcoma after intermediate dose RT for benign conditions would be <1 in 100,000.⁷⁸

Subtopic 2/ Non-Malignant Risks

• Acute Effects

Acute effects may include RT dermatitis or urethritis, although this is sparsely reported in the literature and appears to be dose-dependent, with little to no toxicity amongst series utilizing ≤10-20 Gy total dose, which is the dose range most commonly reported. Rodrigues et al. described no cases of RT-induced morbidity such as erythema or urethritis among 38 patients treated with 9-18 Gy at 3 Gy per fraction.⁴³ In Incrocci et al.’s report of 179 patients treated with 12-13.5 Gy at 1.5-2 Gy per fraction, no RT-related complications occurred except for transient dysuria in 1 patient.⁴⁴ However, in studies that utilized doses ≥30 Gy, reported skin toxicity rates are

generally higher. In a series utilizing 30-40 Gy at 2 Gy per fraction, 28% developed mild acute dermatitis and 4% mild urethritis, with no long-term side effects reported.⁶⁹ In another series of 83 patients treated with 32 Gy in 8 fractions at 4 Gy per fraction, transient erythema developed in 39% and 10% reported transient or chronic dryness.⁴⁷

- **Late Effects**

Late effects of the skin have been reported after RT for PD, albeit mainly among studies that utilized RT doses higher than ≥ 30 Gy. In the report by Martin et al., who gave up to 3 courses of 2100 cGy (6300 cGy total) over a period of 9 months to 3 years, patients developed painless telangiectasias on the treated skin, and 1 patient required surgery because of edema of the foreskin.⁶³ In the study by Pietsch et al. utilizing 32 Gy in 8 fractions, chronic toxicities included 12% with telangiectasias in the RT field, 19% with atrophic skin, and 6% with paresthesia in the irradiated area.⁴⁷

In addition, there has been concern that RT may actually promote further fibrosis. RT has been reported to result in increased fibrogenic cytokine expression by PD fibroblasts.⁴⁶ One case report describes a 25-year old man who developed new onset impotence 5 months after being treated for PD with 6 fractions of 200 rad (total dose 1200 rad) using 250 kV orthovoltage RT.⁸¹ Upon surgical placement of penile prosthesis, he was found to have extensive corporeal fibrosis. Histologic analysis revealed arterial vasculopathy and replacement of trabecular smooth muscle with dense fibrotic tissue.

In the report by Carson et al., 3 out of 40 (7.5%) patients treated with orthovoltage RT complained of a worsened curvature post-treatment.⁴⁵ Furlow et al. reported that 19.5% of patients experienced worsening of penile curvature after RT, compared to 13% of patients managed with no-treatment.⁶⁴ However, in both of these series, it was not possible to determine if this worsening was due to a late effect of RT or the natural disease course.

There has not been reported evidence that RT precludes future surgery, although there is theoretical concern that RT-induced fibrosis may make surgery more difficult. In the report by Carson et al., 13 patients ultimately underwent penile prosthesis implantation, and surgery was not hampered by the prior RT, but patient numbers were small.⁴⁵

Topic 3/ What is the Role of RT in the Treatment of Peyronie's Disease in Comparison to Other Treatments?

There are no published randomized trials comparing RT with either placebo or other treatment methods. Most of the published studies on RT for PD predated the availability of modern treatments such as collagenase clostridium histolyticum, which has been an important development for the therapeutic management of PD. Collagenase clostridium histolyticum was shown in two large, double-blind, randomized placebo-controlled phase III studies to result in a 34% mean decrease in penile curvature compared to 18% mean decrease in the placebo arm, leading to FDA approval of this treatment for PD in 2013.⁸²

In addition, for patients with PD that is in the stable, chronic phase, surgical treatments such as tunical plication, plaque excision, or penile prosthesis can be considered for correction of penile curvature. Data suggests poorer results for RT in patients with greater chronicity of symptoms prior to treatment and low rates of improvement in established penile plaque or curvature, suggesting there is no clear role for RT in the late disease stage.^{62,65}

Overall, given severe design limitations of retrospective cohort series, lack of efficacy demonstrated in the current literature, and availability of alternate treatment options, RT is not a preferred modality in comparison to other treatments.

