Review Article

Options for management of intra ocular tumors

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The management of intra ocular tumors has undergone a sea change from the era of enucleation or external beam radiation. With the advent of new chemotherapy protocols, globe and vision salvage have become possible in a majority of cases of retinoblastoma. This article is an overview of the various modalities available for the management of intra ocular tumors and their indications. Chemotherapy has been covered elsewhere in this series of articles on ocular oncology. Photocoagulation and cryopexy are easily administered modalities of treatment for small tumors and totally within the ophthalmologist's domain. Slightly larger tumors are treatable with brachytherapy. The susceptibility of the tumors to chemotherapy and radiation decide the choice of treatment and the dosage. Management of intra ocular tumors very often needs a multidisciplinary approach including ophthalmologist, oncologist, radiation physicist, and radiotherapist.

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The management of intra ocular tumors has undergone a significant change over the decades. While retinoblastoma (RB) used to be treated preferentially with external beam radiation in the past, it has been pushed down to the last of the list of options in the present era. Major advances have taken place in the administration of chemotherapy.

This article gives an overview of the management options for intra ocular tumors. Chemotherapy is covered in detail elsewhere in this issue and hence only a passing mention will be made here. Broadly, the topic can be covered under the following headings:

- Observation
- Laser photocoagulation: Thermal laser, thermotherapy (transpupillary thermotherapy [TTT]), photodynamic therapy (PDT)
- Cryotherapy: Trans conjunctival, trans scleral
- Radiation: External beam radiotherapy (EBRT), brachytherapy
- Chemotherapy
- Surgical management: Iridectomy, eye wall resection, enucleation.

Observation

Observation may be acceptable in most cases of nonmalignant tumors and some malignant tumors as well. Once a decision is taken to observe a tumor, baseline documentation of the lesion is a must. This should enable accurate comparison on follow-up visits. Fundus photography (especially montage) is perhaps the best documentation that can accurately describe the extent of lesion two dimensionally. The height of the lesion can be documented by B scan ultrasonography. Yet another way of documentation involves detailed fundus drawing that details the blood vessels and the lesion in relation to various landmarks in the fundus. Optical coherence tomography (OCT) cannot be used to image the tumor itself well but is an excellent tool for early detection of sub retinal fluid that may not lend itself to clinical detection. Observation also involves educating the patient about the symptoms for seeking early review as well as training them on some method of self-monitoring where feasible and applicable. Some of the more important conditions that lend themselves to this modality of management are discussed below.

Choroidal nevus

A choroidal nevus is defined as a choroidal melanocytic lesion not larger than 5 mm in the largest basal diameter and not more than 1 mm in height. While there is no controversy on observation as a modality of treatment in these cases, slightly larger lesions termed variously as indeterminate lesions, nevomas, etc., are also mostly observed unless they have high-risk characteristics. The growth of such lesions has been noted in 0–41% of cases in various studies indicating the heterogeneity of the lesions as well as the difference in the population studied.[1] The risk of malignant transformation of a choroidal nevus is estimated at 1 in 8845.[2]

Optic disc melanocytoma

Melanocytoma of the optic disc is a benign condition that is most commonly identified on routine ophthalmoscopy. A vast majority remain stable on observation while 10% may show some growth over years.[3] Only 2% show tendency for malignant transformation.[3] However, without malignant transformation a melanocytoma can become symptomatic due to the occurrence of infarction leading to papillitis, vascular occlusion, etc.

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Iris melanocytoma

Most cases of iris melanocytoma remain asymptomatic and can be observed. However, occurrence of melanocytomalytic glaucoma may require local excision as a treatment.

Uveal melanoma

Once clinically labeled as "uveal melanoma," the lesion is usually treated. However, as mentioned above, the indeterminate lesions are observed in some centers, while others choose to treat them as well. Perhaps the best indication for treatment in such cases is evidence of the growth of the lesion for which the lesion would have to be observed for some time at least.

Circumscribed choroidal hemangioma

Asymptomatic extra macular choroidal hemangioma with no sub retinal fluid can be observed.[4] OCT will help in the follow-up to detect the early occurrence of sub retinal fluid. If macular edema/fluid is long standing with no potential for recovery of vision, one may opt to observe such eyes as well.

Diffuse choroidal hemangioma

In the absence of secondary retinal detachment, observation is the best approach. Even where there is secondary retinal detachment, the aim of treatment is only to induce resolution of the subretinal fluid and not total destruction of the tumor. Hence once this goal is achieved, one would only follow them up with observation.

