# Ocular Oncology and Pathology 2018

## Hot Topics in Ocular Pathology and Oncology—An Update

**Program Directors**
Patricia Chévez-Barrios MD and Dan S Gombos MD

**In conjunction with the American Association of Ophthalmic Oncologists and Pathologists**

McCormick Place
Chicago, Illinois
Saturday, Oct. 27, 2018

Presented by:
The American Academy of Ophthalmology

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On behalf of the American Academy of Ophthalmology and the American Association of Ophthalmic Oncologists and Pathologists, it is our pleasure to welcome you to Chicago and **Ocular Oncology and Pathology 2018: Hot Topics in Ocular Pathology and Oncology—An Update.**

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## 2018 Ocular Oncology and Pathology Subspecialty Day Learning Objectives

Upon completion of this activity, participants should be able to:

- Identify clinical and pathologic features of certain tumors, such as ocular melanoma, retinoblastoma, and conjunctival premalignant lesions
- Identify and manage treatment complications such as second tumors and metastasis
- Recognize advances in liquid biopsies and ocular pathology
- Determine when a patient should be referred to an ocular oncology center and when to consult an ocular pathologist

## 2018 Ocular Oncology and Pathology Subspecialty Day Target Audience

The intended audience for this program is ocular oncology and pathology surgeons, comprehensive ophthalmologists with an interest in anterior segment, and allied health personnel who are performing or assisting with ocular oncology and pathology surgery.

## 2018 Ocular Oncology and Pathology Subspecialty Day CME Credit

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The Academy designates this live activity for a maximum of 7 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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# Ocular Oncology and Pathology 2018: Hot Topics in Ocular Pathology and Oncology—An Update

## In conjunction with the American Association of Ophthalmic Oncologists and Pathologists

### SATURDAY, OCT. 27

| | | | |
|---|---|---|---|
| 7:00 AM | CONTINENTAL BREAKFAST | | |
| 8:00 AM | Welcome and Introductions | Patricia Chévez-Barrios MD*<br>Dan S Gombos MD* | |

**Section I: Oncologist and Pathologist Hand in Hand**

Moderators: Bita Esmaeli MD FACS and Hans E Grossniklaus MD*

| | | | |
|---|---|---|---|
| 8:05 AM | Uveitis vs. Lymphoma: Clinical Approach to Diagnosis | Jose S Pulido MD MS* | 1 |
| 8:12 AM | Uveitis vs. Lymphoma: Laboratory and Molecular Diagnosis | Diva R Salomão MD | 3 |
| 8:19 AM | Update on Histopathologic Clinical Correlates in Retinoblastoma | Patricia Chévez-Barrios MD* | 5 |
| 8:26 AM | Clinical Pearls and Treatment of Vitreous Seeds | Jasmine H Francis MD | 7 |
| 8:33 AM | Sarcoidosis and the Eye: Clinical and Pathologic Diagnosis | Narsing A Rao MD | 8 |
| 8:40 AM | Mechanisms of Neural and Retinal Invasive Uveal Melanoma | Hans E Grossniklaus MD* | 9 |
| 8:47 AM | Conjunctival Melanosis: PAM vs. C-MIN | Tatyana Milman MD | 10 |
| 8:54 AM | Treatment of Conjunctival Melanocytic Lesions | Jacob J Pe'er MD | 12 |
| 9:01 AM | DICER1 and Medulloepithelioma | Maria Miguelina de la Garza MD | 13 |
| 9:08 AM | Update on Diagnosis and Treatment of Medulloepithelioma | Jonathan W Kim MD | 14 |

**Section II: Pro and Con Debate and Roundtable on Retinoblastoma**

Moderators: Dan S Gombos MD* and Jonathan W Kim MD

| | | | |
|---|---|---|---|
| 9:15 AM | Intra-arterial Chemotherapy Does Not Increase the Risk of Secondary and Metastatic Disease | David H Abramson MD FACS | 16 |
| 9:20 AM | We Don't Know if Intra-arterial Chemotherapy Increases the Risk of Secondary and Metastatic Disease | Ann-Marie Leahey MD | 17 |
| 9:25 AM | There Is Consensus on the Use of Intra-arterial Chemotherapy for Unilateral Retinoblastoma | Dan S Gombos MD* | 19 |
| 9:30 AM | There Is No Consensus on the Role of Intra-arterial Chemotherapy for Unilateral Retinoblastoma | Mandeep S Sagoo MBBChir PhD | 20 |
| 9:35 AM | Roundtable and Debate<br>Panel Moderator: Jonathan W Kim MD<br>Panelists: David H Abramson MD FACS, Murali Chintagumpala MD, Dan S Gombos MD*, Ann-Marie Leahey, and Mandeep S Sagoo MBBChir PhD | | |
| 10:05 AM | REFRESHMENT BREAK and AAO 2018 EXHIBITS | | |

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.

## Section III: Hot Topics in Retinoblastoma

Moderators: Jesse L Berry MD* and David J Wilson MD



## Section IV: Uveal Melanoma—Hot and Spicy Topics

Moderators: Paul J Bryar MD and Carol L Shields MD*



## Section V: Uveal Melanoma—Pro and Con Debate

Moderators: Prithvi Mruthyunjaya MD* and Arun D Singh MD*



## Section VI: Multicenter Trials in Ocular Oncology—2018 Update

Moderators: Sander Dubovy MD and Amy C Schefler MD*



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# Uveitis vs. Lymphoma: Clinical Approach to Diagnosis

*Jose S Pulido MD MS*

## Introduction

Intraocular lymphoma is comprised of the following:

- Vitreoretinal lymphoma, which is 95% of the time diffuse large B-cell lymphoma (DLBCL) and 5% of the time T-cell lymphoma
- Choroidal lymphoma, which is usually B-cell lymphoma and mainly small B-cell lymphoma and only 20% diffuse large B-cell
- Iridial lymphoma, usually seen in immunocompromised patients, involves many times Epstein-Barr virus–driven diffuse large B-cell lymphoma

## Vitreoretinal Lymphoma: DLBCL

- Primary
  - No known history of lymphoma
  - Can have history of chronic lymphocytic leukemia (CLL), and thus the patient has had a Richter transformation which is seen in about 6% of patients with CLL.
- Secondary
  - Either associated with primary CNS lymphoma or systemic DLBCL
  - Generally, patients tend to notice floaters, and the floaters are in marked increase in comparison to the level of vision loss (ie, if the patient really had uveitis and there were as many cells as there are in a comparable case of vitreoretinal lymphoma, the vision would be markedly worse). Similarly, OCT and fluorescein angiography generally shows much less cystoid macular edema than one would expect from a comparable case of uveitis.
  - Additionally, the patient has been followed with the diagnosis of "uveitis" on average for 6 months before the thought of the possibility of vitreoretinal lymphoma has been entertained.

When the patient arrives, systemic evaluation and MRI of the brain needs to be done if the patient is considered to have vitreoretinal lymphoma. The vitreal cells tend to be larger than inflammatory cells and do not tend to clump. They attach to the vitreal fibers and sway with the fibers.

If there is retinal involvement, early on it tends to be sub–retinal pigment epithelium (RPE). It never extends posterior to the Bruch membrane so that there is no need to do a choroidal biopsy. If the patient has had a vitrectomy already and there are only a few sub-RPE deposits, the chances of a positive polymerase chain reaction (PCR) or histology are very small from that eye. Try the other eye if there are plenty of cells.

Later, there are intraretinal cells and large accumulations of subretinal cells. The center of the subretinal cells is not good to biopsy because the cells have undergone apoptosis. Vitrectomy is far better than just biopsy because it decreases markedly the amount of proliferating cells and it increases the oxygenation of the vitreous, which affects the DLBCL cells. Also it helps to break down the blood–retina barrier, which allows T-cells to enter.

Send the cells for cytospin in RPMI solution and in ice. Cytospin can then be sent for histology and PCR for MYD88.

DLBCL vitreoretinal lymphoma with secondary T-cells in the vitreous. Only in 15% of primary cases or if the eye has had prior vitrectomy. PCR still is helpful in the primary cases.

## T-Cell Vitreoretinal Lymphoma

Rare; many times associated with mycosis fungoides.

## Choroidal Lymphoma

Many times these are primary and not associated with systemic disease. Most times these cases are small B-cell lymphoma, which is very responsive to low grade 20-Gy radiation. Sometimes the choroidal lymphoma can be DLBCL, and in these cases, there can be extension into the orbit.

- Vision tends to be good and there are rare cells in the vitreous.
- Choroid is whitish.
- OCT shows the choroid is lumpy-bumpy, as described by the Shieldses, and the normal choroidal vasculature is replaced by infiltration of hyperreflective cells.
- Ultrasound has low internal reflectivity if it is thick enough to measure.
- No cystoid macular edema is usually present.
- PET scan should be done since CNS involvement is not generally associated, and most times the PET scan is negative.
- Differential diagnosis are granulomas—either infectious, including TB and syphilis, or noninfectious, like sarcoid, common variable immunodeficiency.
- Evaluation of the orbit and lacrimal glands and conjunctiva should be done and biopsied. If that is negative, then retinal choroidal biopsy should be done. Vitrector is fine.

## Iridial Lymphoma

- Usually DLBCL. Many times associated with immunosuppression or with involvement of other parts of the eye or orbit. Biopsy is helpful, and then EBV PCR and EBV immunostaining should be performed.
- Decrease in immunosuppression should be done. There tends to be keratic precipitates and reactive T-cells.

## Selected Readings

1. Pulido JS, Johnston PB, Nowakowski GS, Castellino A, Raja H. The diagnosis and treatment of primary vitreoretinal lymphoma: a review. *Int J Retina Vitreous*. Epub before print 2018 May 7. doi: 10.1186/s40942-018-0120-4. Erratum in: *Int J Retina Vitreous*. 2018 Jun 4;4:22.
2. Shields CL, Arepalli S, Pellegrini M, Mashayekhi A, Shields JA. Choroidal lymphoma shows calm, rippled, or undulating topography on enhanced depth imaging optical coherence tomography in 14 eyes. *Retina* 2014; 34(7):1347-1353.
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# Uveitis vs. Lymphoma: Laboratory and Molecular Diagnosis

***Diva Regina Salomão MD***

1. Intraocular lymphomas are rare, accounting for less than 1% of all non-Hodgkin lymphomas.[1,2]
2. Intraocular lymphomas can be divided into vitreoretinal lymphomas (VRL), considered a subset of CNS lymphoma and most commonly large-cell lymphomas, and primary uveal lymphomas, which are often low-grade lymphomas.
3. Clinically, patients with VRL may have symptoms that mimic chronic uveitis. Since VRL cases may respond temporarily to systemic corticosteroids, the correct diagnosis is often delayed. Intraocular lymphoma is considered the one of the greatest masqueraders.[3,4]
4. The diagnosis of intraocular lymphoma is often challenging and most commonly based on the interpretation of small and scant specimens, such as vitreous and subretinal aspirates, occasionally a small retinal or choroidal biopsy.
5. Cytological examination is considered the gold standard for the diagnosis of intraocular lymphoma. Cytology of VRL cases show large, atypical lymphoid cells with scant cytoplasm, pleomorphic nuclei, and prominent nucleoli, as most VRL are large-cell lymphomas with a B-cell phenotype. Phenotyping is required to prove clonality and to classify the lymphoma type according to the latest WHO classification for non-Hodgkin lymphomas.
6. Although vitreous cytology provides quick and valuable information when it is adequate, there are several limitations to this technique. Many reactive lymphocytes can mask a malignant cell population if only a few atypical lymphoid cells are present. In addition, degenerative changes, lack of specimen cellularity, and prior steroid treatment may interfere with making the diagnosis.
7. A number of laboratory methods are used as ancillary techniques to confirm the diagnosis of vitreoretinal lymphoma. The choice of method varies with the type of specimen, the availability of the test in the laboratory, and the pathologist's experience with a specific test.
   - Immunophenotyping by using immunostains in the paraffin sections of cell block preparations has become the standard practice in cases of lymphoma. The advantage is the familiarity of this technique to most pathologists, the availability of the stains in most laboratories, and the evaluation of morphology in conjunction with the staining pattern.
   - Multicolor flow cytometry has a reported sensitivity of 82% and specificity of 100%, but again, it depends on the cellularity of provided specimen.[5]
   - Molecular studies have been used to identify clonal immunoglobulin gene rearrangements by polymerase chain reaction (PCR) analysis in specimens with low cellularity or with equivocal results in the immunostains.[6,7]
   - Some centers use interleukin level (IL) in aqueous humor and the vitreous as supportive evidence of the diagnosis of intraocular lymphoma. In fact, the sensitivity is high (80% to 90%) for IL-10 measurement and/or the ratio of IL10:IL6.[8-11]
   - As the majority of large, diffuse vitreoretinal B-cell lymphomas have shown Myd99-L2655P mutation, this PCR test has proven to be very useful as an ancillary diagnostic tool in scarcely cellular specimens.[12-14]
8. Good communication between the ophthalmologist and the laboratory / pathologist who will be handling these small specimens, prior to sending the material, is a key component in planning specimen processing and successfully obtaining a correct diagnosis.

