Review Article - Narrative Review

Taiwan J Ophthalmol 2025;15:62-72

Access this article online

Quick Response Code:

Website: http://journals.lww.com/TJOP

DOI: 10.4103/tjo.TJO-D-24-00108

Innovations in brachytherapy

Joshua Lim[1,2,3], Alvin Wei Jun Teo[1], Tian Rui Siow[4], Kwang Ping Chan[4], Gavin Siew Wei Tan[1,2,3]*

Abstract:

Plaque brachytherapy plays an essential role in the management of intraocular tumors, allowing localized treatment while minimizing damage to surrounding structures. Since the earliest reports of sutured radon seeds used in glioma treatment in the 1920s, plaque brachytherapy in the field of ocular oncology has continued to expand and improve significantly. Today, a wide variety of ocular conditions, both oncologic and not can be treated using plaque brachytherapy. Continued innovations have also improved clinical safety and efficacy for both providers and patients alike. The use of new radioisotopes, combined with continued refinement in plaque design and applicators alongside radiation dose planning are some of novel methods used to maximize coverage and reduce radiation exposure to critical eye structures. In this paper, we will discuss promising future developments that will continue to revolutionize treatment.

Keywords:

Brachytherapy, innovations, ocular brachytherapy, ocular tumors

Introduction

Brachytherapy utilizes radioactive isotopes set in a plaque or an applicator to deliver radiation to tumors. It plays an important role in preserving sight and survival in patients with ocular tumors. It has improved significantly since the earliest reports featuring sutured Radon seeds for treatment of glioma.[1] A wide variety of ocular conditions can now be addressed using plaque brachytherapy.[2-4] Plaques are sutured onto the external sclera in close proximity to tumors to deliver treatment doses of radiation. Innovations in the field today focus on optimization of radioactive dose delivery through accurate plaque placement, radiation dose planning, expansion into more effective radioisotopes, or even novel surgical or planning strategies to minimize unwanted radioactive side effects. These innovations aim to improve local control and survival outcomes while reducing radiation related complications. This review will explore various aspects of the abovementioned innovations.

Novel Radiation Sources

Earliest radiation sources such as Radon-222, Gold-198, and Cobalt-60 (Co-60) are primarily photon emitters (gamma rays or X-rays). They possess high energy and the inability to be shielded from the ocular surface, resulting in significant radiation complications such as maculopathy, optic neuropathy, exudative retinal detachment and cataract formation.[5] External beam radiotherapy (EBRT) presents an alternative strategy however localizing ocular tumors within the column of radiation (mobile target volume) becomes a challenge. To overcome this, the area of irradiation can be increased, though resulting in relatively higher incidences of anterior segment complications.[6] Impetus towards reducing these complications have spurred development of alternative radioactive sources in brachytherapy. A summary of commonly used radioisotopes is found in Table 1. Radioisotope choice ultimately is dependent on factors such as target volume, dose prescription, implant duration, surrounding collateral structures, and overall plaque design.

[1]Singapore National Eye Centre, [2]Singapore Eye Research Institute, [3]Ophthalmology and Visual Sciences Academic Clinical Programme, Duke-NUS Medical School, [4]National Cancer Centre Singapore, Singapore

***Address for correspondence:**
Prof. Gavin Siew Wei Tan, Singapore National Eye Center, 11 Third Hospital Avenue, 168751 Singapore.
E-mail: gmstansw@nus. edu.sg

Submission: 11-09-2024
Accepted: 04-11-2024
Published: 25-02-2025

How to cite this article: Lim J, Teo AW, Siow TR, Chan KP, Tan GS. Innovations in brachytherapy. Taiwan J Ophthalmol 2025;15:62-72.

Table 1: Commonly used radioisotopes in brachytherapy

Radioisotope	Type	Main decay	Half-life $t_{1/2}$
Cobalt-60	High energy	γ	1925.21 days
Iodine-125	Low energy	γ	59.39 days
Palladium-103	Low energy	γ	17 days
Ruthenium-106	Low energy	β	371.50 days
Strontium-90	High energy	β	28.80 years
Yttrium-90	High energy	β	2.66 days

As alternative low-energy radioisotope strategies emerged, Co-60 ultimately fell out of favor as it was high in energy and could not be shielded externally on the ocular surface, resulting in significant collateral side effects.[7] The impetus towards reducing radiation-induced complications then led to the use of alternative radioactive sources such as Iodine-125 (I-125) and Palladium-103 (Pd-103).

I-125 sources have similar dose penetrations compared to Co-60 but can be easily shielded by a 0.5 mm gold cover, thereby increasing the total radiation absorbed by target tissues while reducing radiation-induced complications.[8] I-125 was therefore the radioactive isotope of choice in the COMS study due to its ability to be totally shielded, markedly reducing the radiation effects not just to collateral tissue, but for the surgeon implanting the plaque as well, whilst still maintaining efficacy in emitting useful amounts of radiation.[9] It is currently the commonest radioisotope used in the treatment of ocular tumors.[10,11]

The impetus toward reducing radiation-induced complications then led to the use of other radioisotopes like Pd-103. It was first described in the 1990s for choroidal melanoma treatment.[12] Low energy gamma photons emitted by Pd-103 are more readily absorbed by adjacent biological tissue compared to I-125, reducing the total amount of radiation being absorbed across ocular tissue.[13] The utility of Pd-103 has been reported in multifocal or large iris melanomas previously deemed curable only by enucleation and in nonadvanced primary multifocal iris melanomas with good outcomes and side effect profiles.[14,15] Modest dose reduction of dosimetry to structures such as the lens, optic nerve, and fovea were noted when Pd-103 was compared to standard I-125 radiation.[13]

Beta radiation sources like Ruthenium-106 (Ru-106) soon emerged with potential to further reduce radiation related complications. As a low-energy emitter, it possesses a much steeper radiation gradient compared to I-125, with dose rates exhibiting dramatic drop offs between 1 mm (110 mGy/min) to 10 mm (10 mGy/min) depth, thereby further reducing risk of collateral damage.[16-18] Studies comparing dose fall off curves between Ru-106 and I-125 have demonstrated that for every millimeter of penetration into tissue, the dose penetration of Ru-106 is threefold faster than that of I-125.[19] As such, Ru-106 is considered over I-125 for primary treatment of shallow tumors with an apex height of no more than 5 mm.[17,20] Many reports have demonstrated its efficacy in this respect with low rates of post radiation side effects.[21-23] Beyond the perceived upper limit of 5 mm, Ru-106 has also been used in adjuvant treatment for large tumors > 5 mm, after tumor resection, to reduce risk of local disease recurrence. Jiang *et al*. found comparable outcomes between tumors <5 mm and >5 mm thickness after treatment with Ru-106.[23]

The isotopes described up to this point mainly utilize low-dose rate (LDR) brachytherapy, involving suturing a radioactive implant to the area of interest and leaving it in place for a few days to achieve treatment effect. High-dose rate (HDR) brachytherapy, on the other hand is a treatment strategy that involves delivering concentrated, high doses of radiation with steeper dose gradients over reduced durations.