Variant Cases

Variant cases (**Tables 2 - 6**) were developed as examples for these guidelines to illustrate practical applications of consensus recommendations.

CONCLUSIONS/SUMMARY OF RECOMMENDATIONS

1. The panel recommends that RT is usually not appropriate treatment for the typical case of pain associated with early active-phase, treatment-naïve PD. [**Table 2. Variant 1**] However, RT may have a role in treatment of pain in a patient with active-phase PD unresponsive to NSAIDs and ESWT, and who is not a candidate for intralesional collagenase clostridium histolyticum.
2. The panel recommends that RT is usually not appropriate treatment for the typical case of deformity associated with active-phase PD after failed conservative therapies. [**Variants 2 and 3**]
3. The panel recommends that RT is usually not appropriate treatment for the typical case of deformity associated with stable chronic-phase PD unresponsive to intralesional therapy. [**Variant 4**]
4. The panel recommends that RT is usually not appropriate treatment for the typical case of erectile dysfunction associated with stable chronic-phase PD. [**Variant 5**]

DISCUSSION

It should be noted that much of the data on RT for PD is based on older studies including a heterogeneous mix of prior treatments, RT techniques, and dose-fractionation schedules, limiting comparisons of results from different series. Dose schemes ranged widely between a total dose of 2.2 Gy to 40 Gy, administered at 2.0-3.0 Gy per fraction.^{43-45,47,60,62-65,67,69} In addition, inclusion criteria were minimally reported and it is likely that there was a range of PD severity included in these studies. The majority were retrospective single cohort studies, with the exception of the study by Furlow et al., which included 2 RT dose fractionation groups (1 treatment of 2.2 to 5.5 Gy vs. 2 treatments with total 4.4 to 11 Gy) and a no-treatment comparison group. However, this was not a randomized comparison and it is unclear how patients were selected for different approaches.⁶⁴ The follow up periods for the body of evidence were variable and relatively short, limiting full evaluation of long-term efficacy and side-effects of RT.

Across the literature on RT for PD, a lack of objective outcomes further hampers interpretation of the data. Outcome measures were mostly based on subjective patient- or physician-based reporting of pain, changes penile curvature and plaques, or erectile function, which correlate poorly with objective measurement protocols such as validated pain scales, curvature measurements, or erectile function tests. It is important to note that the vast majority of published outcome data was derived from questionnaire-based follow-up, sometimes obtained up to 5-10 years post-treatment⁶⁷, and thus subject to recall bias as well as selection bias due to low questionnaire response rates.

Some studies reported faster resolution of pain following RT, but could not rule out the possibility that any improvement was due to the natural disease course.⁶⁴ It should be noted that many patients with PD experience spontaneous symptom resolution, and the nature and severity of symptoms can change over time, which further limits the ability to evaluate the efficacy of RT in this disease.

Intermediate-dose RT is used for Dupuytren's disease and Ledderhose disease, hyperproliferative disorders which share pathophysiologic features with PD. However, an extremely important difference between PD and these other hyperproliferative disorders is that PD is a condition affecting an organ whose function relies on adequate vascular inflow, veno-occlusive function from pressurization of the corporal bodies, and associated neural input. A primary concern with RT to the penis for treatment of PD is the impact on erectile rigidity, which for these patients is often already compromised. Unfortunately, erectile dysfunction rates before and after treatment are not well reported, and in many studies, it is not even mentioned.

RT-induced erectile dysfunction may be mediated by damage to the erectile tissue vasculature, nerves, and smooth muscle. The exact mechanisms are yet to be fully elucidated but RT is known to cause vascular injury, with early injury mediated by increased permeability of the microvasculature, which is particularly radiosensitive, and delayed injury via development of fibrotic, occlusive lesions that result in reduced blood flow.⁸³ Delayed lesions in small or medium sized arteries, most commonly manifested as intimal fibrosis, can be seen 3-6 months to many years post-RT, and constitute an important mechanism of RT-induced ischemia and long-term tissue damage.⁸³ Rat experiments have demonstrated an RT-induced decrease in the number of nitric oxide synthase-containing nerve fibers per penile segment after 10-20 Gy delivered to the prostate, with a corresponding decrease in maximal intracavernous pressure induced by electric stimulation.⁸⁴ Of note, 10-20 Gy falls well within the range of doses used in PD studies.

