Review Article

Expanded Indications of Plaque Brachytherapy

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Abstract

Radiotherapy is now a widely accepted treatment modality in oncology. Plaque brachytherapy is an effective eye and vision sparing alternative to enucleation for patients with intraocular tumours. The most common indication for brachytherapy is malignant tumours like retinoblastoma and uveal melanoma. Over the years, brachytherapy is being increasingly used for other conditions affecting the eye and ocular adnexa. These include ocular surface tumours and some benign lesions where traditional methods of treatment have failed such as retinal capillary hemangiomas, vaso-proliferative tumours, choroidal hemangiomas and choroidal neovascularization in age-related macular degeneration. The expanded applications of plaque therapy are summarized in this review.

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Introduction

Radiation therapy is an important therapeutic modality in ocular oncology. There are various ways of administering radiotherapy to ocular or orbital tumours. It can be delivered as external beam radiotherapy, stereotactic radiosurgery, particle radiation therapy or plaque brachytherapy.[1] Brachytherapy delivers radiation close to the target by surgically placing the radioactive source at the site of the intended target which aids in delivering relatively high doses of radiation to smaller, better-defined areas. It involves placing a radioactive material surgically inside the body adjacent to the required site of therapy.[2,3] It can be used as a single mode of therapy or it can combined with External Beam Radiotherapy. The combination treatment allows for a higher dose of radiation to reach the tumour site while reducing the exposure of normal ocular structures. Brachytherapy can be temporary or permanent.[4] Temporary brachytherapy involves the implantation of radioactive material in or near the tumour site for a few hours or days. It is usually preferred for tumours near radiosensitive structures such as the ocular tissue. Permanent brachytherapy is the implantation of radioactive material in the tumour tissue for months together.[4]

It is since 1930s that brachytherapy has been used to treat intraocular tumours.[5] The various sources described are ^{60}Co, ^{106}Ru, ^{125}I, ^{103}Pd, ^{90}Sr, and ^{131}Cs.[6,7] Modern plaques include assemblies of gold shells with low-energy photon seeds (^{125}I, ^{103}Pd, and ^{131}Cs) or solid beta (^{106}Ru and ^{90}Sr) plaques.[8] Brachytherapy can be delivered to the eye via two approaches, ab-externo or episcleral approach for tumours (Figure 1) and ab-interno or epimacular brachytherapy for neovascular age-related macular degeneration (AMD).[9]

Indications for Brachytherapy

Radiation can be used as primary therapy, adjuvant therapy or as a palliative treatment. The most common indication for brachytherapy is malignant tumours like retinoblastoma[10,11] and uveal melanoma.[12,13] In addition, brachytherapy is being increasingly used for other conditions affecting the eye and ocular adnexa. These include ocular surface tumours and some benign lesions where traditional methods of treatment have failed such as retinal capillary hemangiomas (RCH), vaso-proliferativetumours (VPTs), choroidal hemangiomas, and choroidal neovascularization in age-related macular degeneration (AMD).[14] Its anti-fibroblast effect is also being utilized in glaucoma surgeries and in pterygium to avoid recurrence.[15,16]

Uveal Melanoma

The most common indication for brachytherapy is choroidal melanoma but indications have expanded since the 2003 ABS (American Brachytherapy Society) guidelines.[9] Brachytherapy is now indicated for most uveal melanomas. This includes melanomas of the iris, ciliary body, choroid, subfoveal, circumpapillary, peripapillary melanomas and those with limited extrascleral extension.

The Brachytherapy exclusion criteria according to ABS-OOTF (The American Brachytherapy Society - Ophthalmic Oncology Task Force) recommendation includes those with no perception of light, gross extrascleral extension and a painful blind eye.[1]

Retinoblastoma

Brachytherapy is not a primary treatment for retinoblastoma.[17-19] It is used as a secondary treatment option when the conservative treatment modalities like cryotherapy,

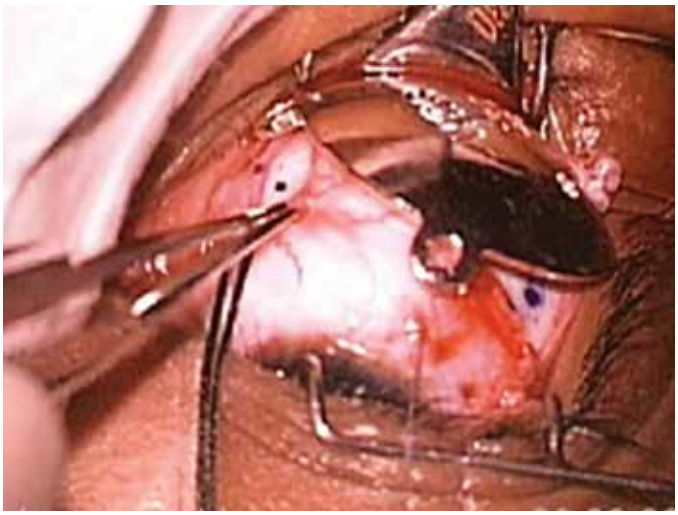

Figure 1: *Ruthenium plaque for treatment of intra-ocular tumours*

systemic or intra-arterial chemotherapy fail to regress the tumour.[20] The ideal tumours for primary brachytherapy as recommended by The ABS-OOTF (Level 2 Consensus) are unilateral tumours located anterior to the equator. It serves as a secondary treatment modality for residual and recurrent tumours. The presence of anterior segment involvement and juxta papillary location are the exclusion criteria for plaque brachytherapy.[21,22]