Strontium-90 (Sr-90) is the first beta-emitter with HDR properties used in the treatment of ocular tumors.[24] Sr-90 exhibits steep dose drop off properties similar to Ru-106 (100% at 2 mm, 60.8% and 28.9% at 3 mm and 4 mm, respectively), lending its utility to the treatment of surface tumors. Sr-90 applicators have been used to treat pterygia or ocular surface squamous neoplasia (OSSN), with good 5-year local control rates (90.5%) and few complications.[25] The use of combination Sr-/Y-90 applicators have also been described in a group of patients with early pterygia, but did not undergo surgery. Reduction in size, and no progression or recurrences in pterygia have been reported even after extensive follow up.[25] Other studies involving Sr-90 as an adjuvant to pterygium surgery have also reported good postoperative outcomes.[26]

At one time, ophthalmic Strontium-90/Yttrium-90 (Sr-90/Y-90) applicators were commonly and widely used in ophthalmology. It had specific indications and was clinically effective.[27,28] However, the applicators' bulk and 29-year half-life ultimately made it commercially nonviable. Meanwhile, Liberty Vision Corporation developed a novel monoisotopic Y-90 beta disc source (LV ^{90}Y disc, Portsmouth, NH) and two hand-held ophthalmic applicators. Each applicator (iWand A® and iWand P®) contains a receptacle for the radioisotope disc and offers unique capabilities. In 2020, the Y-90 disc was cleared by the United States Food and Drug Administration (FDA) for episcleral treatment of tumors and benign growths.[29] Considered a radiosimilar to a predicate Sr-90/Y-90 device, it is improved due to simplified mono-isotopic

Y-90 isodose calculations, and its shorter 64-h half-life that allows for decay in storage to disposal.

The iWand A® was developed for applications on the anterior portion of the eye. Its nodular head was created to shield beta radiation in all directions, except the anterior aperture [Figure 1]. It comprises a 6-mm Y-90 radioactive disc, mounted within a well surrounded by 2 mm of shielding. Thus, a 10-mm circumference active surface has been placed on the eye for short treatment durations (range 6–13 min for malignant tumors), yielding HDR 25–30 Gy to the prescribed tissue depth. HDR doses and thus treatment durations are converted from LDR standards prior to treatment.

Combination Y-90 disc/Wand A® has been used to treat malignant OSSN and anterior uveal melanomas.[29] The iWand P® applicator is the first light guided, light defined brachytherapy treatment. The applicator tip comprises and well for the disc, which is surrounded by 4 lights. When placed behind, the lights are visible through the dilated pupil, and help guide the Y-90 beta source into place beneath the choroidal neoplasm [Figure 2]. To date, patients have benefited by excellent local tumor control and no short-term side effects.[30] Besides Y-90, other HDR radioisotopes such as selenium-75 (Se-75) and ytterbium-169 (Yb-169) are currently being explored. Larger studies will be needed in the future to evaluate the efficacy and effects of these new isotopes on various ocular tumors.[31,32]

Expanded Indications

Conjunctival tumors

The anti-scarring effects of beta-radiation were first recognized in the 1990s and was proven to be a useful adjuvant in conjunctival-based procedures such as trabeculectomy[33] and pterygium surgery.[34] This gave way to utilizing ionizing radiation as a treatment strategy for OSSN. Beta and gamma radiation were then utilized as an adjuvant therapy for OSSN management[35] following wide local excision to prevent recurrence.[36] Despite initial successes, cryotherapy and targeted immunotherapy gained favor over ionizing radiation as the main adjunct following surgical excision of OSSN.[37,38] However, radiotherapy use as a secondary adjuvant for specific cases is a treatment strategy that has gained renewed interest. In one series, 15 eyes with deep invasive squamous cell carcinoma (SCC) had adjuvant treatment with I-125 following local therapy as an alternative to enucleation. All cases were complex SCCs, having had multiple recurrences following either excisional biopsy (53%) with cryotherapy (33%) or topical immunotherapy (33%). Mean apex doses of 56 Gy over a mean of 132 h was administered. Follow-up duration was 7–96 months after plaque removal. Despite a majority satisfactory tumor control reported, 4 patients eventually required enucleation owing to further progression of the lesion despite brachytherapy.[39] Other groups have described a similar treatment approach with Ru-106. The plaque was administered as an addition to conventional excision and local chemotherapy with OSSN of variable base diameters ranging between 3 and 28 mm. This achieved good tumor control and no recurrences of disease during the follow up period. Radiation induced complications, such as secondary glaucoma or scleral melt were reported.[40]

Anterior segment tumors

Anterior segment tumors originate from the iris or ciliary body and can be benign or malignant. An extensive and comprehensive review of this condition has been covered by Marigo and Finger in 2003.[41] Historically, first-line treatment would include radical surgical resection for focal iris lesions. Widespread or diffuse lesions require radical treatment with wide iridectomy, irdidocyclectomy, or lamellar sclerouvectomy.[42,43] These procedures are morbid, technically complex and extensive, often leading to high rates of complications.[41] Strategies today favor conservative approaches, with

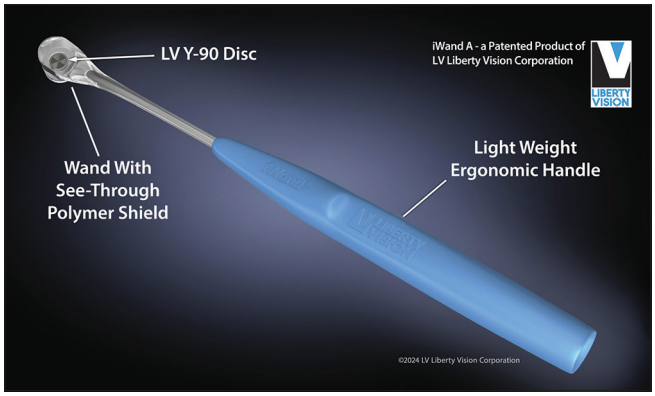

Figure 1: The iWand A®. The device comprises an applicator with an attached Y-90 disc. The radioactive disc is surrounded by custom-made beta radiation shielding material to prevent unwanted lateral absorption of radioactive doses[29]

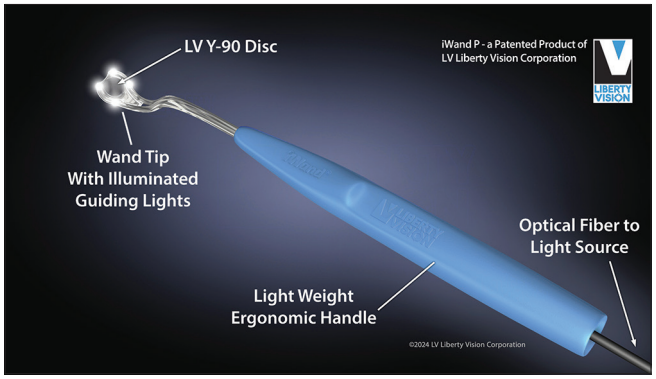

Figure 2: The iWand P®. The device has additional illuminated guide lights surrounding the applicator with attached Y-90 disc. This design allows for intraoperative siting of the radioactive disc via scleral back illumination[29]

brachytherapy playing an essential role in the treatment of these tumors. Shields reported the use of I-125 plaque brachytherapy for the treatment of nonresectable iris melanoma with good rates of tumor regression (93%) during a mean follow-up of 26 months. A large proportion of patients maintained similar or better vision postoperatively. However, complications such as corneal edema without melt, iris vasculopathy that did not amount to frank neovascular glaucoma and various degrees of postradiation cataract formation was documented.[44]

Similarly, Finger reported on using Pd-103 plaques for resectable iris and ciliary body tumors. In these reports, there was an average of 47% reduction in tumor thickness, with no eyes reporting loss of local control and no eye being enucleated after 56 months. In addition, there was no radiation retinopathy or optic neuropathy due to significant distance between the plaque and these ocular structures, and due to radioisotope choice.[45] Other reports have demonstrated similar duration of follow-up with significantly fewer complications, with no radiation retinopathy or optic neuropathy.[15,45]

