346 Retinoblastoma: Clinical

Tuesday, May 09, 2017 11:00 AM-12:45 PM

Exhibit/Poster Hall Poster Session

Program #/Board # Range: 3330–3342/B0606–B0618 **Organizing Section:** Anatomy and Pathology/Oncology

Program Number: 3330 Poster Board Number: B0606

Presentation Time: 11:00 AM-12:45 PM

Developing a novel documentation system for retinoblastoma *Lesley Everett*¹, *Joyce Meza*², *Armin Afshar*², *Bertil E. Damato*². ¹Department of Ophthalmology, University of California, San Francisco, San Francisco, CA; ²Department of Ophthalmology, Ocular Oncology Service, University of California, San Francisco, San Francisco, CA.

Purpose: Accurate documentation of eyes with retinoblastoma facilitates treatment and improves research opportunities. The International Retinoblastoma Classification (IRC) stages disease only according to ocular status. However, it must evolve with therapeutic advances and such evolution requires data granularity not provided with current staging. Further, in patients with multiple tumors, IRC staging does not provide sufficient information for safe patient care. The aim of this study was to develop a system for documenting multiple retinoblastomas in the same eye to enhance treatment as well as opportunities for improving disease staging for research.

Methods: Retinoblastomas were named according to: ocular location; meridian (in clock minutes); retinal location; status; vitreous seeding; retinal seeding; and treatment. Data was documented prospectively with fundus drawings on an iPad using a customized template, fundus photographs, and customized document flow sheets on our electronic medical record (EMR) system. Data was downloaded into Excel spreadsheets and analyzed using SPSS and Stata.

Results: Forty-one tumors in 29 patients (17 female, 12 male) involved the left eye (13 patients), right eye (5 patients) or both eyes (11 patients). Tumors were located in the macula (16.8%), post-equatorial retina (16.3%), equatorial retina (14.8%), pre-equatorial retina (25.6%) and ora (18.6%) with 6.3% and 1.7% of tumors showing sub-retinal and vitreous seeds, respectively. Documentation was found to be feasible during examinations under anesthesia. Data downloaded from our EMR allowed automated retinal plots, tables, and analyses for individuals and groups of patients.

<u>Conclusions</u>: The UCSF documentation system for retinoblastomas facilitates patient care and should enhance opportunities for multicenter studies aimed at validating and improving the staging of retinoblastoma.

Commercial Relationships: Lesley Everett, None; Joyce Meza, None; Armin Afshar, None; Bertil E. Damato, None Support: Giannini Foundation (Research funding, Dr. Damato), That Man May See, Inc. (Dr. Afshar), and Research to Prevent Blindness (Dr. Afshar)

Program Number: 3331 Poster Board Number: B0607

Presentation Time: 11:00 AM-12:45 PM

Immediate and Delayed Microstructural Effects of Cryotherapy for Retinoblastoma Imaged by Optical Coherence Tomography Thamolwan Surakiatchanukul, Emil Anthony T. Say, Carol L. Shields. Ocular Oncology Service, Wills Eye Hospital, Philadelphia, PA. Purpose: To describe immediate and delayed microstructural effects of cryotherapy for retinoblastoma using optical coherence tomography (OCT).

Methods: Descriptive non-comparative case series.

Results: Six eyes of 5 patients with active retinoblastoma were scanned with intraoperative OCT before and after cryotherapy. Of

the 6 active tumors, there were 1 newly detected intraretinal tumor (IRT), 4 residual/recurrent IRT, and 1 subretinal seed (SRS). Before treatment, the 5 IRT appeared hyperreflective on OCT and appeared to originate from the middle or outer retina, while the 1 SRS was located in the subretinal space without overlying fluid, edema, or loss of retinal architecture. (Figure 1) All tumors were treated focally with cryotherapy. One IRT was imaged immediately (within 2 minutes) following cryotherapy, and demonstrated increased tumor reflectivity and thickness without cystoid edema or subretinal fluid. (Figure 2) On follow-up, all treated tumors demonstrated regression with reduced thickness, and OCT showed loss of retinal (6/6, 100%) or choroidal (3/6, 50%) structure and no cystoid edema (6/6, 100%). (Figure 1-2) Two (2/6, 33%) tumors appeared having residual internal limiting membrane with cavitary loss of retinal architecture, while 2 (2/6, 33%) had hyperreflective residua over the regressed scar requiring subsequent treatment.

<u>Conclusions:</u> By OCT, cryotherapy for retinoblastoma results in immediate increase in tumor reflectivity and thickness and later tumor regression, as well as retinal and choroidal thinning. Residual active tumor appears as hyperreflective material on OCT and may require further therapy.