## References


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4. Rothova A, Ooijman F, Kerkhoff F, et al. Uveitis masquerade syndromes. *Ophthalmology* 2001; 108:386-399.
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14. Raja H, Salomão DR, Viswanatha DS, Pulido JS. Prevalence of MYD88 L265P mutation in histologically proven, diffuse large B-cell vitreoretinal lymphoma. *Retina* 2016; 36(3):624-628.

# Update on Histopathologic Clinical Correlates in Retinoblastoma

***Patricia Chévez-Barrios MD***

Retinoblastoma is the most common primary malignant ocular tumor of childhood (and worldwide the most common primary malignant ocular tumor). It usually occurs in children under 4 years of age. Most tumors have a genetic variant in the Rb1 gene, which can be inherited. Cure rates in developed countries reach 95%-98% of cases. In continents such as Africa (death rate of 70%) or Asia (death rate of 42%) late diagnosis with advanced invasive extraocular tumors is associated with micrometastasis that results in the high mortality rate.

Correct assessment of features that may increase the possibilities of metastasis aids in the decision to implement adjuvant therapies. Thus, the pathologist must *handle the enucleated eye* to effectively evaluate choroidal invasion, optic nerve invasion, and extraocular invasion. Fresh tumor is required to evaluate genetic variants in Rb to select screening schedules for the patient and family members. The optic nerve margin is obtained before any opening or manipulation of the fresh eye to avoid contamination with fresh tumor. After obtaining tumor (by a scleral window or through needle aspiration) the eye is fixed for at least 48 hours and then cut to obtain a central pupil–optic nerve (PO) section (with intact optic nerve at the center of this segment) and the two calottes (caps of equatorial tissue). The calottes are then further sectioned anterior-posteriorly and submitted entirely for histologic examination. In 4 blocks the entire eye is submitted: (1) PO section, (2) one calotte in segments, (3) the other calotte in segments, and (4) cross-section of optic nerve margin. Histologic sections of the PO should include the center of the optic nerve (head, laminar, and postlaminar portions) with central vessels. Massive choroidal invasion is defined as 3 mm or more of tumor in the choroid.

Vitreous seeds are classified clinically to correlate with treatment schedules of intravitreous chemotherapy. Histopathologic findings correlate with clinical outcomes of tumor seeds after treatment (see Table 1).

The Children's Oncology Group (COG) prospective trial studied unilateral enucleated eyes with central pathology review and recommended treatment vs. observation based on high-risk histopathologic features (HRF: massive choroidal invasion ≥ 3 mm, postlaminar optic nerve invasion (PLONI), or concomitant choroidal and optic nerve invasion). The main finding was that massive posterior peripapillary choroidal invasion concomitant with retrolaminar invasion had the worst prognosis for recurrence in CNS and death of disease. All of these patients were treated adjuvantly but recurred in CNS. With this study and others we now know that patients with systemic metastasis in bone marrow or soft tissues can be cured and that most treatment failures are associated with CNS relapse. This relapse may be present after treatment for systemic metastasis or adjuvant treatment in HRFs. "Liquid biopsy" of blood, CSF, or aqueous humor is now possible and probably of prognostic value if there is a signature genetic / molecular marker that is associated with CNS recurrence.

The latest edition (8th) of the American Joint Commission on Cancer (*AJCC*) has grouped the HRFs in the categories of pT3a (> 3-mm choroid invasion), b (PLONI), c (inner scleral invasion), d (outer scleral / emissaries invasion), and pT4 (extraocular extension), and for the first time there is a stage group assigned accordingly to Rb patients. AJCC 8 has added for the first time for any cancer the "H = hereditary" category because it has prognostic significance for both the patient and the family.

**Table 1. Vitreous Seeds**

| Type | Histopathology | Clinical Classification and Outcomes After Treatment |
|---|---|---|
| Type 1<br>• Dust | • Scattered macrophages, necrotic cells, and rare viable single or small groups of tumor cells | • Dust-like opacities in vitreous sometimes over tumor<br>• Respond adequately to treatment |
| Type 2<br>• Sphere<br>• Solid translucent | • Spheres made of tumor cells with solid center composed by tumor cells. The periphery sheds tumor cells into the adjacent vitreous. | • Solid translucent spherical-shaped densities in the vitreous sometimes associated with dust<br>• Respond to treatment well |
| Type 2<br>• Sphere<br>• Central white / yellow | • Spheres made of tumor cells with center composed by necrotic cells. They may be associated with cloud-type seeds at periphery. | • Spherical-shaped densities with central white or yellow centers in the vitreous sometimes associated with dust<br>• Respond to treatment well |
| Type 3<br>• Cloud | • Vastly made of necrotic cells with peripheral partial rim of open spheres with central necrosis. Center also has macrophages and rare scattered single tumor cells. | • Large dense white or cream opacities with globular or sheet shape. Dust and spheres may be present at the edge.<br>• Do not respond well to treatment; require several injections |

**Table 2. AJCC 8th Ed., 2017: Pathological Stages (pTNMH)**

| When ***pT*** is … | & ***N*** is … | & ***M*** is … | & ***H*** is … | The Pathological ***Stage Group*** is … |
|---|---|---|---|---|
| pT1, pT2, pT3 | pN0 | cM0 | Any | I |
| pT4 | pN0 | cM0 | Any | II |
| Any | pN1 | cM0 | Any | III |
| Any | Any | cM1 or pM1 | Any | IV |

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# Clinical Pearls and Treatment of Vitreous Seeds

***Jasmine H Francis MD, Scott E Brodie MD, Y Pierre Gobin MD, and David H Abramson MD FACS***

I. Definition of Vitreous Seeds
II. Classification of Vitreous Seeds
  A. 3 classes of vitreous seeds
  B. Clinical characteristics of vitreous seeds
  C. Response to treatment of each seed class
III. Historical Treatment of Vitreous Seeds
  A. Efficacy of vitreous seed treatment with historical modalities
  B. Preclinical and early clinical literature on intravitreous chemotherapy
IV. Modern-day Treatment of Vitreous Seeds
  A. Procedure of intravitreous chemotherapy
  B. Efficacy of intravitreous chemotherapy
  C. Toxicity of intravitreous chemotherapy
  D. Safety of intravitreous chemotherapy
  E. Impact of Intravitreous Chemotherapy
    1. On primary treatment of vitreous seeds
    2. On recurrence of vitreous seeds
V. Special Considerations

# Sarcoidosis and the Eye: Clinical and Pathologic Diagnosis

*Narsing A Rao MD*

Sarcoidosis is a multisystem granulomatous inflammatory disorder of unknown etiology. It most commonly presents with bilateral hilar adenopathy and pulmonary, ocular, and skin changes.

It affects individuals of all racial and ethnic groups and all ages, peaking at 20 to 39 years.

In the United States, adjusted annual incidence among African Americans is 35.5 cases per 100,000; and among white Americans, 10.9 per 100,000.

Diagnosis of sarcoidosis is established with clinical features, radiologic changes, and supported by biopsy of selected sites:

1. Ophthalmic clinical features include ocular sicca, enlarged lacrimal glands, orbital mass, eyelid granuloma, conjunctival granuloma, granulomatous uveitis (anterior, intermediate, posterior, pan), choroidal or optic nerve granuloma, retinal vasculitis, and facial nerve palsy. Common ophthalmic clinical features are bilateral intraocular inflammation (86%); snowballs or string of pearls–like vitreous opacities (50%); mutton-fat keratic precipitates, iris nodules, or both (46%); and multiple chorioretinal peripheral lesions (45%).
2. Radiographic changes revealing bilateral hilar adenopathy
3. Pulmonary changes
4. Supported by biopsy of the involved organ that is easily accessible: conjunctiva, lacrimal gland, skin, peripheral lymph nodes, transbronchial biopsy by bronchoscopy (yield of 85% when multiple lung segments samples are examined). If the lung biopsy is negative, biopsy of intrathoracic lymph nodes provides diagnostic yield of 82%.
5. Biopsy revealing granulomatous inflammation, negative for microbes with acid-fast, stains for fungi, absence of foreign material. Although these histologic features support diagnosis of sarcoidosis, the histopathology is not diagnostic, requiring exclusion of various causes of granulomatous inflammation and negative culture for organisms.
6. Angiotensin-converting enzyme (ACE) levels are high in about 60% of patients, with positive and negative predictive values of 84% and 74%, respectively.

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# Mechanisms of Neural and Retinal Invasive Uveal Melanoma

***Hans E Grossniklaus MD***

I. Types of Neural Invasive Uveal Melanoma
   A. Retinoinvasive melanoma
   B. Optic nerve invasion of uveal melanoma
   C. Metastatic melanoma to the retina and vitreous

II. Retinoinvasive Melanoma
   A. 0.4% of melanoma eyes enucleated
   B. Site noncontiguous with uveal tumor
   C. Most commonly iris / ciliary body "ring" melanoma
   D. Presentation to enucleation averages 8 years
   E. Increased IOP, invasion of optic nerve, retrocorneal involvement

III. Optic Nerve Invasion of Uveal Melanoma
   A. 0.6%-6.9% of melanoma eyes enucleated
   B. Associated with poor prognosis
   C. Rarely extends to optic chiasm causing visual field defect
   D. Loss of light perception reported sign
   E. Transvitreal invasion
      1. Dispersion of melanoma cells into vitreous
      2. Extravasation of melanoma cells through adjacent retinal vessels into vitreous or migration of melanoma cells with vitreous hemorrhage
   F. Retinal invasion
      1. Neuroretinal tumor spread after Bruch membrane rupture
      2. Spreading of melanoma cells on retinal surface
   G. Peripapillary invasion
      1. Extension between end of Bruch membrane and border tissue
      2. Extension through border tissue
   H. Combined mechanism

IV. Metastatic Melanoma to Retina and Vitreous
   A. Approximately 17 patients in literature
   B. Vitreous may be only clinical site of metastasis.
   C. 1/3 bilateral
   D. Mean interval of cutaneous melanoma to metastasis: 4.1 years
   E. Cerebral metastasis in approximately 50% of patients
   F. Melanoma cells invade vitreous through retinal vessels.
   G. Melanoma cells may "co-opt" retinal vessels.
   H. May be becoming more common with checkpoint inhibitors

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# Conjunctival Melanosis: PAM vs. C-MIN

*Tatyana Milman MD*

The terminology used by ophthalmologists for melanocytic lesions evolved separately from classification of melanocytic proliferations at other anatomic locations. It was significantly influenced by the unique morbidity and management issues pertinent to this location and the reluctance of ophthalmologists to prescribe radical surgical therapy unless absolutely necessary.

The term "conjunctival melanosis" refers to the localized or diffuse pigmentation of the conjunctiva. Some forms of conjunctival pigmentation are secondary to the use of topical medications that deposit pigment in the conjunctiva, or in systemic conditions, such as Addison disease. Conjunctival pigmentation and intraepithelial melanocytic hyperplasia can also occur in response to local inflammation or nonmelanocytic conjunctival neoplasm. Collectively, all of these conditions are secondary, not primary, and they are known as "secondary acquired melanosis" in a clinical context. In addition, some patients who have a dark skin tone have bilateral conjunctival pigmentation that is typically more intense at the limbus, known as "complexion-related conjunctival pigmentation," also referred to as "racial melanosis" and "constitutional melanosis."

The term "primary acquired melanosis (PAM)" is applied by clinicians to cases that are not secondary to a known cause and arise de novo, usually in middle age or older, lightly complexioned individuals. These lesions tend to be unilateral or asymmetrical, flat, slowly growing areas of pigmentation with a predilection for the bulbar conjunctiva. What the ophthalmologist calls PAM may histopathologically range from intraepithelial melanin pigment deposit without melanocytic hyperplasia or atypia to atypical melanocytic proliferation (melanoma in situ) with a high risk of progression to invasive melanoma.