Alternatives like Ru-106 have also been utilized.[15,46] Ru-106 was found to be effective in the treatment of iris and iridociliary melanoma and had lower measured levels of radiation outside the treatment zone.[21,47] A larger series by Razzaq *et al*. followed 36 patients treated with Ru-106 for a duration of 6.5 years. It reported good tumor outcomes with no incidences of complications like corneal opacities despite average max doses of 53 Gy delivered.[22] Good outcomes were also demonstrated in a recent retrospective review with a follow-up time between 24 and 265 months,[48] and in a systematic review analyzing 12 retrospective and prospective studies comparing I-125, Ru-106, and Pd-103. Unsurprisingly, the multivariate analysis of the systematic review suggested that while higher doses of radiation were associated with cataract and glaucoma, this was especially seen with the use of I-125 plaques.[15,49]

Other innovations such as Finger's amniotic membrane buffer technique have been developed to reduce radiation complications. There, a 0.1 mm thin layer of amniotic membrane is interposed between the gold plaque seed carrier and the cornea have been developed to reduce radiation complications.[50,51] As previously mentioned, innovations such as the iWand A® can decrease the extent of surgery and dwell time needed compared to LDR plaque surgery.[29]

Choroidal hemangioma

Photodynamic therapy has taken a central role in the treatment strategy of most circumscribed choroidal hemangiomas,[52] but challenges remain in addressing the diffuse forms. Choroidal hemangioma has been treated using ionizing radiation since the 1930s and 50s.[5,53] External beam radiotherapy (EBRT) is utilized in the treatment of these lesions associated with serous retinal detachments.[54,55] Treatment with EBRT may require multiple sessions over weeks, and risk collateral damage and secondary malignancies especially in pediatric groups.[55,56] Plaque brachytherapy has been utilized since the early 1970s and 80s.[57] Throughout the years, treatment outcomes and safety profiles of Cu-60,[57] I-125[58] and Ru-106[59,60] have been described. Complete subretinal fluid resolution has been reported so far in all cases treated with brachytherapy. Collateral radioactive damage is circumvented in most studies through the use of low energy beta emitters like Ru-106, with significantly lower apex doses.[59,61] In diffuse choroidal hemangioma associated with Sturge–Weber Syndrome, Yu *et al*. found that brachytherapy applied to the thickest tumor region with Ru-106 isotope (mean doses of 83 Gy) as opposed to targeting the entire tumor can reduce tumor size and subretinal fluid effectively. In their study, despite a higher-than-average scleral contact dose, no complications like scleral melt were reported.[60] Ideal plaque size remains contended, with some utilizing custom-made plaques attempting to encompass the entirety of the tumor with 2 mm margins, and others utilizing smaller plaques targeting just under the thickest point of the tumor. Future directions will likely explore if and how lower doses of radiation will affect tumor response. EBRT studies in circumscribed hemangioma have reported utilizing equivalence doses as low as 16.4 Gy.[62] Novel strategies utilizing HDR and newer isotopes can potentially allow for shorter duration, lower dose treatments, especially in cases of diffuse hemangiomas in the future.

Retinoblastoma

As per the American Brachytherapy Society guidelines, retinoblastomas treated with primary brachytherapy are unilateral, solitary, and anteriorly located.[63] Brachytherapy can be used as adjuvant or secondary treatment in residual or recurrent tumors irrespective of location. Various radioisotopes have been utilized, with recurrence rates between 12% and 17%, reported in some early studies.[64,65] Most recently, Pd-103 has been utilized with good long-term outcomes in a case report by Maheshwari *et al*.[66] Ru-106 has also been combined with intravitreal chemotherapy to treat grade D retinoblastomas with vitreous seeding as first- or second-line therapy following chemoreduction to improve overall outcomes.[67] High globe salvage rates (66.7%) with good therapeutic response were reported in the group with mean tumor heights of 6.0 ± 2.5 mm receiving brachytherapy as first-line treatment. Second-line therapy patients with mean tumor heights of 9.0 ± 1.3 mm, reported higher incidences of

complications such as intraocular hemorrhage and serous retinal detachment.[67] However, it is more convenient that external beam radiation requiring fewer sessions, and avoiding complications such as facial hypoplasia and secondary tumors.[68]

Eyelid tumors

Nonmelanotic eyelid tumors are usually excised; however other factors such as tumor size, site and patient fitness can influence treatment options.[69] EBRT has been an effective treatment modality, especially where there is difficulty obtaining good surgical clearance margins. Brachytherapy remains a viable option in patients who have multiple comorbidities, poor expected cosmesis or who decline invasive surgery.[70] Improved brachytherapy strategies in combination with innovation may lead to more promising outcomes. Recent studies have looked at custom made molds afterloaded with HDR Iridium-192 for the treatment of eyelid basal cell carcinomas. Good survival and cosmetic outcomes have been reported, with common complications consisting of conjunctival and periorbital erythema.[71,72]

Vasoproliferative tumors

Vasoproliferative tumors are potentially vision-threatening benign, vascular lesions associated with widespread exudation and subretinal fluid. Cryotherapy has been the traditional first line of treatment, however has been shown to result in paradoxical massive subretinal exudation, fluid, and hemorrhage with excessive use.[73,74] The efficacy of laser therapy can largely be limited by the peripheral location of the lesion, and no convincing evidence yet exists for the use of anti-vascular endothelial growth factors.[75] To date, Ru-106 and I-125 brachytherapy has been utilized in these lesions with varying degrees of success.[74] Given its steep fall off gradient, Ru-106 allows for higher apex doses while sparing surrounding ocular tissues, but may lead to errors in delivering optimal radiation to the tumor apex.[74] Cohen *et al*. reported the effectiveness of I-125 plaques in the treatment of larger tumors > 2.5 mm thick, due to its higher dose penetration.[76] Apart from its role as a primary modality of treatment, brachytherapy may be used also as salvage therapy in cases that are refractory to initial strategies of treatment.[74] Similarly, cases which remain refractory to brachytherapy as the initial form of therapy may also require a combination approach; more studies in this area are warranted to determine the relative efficacy between these various modalities of treatment.

Retinal capillary hemangioblastoma

Retinal hemangioblastoma are rare benign tumors characterized by a pink, nodular appearance with dilated and tortuous feeding and draining blood vessels. These tumors can exudate involving both the macula and retinal peripheries.[77] There is currently no consensus regarding the optimal treatment, with ablative therapies being commonly used by physicians.[77] The use of plaque brachytherapy in the management of these lesions is sparse in the current literature. One retrospective case series by Kreusel *et al*. reported 25 eyes that achieved lesion resolution following Ru-106 brachytherapy. However, a significant proportion of eyes in that report had worsening visual acuity, recurrence of exudation or tractional retinal detachments.[78] A more recent study by Dalbah *et al*. reported that although 79.1% of patients had tumor inactivation, up to 50% of eyes post Ru-106 brachytherapy treatment required eventual additional vitreoretinal surgery.[79] Ultimately, the role of plaque brachytherapy might be confined to cases which are refractive to laser treatment, or lesions larger than 1.5 mm.[80]

Plaque Innovations

Plaque design

The COMS study standardized the use of the I-125 COMS plaque, comprising of a gold alloy shell and silastic insert designed to fit the eye curvature.[81] The inherent thickness of the plaque required occasional muscle disinsertion to gain access to lesions. Locations near structures like the optic nerve have been addressed by innovations and plaque modifications in the form of a slotted design, allowing the optic nerve sheath to fit into the seed carrier with compensations made to dosimetry planning and radioactive seed arrangement. While optimization of dose distribution remains challenging,[82] 12-year results from Finger's Slotted Pd-103 plaques in the treatment of choroidal melanoma near or touching the optic nerve, however have demonstrated excellent local tumor control rates (98%), reflecting the ability of slotted designs to overcome the physical barrier of the optic nerve to effectively treat posterior pole tumors.[83] This will likely improve as innovations to effectively model and predict dose delivery for eccentric plaque placement and non-uniform isotope loading improve.

