Radiation Therapy for Benign Disease

Keloids, Macular Degeneration, Orbital Pseudotumor, Pterygium, Peyronie Disease, Trigeminal Neuralgia

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KEYWORDS

• Radiation therapy • Benign disease • Keloids • Macular degeneration
• Orbital pseudotumor • Pterygium • Peyronie disease • Trigeminal neuralgia

KEY POINTS

- Although the use of ionizing radiation on malignant conditions has been well established, its application on benign conditions has not been fully accepted and has been inadequately recognized by health care providers outside of radiation therapy.
- Radiation therapy has been shown to be effective as one of the treatment modalities for several benign conditions.
- Most patients experience no or very few symptomatic side effects and achieve good long-term control and improved quality of life.
- Clinicians must still carefully balance all of the potential risks against the benefits before proceeding with radiation therapy, especially in younger patients and children.

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KELOIDS

Keloids are benign dermal disorders that consist of raised scars formed from excessive tissue proliferation and excess collagen in the skin, mostly resulting from pathologic wound healing after injuries to the deep dermis, including surgery, trauma, and burn injuries.[1] Some other inciting events include body piercings, acne, insect bites, and vaccinations. However, some keloids form spontaneously and usually in areas with high skin tension, such as presternal, back, and posterior neck regions. Although sometimes painful and pruritic, keloids are usually asymptomatic and mainly of cosmetic concern.[2–4]

The exact pathophysiologic mechanisms causing keloid formation are unknown. Unlike hypertrophic scars, keloids extend beyond the boundary of the original site of injury. Fibroblasts in keloids seem to have different properties compared with normal skin of hypertrophic scars, because they show greater capacity to proliferate and produce high levels of primarily type I collagen, elastin, fibronectin, and proteoglycan.[5–7] In contrast, hypertrophic scars only show a modest increase in collagen production and respond normally to growth factors.[8] Several studies have shown an association between transforming growth factor-β and increased collagen or fibronectin synthesis by keloid fibroblasts.[8–10] It is hypothesized that radiation acts on fibroblasts to prevent their repopulation after excision, modulates humoral or cellular factors that would otherwise recruit or stimulate fibroblasts, or inhibits angiogenesis.[11,12]

Keloids are common, occurring in 5% to 15% of wounds and affecting both sexes equally.[13] They mainly affect people 10 to 30 years old[14] and are more commonly seen in those with family history of keloids.[15] Marneros and colleagues[16] studied 14 pedigrees and determined that keloids were an autosomal dominant entity with incomplete penetrance and variable expression. Keloids are more prominent in those with darker skin phototypes, such as black and Hispanic populations, in which the incidence is 4.5% to 16%.[17,18] **Fig. 1** shows a common keloid occurring after ear piercing in a female African American.

Although there have been many articles and studies done on management of keloids, there is no universally accepted treatment protocol for them. Choice of treatment modality often depends on factors such as size, depth, and location of the

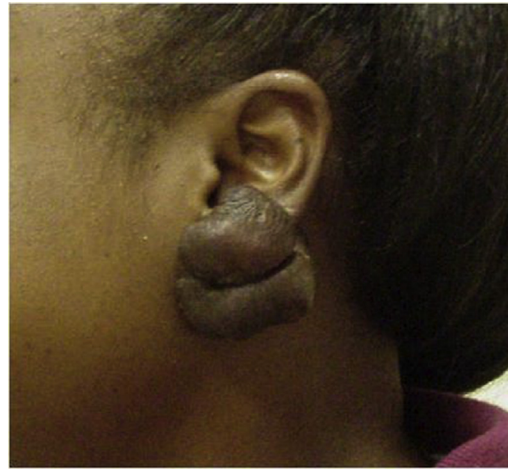

Fig. 1. A keloid develops slowly after ear piercing in a female African American.

lesion as well as the patient's age and prior response to treatment.[19] Radiation is usually indicated for recurrent keloids or keloids suspected to be at high risk of recurrence because of marginal resections, wider spread, or unfavorable locations.[20] Recurrence rates after surgical debulking or resection range from 45% to 100%[21] and are lowest in earlobe keloids.[22] With adjuvant radiation therapy, there is a 60% to 90% success rate in preventing new scar formation and achieving good cosmetic outcomes.[13,23,24] Other treatment modalities that keloids respond to include pressure therapy, cryotherapy, intralesional injections of corticosteroid, interferon and fluorouracil, pulsed-dye laser treatment, and topical silicone and other dressings.

Radiation therapy can be applied in the form of low-energy x-rays (150–200 kV), low-energy electrons (4–10 MeV), or brachytherapy.[25] Radiation can most effectively prevent keloid recurrence when it is started within 24 hours after surgical excision.[1,26] Borok and colleagues[27] reported a 2.4% recurrence rate within 50 years on 393 keloids in 250 patients after excision. In a 2011 meta-analysis, Flickinger[22] determined from a review of 2515 resected keloids that earlobe location, biologically effective dose, and treatment with electron beam or Co-60 versus other techniques, including x-rays and Sr-90, were correlated with decreased keloid recurrence by multivariate stepwise logistic regression analysis. In addition, postoperative keloid radiotherapy requires moderately high doses with a limited number of fractions and high doses per fraction to obtain optimum results, given that the dose-response function for keloids has a low α/β ratio. Using electron beam radiation, 18.3 to 19.2 Gy achieves 95% control of earlobe keloids, whereas 23.4 to 24.8 Gy achieves 95% control of other sites. Electron beam or Co-60 were thought to achieve lower rates of recurrence of resected keloids because of their less rapid dose decline with depth. Multiple studies have shown that a biologic equivalent dose 2 Gy (BED_2) greater than 35 Gy (ie, 13 Gy/1 fraction, 16 Gy/2 fractions, 18 Gy/3 fractions) yields favorable local control across all keloid sites.[22,23] The most commonly seen side effects of radiation therapy are hyperpigmentation, pruritus, and erythema.[24] **Table 1** summarizes the results from several radiation therapy studies on keloids.