Various histological nomenclatures have been proposed to describe the pathology of lesions that ophthalmologists call PAM. These include PAM with and without atypia, low-risk and high-risk PAM, conjunctival intraepithelial melanocytic neoplasia (C-MIN) with and without atypia, and intraepithelial melanocytic proliferation (IMP) with and without atypia. These nomenclatures with their corresponding histopathology are summarized in Table 1.

All proposed classification schemes have strengths and weaknesses, which are summarized in Table 2.

These classification schemes will be integrated into the upcoming fourth edition of the *WHO Classification of Tumours of the Eye*.

**Table 1.**

| Histopathology | Differential Diagnosis and Terminology |
|---|---|
| Increased production of melanin by melanocytes that are normal in size, location, and number | Racial or complexion-associated melanosis<br>PAM without atypia<br>(Synonyms: primary conjunctival hypermelanosis, epithelial non-proliferative melanocytic pigmentation)<br>Ephelis (freckle) |
| Mild melanocytic hyperplasia (eg, idiopathic, ultraviolet-induced, post-inflammatory, unrelated tumor) and early melanocytic neoplasia with well-preserved and functioning basal dendritic melanocytes | PAM without atypia<br>(Synonyms: C-MIN without atypia, IMP without atypia) |
| Proliferations composed of cells with aberrant nuclear characteristics<br>Intraepithelial migration and nesting are common. | PAM with atypia<br>(Synonyms: C-MIN with atypia / melanoma in situ, IMP with atypia) |
| Cytologic features that are indeterminate or fall between categories<br>Microscopic interpretation is hampered by the small size of the specimen, poor sectioning, and staining, or crush artifact. | Intraepithelial melanocytic proliferation of indeterminate biological behavior |

**Table 2.**

| Nomenclature | Strength | Limitation |
|---|---|---|
| Primary acquired melanosis (PAM) | 1. Clinical-pathologic correlations with outcome data available<br>2. Easy to use | 1. Heterogeneity of lesions, particularly in no atypia to low/moderate atypia categories<br>2. Definitional overlap with conjunctival epithelial hypermelanosis and PAM without atypia<br>3. Potential for intra- and interobserver variability<br>4. Concept of melanoma in situ not well defined |
| Conjunctival melanocytic intraepithelial neoplasia (C-MIN) | 1. Attempts to minimize intra- and interobserver variability through systematic histopathologic classification approach<br>2. Distinguishes conjunctival epithelial hyperpigmentation from melanocytic proliferations<br>3. Defines the concept of melanoma in situ | 1. No clinical-pathologic correlations with outcome data available<br>2. Time consuming to use in clinical practice if rigorous scoring system is followed<br>3. Implies all melanocytic proliferations are neoplastic<br>4. Intra- and interobserver variability not assessed |
| Intraepithelial melanocytic proliferation (IMP) | 1. Conceptually similar to dermatopathology terminology<br>2. Distinguishes conjunctival epithelial hyperpigmentation from melanocytic proliferations<br>3. Adds immunohistochemical characterization to classification | 1. No clinical-pathologic correlations with outcome data available<br>2. Intra- and interobserver variability not assessed |

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# Treatment of Conjunctival Melanocytic Lesions

***Jacob J Pe'er MD***

Conjunctival pigmented lesions, all arising from conjunctival melanocytes, include nevi, primary acquired melanosis (PAM), and melanoma. The benign nevi and PAM without atypia can be treated by observation or surgical excision. PAM with atypia has been treated in recent years by topical chemotherapy. Conjunctival melanoma should always be treated by surgical excision and additional adjuvant treatment such as topical chemotherapy or brachytherapy. In recent years advances have been made in treating metastatic melanoma.

# DICER1 and Medulloepithelioma

***Maria Miguelina de la Garza MD, Austin Nakatsuka MD, Dan S Gombos MD, and Patricia Chévez-Barrios MD***

We present a case of an 8-year-old white male referred to the clinic for evaluation of right eye leukocoria and progressive right vision loss. His past medical history was relevant for pleuropulmonary blastoma of the right lung found in utero and diagnosed at 3 months of age after right middle lobectomy. The tumor was found to harbor *DICER1* mutation. On examination, visual acuity in the right eye was light perception. The right pupil was poorly reactive with corectopia. The right iris showed a posterior, hyperpigmented, and vascularized mass at 8 hours that extended anteriorly to the lens. MRI of the orbits with and without contrast showed a rim-enhancing lesion involving the right ciliary body. Based on the clinical presentation and the history of *DICER1* mutation, the patient had a right eye enucleation. On gross examination a mass was identified on the inferior temporal aspect of the ciliary body. The lens was cataractous and completely surrounded by membrane and tumor. The tumor had tan-white to yellow areas with prominent vasculature, some surrounded by black pigment.

On microscopic examination the ciliary body mass showed cords of primitive neuroepithelial cells that resembled embryonic retina, surrounded by a loose mesenchymal tissue rich in hyaluronic acid. The substance was better seen with the Alcian blue with and without hyaluronidase. These cords were lined externally by a thin basement membrane, while the inner aspect was lined by a series of terminal bars. The tumor extended to the iris through a cyclitic membrane. There were occasional mitoses in the neoplastic epithelium; however, no high-grade malignant or teratoid features were seen. The ciliary body mass was diagnosed as a benign nonteratoid medulloepithelioma, confined to the eye without extraocular extension.

The name "medulloepithelioma" derives from the histological resemblance of the tumor to the neuroepithelium of the embryonic neural tube and because of the histopathological resemblance to medulloepithelioma of the brain described by Bailey and Cushing. Intraocular medulloepitheliomas arise from the nonpigmented epithelium of the ciliary body and from the optic nerve, or retina. It is thought to derive from the embryonic medullary epithelium composing the inner layer of the anterior optic cup.

Ciliary body medulloepitheliomas (CBMEs) present during the first decade of life, with a mean of 5 years of age, in 75% to 90% of cases. The patients complain of poor vision or blindness (41%), pain (30%), leukocoria (18%), strabismus, or red painful eye. On examination the patients present with iris neovascularization and secondary glaucoma (44% to 60%), cataract (26%), retinal detachment, and a lightly pigmented or amelanotic cystic mass in the ciliary body (56%-61%). A retrolental neoplastic cyclitic membrane is also found in 50% of cases. The current treatment consists of enucleation or, in rare cases, iridocyclectomy. However, any form of local management of medulloepithelioma shows a high recurrence rate. On gross examination the tumors show a white-gray to yellow cut surface with intratumoral clear cysts located in the ciliary body and between the ciliary body and lens. A neoplastic cyclitic membrane usually covers the posterior surface of the lens, and remnants of the hyaloid artery can rarely be seen (23%).

Most ciliary medulloepitheliomas are sporadic; however, some patients may harbor DICER1 syndrome (5%). DICER1 is a ribonuclease required for the final production of microRNA (miRNA). These miRNAs then target messenger RNA (mRNA) expressed in embryologic and early developmental stages to regulate gene expression. Germline heterozygous mutations in the DICER1 gene (14q31) are seen in familial pleuropulmonary blastoma (PPB) syndrome. Patients with this syndrome can develop pleuropulmonary blastoma, cystic nephroma, rhabdomyosarcoma, thyroid cancer, stromal-cell ovarian tumors, and intraocular medulloepithelioma. Only 1% to 3% of PPB patients will manifest with CBME. In a recent study, 22% of DICER1 carriers harbored ocular abnormalities such as optic nerve abnormality, macular Drüsen, and retinal pigmentary abnormality, proving that DICER1 is needed for the normal development of the eye.

We present the above case to review CBMEs in the setting of DICER1 mutation. Our case presented with the classic clinical, radiological, and histological features of CBME. Early recognition of these features can avoid misdiagnosis and mistreatment of these tumors.

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# Update on Diagnosis and Treatment of Medulloepitheliomas

## Intraocular Medulloepithelioma

***Jonathan W Kim MD***

I. Introduction

A. Congenital, nonhereditary tumor of the nonpigmented ciliary epithelium, usually diagnosed in childhood

B. Second most common primary intraocular neoplasm during the first decade of life

C. Commonly used clinical name: diktyoma

II. Epidemiology

A. No reliable population-based information on incidence or prevalence

B. No sex or racial predilection

C. Median age of 2-5 years

1. 11 cases reported in persons older than 20 years

2. Oldest documented case is 79 years.

3. Most cases in adults are malignant.

III. Pathology

A. Classified into nonteratoid and teratoid medulloepitheliomas, benign or malignant

B. Most commonly, pseudostratified epithelium resembling medullary epithelium of the embryonic neural tube or developing neurosensory retina, surrounded by loose mesenchymal tissue rich in hyaluronic acid (eg, combination of primitive neuroepithelium and hypocellular stroma)

C. When the medullary epithelium folds so that the vitreous surface faces inward, it creates cysts rich in hyaluronic acid. Such proliferating cysts can be a part of the mass or detach from the main tumor and appear as free-floating cysts in the anterior or posterior segment of the eye.

D. Both Homer Wright and Flexner-Wintersteiner rosettes can be observed among undifferentiated neuroblasts. Calcification is uncommon.

E. The term "teratoid medulloepithelioma" applies when heteroplastic tissue is present. Mature hyaline cartilage is the most common heteroplastic element, but neuroglial tissue resembling disorganized brain and rhabdomyoblasts have also been described. More than a third of contain heteroplastic elements, usually hyaline cartilage, rhabdomyoblasts, or brainlike tissue. Those with heteroplastic tissue are designated teratoid medulloepitheliomas.

F. There is no universally agreed-upon histologic criteria for malignancy, but 2/3 of cases are thought to be malignant.

IV. Clinical Features

A. Irregularly shaped ciliary body and/or iris masses with smooth surfaces and gray to fleshy pink color. Intrinsic vessels are occasionally noted, visible on or close to the surface.

B. Approximately half of cases have cysts noted within the lesion or in the anterior chamber. Malignant retrolental membranes have also been described.

C. Frequent ocular associations of subluxation of the lens, cataract, or glaucoma

D. Typically, tumors are slow growing and not visible until they enlarge enough to protrude into the pupil, distort the iris, or invade the adjacent tissues.

E. Differential diagnosis includes acquired neoplasms of the nonpigmented or pigmented ciliary body epithelium, adenomatous hyperplasia, Fuchs adenoma and carcinoma, and metastatic tumors such as neuroblastoma.

F. 20% may show signs of persistent fetal vasculature.

G. Rare association with pleuro-pulmonary blastoma reported in 1 study

V. Management

A. Surgical enucleation has been the standard therapy for intraocular medulloepithelioma once the diagnosis has been established.

B. Globe-conserving therapies have been more commonly employed over the past 2 decades.

C. Surgical excision (iridocyclectomy) has been utilized with varying degrees of success, but because it has an unacceptably high recurrence rate overall it is generally not recommended.

D. Brachytherapy has been used successfully in recent series and is the most effective globe-sparing therapy. Fine needle aspiration biopsy (FNAB) may be performed prior to brachytherapy but is not considered to be necessary in all cases.

E. The polymorphic nature of medulloepithelioma means that sample variation can affect the accuracy of aspiration cytology. The risk of tumor seeding with FNAB is unknown, but risks are likely similar to those with retinoblastoma.

F. Treatment options include careful observation for documentation of growth, brachytherapy, or enucleation. FNAB can be used to confirm the diagnosis before brachytherapy or enucleation.

VI. Prognosis

A. Series by Broughton and Zimmerman showed extraocular extension in 20% and tumor-related death in 12%. All deaths were related to malignant tumors causing extraocular extension, orbital recurrence following enucleation followed by lymphatic or central nervous system spread.

B. If extraocular disease can be prevented, mortality is thought to be negligible. Extraocular extension can occur from aggressive tumor invasion or following surgical biopsy or excision.