We recognize that current literature contains insufficient evidence to recommend the routine use of RT for the treatment of PD. RT for treatment of PD generally should not be considered outside of a clinical trial. Well-designed sham-controlled randomized trials using consistent dose fractionation schedules, modern RT techniques, uniform inclusion criteria, objective outcome measures, and longer follow up would be required to fully evaluate the utility of RT for treatment of PD.

SUMMARY OF EVIDENCE

This section summarizes the references on the evidence table.

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).

Supporting Documents

For additional information on the ARS Appropriate Use Criteria methodology and other supporting documents go to <http://www.americanradiumsociety.org/page/aucmethodology>.

The American Radium Society™ Appropriate Use Criteria and its expert panels have developed criteria for determining appropriate procedures for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide treating and referring physicians in making decisions regarding diagnosis and treatment of cancers and related or associated conditions. Generally, the complexity and severity of a patient’s clinical condition should dictate the selection of appropriate diagnostic procedures or treatments. Only those examinations or treatments generally used for evaluation of the patient’s condition are ranked. Other procedures necessary to evaluate or treat other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate procedures or treatments. Procedures, techniques, or other interventions classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment, applications, and treatment protocols should be encouraged. The ultimate decision regarding the appropriate use of any specific examination or treatment must be made by the referring physician and oncologist in light of all the circumstances presented in an individual examination.

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Table 1. Select Studies Evaluating RT in the Treatment of Peyronie's Disease (Induratio Penis Plastica)

Author	Year	Study Type (Study Quality)	Number of Patients	Radiation Technique	Dose/ Fractionation	Result
Feder	1971	Retrospective (3)	46	Orthovoltage	1.5-2 Gy x 4 fractions; Total dose 6-8 Gy	Pain: 67% improved "Deformity": 39% improved
Byström et al.	1971	Retrospective (3)	19	Orthovoltage	Total dose 12 Gy	21% with "improvement" but no mention of what specific outcomes improved
Helvie et al.	1972	Retrospective (3)	40	Orthovoltage	3 Gy x 3-8 fractions; Total dose 9 to 24 Gy	Pain: 52% improved Penile curvature: 21% improved
Martin et al.	1972	Retrospective (3)	77	Orthovoltage	3 Gy x 7 fractions; Total dose 21 Gy, repeated up to 2 times	Pain: 90% improved Penile curvature: 75% improved
Furlow et al.	1975	Retrospective (3)	90	Orthovoltage (n=51) No treatment (n=26) Radium or non-RT treatments (n=13)	Orthovoltage: 250-600 roentgens as a single dose, repeated up to 2 times	Single Orthovoltage RT dose: Pain improved in 100%, curvature improved in 50%. No treatment: Pain improved in 100%, curvature improved in 52%
Mira et al.	1980	Retrospective (3)	56	Orthovoltage	Total dose 600-2100 roentgens, mostly at 200 roentgens per fraction given 3x/week	Pain: 70% improved, >50% complete resolution Induration and penile deviation: 50% partial response, 0% complete response
Alth et al.	1985	Retrospective (3)	636	Radium	5.5-6.6 Gy in core of penis	Pain: 90.5% improved Penile curvature: 52.8% improved
Carson et al.	1985	Retrospective (3)	40	Orthovoltage	Total dose 6-16 Gy (average 9 Gy)	Pain: 78.5% improved Penile curvature: 6.3% improved Plaque: 13.3% improved
Viljoen et al.	1993	Retrospective (3)	98	Orthovoltage	2.5 Gy x10; Total dose 25 Gy	Pain: 84% improved Penile curvature: 38.6% improved Erectile function: 7% improved
Rodrigues et al.	1995	Retrospective (3)	38	Orthovoltage	3 Gy x 3 fractions on alternating days; Total dose 9 Gy	Pain: 76% improved Penile Curvature: 48% improved Erectile function: 60% improved
Koren et al.	1996	Retrospective (3)	155	Iridium-192	Median 9.45 Gy (range: 7.21-13.2 Gy)	Pain: 61.4% improved
Incrocci et al.	2000	Retrospective (3)	179	Orthovoltage or electrons	Orthovoltage: 1.5 Gy x 9; Total dose 13.5 Gy Electrons: 2 Gy x 6; Total dose 12 Gy	Pain: 83% improved by 3 months Penile curvature: 23% improved Erectile function: 8% improved
Niewald et al.	2005	Retrospective (3)	101	Co-60, 4-6 MV photons, or 5-8 MeV electrons	2 Gy x 15-20 fractions; Total dose 30-40 Gy	Pain: 50% improved Penile curvature: 47% improved Induration: 52% improved
Pietsch et al.	2018	Retrospective (3)	83	Orthovoltage	4 Gy x 8 fractions; Total dose 12 Gy	Pain: 71% improved Penile curvature: 49% improved Induration: 42% improved