Most studies on the radiation treatment of keloids are either retrospective studies or meta-analyses. A meta-analysis by Mankowski and colleagues[28] analyzed 72 studies of 9048 keloids and showed that, among brachytherapy, electron, and x-ray treatment modalities, postoperative brachytherapy yielded the lowest recurrence rate of 15%. High-dose brachytherapy is an alternative for patients who are resistant to adjuvant external beam radiation therapy and has been shown to result in a recurrence rate of 4.7% to 21%.[29–32] Jiang and colleagues[32] did a prospective trial of 29 patients with 37 recurrent keloids, in which all patients received 18 Gy in 3 fractions within 36 hours of local excision, with a subsequent 8.1% recurrence rate after a median follow-up of 49.7 months and complete resolution of pretherapeutic symptoms without recurrence.

MACULAR DEGENERATION

Macular degeneration is a common disease of the eye, characterized by deterioration of the central area of the retina known as the macula and resulting in blurry, distorted, or lost central vision. Age-related macular degeneration (AMD) is a major cause of visual impairment in the United States for people more than 65 years of age and is the leading cause of legal blindness in Western countries.[38] Approximately 30 million people worldwide are blind because of this disease.[39] The 2 common forms of macular degeneration are dry and wet. Dry AMD is the most common form, accounting for 90% of all AMD. The classic lesion in the dry form is geographic atrophy, which causes

Table 1
Summary of selected treatment results of keloids

Study	No. Patients	Cohort	No. Lesions	Dose	Response Rate (%)	Notes/Findings
Jiang et al,[32] 2018	29	HDR brachytherapy	37	18 Gy/3 fx	91.9	All patients started with recurrent keloids
Kim et al,[33] 2015	28	WLE + RT	39	12 Gy/3 fx (group 1) or 15 Gy/3 fx (group 2)	50 (group 1), 50 (group 2)	Recurrence was indirectly assessed by observing for reelevation of keloids
Shen et al,[34] 2015	568	WLE + RT	834	18 Gy/2 fx	90.41	Electron beam of 6 or 7 MeV was used
Emad et al,[35] 2010	26	WLE + RT (group A), cryotherapy + intralesional steroid (group B)	76	12 Gy/3 fx (group A)	70.4 (group A), 68.8 (group B)	Treatment using surgery plus immediate radiotherapy was more efficacious and safer than cryotherapy and adjuvant steroid injection
Malaker et al,[36] 2004	64	RT alone	86	37.5 Gy/5 fx	97	Unresectable keloids; 63% satisfied with outcome
Lo et al,[37] 1990	199	WLE + RT	354	2–20 Gy/1 fx	87 (≥9 Gy); 43 (<9 Gy)	Difference nonsignificant statistically
Borok et al,[27] 1988	250	WLE + RT	393	4–16 Gy/varied fx	98	Excellent cosmetic results in 92% of pts; recommend 12 y in 3 fx

Abbreviations: fx, fractions; HDR, high dose rate; RT, radiation therapy; WLE, wide local excision.

severe central visual loss (Fig. 2). In most cases, this loss is self-limited and causes no dramatic visual deterioration. No treatment can reverse the progression of this type of AMD. Approximately 20% of patients who have dry AMD progress to wet AMD over a 5-year period.[40] Wet macular degeneration is less common but is more severe than the dry form. It accounts for 10% of all AMD but results in 90% of all blindness from the disease. Wet macular degeneration is characterized by choroidal neovascularization macular degeneration, which is the development of abnormal vessels beneath the retinal pigment of the retina. These vessels can bleed and eventually cause macular scarring, resulting in profound loss of central vision. The pathophysiology of macular degeneration is not completely understood. Some of the causal factors that have been proposed include primary retinal pigment epithelium, Bruch membrane senescence, genetic susceptibility, primary ocular perfusion abnormalities, and oxidative injury.[41] Several therapeutic strategies are available to treat macular degeneration, but the progression of disease often cannot be reversed. Laser treatment has shown some potential benefit and may halt or decrease vision loss. Often, a scar is left and may produce a permanent loss of vision secondary to damage of the overlying retina.

Subretinal surgery may be an option but does not always give optimal results.[42] In photodynamic therapy, a light-activated drug, verteporfin, is given intravenously and a laser is used to close the abnormal vessels while leaving the retina intact.[43] Intravitreal anti–vascular endothelial growth factor (VEGF) drugs are the mainstay of treatment, with multiple approved drugs, including bevacizumab, ranibizumab, and aflibercept. They function by inhibiting angiogenesis and permeability.[44]

The treatment with ionizing radiation is to prevent the proliferation of endothelial cells necessary for neovascularization as well as inhibiting inflammation and fibrosis. It induces the regression of vascular tissue and inhibits growth of new blood vessels. Some advantages in treating AMD with low-dose radiotherapy include the absence of iatrogenic mechanical or laser damage, absence of systemic side effects, and absence of local side effects caused by ocular injection. An additional advantage for patients who have primarily large, occult choroidal neovascularization is that radiation can be used for this type of macular degeneration. One of the major potential side effects is radiation retinopathy, which is dose dependent.[45] Some of the common techniques include 6-MV to 9-MV photons with a lateral-port half-beam technique, episcleral brachytherapy with strontium-90 plaques, and more recently proton