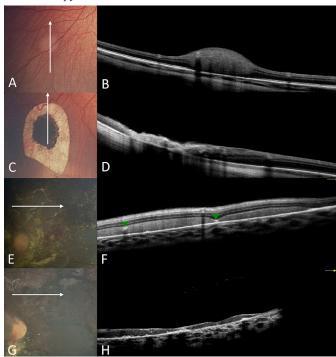


Figure 1. Retinoblastoma imaged by optical coherence tomography (OCT) before and after cryotherapy. (A-D) Newly-detected retinoblastoma in a patient with germline retinoblastoma. (A, B) The gray-white tumor deep to the nerve fiber layer (NFL) originated in the outer nuclear layer on OCT. After cryotherapy (C, D), the scar became flat with central retinal pigment epithelium (RPE) hyperplasia, corresponding to RPE thickening on OCT. (E-H) Multifocal recurrent subretinal seeds (SRS) after intra-arterial chemotherapy. (E, F) The SRS superior to the disc with surrounding exudation corresponded to hyperreflective areas in the subretinal space with focal hyperreflective lesions (green arrowhead) consistent with exudation. Following cryotherapy (G, H), SRS resolved, leaving thinned retina with focal loss of tissue and intact choroid.

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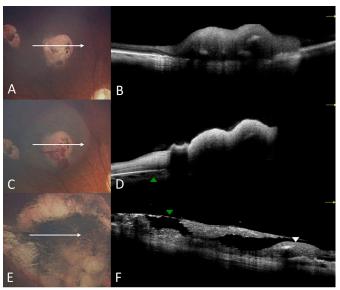


Figure 2. Recurrence in only remaining eye of bilateral retinoblastoma imaged by OCT. (A, B) Central residua appeared as retinal thickening with intra-lesional hyperreflectivity representing calcification by OCT. Immediately after cryotherapy (C, D), retinal edema surrounding the scar corresponded to increased retinal and tumor reflectivity with posterior shadowing (green arrowhead). After additional cryotherapy sessions (E, F), the flat scar contained strands of ILM (green arrowhead) with loss of intervening retinal tissue on OCT. Focal hyperreflectivity nasally (white arrowhead) likely represented regressed residua.

Commercial Relationships: Thamolwan Surakiatchanukul; Emil Anthony T. Say, None; Carol L. Shields, None

Program Number: 3332 Poster Board Number: B0608

Presentation Time: 11:00 AM-12:45 PM

Automatic Segmentation of Retinoblastoma in Fundus Image Photography using Convolutional Neural Networks

Carlos Ciller^{2, 1}, Sandro Ivo S. De Zanet³, Stefanos Apostolopoulos¹, Francis L. Munier⁴, Sebastian Wolf⁵, Jean-Philippe Thiran^{6, 2}, Meritxell Bach Cuadra^{7, 2}, Raphael Sznitman^{1, 5}. ¹Ophthalmic Technologies Laboratory, ARTORG Center, University of Bern, Bern, Switzerland; ²Department of Radiology, University of Lausanne, Lausanne, Switzerland; ³Computer Vision Lab (CVLab), EPFL, Lausanne, Switzerland; ⁴Unit of Pediatric Ocular Oncology, Jules Gonin Eye Hospital, Lausanne, Switzerland; ⁵Department of Ophthalmology, Inselspital, Bern University Hospital, Bern, Switzerland; ⁶Laboratory of Signal Processing 5 (LTS5), EPFL, Lausanne, Switzerland; ⁷Signal Processing Core, CIBM, Lausanne, Switzerland.

Purpose: Retinoblastoma is the most common form of ocular cancer in children. Locating newly-formed tumors in images of the retinal wall and estimating their growth pattern are significant challenges in the evaluation and tracking of the disease progression. In order to perform these tasks, ophthalmologists need to analyze images from different screening sessions and to annotate them, which is both time-consuming and tedious. Here, we present a method for the automatic segmentation of retinoblastoma in fundus, paving the way towards longitudinal tracking of ocular tumors.

Methods: Our data set is composed of 1186 fundus images with size 640 x 480 pixels from 28 pathological children eyes. Imaging was performed with a Retcam (Clarity Medical Systems, Pleasanton (CA), US) Fundus pediatric camera, with the patients under general anesthesia. The images were manually annotated by an expert ophthalmologist.

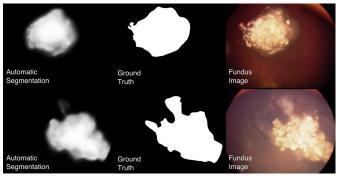
We achieve automatic segmentation of retinoblastoma by using a convolutional neural network (CNN) with an architecture known as *U-Net* (Ronneberger et al. in 2015). We trained the network with

a reduced number of filters and use data augmentation techniques to enlarge the number of training samples (mirroring on the x and y axes). We furthermore modified the *U-Net* architecture with a seven-layer-deep structure with a geometrically increasing number of feature maps at every level.

We quantitatively evaluate our segmentation method with a 7-fold cross validation, testing on 4 of the 28 subjects every time and training on the rest (24). The resulting segmentation is assessed by the overlapping Dice Similarity Coefficient (DSC), with the manual segmentation used as the ground truth.