Abbreviations:

MV: megavoltage

MeV: mega electron volt

n: number

Gy: Gray

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 M Meta-analysis

Table 2: Variant 1: Early Active-Phase, Treatment-Naïve Peyronie’s Disease

A 48-year-old man presents with a 4-month history of PD in the active phase. He reports moderate penile pain during erections (6/10) and has developed a 25° dorsal curvature. Examination reveals a palpable, noncalcified dorsal plaque. He has not received any prior PD-specific treatment. Erectile function is normal and sufficient for intercourse, with an International Index of Erectile Function-5 (IIEF-5) score of 24/25. He is seeking treatment recommendations for pain.

Treatment Options	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Radiotherapy	U	1	4	7	1	0	0	0	0	0	3		L	↑

Variant Discussion:

This patient has active-phase PD, characterized by a 4-month history of penile pain, progressive 25° dorsal curvature, and a noncalcified plaque. During the active-phase (typically the first 6–12 months after symptom onset) ongoing inflammation and plaque remodeling provide the strongest theoretical rationale for radiation therapy, as its proposed anti-inflammatory effects could reduce penile pain before mature fibrosis develops. However, the patient's curvature remains <30°, below the Food and Drug Administration (FDA) approved threshold for intralesional collagenase clostridium histolyticum, and surgery is generally deferred during the active-phase, leaving conservative management as the standard approach. Despite this biologic rationale, evidence supporting radiation therapy is limited to retrospective, uncontrolled case series reporting improvement in penile pain but inconsistent effects on curvature, plaque progression, erectile function, or subsequent intervention. Because penile pain often resolves spontaneously during the natural history of active-phase PD, any observed benefit cannot be distinguished from spontaneous improvement in the absence of randomized controlled trials.

Extracorporeal shockwave therapy (ESWT) provides an important comparator because it targets the same symptom through anti-inflammatory and analgesic mechanisms without exposing the penis to ionizing radiation. Unlike radiation therapy, ESWT has been evaluated in sham-controlled randomized trials and systematic reviews demonstrating low-certainty but consistent improvement in penile pain, including durable long-term pain relief, high patient satisfaction, and low rates of subsequent surgery. Similar to radiation, however, ESWT has not demonstrated meaningful improvement in penile curvature.

Although this variant represents the clinical scenario in which radiotherapy has its strongest rationale, its potential value as a treatment option is reduced by preserved erectile function (IIEF-5 24/25), mild curvature, availability of conservative management, and the presence of a better-studied alternative therapies. However, radiotherapy may have a role in treatment of pain in a patient with active-phase PD unresponsive to NSAIDs and ESWT, and who is not a candidate for intralesional collagenase clostridium histolyticum.

Table 3: Variant 2: Active-Phase Peyronie's Disease After Failed Conservative Therapy

A 55-year-old man presents with an 8-month history of active-phase PD characterized by persistent penile pain (4/10) and progressive left lateral curvature, increasing from 20° to 40° over the past 4 months. Physical examination demonstrates a noncalcified plaque. He previously completed treatment with NSAIDs and a 3-month course of penile traction therapy without symptomatic improvement. Erectile function remains normal, with an IIEF-5 score of 23/25, but he notes psychological distress due to the inability to have intercourse due to pain and curvature. He is seeking treatment recommendation for pain and curvature.