Silastic membrane inserts in COMS plaques attenuate about 10% of total radiometric dose due to the membrane having a higher effective atomic number than water.[84,85] Seed placement is also limited by insert positioning and can affect dosimetry calculations, resulting in dose inhomogeneity. Newer plaque designs such as the eye physics (EP) second and third generation plaques (EP, LLC, Los Alamitos, CA, USA) were developed in conjunction with plaque simulator (EP, LLC, Los Alamitos, CA, USA) treatment planning system (TPS).[86] Being thinner than COMS plaques, its placement is potentially less traumatic to recti and better tolerated by patients. These plaques also have an improved design made of 18 carat gold with a treatment face containing

a collimated slotted design, with varying depths of individual slots within the plaque. Radioactive seeds are subsequently glued in, doing away for the need of silastic inserts.[86] This improvement results in radioactive seeds being closer to the tumor, maximizing the inverse square law effect and reducing lateral exposure to surrounding structures.[87] The ability to fix multiple seed onto these plaques allow for lower individual seed intensity by varying the angle of irradiation and offsetting sources at different distances from the sclera.[88] Slot depths deeper towards the center and shallower in the periphery ensures that the collimating gold edges absorb much of the laterally directed radiation from each radioactive seed. Third-generation plaques are designed in tandem with TPS and can be prototyped with stereolithographic 3D printing technology to better fit atypical eyes and optimize lesion coverage.

Optimization of plaque placement

Accurate intraoperative plaque placement is key for delivering optimal doses to tumors. Various techniques such as postoperative ultrasonography,[89] intraoperative transillumination,[90] and postoperative magnetic resonance imaging (MRI)[91] have been described. The use of intraoperative ultrasonography is a straightforward and effective step in providing surgeons real time confirmation of plaque position, especially in more challenging posterior or peripapillary cases.[92] In a series of 117 eyes, Tabandeh *et al*. reported 24% of eyes requiring plaque repositioning following intraoperative confirmation with ultrasound. 71.4% of plaques requiring repositioning were in posteriorly located tumors. The group found that intraoperative ultrasonography provided excellent imaging of the tumor plaque interface even without clear ocular media. Grimes *et al*. similarly compared 24-month rates of local tumor control between patients that had intraoperative ultrasound verification of plaque position versus a historic cohort that did not utilize this method of verification. It demonstrated a 24-month local recurrence rate of 0.9% in the former group, a significant improvement from 2% 24-month recurrence rates in their historic controls.[93] The use of intraoperative ultrasound has since become an advocated surgical step by many groups to ensure optimal plaque placement and centration. A hypoacoustic signal attenuation caused by the plaque can be appreciated when the plaque is positioned correctly posterior to the tumor [Figure 3].[94,95] Experimental methods utilizing the Cherenkov radiation effect, whereby charged particles induce a faint visible light when travelling faster than the speed of light in a given dielectric medium have been proposed.[96] Patients following Ru-106 brachytherapy had fundus photos taken by a highly sensitive camera tuned to obtain Cherenkov Luminescence Imaging. In all patients studied, this method revealed circular areas of light corresponding to the size and location of the plaque. However, obtaining these results were technically demanding; patients had to be still for long exposures in total darkness for acceptable image quality processing. In addition, these methods cannot be applied to gamma emission isotopes like I-125 and Pd-103 as they do not induce Cherenkov luminescence, limiting potential applications.[97]

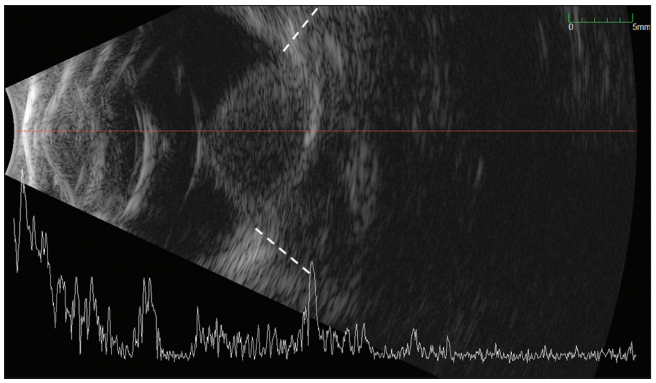

Figure 3: Intraoperative B-scan capture demonstrating the utility of intraoperative ultrasound plaque position confirmation. Hypoacoustic shadow attenuation can be appreciated posterior to the limits of the tumor when the plaque is positioned correctly (Dashed lines)

Dosing Precision and Protection

Radiation planning: Two-dimensional versus three-dimensional

In conventional ocular brachytherapy, two-dimensional (2D) methods comprising of assembled fundus photos or A/B scan ultrasounds are used to map lesions for plaque placement. Dosimetric calculations are based on central axis dose calculations to single points like the tumor apex. However, no volumetric measurements are taken into account with this method. While 2D image-based brachytherapy is generally sufficient for dosimetric calculations to be performed as ocular tumors are generally confined within a sphere, there is a shift towards 3D modeling to optimize these calculations, especially in tumors of irregular shape.[98] MRI or computed tomography are important modalities used to map relational structures to the tumor. Images from these modalities are then input into planning software like TPS to calculate 3D volume-based dosimetric planning.[99] These planning methods, when compared to the original COMS, have been shown in simulation studies to reduce radiation doses for choriodal melanoma.[99] Similar Monte Carlo simulations with Ru-106 dosimetry planning have also reported greater effective delivery of radiation doses to tissue.[100] Future innovations will likely utilize modalities like ultra-high-field MRI to better facilitate the accuracy of tumor contouring compared to conventional ultrasound methods.[101,102]

Intraocular shielding

The concept of intraocular radiation blocking was first proposed by Finger *et al*., where iodine based liquid

radiopaque contrast agents (iophendylate, iohexol, and iopamidol) were experimentally inserted into a rabbit eye model to simulate intraocular radiation blocking.[103] Studies have estimated that up to 40% of emissions undergo photoelectric absorption, with the remainder 60% scattered into the intraocular space.[104] Blocking agents such as iophendylate increase the probability of photoelectric absorption and hence proportionately increases attenuation of surrounding tissue.[103] Since then, various candidate vitreous substitutes have been assessed. Cadaveric *ex vivo* measurements and Monte Carlo simulation studies by Oliver *et al*. demonstrated good radiation attenuation (55%) using 1000-cSt silicone oil compared with saline.[105] The effects of vitreous substitution with silicone oil on radiation attenuation and side effects such as radiation retinopathy, cystoid macular edema and cataract formation has since been clinically demonstrated with the use of I-125 plaques.[106] This clinical adjunct is, however not without potential risks. McCannel's original case series of 20 consecutive patients reported intraoperative complications such as retinal tears, serous retinal detachment under oil, macular hole, and epiretinal membranes formation.[106] Due to potential intra- and postoperative complications, some authors have proposed that the indications of vitrectomy and silicone oil endotamponade be reserved for select cases like posterior pole tumors, or in only functional eyed patients.[107] Recent experimentation with material composed of a mixing ratio of 1:1 tungsten-silicone (Wolfram) for the purposes of both extraocular and intraocular shielding was conducted on a set up mimicking the intraocular milieu. Shielding effects of 92%–98% was demonstrated in I-125 seeds fully covered by Wolfram; this shielding effect decreased to 35%–85% if partially covered. Additional *in vivo* experiments assessing the biological safety of Wolfram did not show any significant histopathological changes to the ocular adnexa. Nonreactive tungsten deposits were however documented on the surface of the retina and within vitreous. Its potential long-term impact is unknown.[108] Further *in vivo* evaluation of this innovation and its long-term impact is required, before human trials can be performed.

