Eckert & Ziegler

White Paper

THERAPEUTIC MODALITIES FOR UVEAL MELANOMA AND RETINOBLASTOMA: PROS AND CONS

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SUMMARY

Ruthenium Brachytherapy

In most centers in Europe and many other countries around the world, ruthenium plaque radiotherapy is the first choice of treatment for uveal melanoma not exceeding 5 mm in thickness. This is because of the reduced risk of collateral damage to optic nerve, macula and lens. In addition, because ruthenium plaques can be re-used for up to a year, they are more cost effective than other forms of radiotherapy if enough patients are treated. The slim design makes plaque insertion easier, especially in children. The proven high standard of manufacture and dosimetry enhances reliability and safety.

Iodine Brachytherapy

The greater range of the iodine-125 gamma radiation enables treatment of tumors that are too large for ruthenium brachytherapy. However, this is associated with greater risk of visual loss, because of collateral damage to important ocular structures, and the development of a painful eye requiring enucleation because of toxic tumor syndrome. Iodine plaques are bulky and therefore more difficult to position, especially in children.

Palladium Brachytherapy

Palladium brachytherapy causes less collateral damage than iodine brachytherapy but is expensive and not widely used.

Proton Beam Radiotherapy

Proton beam radiotherapy reduces the risk of local recurrence with small, juxtapapillary tumors, which are difficult to treat with plaque brachytherapy. The newer, high-energy beams are less finely focused than those produced by older cyclotrons, which are now reaching the end of their lifespan; the risk of collateral damage to healthy ocular structures is therefore greater. This form of treatment damages superficial tissues that cannot be retracted from the proton beam. This can result in a watery eye with medial tumors or keratinization of the superior palpebral conjunctiva and corneal damage with superior tumors, as well as lash loss, skin depigmentation and other cosmetic defects. As with iodine brachytherapy, proton beam radiation of large tumors is associated with increased risk of tumor recurrence, visual loss and a severe pain from neovascular glaucoma.

Stereotactic Radiotherapy

This form of radiotherapy is reported to cause more side effects than proton beam radiotherapy and therefore tends to be used only when proton beam radiotherapy and brachytherapy are not possible.

Iridectomy

Excision of iris tumors results in enlarged pupils, causing photophobia and a cosmetic defect, and is associated with a significant tumor recurrence rate so that it has largely been replaced by plaque or proton beam radiotherapy.

Exoresection, Cyclectomy, Eyewall Resection

Trans-scleral excisions of ciliary body and choroidal tumors are highly complex procedures, which are therefore performed only rarely in very few centers and then only when radiotherapy is unlikely to conserve the eye and useful vision.

Endoresection

Endoresection of choroidal melanoma with a vitreous cutter can conserve vision in some eyes with juxtapapillary tumors, which would otherwise develop radiation-induced optic neuropathy following plaque brachytherapy, proton beam radiotherapy or stereotactic radiotherapy. However, this operation is highly controversial because of reports of fatal gas embolism following the use of air or perfluorocarbon liquid to flatten the retina. There are also concerns regarding the possibility of tumor dissemination intraocularly and systemically.

Transpupillary Thermotherapy

This laser treatment is associated with a high tumor recurrence rate so that it is rarely performed, except for very small tumors or, after radiotherapy, for exudation or suspected recurrence.

Photodynamic Therapy (PDT)

PDT with verteporfin has not gained wide acceptance because it has a high failure rate. PDT with Au-011 is still experimental.

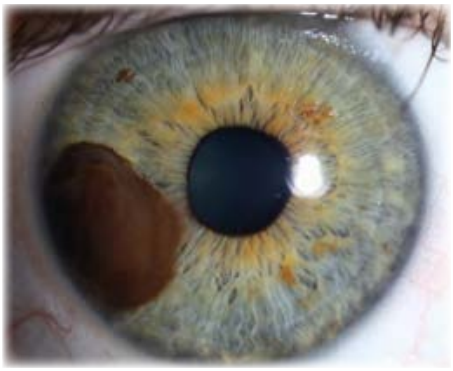
Enucleation

This operation is generally reserved for eyes that are unlikely to remain comfortable and with useful vision after other forms of treatment. Quality-of-life studies have shown wellbeing to be similar to that after radiotherapy adjusting for other factors, such as social support, general health and financial status.

INTRODUCTION

Uveal Melanoma

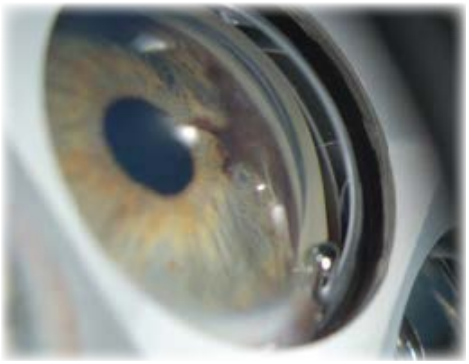
Uveal melanoma is the most common primary, intraocular malignancy.[1] Ocular treatment of this cancer is aimed at preventing metastatic disease, if possible, also conserving the eye and vision; however, about 50% of patients with uveal melanoma develop metastases, despite successful treatment of the ocular tumor.[2] This is because the tumor has already metastasized by the time of treatment.[3] It is not known whether the remaining patients survive because of their ocular treatment or because their tumor did not have metastatic potential at the time of treatment and would never have developed such potential even without receiving treatment.



Iris Melanoma

Another aim of ocular treatment is to prevent the eye from becoming painful and unsightly as a result of neovascular glaucoma, inflammation, or even proptosis.

For many years, the standard treatment was enucleation. This has largely been replaced, whenever possible, by some form of radiotherapy, laser treatment or excision, with each of these performed in isolation or in various combinations. For example, radiotherapy may be followed by laser treatment and local resection may be followed by (adjunctive) radiotherapy or preceded by (neoadjuvant) radiotherapy.



Gonioscopy showing tumor spread around the angle.

The therapeutic modalities deployed at each ocular oncology center depend not only on the size and location of the tumor but also the patient's preferences and, to some extent, the methods that were previously available at that center.[4] For example, patients attending one center may be treated with brachytherapy because proton beam radiotherapy is not available there whereas patients attending a different center with an identical tumor are treated with proton beam radiotherapy because of lack of expertise with brachytherapy.

1 Jager MJ, Shields CL, Cebulla CM, Abdel-Rahman MH, Grossniklaus HE, Stern MH, et al. Uveal melanoma. Nat Rev Dis Primers. 2020;6(1):24.

2 Kujala E, Mäkitie T, Kivelä T. Very long-term prognosis of patients with malignant uveal melanoma. Invest Ophthalmol Vis Sci. 2003;44(11):4651-9.

3 Eskelin S, Pyrhönen S, Summanen P, Hahka-Kemppinen M, Kivelä T. Tumor doubling times in metastatic malignant melanoma of the uvea: tumor progression before and after treatment. Ophthalmology. 2000;107(8):1443-9.

4 Damato B, Heimann H. Personalized treatment of uveal melanoma. Eye (Lond). 2013;27(2):172-9.

Retinoblastoma

Retinoblastoma

Retinoblastoma is an aggressive intraocular cancer that usually presents in the first two years of life. In almost all cases it occurs as a result of biallelic (i.e., both maternal and paternal) mutations of the *RB1* gene.[5] If the first mutation is inherited from a parent, it is present throughout the body. If it occurs during fetal development, the mutation is present in only part of the body (i.e., mosaicism). If it arises in a developing retinal cell, the mutation occurs only in tumor cells derived from that cell. The main priority of treatment is to preserve life by preventing metastatic death and tumor spread along the optic nerve to the brain. Conservation of the eye with useful vision is attempted only if the chances of success are good enough to justify prolonged and intensive treatment with numerous interventions and investigations under general anesthesia.

Treatment is selected according to the size and extent of any intraocular tumors, as categorized by the International Retinoblastoma Classification.[6] Small tumors, less than 3 mm in diameter, are generally treated with laser therapy or cryotherapy, according to whether they are posterior or anterior, respectively. Larger tumors confined to the retina are treated with systemic or intra-arterial chemotherapy, including intravitreal chemotherapy if vitreous seeds are present. Tumors extending beyond the retina into optic nerve, choroid, ciliary body, or anterior segment of the eye are treated by enucleation. Systemic adjuvant therapy is administered if histological examination of the enucleated eye indicates an increased risk of orbital tumor recurrence or metastatic disease. In patients with a germline mutation, radiotherapy is avoided because of the risk of inducing second malignant neoplasms. Some tumors resistant to other forms of treatment are treated with radiotherapy, in which case brachytherapy or proton beam radiotherapy is usually selected to avoid irradiating healthy tissues. Ocular conservation is more likely to be attempted if tumors are present in both eyes.

Caveats

It is difficult to compare outcomes between centers because the same therapeutic modality may be deployed differently in the different centers and because of variation in measurements of tumor dimensions and outcomes such as visual acuity. Outcomes are greatly influenced by the skills of the team performing the treatment as well as the success with which any side effects and complications are managed. This literature review is not comprehensive and therefore subject to bias induced by the author's personal experience.