Treatment Options	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Radiotherapy	U	0	3	10	0	0	0	0	0	0	3		L	↑

Variant Discussion:

This patient represents progressive active-phase PD with an 8-month history of persistent penile pain, documented curvature progression from 20° to 40° despite NSAIDs and penile traction therapy, and preserved erectile function (IIEF-5 23/25). The dominant clinical concern is progressive deformity resulting in functional impairment rather than pain alone. The patient's 40° curvature exceeds the threshold for FDA-approved intralesional collagenase clostridium histolyticum therapy, but its use in the active-phase is off-label.

Although some studies have reported stabilization of disease following radiotherapy, it remains unclear whether this reflects a true treatment effect or the natural disease course, as PD spontaneously stabilizes in a substantial proportion of patients over time. In contrast, high-quality randomized trials support intralesional collagenase clostridium histolyticum for men with curvature between 30° and 90°, demonstrating significant improvements in penile curvature and patient-reported bother, with evidence supporting its use in both active-phase and stable-phase disease.

Evidence demonstrating consistent meaningful improvement in curvature with radiotherapy is lacking. Given this patient's progressive deformity despite conservative therapy, preserved erectile function, and availability of FDA-approved therapies supported by stronger evidence, radiotherapy is not considered an appropriate next step in the management of PD in this case.

Table 4: Variant 3: Active-Phase Peyronie's Disease with Severe Progressive Deformity

A 60-year-old man has a 10-month history of active-phase PD with progressive deformity despite only mild penile pain (1–2/10). He has developed a 60° dorsal curvature with an associated hourglass deformity. Examination reveals a noncalcified plaque. Previous treatment with pentoxifylline and penile traction failed to prevent progression. He has mild erectile dysfunction that responds to phosphodiesterase type 5 inhibitors, with an IIEF-5 score of 19/25. He is seeking treatment recommendations for deformity.

Treatment Options	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Radiotherapy	U	4	6	2	0	0	0	0	0	0	2		L	↑

Variant Discussion:

This patient has complex, progressive active-phase PD, characterized by a 10-month history of worsening deformity despite pentoxifylline and penile traction therapy, a 60° dorsal curvature with an associated hourglass deformity, and mild erectile dysfunction responsive to PDE5 inhibitors (IIEF-5 19/25). Unlike the preceding variants, the primary clinical problem is severe structural deformity causing functional impairment rather than penile pain. The combination of severe curvature and hourglass deformity places the patient within a subgroup that often requires definitive intervention, with preserved erectile function making him a potential candidate for reconstructive surgery once the disease stabilizes.

No studies have specifically evaluated radiotherapy in patients with complex deformities such as hourglass deformity or severe curvature, and no randomized controlled trials have demonstrated a benefit for deformity correction. Evidence-based alternatives—including intralesional collagenase clostridium histolyticum and plaque incision with grafting for appropriate surgical candidates—have demonstrated substantially greater efficacy for curvature correction, with surgical reconstruction providing the most reliable correction of both severe curvature and hourglass deformity.

Given this patient's progressive complex deformity, minimal pain, preserved but vulnerable erectile function, radiation therapy is unlikely to address his primary treatment goals and would unnecessarily expose erectile tissues to radiation. Evidence supports escalation to intralesional therapy and early surgical consultation in this case.

Table 5: Variant 4: Stable Chronic-Phase Peyronie's Disease After Intralesional Therapy

A 62-year-old man presents with stable chronic-phase PD of 24 months' duration. He reports no penile pain, and his 55° dorsal curvature has remained unchanged for more than 9 months. Examination demonstrates a partially calcified dorsal plaque. He previously completed a course of intralesional collagenase injections but continues to experience bothersome deformity affecting intercourse. Erectile function is otherwise normal, with an IIEF-5 score of 24/25. He is seeking treatment recommendations for deformity.