# Intra-arterial Chemotherapy Does Not Increase the Risk of Secondary and Metastatic Disease

*David H Abramson MD FACS*

## Secondary Cancers

Intra-arterial chemotherapy does not increase the incidence of secondary cancers but is associated with a lower incidence of secondary cancers than in the past as a result of the elimination of external beam irradiation (which induces sarcomas) and systemic chemotherapy (secondary leukemias). Secondary cancers unrelated to treatment (but related to germline Rb1 defects) continue to develop in patients who are treated with intra-arterial chemotherapy.[1]

## Metastatic Deaths

Metastatic deaths from retinoblastoma are not increased (or even common) in patients treated with intra-arterial chemotherapy.[1]

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Abramson *et al. Int J Retin Vitr (2017) 3:40*
DOI 10.1186/s40942-017-0093-8

International Journal of Retina and Vitreous

COMMENTARY Open Access

Metastatic deaths in retinoblastoma patients treated with intraarterial chemotherapy (ophthalmic artery chemosurgery) worldwide

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**Abstract**

**Background:** Ophthalmic artery chemosurgery [OAC, intra-arterial chemotherapy (IAC)] was introduced in 2006 as treatment modality for intraocular retinoblastoma. The purpose of this commentary is to retrospectively review the incidence of metastatic deaths in retinoblastoma patients treated with OAC worldwide over a 10 year period. Retrospective data regarding metastatic deaths was collected from six international retinoblastoma centers (New York City USA, Philadelphia USA, Sao Paulo Brazil, Siena Italy, Lausanne Switzerland and Buenos Aires Argentina). All retinoblastoma patients from these centers (naive and recurrent, unilateral and bilateral) treated with OAC/IAC since 2006 have been included in this study. Data regarding number of patients, number of OAC/IAC infusions, number unilateral and bilateral, number treated for naive disease or salvage and number of metastatic deaths have been assessed. Over a 10-year period of time 1139 patients received OAC/IAC for 4396 infusions. At last follow-up there were only three metastatic deaths (all treated in Buenos Aires).

**Conclusion:** The current survey assessed the recorded risk of metastatic deaths in six retinoblastoma centers worldwide in children with retinoblastoma (unilateral or bilateral) treated with OAC/IAC as primary or secondary therapy. Overall, the observed risk for metastatic deaths from retinoblastoma was <1% in OAC/IAC treated children.

**Keywords:** Intra-arterial (intrarterial) chemotherapy (IAC), Metastatic death, Ophthalmic artery chemosurgery (OAC), Retinoblastoma (Rb), Melphalan

Figure 1.

# We Don't Know if Intra-arterial Chemotherapy Increases the Risk of Secondary and Metastatic Disease

*Anne Marie Leahey MD*

## We Don't Know the Rate of Secondary Cancers After Intra-arterial Chemotherapy

Recently Habib et al published a single-institution retrospective case series entitled "Second primary malignancies (SPM) in retinoblastoma (RB) patients treated with intra-arterial chemotherapy (IAC): the first 10 years." The authors report a Kaplan-Meier estimate of SPM development of 2.7% at 5 years in their cohort of 214 patients with heritable RB. They conclude that the rate of SPM development following IAC "is comparable" to previously published results of other treatment modalities.[1]

There are three things to consider. First, the median follow-up of the cohort is 2.5 years, and the 95% confidence interval surrounding the Kaplan-Meier estimate is 0% to 25%. Two years is simply too short an interval to study the rate of second cancers. Additionally, the authors do not have complete follow-up of their cohort, as evidenced by the published report of one of their patients who died of acute myeloid leukemia at another hospital following treatment of widely disseminated metastatic disease.[2] It should be noted that the agents and doses of chemotherapy needed to treat metastases are higher than those used to treat intraocular disease and are known to increase the risk of AML. The point is that the development of metastatic disease is to be avoided. A systematic reviewed of IAC published in 2016[3] estimated the risk of metastatic disease following IAC to be 2.1% to 4.8%. Metastatic disease to the central nervous system (Stage 4b) is usually fatal, and published results of stem cell transplantation for Stage 4a disease reveal a 5-year event-free survival rate of only 59%.[4]

Also of concern is that 4 patients in their series developed pineoblastoma. Three have died, and the fourth patient had only 1 month of follow-up at the time of publication. There is disagreement about why the observed rates of pineoblastoma fell in the 1990s with the advent of systemic chemotherapy. Some believed that the avoidance of external beam radiotherapy led to this important decline. However, does this explain that the tumors are not equally distributed randomly throughout the radiation field but rather to a distinct midline location which shares an embryologic origin with cells of the retina? Single-institution data have shown a statistically decreased rate of pineoblastoma following carboplatin, etoposide, and vincristine in patients with heritable RB compared to patients with heritable RB treated with surgery alone.[5] These data support the hypothesis that systemic chemotherapy may prevent pineoblastoma.

It will be important to gather more data on this important topic, and an international consortium called the IRiSC has begun work to gather data on a cohort of 10,000 patients from the Americas, Europe, and Asia to attempt to correlate second cancers with treatments received. A secondary aim is to attempt genotype–phenotype correlations of the RB1 germline mutations with subsequent second malignancies. The data available today are simply too limited to let us know with certainty what the rate of second cancers is after IAC.

## We Don't Know the Risk of Metastatic Disease Following Intra-arterial Chemotherapy

A recent publication entitled "Metastatic deaths in retinoblastoma patients treated with intra-arterial chemotherapy (ophthalmic artery chemosurgery) worldwide" reported that over a 10-year period the "observed risk" for metastatic deaths was less than 1%.[6] This sounds reassuring, but it is important to note that the results were obtained by a survey of 6 centers. Case series and poor quality cohort or case-control studies are considered by the Oxford Centre of Evidence-Based Medicine's level of evidence as low-level evidence.[7] A survey report falls below that level.

As pointed out by Soliman et al, the length of follow-up and completeness of follow-up are unknown.[8] While there are only 3 deaths reported there is no mention of the number of patients who developed metastatic disease overall. Furthermore, there is only 1 line of data in a single table. Additionally, this is a survey of 6 experienced centers and may not be generalizable to teams worldwide, especially those with lower patient volumes. It is possible that for teams with less experience and different populations the risk of metastasis could be higher.

While ocular salvage rates of 96% at 1 year following IAC are exciting,[9] it has been stressed by others that "eye salvage is only valuable when achieved without risk to life."[3] Metastatic RB is unquestionably a risk to life, and we need rigorous prospective studies with adequate follow-up to assess the risk of this critical endpoint.

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# There Is Consensus on the Use of Intra-arterial Chemotherapy for Unilateral Retinoblastoma

***Dan S Gombos MD***

I. Treatment Options for Unilateral Retinoblastoma
   A. Enucleation
   B. Intravenous chemotherapy
   C. Intra-arterial chemotherapy (IAC)
   D. Intravitreal chemotherapy
   E. Periocular chemotherapy
   F. Radiation therapy
   G. Laser therapy
   H. Cryotherapy
II. Historic Approaches Prior to IAC
III. Outcomes With Intravenous Chemotherapy
   A. Group B C D
   B. Adjuvant therapy with radiation and/or periocular chemotherapy
IV. Increased Facility and Use of IAC
   A. Decade of experience
   B. Worldwide access
V. Salvage Rates for Groups A B C D E
VI. Greater Understanding of Risks and Complications
VII. Improved Outcomes With Increased Use
VIII. Consensus on IAC Contraindications
   A. Extraocular disease
   B. Neovascular glaucoma
IX. Use as Primary vs. Salvage Therapy
X. Common Treatment Regimens
   A. Melphalan / carboplatin / topotecan
   B. Doses and cycles

## Selected Readings

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# There Is No Consensus on the Role of Intra-arterial Chemotherapy for Unilateral Retinoblastoma

***Mandeep S Sagoo MBBChir PhD***

The management of a rare cancer such as retinoblastoma is dependent on many factors. Unilateral retinoblastoma can be managed with a range of treatments, such as laser, cryotherapy, brachytherapy, chemotherapy, or even enucleation. Chemotherapy may take the form of systemic, intra-arterial, or intravitreal chemotherapy. While there are areas of agreement in the use of intra-arterial chemotherapy, there still exist practice differences as to the indications for its use. Use of intra-arterial chemotherapy is dependent on the following:

- International Classification of Retinoblastoma (ICRB) or TNMH group
- Laterality
- Age of patient
- Experience and availability of different treatment modalities
- Complication profile
- Parental wishes

Various scenarios require the optimal treatment modality, and hence consensus does not yet exist on the role of intra-arterial chemotherapy.

# 2018 Advocating for the Profession and Patients

## Ocular Oncology and Pathology Subspecialty Day

***Gareth M Lema MD PhD***

Ophthalmology's goal to protect sight and empower lives requires active participation and commitment to advocacy from every ophthalmologist. Contributions to the following three critical funds are a part of that commitment:

- OPHTHPAC® Fund
- Surgical Scope Fund (SSF)
- State Eye PAC

Please join the dedicated community of ophthalmologists who are contributing to protect quality patient eye care for everyone. The OPHTHPAC Committee is identifying Congressional Advocates in each state to maintain close relationships with federal legislators in order to advance ophthalmology and patient causes. At Mid-Year Forum 2018, we honored nine of those legislators with the Academy's Visionary Award. This served to recognize them for addressing issues important to us and to our patients. The Academy's Secretariat for State Affairs is collaborating closely with state ophthalmology society leaders to protect Surgery by Surgeons at the state level.

Our mission of "protecting sight and empowering lives" requires robust funding of both the Surgical Scope Fund and the OPHTHPAC Fund. Each of us has a responsibility to ensure that these funds are strong.

### OPHTHPAC® Fund

OPHTHPAC is a crucial part of the Academy's strategy to protect and advance ophthalmology's interests in key areas, including physician payments from Medicare and protecting ophthalmology from federal scope-of-practice threats. Established in 1985, OPHTHPAC is one of the oldest, largest, and most successful political action committees in the physician community. We are very successful in representing your profession to the U.S. Congress.

Advocating for our issues in Congress is a continuous battle, and OPHTHPAC is always under financial pressure to support our incumbent friends as well as to make new friends among candidates. These relationships allow us to have a seat at the table with legislators who are willing to work on issues important to us and our patients.

The relationships OPHTHPAC builds with members of Congress is contingent on the financial support we receive from Academy members. Academy member support of OPHTHPAC allows us to advance ophthalmology's federal issues. We need to increase the number of our colleagues who contribute to OPHTHPAC and to the other funds. Right now, major transformations are taking place in health care. To ensure that our federal fight and our PAC remain strong, we need the support of every ophthalmologist to better our profession and ensure quality eye care for our patients.

Among the significant impacts made by OPHTHPAC are the following:

- Secured relief from the burdens and penalties associated with the existing Medicare quality improvement programs for 2018
- Halted applications of MIPS penalties to Part B drug payments to physicians
- Convinced CMS to revisit drastic cuts to retina and glaucoma surgical codes
- Halted the flawed Part B Drug Demonstration
- Derailed an onerous global surgery payment data collection plan
- Continued efforts in collaboration with subspecialty societies to preserve access to compounded and repackaged drugs such as Avastin

Contributions to OPHTHPAC can be made here at AAO 2018, or online at www.aao.org/ophthpac by clicking "Join." You can also learn more by texting "OPHTH" to 51555.

Leaders of the American Association of Ophthalmic Oncologists and Pathologists (AAOOP) are part of the American Academy of Ophthalmology's Ophthalmic Advocacy Leadership Group (OALG), which meets annually in January in Washington, D.C., to provide critical input and to discuss and collaborate on the Academy's advocacy agenda. At the January 2018 OALG meeting, panel discussions took place on the outlook for Medicare reimbursement and implementation of the Merit-based Incentive Payment System (MIPS), as well as specialty research related to the IRIS™ Registry. In addition, meeting participants discussed the changing paradigm for optometric scope battles, held a roundtable to discuss challenges for surgical subspecialties, and considered how telemedicine could impact ophthalmology.

At Mid-Year Forum 2018, the Academy and AAOOP ensured a strong presence of ocular oncologists and pathologists to support ophthalmology's priorities. Ophthalmologists visited members of Congress and their key health staff to discuss ophthalmology priorities as part of Congressional Advocacy Day. The AAOOP remains a crucial partner with the Academy in its ongoing federal and state advocacy initiatives.

### Surgical Scope Fund

Thanks to contributions to the 2018 Surgical Scope Fund (SSF) from ophthalmologists across the country, the Academy's Surgery by Surgeons initiative has had a successful year preserving patient surgical safety and surgical standards in state legislatures across the country. The SSF is key to the Academy's Surgery by Surgeons campaign. If you have not yet made a 2018 SSF contribution, visit our contribution booth at AAO 2018 or contribute online at www.aao.org/ssf. If you already have made that 2018 contribution, please consider making a crucially needed supplemental contribution.