Dose reduction strategies/dual source planning

Considerations for dosimetry include tumor base dimensions and apex height.[109] Margins of 2 mm around tumor circumference are applied to ensure sufficient dosing across the tumor.[110] The COMS planning norms of 85 Gy are prescribed either to a minimum of 5 mm or to the maximal tumor apex height if >5 mm. This can result in unwanted radiation dosages to peripheral structures in small-to-medium-sized tumors.[111,112] Studies have explored the effects of reduced dose planning in the treatment of these tumors and their outcomes.[113] One of the largest studies by Perez *et al*. showed that in patients with tumor heights <5 mm, those receiving lower doses had comparable tumor control outcomes compared to those receiving conventional 85 Gy over a 5-year period.[114]

Dosage effects of dual source strength seed loading in various plaque designs have also been investigated.[115] EP plaques were planned to 3 different scenarios; a circular 19.9 mm plaque for shallow <5.5 mm tumors with large base dimensions, a notched plaque for tumors very close to the optic nerve, and a small diameter 18.5 mm plaque for very shallow <3.0 mm tumors with moderate base dimensions. In each plaque, a mix of source strength seeds were utilized in specific conformations. Simulation results from the 3 scenarios were varied, being largely dependent on the location of the higher source strength seeds. In some cases, general reduction in radiometric dosages to adjacent structures were demonstrated. Notched plaques demonstrated higher dosages to optic nerve due to inherent positioning of the higher source strength seed. Despite variations in results, the study demonstrated the potential for dose optimization with case-by-case planning and selective high source strength seed positioning.[115] Another experimental plaque consisting of dual isotope core of Pd-103 and Ru-106 has reported higher combined dose rates to the tumor with slightly higher doses to surrounding tissue compared to monoisotope models.[116]

Novel studies are emerging surrounding the use of nanoparticle enhanced brachytherapy strategies. Gold, bismuth, and lutetium-177 are some early proposed radiosensitizers.[117] Modeling studies involving gold nanoparticle (GNP) effects have demonstrated the potential for significant increase of dosages within sequestered areas of GNP and no significant changes in adsorbed doses by other parts of the eye models.[118] Future innovations into this field of study will likely optimize our ability to accurately direct and concentrate these radiosensitizers into the substance of the tumor.[119]

Conclusion

Since the inception of plaque brachytherapy as a treatment option for choroidal melanoma, increased understanding and innovations have led to the expanded indications of this modality of treatment. The future will see increasing utilization of precision dosimetric planning, and further discoveries and innovations to isotope utilization and plaque design that will result in greater therapeutic efficacy and safer dose delivery with fewer side effects of radiation therapy. The challenge will remain having large enough studies to prove the superiority of these innovations, especially for the rarer indications.

Acknowledgement

The authors would like to acknowledge LV Liberty Vision Corporation for the use of illustrations for the iWand, and the kind contributions from Dr Paul T Finger, MD to the relevant sections.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

References

1. Barkan H. Bilateral glioma treated by radium. Arch Ophthalmol 1934;11.
2. Brewington BY, Shao YF, Davidorf FH, Cebulla CM. Brachytherapy for patients with uveal melanoma: Historical perspectives and future treatment directions. Clin Ophthalmol 2018;12:925-34.
3. Shields JA, Shields CL. Management of posterior uveal melanoma: Past, present, and future: The 2014 Charles L. Schepens lecture. Ophthalmology 2015;122:414-28.
4. Shields JA, Shields CL, De Potter P, Cu-Unjieng A, Hernandez C, Brady LW. Plaque radiotherapy for uveal melanoma. Int Ophthalmol Clin 1993;33:129-35.
5. Moore RF. The value of radium in intraocular lesions. Trans Ophthalmol Soc UK 1935;55:3-26.
6. Finger PT. Radiation therapy for choroidal melanoma. Surv Ophthalmol 1997;42:215-32.
7. Stallard HB. Radiotherapy for malignant melanoma of the choroid. Br J Ophthalmol 1966;50:147-55.
8. Echegaray JJ, Bechrakis NE, Singh N, Bellerive C, Singh AD. Iodine-125 brachytherapy for uveal melanoma: A systematic review of radiation dose. Ocul Oncol Pathol 2017;3:193-8.
9. Earle J, Kline RW, Robertson DM. Selection of iodine 125 for the collaborative ocular melanoma study. Arch Ophthalmol 1987;105:763-4.
10. Rusňák Š, Hecová L, Kasl Z, Sobotová M, Hauer L. Therapy of uveal melanoma a review. Cesk Slov Oftalmol 2020;77:1-13.
11. Wei S, Li C, Li M, Xiong Y, Jiang Y, Sun H, *et al.* Radioactive iodine-125 in tumor therapy: Advances and future directions. Front Oncol 2021;11:717180.
12. Finger PT, Berson A, Szechter A. Palladium-103 plaque radiotherapy for choroidal melanoma: Results of a 7-year study. Ophthalmology 1999;106:606-13.
13. Finger PT, Zhou D, Kalach N, Semenova E, Choi W. (103)Pd versus (125)I ophthalmic plaque brachytherapy: Preoperative comparative radiation dosimetry for 319 uveal melanomas. J Radiat Oncol 2014;3:409-16.
14. Petousis V, Finger PT, Milman T. Multifocal iris melanoma treated with total anterior segment palladium-103 plaque radiation therapy. Graefes Arch Clin Exp Ophthalmol 2011;249:937-40.
15. Finger PT, Tomar AS, Chin KJ. Palladium-103 plaque therapy for multifocal iris melanoma: Radiation of the entire anterior segment of the eye. Eur J Ophthalmol 2021;31:1375-83.
16. Wilkinson DA, Kolar M, Fleming PA, Singh AD. Dosimetric comparison of 106Ru and 125I plaques for treatment of shallow (<or=5 mm) choroidal melanoma lesions. Br J Radiol 2008;81:784-9.
17. Fili M, Lundell G, Lundell M, Seregard S. High dose rate and low dose rate ruthenium brachytherapy for uveal melanoma. No association with ocular outcome. Br J Ophthalmol 2014;98:1349-54.
18. Pe'er J. Ruthenium-106 brachytherapy. Dev Ophthalmol 2012;49:27-40.
19. Filì M, Trocme E, Bergman L, See TR, André H, Bartuma K, *et al.* Ruthenium-106 versus iodine-125 plaque brachytherapy of 571 choroidal melanomas with a thickness of ≥5.5 mm. Br J Ophthalmol 2020;104:26-32.
20. Seregard S, Damato B. Uveal Malignant Melanoma: Management Options for Brachytherapy. In: Damato B, Singh A. (eds) Clinical Ophthalmic Oncology. Springer, Berlin, Heidelberg; 2014. [doi: 10.1007/978-3-642-54255-8_13].
21. Keizer R, Tjho-Heslinga R, Verbeek A, Keunen J. Ruthenium Brachytherapy of 24 Iris and Iridociliary Melanomas. International Conference of Ocular Oncology Abstract; 2004; 2004.
22. Razzaq L, Keunen JE, Schalij-Delfos NE, Creutzberg CL, Ketelaars M, de Keizer RJ. Ruthenium plaque radiation therapy for iris and iridociliary melanomas. Acta Ophthalmol 2012;90:291-6.
23. Jiang P, Purtskhvanidze K, Kandzia G, Neumann D, Luetzen U, Siebert FA, *et al.* (106) Ruthenium eye plaque brachytherapy in the management of medium sized uveal melanoma. Radiat Oncol 2020;15:183.
24. Chakravarty R, Dash A, Pillai MR. Availability of yttrium-90 from strontium-90: A nuclear medicine perspective. Cancer Biother Radiopharm 2012;27:621-41.
25. Pajic B, Greiner RH. Long term results of non-surgical, exclusive strontium-/yttrium-90 beta-irradiation of pterygia. Radiother Oncol 2005;74:25-9.
26. Qin XJ, Chen HM, Guo L, Guo YY. Low-dose strontium-90 irradiation is effective in preventing the recurrence of pterygia: A ten-year study. PLoS One 2012;7:e43500.
27. Jaakkola A, Heikkonen J, Tommila P, Laatikainen L, Immonen I. Strontium plaque irradiation of subfoveal neovascular membranes in age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 1998;236:24-30.
28. Cohen VM, Papastefanou VP, Liu S, Stoker I, Hungerford JL. The use of strontium-90 beta radiotherapy as adjuvant treatment for conjunctival melanoma. J Oncol 2013;2013:349162.
29. Finger PT, Stewart R, Rivard MJ, Beers RJ, Kamen J, Lama S, *et al.* First clinical implementation of yttrium-90 disc brachytherapy after FDA clearance. Brachytherapy 2023;22:416-27.
30. Finger PT. High-dose-rate yttrium-90 ((90)Y) episcleral plaque brachytherapy for iris and iridociliary melanoma. Ophthalmol Sci 2024;4:100513.
31. Dupere JM, Munro JJ 3rd, Medich DC. Intensity modulated high dose rate ocular brachytherapy using Se-75. Brachytherapy 2021;20:1312-22.
32. Dupere JM, Munro JJ 3rd, Medich DC. Shielded high dose rate ocular brachytherapy using Yb-169. Phys Med Biol 2021;66. [doi: 10.1088/1361-6560/ac02d6].
33. Murdoch I, Puertas R, Hamedani M, Khaw PT. Long-term safety and outcomes of β-radiation for trabeculectomy. J Glaucoma 2023;32:171-7.
34. Jürgenliemk-Schulz IM, Hartman LJ, Roesink JM, Tersteeg RJ, van Der Tweel I, Kal HB, *et al.* Prevention of pterygium recurrence by postoperative single-dose beta-irradiation: A prospective randomized clinical double-blind trial. Int J Radiat Oncol Biol Phys 2004;59:1138-47.
35. Kearsley JH, Fitchew RS, Taylor RG. Adjunctive radiotherapy with strontium-90 in the treatment of conjunctival squamous cell carcinoma. Int J Radiat Oncol Biol Phys 1988;14:435-43.
36. Erie JC, Campbell RJ, Liesegang TJ. Conjunctival and corneal intraepithelial and invasive neoplasia. Ophthalmology 1986;93:176-83.