Results: Through the 7-fold cross-validation we obtain a DSC of $71.84\pm23.70\%$ when using a smooth DSC as an objective function compared to a DSC of $62.45\pm19.63\%$ when using binary cross-entropy. The testing time for the automatic segmentation is on average < 1 second, which, compared to manual delineation taking 1-2 minutes, results in a \sim 100x speed increase.

<u>Conclusions:</u> We have shown a fast segmentation tool that provides a significant benefit for the task of segmenting retinoblastoma in fundus images. In the future, this tool will be used to simplify longitudinal tracking of ocular tumors and the evaluation of competing treatment strategies.



Results of automatic segmentation of retinoblastoma in fundus. Commercial Relationships: Carlos Ciller; Sandro Ivo S. De Zanet, None; Stefanos Apostolopoulos, None; Francis L. Munier, None; Sebastian Wolf, None; Jean-Philippe Thiran, None; Meritxell Bach Cuadra, None; Raphael Sznitman, None

Program Number: 3333 Poster Board Number: B0609

Presentation Time: 11:00 AM-12:45 PM

Development of a technique for assessment of retinoblastoma cell dissemination after intravitreal injection of chemotherapy URSULA A. WINTER¹, Michael Nicolas², Francis L. Munier², Mariana Sgroi¹, Adriana Fandiño¹, Guillermo Chantada¹, Paula Schaiquevich¹. ¹Hospital J.P Garrahan, Buenos Aires, Argentina; ²Jules-Gonin Eye Hospital, Lausanne, Switzerland. Purpose: Intravitreal chemotherapy is part of the conservative treatment strategy for intraocular retinoblastoma management. The technique developed by Munier F. et al (Br J Ophthalmol., 2012) proposes several recommendations to minimize extraocular tumor dissemination after the injection of the drugs.

Despite well documented tumor regression, it is necessary to assess for potential risks of tumor cell dissemination from the needle track after the injection. Thus, our aim was to develop a specific, sensitive and simple technique of tumor cell assessment in the wound after intravitreal injections in retinoblastoma patients treated in two reference clinical centers in Argentina and Switzerland.

Methods: After performing the intravitreal injection of chemotherapy followed by cryotherapy, a 3mm diameter circular paper filter (Whatman®42 Sigma-Aldrich) was placed on the scar and another piece of paper on the cryo-tip probe. Then, each paper was placed in

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a tube and PBS were added. After 1min, the supernatant was removed and the tube with the paper was subjected to freeze and thaw cycles. Then, cDNA was obtained by RT-PCR (SuperscriptIII, Life Technologies) to evaluate the expression of a lineage-specific gene marker CRX (cone-rod homeobox-containing gene). RTq-PCR was performed using SYBR®Green Master Mix (Life Technologies) and a Real-Time PCR system (ABI). A calibration curve was performed using WERI-Rb1 (ATCC). CRX was considered positive if Ct value of each replica was less than 40 and S.D between replicates was less than 0.5.

The study protocol and informed consent were approved by the by the Institutional Review Boards of both countries.

Results: The developed technique allows detecting as low as one retinoblastoma cell. Primer specificities were confirmed by melting curve analysis with single peaks. The efficiencies of CRX and gapdh genes were between 80 and 120 % with associated correlation coefficients ≥0.95.

A total of 19 cycles of intravitreal chemotherapy were evaluated until the present report. In all cases, samples from the wound of injection or the cryo-tip probe resulted CRX negative.

<u>Conclusions:</u> The developed technique is precise and sensitive allowing detecting as low as one retinoblastoma cell. This technique is tool to aid in assessing the performance and safety of intravitreal injection of chemotherapy in intraocular retinoblastoma management.

Commercial Relationships: URSULA A. WINTER, None; Michael Nicolas, None; Francis L. Munier, None; Mariana Sgroi, None; Adriana Fandiño, None; Guillermo Chantada, None; Paula Schaiquevich, None

Support: This work was supported by The National Scientific and Technical Research Council-Argentina (CONICET, PIP #11220120100383CO01); Fund for Ophthalmic Knowledge, New York, NY, USA; and Fundación Natalie D Flexer de Ayuda al Niño con Cáncer, Buenos Aires, Argentina.

Program Number: 3334 Poster Board Number: B0610 Presentation Time: 11:00 AM-12:45 PM

Magnetic resonance imaging features of the optic nerve in enucleated retinoblastoma patients

Ramon Lee^{1, 2}, Jesse L. Berry^{1, 2}, Ingy Madi^{1, 2}, Emily Zolfaghari^{1, 2}, Jonathan W. Kim^{1, 2}. ¹The Vision Center at Children's Hospital Los Angeles, Department of Ophthalmology, Keck School of Medicine of University of Southern California, Los Angeles, CA; ²USC Roski Eye Institute, Department of Ophthalmology, Keck School of Medicine of University of Southern California, Los Angeles, CA.

Purpose: The aim of this retrospective review was to determine the role of gadolinium-enhanced magnetic resonance imaging in the assessment of optic nerve of retinoblastoma patients post-enucleation by detecting signs of contrast enhancement and/or thickening along the cut end of the nerve.