Treatment Options	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Radiotherapy	U	5	5	2	0	0	0	0	0	0	2		L	↑

Variant Discussion:

This patient has stable chronic-phase PD, demonstrated by a 24-month disease duration, absence of penile pain, stable 55° dorsal curvature for more than 9 months, and a partially calcified plaque following a completed course of intralesional collagenase clostridium histolyticum. These findings indicate mature fibrotic disease, for which surgical correction is the recommended definitive treatment in patients with preserved erectile function. Plaque calcification is associated with reduced responsiveness to nonsurgical therapies and a greater likelihood of requiring surgery, further supporting this patient's candidacy for operative management.

No studies have specifically evaluated radiotherapy after failed collagenase clostridium histolyticum treatment. Surgical correction is the recommended therapy for patients with stable chronic-phase disease, bothersome curvature, and preserved erectile function. Tunical plication or plaque incision with grafting provide substantially higher rates of curvature correction than any reported with radiotherapy and have demonstrated excellent outcomes even after unsuccessful collagenase clostridium histolyticum therapy.

In this patient, radiotherapy offers little potential benefit because pain is no longer present, the plaque is mature and partially calcified, and the most effective nonsurgical treatment (intralesional therapy) has already failed. Pursuing radiotherapy could delay definitive surgical management without evidence of meaningful improvement in deformity.

Table 6: Variant 5: Variant 5: Stable Chronic-Phase Peyronie's Disease with Concomitant Erectile Dysfunction

A 67-year-old man has a 30-month history of stable chronic-phase PD with no penile pain. He has a stable 45° ventral curvature associated with a calcified ventral plaque. He has not undergone PD-specific treatment and has moderate erectile dysfunction despite phosphodiesterase type 5 inhibitor therapy, with an IIEF-5 score of 14/25. He is seeking further improvement and is interested in treatment recommendations for deformity and erectile dysfunction.

Treatment Options	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Radiotherapy	U	8	3	1	0	0	0	0	0	0	1		L	↑

Variant Discussion:

This patient has stable chronic-phase PD with a 30-month history of stable 45° ventral curvature, a calcified plaque, and no penile pain. The defining feature of this variant is moderate erectile dysfunction (IIEF-5 14/25) refractory to PDE5 inhibitor therapy, making erectile function—not curvature alone—the primary driver of treatment selection. Inflatable penile prosthesis is the preferred definitive treatment for patients with stable chronic-phase PD and erectile dysfunction that is unresponsive to medical therapy.

Although emerging data suggest collagenase clostridium histolyticum may improve ventral curvature in appropriately selected patients, its use for ventral plaques remains off-label. More importantly, this patient's calcified plaque, refractory erectile dysfunction, and mature stable disease make collagenase clostridium histolyticum unlikely to restore overall sexual function, even if modest curvature improvement were achieved. In contrast, inflatable penile prosthesis addresses both erectile dysfunction and penile deformity, providing high rates of patient satisfaction and functional recovery.

Given this patient's stable chronic-phase disease, absence of pain, and clear surgical indication, radiotherapy is unlikely to provide meaningful clinical benefit and may further compromise erectile function. Accordingly, inflatable penile prosthesis represents definitive treatment, whereas radiotherapy is not recommended in this clinical scenario.

Please refer to the supporting documentation for a more complete discussion of the concepts and definitions below.

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate

Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

SOE: S Strong; M Moderate; L Limited; EC Expert Consensus; EO Expert Opinion

SOR: ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak

APPENDIX A: Search Documentation: Radiotherapy for Peyronie’s Disease

Date: June 24, 2026

Database (and platforms): PubMed MEDLINE

Search Set	Search Query
1 PD MeSH	"Penile Induration"[Mesh]
2 PD Keywords [title/abstract]	"Peyronie Disease"[tiab] OR "Peyronie's Disease"[tiab] OR "Peyronies Disease"[tiab] OR "Penile Fibromatosis"[tiab] OR "Penile induration"[tiab]
3	#1 OR #2
4 RT MeSH	"Brachytherapy"[Mesh] OR "Radiotherapy"[Mesh] OR radiotherapy[sh]
5 RT Keywords [title/abstract]	"Radiotherapy"[tiab] OR "Radiotherapies"[tiab] OR "Brachytherapy"[tiab] OR "Brachytherapies"[tiab] OR "Radiation therapy"[tiab] OR "Radiation Therapies"[tiab] OR "Radiation Treatment"[tiab] OR "Radiation Treatments"[tiab] OR "External beam radiation"[tiab] OR "External radiation"[tiab] OR "Teletherapy"[tiab] OR EBRT[tiab]
6	#4 OR #5
7	#3 AND #6
8	Publication date: 1970 – June 24, 2026

Also include any filters used, and those results, above: English Language, Publication Years, etc.