37. Basti S, Macsai MS. Ocular surface squamous neoplasia: A review. Cornea 2003;22:687-704.
38. Shields JA, Shields CL, De Potter P. Surgical management of conjunctival tumors. The 1994 Lynn B. McMahan Lecture. Arch Ophthalmol 1997;115:808-15.
39. Arepalli S, Kaliki S, Shields CL, Emrich J, Komarnicky L, Shields JA. Plaque radiotherapy in the management of scleral-invasive conjunctival squamous cell carcinoma: An analysis of 15 eyes. JAMA Ophthalmol 2014;132:691-6.
40. Rahal A, Meller D, Manthey A, Bechrakis N, Guberina M, Stuschke M, *et al.* Brachytherapy as a curative option for ocular surface squamous neoplasia. Int Ophthalmol 2023;43:1861-5.
41. Marigo FA, Finger PT. Anterior segment tumors: Current concepts and innovations. Surv Ophthalmol 2003;48:569-93.
42. Dyson C. Iridocyclectomy with lamellar scleral resection. Can J Ophthalmol 1972;7:297-301.
43. Hager G. Results following iridocyclectomy using scleral step incision and lamellar scleral resection. Klin Monbl Augenheilkd 1973;162:585-90.
44. Shields CL, Shields JA, De Potter P, Singh AD, Hernandez C, Brady LW. Treatment of non-resectable malignant iris tumours with custom designed plaque radiotherapy. Br J Ophthalmol 1995;79:306-12.
45. Finger PT. Plaque radiation therapy for malignant melanoma of the iris and ciliary body. Am J Ophthalmol 2001;132:328-35.
46. Finger PT, Chin KJ, Duvall G. Palladium-103 ophthalmic plaque radiation therapy for choroidal melanoma: 400 treated patients. Ophthalmology 2009;116:790-6, 796.e1.
47. Kuiper N, Tjho-Heslinga R, Verbeek A, Keunen JE. An anterior segment calculation diagram for 106 ruth brachytherapy of iris and iridociliair melanomas, the preliminary results of the therapy. Invest Ophthalmol Vis Sci 2002;43:1150.
48. Zwolin Ska E, Główka L, Chicheł A, Rospond-Kubiak I. Ruthenium brachytherapy for iris melanoma. J Contemp Brachytherapy 2023;15:344-9.
49. Karimi S, Arabi A, Shahraki T. Plaque brachytherapy in iris and iridociliary melanoma: A systematic review of efficacy and complications. J Contemp Brachytherapy 2021;13:46-50.
50. Finger PT. Finger's amniotic membrane buffer technique: Protecting the cornea during radiation plaque therapy. Arch Ophthalmol 2008;126:531-4.
51. Semenova E, Finger PT. Amniotic membrane corneal buffering during plaque radiation therapy for anterior uveal melanoma. Ophthalmic Surg Lasers Imaging Retina 2013;44:477-82.
52. Shields CL, Honavar SG, Shields JA, Cater J, Demirci H. Circumscribed choroidal hemangioma: Clinical manifestations and factors predictive of visual outcome in 200 consecutive cases. Ophthalmology 2001;108:2237-48.
53. Maclean AL, Maumenee AE. Hemangioma of the choroid. Am J Ophthalmol 1960;50:3-11.
54. Scott TA, Augsburger JJ, Brady LW, Hernandez C, Woodleigh R. Low dose ocular irradiation for diffuse choroidal hemangiomas associated with bullous nonrhegmatogenous retinal detachment. Retina 1991;11:389-93.
55. Madreperla SA, Hungerford JL, Plowman PN, Laganowski HC, Gregory PT. Choroidal hemangiomas: Visual and anatomic results of treatment by photocoagulation or radiation therapy. Ophthalmology 1997;104:1773-8.
56. Ritland JS, Eide N, Tausjø J. External beam irradiation therapy for choroidal haemangiomas. Visual and anatomical results after a dose of 20 to 25 GY. Acta Ophthalmol Scand 2001;79:184-6.
57. Zografos L, Bercher L, Chamot L, Gailloud C, Raimondi S, Egger E. Cobalt-60 treatment of choroidal hemangiomas. Am J Ophthalmol 1996;121:190-9.
58. Arepalli S, Shields CL, Kaliki S, Emrich J, Komarnicky L, Shields JA. Diffuse choroidal hemangioma management with plaque radiotherapy in 5 cases. Ophthalmology 2013;120:2358-59, 2359.e1-2.
59. Murthy R, Hanovaz SG, Naik M, Gopi S, Reddy VA. Ruthenium-106 plaque brachytherapy for the treatment of diffuse choroidal haemangioma in Sturge-Weber syndrome. Indian J Ophthalmol 2005;53:274-5.
60. Yu YY, Li XX, Liang JH. Ruthenium-106 plaque brachytherapy for the treatment of diffuse choroidal hemangioma in Sturge-Weber syndrome. Int J Ophthalmol 2020;13:513-7.
61. Kubicka-Trząska A, Karska-Basta I, Oleksy P, Romanowska-Dixon B. Management of diffuse choroidal hemangioma in Sturge-Weber syndrome with ruthenium-106 plaque radiotherapy. Graefes Arch Clin Exp Ophthalmol 2015;253:2015-9.
62. Chan RV, Yonekawa Y, Lane AM, Skondra D, Munzenrider JE, Collier JM, *et al.* Proton beam irradiation using a light-field technique for the treatment of choroidal hemangiomas. Ophthalmologica 2010;224:209-16.
63. American Brachytherapy Society, Ophthalmic Oncology Task Force Electronic Address: paulfinger@eyecancercom, ABS-OOTF Committee. The American brachytherapy society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. Brachytherapy 2014;13:1-14.
64. Shields CL, Shields JA, De Potter P, Minelli S, Hernandez C, Brady LW, *et al.* Plaque radiotherapy in the management of retinoblastoma. Use as a primary and secondary treatment. Ophthalmology 1993;100:216-24.
65. Amendola BE, Markoe AM, Augsburger JJ, Karlsson UL, Giblin M, Shields JA, *et al.* Analysis of treatment results in 36 children with retinoblastoma treated by scleral plaque irradiation. Int J Radiat Oncol Biol Phys 1989;17:63-70.
66. Maheshwari A, Finger PT. Palladium-103 plaque brachytherapy for retinoblastoma: Long term follow up. Am J Ophthalmol Case Rep 2022;27:101636.
67. Schlüter S, Bornfeld N, Valiyev E, Flühs D, Stuschke M, Bechrakis NE, *et al.* Combination of brachytherapy and intravitreal chemotherapy in the treatment of retinoblastoma with vitreous seeding. Ocul Oncol Pathol 2022;8:64-70.
68. Shields CL, Shields JA, Cater J, Othmane I, Singh AD, Micaily B. Plaque radiotherapy for retinoblastoma: Long-term tumor control and treatment complications in 208 tumors. Ophthalmology 2001;108:2116-21.
69. Avril MF, Auperin A, Margulis A, Gerbaulet A, Duvillard P, Benhamou E, *et al.* Basal cell carcinoma of the face: Surgery or radiotherapy? Results of a randomized study. Br J Cancer 1997;76:100-6.
70. Cisek P, Kieszko D, Bilski M, Dębicki R, Grywalska E, Hrynkiewicz R, *et al.* Interstitial HDR brachytherapy in the treatment of non-melanocytic skin cancers around the eye. Cancers (Basel) 2021;13:1425.
71. Krzysztofiak T, Suchorzepka M, Tukiendorf A, Wojcieszek P, Kamińska-Winciorek G. Basal cell carcinoma after high dose rate brachytherapy: Medium-term dermoscopic evaluation of cancer's response. Dermatol Ther (Heidelb) 2023;13:2063-78.
72. Vavassori A, Riva G, Durante S, Fodor C, Comi S, Cambria R, *et al.* Mould-based surface high-dose-rate brachytherapy for eyelid carcinoma. J Contemp Brachytherapy 2019;11:443-8.
73. Anastassiou G, Bornfeld N, Schueler AO, Schilling H, Weber S, Fluehs D, *et al.* Ruthenium-106 plaque brachytherapy for symptomatic vasoproliferative tumours of the retina. Br J Ophthalmol 2006;90:447-50.
74. Case MJ, Lentz C, Duffy EW, Magrath GN, Cooper SL. Large vasoproliferative retinal tumor refractory to cryotherapy treated with salvage I-125 plaque radiation therapy. Adv Radiat Oncol 2022;7:100972.
75. Chu TW, Tsai SH, Chen LJ. Retinal vasoproliferative tumor regression after intravitreal aflibercept. Taiwan J Ophthalmol 2023;13:249-52.
76. Cohen VM, Shields CL, Demirci H, Shields JA. Iodine I 125 plaque