Methods: Eligible patients underwent enucleation for retinoblastoma between January 2008 and December 2015. Overall, 90 enucleated eyes for 88 patients were included. Post-contrast MRI of the orbit was performed both pre-enucleation, for evaluation of optic nerve and trilateral disease, and post-enucleation for routine screening. The primary outcome measures were contrast enhancement along the cut end of the optic nerve, abnormal optic nerve thickening, presence of orbital disease, and/or trilateral retinoblastoma post-enucleation. Based on radiologist assessment, optic nerve enhancement was categorized into 3 subgroups: mild, moderate, or severe. Tumor extension into the optic nerve on histopathology was also assessed and categorized as pre- or post-laminar invasion.

Results: Overall, 41 of 50 eyes (82%) of post-enucleation patients demonstrated contrast enhancement along the cut end of the optic

nerve post-enucleation at a mean interval of 10 months. Of these, 20 demonstrated moderate enhancement and 7 mild; the severity of enhancement was not described for 14 patients. The enhancement was noted to be stable or resolved on follow-up imaging. Among the 88 patients, 38 patients received systemic chemoreduction with CEV pre-enucleation; there was no association between chemotherapy administration and optic nerve enhancement. Histopathologic post-laminar optic nerve invasion was reported in 6 eyes and preenucleation optic nerve enhancement was detected in 3 of these eyes. No child required a biopsy secondary to optic nerve findings. None of these patients were found to have subsequent orbital or metastatic disease at last exam under anesthesia (average 13 months, range 1-59) or last follow-up visit (average 29 months, range 1-71). **Conclusions:** Optic nerve contrast enhancement on follow-up MRI post-enucleation for retinoblastoma is a common finding and appears to be consistent with normal post-surgical scarring and granulation tissue, and not active tumor. The presence or absence of post-enucleation enhancement did not correlate with preenucleation chemotherapy or the presence of optic nerve invasion on histopathology.

Commercial Relationships: Ramon Lee, None; Jesse L. Berry, None; Ingy Madi, None; Emily Zolfaghari, None; Jonathan W. Kim, None

Program Number: 3335 Poster Board Number: B0611 Presentation Time: 11:00 AM-12:45 PM Optic Nerve Obscuration in Retinoblastoma: a Risk Factor for Optic Nerve Invasion?

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¹Ophthalmology, Children's Hospital, Los Angeles, Los Angeles, CA;

²USC Roski Eye Institute, Los Angeles, CA; ³The Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, Los Angeles, CA.

Purpose: Obscuration of the optic nerve is a common finding in advanced intraocular retinoblastoma, but there are no previous studies examining its risk for optic nerve invasion. The objective of this study is to evaluate the risk of optic nerve invasion associated with optic nerve obscuration either at diagnosis or that persists during treatment. In addition, a case series of 4 patients with advanced retinoblastoma and complete obscuration of the optic nerve by tumor that persisted throughout treatment is presented.

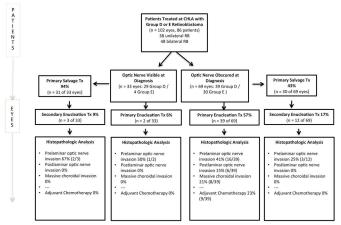
Methods: Retrospective review from 2011-2016 of patients at Children's Hospital Los Angeles with advanced retinoblastoma (Group D/E) with complete obscuration of the optic nerve at diagnosis and a second group of patients who had persistent obscuration through the course of therapy. RetCam fundus photographs from examination under anesthesia (EUA) at diagnosis, and each subsequent EUA, were evaluated for completed obscuration of the optic nerve by the tumor.

Results: Advanced retinoblastoma was diagnosed in 102 eyes of 86 patients. The optic nerve was obscured in 69 eyes (68%) at diagnosis. Of these, 30 (43%) underwent salvage therapy and 39 (57%) primary enucleation. Histopathologic analysis of primarily enucleated eyes with optic nerve obscuration showed 41% pre-laminar invasion and 15% post-laminar invasion. Four eyes in the salvage group had persistent nerve obscuration throughout treatment; 2 were subsequently enucleated without evidence of optic nerve invasion. Average follow up was 23.5 months (range 1-62 months).

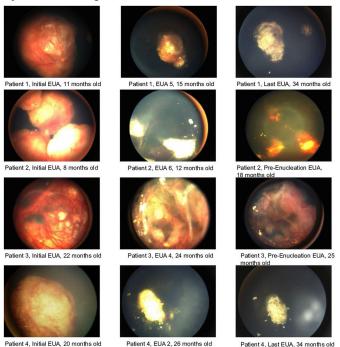
<u>Conclusions:</u> Optic nerve obscuration at diagnosis may be associated with higher-risk pathologic features including post-laminar optic nerve invasion. While persistent post-treatment obscuration of the optic nerve by retinoblastoma is a relatively poor prognostic sign for

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both globe salvage and vision, it does not appear, in this small cohort, to increase the risk of optic nerve invasion during or after treatment. With appropriate control of the intraocular tumor, these eyes can be safely salvaged.