5 Dimaras H, Corson TW. Retinoblastoma, the visible CNS tumor: A review. J Neurosci Res. 2019;97(1):29-44.

6 Ancona-Lezama D, Dalvin LA, Shields CL. Modern treatment of retinoblastoma: A 2020 review. Indian J Ophthalmol. 2020;68(11):2356-65.

Aims

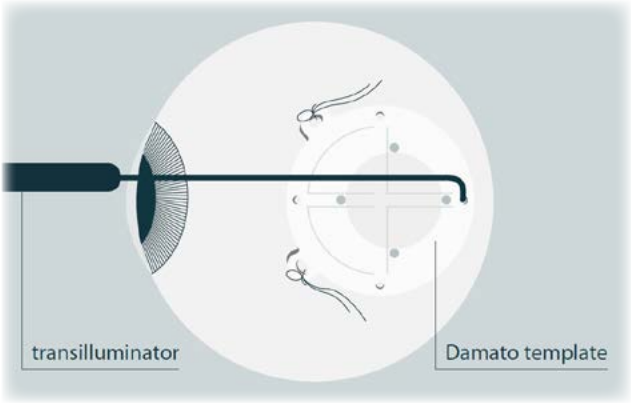
The aims of this document are to describe the available therapeutic modalities for uveal melanomas and retinoblastoma and to highlight the advantages and disadvantages of each type of treatment.

RUTHENIUM BRACHYTHERAPY

Ruthenium-106 brachytherapy is the first choice of treatment for most uveal melanomas in Europe. It is delivered with a saucer-shaped applicator, containing a film of ruthenium-106 that is sandwiched between a thin inner and a thick outer plate of silver.

The applicator is sutured to the wall of the eye overlying the intraocular tumor. The applicator is removed after a specified number of hours according to dose required at a specific distance from the internal plaque surface and according to the age (and hence the activity) of the applicator.

Ruthenium-106 Applicators



Transilluminator shining light through a perforation in a template

Accurate positioning of the plaque over the tumor is achieved more reliably if any overlying extraocular muscles are detached and if a template is used together with a transilluminator that is shone through perforations in the template at known distances from the edge of the template. While performing transillumination through these perforations, the surgeon examines the back of the eye with a binocular indirect ophthalmoscope to determine the distance between each spot of light (from the transilluminator) and the tumor margin (i.e., 'sunset sign'). When the applicator is removed, any detached muscles are sutured back in place.

A minimum dose of approximately 85 to 100 Gy is delivered to the tumor apex over 2 to 7 days. Damato also specifies a minimum scleral dose of 350 Gy, which ensures visible choroidal atrophy six months post-operatively, enabling confirmation of previous plaque position; however, he positions the posterior plaque edge at the posterior tumor margin, using side-scatter of radiation to achieve the required safety margin.

With correct technique and good patient selection, the chances of local tumor control are better than 90%.[7] The chances of conserving vision of 20/40 or better are about 75% if the tumor does not extend less than 3 mm from the optic disc or fovea.[8]

7 Damato B, Patel I, Campbell IR, Mayles HM, Errington RD. Local tumor control after 106Ru brachytherapy of choroidal melanoma. Int J Radiat Oncol Biol Phys. 2005;63(2):385-91.

8 Damato B, Patel I, Campbell IR, Mayles HM, Errington RD. Visual acuity after Ruthenium(106) brachytherapy of choroidal melanomas. Int J Radiat Oncol Biol Phys. 2005;63(2):392-400.

The main complications are:

- Scleral thinning or necrosis, especially if irradiated sclera is left unprotected by conjunctiva after plaque removal
- Visual loss from collateral damage to optic nerve, fovea and lens (depending on plaque position)
- 'Toxic tumor syndrome' (a term coined by the author) with release of fluid and angiogenic factors from the irradiated tumor causing macular edema, retinal detachment, iris neovascularization and neovascular glaucoma (depending on tumor size)[9]
- Local tumor recurrence (also rare), which in addition to requiring further treatment may perhaps result in metastatic disease in some patients.[10]

Advantages

Uveal Melanoma

- Radiation is localized to the tumor, because of short range of beta radiation, so that compared to iodine-125 brachytherapy there is relatively low risk of radiation-induced optic neuropathy, radiation-induced macular atrophy, and cataract, unless the ruthenium applicator needs to be placed close to these structures.[10, 11]
- The limited range also reduces the incidence and severity of radiation vasculopathy in patients with diabetes mellitus, who tend to develop sight-threatening diabetic retinopathy even in the absence of radiation.[12]
- A review of 21 studies reports that with good patient selection high rates of local tumor control can be achieved with ruthenium brachytherapy.[13]
- As with other forms of brachytherapy, no damage is caused to eyelid and canaliculi, so that loss of lashes, eyelid scarring, skin de-pigmentation and a watery eye do not occur. This is unlike proton beam radiotherapy, which causes these problems if it is not possible to retract the eyelids out of the beam. With brachytherapy there is no risk of damage to the muco-cutaneous junction at the upper lid margin and therefore no risk of keratinization of superior tarsal conjunctiva and hence no painful corneal abrasion from such keratin. This is unlike proton beam radiotherapy if the upper eyelid margin cannot be retracted out of the radiation field.[14]

9 Damato B. Vasculopathy After Treatment of Choroidal Melanoma. In: Joussen AM, Gardner TW, Kirchhof B, Ryan SJ, editors. Retinal Vascular Disease. Heidelberg: Springer; 2007. p. 582-91.

10 Stålhammar G, Seregard S, Damato B. Uveal melanoma: brachytherapy. In: Damato B, Singh A, editors. Clinical Ophthalmic Oncology Uveal Tumors. 3rd ed. Switzerland: Springer Nature; 2019. p. 201-17.

11 Stöckel E, Eichmann M, Flühs D, Sommer H, Biewald E, Bornfeld N, et al. Dose Distributions and Treatment Margins in Ocular Brachytherapy with 106Ru Eye Plaques. Ocul Oncol Pathol. 2018;4(2):122-8.

12 Viebahn M, Barricks ME, Osterloh MD. Synergism between diabetic and radiation retinopathy: case report and review. Br J Ophthalmol. 1991;75(10):629-32.

13 Karimi S, Arabi A, Siavashpour Z, Shahraki T, Ansari I. Efficacy and complications of ruthenium-106 brachytherapy for uveal melanoma: a systematic review and meta-analysis. J Contemp Brachytherapy. 2021;13(3):358-64.

14 Konstantinidis L, Roberts D, Errington RD, Kacperek A, Heimann H, Damato B. Transpalpebral proton beam radiotherapy of choroidal melanoma. Br J Ophthalmol. 2015;99(2):232-5.

- Because of the long half-life of around 374 days, the same applicator can be used with many patients over a 1-year period, reducing cost per patient if enough patients are treated each year.
- Compared to other forms of radiotherapy, there is less tendency for ruthenium brachytherapy to be followed by visual loss from exudation, because the high beta radiation dose at the base of the tumor causes vascular closure in this area.[15]
- Brachytherapy of iris melanoma avoids the iris coloboma that usually occurs after iridectomy so that there is less photophobia (i.e., intolerance of bright light).[16] Although the dosimetry with brachytherapy is not as favorable as with proton beam radiotherapy, because the plaque delivers a higher dose of radiation to the cornea than to the tumor, in practice this does not seem to be a problem.[17]
- Ruthenium plaques are thin and therefore easier to position than bulky iodine plaques.

Retinoblastoma

- The limited range of beta radiation is also an advantage in patients with germline retinoblastoma, in whom exposure to ionizing radiation increases the risk of second malignant neoplasms.[18]

Challenges

Uveal Melanoma

- Treatment of juxtapapillary tumors is associated with a higher recurrence rate, because of difficulty positioning the plaque adequately and because of the low radiation dose delivered to the optic disc edge. Except for thick tumors overhanging the optic disc, these problems can be overcome by using a template to ensure correct plaque position and by delivering a high scleral dose.[19]

Retinoblastoma

- Some surgeons find it challenging to treat retinoblastoma with brachytherapy because they find it difficult to localize the tumor, which unlike melanoma does not cast a shadow on the sclera with transpupillary transillumination. This problem is easily overcome using a Damato Template together with the right-angled, 25G transilluminator that is designed for use with this template.

15 Chiam PJ, Coupland SE, Kalirai H, Groenewald C, Heimann H, Damato BE. Does choroidal melanoma regression correlate with chromosome 3 loss after ruthenium brachytherapy? Br J Ophthalmol. 2014;98(7):967-71.

16 Marinkovic M, Horeweg N, Laman MS, Bleeker JC, Ketelaars M, Peters FP, et al. Ruthenium-106 brachytherapy for iris and iridociliary melanomas. Br J Ophthalmol. 2018;102(8):1154-9.

17 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(1):46-50.

18 Temming P, Arendt M, Viehmann A, Eisele L, Le Guin CH, Schündeln MM, et al. Incidence of second cancers after radiotherapy and systemic chemotherapy in heritable retinoblastoma survivors: A report from the German reference center. Pediatr Blood Cancer. 2017;64(1):71-80.