The SSF provides grants to state ophthalmology societies in support of their efforts to derail optometric surgery proposals that pose a threat to patient safety. Since its inception, the

Surgery by Surgeons campaign and the SSF, in partnership with state ophthalmology societies, has helped 34 state/territorial ophthalmology societies reject optometric scope-of-practice expansion into surgery.

To date in 2018, thanks to financial resources from the SSF, the Surgery by Surgeons campaign has netted patient safety and surgery standard preservation victories in the following battleground states:

- Florida
- Iowa
- Maryland
- Mississippi
- Nebraska
- North Carolina
- South Carolina
- Vermont
- Virginia

The 2018 battle is far from over, though. For example, California, Illinois, Massachusetts, and Pennsylvania are currently under assault. Furthermore, as of submission of this update in June 2018, the optometric surgery push had sprouted in six additional states.

Dollars from the SSF are critical in the state surgery campaigns. In each of these legislative battles, the benefits from SSF distributions are abundantly clear. The best lobbyists and public relations consultants are contracted as necessary. Additionally, media campaigns (including TV, radio, and social media) are launched to educate the voting public when needed. This helps to secure success in protecting patient safety by thwarting optometry's attempts at expanding its scope of practice to include surgery privileges.

Each of these endeavors is very expensive, and no one state has the resources to wage one of these battles on its own. Ophthalmologists must join together and donate to the SSF to fight for patient safety when a state faces a scope battle over optometric surgery.

The Secretariat for State Affairs thanks subspecialty societies who joined state ophthalmology societies in contributing to the SSF in 2017. These ophthalmic organizations complete the necessary SSF support structure for the creation and implementation of successful Surgery by Surgeons campaigns.

## State Eye PAC

It is increasingly important for all ophthalmologists to support their respective State Eye PACs because campaign contributions to legislators at the state level must come from individual ophthalmologists and cannot come from the Academy, OPHTHPAC, or the SSF. The presence of a strong State Eye PAC providing financial support for campaign contributions and legislative education to elect ophthalmology-friendly candidates to the state legislature is critical, as scope-of-practice battles and many regulatory issues are all fought on the state level.

## ACTION REQUESTED: *Advocate for Your Profession & Your Patients*

Academy SSF contributions are used to support the infrastructure necessary in state legislative / regulatory battles and for public education. State PAC and OPHTHPAC contributions are necessary at the state and federal level, respectively, to help elect officials who will support the interests of our patients. Contributions to *each* of these three funds are necessary and help us protect sight and empower lives. SSF contributions are completely confidential and may be made with corporate checks or credit cards, unlike PAC contributions, which must be made by individuals and are subject to reporting requirements.

Please respond to your Academy colleagues and be part of the community that contributes to OPHTHPAC, the Surgical Scope Fund, and your State Eye PAC. Please be part of the community advocating for your patients now.

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| Political grassroots activities, lobbyists, PR and media campaigns<br>No funds may be used for campaign contributions or PACs. | Campaign contributions, legislative education | Campaign contributions, legislative education |
| Contributions: Unlimited<br>Individual, practice, and organization | Contributions: Limited to $5,000 | Contribution limits vary based on state regulations. |
| Contributions are 100% confidential. | Contributions above $200 are on the public record. | Contributions are on the public record depending upon state statutes. |

# Aqueous Humor as a Surrogate Tumor Biopsy for Retinoblastoma

***Jesse L Berry MD, Liya Xu PhD, Irsan Kooi PhD, A Linn Murphree MD, Rishvanth Prabakar PhD, Mark Reid PhD, Kevin Stachelek BS, Bao Han A Le, Rima Jubran MD, Lisa Welter, Bibian Jin Reiser MD, Patricia Chevez-Barrios MD, Thomas C Lee MD, Peter Kuhn PhD, Jonathan W Kim MD, David Cobrinik MD PhD, and James Hicks PhD***

**No FDA-approved indications will be discussed.**

I. Why Do We Want a Biopsy in Retinoblastoma (RB)?

II. Why Is the Aqueous a Safe Option?

III. What Do We Know About the DNA in the Aqueous?

IV. What Is Known About RB-related Somatic Copy Number Alterations (RB SCNAs) in Tumors?

V. Can We Find RB SCNAs in the Small Amount of DNA in the Aqueous Humor?

VI. Can SCNAs Provide Additional Objective Information That Improves Upon Our Clinical Models of Prognostication for Globe Salvage in RB?

VII. Are There Other Aqueous Humor Biomarkers Such as *RB1*, *MYCN*, and miRNA That May Be Useful in the Future?

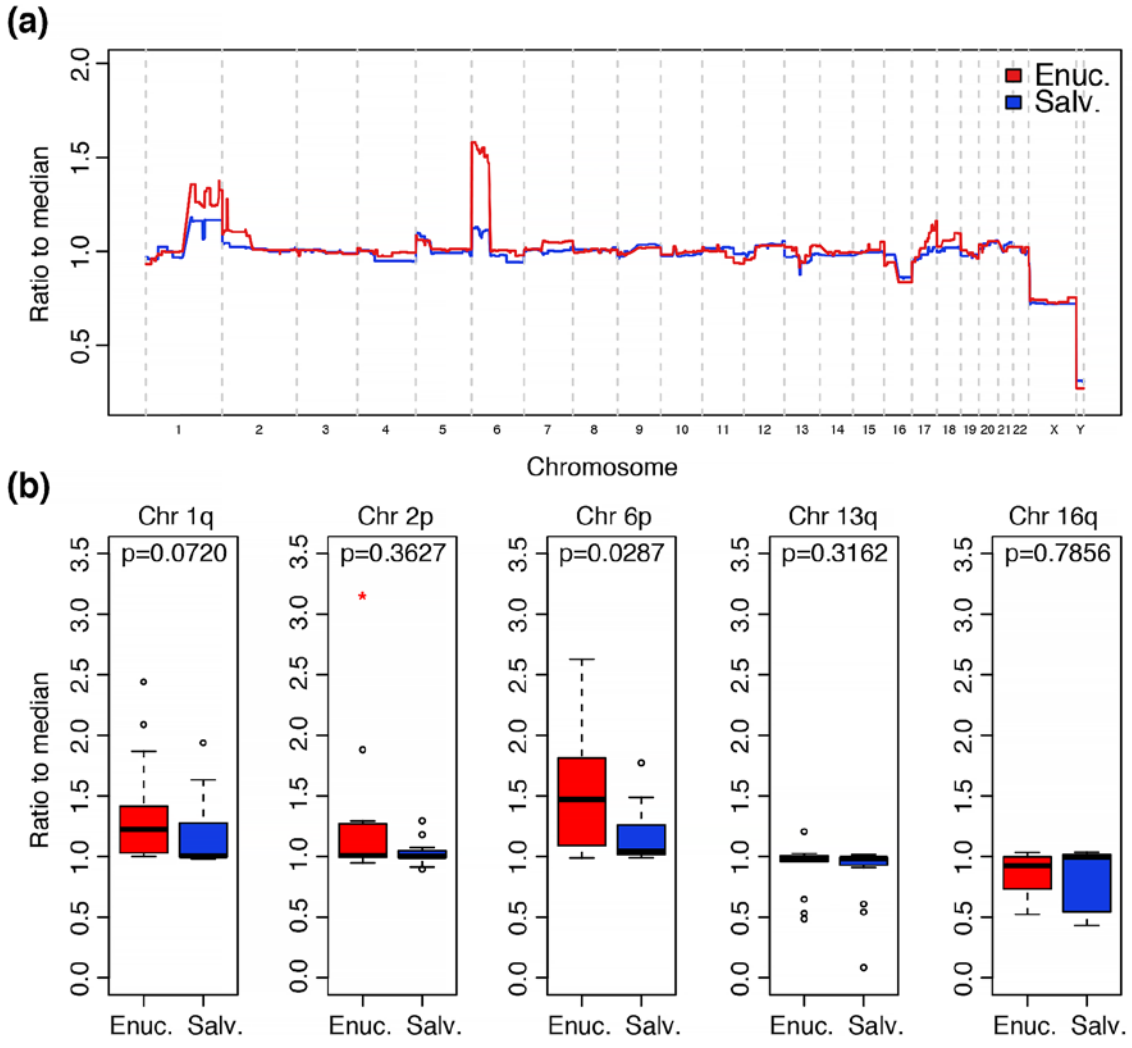


Figure 1. (a) Composite somatic copy number alteration (CNA) profile from cell-free DNA in the aqueous humor (AH) samples from enucleated eyes (Enuc, red) and salvaged eyes (Salv, blue). (b). Box plot demonstrating the range of amplitude changes for the enucleated (Enuc) vs. salvaged (Salv) eyes; the black bar represents the median while the green bar represents the mean (of the ratio to median). The sample with focal *MYCN* gain is shown as a red asterisk in the Chr 2p plot. The mean of the ratio to median amplitude of Chr 6p gain is significantly greater in enucleated eyes ($P$ = .001), which may be both from the increased copy number of the amplified region and an increase in the total fraction of tumor-derived DNA in the AH of enucleated eyes.

# Approach to Group E Eyes

***Luiz Fernando Teixeira MD***

I. Introduction

A. International Classification of Retinoblastoma (ICRB)

The International Classification of Retinoblastoma (ICRB) is a grouping system based on the natural history of the intraocular disease; it predicts the probability of salvage for eyes during the systemic chemotherapy era. Recent publications showed the same predictive results for intra-arterial chemotherapy. The eyes are classified by extension and dissemination of intraocular tumor (groups A–E).

B. Definition of Group E in most publications: Very High Risk Eyes (Consensus)

1. CHLA version

Unsalvageable eyes (destroyed anatomically and/or functionally) with one or more of the following:

a. Neovascular glaucoma

b. Massive intraocular hemorrhage

c. Massive tumor necrosis associated with aseptic orbital cellulitis

d. Tumor anterior to anterior vitreous face

e. Tumor touching the lens

f. Anterior segment tumor

g. Diffuse infiltrating retinoblastoma

h. Phthisis or pre-phthisis

2. Philadelphia version

Extensive retinoblastoma occupying > 50% of the globe with or without the following:

a. Neovascular glaucoma

b. Opaque media from hemorrhage in anterior chamber, vitreous, or subretinal space

c. Invasion of postlaminar optic nerve, choroid, sclera, orbit, anterior chamber

3. Some publications use a combination of the two versions, and some papers don't include a definition of Group E eyes.

4. Differences in the definition of Group E eyes make it difficult to compare the results of published studies.

II. Important Aspects of Group E Eyes

A. High-risk histopathology features (HRHFs) in primary enucleated Group E eyes

1. Clinical findings related to Group E eyes that predict HRHFs include glaucoma and/or buphthalmia, iris neovascularization, hyphema, pseudohypopyon, and aseptic orbital cellulitis.

2. 24%-61% of Group E eyes present with HRHFs.

a. Invasion of the post-laminar optic nerve

b. Massive (> 3 mm) choroidal invasion

c. Scleral invasion / extraocular invasion

d. Combination of focal posterior uveal invasion (< 3 mm in diameter) with any degree of nonretrolaminar optic nerve invasion

e. Anterior chamber invasion (iris infiltration and ciliary body infiltration)

3. Studies

a. Kaliki et al.

i. Philadelphia, USA

ii. 432 Group E eyes

iii. 24% (102/432 eyes) with HRHFs (1,2,4 e 5)

b. Berry et al.

i. Los Angeles, USA

ii. 143 Group E eyes

iii. 35.7% (51/143) with HRHFs (1,2,3 e 5)

c. Kaliki et al.

i. Hyderabad, India

ii. 353 Group E eyes

iii. 39% (137/353 eyes) with HRHFs (1,2,3,4 e 5)

d. Brennan et al.

i. Memphis, USA

ii. 86 Group E eyes

iii. 43% (37/86 eyes) with HRHFs (1,2,3 e 5)

e. Youssef et al.

i. Amman, Jordan

ii. 18 Group E eyes

iii. 61% (11/18 eyes) with HRFHs (1,2,3 e 5)

B. Orbital recurrence after primary enucleation for group E eyes
   1. Berry et al.
      a. Los Angeles, USA
      b. 143 Group E eyes
      c. Orbital recurrence: 0.7% (1/143)

C. Metastatic disease after primary enucleation for group E eyes:
   1. Kaliki et al.
      a. Philadelphia, USA
      b. 432 Group E eyes
      c. Metastatic disease in 10% of the Group E eyes with HRHFs (10/102 eyes) or 2% of total Group E eyes in the study
   2. Berry et al.
      a. Los Angeles, USA
      b. 143 Group E eyes
      c. Metastatic disease: 0.7% (1/143), no deaths
   3. Zhao et al.
      a. Beijing, China
      b. 37 Group E eyes
      c. No cases (0%) of metastatic disease

III. Management of Patients With Group E Eyes

A. Staging the patient
   1. MRI brain and orbits: 1.5 T / 3.0 T
      a. Sensitive and accurate for extraocular tumor extent and extensive optic nerve invasion
      b. Limited diagnostic accuracy in detecting microscopic invasion of optic nerve and choroid
   2. Diagnostic lumbar puncture and bone marrow aspiration
      a. Most Group E eyes present negative results for lumbar puncture and bone marrow tap at diagnostic.
      b. There is no specific guideline in the literature for Group E eyes.