Consort Diagram showing Clinical and Pathologic features of Advanced Retinoblastoma Eyes with and without Obscuration of the Optic Nerve at Diagnosis.



Fundus Photos of Four patients with Advanced Retinoblastoma with Persistent Obscuration of the Optic Nerve through the course of therapy. Patient 2 and 3 were enucleated; Patient 1 and 4 were salvaged with full control of the intraocular disease.

Commercial Relationships: Emily J. Zolfaghari, None; Jesse L. Berry, None; Alexander Chen, None; A. Linn Murphree, None; Rima Jubran, None; Jonathan W. Kim, None Support: Retinoblastoma International, Inc.; The Institute for Families, Inc., Children's Hospital Los Angeles; An unrestricted departmental grant from Research to Prevent Blindness **Program Number:** 3336 **Poster Board Number:** B0612

Presentation Time: 11:00 AM-12:45 PM

Treatment of Group B Retinoblastoma with Chemotherapy Alone without Laser Consolidation Therapy

Arezu Haghighi¹, Emily J. Zolfaghari², Jonathan Kim², Hassan A. Aziz², Kathleen McGovern², Rima Jubran², A. Linn Murphree², Jesse L. Berry¹. ¹Ophthalmology, University of Southern California Roski Eye Institute, Pasadena, CA; ²Children's Hospital Los Angeles, Los Angeles, CA.

Purpose: Group B retinoblastoma tumors are conventionally treated with 3-6 cycles of systemic chemotherapy and local consolidation with laser therapy. Using this treatment approach, salvage rates of Group B retinoblastoma approach 90-100%. However, the added benefit of laser consolidation therapy as well as the exact timing of this therapy has yet been elucidated. This study presents a case series of four Group B patients with tumors located within or adjacent to the fovea that were treated with chemotherapy alone without laser consolidation therapy.

Methods: A case series (4) of Group B eyes treated with chemotherapy alone were obtained from a retrospective chart review with data collection from a 20-year period spanning January 1, 1995 to January 1, 2016. Inclusion criteria included patients diagnosed at CHLA with Group B retinoblastoma in at least one eye, at least one tumor involving the posterior pole, and Retcam photos available for comparison at diagnosis, during and after the completion of chemoreduction. Patient were treated with 2-6 cycles of chemotherapy every 28 days with follow-up every 4-6 weeks during treatment. EUA was performed and Retcam images were obtained at every follow-up visit. From the Retcam images, tumor dimensions and distance of tumor to the fovea and optic nerve were recorded. **Results:** Three of four eyes in this series showed complete tumor control. One eye showed initial response to chemotherapy and 6 cycle were given—this eye was not treated with laser however there was a large late tumor recurrence, and given this was a unilateral case with tumor involving >50% of the macula it was decided to proceed with enucleation rather than further salvage therapy. One of the four eyes showed complete resolution of the tumor without scar. Amongst the salvaged eyes, a steady decline in tumor dimensions was noted at every follow-up visit with chemotherapy alone with one case showing a slight increase in tumor dimensions at the final visit; this phenomenon has been observed amongst a larger study cohort and could be attributed to an increase in the choreoretinal scar size. Final visual acuity was 20/20, 20/40, and 20/400 in the salvaged eyes, which correlated with macular involvement.

of patients with tumors at or adjacent to the fovea, systemic chemotherapy alone without laser consolidation may be curative. Commercial Relationships: Arezu Haghighi, None; Emily J. Zolfaghari, None; Jonathan Kim, None; Hassan A. Aziz, None; Kathleen McGovern, None; Rima Jubran, None; A. Linn Murphree, None; Jesse L. Berry, None Support: Retinoblastoma International, Inc.; The Institute for Empilies Line, Children's Hospital Los Appelos: Research to Prevent

Conclusions: The results of this study show that in a small cohort

Families, Inc., Children's Hospital Los Angeles; Research to Prevent Blindness; UL1TR001855 and UL1TR000130 from the National Center for Advancing Translational Sciences (NCATS)

Program Number: 3337 Poster Board Number: B0613

Presentation Time: 11:00 AM-12:45 PM

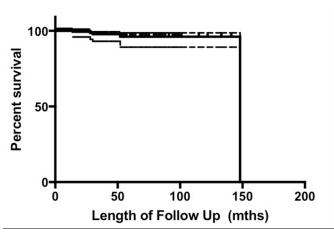
Second Primary Malignancies in Retinoblastoma Patients
Treated with Intraarterial Chemotherapy: The First Ten Years
Larissa Habib¹, Jasmine H. Francis¹.², Pierre Gobin², Brian Marr¹.²,
Ira J. Dunkel³, David H. Abramson¹.².¹Ophthalmic Oncology,
Memorial Sloan Kettering Cancer Center, New York, NY; ²Weill
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Sloan Kettering Cancer Center, New York, NY.