19 Fili M, Astrahan M, Stålhammar G. Long-term outcomes after enucleation or plaque brachytherapy of choroidal melanomas touching the optic disc. Brachytherapy. 2021;20(6):1245-56

Disadvantages

Uveal Melanoma

- Ruthenium brachytherapy is not recommended for tumors more than 5 mm in thickness, although some success has been reported with larger tumors.[20] Thicker tumors can be treated with other methods, such as iodine brachytherapy, proton beam radiotherapy and stereotactic radiotherapy; however the chances of achieving local tumor control and conserving useful vision are reduced.

IODINE BRACHYTHERAPY

Iodine-125 is the isotope that is currently most widely used in the United States. The applicator consists of a concave shell with iodine-125 seeds attached to its inner surface by means of a silicone insert or medical-grade adhesives. As with ruthenium applicators, iodine-125 plaques are sutured to the globe directly adjacent to the tumor by means of eyelets.

COMS Eye Applicator with I-125 Ophthalmic Seeds

Advantages

Uveal Melanoma

- With iodine plaques, it is possible to treat uveal melanomas exceeding 5 mm in thickness.[21]
- Because of their longer range of radiation and the relatively high side-scatter, iodine plaques have a lower rate of treatment failure with melanomas involving the optic disc margin, with which posterior plaque placement is prevented by the thickness of the optic nerve.[22]
- As with ruthenium brachytherapy, iodine brachytherapy does not cause eyelid damage.[23]
- It is possible to improve dosimetry by adjusting the number and distribution of seeds in the applicator, especially with collimation as well as advanced computer modeling.[24]

20 Kaiserman N, Kaiserman I, Hendler K, Frenkel S, Pe'er J. Ruthenium-106 plaque brachytherapy for thick posterior uveal melanomas. Br J Ophthalmol. 2009;93(9):1167-71.

21 Reichstein D, Karan K. Plaque brachytherapy for posterior uveal melanoma in 2018: improved techniques and expanded indications. Curr Opin Ophthalmol. 2018;29(3):191-8.

22 Hegde JV, McCannel TA, McCannel CA, Lamb J, Wang PC, Veruttipong D, et al. Juxtapapillary and circumpapillary choroidal melanoma: globe-sparing treatment outcomes with iodine-125 notched plaque brachytherapy. Graefes Arch Clin Exp Ophthalmol. 2017;255(9):1843-50.

23 Bolling JP, Dagan R, Rutenberg M, Mamalui-Hunter M, Buskirk SJ, Heckman MG, et al. Treatment of Uveal Melanoma With Radioactive Iodine 125 Implant Compared With Proton Beam Radiotherapy. Mayo Clin Proc Innov Qual Outcomes. 2022;6(1):27-36.

24 Le BHA, 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(6):981-9.

- In centers treating small numbers of patients the cost per patient using iodine seeds may be less than with ruthenium brachytherapy.

Retinoblastoma

- Iodine brachytherapy may be useful as salvage therapy for retinoblastomas that have not responded adequately to other forms of therapy.[25]

Challenges

Uveal Melanoma

- Treatment of large choroidal melanomas is associated with an increased risk of a blind and painful eye from toxic tumor syndrome.[26] This toxicity may be prevented or reduced with prophylactic anti-angiogenic therapy in some patients.[27]

Disadvantages

Uveal Melanoma

- Large choroidal melanomas are more likely to recur after radiotherapy, although less so than with ruthenium.[28, 29]
- The long range of radiation is more likely to cause collateral damage to the optic nerve, macula and lens, than ruthenium plaque radiotherapy.[30] Such collateral damage is reported to be less with Eye Physics plaques than with COMS plaques, because of improved collimation of the radiation.[24]
- Iodine applicators are bulky and therefore more difficult to position accurately than ruthenium applicators.
- Because of their bulk, iodine plaques are more likely to require detachment of an extraocular muscle and this increases the risk of diplopia, with one study reporting an incidence of 32.5%.[23]

25 Soliman SE, Bansal A, De Nicola ML, Bhambhwani V, Laperriere N, Gallie BL, et al. Applications of iodine-125 plaque radiotherapy for residual or recurrent retinoblastoma. Can J Ophthalmol. 2021;56(5):317-24

26 Groenewald C, Konstantinidis L, Damato B. Effects of radiotherapy on uveal melanomas and adjacent tissues. Eye (Lond). 2013;27(2):163-71.

27 Chang M, Dalvin LA, Mazloumi M, Martin A, Yaghy A, Yang X, et al. Prophylactic Intravitreal Bevacizumab After Plaque Radiotherapy for Uveal Melanoma: Analysis of Visual Acuity, Tumor Response, and Radiation Complications in 1131 Eyes Based on Patient Age. Asia Pac J Ophthalmol (Phila). 2020;9(1):29-38.

28 Jampol LM, Moy CS, Murray TG, Reynolds SM, Albert DM, Schachat AP, et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: IV. Local treatment failure and enucleation in the first 5 years after brachytherapy. COMS report no. 19. Ophthalmology. 2002;109(12):2197-206.

29 Filì M, Trocme E, Bergman L, See TRO, 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(1):26-32.

30 Oare C, Sun S, Dusenbery K, Reynolds M, Koozekanani D, Gerbi B, et al. Analysis of dose to the macula, optic disc, and lens in relation to vision toxicities - A retrospective study using COMS eye plaques. Phys Med. 2022;101:71-8.

- Iodine-125 has a half-life of 60 days so that each plaque is used for only one or two patients, increasing costs.

Retinoblastoma

- The long range of radiation increases the radiation dose to healthy tissues around the eye, increasing the risk of second malignant neoplasms in patients with a germline retinoblastoma.[18]
- The long range of radiation also increases the risk of collateral damage to optic nerve and other intraocular structures.
- The challenge of accurately positioning the bulky applicator is even greater when treating children.

PALLADIUM BRACHYTHERAPY

Palladium brachytherapy is administered with a saucer-shaped applicator containing palladium-103 seeds, which have a 25% lower energy than iodine-125 so that collateral damage to optic nerve, macula and lens is less. A dose of 73 Gy is delivered to the tumor apex over 5-7 days.

Advantages

Uveal Melanoma

- Unlike proton beam and stereotactic radiotherapy, palladium brachytherapy does not cause eyelid damage (as is the case with other forms of brachytherapy).[31]
- Palladium brachytherapy also causes less collateral damage to optic nerve and macula than iodine brachytherapy.[31, 32]
- A comparison of palladium versus iodine brachytherapy reports equivalent rates of local tumor control with less radiation toxicity after palladium brachytherapy.[32]

Retinoblastoma

- Maheshwari and Finger have reported successful pallidum plaque treatment of an 8-year-old girl with solitary retinoblastoma.[33]

31 Finger PT, Chin KJ, Duvall G, Group P-fCMS. Palladium-103 ophthalmic plaque radiation therapy for choroidal melanoma: 400 treated patients. Ophthalmology. 2009;116(4):790-6, 6.e1.

32 Patel KR, Prabhu RS, Switchenko JM, Chowdhary M, Craven C, Mendoza P, et al. Visual acuity, oncologic, and toxicity outcomes with 103 Pd vs. 125I plaque treatment for choroidal melanoma. Brachytherapy. 2017;16(3):646-53.

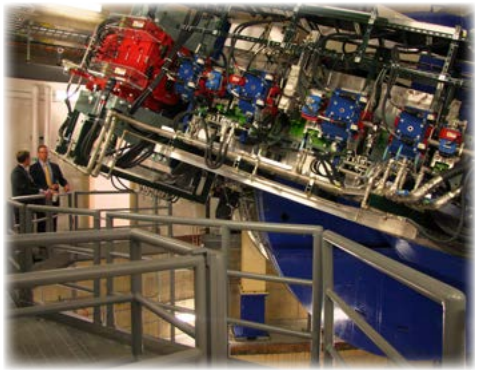
33 Maheshwari A, Finger PT. Palladium-103 plaque brachytherapy for retinoblastoma: Long term follow up. Am J Ophthalmol Case Rep. 2022;27:101636.

Disadvantages

- Palladium brachytherapy is more expensive than iodine brachytherapy.[31]

PROTON BEAM RADIOTHERAPY

With proton beam radiotherapy, protons are directed at the tumor where they release ionizing radiation at the depth where they stop moving so that the dose-depth curve shows a 'Bragg Peak' (i.e., focusing within the tumor) with some sparing of superficial tissues.



Proton therapy synchrocyclotron at the Mayo Clinic in Rochester, Minnesota

Cyclotrons enabling proton beam radiotherapy of the eye are increasing in number around the world, but newer devices emit higher-energy beams that are not as well focused as the older, low-energy beams.

The treatment involves the following steps:

- Tumor and ocular measurements with ultrasonography, MRI and/or CT
- Insertion of fiducial, tantalum markers at known distances from tumor margins, limbus, and each other
- Simulation and preparation of treatment plans
- A course of radiotherapy on 4 or 5 consecutive days to deliver a dose of 50-70 Gy

During the treatment the patient is asked to look at a fixation target. The face is held immobile with a face mask and dental bite, which are individualized for each patient.

