

## Answers to Audience Questions - WSPOS World Wide Webinars

### WWW 16 – Season 2 – Retinoblastoma



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1. How to manage recurrent RB after enucleating and chemotherapy are done with?

MP: I presume this refers to extraocular RB if the eye has been enucleated. It depends on the site of recurrence. If it is in the orbit, the child needs staging with MRI, LP and bone marrow biopsy. The orbital disease can be treated with radiation (proton beam if possible) but the child will also need high dose chemotherapy with the ARET protocol. If it is metastatic disease, ARET protocol chemo after staging, but the prognosis is very poor if there is CNS metastasis.

CS: I have nothing to add to MP's answer (above).

2. Christina: Which one of all those imaging investigations is the most important.

CS: There is unfortunately no general answer to this as each of the ancillary testing has specific information to bring and help the individual therapeutic decision making.

3. Does IAC have a risk of systemic dissemination through the optic nerve?

MP: Although it has been suggested by some clinicians that IAC can sterilise the optic nerve with the high doses of drugs delivered, we have seen 2 cases treated with IAC, and subsequent enucleation where disease was present in the optic nerve. There is therefore risk of systemic dissemination if there is definitive involvement of the optic nerve on MRI. We will enucleate all such cases, along with pre and post enucleation chemo.

AS: Yes, IAC does not offer adjuvant protection from mets – IVC does. The numbers may be too small to prove but there is enough general info to reach this conclusion.

CS: I also agree with MP. When there is a suspicion of intralaminar (or further) optic nerve invasion, the eye should be enucleated without delay. We have also recently seen a unilateral case treated previously with IAC that we enucleated despite visual potential for a suspicion of intralaminar optic nerve relapse on OCT and MRI that was confirmed on histopathology.

4. Arun: What are your preferred parameters for TTT (in order to avoid ILM damage)

AS: I use indirect system with spot size of 2 mm. Start with the lowest energy around 150mW and go up to increments of 50 mw (until faint white uptake). Hesitant to go over 500 mW.

5. What are the preferred Laser settings for TTT using the Diode laser or the Double frequency green laser?

MP: We use the indirect laser delivery for infrared laser, parameters depend on the amount of pigment in the fundus, and whether lasering near the posterior pole or periphery, or over calcium or depigmented scar. Typical energy varies

from 200-1000MW. Lower energies are used if there is more pigment, or in periphery of retina. Higher in all other cases.

CS: We use the 810nm infrared diode laser, with a preference for a transpupillary application with an adaptor coupled to an operating microscope through a 3-mirror lens contact. Compared to the indirect ophthalmoscopy where the spot is variable, the microscope adaptor allows to set the spot size as well to achieve uniform delivery of the laser on the to be treated lesion. The laser power setting can vary from 100 to 1200 mW, depending on the tumor size, localisation and underlying level of pigmentation. Duration depends on the clinical response. Usually, the lesion is treated until a whitening appears. Intravenous indocyanine green can be used concomitantly to promote a potentiated laser response for some tumors refractory to simple thermotherapy alone (Francis JH, Abramson DH, Brodie SE, Marr BP, 2013, Indocyanine green enhanced chemosurgery for retinoblastoma. Br J Ophthalmol, 97, 164-168)

AM: We use both laser types for transpupillary thermotherapy (indirect and adapted to an operating microscope). I agree with MP and CS regarding the laser parameters. Typically, we treat less than a minute a very small lesion (1 mm diameter approximately), a few minutes a middle-sized lesion (a few mm) and 20 minutes larger lesions (> 10 mm diameter).

6. Arun: How would you treat if there resected optic nerve shows involvement after enucleation? just iv chemotherapy?

VR: Once, the cut section of optic nerve shows involvement, we treat it as an Orbital Rb. The protocol is to start High-dose systemic intravenous chemotherapy 12 cycles followed by external beam radiotherapy to the orbit.

AS: Just IV chemo is NOT sufficient for transection margin positive RB. Need RT.

AM: I fully agree with VR and AS. RT can be external beam or orbital brachytherapy (although very few centres worldwide are able to perform this technique).

7. Was Alexandre concerned about ac tap in the case he presented with active AC disease atypical presentation? Was iVIC given at same time?

AM: No in these cases AC tap is an efficient way to diagnose Rb. The risk of dissemination to the orbit is low when performing AC tap at the limbus. Distilled water can be added on the ocular surface to destroy any residual malignant cell. iVIC will be given at the same time once the diagnosis is established and according to the planned treatment scheme. We suggest alternating intracamerular and intravitreal injections. As pointed below (Question 8) the Lausanne Group has published their protocol for UBM-guided intracamerular within the posterior chamber.

8. For patients with hypopyon and ciliary process involvement, is any further treatment like plaque or IAC or IVC suggested? or just enucleation?

MP: Francis Munier, Christina and colleagues have published their protocol for treating such cases with IvitC. I would add plaque if there is localised ciliary body involvement.