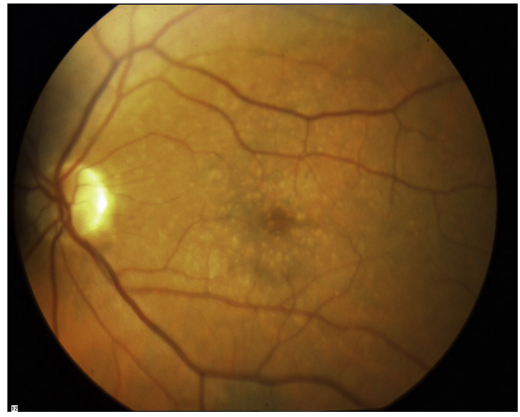

Fig. 2. Macular degeneration with atrophic-appearing macula.

therapy, kilovoltage stereotactic radiotherapy (SRT), and epimacular brachytherapy (EMBT).

External beam SRT allows more accurate delivery of dose than a half-beam technique with external beam radiotherapy would, with potential benefits of allowing for dose decline and dose escalation. Multiple commercial systems are available. SRT was evaluated in a randomized trial of 16-Gy or 24-Gy SRT using the IRay system or sham radiation therapy in patients previously treated with anti-VEGF injections. Patients treated with radiation had a significant reduction in intravitreal injections over 2 years, and only 1% of eyes had microvascular changes related to radiation that possibly affected vision.[46] Long-term follow-up showed 30.3% of cases treated developed retinal microvascular abnormalities, although this contributed to vision loss in only 5 out of 37 cases.[47]

EMBT uses an intraocular probe containing a radioactive source that emits β radiation. A randomized trial did not support use of EMBT with anti-VEGF versus VEGF alone in a randomized trial.[48] A recent trial treated patients with a combination of proton therapy and anti-VEGF with ranibizumab, the first study using this combination therapy. Proton therapy has an advantage of limited distal dose because of the properties of the Bragg peak. There was no change in visual acuity at 24 months, but, for newly diagnosed patients, there was some improvement in visual acuity; fewer injections of ranibizumab were noted than with the standard protocol and no cases of radiation retinopathy were reported at 3 years.[49]

Although several clinical studies have shown some benefit with radiation therapy, conclusive data have not been established despite multiple trials, many of which were completed before anti-VEGF therapy became standard-of-care treatment. **Table 2** presents some of the recent radiation treatment results.

ORBITAL PSEUDOTUMOR

Orbital pseudotumor, also called idiopathic orbital inflammation, is an inflammatory process of unknown cause that sometimes results in a palpable mass resembling a tumor. It can affect the orbit in its entirety or parts of the orbit, such as the extraocular muscles, lacrimal gland, fat, and sclera. In addition to a palpable mass, orbital pseudotumor may present as pain, edema, proptosis, chemosis, ophthalmoplegia, and diplopia.[57] It can manifest acutely or chronically, and it presents bilaterally around 25% of the time. Distant metastases are rare, but local recurrence is common. To date, there have been no data to suggest a distribution based on age, gender, or race. Orbital pseudotumor is generally a diagnosis of exclusion. Other causes to rule out include neoplasms, infection, Graves ophthalmology, ocular lymphoma, sarcoidosis, orbital myositis, scleritis, Sjögren disease, and Wegener granulomatosis. An appropriate work-up includes a physical examination, medical history, laboratory work, and imaging.[58] Usually, there are nonspecific markers of inflammation found on serologic studies. Computed tomography (CT) scans may show soft tissue swelling and inflammation, but contrast-enhanced MRI with fat saturation is recommended. Some clinicians argue a biopsy is not required for diagnosis, but it is often obtained in order to rule out other causes. Histopathology shows infiltrative inflammatory cells that can be further classified as lymphoid (necessitating flow cytometry to rule out lymphoma), granulomatous, or sclerosing.[59] Besides a biopsy, a diagnosis can be confirmed by an improvement of symptoms on a trial of systemic corticosteroids, which then are slowly tapered. Although most patients experience an improvement, only approximately 50% of patients have a complete resolution of symptoms. Radiation therapy can be