Advantages

Uveal Melanoma

- The treatment planning adjusts for any inaccurate measurements of tumor dimensions or tantalum marker locations. In some cases (e.g., small, posterior tumors), the risk of local treatment failure is therefore less than with brachytherapy, which depends on the ability to place the plaque precisely at its desired location.[34]

34 Damato B, Kacperek A, Chopra M, Campbell IR, Errington RD. Proton beam radiotherapy of choroidal melanoma: The Liverpool-Clatterbridge experience. Int J Radiat Oncol Biol Phys. 2005;62(5):1405-11.

- With proton beam radiotherapy, there is no limit to the size of tumor that can be treated. However, with large tumors the results are disappointing, with a study from Boston reporting ten-year retention of vision better than 20/200 in only 9% of cases.[35] Further, this study reported ocular retention in only 70.4% and tumor recurrence in 12.5%. Quality of life is probably better after enucleation in such cases.[36]
- Proton beam radiotherapy for iris melanoma is highly effective and does not require any surgical procedures.[37, 38, 39, 40] Irradiation of the entire anterior segment can conserve some eyes with extensive diffuse iris melanoma.[41]

Retinoblastoma

- Proton beam radiotherapy may be useful as rescue therapy after other methods have failed to achieve local tumor control.[42, 43]

Challenges

Recurrent iris melanoma following proton beam radiotherapy

Uveal Melanoma

- Proton beam radiotherapy of iris melanoma can be complicated by local tumor recurrence if the extent of the tumor is underestimated clinically or if diffuse seeding is not detected.[44]

35 Papakostas TD, Lane AM, Morrison M, Gragoudas ES, Kim IK. Long-term Outcomes After Proton Beam Irradiation in Patients With Large Choroidal Melanomas. JAMA Ophthalmol. 2017;135(11):1191-6.

36 Damato B, Hope-Stone L, Cooper B, Brown S, Heimann H, Dunn L. Patient-Reported Outcomes and Quality of Life after Treatment for Choroidal Melanoma. Ocul Oncol Pathol. 2019;5(6):402-11.

37 Oxenreiter MM, Lane AM, Aronow MB, Shih H, Trofimov AV, Kim IK, et al. Proton beam irradiation of uveal melanoma involving the iris, ciliary body and anterior choroid without surgical localisation (light field). Br J Ophthalmol. 2022;106(4):518-21.

38 Damato B, Kacperek A, Chopra M, Sheen MA, Campbell IR, Errington RD. Proton beam radiotherapy of iris melanoma. Int J Radiat Oncol Biol Phys. 2005;63(1):109-15.

39 Hauzinger JA, Blatsios G, Haas G, Zehetner C, Velez-Escola L, Nowosielski Y, et al. Proton beam radiation for iris melanoma: case series and review of literature. BMJ Open Ophthalmol. 2021;6(1):e000683.

40 Gollrad J, Boeker A, Vitzthum S, Besserer A, Heufelder J, Gauger U, et al. Proton therapy for 166 patients with iris melanoma: side effects and oncological outcome. Ophthalmol Retina. 2022.

41 Konstantinidis L, Roberts D, Errington RD, Kacperek A, Damato B. Whole anterior segment proton beam radiotherapy for diffuse iris melanoma. Br J Ophthalmol. 2013;97(4):471-4.

42 Biewald E, Kiefer T, Geismar D, Schlüter S, Manthey A, Westekemper H, et al. Feasibility of Proton Beam Therapy as a Rescue Therapy in Heavily Pre-Treated Retinoblastoma Eyes. Cancers (Basel). 2021;13(8).

43 Mouw KW, Yeap BY, Caruso P, Fay A, Misra M, Sethi RV, et al. Analysis of patient outcomes following proton radiation therapy for retinoblastoma. Adv Radiat Oncol. 2017;2(1):44-52.

44 Sandinha MT, Kacperek A, Errington RD, Coupland SE, Damato B. Recurrence of iris melanoma after proton beam therapy. Br J Ophthalmol. 2014;98(4):484-7.

- Extensive irradiation of the iris is associated with glaucoma, although it is uncertain as to whether this is due to the radiation or tumor growth in the trabecular meshwork obstructing aqueous outflow.[40] Other side effects include cataract in most cases and corneal stem cell deficiency in a minority.

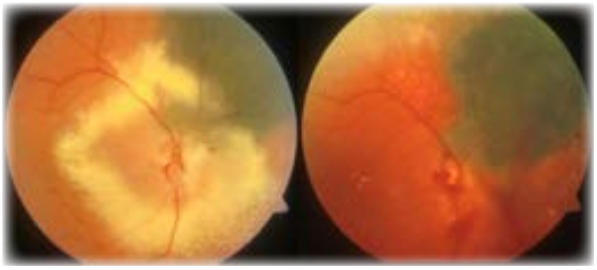
Retinoblastoma

- In babies, proton beam radiotherapy for retinoblastoma requires several general anesthetics, which may be a problem in some centers.
- In patients with germline retinoblastoma, irradiation of the eyelids may result in a second malignant neoplasm (e.g., sebaceous gland carcinoma) in later life. In some cases, this risk may be reduced by adjusting the entry side and angle of the proton beam, depending on tumor location.[45]

Disadvantages

Uveal Melanoma

- When it is necessary to convert the sharp Bragg Peak into multiple adjacent Bragg Peaks to achieve a 'plateau' of high-dose radiation, because the tumor is large, the relative sparing of superficial tissues is diminished. This can result in a canalicular damage and a watery eye if the tumor is medial, superior tarsal conjunctival keratinization and corneal abrasion if the tumor is superior, and cosmetic changes irrespective of tumor location (i.e., loss of lashes, depigmentation of eyelid skin).
- Proton beam radiotherapy is not widely available. Although the number of centers providing this treatment is increasing, these now provide high-energy beams, which have a wider 'penumbra' than older cyclotrons, so that there is more collateral damage to healthy ocular structures, such as the optic nerve, macula and lens. Another problem is that if the demand on a proton beam service is excessive, patients with more urgent needs (e.g., life-threatening brain tumors) may be prioritized over those with an ocular tumor, in whom treatment is aimed at conserving the eye, hopefully with useful vision (which depends not only on the vision in the treated eye but the quality of vision in the fellow eye).
- The relatively low dose of radiation near the tumor base, compared to ruthenium brachytherapy, may be the reason why there is more exudation after proton beam radiotherapy than after ruthenium treatment and, therefore, why mmacular edema is more common and severe. This is because, unlike ruthenium brachytherapy, the radiation dose does not obliterate the vasculature near the tumor base so that these irradiated blood vessels leak fluid.[46]



Exudation (left) followed by vitreous hemorrhage (right) after proton beam radiotherapy

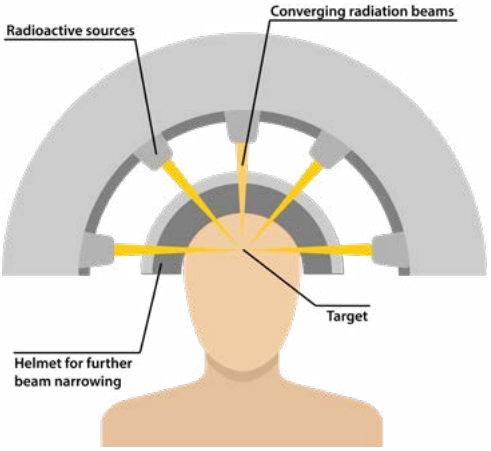
45 Krengli M, Hug EB, Adams JA, Smith AR, Tarbell NJ, Munzenrider JE. Proton radiation therapy for retinoblastoma: comparison of various intraocular tumor locations and beam arrangements. Int J Radiat Oncol Biol Phys. 2005;61(2):583-93.

46 Damato B. Predicting Choroidal Melanoma Regression after Brachytherapy. Ophthalmology. 2018;125(5):755-6.

Retinoblastoma

- Proton beam radiotherapy in early life can cause orbital hypoplasia, with facial disfigurement if bone is included in the radiation field.[45]

STEREOTACTIC RADIOTHERAPY



Functionality of stereotactic radiotherapy

With stereotactic radiotherapy, multiple fine radiation beams are focused on the tumor from different directions, either in a single session ('stereotactic radiosurgery') or over several days ('fractionated stereotactic radiotherapy').

Leksell Gamma Knife radiosurgery involves the placement of a cup-shaped frame over the patient's head and administering a dose of approximately 20-60 Gy from 201 cobalt-60 sources in a single fraction.

Cyberknife robotic radiosurgery is delivered in a single fraction with a 6 MV linear accelerator mounted on a robotic arm, with stereoscopic x-ray imaging to localize the target tissue.

Fractionated stereotactic radiotherapy is administered with a linear accelerator (LINAC) with a total of 50 Gy delivered over five consecutive days.