CS: When dealing with such cases, you always have to think to also treat the source of seeding. Pseudohypopyon can be managed with intracameral chemotherapy. We usually give concomitant intravitreal chemotherapy to avoid any cross contamination with the vitreous. If you have concomitant ciliary body/pars plicata involvement, you need to use a plaque brachytherapy, as such relapses do not respond to IAC due to the poor vascular supply. (Munier F.L, Moulin A, Gaillard MC, Bongiovanni M, Decembri S, Houghton S, Beck-Popovic M, Stathopoulos C, 2018. Intracameral chemotherapy for globe salvage in retinoblastoma with second anterior chamber invasion, Ophthalmology 125, 615-617)

9. Any role of lactate dehydrogenase in diagnosis?

JB: re LDH in the AH, no, there is no role for this at this time. There were past studies on LDH in the aqueous humor from enucleated eyes but never a clear objective threshold -- an exam from an ocular oncologist would be higher sensitivity. Now with improved sequencing techniques we can directly evaluate for RB1 mutations and secondary chromosomal alterations which are much more sensitive and specific for the diagnosis for RB.

MP: No

CS: No

AM: Not in our current practice

10. I have a case with bilateral retinoblastoma, has already received IAC, IVC, and proton. But once stop IVC, tumour recurrent and even progression. Didn't know what can do next except enucleation.

MP: Has the retinal disease been completely eradicated? If so, IVC can be repeated. If there is retinal disease, local treatment or plaque can be tried. In some cases, enucleation is the only option sadly.

CS: This is too difficult to answer without more details on the given treatments (doses, drug combination, the time of the relapse since the last treatment and especially the type of the relapse, etc.), but as Manoj said, sometimes very resistant tumor can progress despite all the treatments have been attempted and enucleation becomes the best option to keep the child safe from metastasis.

11. Are there any special considerations when doing a cataract Sx. in an RB child?

MP: Cataract surgery may be required to enable visualisation of the fundus during active treatment or active follow-up i.e., within 2 years of last treatment. It may also be needed later for visual reasons, once the risk of active disease has passed.

If surgery is performed to permit visualisation, use a clear corneal incision to minimise risk of spread (although risk very small). Large anterior capsulotomy, and if capsulorrhexis performed, make radial incisions to prevent capsular phimosis, remember, the aim is to maximise view. Avoid removal of PC, and if PC opacifies, you can perform YAG laser under GA later. Polish the PC to minimise PCO. Meticulous removal of lens matter. Suture all wounds. We don't use intracameral Melphalan. No IOL

If performed later, capsulorrhexis and IOL in bag, with careful removal of lens matter and polishing. If needed, PC rhexis can be performed at the same time if patient is more than 2 years post last treatment and no signs of activity for 2 years.

CS: Clear cornea incision should indeed be always preferred. Depending on the treatment –free interval time and/or tumor localisation as well the frequency of follow-ups, ancillary testing (including pre-operative MRI) may be indicated to exclude tumor exteriorisation. Preoperative intravitreal Melphalan may also be given in specific cases to sterilize the vitreous especially if posterior capsulotomy is planned (sometimes inevitable due to the density of the opacification). Also, lens removal/anterior vitrectomy material should always be sent for cytopathology analysis to exclude active tumor cells.

AM: I agree with MP to respect at least a 2-year interval since the last active sign of the tumor.

12. How would you manage the PCO?

MP: Answered above

CS: There is now a supine YAG laser, that can be used to perform capsulotomies in young children.

13. When do you start examination without anaesthesia in a child who has been treated conservatively?

VR: There is no clear-cut age cut-off, however any time the child does allows for a complete dilated fundus examination in Op clinic we can follow up without EUA. Ideally, in our practice child older than 6 years do allow for a detailed fundus examination.

MP: I suggest reading our publication on this subject which should answer this question. Batra R, Abbott J, Jenkinson H, Ainsworth JR, Cole T, Parulekar MV, Kearns P. Long-term retinoblastoma follow-up with or without general anaesthesia. *Pediatr Blood Cancer*. 2014 Feb;61(2):260-4.

AS: I would go with age (usually after 4 years) and at least 2 years of stability.

CS: We usually start to see children on an outpatient basis after the age of 4 years old and usually a 2 year-treatment-free interval. Of course, depending on the child compliance and the localisation of the tumor(s) that need to be followed, some children may be require a longer follow-up under anesthesia.

AM: Exact same answer as AS and CS - at least 4-year-old and 2-year stability.

14. Do you suggest routine screening of fundus for new-born?

VR: Yes, considering neonatal retinoblastoma constitutes 7-10% of total number of Rb cases diagnosed globally per year. Routine fundus screening of new-borns would diagnose them at an early stage.

MP: Only if they are at increased risk of RB. I suggest this paper which should answer the situations when one should screen. Skalet AH, Gombos DS, Gallie BL, Kim JW, Shields CL, Marr BP, Plon SE, Chévez-Barríos P. Screening Children at Risk for Retinoblastoma: Consensus Report from the American Association of Ophthalmic Oncologists and Pathologists. *Ophthalmology*. 2018 Mar;125(3):453-458

AS: This is now available as an APP : Singh N, DeBenedictis MJ, Singh AD. An Online Application for Retinoblastoma Surveillance. *Ocul Oncol Pathol*. 2020 Oct;6(5):376-380.

CS: I agree with MP. Of course, children whose parents notice suspicious signs of rb (leucocoria, strabismus) should also undergo dilated fundus examination.

AM : I agree that new-borns with family history of retinoblastoma (or retinoma/retinocytoma) should undergo fundus screening at birth and then adjusted to the risk level (see publication recommended by MP). The issue limiting a wider routine screening for the whole population is the availability of ophthalmologists required for this task, and the low incidence of retinoblastoma that would not make such a screening efficient.