B. Eye treatment
   1. Primary enucleation
      a. Indications
         i. Any Group E eye with phthisis, buphthalmos, advanced neovascular glaucoma or anterior segment involvement (consensus)
         ii. All unilateral Group E eyes (not a consensus)
         iii. Most Group E eyes in bilateral cases: Group A/E, B/E eyes (not a consensus)
      b. Important considerations
         i. Long optic nerve stump is extremely important.
         ii. Harvest of fresh tumor for RB1 testing or other research uses
         iii. Proper pathology examination of enucleated eye
         iv. Eyes with HRHFs need adjuvant systemic chemotherapy to decrease the risk of metastatic disease.
      c. Special conditions

         For eyes with buphthalmia and glaucoma or massive necrosis with aseptic cellulitis, consider neoadjuvant chemotherapy followed by secondary enucleation. Also: Complete systemic chemotherapy treatment after the eye removal regardless of the presence or absence of HRHFs in the pathology exam.
   2. Conservative treatment
      a. Indications
         i. Advanced bilateral retinoblastoma groups: C/E, D/E, E/E eyes or EO/Group E except Group E eyes with phthisis, buphthalmos, advanced neovascular glaucoma, or anterior segment involvement
         ii. Specific unilateral cases (not a consensus)
         iii. Cultural / familial reasons
      b. Important considerations
         i. Discussion with the family about risks and benefits of treatment
         ii. Close follow-up of the patient
         iii. Prompt secondary enucleation if necessary and proper pathology examination of enucleated eye
         iv. Eyes with HRHFs need adjuvant systemic chemotherapy to decrease the risk of metastatic disease.
   3. Systemic chemotherapy
      a. Systemic chemotherapy alone has a high incidence of intraocular recurrence and a high enucleation rate in Group E eyes. The use of adjuvant external beam radiotherapy (EBRT) and periocular chemotherapy increases the rate of saved eyes.
      b. Studies
         i. Berry et al.
            (a) Los Angeles, USA
            (b) Systemic chemotherapy (CEV, 6 cycles high carbo dose + local treatment + EBRT 36 Gy for persistent tumor or recurrence)

(c) 37 Group E eyes

(d) No orbital recurrence

(e) 1 case of metastatic disease with death (2.7%); 10 saved eyes (25.6%)

ii. Shields et al.

(a) Philadelphia, USA

(b) Systemic chemotherapy (CEV, 6 cycles + local treatment)

(c) 64 Group E eyes

(d) 16 saved eyes (25%)

(e) With EBRT, improved the number of salvaged eyes (50%-83%)

iii. Manjandavida et al.

(a) India

(b) Systemic chemotherapy (high-dose CEV, 6-12 cycles + periocular carboplatin as needed + EBRT as needed)

(c) 40 Group E eyes

(d) 23 saved eyes (57.5%)

c. Metastatic disease after systemic treatment for Group E eyes

i. Berry et al.

(a) Los Angeles, USA

(b) Systemic chemotherapy (CEV, 6 cycles high carbo dose + local treatment + EBRT 36 Gy for persistent tumor or recurrence)

(c) 37 Group E eyes

(d) No orbital recurrence

(e) 1 case of metastatic disease with death (2.7%)

ii. Zhao et al.

(a) Beijing, China

(b) Systemic chemotherapy

(c) 45 Group E eyes

(d) 4 cases of metastatic disease with death (8.9%)

4. Intra-arterial chemotherapy

a. Intra-arterial chemotherapy has improved the treatment of advanced Group E eyes, naïve or not, and decreased the use of EBRT. The use of multiagent chemotherapy for intra-arterial chemotherapy and the use of adjuvant intravitreal chemotherapy improved the rate of eye salvage.

b. Studies

i. Suzuki et al.

(a) Tokyo, Japan

(b) Intra-arterial chemotherapy (balloon; melphalan), other treatments were used (EBRT, systemic chemotherapy, local).

(c) 18 Group E eyes

(d) Saved eyes: 30%

ii. Abramson et al.

(a) New York, USA

(b) Intra-arterial chemotherapy (catheter or balloon as needed; melphalan / topotecan / carboplatin)

(c) 63 Group E naïve and rescue eyes

(d) Saved eyes: 70.1%

iii. Shields et al.

(a) Philadelphia, USA

(b) Intra-arterial chemotherapy (catheter or balloon as needed; melphalan / topotecan / carboplatin)

(c) 14 Group E eyes

(d) Saved eyes: 36%

iv. Chen et al.

(a) Guangzhou, China

(b) Intra-arterial chemotherapy (catheter; melphalan / topotecan)

(c) 29 Group E naïve and rescue eyes

(d) Saved eyes: 62%

c. Metastatic disease after intra-arterial chemotherapy treatment for Group E eyes

i. Abramson et al.

(a) New York, USA

(b) Intra-arterial chemotherapy

(c) 63 Group E naïve and rescue eyes

(d) Metastatic disease: 15%

ii. Shields et al.

(a) Philadelphia, USA

(b) Intra-arterial chemotherapy

(c) 14 Group E eyes

(d) Metastatic disease: 0%

5. Combined systemic and intra-arterial chemotherapies:
    a. Combined systemic and intra-arterial chemotherapy can be used for advanced intraocular retinoblastoma. This combination can decrease the possibility of metastatic disease in eyes with possible HRHFs.
    b. Shields
        i. Philadelphia, USA
        ii. 8 Group E eyes
        iii. Systemic chemotherapy + intra-arterial chemotherapy
        iv. Saved eyes: 50%
        v. No metastatic disease

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# Vitrectomy and Endoresection of Refractory Intraocular Retinoblastoma

***Brenda L Gallie MD, Junyang Zhao MD, Qiyan Li MD, and Kahaki Kimani MD***

We reported that surgical removal of retinoblastoma that had failed all other conventional therapies to control intraocular tumor achieved tumor control and useful vision for selected eyes with refractory retinoblastoma, without extraocular spread.[1] In the first 6 months of 2013, the only remaining eyes of 21 children were treated by pars plana vitrectomy (PPV) to remove active vitreous seeds and resect the tumor source of the seeds. All children had received systemic chemotherapy; melphalan was used in the surgical irrigation and subconjunctival post operatively. Results are summarized in Figure 1.

With minimal subsequent treatments, 18 only eyes of 21 children whose retinoblastoma was not controlled with systemic, intra-arterial, or intravitreal chemotherapy and focal therapy were saved, with vision better than legal blindness in 14 eyes. Recurrence of tumor in 2 eyes was treated by enucleation with no high-risk pathological features. One child was lost to follow-up after enucleation of the last eye was refused following failure of repeat PPV for recurrent tumor; after publication we learned that this child died of metastatic disease.[2] This child did not die of complications of PPV; when last seen the tumor was clearly intraocular with 20/100 vision, and timely enucleation would have saved the child's life. Instead, the long and costly investment by child and family to saving an eye and vision led the parents to value that dangerous eye more than the life of the child. A prime area to study is how parents make choices for their child. We propose that high-quality evidence at first diagnosis may help parents to prioritize life in their treatment choices.

For the many children in China with recurrent disease after all standard therapies, a direct and definitive therapy to save remaining eyes was needed. Based on these first 21 children, in 2013, 159 children (174 eyes) were treated with PPV and retinoblastoma resection, with 4.2 years follow-up following PPV (manuscript in preparation). Ten children (8%) died and 6 (4%) were lost-to-follow-up, presumed dead (not different from national rates). Of evaluable eyes, 81% that otherwise would have been lost have been salvaged. Through this study, criteria for PPV and retinoblastoma resection have been refined. Many children have been treated with careful, timely PPV who have shorter follow-up.

This unconventional approach to retinoblastoma grew from the necessity to treat many patients efficiently, without expensive long, drawn-out efforts with many different approaches.

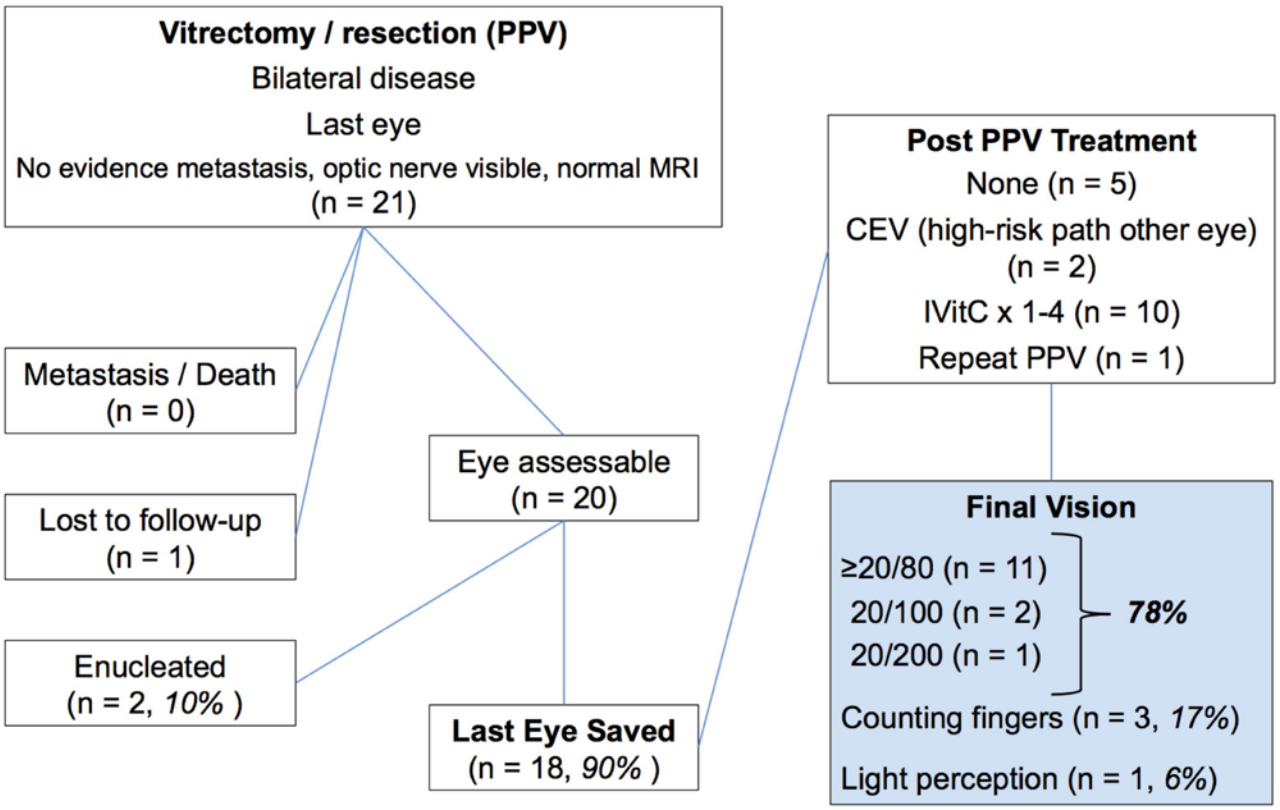


Figure 1. Flow diagram of outcomes of PPV and resection for 21 children with refractory intraocular retinoblastoma (from reference 1).