Advantages

Uveal Melanoma

- Fractionated stereotactic radiotherapy is possible for tumors up to 12 mm in thickness and up to 16 mm in diameter.
- Unlike proton beam radiotherapy, insertion of fiducial tantalum markers for radiographic tumor localization is not required. Apart from avoiding the need for surgery, this allows treatment planning even when the tumor is obscured by media opacities, such as vitreous hemorrhage.
- Facilities for stereotactic radiotherapy are more widely available than for proton beam radiotherapy

Retinoblastoma

- A team in Moscow has reported stereotactic gamma knife radiosurgery in 19 eyes of 18 patients whose parents refused enucleation.[47]

47 Yarovoy AA, Golanov AV, Yarovaya VA, Kostjuchenko VV, Volodin DP. Stereotactic Gamma Knife® Radiosurgery of Intraocular Retinoblastoma: Six-Year Experience. Cureus. 2022;14(9):e28751.

Disadvantages

Uveal Melanoma

- Several studies report worse conservation of vision with stereotactic radiotherapy than with proton beam radiotherapy as well as iodine and ruthenium brachytherapy (although reference groups were not identical).[48, 49, 50, 51, 52] The worse ocular morbidity after stereotactic radiotherapy is likely to be caused by greater collateral damage to optic nerve and macula.[53]
- Other side-effects of stereotactic radiotherapy include cataract, neovascular glaucoma, optic neuropathy, radiation retinopathy, vitreous hemorrhage, and keratoconjunctivitis sicca.[49, 54]

Retinoblastoma

- Stereotactic radiotherapy exposes non-ocular tissues in the head to low doses of radiation and may result in second malignant neoplasms in patients with germline retinoblastoma.[47]

EXORESECTION

- Exoresection (also known as trans-scleral local resection or eyewall resection) refers to en bloc excision of the intact tumor through a large opening in the wall of the eye.[55] Variations of exoresection include iridectomy (iris), iridocyclectomy (iris and ciliary body), cyclochoroidectomy (ciliary body and choroid) and choroidectomy (choroid).
- For tumors not extending to the anterior chamber angle, iridectomy involves excising the tumor with a surround of healthy tissue and this is done through a circumferential corneal incision.

48 Sikuade MJ, Salvi S, Rundle PA, Errington DG, Kacperek A, Rennie IG. Outcomes of treatment with stereotactic radiosurgery or proton beam therapy for choroidal melanoma. Eye (Lond). 2015;29(9):1194-8.

49 Muller K, Naus N, Nowak PJ, Schmitz PI, de Pan C, van Santen CA, et al. Fractionated stereotactic radiotherapy for uveal melanoma, late clinical results. Radiother Oncol. 2012;102(2):219-24.

50 Guleser UY, Sarici AM, Ucar D, Gonen B, Sengul Samanci N, Özgüroğlu M. Comparison of iodine-125 plaque brachytherapy and gamma knife stereotactic radiosurgery treatment outcomes for uveal melanoma patients. Graefes Arch Clin Exp Ophthalmol. 2022;260(4):1337-43.

51 Krema H, Heydarian M, Beiki-Ardakani A, Weisbrod D, Xu W, Laperriere NJ, et al. Dosimetric and late radiation toxicity comparison between iodine-125 brachytherapy and stereotactic radiation therapy for juxtapapillary choroidal melanoma. Int J Radiat Oncol Biol Phys. 2013;86(3):510-5.

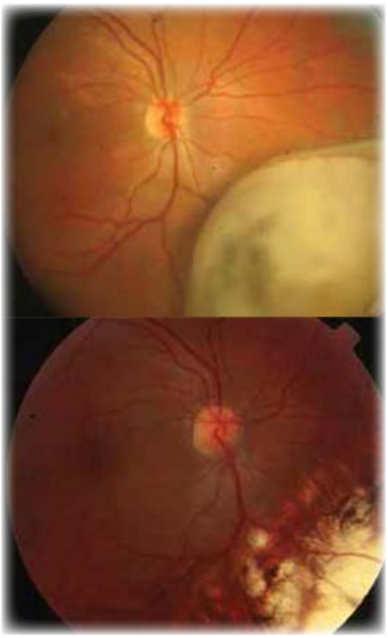
52 Mazzini C, Pieretti G, Vicini G, Nicolosi C, Scoccianti S, Pertici M, et al. Clinical outcomes and secondary glaucoma after gamma-knife radiosurgery and Ruthenium-106 brachytherapy for uveal melanoma: a single institution experience. Melanoma Res. 2021;31(1):38-48.

53 Höcht S, Stark R, Seiler F, Heufelder J, Bechrakis NE, Cordini D, et al. Proton or stereotactic photon irradiation for posterior uveal melanoma? A planning intercomparison. Strahlenther Onkol. 2005;181(12):783-8.

54 van Beek JGM, Ramdas WD, Angi M, van Rij CM, Naus NC, Kacperek A, et al. Local tumour control and radiation side effects for fractionated stereotactic photon beam radiotherapy compared to proton beam radiotherapy in uveal melanoma. Radiother Oncol. 2021;157:219-24.

55 Damato BE. Local resection of uveal melanoma. Dev Ophthalmol. 2012;49:66-80.

- Iridocyclectomy is performed by preparing a lamellar scleral flap, hinged at the corneal limbus, then excising the iris and ciliary body together with the deep scleral lamella. Next, the lamellar scleral flap is closed with sutures and, in selected cases, adjunctive plaque brachytherapy is administered about four weeks later, once wound healing has occurred.[56] Hypotensive anesthesia is not required as hemorrhage is not severe.
- Choroidectomy is performed by preparing a large, lamellar scleral flap, hinged posteriorly and softening the globe by core vitrectomy. The tumor is then excised together with the deep scleral lamella, followed by closure of the scleral flap with sutures. Finally, the globe is filled with balanced salt solution and adjunctive brachytherapy is administered. Profound systemic hypotension is required to control hemorrhage.[55, 57]
- Iridectomy is not too difficult, but iridocyclectomy requires special expertise and choroidectomy is a highly complex procedure so that it has been performed only rarely by very few ocular oncologists.



Choroidal melanoma before and after exoresection by the author

Advantages

Iris Melanoma

- Iridectomy provides a tissue for diagnosis.
- Resection is less likely to cause cataract and corneal problems than radiotherapy.[58]

Ciliary Body Melanoma

- Excision provides tissue for diagnosis, which is especially useful as ciliary body tumors are more likely to be conditions other than melanoma (e.g., neurilemmoma/schwannoma, leiomyoma, etc).

Choroidal Melanoma

- If performed by an experienced surgeon, exoresection can conserve the eye and vision when radiotherapy is likely to result in a blind and painful eye from toxic tumor syndrome on account of large tumor size.[55]

56 Rospond-Kubiak I, Damato B. The surgical approach to the management of anterior uveal melanomas. Eye (Lond). 2014;28(6):741-7.

57 Shields JA, Shields CL, Shah P, Sivalingam V. Partial lamellar sclerouvectomy for ciliary body and choroidal tumors. Ophthalmology. 1991;98(6):971-83.

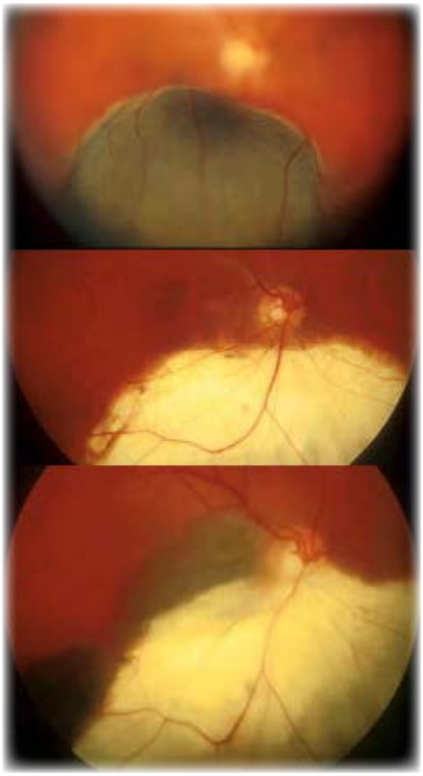
58 Popovic M, Ahmed IIK, DiGiovanni J, Shields CL. Radiotherapeutic and surgical management of iris melanoma: A review. Surv Ophthalmol. 2017;62(3):302-11.

- In some cases, exoresection offers the best opportunity to conserve the eye that has developed toxic tumor syndrome after radiotherapy.[59]

Retinoblastoma

- Exoresection is contraindicated because of the high risk of tumor seeding into surrounding tissues.

Challenges



Local recurrence three years after exoresection

Iris Melanoma

- Tumor excision may be incomplete so that the patient requires salvage therapy consisting of brachytherapy, proton beam radiotherapy or enucleation, performed either immediately or if close monitoring reveals local tumor re-growth.

Ciliary Body Melanoma

- Cyclectomy is a highly skilled procedure, which can result in hypotony, retinal detachment and other severe complications with loss of the eye if not performed correctly.
- A serious complication is local tumor recurrence. This risk can be mitigated by administering adjunctive plaque radiotherapy; however, this radiotherapy can cause cyclodialysis (detachment of the ciliary body from the sclera) and severe hypotony (low intraocular pressure) unless the surgeon is aware of the need to delay the radiotherapy for several weeks until adhesions have developed between the ciliary body and the sclera.