Table 2
Summary of selected treatment results of macular degeneration

Study	No. Patients/Eyes	Treatment	Results	Notes
Park et al,[49] 2012	6	24 CGE proton therapy/2 fx 24 h apart with 4 monthly injections ranibizumab	No change VA at 24 mo; no radiation retinopathy at 3 y	Fewer injections of ranibizumab than would be standard
Jackson et al,[46] 2015	230	16 Gy vs 24 Gy SRT vs sham RT; all received concurrent ranibizumab	SRT reduces intravitreal injections at 2 y; 30.3% of cases developed microvascular abnormalities at 3 y; no improvement VA with SRT	—
Jackson et al,[48] 2016	363	Ranibizumab monotherapy vs 24 Gy EMBT + ranibizumab	No difference in PRN ranibizumab injections, mean VA change −4.8 vs −0.9 letters favoring EMBT, proportion of patients losing fewer than 15 letters 84% EMBT vs 92%	One patient with RT-induced retinal vascular abnormality; safety good but only 12 mo follow-up
Jaakkola et al,[50] 2005	86/88	15 Gy 12.6 Gy (Sr90)	VA loss >3 lines: Control 84% RT 80%	No long-term benefits (at 3.5 mo)
Marcus et al,[51] 2004	88 (randomized RT vs no RT)	20 Gy/fx	At 6 mo, 26% vs 43% 3-line VA loss At 12 mo, 42% vs 49% 3-line VA loss	RT had a short-term benefit in preserving visual acuity
Prettenhofer et al,[52] 2004	80	14.4 Gy 25.2 Gy	VA deteriorated in 85% (14.4 Gy) and 65% (25.2 Gy) of patients	After 4 y, irradiated eyes were similar to the natural course of the disease
Hart et al,[53] 2002	203 (randomized to RT vs no RT)	12 Gy/6 fx	RT better than control group but not statistical significance	Negative trial
Valmaggia et al,[54] 2002	161 (prospective double-blinded study)	1 Gy/4 fx vs 8 Gy/4 fx vs 16 Gy/4 fx	No difference among treatment groups. Classic CNV, initial VA >20/100 benefited more from higher doses	Higher doses resulted in stabilization of the VA without any difference in efficacy
Schittkowski et al,[55] 2001	118/126	20 Gy in 2 wk	VA decreased but most had decreased metamorphopsia and increased color and contrast perception with RT	8 patients reported epiphora, and 4 patients complained of transient sicca syndrome
Kobayashi & Kobayashi,[56] 2000	101 (randomized RT vs no RT)	20 Gy in 2 wk	Smaller choroidal neovascular membrane or better baseline VA benefited. Mean VA 20/168 vs 20/327	RT seems to have a beneficial effect in selected patients

Abbreviations: CGE, cobalt gray equivalent; CNV, choroidal neovascularization; PRN, as needed; VA, visual acuity.

considered when there is a lack of response to steroids, a recurrence after steroids, or an inability to tolerate steroids. Treatment is delivered using en face electron therapy, opposed lateral field three-dimensional conformal radiation therapy, or intensity modulated radiation therapy (IMRT). **Fig. 3** shows a right orbital pseudotumor treated with IMRT. Radiation doses range from 2000 to 3000 cGy given at 180 to 200 cGy per fraction. **Table 3** provides a summary of radiation therapy results.[60–67] Using proper radiation techniques, such as lens shielding, these studies show a good local control rate with minimal morbidity. patients who are older at the time of diagnosis and who have a complete response to radiation therapy were significantly less likely to experience a recurrence of symptoms. Outside of radiation therapy, other treatment modalities include immunosuppressive agents (cyclosporine, tacrolimus), cytotoxic agents (azathioprine, cyclophosphamide, methotrexate), biologic agents (rituximab, infliximab), and surgery for lesions that are well localized or lesions that are refractory to other treatment modalities.[57,68] However, although an orbital pseudotumor may start as a benign process, it may progress and compress critical orbital structures, such as the optic nerve, leading to optic nerve atrophy and vision loss.

PTERYGIUM

A pterygium is a triangular wedge, usually of medial nasal conjunctiva, that extends onto the cornea. It is sometimes confused with pinguecula, which is a similar disorder that arises from but remains confined to the conjunctiva. The name pterygium describes the shape of the tissue, which resembles a wing. Although considered a benign proliferation of subconjunctival fibroblasts, pterygia can block the visual axis, directly reducing visual acuity, and induce astigmatism. It also is of concern to patients because of the abnormal appearance of the eye and often is associated with redness and irritation, which can make wearing contact lenses uncomfortable. Pterygia occur most commonly in tropical regions where there is a high rate of sun exposure.[69] Lower rates of pterygium are associated with using sunglasses, using prescription glasses, and smoking cigarettes.[70] Diagnosis is made clinically by

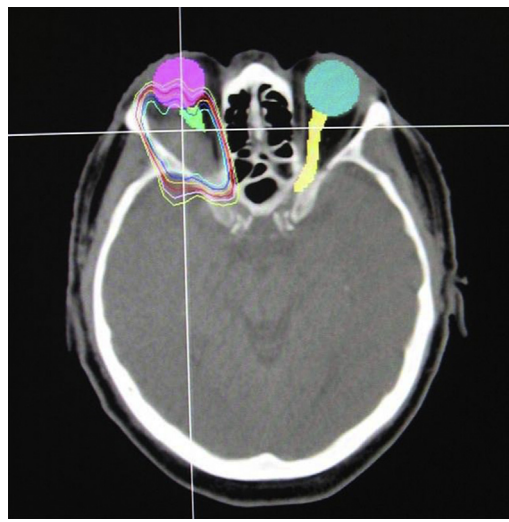

Fig. 3. A right orbital pseudotumor treated with IMRT.

Table 3
Summary of selected treatment results of orbital pseudotumor

Study	No. Patients (Orbits)	Radiation Therapy Treatment	Outcomes	Comments
Mokhtech et al,[67] 2018	20 (24)	20 Gy (4.8–40 Gy) at 2 Gy (0.8–2 Gy)/fx	40% CR, 35% PR, 20% SD, 5% DP	Most common toxicities; cataracts (10%) and dry eye (10%)
Prabhu et al,[66] 2013	20 (26)	Median 27 Gy (25.2–30.6 Gy)	35% PR, 5% CR with reduction in steroids, 45% CR with cessation of steroids	Older age and complete clinical response to RT reduced symptom recurrence
Matthiesen et al,[65] 2011	16 (20)	Mean 20 Gy (14–30 Gy)	25% CR with reduction in steroids, 56.3% CR with cessation of steroids, 18.7% required same steroid dose	3 patients received orbital retreatment. No increased morbidity noted on follow-up
Keleti et al,[64] 1992	28 benign, 20 lymphoma, 17 indeterminate	20–30 Gy/10–15 fx	RT efficacious in all groups. 84% DFS at 42 mo med FU; benign group did better	Cataracts developed in 46% of the patients treated with anterior-posterior fields
Lanciano et al,[63] 1990	23 (26)	20 Gy/10 fx	Overall CR 66%; soft tissue swelling 87% CR; proptosis 82% CR; extraocular dysfunction 78%; pain 75% CR; durable LC 77% (median FU 41 mo)	70% recurrence during steroid taper, 17% no response to steroids, 13% no steroids treatment before RT
Mittal et al,[62] 1986	20 benign, 12 lymphoma, 10 indeterminate	Mean 25 Gy	100% ultimate control rate	Very high local control, minimal morbidity
Austin-Seymour et al,[61] 1985	20 (20)	Mean 23.6 Gy (20–30 Gy)	75% complete resolution	Most steroid-refractory disease; no complications
Sergott et al,[60] 1981	19 (21)	10–20 Gy	Improvement 74% (decreased proptosis, lid edema, and conjunctival injection; improved ocular motility and VA	79% recurrence during steroid taper before RT. RT responders remained recurrence free × 25 mo FU with no further steroids