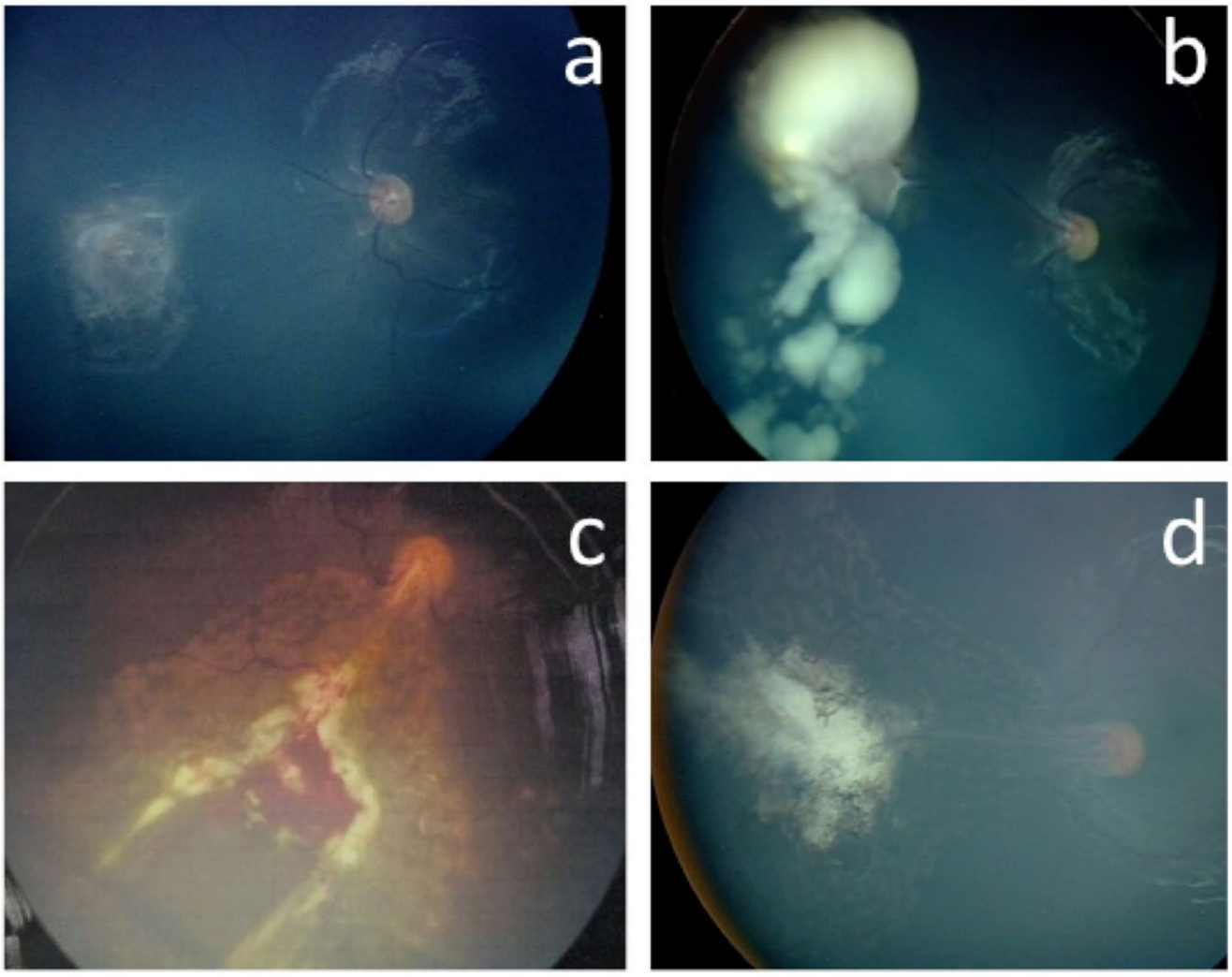


Figure 2.

The median time from initial diagnosis to PPV is 0.6 years while many therapies were used and failed, while after PPV few subsequent interventions were required over a median 4.2 years follow-up. For good reasons, surgical resection of retinoblastoma has been taboo, considering the risks to disseminate tumor and lead to death. The success of the Chinese program depends on multidisciplinary teamwork and careful technique to select eligible eyes and avoid tumor dissemination.

We present 1 case showing the value of PPV and tumor resection with global collaboration. The right eye of a child in Nairobi, Kenya, was enucleated at diagnosis with massive choroidal invasion and optic nerve involvement past the lamina cribosa but not to the cut end. The child received 6 cycles of vincristine, etopside, carboplatin (VEC) systemic chemotherapy. The left eye (Figure 2a) was concurrently treated with laser for a nasal tumor.

One year later recurrence was treated with 4 cycles of VEC, with poor response (Figure 2b); enucleation of last eye was considered. With global collaboration and support, the child traveled to China for PPV and endoresection (Figure 2c); 3 months later she returned to China for silicone oil removal. At recent 2.5-year follow-up, the child remains well with 6/6 vision in her remaining eye (Figure 2d).

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# IAC 1. Correlation of Ocular Vasculature and Treatment Outcomes

***Stephen R Chen MD***

I. Overview of Ocular Vasculature
   A. Embryologic vascular development[1,2]
   B. Normal variants in vascular anatomy

II. Anatomic Considerations for Intra-arterial Chemotherapy (IAC)
   A. Anatomic variation of the carotid siphon[3]
   B. Approach to normal variants[4-6]
   C. Effects of blood flow pattern

III. Reported and Observed Variation Outcomes[7]
   A. Vessels visualized
   B. Location infused

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# IAC 2. Angiographic Findings Pre and Post Therapy

## Ocular/Orbital Vascular Alterations and Their Impact on Intra-Arterial Chemotherapy for Retinoblastoma

***Timothy G Murray MD MBA***

I. Intra-arterial chemotherapy (IAC) has revolutionized the ocular oncologist's approach to advanced intraocular retinoblastoma. Intra-arterial chemotherapy has greatly reduced the enucleation rate while maintaining improved ocular function. Significantly, the systemic complications of therapy are decreased. During the 3-decade evolution from enucleation to external beam radiotherapy to systemic chemotherapy, we saw shifting treatment morbidities. As expected, the delivery of IAC does impact orbital and ocular structures.

A. Orbital vasculature

Prior to the advent of IAC our understanding of orbital vascular variations remained limited. The use of angiography preceding IAC has enabled an enhanced understanding of orbital vasculature and both its normal variants and pathologic responses.

B. Ophthalmic vasculature

Ophthalmic vasculature has been extensively evaluated in the adult population with the use of both intravenous fluorescein angiography (IVFA) and indocyanine angiography. With the advent of wide-field fluorescein angiography, particularly with intraoperative assessment, the pediatric retina has been imaged with a recent focus on both normal eyes and pathologic eyes. Retinoblastoma was one of the earliest diseases evaluated with IVFA imaging.

II. IAC delivery hinges on vascular access to the involved globe. Typically access is obtained through the ophthalmic artery, but normal and pathologic variants may limit access to this primary approach. Pretreatment angiography is critical to determining vascular access, vascular caliber, and flow. Additionally, anomalies of the vasculature may require re-assessment of treatment approach, or even preclude the ability to treat.

A. Orbital vascular alterations: primary IAC

Orbital vascular alterations are seen in roughly 9% of untreated eyes. These preclude treatment in less than 1% of cases. Vascular alterations may increase related to the number of intra-arterial treatment courses and may be as high as 24% after 6 IAC treatment cycles. These alterations may require alternative vascular access in as many as 1 in 5 treatments.

B. Orbital vascular alterations: secondary IAC

Prior treatments have shown significant impact on orbital vasculature. Interestingly, vascular effects are differentiated by the type and extent of prior treatment. Of note, systemic chemotherapy combined with transpupillary laser tumor ablation does not appear to impact orbital vasculature. External beam radiotherapy is noted to reduce both vascular caliber and flow in approximately 25%. Vascular access did not appear compromised in any of these eyes, and all eyes *did* respond to IAC with tumor response. Focal therapies, including cryoablation and periocular chemotherapy, showed vascular alterations in over 60% of eyes undergoing secondary IAC.

III. Ophthalmic vascular alterations are known to be associated with retinoblastoma tumor extent, location, inflammatory alterations, and associated retinal detachment. In these advanced eyes, retinal vascular alterations are typically present in virtually 100% of eyes. Typically, these vascular alterations have not precluded treatment. Tumor vascular alterations are ubiquitous, while secondary vascular alterations—including vascular occlusion (both venous and arterial), anomalous vasculature, and ischemia—are more variable.

A. Ophthalmic vascular alterations in the tumor bed include intrinsic tumor vessels, secondary retinal vascular involvement, hemorrhage, and inflammatory necrosis. Typically, these changes will evolve during IAC, particularly when coupled with direct transpupillary tumor ablation.

B. Ophthalmic vascular alterations associated with IAC treatment include the entire perfusion tree of the ophthalmic artery. Vascular alterations seem more profound in the choroidal perfusion than in the retinal vasculature, but these findings do appear to be independent. Choroidal vascular alterations may approach 50% of treated eyes and again appear to exhibit a treatment burden effect. Retinal vascular alterations are more variable but include arterial and venous occlusion, induced hemorrhage, and ischemic vasculopathy that is seen in approximately 15% of treated eyes.

IV. Advances in treatment approach have decreased IAC treatment-associated vascular complications for both choroidal and retinal vascular compromise. A shift to flow-directed vascular access and an understanding that occlusion of the ophthalmic artery during treatment is not necessary to achieve chemotherapy delivery have enabled a decrease in vascular complications. Further, alternative vascular access appears to mitigate, to some degree, issues with primary vascular access when the ophthalmic artery is compromised.

V. IAC is a major advance in the treatment armamentarium of the pediatric ocular oncologist. This treatment brings both significant reward to our patients but also variations in treatment morbidity. As with all advanced treatments, ongoing review to target best indications for treatment and best IAC delivery strategies and to focus on unique concerns for this specialized treatment is required for each specialist and institution engaged in the treatment of these complex children.

VI. IAC will remain a major tool in the treatment of advanced retinoblastoma, achieving increased anatomic and functional globe retention. An understanding of the unique impact of the orbital *and* ophthalmic vasculature is key to enhancing IAC treatment benefit while minimizing treatment-associated complications. Ongoing dissemination of best practices for IAC continues to decrease treatment-related morbidity.

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# IAC 3. Histopathologic Correlation of Post-treatment Vascular Changes in a Non-human Primate Model

***Matthew W Wilson MD***

I. Non-human Primate (NHP) Model of Super Selective Intra-Ophthalmic Artery Chemotherapy (SSIOAC)
   A. Approved by Institutional Animal Care and Utilization Committee
   B. 6 NHPs
   C. Treated 3 cycles every 3 weeks of SSIOAC per published guidelines
      1. 3 treated with 5 mg melphalan/30 cc over 30 minutes
      2. 3 treated with 30 mg carboplatin/30 cc NS over 30 minutes
   D. Real-time imaging performed during infusion
      1. Optic nerve pallor
      2. Retinal artery narrowing
      3. Retinal edema
      4. Precipitates
      5. Choroidal blanching
   E. Post-infusion intravenous fluorescein angiogram
      1. Delayed choroidal filling
      2. Choroidal filling defects
      3. Optic nerve edema
      4. Retinal artery narrowing
      5. Vascular sheathing
      6. Truncation of retinal arterial tree
      7. Leakage / hyperfluorescence
   F. Weekly dilated fundus examinations
      1. Nerve fiber layer infarcts
      2. Hemorrhage
      3. Choroidal scarring
      4. Anisocoria
      5. Upper eyelid edema

II. Final Infusion
   A. Intraocular pharmacokinetics
   B. Systemic pharmacokinetics
   C. Bilateral enucleations
   D. NHP euthanized
   E. NHP perfused with formalin

III. Ocular Pathology
   A. Injected with 1 cc 0.4% paraformaldehyde
   B. Placed in 10% formaldehyde
   C. Fixated for > 48 hours
   D. Globes were grossed.
      1. Caps submitted for electron microscopy
      2. Pupil optic nerve section completely sectioned ~500 slides
   E. Observed ocular pathologies
      1. Endothelial cell trauma
      2. Retinal vascular occlusion
      3. Choroidal vascular occlusion
      4. Short posterior ciliary artery occlusion
      5. Foreign material
      6. Central retinal artery thrombosis

IV. Orbital Pathology
   A. Ophthalmic artery dissection
   B. Central retinal artery dissection
   C. Fracturing of internal elastic lamina
   D. Eyelid thrombosis

V. Validation of the NHP Model

V. Melphalan Induces Retinal Endothelial Cell Inflammation
   A. In vitro cell assays
   B. Flow chamber

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# AAOOP Consensus Guidelines for Screening Children at Risk for Retinoblastoma: One-Year Update

***Alison Skalet MD PhD***

In 2018, the first U.S. guidelines for screening children at risk for retinoblastoma due to family history of the disease were published.[1] This consensus statement was the product of a panel created within the American Association of Ophthalmic Oncologists and Pathologists (AAOOP) that comprised senior leaders in retinoblastoma care representing major North American centers. Ocular oncologists, ophthalmic pathologists, and geneticists with expertise in retinoblastoma care were included.