Purpose: Survivors of retinoblastoma carry a lifetime risk of secondary malignancies. It is well established that external beam radiation increases this risk, however, the long-term risk of intraarterial chemotherapy remains unknown. We report on ten years of experience with intraarterial chemotherapy and the rate of second primary malignancy (SPM) development.

Methods: This is a retrospective review approved by the Memorial Sloan Kettering Cancer Center (MSKCC) institutional review board (IRB) of all patients who received intraarterial therapy over a ten-year period, May 2006 to November 2016. The clinical characteristics including age at first treatment, sex, laterality, genetics, family history and adjunctive therapy were collected. Second tumor free survival in bilateral and unilateral with family history or confirmed germline mutation was estimated using the Kaplan-Meier method.

Results: Twenty-nine unilateral patients with family history or confirmed germline mutation and 205 bilateral patients were analyzed. One patient was excluded as she presented with trilateral disease. Over the study period 5 patients developed a SPM. Of those, 4 were pineal tumors in patients that had not received external beam radiation (EBR) and 1 was an osteogenic sarcoma of the orbit in a patient that did receive EBR. All of the patients with SPM were bilateral patients in this cohort. Kaplan Meier analysis estimates the likelihood of developing a second cancer to be 3.7% at 5 years (95% CI 2.4 – 6.9). (Figure 1)

Conclusions: In our ten-year experience we have found that SPM development in patients treated with intraarterial chemotherapy was comparable to previously published rates for germline patients.^{1,2} In the first ten years, intrarterial chemotherapy did not increase the known incidence of second malignancies and the most common second malignancy was a pineal tumor. This cohort will continue to be followed to establish the rate of development with extended follow up.



Commercial Relationships: Larissa Habib; Jasmine H. Francis, None; Pierre Gobin, None; Brian Marr, None; Ira J. Dunkel, None; David H. Abramson, None **Program Number:** 3338 **Poster Board Number:** B0614

Presentation Time: 11:00 AM-12:45 PM

Anti-VEGF therapy for secondary neovascularization following intra-arterial chemotherapy for advanced retinoblastoma

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Ciara Bergin¹, Susan Houghton¹, Alexandre Moulin¹,

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Eye Hospital, Lausanne, Switzerland; ²Neuroradiology Unit, Centre
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Hematology Oncology Unit, Centre Hospitalier Universitaire

Vaudois, Lausanne, Switzerland.

Purpose: Primary neovascularization in retinoblastoma is still considered an indication for enucleation (Group E), as well as in secondary cases, habitually related to radiotherapy. We investigated the use of anti-VEGF therapy in secondary vasoproliferative disease for globe salvage after intra-arterial chemotherapy (IAC). Methods: Retrospective review of consecutive retinoblastoma patients with progression of proliferative retinopathy and/or rubeosis despite cryo-photo-ablation of the ischemic retina, or inability to perform cryo-ablation due to hematovitreous and/or retinal detachment. Anterior and posterior segment status was monitored under anesthesia by photography and fluorescein angiography, and intravitreal anti-VEGF (ranibizumab and/or aflibercept) administered according to the safety-enhanced technique.

Results: From November 2010 to May 2016, 24 patients (26 eyes) with advanced retinoblastoma complied with the inclusion criteria, having received IAC and developed secondary neovascularization. Three eyes received IAC only; 23/26 underwent prior systemic chemotherapy (IVC) with/without radiotherapy (6/17 respectively). Anti-VEGF was administered at a mean interval of 6.4 (median 2.5) months after IAC.

Vasoproliferative complications were classified as: rubeosis with/ without localized retinal neovascularization or extended fibrovascular membrane. A total of 46 injections were administered, a single injection for 13 eyes (50%), multiple injections for 13 eyes (50%). 9/26 eyes (34.6%) were ultimately enucleated: 6 for progressive disease. Three had intermediate histopathologic risk factors and received adjuvant IVC. Mean follow-up for globe salvage was 19.4 months. All patients are alive without metastases.

Conclusions: IAC is identified as a novel risk factor for secondary neovascularization related to ischemic retinopathy with/without retinal detachment. In our series, anti-VEGF enabled 23 (63.8%) eyes to be salvaged, by providing the conditions to continue conservative treatment i.e. angiography-directed therapy of any ischemic retinopathy; subsequent retinal detachment surgery as necessary, and continued tumor-related management.

Commercial Relationships: Francis L. Munier, None; Marie-Claire Gaillard, None; Francesco Puccinelli, None; Ciara Bergin, None; Susan Houghton, None; Alexandre Moulin, None; Maja Beck-Popovic, None

Program Number: 3339 Poster Board Number: B0615

Presentation Time: 11:00 AM-12:45 PM

Choroidal infarction following ophthalmic artery chemotherapy Kelley Bohm¹, Pierre Gobin², Jasmine H. Francis¹, Brian Marr¹, Anahita Dabo-Trubelja³, Paul H. Dalecki³, David H. Abramson¹. ¹Ophthalmic Oncology Dept., Memorial Sloan Kettering Cancer Center, NEW YORK, NY; ²Interventional Neuroradiology Dept., Weill Cornell Medical College, New York, NY; ³Anesthesia Dept., Memorial Sloan Kettering Cancer Center, New York, NY.