Abbreviations: CR, complete response; DFS, disease-free survival; DP, disease progression; FU, follow-up; LC, local control; PR, partial response; SD, stable disease.

recognizing the classic appearance of a wedge-shaped growth onto the cornea. **Fig. 4** shows a typical medial (nasal) pterygium that is extending onto the cornea. There is no commonly accepted scale for grading the severity of pterygia. Although surgery has been the primary therapy for this condition, recurrence rates are high, at 20% to 67%.[71] Medications can be used for symptomatic relief but do not stop progression. Postoperative radiation using a strontium-90/yttrium-90 beta-emitting contact applicator has been shown to reduce recurrence rates significantly, to 20% or less,[71,72] and in a randomized trial has shown to be significantly more effective than observation, with recurrence rates of 68% versus 0% with radiation therapy at a median follow-up of 14 months.[73]

Because pterygium is often considered a trivial problem, most datasets are small, and more evidence-based data are needed. The largest study analyzing the use of postoperative radiation in the treatment of pterygium was performed by Van den Brenk,[74] who found that using prophylactic postoperative beta radiation treatment with a strontium-90 applicator resulted in recurrences of only 1.4% of 1300 pterygia in 1064 patients (**Table 4**). Treatment consisted of 8 to 10 Gy given immediately after surgery followed by 2 more treatments at 7-day intervals. Local control is best when the radiation is given immediately after surgery,[75] with most published protocols requiring treatment within 3 days.[76–78] A retrospective study comparing high-dose (n = 28; 40 Gy in 2 fractions 1 week apart) and low-dose (n = 67; 20 Gy in a single fraction) strontium-90 treatment of pterygium suggested a benefit to higher doses. All recurrences (11) occurred in the low-dose group, with older age a marginal negative predictor of recurrence in the low-dose group, with no severe complications, including scleromalacia, occurring in either dose group with a median follow-up of 10 years.[79]

Kal and colleagues[80] performed a meta-analysis and found that recurrence rates for pterygia were less than or equal to 10% with a BED greater than or equal to 30. However, 2 randomized trials comparing dosing regimens in pterygia did not show improved control with higher doses. The first randomized patients to 30 Gy in 3 fractions over 15 days or 40 Gy in 4 fractions in 22 days, with no significant difference in 2-year local control (85% vs 75%) and no serious acute or late complications in either arm.[78] The second randomized patients to 35 Gy in 7 fractions (3 d/wk) or 20 Gy in 10 fractions (5 d/wk) using strontium-90 applicators. There was no significant difference in crude recurrence rates (7.1% vs 6.7%) or pterygium control (92.3% vs 93.9%; $P = .616$). Excellent or good cosmetic effect was favored in the lower-dose group (92% vs 70%; $P = .034$), and scleromalacia was more common in the high-dose group (5.6% vs 0%; $P = .17$).[77]

Other dosing schedules are also effective, as shown in **Table 4**. The primary use of radiation therapy as a nonsurgical treatment of pterygium also has been successful in

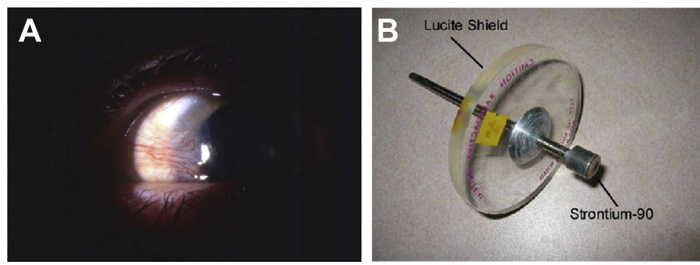

Fig. 4. Pterygium of the left eye. (*A*) The medial conjunctival tissue extends laterally onto the cornea, affecting the patient's vision. (*B*) The strontium eye applicator.