Laser Treatment

Laser is a collimated, monochromatic, and coherent beam of high energy that can be brought to a fine focus. Three wavelengths are of importance in the management of intra ocular tumors by thermal photocoagulation-the green laser of 532 nm, the diode laser of 810 nm and the yellow dye laser of 577 nm.[5] The effect on the tissue will depend on the absorption spectrum of the chromophores present in the eye (melanin in retinal pigment epithelium [RPE] and choroid, hemoglobin in red blood cells, xanthophyll, lipofuscin, rhodopsin, and cone pigments). All the three lasers are absorbed by melanin of the RPE and choroid while green and yellow lasers are also absorbed by hemoglobin (yellow laser more than green).

Photodynamic therapy enables the production of laser effect in tissues without pigment, by utilizing the absorption spectra of photosensitive dyes that are injected before application of the laser energy. The most common example is the use of verteporfin coupled with a 689 nm laser.[6]

The aim of laser treatment in intra ocular tumors is total destruction or at least reduction of the tumor mass. The following methods are in use.

Thermal photocoagulation

Reasonably, high levels of energy are delivered to coagulate the lesion with temperatures reaching above 65°C. This treatment can be administered with the traditional green laser, yellow or the diode laser.

Trans pupillary thermotherapy (transpupillary thermotherapy)

In this modality of laser administration, relatively low energy is delivered for long periods of time so that the tumor is heated slowly to 60–65°C. This achieves greater penetration of the tumor mass by the laser resulting in greater necrosis in the depths of the tumor compared to thermal laser. The diode (810 nm) laser is used for this purpose. With TTT attachment, large spot sizes are selected to cover the tumor with least number of applications.

Photodynamic therapy

Photodynamic therapy involves the injection of a photosensitive dye (verteporfin) followed by exposure of the area of interest to a laser of wavelength 689 nm. A dose of 600 mw/cm^2 is delivered for 83 s. The effect on the tissue is by the liberation of free oxygen radicals and not by heat production. Although originally developed for the treatment of the choroidal neovascular membrane, the modality has found application in tumors like choroidal hemangioma, amelanotic melanoma, retinal hemangioblastoma, metastatic lesions of the eye, etc.

Laser delivery

Delivery of laser can be through slit lamp, indirect ophthalmoscope or via a cable coupled to the operating microscope. The TTT mode enables use of large spot sizes. The operating microscope attachment is especially useful while treating children under general anesthesia.

Applications

Retinoblastoma

In the treatment of RB, laser (thermal/TTT) is used as primary modality of treatment only for very small tumors.[7] In most cases, however, it is used as an adjunct. Tumors are regressed with chemotherapy and then subjected to laser treatment to achieve total destruction. Tumors of up to 3 mm basal diameter and height of about 2 mm are amenable for laser treatment. The laser is applied around the tumor to cut off the blood supply. Direct treatment of the tumor can also be done although there are concerns about the vitreous dissemination of tumor cells. Direct treatment of RB can be more safely done with TTT rather than by thermal photocoagulation. With TTT, the end point of each burn is the development of mild opalescence in the tumor. One can combine the treatment surrounding the tumor with thermal coagulation followed by TTT of the tumor itself. Figs. 1 and 2 depict the RB tumor immediately after laser photocoagulation and the subsequent regression.

Tumors bordering the macula are best allowed to shrink with chemotherapy till it is safe to destroy the residue without compromising the fovea. However, it may not always be possible to preserve the fovea-especially where the epicenter of the tumor lies in the foveal location, and it shrinks toward and not away from fovea.

Shields *et al*. have shown a success of 85.6% in achieving complete tumor regression. The risk factors for tumor recurrence were male sex, inability to produce a color change in the tumor with TTT and tumors being treated after chemo reduction.[8]

Unlike cryotherapy, the laser can be used for posterior as well as anterior lesions without much change in technique. Extremely anterior lesions bordering on the ora serrata can be treated using indentation and indirect ophthalmoscopic delivery.