radiotherapy for vasoproliferative tumors of the retina in 30 eyes. Arch Ophthalmol 2008;126:1245-51.
77. Huang Y, Hu W, Huang X. Retinal hemangioblastoma in a patient with von hippel-lindau disease: A case report and literature review. Front Oncol 2022;12:963469.
78. Kreusel KM, Bornfeld N, Lommatzsch A, Wessing A, Foerster MH. Ruthenium-106 brachytherapy for peripheral retinal capillary hemangioma. Ophthalmology 1998;105:1386-92.
79. Dalbah S, Bechrakis NE, Thomasen H, Flühs D, Rating P, Guberina M, *et al.* Brachytherapy for peripheral retinal capillary haemangioblastoma in von hippel-lindau disease. Klin Monbl Augenheilkd 2021;238:781-7.
80. Wiley HE, Krivosic V, Gaudric A, Gorin MB, Shields C, Shields J, *et al.* Management of retinal hemangioblastoma in von hippel-lindau disease. Retina 2019;39:2254-63.
81. Diener M, Hawkins BS, Fine SL, Earle JD, Straatsma BR, Mowery RL, *et al.* Design and methods of a clinical trial for a rare condition: The collaborative ocular melanoma study. COMS report no. 3. Control Clin Trials 1993;14:362-91.
82. Semeniuk O, Malkov V, Chamberland MJ, Weersink RA. Monte Carlo investigation of dose distribution of uniformly and non-uniformly loaded standard and notched eye plaques. J Appl Clin Med Phys 2023;24:e14149.
83. Maheshwari A, Finger PT. A 12-year study of slotted palladium-103 plaque radiation therapy for choroidal melanoma: Near, touching, or surrounding the optic nerve. Am J Ophthalmol 2018;188:60-9.
84. Binder C, Mruthyunjaya P, Schefler AC, Seider MI, Crilly R, Hung A, *et al.* Practice patterns for the treatment of uveal melanoma with iodine-125 plaque brachytherapy: Ocular oncology study consortium report 5. Ocul Oncol Pathol 2020;6:210-8.
85. Beaulieu L, Carlsson Tedgren A, Carrier JF, Davis SD, Mourtada F, Rivard MJ, *et al.* Report of the task group 186 on model-based dose calculation methods in brachytherapy beyond the TG-43 formalism: Current status and recommendations for clinical implementation. Med Phys 2012;39:6208-36.
86. Le BH, Kim JW, Deng H, Rayess N, Jennelle RL, Zhou SY, *et al.* Outcomes of choroidal melanomas treated with eye physics plaques: A 25-year review. Brachytherapy 2018;17:981-9.
87. Marcié S, Gerard JP, Dejean C, Feuillade J, Gautier M, Montagné L, *et al.* The inverse square law: A basic principle in brachytherapy. Cancer Radiother 2022;26:1075-7.
88. Astrahan MA. Improved treatment planning for COMS eye plaques. Int J Radiat Oncol Biol Phys 2005;61:1227-42.
89. Williams DF, Mieler WF, Lewandowski M, Greenberg M. Echographic verification of radioactive plaque position in the treatment of melanomas. Arch Ophthalmol 1988;106:1623-4.
90. Finger PT, Iezzi R, Esteveo ML, Szechter A, Rosen RB, Berson A. Diode-light transillumination for ophthalmic plaque localization around juxtapapillary choroidal melanomas. Int J Radiat Oncol Biol Phys 1999;44:887-90.
91. Hanna SL, Lemmi MA, Langston JW, Fontanesi J, Brooks HL Jr., Gronemeyer S. Treatment of choroidal melanoma: MR imaging in the assessment of radioactive plaque position. Radiology 1990;176:851-3.
92. Tabandeh H, Chaudhry NA, Murray TG, Ehlies F, Hughes R, Scott IU, *et al.* Intraoperative echographic localization of iodine-125 episcleral plaque for brachytherapy of choroidal melanoma. Am J Ophthalmol 2000;129:199-204.
93. Grimes JM, Zhou H, Dal Col AK, Gershkovich A, Bogomolny D, Marr BP. Ultrasound verification of plaque brachytherapy placement in patients treated for primary uveal melanoma: A single-center experience. Ocul Oncol Pathol 2023;9:17-24.
94. Ces AP, Rodriguez MB, Sueiro JM, Castro AM, Busto RL, Rodriguez PS, *et al.* Intra-operative ocular ultrasonography of iodine-125 brachytherapy plaques in patients with uveal melanoma. J Contemp Brachytherapy 2021;13:126-34.
95. Wong AJ, Teh BS, Nguyen BT, Pino R, Bretana ME, Bernicker EH, *et al.* Three-year outcomes of uveal melanoma treated with intra-operative ultrasound-guided iodine-125 brachytherapy using custom-built eye plaques. J Contemp Brachytherapy 2022;14:130-9.
96. Cherenkov PA. Visible light from clear liquids under the action of gamma radiation. C.R. (DokI.) Acad. Sci. URSS 1934;2:451-4. [Phyaico-Mathematicat Institute V.A. Stekiova. Academy of Science. Leningrad. USSRI].
97. Krohn J, Chen YC, Stabo-Eeg NO, Hamre B. Cherenkov luminescence imaging for assessment of radioactive plaque position in brachytherapy of uveal melanoma: An *in vivo* feasibility study. Transl Vis Sci Technol 2020;9:42.
98. Itami J. Modern development of high-dose-rate brachytherapy. Jpn J Clin Oncol 2020;50:490-501.
99. Krintz AL, Hanson WF, Ibbott GS, Followill DS. A reanalysis of the collaborative ocular melanoma study medium tumor trial eye plaque dosimetry. Int J Radiat Oncol Biol Phys 2003;56:889-98.
100. Espensen CA, Kiilgaard JF, Klemp K, Gothelf A, Appelt AL, Fog LS. 3D image-guided treatment planning for ruthenium-106 brachytherapy of choroidal melanomas. Acta Ophthalmol 2021;99:e654-60.
101. Beenakker JW, Ferreira TA, Soemarwoto KP, Genders SW, Teeuwisse WM, Webb AG, *et al.* Clinical evaluation of ultra-high-field MRI for three-dimensional visualisation of tumour size in uveal melanoma patients, with direct relevance to treatment planning. Magn Reson Mater Phys Biol Med 2016;29:571-7.
102. Zoberi JE, Garcia-Ramirez J, Hedrick S, Rodriguez V, Bertelsman CG, Mackey S, *et al.* MRI-based treatment planning and dose delivery verification for intraocular melanoma brachytherapy. Brachytherapy 2018;17:31-9.
103. Finger PT, Ho TK, Fastenberg DM, Hyman RA, Stroh EM, Packer S, *et al.* Intraocular radiation blocking. Invest Ophthalmol Vis Sci 1990;31:1724-30.
104. Curry TS, Dowdey JE, Murry RC. Christensen's Physics of Diagnostic Radiology. PA, USA: Lippincott Williams and Wilkins; 1990.
105. Oliver SC, Leu MY, DeMarco JJ, Chow PE, Lee SP, McCannel TA. Attenuation of iodine 125 radiation with vitreous substitutes in the treatment of uveal melanoma. Arch Ophthalmol 2010;128:888-93.
106. McCannel TA, McCannel CA. Iodine 125 brachytherapy with vitrectomy and silicone oil in the treatment of uveal melanoma: 1-to-1 matched case-control series. Int J Radiat Oncol Biol Phys 2014;89:347-52.
107. Ahuja Y, Kapoor KG, Thomson RM, Furutani KM, Shultz RW, Stafford SL, *et al.* The effects of intraocular silicone oil placement prior to iodine 125 brachytherapy for uveal melanoma: A clinical case series. Eye (Lond) 2012;26:1487-9.
108. Sokolenko EA, Flühs D, Lalos F, Meyer P, Fiorentzis M, Lindziute M, *et al.* Wolfram-silicone implants as effective radiation shielding for ocular brachytherapy: Dosimetric features and *in vivo* animal study on biocompatibility. Can J Ophthalmol 2024;59:e515-24.
109. Nath R, Anderson LL, Luxton G, Weaver KA, Williamson JF, Meigooni AS. Dosimetry of interstitial brachytherapy sources: Recommendations of the AAPM radiation therapy committee task group no. 43. American Association of Physicists in Medicine. Med Phys 1995;22:209-34.
110. Gagne NL, Rivard MJ. Quantifying the dosimetric influences of radiation coverage and brachytherapy implant placement uncertainty on eye plaque size selection. Brachytherapy 2013;12:508-20.
111. Oellers P, Mowery YM, Perez BA, Stinnett S, Mettu P, Vajzovic L, *et al.* Efficacy and safety of low-dose iodine plaque brachytherapy