Table 4
Summary of selected treatment results of pterygium

Study	No. Lesions	Dose	Recurrence (%)	Comments
Viani et al,[77] 2012	216	5 Gy × 7 vs 2 Gy × 10 (randomized)	3-y LC 93.8% (35 Gy) vs 92.3% (20 Gy), $P = .616$	Significant benefit in lower group for cosmetic effect ($P = .034$), photophobia ($P = .02$), irritation ($P = .001$), scleromalacia ($P = .017$)
Nakamatsu et al,[78] 2011	74	30 Gy × 3 (15 d) vs 40 Gy × 4 (22 d) (randomized)	2-y LC 85% (30 Gy) vs 75% (40 Gy); no significant difference	No serious acute/late toxicity in either arm. Supports lower dose
Yamada et al,[79] 2011	95	40 Gy (n = 28) vs 20 Gy (n = 67) (retrospective)	Crude rates 0 vs 16.4	Suggests benefit for higher doses, including for larger size pterygia and in younger patients
Schultze et al,[87] 1996	64	5 Gy × 6	12.5 (median FU 5.5 y)	0% recurrence for primary lesions treated within 3 d after surgery
Paryani et al,[88] 1994	825	10 Gy × 6	1.7 (median FU 8 y)	No complications with higher doses
Dusenbery et al,[76] 1992	36 (recurrent lesions)	24 Gy (median) in 2–4 fractions	8	36% complications, higher if previously irradiated
Monselise et al,[89] 1984	135	6 Gy × 3	7.4	Relatively low doses
Alaniz-Camino,[72] 1982	485	7–8 Gy × 4	4.3	—
Van Den Brenk,[74] 1968	1300	8–10 Gy × 3	1.7	Largest series reported

reducing the size of pterygia.[81,82] Acute self-limited side effects of radiation include ocular irritation, scleral atrophy, and neovascularization. No late complications or side effects have been reported with fractionated therapy. Major complications, such as severe scleromalacia and corneal ulceration, have been seen in 4% to 5% of patients receiving single fractions of 20 to 22 Gy given postoperatively,[83] but rates can be lower or even absent in lower-dose treatments.[77,78] Significant complications have been reported in patients who received reirradiation.[76] Alternative methods for preventing recurrence include intraoperative or postoperative mitomycin C, postoperative thiotepa solution, postoperative 5-fluorouracil, and conjunctival autografting.[84–86] Successful prevention of pterygium involves educating the public to wear sunglasses, particularly those who spend significant time outdoors.

PEYRONIE DISEASE

Named after the personal physician of King Louis XVI of France, Francois Gigot de la Peyronie, who in 1743 described "rosary beads" of scar tissue extending the full length of the dorsal penis, Peyronie disease (PD) occurs in 3% to 5% of men between the ages of 40 and 70 years.[90,91] However, the true prevalence of PD may be underestimated because some men may are reluctant to report because of embarrassment and some attribute the condition to aging.

Also known as induratio penis plastica, PD is a localized connective tissue disorder characterized by severe curvature of the erected penis.[92] Scarring and formation of plaques that do not stretch with erection are thought to occur as a result of penile injury, trauma, or other nonspecific inflammation of the tunica albuginea.[90,91] Patients may initially present with painful erections, curvature, distortion and shortening of the penis, and psychological issues caused by associated physiologic or functional impotence.[93,94] Some degree of erectile dysfunction, either as a direct result of or in association with PD, has been observed in as many as 40% of affected men.[93]

Diagnosis is usually apparent from patient history and penile examination. A well-defined plaque or induration can be palpated on physical examination, especially in classic PD. Several imaging modalities have been applied to diagnose PD, including ultrasonography, plain radiography, CT, and MRI. Ultrasonography has the highest sensitivity for plaques in the tunica albuginea compared with other methods.[95]

Disease stabilization may take up to 6 months and occurs in approximately half of the cases. Reassurance alone is appropriate for patients who have minimal pain or deformity. PD has an overall spontaneous regression rate of 13%.[96] Penile pain occurs primarily during erection and usually resolves with 12 to 24 months of initial onset. Mulhall and colleagues[97] showed about 90% of 246 men who did not receive medical or surgical intervention reported complete resolution of pain at a mean follow-up of 18 months. At this moment, there are no placebo-controlled randomized trials that evaluate conservative therapy to reduce inflammation and pain in early-stage PD. Therefore, treatment of PD is symptom directed and it can include pentoxifylline, vitamin E, ibuprofen, and colchicine.[91,96] In addition to oral therapies, intralesional drug therapy is another potential option. Collagenase clostridium histolyticum is the only intralesional treatment approved by US Food and Drug Administration (FDA) for PD.[98] Other potential options include interferon alfa-2b, verapamil, and corticosteroids. Topical therapy is not recommended for the treatment of PD outside of clinical trials. Surgery to straighten the penis is indicated if the curvature interferes with sexual intercourse, and penile prosthesis is the treatment of choice for PD with erectile dysfunction.[91] Penile traction therapy has shown some efficacy in small case studies.[99,100] Iontophoresis, electromotive drug administration, has also been used but it needs further studies.[101] Extracorporeal shockwave therapy is currently under investigation.

Low-dose radiation therapy has been used to relieve pain and to improve plaque resolution.[93,102,103] External beam radiation, electron, and brachytherapy techniques using isotopic molds have been reported, with doses ranging from 250 to 2000 cGy.[92,96,104] **Table 5** presents some of the results of radiation therapy. The patient must be counseled, and special care must be given to gonadal protection and shielding. The potential for either spontaneous regression or progression must be considered. **Fig. 5** shows a patient who has PD being treated with electrons. The wax-coated shields protect the scrotum and the base of penis.