Choroidal Melanoma

- Local tumor recurrence is a serious complication but can usually be prevented by administering brachytherapy with a 25 mm ruthenium plaque.[60, 61]

59 Konstantinidis L, Groenewald C, Coupland SE, Damato B. Trans-scleral local resection of toxic choroidal melanoma after proton beam radiotherapy. Br J Ophthalmol. 2014;98(6):775-9.

60 Damato BE, Paul J, Foulds WS. Risk factors for residual and recurrent uveal melanoma after trans-scleral local resection. Br J Ophthalmol. 1996;80(2):102-8.

61 Damato B. Adjunctive plaque radiotherapy after local resection of uveal melanoma. Front Radiat Ther Oncol. 1997;30:123-32.

Disadvantages

Iris Melanoma

- Iridectomy results in an iris coloboma (i.e., iris defect), which causes a cosmetic defect and light intolerance.[62] In some patients this can be treated with a painted contact lens, an artificial iris implant, or suturing of the iris.

Choroidal Melanoma

- Exoresection for choroidal melanoma is rarely if ever performed today because it needs a high level of surgical expertise as well as an experienced anesthetist who can safely induce profound hypotensive anesthesia (i.e., with lowering of the blood pressure) for prolonged periods. The main complications are expulsive hemorrhage, rhegmatogenous retinal detachment and local tumor relapse.
- Exoresection can take several hours to perform, and this can be a deterrent in high volume specialties such as ophthalmology.

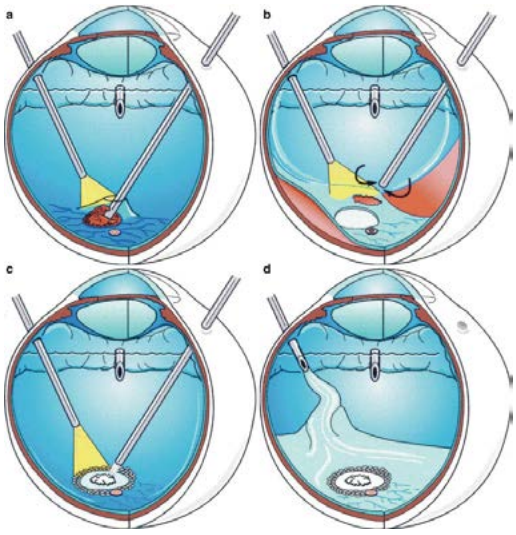
Retinoblastoma

- Not applicable.

ENDORESECTION

Endoresection of choroidal melanoma is a term coined by Damato for piecemeal removal of a tumor with a vitreous cutter.[63] The procedure involves:

- Total vitrectomy
- Tumor removal through a retinotomy
- Endolaser around the retinotomy to prevent retinal detachment ('retinopexy')
- Endolaser to the scleral bed to destroy any tumor remnants
- Silicone fill to prevent post-operative vitreous hemorrhage and retinal detachment with removal of the silicone after about 12 weeks



Endoresection of choroidal melanoma

62 Abouzeid H, Moeckli R, Gaillard MC, Beck-Popovic M, Pica A, Zografos L, et al. (106)Ruthenium brachytherapy for retinoblastoma. Int J Radiat Oncol Biol Phys. 2008;71(3):821-8.

63 Damato B, Groenewald C, McGalliard J, Wong D. Endoresection of choroidal melanoma. Br J Ophthalmol. 1998;82(3):213-8.

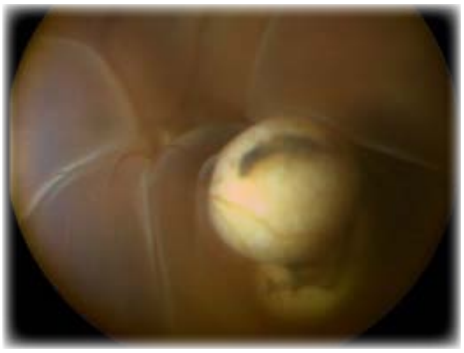
The silicone oil tends to cause cataract, which is usually treated at the time of oil removal. Some authors advocate adjunctive plaque radiotherapy after the endoresection, either selectively or in all patients, to prevent local tumor recurrence.

A few authors advocate neoadjuvant radiotherapy before the endoresection because of concerns that the procedure may disseminate tumor cells throughout the body to cause metastatic disease.[64] Flattening of the retina during the operation with air or perfluorocarbon liquid has been complicated by fatal gas embolism.[65, 66, 67] Although rare, this complication has diminished enthusiasm for this procedure.

Advantages

Choroidal Melanoma

- If performed by an experienced surgeon, endoresection can conserve vision in eyes with a juxtapapillary melanoma (i.e., melanoma very close to optic disc) that would otherwise become blind as a result of optic neuropathy caused by brachytherapy, proton beam radiotherapy, or any other form of radiotherapy.[68]
- Good results can be achieved with thick tumors.[69] Some have reported better visual outcomes than iodine brachytherapy.[70]
- Endoresection is useful for removing toxic tumor after radiotherapy for choroidal melanoma, as a treatment for severe retinal detachment or exudation.[9]



Severe exudative retinal detachment after proton beam radiotherapy of a choroidal melanoma, which was successfully treated by endoresection of the toxic tumor

64 Guberina M, Sokolenko E, Guberina N, Dalbah S, Pöttgen C, Lübcke W, et al. Feasibility, Method and Early Outcome of Image-Guided Volumetric Modulated Arc Radiosurgery Followed by Resection for AJCC Stage IIA-IIIB High-Risk Large Intraocular Melanoma. Cancers (Basel). 2022;14(19).

65 Rojanaporn D, Tipsuriyaporn B, Chulalaksiriboon P, Virankabutra T, Morakul S, Damato B. Fatal Air Embolism after Choroidal Melanoma Endoresection without Air Infusion: A Case Report. Ocul Oncol Pathol. 2021;7(5):321-5.

66 Ruschen H, Romano MR, Ferrara M, Loh GK, Wickham L, Damato BE, et al. Perfluorocarbon syndrome-a possible, overlooked source of fatal gas embolism following uveal-melanoma endoresection. Eye (Lond). 2022.

67 Rice JC, Liebenberg L, Scholtz RP, Torr G. Fatal air embolism during endoresection of choroidal melanoma. Retin Cases Brief Rep. 2014;8(2):127-9.

68 Konstantinidis L, Groenewald C, Coupland SE, Damato B. Long-term outcome of primary endoresection of choroidal melanoma. Br J Ophthalmol. 2014;98(1):82-5.

69 Garcia-Arumi J, Leila M, Zapata MA, Velázquez D, Dinares-Fernandez MC, Tresserra F, et al. Endoresection technique with/without brachytherapy for management of high posterior choroidal melanoma: extended follow-up results. Retina. 2015;35(4):628-37

70 Rice JC, Stannard C, Cook C, Lecuona K, Myer L, Scholtz RP. Brachytherapy and endoresection for choroidal melanoma: a cohort study. Br J Ophthalmol. 2014;98(1):86-91.

Retinoblastoma

- Retinoblastoma is generally regarded as an absolute contraindication to endoresection although tumor removal with a vitreous cutter is being pioneered in China with precautions to prevent tumor seeding.[71, 72]

Disadvantages

Choroidal Melanoma

- Fatal gas embolism can occur during or soon after endoresection when performed with infusion of air or perfluorocarbon liquid into the eye and if these enter the general circulation through the vortex veins.[65, 66, 67]
- Ocular complications include retinal detachment from entry site tears, hemorrhage, cataract, and local tumor relapse.[68]
- Incomplete tumor resection can result in extraocular extension as well as spread into the vitreous through the retinotomy.[73, 74]

Retinoblastoma

- High risk of seeding tumor cells into orbit.

TRANSPUPILLARY THERMOTHERAPY

Transpupillary thermotherapy (TTT) involves gentle heating of the tumor to 45-65°C for about one minute. It is administered at a slit-lamp or down an operating microscope.[75] The technique comprises retrobulbar or peribulbar injection of local anesthetic followed by 3 mm diode laser applications to the entire tumor surface and 1.5 mm of the surrounding choroid, with power adjusted to produce retinal blanching after 45 seconds. The procedure is repeated approximately every 2 months until total flattening of the tumor is achieved.

71 Zhao J, Li Q, Wu S, Jin L, Ma X, Jin M, et al. Pars Plana Vitrectomy and Endoresection of Refractory Intraocular Retinoblastoma. Ophthalmology. 2018;125(2):320-2.

72 Zhao J, Li Q, Feng ZX, Zhang J, Wu S, Jin L, et al. Tylectomy Safety in Salvage of Eyes with Retinoblastoma. Cancers (Basel). 2021;13(22).

73 Damato B, Wong D, Green FD, Mackenzie JM. Intrascleral recurrence of uveal melanoma after transretinal "endoresection". Br J Ophthalmol. 2001;85(1):114-5.

74 Hadden PW, Hiscott PS, Damato BE. Histopathology of eyes enucleated after endoresection of choroidal melanoma. Ophthalmology. 2004;111(1):154-60.