<u>Purpose:</u> To describe choroidal infarction after ophthalmic artery chemotherapy in patients who had at least one mutated copy of the methylenetetrahydrofolate reductase (MTHFR) gene and received

inhaled nitrous oxide with anesthesia during ophthalmic artery chemosurgery (OAC).

Methods: Single center retrospective review of pediatric patients with advanced retinoblastoma (diagnosed as International Classification Groups D and E) who received OAC and developed choroidal infarcts. All patients had at least one mutated copy of the MTHFR gene (mutations in either the C677T or A1298C alleles on chromosome 1p at position 36.22) and received inhaled nitrous oxide induction anesthesia (between 5 to 10 minutes duration) during the preceding OAC. Indirect ophthalmoscopy, RetCam digital photography, ocular coherence tomography (OCT) and in some of the patients, fluorescein angiography (FA) was used to describe fundus findings.

Results: Six advanced retinoblastoma patients ages 10 to 58 months (3 males, 3 females) experienced choroidal infarcts within the one-month period after OAC in which nitrous oxide induction was used for the procedure. All 6 patients had abnormalities in MTHFR: two were homozygous for the C677T mutation of the MTHFR gene, two were heterozygous for C677T, one was heterozygous for A1298C, and one was heterozygous for both C677T and A1298C. In all 6 patients, indirect ophthalmoscopy and fundus photography showed marked disturbance of the retinal pigment epithelium and OCT confirmed marked thinning of the choroid. Follow-up time for these patients ranged from 6 to 49 months (median 14.5 months).

<u>Conclusions:</u> Choroidal infarction in eyes treated with OAC developed in children who were both deficient in at least one working allele of the MTHFR gene (heterozygous or homozygous) and received nitrous oxide induction anesthesia during ophthalmic artery chemosurgery.

Commercial Relationships: Kelley Bohm, None; Pierre Gobin, None; Jasmine H. Francis, None; Brian Marr, None; Anahita Dabo-Trubelja, None; Paul H. Dalecki, None; David H. Abramson, None

Program Number: 3340 Poster Board Number: B0616

Presentation Time: 11:00 AM-12:45 PM

A comparison of retinoblastoma vitreous seed clouds (class 3) treated with ophthalmic artery chemosurgery with or without intravitreous chemotherapy

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Purpose: Class 3 retinoblastoma vitreous seeds, or clouds, have the distinctive clinical profile because they occur more commonly in older patients with unilateral disease and peripheral tumors. They receive the highest amount of intravitreous melphalan and take the longest time to regress. This study compares efficacy and toxicity of treatment between ophthalmic artery chemosurgery with or without intravitreous chemotherapy.

Methods: 40 eyes containing clouds (class 3 vitreous seeds) of 40 retinoblastoma patients (19 treated with OAC alone and 21 treated with OAC and intravitreous (OAC/IVit) were investigated. The outcomes measures of ocular survival, disease-free survival and time to regression of seeds were analyzed with Kaplan-Meier estimates. Ocular toxicity was evaluated by clinical findings and electroretinography (ERG): 30 Hz flicker responses were recorded at baseline, immediately prior to each injection and at each follow-up visit. Continuous variables (age, follow-up time) were compared with a Students' t-test and categorical variables (laterality, disease status, etc) were compared with Fisher's Exact Test.

Results: There were no disease or treatment-related deaths and no metastatic disease. No patient developed externalization of tumor. There was no significant difference in the age, laterality or disease and disease status (naïve vs prior treated) between the two groups. The time to regression was significantly shorter for eyes treated with OAC/IVit (5.6mos), compared to eyes treated with OAC alone (14.6 mos, p<0.001). The 18-month Kaplan-Meier estimates of disease-free survival were significantly worse for the OAC alone group: 67.1% (95%CI 40.9-83.6), compared to the OAC/IVit group: 94.1% (95%CI 65-99.1), (p=0.05). The 36-month Kaplan-Meier estimate of ocular survival 83.3% (95%CI 56.7-94.3) for the OAC alone and 100% for the OAC/IVit, p=0.16. Changes in electroretinogram responses were not significantly different between the two groups.

<u>Conclusions:</u> Treating vitreous seed clouds with OAC *and* intravitreous chemotherapy, compared to OAC alone, results in a shorter time to regression and is associated with fewer recurrences requiring additional treatment. The toxicity to the retina appears to be equivalent between the two groups.