Table 5
Summary of selected treatment results of Peyronie disease

Study	No. of Patients	RT Treatment	Outcome	Comments
Pietsch et al,[102] 2018	83	32 Gy in 8 fx superficial x-ray	78% patients reported some response. 47% had symptom regression. Only 7% reported PD progression. Penile curvature was improved in 49% of patients	71% reported substantial pain relief. Transient erythema in 38.6% and 9.6% reported transient or chronic dryness. No severe side effects
Niewald et al,[103] 2006	154	30 or 36 Gy at 2 Gy per fx Co-60 gamma rays or 4-MV/6-MV photon beams	Improvement of deviation in 47%, reduction of number of foci in 32%, reduction of size of foci in 49%, and less induration in 52%. 50% reported pain relief	28 patients with mild acute dermatitis and only 4 patients with mild urethritis. No long-term side effects
Incrocci et al,[93] 2000	179	13.5 Gy/9 fx x-rays or 12 Gy/6 fx electrons	Pain relief 83% Deformity improved 23% Sexually active 72% Erectile dysfunction 48% Dissatisfied 49%	82% responded to questionnaire regarding sexual function. 29% had post-RT penile surgery
Koren et al,[92] 1996	265	Iridium-192 moulage	Success 66.4% fibromatous foci: CR 9% PR>50%: 29.7% PR<50%: 27.7% Pain relief: 61.4%	Pain relief and regression of deviation correlated with improved erectile function. 41 pretreated with potassium p-aminobenzoate, vitamins, topical corticosteroids, or RT
Rodrigues et al,[90] 1995	38	9 Gy/5 fx x-rays. Reirradiation for minimal response: 9 Gy/5 fx (16 patients)	Pain relief 66% (CR 12%, PR 54%). Improved curvature 40% Sexual function 47% Plaque: CR 24%, PR 8% Reirradiated group: pain relief 25% Improved curvature 28% Sexual function 28%	No RT morbidity Vitamin E effects not clear
Viljoen et al,[94] 1993	98	25 Gy (10 × 2.5 2.5 Gy), x-rays	Pain relief: 84% Angulation improved: 38.6% Sexual function: 87.2%	Progression in 18% Decline in sexual activity seemed age related

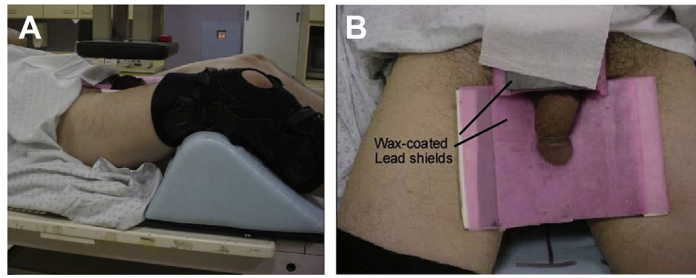

Fig. 5. Radiation treatment setup for Peyronie disease. (*A*) The patient is treated in a supine frog-legged position. (*B*) With proper lead shields, only the penis is exposed to radiation. (*Courtesy of* J. Mira, MD, San Antonio, TX.)

TRIGEMINAL NEURALGIA

Trigeminal neuralgia (TN) is characterized by recurrent brief episodes of unilateral electric shock–like pains, abrupt in onset and termination, in the distribution of 1 or more divisions of the trigeminal nerve (V1, ophthalmic; V2, maxillary; V3, mandibular), typically triggered by innocuous stimuli. TN is uncommon, with an annual incidence of 4 to 13 per 100,000 people.[105] It affects women more than men. Most cases of TN are caused by compression of the trigeminal nerve root by an aberrant loop of an artery or vein, usually in the root entry zone.[106] According to the International Classification of Headache Disorders, Third Edition (ICHD-3), TN is divided into classic TN, secondary TN, and idiopathic TN.[107] Classic TN includes cases caused by vascular compression. Secondary TN is caused by an underlying disease such as multiple sclerosis or a tumor along the trigeminal nerve. TN without clear cause is categorized as idiopathic.

TN is usually unilateral but it is bilateral occasionally. V2 and V3 subdivisions are more commonly involved than V1. Autonomic symptoms may include lacrimation, conjunctival injection, and rhinorrhea.[108] The diagnostic criteria for TN are listed in the ICHD-3.[107] It is recommended that all patients with suspected TN get brain MRI with and without contrast to look for an underlying cause such as brain lesion, demyelinating disease, or vascular compression. The preferred imaging modality is high-resolution MRI with thin cuts through the region of the trigeminal ganglion and heavy T2 weighting, a constructive interference in steady-state fusion study.[108] If a patient cannot get MRI, a CT cisternogram can be obtained. Sometimes TN can be confused with postherpetic neuralgia. Isolated involvement of the V1 subdivision is less than 5% in TN but very common in postherpetic neuralgia.[109] Dental causes of pain sometimes can be misdiagnosed as TN. Dental pain is usually continuous, intraoral pain that is dull or throbbing.

Carbamazepine is the first-line initial treatment of TN. Several randomized trials have shown its effectiveness (200–2400 mg daily).[110–112] Some studies suggest oxcarbazepine, clonazepam, gabapentin, baclofen, and lamotrigine can also be beneficial. Botulinum toxin injections may be beneficial for patients who do not respond to first-line medical therapies.[113] For patients with medically refractory TN, surgical options include microvascular decompression, rhizotomy with radiofrequency thermocoagulation, mechanical balloon compression, glycerol injection, and peripheral neurectomy and nerve block.[114,115]

Stereotactic radiosurgery (SRS) is a minimally invasive option for TN. It is preferred for patients with medically refractory TN who are not good surgical candidates. It aims at the proximal trigeminal nerve root. A typical dose of 70 to 90 Gy in a single fraction is prescribed to the 100% isodose line via a 4-mm cone. Stereotactic frame and high-