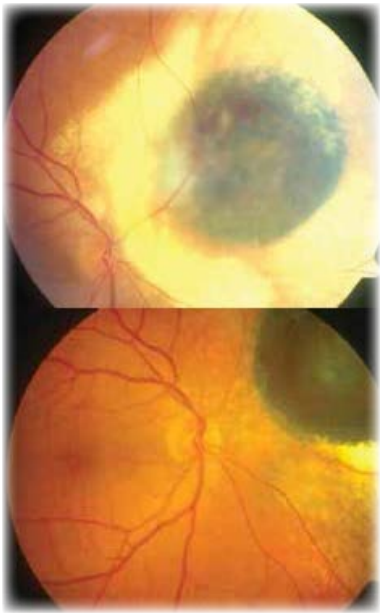
75 ournée-de Korver JG, Keunen JE. Thermotherapy in the management of choroidal melanoma. Prog Retin Eye Res. 2002;21(3):303-17.

Osterhuis et al, who developed TTT, intended it to be administered together with brachytherapy ('sandwich therapy'); however, this was discontinued in most centers. The largest series has been reported by Shields et al, who advocated TTT for post-equatorial melanomas not exceeding 12 mm in diameter and/or 4 mm in thickness.[76]

Advantages

Choroidal Melanoma

- Transpupillary thermotherapy is less 'invasive' than other procedures, requiring only a local anesthetic injection so that it can be performed as an outpatient procedure.
- The laser burns can be applied very precisely so that optic nerve function can be preserved even if the tumor is juxtapapillary.
- TTT can be effective in arresting exudation from an irradiated choroidal melanoma, so that the visual acuity may improve if any subretinal fluid involves the fovea.[9]
- TTT can allow the eye to be conserved if a patient develops a small area of recurrence after previous radiotherapy.



Exudation from an irradiated choroidal melanoma, with resolution after TTT

Retinoblastoma

- Small retinoblastomas up to 3 mm in diameter can successfully be treated with diode or argon laser, especially if located at the equator or more posteriorly.[77] Thermotherapy is also useful as consolidation treatment for retinoblastoma after chemotherapy.[78] The techniques used for retinoblastoma are different from TTT developed for choroidal melanoma.

Disadvantages

Melanoma

- TTT is less reliable than radiotherapy so that there is a greater risk of local tumor recurrence. Using Kaplan-Meier estimates, the Shields group reported a 22% recurrence rate at 3 years.[76]
- TTT can cause several complications, which include retinal vascular occlusion, retinal traction with distortion and possibly detachment, macular edema, neovascularization, and cataract.[76]

76 Shields CL, Shields JA, Perez N, Singh AD, Cater J. Primary transpupillary thermotherapy for small choroidal melanoma in 256 consecutive cases: outcomes and limitations. Ophthalmology. 2002;109(2):225-34.

77 Shields CL, Santos MC, Diniz W, Gündüz K, Mercado G, Cater JR, et al. Thermotherapy for retinoblastoma. Arch Ophthalmol. 1999;117(7):885-93.

78 Shields CL, Honavar SG, Meadows AT, Shields JA, Demirci H, Singh A, et al. Chemoreduction plus focal therapy for retinoblastoma: factors predictive of need for treatment with external beam radiotherapy or enucleation. Am J Ophthalmol. 2002;133(5):657-64.

Retinoblastoma

- Inadequate laser treatment may result in local treatment failure so that the tumor requires intra-arterial or systemic chemotherapy.
- Excessive laser power may cause 'explosions', with tumor seeding into the vitreous cavity, requiring intra-vitreal chemotherapy.[79]
- Laser treatment of pre-equatorial tumors may result in inadvertent iris burns, with the formation of posterior synechiae (i.e., scars attaching the iris margin to the lens), which prevent pupillary dilatation so that it is difficult to examine the retina and treat any active disease in the posterior segment of the globe.

VERTEPORFIN PHOTODYNAMIC THERAPY

Standard photodynamic therapy (PDT) involves the intravenous injection of a photosensitizer, verteporfin, followed by an 83- to 166-second application of 689 nm laser with irradiance of 600 mW/cm^2 to induce necrosis and apoptosis of the tumor and damage to the tumor vasculature.

Advantages

- Local control of small, amelanotic melanomas with minimal or no collateral damage to healthy ocular tissues.[80, 81, 82]

Disadvantages

- High local treatment failure rate.[81, 82] Such failure may increase the risk of extraocular tumor extension and metastasis.

79 Gombos DS, Cauchi PA, Hungerford JL, Addison P, Coen PG, Kingston JE. Vitreous relapse following primary chemotherapy for retinoblastoma: is adjuvant diode laser a risk factor? Br J Ophthalmol. 2006;90(9):1168-72.

80 Campbell WG, Pejnovic TM. Treatment of amelanotic choroidal melanoma with photodynamic therapy. Retina. 2012;32(7):1356-62.

81 Rundle P. Treatment of posterior uveal melanoma with multi-dose photodynamic therapy. Br J Ophthalmol. 2014;98(4):494-7.

82 Turkoglu EB, Pointdujour-Lim R, Mashayekhi A, Shields CL. Photodynamic therapy as primary treatment for small choroidal melanoma. Retina. 2019;39(7):1319-25.

AURA PHOTODYNAMIC THERAPY

Belzupacap Sarotalocan (AU-011) is a first-in-class targeted therapy for choroidal melanoma consisting of a virus-like particle conjungated with phthalocyanine dye.[83] This attaches to tumor-specific heparan sulphate proteoglycans on the surface of malignant cells. When exposed to light with a wavelength of 689 nm, single oxygen is released, which disrupts cell membranes and organelles, causing tumor cell necrosis. The damaged tumor cells release neoantigens, which activate T cells to kill the tumor cells. This therapeutic agent is administered into the suprachoroidal space, using a special device.[84]

During a phase 2 trial in a cohort of 9 patients with small choroidal melanomas, tumor control was reported in 8 cases after a mean follow up of 6 months, with the growth rate reducing substantially. Vision was preserved in 8 patients.[85]

Preclinical studies suggest that AU-011 may be effective in the treatment of choroidal metastases. However, metastases tend to grow rapidly so that it may not be possible to eradicate these tumors in vivo.

Advantages

- If long-term studies show no recurrences after AU-011 treatment for uveal melanoma, an advantage of this treatment would be the avoidance of visual loss from radiation-induced ocular morbidity after plaque brachytherapy or proton beam/stereotactic radiotherapy. Similarly, with choroidal metastases, AU-011 treatment may avoid the need for external beam radiotherapy.

Disadvantages

- AU-011 should be considered experimental until its efficacy if proven, and this is likely to take several years as recurrent tumors may take time to develop. Many oncologists are unlikely to be reassured by slowing down of tumor growth as they would feel more confident if it is completely eradicated. This is because of concerns that local treatment failure may increase the risk of metastatic death. Studies have shown that local tumor recurrence is associated with higher metastatic mortality.[86] However, it has not yet been possible to conclude whether this is because recurrence is the source of the fatal metastasis or whether the recurrence is only an indicator that the tumor is more aggressive.
- The latest protocol for AU-011 therapy would involve treatment on 9 separate occassions over 11 weeks. If the therapy is not available in general ophthalmic clinics, it would be difficult for many patients to attend an ocular oncology centre so frequently, especially if they live far from the oncology center.

83 Kines RC, Varsavsky I, Choudhary S, Bhattacharya D, Spring S, McLaughlin R, et al. An Infrared Dye-Conjugated Virus-like Particle for the Treatment of Primary Uveal Melanoma. Mol Cancer Ther. 2018;17(2):565-74.

84 Wan CR, Muya L, Kansara V, Ciulla TA. Suprachoroidal Delivery of Small Molecules, Nanoparticles, Gene and Cell Therapies for Ocular Diseases. Pharmaceutics. 2021;13(2).

85 Kim IK, on Behalf of the AU-011 Investigator Group, oral presentation, American Academy of Ophthalmology, October 2022

86 Force OOT. Local Recurrence Significantly Increases the Risk of Metastatic Uveal Melanoma. Ophthalmology. 2016;123(1):86-91.

ENUCLEATION

Enucleation is the term widely used for amputation of the eye. The operation involves:

- Detachment of all the extraocular muscles
- Removal of the eye by cutting the optic nerve
- Insertion of an a hydroxyapatite, acrylic, silicone or other implant into the orbit
- Suturing of extraocular muscles to the implant
- Suturing of tenons capsule and conjunctiva
- Insertion of a conformer to maintain the fornices and eyelid shape during healing
- Application of a pressure bandage for 1-2 days
- Replacement of the conformer with an ocular prosthesis once healing has occurred, usually about 6 weeks after the enucleation

There are many variations in enucleation technique. Some authors prefer porous orbital implants (e.g., hydroxyapatite) and others prefer non-porous implants (e.g., silicone, acrylic). Porous implants are relatively expensive and difficult to remove if they extrude through the conjunctiva. A randomized study found that porous and non-porous implants provide similar results.[87]

Enucleation is indicated when radiotherapy, local excision or laser therapy are unlikely to conserve what the patient considers to be a useful eye or when the chances of complications after eye-conserving treatments are considered to be excessively high.