Commercial Relationships: Jasmine H. Francis, None; Saipriya Iyer, None; Pierre Gobin, None; Brian Marr, None; Scott E. Brodie, None; David H. Abramson, None

Program Number: 3341 Poster Board Number: B0617 Presentation Time: 11:00 AM-12:45 PM Retinoblastoma in India: Clinical presentation and outcome in

1457 patients (2074 eyes)
Swathi Kaliki, Anamika Patel, Sadiya Iram, Vijay Anand
Reddy Palkonda, Ashik Mohamed, George Ramappa. Ocular

Oncology, L V Prasad Eye Institute, Hyderabad, India. **Purpose:** India peaks the predicted incidence of retinoblastoma in the world with over 1400 of 8000 new cases diagnosed each year. In this report, we studied the clinical presentation, treatment, and outcome of patients with retinoblastoma (RB) in India. We performed a retrospective clinical study on 1457 patients (2074 eyes) with

<u>Methods:</u> All patients diagnosed with retinoblastoma and with adequate documentation of presenting signs and clinical details were included in the study. The treatment modalities and outcome (metastasis and death) were analyzed.

Results: The mean age at presentation of RB was 29 months (median, 24 months; range; <1 to 370 months). There were 812 (56%) males and 645 (44%) females with unilateral presentation of RB in 57% (n=834) and bilateral in 43% (n=623). Family history of RB was present in 4% (n=55). The most common presenting complaints included leukocoria (n=1100; 75%), proptosis (n=91; 6%), strabismus (n=77; 5%), and red eye (n=68; 5%). Most (n=1889; 91%) tumors were intraocular in location and 185 (n=185; 9%) had extraocular tumor extension at presentation. Based on International Classification of Intraocular Retinoblastoma, the tumors were classified as group A (n=107; 6%), B (n=278; 15%), C (n=127; 7%), D (n=414; 22%), or E (n=963; 51%). Based on International Staging of Retinoblastoma, the tumors were classified as stage 0 (n=933; 45%), I (n=925; 45%), II (n=31; 2%), III (n=131; 6%), or IV (n=54; 3%). Based on Tumor Node Metastasis classification, the tumors belonged to T1 (n=385; 19%), T2 (n=541; 26%), T3 (n=963; 46%), or T4 (n=185; 9%). The most common modalities of primary treatment included systemic chemotherapy (n=1171; 60%) and enucleation (n=674; 35%). At a mean follow-up period of 44 months (median, 30 months; range, 3 to 234 months), 92% (n=1206) were alive and 108 (8%) patients died due to RB. Based on Kaplan-Meier analysis, the survival at 1, 3, 5, and 10 years was 94%, 91%, 90%, and 89% respectively.

Conclusions: The most common presenting signs of RB in Asian Indian population are leukocoria and proptosis. Though most patients present with advanced disease compared to western studies, with appropriate treatment, the survival rate is favorable at 92%. Commercial Relationships: Swathi Kaliki, None; Anamika Patel, None; Sadiya Iram, None; Vijay Anand Reddy Palkonda, None; Ashik Mohamed, None; George Ramappa, None

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Presentation Time: 11:00 AM-12:45 PM

Are plasma levels of 8-hydroxy-2'-deoxyguanosine associated with an increased risk of unilateral sporadic Retinoblastoma? Bhavna Chawla¹, Shilpa Bisht², Rima Dada². ¹Dr Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India; ²Laboratory for Molecular Reproduction and Genetics, Department of Anatomy, All India Institute of Medical Sciences, New Delhi, India.

Purpose:

Oxidative stress (OS) is associated with oxidative DNA damage and is documented to be associated with tumorigenesis. Guanine is most susceptible to OS due to its low oxidation potential. This results in the generation of highly mutagenic oxidative base adduct 8-OHdG (8-hydroxy-2'-deoxyguanosine). 8-OHdG has the ability to pair with adenine and results in G:C \rightarrow T:A transversions, which result in single and double strand DNA breaks and therefore, an increased mutation rate. Increased plasma levels of 8-OHdG are associated with the development of colorectal carcinoma, ovarian cancer and prostate

cancer, but the plasma levels of 8-OHdG have not been evaluated in retinoblastoma patients so far. The present study was undertaken to examine whether plasma 8-OHdG could be a probable factor for the development of unilateral sporadic retinoblastoma.

Methods: Cases of unilateral sporadic retinoblastoma who presented to our Centre between 2014-2015 were studied. Demographic and clinical features were noted. Blood samples were taken from the patients. DNA isolation, PCR and Sanger's sequencing was performed to exclude cases with germline mutation in the *RB1* gene. 8-OHdG levels were determined in the blood plasma of cases and age matched healthy controls by ELISA (DNA/RNA Oxidative Damage EIA kit from Cayman Chemical, Ann Arbor, MI) and compared between the two groups.

Results:

The study included 36 cases and 36 controls. The mean age of presentation in retinoblastoma children was 22.6 ± 10.8 months. 8-OHdG plasma levels were found to be significantly higher (p value= 0.016) in cases (7579 ± 58 pg/ml) as compared to controls (6179 ± 78 pg/ml).

<u>Conclusions</u>: This study provides an insight into the possible role of oxidative DNA adduct 8-OHdG in retinoblastoma pathogenesis. Elevated plasma 8-OHdG levels in unilateral sporadic retinoblastoma patients could predispose to somatic mutations in the *RB1* gene and may be a probable factor for its development.

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