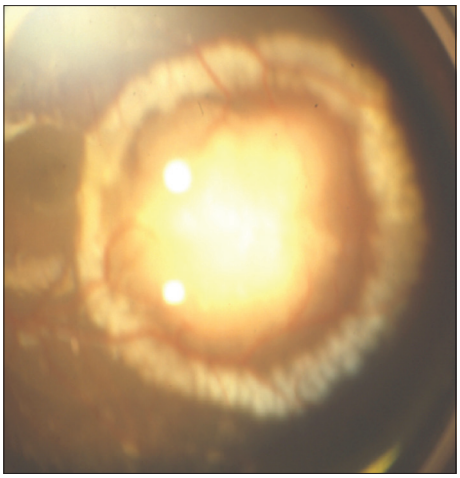

Figure 1: Retinoblastoma tumor surrounded by fresh laser marks

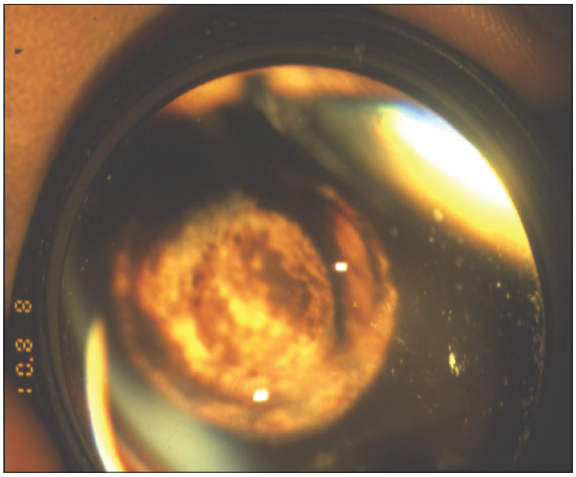

Figure 2: Same tumor showing good regression

Retinal capillary hemangioma

Small capillary hemangiomas are amenable for direct thermal photocoagulation-either as direct treatment or coupled with feeder vessel treatment. Green laser or yellow laser can be used. Yellow laser has a high uptake by both oxygenated and reduced hemoglobin in addition to melanin, and hence on a theoretical basis, appears ideal for treatment of a predominantly vascular tumor.[9] Small extra papillary tumors of 1.5 mm or less are easily treated with good control rate. Repeated treatment is needed. In view of the increasing difficulty in treating large angiomas, most surgeons will choose to treat rather than observe even small angiomas. PDT has also been used in the treatment of capillary hemangiomas with moderate efficacy. Treatment of capillary hemangiomas of the optic disc with PDT could be complicated by the high incidence of compromise of optic nerve and retinal function-especially when high fluency is used (100 mJ).[10]

Choroidal melanoma

Choroidal melanomas are mostly treated by brachytherapy, sometimes aided by additional thermotherapy. Small tumors can potentially be treated with photocoagulation or thermotherapy alone, but have a risk of local recurrence.[11,12]

Choroidal hemangioma

Circumscribed choroidal hemangioma can be treated with thermal laser or TTT, but PDT is superior in achieving a better result with less complication of exudative retinal detachment, fibrosis, and cystoid macular edema.[13,14]

The aim of treatment in choroidal hemangioma is the resolution of secondary retinal detachment. Total destruction of the lesion is neither aimed at nor is achieved in most cases. Hence, lesions without any secondary effects can be observed without treatment.

Diffuse choroidal hemangioma as in Sturge–Weber syndrome is less likely to respond to PDT.

Other tumors

Small choroidal metastasis, vasoproliferative tumors, and on occasion retinal astrocytomas have been treated with laser-thermal as well as TTT.

Cryo Therapy

Cryotherapy involves freezing of the tissue of interest using the principle of Joule–Thomson effect wherein gas at high pressure is forced to exit through a small aperture at the tip of the probe-the sudden expansion of gas produces sudden drop in temperature at the tip leading to freezing. While freezing itself damages the cells, it is the slow thawing that leads to the formation of large intra cellular crystals, which damage cells even more. Repeat freeze-thaw cycles increase the cellular damage. One advantage of cryotherapy is the ability to treat trans conjunctivally/trans sclerally. The damage to the sclera is minimal and negligible while the intra ocular tumor is destroyed.

Procedure

Intra ocular tumors are treated using the retina cryoprobe. In general, lesions located anteriorly are easily treated with cryo since conjunctiva need not be opened. If needed, one can make limited conjunctival opening to reach posteriorly. Skill in indirect ophthalmoscopy and indentation would be important in the accurate treatment of the lesion. The indentation caused by the probe tip is positioned under the center of the lesion and freezing is commenced. Freezing is done till the ice ball totally encloses the tumor mass. The probe is allowed to defreeze completely before freezing again. The cycle is repeated thrice. Topical steroids are usually administered for a few days.