A study by Damato and Lecuona[88] showed the main predictive factors for primary enucleation to be:

- Age more than 60 years - indicating reduced health
- Reduced visual acuity - indicating reduced likelihood of visual conservation
- Posterior extension close to or involving the optic disc and fovea - indicating probable severe visual loss after radiotherapy
- Circumferential spread around the ciliary body, iris, or angle - indicating high risk of local tumor recurrence
- Large basal tumor diameter and/or great tumor height - indicating increased risk of toxic tumor syndrome, local tumor recurrence, and poor visual outcome

In the 1980's, Zimmerman hypothesized that enucleation increased metastatic mortality by physically disseminating tumor cells from the eye into the general circulation during the surgical manipulations.[89] This hypothesis was later disproved by the Collaborative Ocular Melanoma Study (COMS).[90]

87 Ho VWM, Hussain RN, Czanner G, Sen J, Heimann H, Damato BE. Porous Versus Nonporous Orbital Implants After Enucleation for Uveal Melanoma: A Randomized Study. Ophthalmic Plast Reconstr Surg. 2017;33(6):452-8.

88 Damato B, Lecuona K. Conservation of eyes with choroidal melanoma by a multimodality approach to treatment: an audit of 1632 patients. Ophthalmology. 2004;111(5):977-83.

89 Zimmerman LE, McLean IW, Foster WD. Does enucleation of the eye containing a malignant melanoma prevent or accelerate the dissemination of tumour cells. Br J Ophthalmol. 1978;62(6):420-5.

90 Hawkins BS, Group COMS. The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma: IV. Ten-year mortality findings and prognostic factors. COMS report number 24. Am J Ophthalmol. 2004;138(6):936-51.

Choice of treatment is strongly influenced by the patient's preference.[4] For example, when loss of useful vision is highly likely to occur after plaque or proton beam radiotherapy for a juxtapapillary choroidal melanoma some patients opt for such treatment in any case whereas others prefer to have the eye removed.

Advantages

Uveal Melanoma

- Enucleation is the most secure method of eliminating the primary ocular tumor, with minimal or no risk of local tumor relapse and other ocular complications (e.g., cataract, neovascular glaucoma, optic neuropathy). The need for long-term ophthalmic follow up is therefore reduced. This is especially relevant in countries where patients cannot afford the cost of intensive and long-term management after eye-conserving forms of treatment.
- Quality-of-life studies indicate that, after adjusting for non-ophthalmic factors (e.g., social support, general health, financial security), wellbeing after enucleation is not significantly worse than after plaque or proton beam radiotherapy.[36, 91]

Retinoblastoma

- Enucleation provides a quick and complete removal of the primary intraocular tumor, avoiding the need for less reliable methods of treatment, which include systemic chemotherapy, intra-arterial chemotherapy, intra-vitreal chemotherapy, laser therapy and cryotherapy. These are administered in various combinations according to the size and extent of the intraocular disease. All require multiple examinations under anesthesia (e.g., monthly for at least a year) to detect and treat any recurrence or new tumors.
- Irrespective of the status of the fellow eye, enucleation is performed for eyes with very advanced disease (i.e., Group E, with neovascular glaucoma, anterior chamber spread, etc.) and, therefore, minimal likelihood of conserving useful vision.
- Eyes with less advanced but nevertheless severe disease (e.g., Group D, with diffuse vitreal or subretinal seeding) are usually enucleated if the fellow is normal or has tiny retinoblastoma(s) that can confidently be treated successfully with laser and/or cryotherapy.

Disadvantages

- In some individuals, the cosmetic aspect of enucleation is important because of social and occupational consequences.
- If the fellow eye has poor vision, the loss of an eye and useful vision can result in serious handicap so that quality of life is diminished.

91 Damato B, Hope-Stone L, Cooper B, Brown SL, Salmon P, Heimann H, et al. Patient-reported Outcomes and Quality of Life After Treatment of Choroidal Melanoma: A Comparison of Enucleation Versus Radiotherapy in 1596 Patients. Am J Ophthalmol. 2018;193:230-51.

- Even if the fellow eye is healthy, visual difficulties can be significant because of loss of stereopsis (i.e., depth perception) or loss of visual field.[90]
- There may be problems with the socket resulting in ptosis (i.e., drooping upper eyelid), sagging of the lower eyelid, grittiness, mucoid discharge, and watering. In rare cases, the orbital implant extrudes through the overlying conjunctiva, requiring replacement. Some patients develop problems with the prosthesis (i.e., calcific deposits, breakages).[90]

THE AUTHOR'S APPROACH TO TREATMENT FOR UVEAL MELANOMA

The author's first choice of treatment for choroidal and ciliary body melanoma is ruthenium plaque radiotherapy. If the tumor thickness exceeds 5 mm or if the tumor involves optic disc, then he performs iodine brachytherapy or proton beam radiotherapy, whichever modality is available at the hospital he is working in (i.e., ruthenium/iodine brachytherapy in Stockholm and proton beam radiotherapy in London).

If an irido-ciliary melanoma is too thick for ruthenium plaque radiotherapy (i.e., >5 mm), then cyclo-iridectomy is considered.

In Liverpool, he performed several hundred trans-scleral choroidectomies for tumors that were too large for brachytherapy or proton beam radiotherapy and with an excessive risk of toxic tumor syndrome. He has performed retinal endoresections in patients with juxtapapillary tumors and some tumors with toxic tumor syndrome after radiotherapy. These procedures are now being undertaken by his retinal surgical colleagues in Liverpool, whom he trained. This resection is performed after closure of the draining vortex veins to prevent gas embolism. All resections are now followed by adjunctive ruthenium brachytherapy to prevent tumor relapse.

Patients with iris melanoma are treated with ruthenium plaque radiotherapy or, if able to travel to the Clatterbridge Cyclotron Unit, proton beam radiotherapy.

Patients who are unlikely to retain a comfortable and seeing eye after these procedures are advised to undergo enucleation with reassurance (based on his quality-of-life studies on more than 1500 patients) that their quality of life will be similar to that after radiotherapy.

ABOUT THE AUTHOR

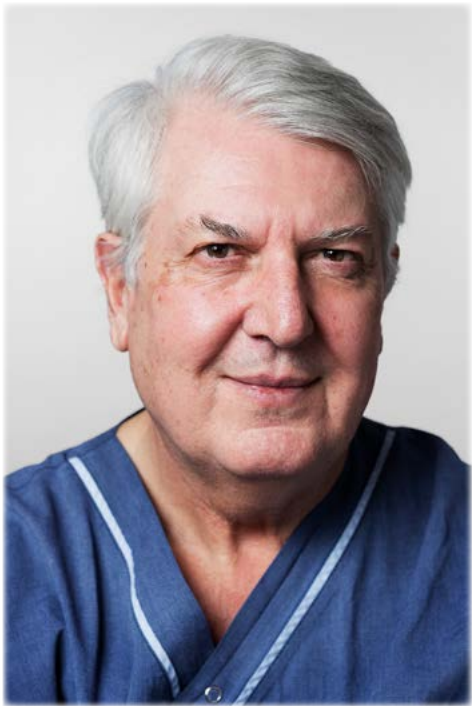
Bertil Damato received his undergraduate education in Malta, where he was born, and his postgraduate training in ophthalmology and ocular oncology under the mentorship of Professor W. Foulds at the Tennent Institute of Ophthalmology in Glasgow.

In 1993, he established the Liverpool Ocular Oncology Centre, which he directed for 20 years, developing the service into one of the largest worldwide, receiving more than 300 patients with ocular melanoma each year.

From 2013 to 2018, he was Professor of Ophthalmology and Radiation Oncology at the University of California, San Francisco, where he directed and renovated the adult and pediatric ocular oncology services.

Between 2018 and 2022, Professor Damato was part-time consultant ocular oncologist at Oxford Eye Hospital, where he established a diagnostic adult tumor service.

Since 2018, he has served as part-time consultant ocular oncologist at Moorfields Eye Hospital, London.



Bertil Damato

Currently, he is consultant ocular oncologist at St Erik Eye Hospital/Karolinska Institutet, Stockholm, Sweden, where he is helping to reorganize the ocular oncology service.

Since entering the field of ocular oncology in 1984, Professor Damato has treated well over 4000 patients with uveal melanoma with ruthenium and iodine brachytherapy, proton beam radiotherapy, iridectomy, cycloiridectomy, cyclo-choroidectomy, choroidectomy, endoresection and enucleation and has made improvements to all these procedures as well as tumor biopsy techniques. He has also pioneered genetic typing of uveal melanoma and multivariable survival prognostication. He has expertise in treatment of retinoblastomas and has developed techniques for coding and documenting individual tumors in addition to status of the whole eye.

Professor Damato has served as President of the European Ocular Oncology Group, the European Vision and Research Association and the International Society of Ocular Oncology. He has published more than 300 scientific articles and authored or co-edited several textbooks. He has received a number of awards, which include the Bjerrum Medal in Denmark, the Cohen Medal in South Africa, the Watson and Ashton Medals in the UK, the Shields Medal in Hong Kong and the Platinum Award of the National Health Service of the UK. He is married to Frankanne and has two children, both doctors.

DISCLOSURE

The author was commissioned by Eckert & Ziegler BEBIG to write this white paper. All views and opinions expressed in this paper reflect those of the author.

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