Ocular Surface Tumours

Ocular surface malignancies including conjunctival melanoma (CM) and squamous cell carcinoma (SCC) are potentially sight- and life-threatening conditions affecting middle-age and elderly individuals.[23,24] They are usually managed by topical chemotherapy or surgical excision.[23,24] Incomplete excision of primary tumours with a positive margin on histopathology is a significant risk factor for recurrence and regional spreads.[25,26] A retrospective, non-comparative, interventional case series by Conway et al[27] described the outcome of patients treated by surgical excision followed by plaque brachy-therapy for primary or recurrent ocular surface malignancies with evidence of deep margin (corneo-scleral) invasion. Eleven consecutive patients presenting with biopsy-proven scleral and/or corneal stromal involvement including 5 conjunctival melanoma (CM) and 6 squamous cell carcinoma (SCC) of the conjunctiva were reviewed. All patients were treated with Iodine-125 plaque with treatment dose 100Gy to a depth of 1.5–2.5 mm.[27] At a mean follow up of 23.4 months (range 12–36 months), none experienced recurrence at the treatment site.[27]

Retinal Capillary Hemangioma

They are benign vascular tumours which are hamartomas arising from the blood vessels of the retina or optic disc. It can be sporadic or a part of syndromic association like in von Hippel Lindau disease (VHL), which is an autosomal-dominant phakomatosis.[28,29] Radiotherapy was one of the first treatment modalities for retinal angiomas. In 1935, Moore sutured radon seeds to the sclera over the tumour site in two patients and successful regression was noted in both the patients.[30] However, radiation therapy failed to emerge as a better treatment modality compared to laser photocoagulation due to wrong case selection and limited experience.[31] Nevertheless, in recent times, radiotherapy is emerging as a new approach for patients who have not been responding to laser and cryotherapy and who have large exudative retinal detachments.[32] Kreusel et al[33] reported a series of 25 cases treated with ruthenium-106 (Ru-106) plaques in 1998. Various reports suggest brachytherapy to be a safe option for managing challenging cases of retinal capillary hemangiomas as well as those cases in which other treatment options have failed. However, larger case series with longer follow-up periods are required to provide long-term safety and efficacy data to support the use of brachytherapy in managing large capillary hemangiomas.[14]

Vasoproliferative Retinal Tumours

The vasoproliferative retinal tumour (VPT) is a benign vascular tumour of the sensory retina. It can be either primary (idiopathic) or secondary to other ocular disease. Two-thirds of VPT are primary and are seen as solitary, small lesions and are located near the ora serrata.[34,35]

Brachytherapy is being seen as a newer treatment modality for larger VPTs (greater than 2 mm in thickness). In 2006, a case series of 35 VPTs treated with Ru-106 plaques was published by Anastassiou and coworkers.[36] They documented a decrease in mean tumour thickness from 2.8 mm to 1.5 mm. Of these, 11% did not respond to treatment, out of which, 3 cases had secondary glaucoma prior to brachytherapy, thus making glaucoma a significant cause of treatment failure. They did not report any case of radiation-induced retinopathy or optic neuropathy. Another case series by Cohen et al reported 30 eyes with VPT treated with I-125 brachytherapy wherein 77 % of cases had exudative retinal detachment.[37] They observed tumour regression in 97% cases and complete resolution of retinal detachment in 65% cases after brachytherapy. Brachytherapy is superior to conventional treatment modalities like laser or cryotherapy as the high-dose radiation emitted by plaques are delivered to a well-defined area, allowing larger tumours to be treated more effectively. Also, the radiation side effects are minimized due to the peripheral location of these tumours.[14]

Choroidal Hemangioma

Choroidal hemangiomas are rare, benign, vascular hamartomas. They can be described as circumscribed or diffuse. Circumscribed choroidal hemangioma (CCH) is a rare congenital solitary tumour, with no associated systemic association.[38] Patients usually present with reduced vision in the late 5th-6th decade which is associated with either exudative retinal detachment or macular edema. Diffuse choroidal hemangiomas (DCHs) are sporadic hamartomas usually seen in association with the Sturge–Weber Syndrome. The affected fundus is sometimes referred to as a 'tomato ketchup fundus.[39]

The role of radiotherapy has been described in the management of both CCH and DCH.[40-42] Mac Lean and associates probably used brachytherapy for the first time for the treatment of choroidal haemangioma.[43] They used trans-scleral diathermy with scleral suturing of radon seeds and presently, episcleral plaque brachytherapy is considered an effective treatment option for large, circumscribed choroidal hemangiomas with sub retinal fluid.[35,44]