Complications

Retinal edema is an expected effect of the cryotherapy. But on occasion, secondary retinal detachment, and retinal hemorrhages can occur. Accidental freezing of unwanted areas is a risk when trans scleral treatment is being done for relatively posterior lesions. In most cases of posterior lesions, the laser would be the treatment of choice. Edema of the eyelids and conjunctiva are common but should resolve in a few days.

Indications

Retinoblastoma

Very small tumors not more than 3 mm in diameter and 2 mm thickness are amenable for cryotherapy as a sole modality of treatment.[15] Vitreous seeds are not usually treatable with cryo unless they are lying in the immediate vicinity of the

tumor. In most cases, however, cryo, like the laser is used as a mode of consolidating the effects of chemotherapy. Tumor recurrences – when small can also be treated with cryo. In addition, cryo can also be done to break the blood-retinal barrier in eyes undergoing chemotherapy in order to improve the penetration of the drug into the vitreous cavity. Cryo can be repeated after 3–4 weeks if needed.

Retinal capillary hemangiomas and vasoproliferative tumors can also be treated with cryotherapy. In a series by Singh *et al*., cryotherapy was used in 23% of cases of retinal capillary hemangioma.[16]

Radiation

Radiation has been one of the first modalities of treatment used in the treatment of RB with excellent tumor control.[17] The Reese-Ellsworth classification is based on the response of RB tumors to radiation. Two developments have altered the role of radiation and pushed it down the list of alternatives-the advent of modern day chemotherapy with use of combination of drugs and the recognition of the increased risk of second tumors in radiation treated patients subsequently. However, radiation is the mainstay in the treatment of choroidal melanoma and is also useful in other intra ocular tumors.

Radiation can be applied by EBRT or locally around the eye as brachytherapy. From the ophthalmologist's perspective, knowledge of teletherapy is needed more to understand the indications and ocular complications rather than the details of the administration. Episcleral plaque is more in the ophthalmologist's domain – at least in its application and removal.

The sources of radiation

- Cobalt-60 unit that emits γ rays as the cobalt-60 decays. Maximum dose is delivered to a depth of 0.5–1 cm with the photon beam
- Linear accelerator uses high-frequency electromagnetic waves to accelerate the electrons and can deliver maximum doses up to 6 cm
- Cyclotron: This instrument delivers neutron and proton beams that are capable of causing more damage to the tissue
- Episcleral plaque brachytherapy usually involves the use of iodine-125 or ruthenium-106. Less commonly iridium-192, palladium-103, and strontium-90 have been used.

I-125 seeds deliver γ rays while ruthenium-106 deliver β rays. Hence, the depth of penetration is greater with I-125. Correspondingly, the dose to the lens is greater with Iodine. The advantage of ruthenium is its long half-life (373.6 days compared to 59.4 days for Iodine). While I-125 seeds are loaded on to a gold plaque, ruthenium can be integrated with a silver applicator. The plaques are of several designs and sizes including notched plaques to accommodate treatment of peripapillary tumors. The dosage of the radiation is calculated using customized software with inputs of the location of the tumor, basal diameter, and height of the tumor. Placement of the plaque is fairly simple and involves careful localization of the tumor on the scleral surface and anchoring the plaque into place by passing sutures through the eyelets anteriorly. On occasions, the recti muscles may need to be disinserted to properly locate the plaque. The plaque is left in position till the required dosage is delivered to the apex of the tumor.

Retinoblastoma

As alluded to, EBRT is performed as a last resort in the management of RB due to the risk of second malignancies. A three-fold increase has been noted in the standardized incidence of new cancers in radiated versus nonradiated RB patients.[18] In general, children above 1-year of age appear to be at less risk of second malignancies compared to those below 1-year of age.[19] In the present era, EBRT would be offered to RB patients only if all other modalities fail. Extra ocular RB would also be treated with EBRT along with high dose chemotherapy. Lens-sparing protocols have a higher risk of relapse compared to modified lateral technique.[20]

Retinoblastoma, being very sensitive to radiation, doses of 35–45 Gy are administered depending on the severity. Newer techniques of radiation for RB include intensity modulated radiation therapy;[21] conformal irradiation and proton beam radiation.[22] In a series of 84 eyes of RB with tumor recurrence after chemoreduction, brachytherapy with I-125 was able to salvage 95% of eyes after 5 years follow-up.[23]

Complications of EBRT in children include dry eye, cataract formation, orbital bone hypoplasia, and increased risk of second malignancies.