for juxtapapillary choroidal melanoma. Am J Ophthalmol 2018;186:32-40.
112. Oellers P, Mruthyunjaya P. Low-dose brachytherapy strategies to treat uveal melanoma: Is less more? Melanoma Manag 2016;3:13-22.
113. Murray TG, Markoe AM, Gold AS, Ehlies F, Bermudez E, Wildner A, *et al.* Long-term followup comparing two treatment dosing strategies of (125) I plaque radiotherapy in the management of small/medium posterior uveal melanoma. J Ophthalmol 2013;2013:517032.
114. Perez BA, Mettu P, Vajzovic L, Rivera D, Alkaissi A, Steffey BA, *et al.* Uveal melanoma treated with iodine-125 episcleral plaque: An analysis of dose on disease control and visual outcomes. Int J Radiat Oncol Biol Phys 2014;89:127-36.
115. Meltsner SG, Kirsch DG, Materin MA, Kim Y, Sheng Y, Craciunescu O. Dual-source strength seed loading for eye plaque brachytherapy using eye physics eye plaques: A feasibility study. J Contemp Brachytherapy 2022;14:590-600.
116. Sharifzadeh M, Chiniforoush TA, Sadeghi M. Design and optimizing a novel ocular plaque brachytherapy with dual-core of (103) Pd and (106) Ru. Phys Med 2021;91:99-104.
117. Zhou R, Zhao D, Beeraka NM, Wang X, Lu P, Song R, *et al.* Novel implications of nanoparticle-enhanced radiotherapy and brachytherapy: Z-effect and tumor hypoxia. Metabolites 2022;12:943.
118. Asadi S, Vaez-zadeh M, Masoudi SF, Rahmani F, Knaup C, Meigooni AS. Gold nanoparticle-based brachytherapy enhancement in choroidal melanoma using a full Monte Carlo model of the human eye. J Appl Clin Med Phys 2015;16:344-57.
119. Masoudi SF, Daryabari FS, Rasouli FS. Distribution modeling of nanoparticles for brachytherapy of human eye tumor. EJNMMI Phys 2020;7:53.