Madreperla et al[41] have described favorable visual outcomes in patients treated with brachytherapy. Of the 23 patients with CCH, 13 were treated with laser photocoagulation, 8 by plaque brachytherapy and 2 by EBRT. Brachytherapy was used for fovea - involving tumours using either I-125 or Ru-106 plaques since photocoagulation is associated with a poor prognosis in such cases. In the brachytherapy treatment group, six of eight eyes had a VA of 6/12 or better at 1 year, and in all eight patients, no re-accumulation of sub-retinal fluid was noted. Of the 13 eyes treated by photocoagulation, 5 (38%) had a VA of 6/12 or better at 1 year and 6 (46%) of 13 had no subretinal fluid.[41] Brachytherapy resulted in regression of the tumour size, whereas the photocoagulation-treated tumours remained unchanged. Plaque brachytherapy should be considered only for choroidal hemangiomas that

have history of treatment failure, or are not candidates for laser and cryotherapy due to subfoveal location or if there is presence of extensive subretinal fluid; this is due to the potential for radiation-induced complications such as cataract, retinopathy and papillopathy.[35,45]

Brachytherapy has also been used in the management of DCH in selected cases where the diffuse area can be covered by brachytherapy. Murthy et al have used Ru-106 brachytherapy in the treatment of a 10-year-old child with DCH and secondary total exudative retinal detachment.[46] They observed a 50% reduction in tumour thickness, resolution of subretinal fluid and improvement of visual acuity from 6/60 to 6/9 at the end of one month without any radiation-related complications. In summary, brachytherapy can be used in the management of choroidal hemangiomas, especially in larger lesions which are not amenable to laser photocoagulation or PDT. Furthermore, brachytherapy can treat both foveal and non-foveal lesions[47] along with a lower re-detachment rate.[41]

Neovascular Age-Related Macular Degeneration

Age-Related Macular Degeneration (AMD) is one of the major contributors to blindness in developed countries. AMD can be of two types; atrophic (dry) AMD and neovascular (wet) AMD. Out of these two types, it is the neovascular AMD in which the role of radiation has been described. The therapeutic effect of radiation in neovascular AMD can be seen with relatively low doses of radiation (15-20 Gy). Radiation causes lengthening of the capillary endothelial cell nuclei resulting in narrowed capillary lumen, capillary occlusion and hence at the end, leading to endothelial cell loss.[48] Proliferating choroidal neovascular (CNV) cells in the radiosensitive cell cycle phase are highly mitotic and hence more easily damaged by low doses of radiation. The retina and optic disc is spared from the effect of radiation as these structures are relatively radio-resistant at lower doses of radiation.[49,50] Therefore, lower doses of ionizing radiation can be effective against proliferating CNV cells while being relatively safer for the retina and optic nerve at the same time.[48]

In 2008, Avila et al[51] described the results of 12 months of Phase I trial in which epimacular brachytherapy was used along with intravitreal bevacizumab for the treatment of neovascular AMD. Most of the other studies have used radiation alone in the treatment of neovascular AMD while this trial used intravitreal bevacizumab in combination with radiation therapy. At the end of one year, 68% of subjects improved or maintained best corrected visual acuity. During follow up, no radiation related side effects were observed and the authors concluded that concurrent use of anti-VEGF with epimacular brachytherapy is safe and efficacious in the treatment of subfoveal CNV secondary to AMD.[51] Dugel et al[52] have reported a 2-year safety and efficacy data from a Phase III, multicenter RCT comparing epimacular brachytherapy with ranibizumab monotherapy for the treatment of neovascular AMD but this study failed to support the routine use of epimacular brachytherapy for treatment of wet AMD, despite an acceptable safety profile.[52] In the study, 2.9% of enrolled patients developed radiation retinopathy even though it did not contribute to the loss of vision. An uncontrolled Phase II study found that enrolled patients appeared to need fewer injections of anti VEGF in the year after epimacular brachytherapy, with 81% maintaining best corrected visual acuity and a lower injection rate.[53] Jackson et al have delivered stereotactic radiotherapy to AMD lesions and found encouraging results.[54] The INTREPID study was a randomized, double masked, sham-controlled clinical trial in which a robotically controlled device was used to deliver 16 or 24 Gy radiation through the inferior sclera to the macula by providing three beams of radiation. At the end of one year, a one-third reduction was seen in the frequency of anti-VEGF therapy as compared to controls and visual acuity was significantly better than controls. No cases of radiation retinopathy were reported at the 1 year results, however, year 2 safety study results showed radiation-induced microvascular changes in a few subjects.[54]

Conclusion

Radiotherapy is now a widely accepted treatment modality in oncology.[72] Plaque brachytherapy is an effective eye and vision sparing alternative to enucleation for patients with intraocular tumours. Over the years, its role has expanded to include other ocular conditions, including benign lesions.

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