Choroidal melanoma

Episcleral brachytherapy is the most common mode of management of choroidal melanoma. The dose to the tumor apex is usually around 80–100 Gy since the tumor is relatively radio-resistant. Tumor regression is not evident usually in the first 3–6 months. Larger tumors and tumors with retinal invasion have a higher risk of failure and increased risk of local recurrence. Complications of brachytherapy would include cataract, optic neuropathy, radiation retinopathy, neovascular glaucoma (NVG), and rarely scleral melt. Enucleation may be needed if there is gross recurrence of tumor or painful blind eye due to NVG.

Repeat brachytherapy may be possible in selected cases. In general, the survival seems to be equal between enucleation and brachytherapy.[24]

For large tumors and those close to the posterior pole, proton beam radiation may be better alternative if globe conservation is desired. However, if the tumor occupies more than 30% of eye volume, even proton beam radiation is not recommended.[25] Tumors close to the macula and optic nerve have poor visual outcome irrespective of the modality of treatment.

Radiation retinopathy

Radiation retinopathy is fairly common with choroidal melanoma in view of the high levels of radiation used. Steroids and anti-VEGF agents are the mainstay in the treatment of radiation retinopathy – especially when associated with macular edema. Vision can be compromised-sometimes on a permanent basis despite treatment. The combination of intravitreal triamcinolone and bevacizumab has been used for radiation-induced macular edema with some efficacy.[26] Secondary retinal detachment caused by necrosis of the tumor can also sometimes respond to intra vitreal steroids.[27] NVG can be treated with intra vitreal bevacizumab.[27] Scleral necrosis and melt may necessitate scleral patch graft.[27]

Table 1: Summary of treatment options in intra ocular tumors

Type of tumor	Observation	Chemotherapy	Laser/Cryo	Radiation	Surgical
Retinoblastoma	All RB s need treatment Only retinocytomas can be observed	Systemic chemo reduction followed by local consolidation Subtenon's carboplatin as addendum Intra vitreal melphalan increasingly used as addendum	Lesions up to 3 mm basal diameter and 2 mm height Cryo/TTT acceptable options Forms important part of consolidation after chemotherapy	Larger residual tumors Brachytherapy if possible EBRT last resort Dose: 35-45 Gy	Enucleation for most group E eyes Treatment failures with no useful vision-especially unilateral
Choroidal melanoma	Indeterminate lesions not showing signs of growth	No role	TTT for lesions less than 4 mm height Not preferred as first choice Cryo not preferred	Brachytherapy is treatment of choice Proton beam radiation better for tumors in posterior pole Dose: 80-100 Gy	Enucleation for most large tumors, tumors in blind eye, failed treatment, NVG, extra ocular extension Eye wall resection with brachytherapy for medium tumors Endo resection: A controversial approach
Metastatic tumors	Patients in terminal illness Patients on systemic chemotherapy	Based on primary tumor	Lesions up to 3 mm basal diameter and 2 mm height	Isolated secondaries can be treated with brachytherapy EBRT	No role
Choroidal hemangioma	Treatment of choice unless secondary complications arise	No role	PDT is treatment of choice Cryo/thermal laser/TTT possible but less preferred	Nonresponsive hemangioma and diffuse hemangioma can be treated with radiation (plaque, EBRT or proton beam) at low doses	No role
Retinal capillary hemangioma	Small, isolated uniocular tumors without secondary effects perhaps can be observed	No role	Treatment of choice Small tumors more easily treated Feeder vessel treatment also done for larger lesions Thermal laser/PDT preferred TTT not used	Brachytherapy can sometimes be used for large tumors	Surgery often needed for secondary complications such as traction/combined rhegmatogenous traction retinal detachments Large tumors excisable but do not alter prognosis much
Vaso proliferative tumors	Mostly would need treatment	Steroids for inflammation No role of chemotherapy	Cryo treatment of choice Thermal laser can be used	Brachytherapy needed on occasion	Surgery for traction retinal detachment
Astrocytoma	Mostly observed	No role	Rarely laser used	No role	No role
Iris nevus	Do not need active treatment	No role	No role	No role	Excision only if signs of growth
Iris/irido-ciliary melanoma	Once growth established, observation not advisable	No role	No role	Trans corneal/scleral brachytherapy possible	Excision if less than 3'O clock hours (90°)
Iris melanocytoma	Mostly observed	No role	No role	No role	Excised if secondary glaucoma present

TTT: Transpupillary thermotherapy, PDT: Photodynamic therapy, EBRT: External beam radiotherapy, NVG: Neovascular glaucoma, RB: Retinoblastoma

Choroidal hemangioma

While PDT is the preferred first approach to the treatment of circumscribed choroidal hemangioma, radiation in the form of lens-sparing EBRT, stereotactic radiotherapy, plaque radiotherapy, and proton beam radiation have been used with varying success. The dosage used is much lower than for melanoma-about 20 Gy is aimed at. For diffuse choroidal hemangioma, radiation may be a better option. As alluded to, the aim of treatment is to induce resolution of secondary retinal detachment.