Date: June 24, 2026

Database (and platforms): Embase

Search Set	Search Query
1 PD Emtree	'peyronie disease'/exp
2 PD :ti,ab,kw	'peyronie disease' OR 'peyronies disease' OR 'peyronie`s disease' OR 'penile fibromatosis' OR 'penile induration'
3	#1 OR #2
4 RT Emtree	'radiotherapy'/exp
5 RT :ti,ab,kw	'radiotherapy' OR 'radiotherapies' OR 'brachytherapy' OR 'brachytherapies' OR 'radiation therapy' OR 'radiation therapies' OR 'radiation treatment' OR 'radiation treatments' OR 'external beam radiation' OR 'external radiation' OR 'teletherapy' OR 'external beam radiotherapy' OR 'EBRT'
6	#4 OR #5
7	#3 AND #6
8	Publication date: 1970 – June 24, 2026

Also include any filters used, and those results, above: English Language, Publication Years, etc.

Date: June 24, 2026

Database (and platforms): Scopus

Search Set	Search Query
1 PD Indexing Terms	'penile induration' OR 'peyronie disease'
2 PD [title/abstract/keywords]	"Peyronie Disease"[tiab] OR "Peyronie's Disease"[tiab] OR "Peyronies Disease"[tiab] OR "Penile Fibromatosis"[tiab] OR "Penile induration"[tiab]
3	#1 OR #2
4 RT MeSH	"Brachytherapy"[Mesh] OR "Radiotherapy"[Mesh] OR radiotherapy[sh]
5 RT Keywords [title/abstract]	"Radiotherapy"[tiab] OR "Radiotherapies"[tiab] OR "Brachytherapy"[tiab] OR "Brachytherapies"[tiab] OR "Radiation therapy"[tiab] OR "Radiation Therapies"[tiab] OR "Radiation Treatment"[tiab] OR "Radiation Treatments"[tiab] OR "External beam radiation"[tiab] OR "External radiation"[tiab] OR "Teletherapy"[tiab] OR EBRT[tiab]
6	#4 OR #5
7	#3 AND #6
8	Publication date: 1970 – June 24, 2026