Table 6
Summary of selected treatment results of trigeminal neuralgia

Study	No. of Patients	Type of TN	RT Treatment	Outcome	Side Effects
Regis et al,[121] 2016	497	Classic	GKS, 70–90 Gy	91.75% pain free in a median time of 10 d (range 1–180 d). Probabilities of remaining pain free without medication at 3, 5, 7, and 10 y were 71.8%, 64.9%, 59.7%, and 45.3%	Hypesthesia rate at 5 y was 20.4%, but remained stable until 14 y. Very bothersome facial hypesthesia was reported in only 3 patients
Lucas et al,[118] 2014	446	Mixed	GKS, 80–97 Gy	Pain relief of BNI 1–3 at 1, 3, and 5 y in 86.1%, 74.3%, and 51.3% of type 1 patients; 79.3%, 46.2%, and 29.3% of type 2 patients; and 62.7%, 50.2%, and 25% of atypical facial pain patients	Only 13% of patients with atypical facial pain achieved BNI 1 response; 42% of patients developed post-GKS radiation surgery trigeminal dysfunction
Young et al,[122] 2013	315	Mixed	GKS, 90 Gy	170 patients (71.4%) were pain free and 213 (89.5%) had at least 50% pain relief	Eighty patients (32.9%) developed numbness after GKS, and 74.5% of patients with numbness had complete pain relief
Marshall et al,[123] 2012	448	Mixed	GKS, 80–97 Gy	By 3 mo after GKS, 86% of patients achieved BNI 1–3 pain scores, with 43% of patients achieving a BNI 1 pain score	26% patients reported facial numbness; 28% reported a post-GKS procedure for relapsed pain, and median time to next procedure was 4.4 y
Kondziolka et al,[124] 2010	503	Idiopathic	GKS, 80 Gy	Significant pain relief was achieved in 73% at 1 y, 65% at 2 y, and 41% at 5 y 43% of 450 patients reported recurrent pain 3–144 mo after initial relief (median 50 mo)	10.5% (53) developed new subjective facial paresthesia; these symptoms resolved in 17 patients
Smith et al,[125] 2011	179	Mixed	LINAC, 70–90 Gy	134 (79.3%) experienced significant relief at a mean of 28.8 mo (range, 5–142 mo). Average time to relief was 1.92 mo (range, 0–6 mo)	Numbness, averaging 2.49 on a subjective scale of 1–5, was experienced by 49.7% of the patients
Herman et al,[119] 2004	18	Recurrent	GKS, median dose of 75 Gy for first SRS and 70 Gy for second SRS	Among those with recurrent pain after initial SRS, 14 patients (93%) achieved excellent or good pain outcomes after repeat SRS	Two patients (11%) reported new or increased facial numbness after retreatment
Hasegawa et al,[120] 2002	31	Recurrent	GKS, median dose of 75 Gy for first SRS and 64 Gy for second SRS	After second SRS, 5 patients had an excellent response, 8 had a good response, 10 had a fair response, and 4 had a poor response. 48% achieved complete pain relief	2 patients (7.4%) experienced new sensory symptoms after first SRS, and 3 (12.7%) experienced new sensory symptoms after second SRS

Abbreviation: GKS, Gamma Knife radiosurgery.

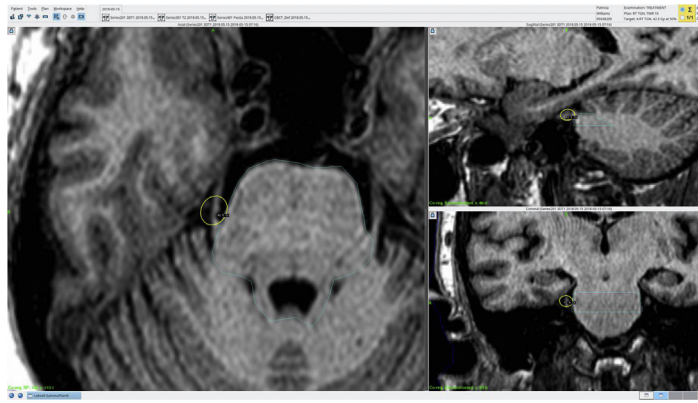

Fig. 6. High-resolution MRI with the target trigeminal nerve clearly identified for Gamma Knife radiosurgery treatment planning.

resolution MRI brain are generally required for treatment planning. The high-dose radiation causes axonal degeneration and necrosis. The major complication is facial numbness/paresthesia (<10%).[116] Both Gamma Knife SRS and linear accelerator (LINAC) SRS have been used. The typical response rate is 60% to 70%. The only prospective controlled trial that included 100 patients with at least 12-month follow-up showed that 83% patients were pain free at last visit. Six patients reported facial paresthesia and 4 patients reported hypesthesia.[117] There are more than 60 retrospective studies that showed the effectiveness of SRS for TN. Lucas and colleagues[118] described an Internet-based nomogram that predicts durability of pain relief based on pretreatment and posttreatment factors following SRS. Barrow Neurologic Institute (BNI) pain scale was used. Some studies suggest that repeat SRS after recurrent TN can still be beneficial with a reasonable safety profile.[119,120] **Fig. 6** shows an example of target delineation on MRI brain. **Table 6** provides a summary of the major studies.

SUMMARY

Although the evidence for radiation therapy efficacy on benign disease is largely retrospective, it has been shown to be quite effective as one of the treatment modalities for several benign conditions. In many cases, patients benefit from adjuvant radiation therapy in a multidisciplinary approach. By following the general radiation safety principles and established guidelines, the risk of major radiation therapy toxicity is low because only lower doses and smaller fields of radiation are normally used than those used to treat cancer. Most patients experience no or very few symptomatic side effects and achieve good long-term control and improved quality of life. However, clinicians must still carefully balance all of the potential risks against the benefits before proceeding with radiation therapy, especially in younger patients and children, who are expected to live long and may be at a higher risk of potential secondary malignancies and other late sequelae.

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