Chemotherapy

Modern day chemotherapy has altered the success of globe salvage in RB dramatically. Experience with new drugs, new

protocols, and new methods of delivery have totally altered the way these tumors are treated. The details of chemotherapy are discussed in detail elsewhere.

Surgical Options

Iridectomy

Iridectomy is indicated in iris melanoma if it is less than 4'O clock hours. Borderline cases are usually observed for evidence of growth before offering excision as an option of treatment. The surgical procedure is fairly straightforward. The anterior chamber can be entered opposite the site of tumor and visco elastic can be injected under the iris. A vitreous scissors or a straight Vanna's scissors can be introduced, and two radial cuts are made on either side of the lesion giving sufficient safety margin. Next, an incision is made at the limbus adjacent to the lesion and anterior chamber entered. The iris with the lesion can be allowed to prolapse (the viscoelastic under the iris helps in the process) and then and the iris is excised by cutting at the base. A minimally invasive technique has been described by Hood *et al*. wherein the tumor is excised from the iris using vitreous forceps and scissors under visco elastic fill through two clear corneal wounds. The free floating iris segment with lesion is aspirated into a clear viscoelastic primed plastic tubing attached to a syringe. The incision needed is only about 3 mm and also permits repair of the iris defect.[28]

Iridocyclectomy

Where the ciliary body is involved in addition to the iris by the tumor, the involved area of the iris, and ciliary body are excised together. A partial thickness scleral flap is made to facilitate the excision of the tumor in toto with a 2 mm safety margin. The zonules of the lens would need to be lysed in the area of excision, without traumatizing the lens itself.

This approach would be needed for melanoma, adenocarcinoma of the iris and ciliary body and for some benign tumors such as leiomyoma. Vitreous disturbance may or may not occur. Since the ciliary body is excised, there is a risk of oral dialysis and retinal detachment subsequently. Retinal detachment (if it occurs) can be managed routinely with pars plana vitrectomy, internal tamponade, and endolaser photocoagulation.

Surgical resection of choroidal melanoma

This procedure involves resection of the tumor from an external or internal approach.

External techniques vary from total eye wall resection (sclera uveo retinectomy) to excision of only the tumor with partial scleral flap while retaining the retina.[29,30] Often the procedure includes placement of an episcleral plaque at the conclusion of the resection procedure. The complications of the resection of the large tumors are significant and include retinal detachment, vitreous hemorrhage, etc. The function of the eye is very often compromised although the eyeball may be retained. The survival of the patients is not altered by this technique. It is perhaps performed for a highly motivated patient, who does not want enucleation.

Endoresection by parsplana approach is an even more controversial surgery and involves piecemeal removal of the tumor with the cutter and managing the retinal break through which the tumor is removed. There exists the risk of local recurrence and spread of the tumor into the vitreous cavity.[31] This is usually performed after the eye has been treated with radiotherapy.

Enucleation

However, undesirable, enucleation remains an important part of the management of intra ocular tumors. The decision to enucleate would need to be taken when the eye is not salvageable. The incidence of up front enucleation in RB has diminished with more patients presenting early in the course of the disease, and better treatment regimens being available to salvage eyes. In general, eyes with RB are enucleated when there are signs of anterior segment involvement or if there is an advanced disease with no hope of visual recovery. The threshold for enucleation would be less in unilateral cases. In bilateral cases, the obviously worse eye with no scope for visual recovery may sometimes be enucleated up front while conservative management is initiated to preserve the better eye. However, there are many cases wherein it is difficult to know which eye will respond better. One can always start chemotherapy and decide on planned enucleation depending on the response to chemotherapy. In this situation, there is a risk that there would be downgrading of the risk for metastasis following enucleation since the picture would have been altered by the up-front chemotherapy.[32]

The indications for enucleation in uveal melanoma include large tumors, blind painful eye, optic nerve invasion, NVG, and extra scleral extension.

Table 1 gives a summary of the various treatment modalities in the important intra ocular tumors.

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