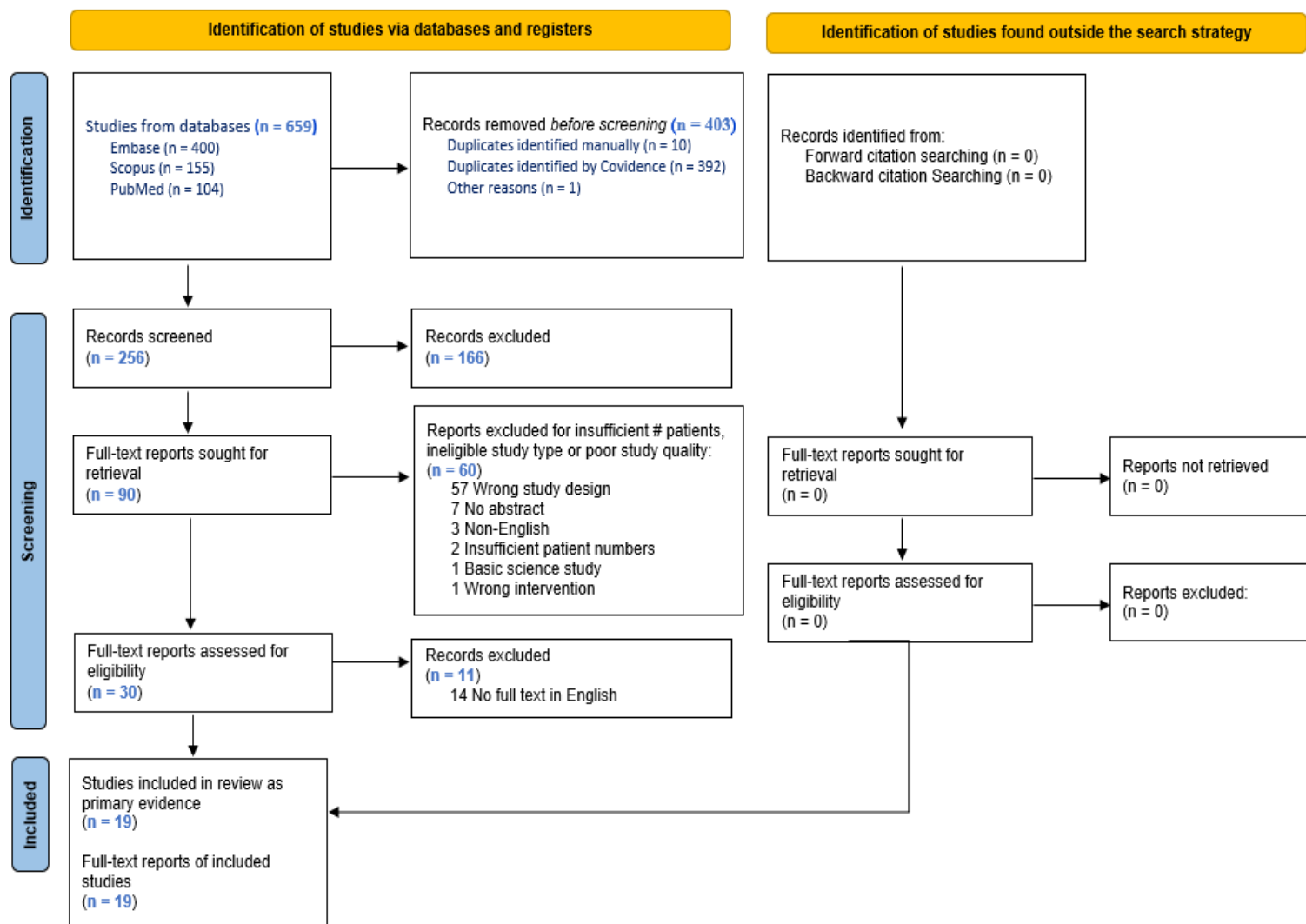
Also include any filters used, and those results, above: English Language, Publication Years, etc.

Keyword strings for searching:

"Radiotherapy" OR "Radiotherapies" OR "Brachytherapy" OR "Brachytherapies" OR "Radiation therapy" OR "Radiation Therapies" OR "Radiation Treatment" OR "Radiation Treatments" OR "External beam radiation" OR "External radiation" OR "Teletherapy" OR 'EBRT'

"Peyronie Disease" OR "Peyronie's Disease" OR "Peyronies Disease" OR "Penile Fibromatosis" OR "Penile induration"

Appendix B: PRISMA 2020 Study Selection Flow Diagram for Radiotherapy for the Treatment of Peyronie's Disease



APPENDIX D: PRISMA CHECKLIST

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	¶2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	¶2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	¶1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	¶1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix A: Search Strategy
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	¶1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	¶1
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	¶1
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	¶1
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Appendix C: Evidence Table
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Variants 1-3 via Strength of Evidence (SOE)
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Appendix B: Flow Diagram
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Appendix B: Flow Diagram
Study characteristics	17	Cite each included study and present its characteristics.	Appendix C: Evidence Table
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appendix C: Evidence Table
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Variants 1-6 via Strength of Evidence (SOE) and Strength of Recommendation (SOR), & section "SUMMARY OF RECOMMENDATIONS"
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	SUMMARY OF LITERATURE REVIEW Topics 1 - 3
	23b	Discuss any limitations of the evidence included in the review.	N/A
	23c	Discuss any limitations of the review processes used.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
	23d	Discuss implications of the results for practice, policy, and future research.	N/A
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Title Page
Competing interests	26	Declare any competing interests of review authors.	Title Page
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	https://www.americanradiumsociety.org/page/aucmethodology

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: <http://www.prisma-statement.org/>