The consensus statement was developed with the goal of creating a simple, rational approach to ophthalmic screening in children at risk that emphasized the importance of genetic testing. The screening approach outlined risk stratification separating children into 4 risk categories: high, intermediate, low, and population risk. It was recommended that all children with risk higher than population risk receive dedicated ophthalmic screening with serial dilated fundus examinations. Initial risk categorization was based on a child's familial relationship to the proband and whether the proband had unilateral or bilateral disease. The recommendation was made to clarify an individual child's risk as soon as possible through genetic testing.

This approach allows care, and it involves risks as well as expenses associated with screening evaluations, to be focused upon the children at highest risk. Screening evaluations with dilated fundus examinations by an ophthalmologist were recommended at high frequencies during early infancy, then at decreasing frequency over time, and proposed examination schedules for children in each risk category requiring dedicated ophthalmic exams were outlined. Examinations until age 7 were recommended.

The AAOOP consensus report was endorsed prior to publication by numerous professional societies in both pediatrics and ophthalmology and underwent extensive constructive peer review during this process as well as standard peer review for publication. Nonetheless, areas of debate have arisen since publication. We understand that not everyone will agree on every point in any consensus, and some providers and centers may choose to screen using a different strategy. However, the AAOOP consensus statement presents a valid and useful system for screening these children, with particular utility for clinicians who are not experts in retinoblastoma care. This talk will focus on the published AAOOP consensus recommendations and areas of ongoing discussion among ocular oncologists regarding best approaches for retinoblastoma screening in children at risk.

## Selected Reading

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# AJCC 8th Edition Update

## The 8th Edition of the AJCC Staging for Retinoblastoma, 2017

***Ashwin C Mallipatna MBBS***

### Clinical Staging

| | | |
|---|---|---|
| **cT1** | | **Intraretinal tumor(s) with subretinal fluid ≤ 5 mm from base of any tumor** |
| | cT1a | Tumors ≤3 mm and further than 1.5 mm from disc and fovea |
| | cT1b | Tumors >3 mm or closer than 1.5 mm from disc or fovea |
| **cT2** | | **Intraocular tumor(s) with retinal detachment, vitreous seeding, or subretinal seeding** |
| | cT2a | Subretinal fluid >5 mm from the base of any tumor |
| | cT2b | Vitreous seeding and/or subretinal seeding |
| **cT3** | | **Advanced intraocular tumor(s)** |
| | cT3a | Phthisis or prephthisis bulbi |
| | cT3b | Tumor invasion of choroid, pars plana, ciliary body, lens, zonules, iris, or anterior chamber |
| | cT3c | Raised IOP with neovascularization and/or buphthalmos |
| | cT3d | Hyphema and/or massive vitreous hemorrhage |
| | cT3e | Aseptic orbital cellulitis |
| **cT4** | | **Extraocular tumor(s) involving orbit, including optic nerve** |
| | cT4a | Radiologic evidence of retrobulbar optic nerve involvement or thickening of optic nerve or involvement of orbital tissues |
| | cT4b | Extraocular tumor clinically evident with proptosis and/or an orbital mass |
| **N1** | | **Evidence of preauricular, submandibular, and cervical lymph node involvement** |
| **M1** | | **Clinical signs of distant metastasis** |
| | M1a | Tumor(s) involving any distant site (eg, bone marrow, liver) |
| | M1b | Tumor involving the CNS (not including trilateral retinoblastoma) |
| **H** | | **Hereditary trait** |
| | HX | Unknown or insufficient evidence of a constitutional *RB1* gene mutation |
| | H0 | Normal *RB1* alleles in blood tested with demonstrated high-sensitivity assays |
| | H1 | Bilateral retinoblastoma, retinoblastoma with an intracranial primitive neuroectodermal tumor (ie, trilateral retinoblastoma), patient with family history of retinoblastoma, or molecular definition of a constitutional *RB1* gene mutation |

*(table continues)*

## Pathological Staging

| | | |
|---|---|---|
| **pT1** | | **Intraocular tumor(s) without any local invasion, or with focal choroidal invasion, or pre- or intralaminar involvement of the optic nerve head** |
| **pT2** | | **Intraocular tumor(s) with local invasion** |
| | pT2a | Concomitant focal choroidal invasion and pre- or intralaminar involvement of the optic nerve head |
| | pT2b | Tumor invasion of stroma of iris and/or trabecular meshwork and/or Schlemm canal |
| **pT3** | | **Intraocular tumor(s) with significant local invasion** |
| | pT3a | Massive choroidal invasion (>3 mm in largest diameter, or multiple foci of focal choroidal involvement totaling >3 mm, or any full-thickness choroidal involvement) |
| | pT3b | Retrolaminar invasion of the optic nerve head, not involving the transected end of the optic nerve |
| | pT3c | Any partial-thickness involvement of the sclera within the inner two thirds |
| | pT3d | Full-thickness invasion into the outer third of the sclera and/or invasion into or around emissary channels |
| **pT4** | | **Extraocular tumor(s) involving orbit, including optic nerve** |
| | pT4a | Evidence of extraocular tumor: tumor at the transected end of the optic nerve, tumor in the meningeal spaces around the optic nerve, full-thickness invasion of the sclera with invasion of the episclera, adjacent adipose tissue, extraocular muscle, bone, conjunctiva, or eyelids. |

Source: Mallipatna AC, Finger PT, et al. Retinoblastoma. In: Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017: ch. 68, 819-831.

# Benefits of PRAME in Prognostic Testing

***J William Harbour MD***

I. PRAME is a testis-specific gene that should not be expressed in normal tissues.
   A. PRAME is likely involved in meiosis.
   B. Inappropriate expression of PRAME in cancer may cause tumor progression

II. PRAME is expressed in a subset of Class 1 and Class 2 uveal melanomas.
   A. About 20% of Class 1 uveal melanomas are PRAME+.
   B. About 30% of Class 2 uveal melanomas are PRAME+.

III. PRAME expression is associated with worse patient outcome.
   A. PRAME expression is associate with shorter time to metastasis and melanoma-specific mortality in both Class 1 and Class 2 uveal melanomas.
   B. Laboratory research confirms that PRAME promotes uveal melanoma metastasis.

IV. PRAME expression is associated with specific driver mutations.
   A. In Class 1 uveal melanomas, PRAME expression is associated with SF3B1 mutations and inversely associated with EIF1AX mutations.
   B. This may allow PRAME to guide the choice of targeted molecular therapy in uveal melanoma.

V. PRAME can be recognized as a tumor antigen by the immune system.
   A. PRAME-directed T-cell therapies and vaccines are being developed and tested for PRAME-expressing cancers.
   B. This may allow PRAME to guide the choice of immune therapy in uveal melanoma.

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# How Cytopathology and Size Enhance Prognostication in Uveal Melanoma

***Juan Ortiz MD***

As management of uveal melanomas (UM) is evolving to minimally invasive techniques (fine needle aspiration [FNA]-guided brachytherapy), the traditional prognostic classification,[1] based on complete histological examination of enucleated eyes, is not applicable in a large number of cases undergoing current treatment modalities. Extensive work has been performed on the cytology of UMs in the "premolecular diagnostic era"; however, little quantified data are available on the significance of the cytological findings in partial FNA samples at the time of gene expression profile (GEP) and brachytherapy.

Initial observations demonstrated prognostic significance in different cell types, with epithelioid cells associated with worse prognosis than spindle cells. However, interobserver variability affected reproducibility, requiring later modifications of the original classification.[1] Prior to the "molecular era," research in cytomorphology continued, and different groups in the 1980s and 1990s emphasized the role of tumor cell types and the correlation of nucleolar features with outcome.[2-6] More recently, Medina et al reported direct correlation between nucleolar size and both tumor height and largest basal dimension, but there was no correlation with cytologic type. The study also showed 100% correlation between cytologic and histologic diagnosis in all eyes that underwent enucleation.[7]

Based on some of these previous observations and unpublished data from our cohort of cytology cases, there is good correlation between cell type and presence of nucleoli. This correlation of cell type–presence of nucleoli is a good internal control that helps to decrease interobserver variability, forcing the interpreter to look for two independent characteristics to come up with a cytological classification. In individual cases, the presence of aggressive cytomorphological features can be compared with other clinical and molecular characteristics associated with higher risk of metastatic disease.

Currently, GEP is statistically superior to clinical and histological findings as a prognostic tool; however, other clinical features, including tumor largest linear basal diameter, tumor thickness, and intraocular location, have been reported to add significant prognostic value.[8] In addition, as with any diagnostic procedure with tissue obtained by FNA, there is the potential risk of misclassification due to tumor heterogeneity,[6,9,10] which could, at least in part, explain why larger tumors with class 1a GEP can have worse progression-free survival (PFS) than smaller tumors with class 2, raising the question of whether multiple FNA samples would increase accuracy.[10]

Despite the fact that GEP is a stronger prognostic tool, our study highlights the importance of adding morphological information to the clinical and molecular profile—first and more importantly, because this relatively inexpensive approach is essential to confirming the presence of tumor cells prior to sending tissue for molecular testing, and secondly, as it could add valuable information to the current clinical and molecular classification of UMs, in particular in those cases when molecular testing is not compatible with the cytological findings (eg, low GEP class in cases with aggressive cytomorphology). In addition, the findings also remind current practitioners that because of the complex biology of UM, no diagnostic technique should be used alone as a single predictive marker. Long-term follow-up studies are needed to confirm these findings.

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# Liquid Biopsies in Uveal Melanoma

*Martine J Jager MD PhD and Jesse L Berry MD*

## Introduction to Liquid Biopsies

Biopsies are usually taken from uveal tumors for diagnostic or prognostic purposes. In general, these are tissue biopsies. Intraocular biopsies may be taken from lesions located in the iris or the choroid, where a lesion can be approached trans-sclerally or through the vitreous and retina. "Liquid biopsy" refers to samples of fluid, which can be, for example, tears, aqueous, vitreous, or blood.

Why would one take a sample of one of these liquids? The goal is to minimize direct tissue disruption from a traditional or fine needle biopsy, while still obtaining adequate tumor biomarkers for evaluation. A liquid biopsy can be used to analyze cytokines, cells, exosomes, enzymes, mRNA, miRNA, DNA, etc.

## Lymphoma

Vitreous biopsies have long been used to diagnose and manage primary vitreoretinal lymphoma (PVRL) through the collection of neoplastic cells from the vitreous cavity. Cells can be analyzed histologically, by immunophenotyping,[1] but also through molecular tests (eg, for mutations in MYD88). Analyzing the levels of cytokines such as interleukin (IL)-10 and IL-6 helps to differentiate between PVRL and non-neoplastic uveitis, with PVRL having a much higher Il-10/IL-6 ratio than uveitis in most studies.[2,3] Aqueous fluid can also be used but shows lower and less pronounced differences.[4] Quantification of microRNAs may be another option to characterize different disease entities, but this is still a work in progress (Tuo 2014). Analysis of vitreous is now routine and standard of care for intraocular / primary vitreoretinal lymphoma.

## Uveal Melanoma

Fine-needle aspiration biopsy is often used for uveal melanoma. Biopsies may be evaluated histologically or cytologically for diagnosis, but more often they are used prognostically to determine either the chromosome status (tumor DNA) or class 1 / class 2 gene expression profile (tumor mRNA) (reviewed by Dogrusöz 2017). The prognostically bad monosomy 3 / class 2 tumors are associated with an inflammatory phenotype.[7,8] Studies on vitreous fluid from uveal melanoma eyes have shown that these fluids can contain a wide variety of cytokines.[9] These cytokines can also be evaluated in the aqueous; IL-8 appears to correlate with tumor size and vascular endothelial growth factor (VEGF) and is highly expressed in melanoma eyes as compared to cataract controls.[10]

We wondered whether taking a sample of aqueous would allow us to differentiate between the 2 tumor types and give an indication of the prognosis for metastatic disease. An analysis of cancer-related cytokines and unsupervised clustering showed the presence of 3 clusters, 1 of which was associated with monosomy 3, but also with ciliary body involvement (unpublished). This indicates that genetics as well as the location of the tumor may be important determinants of the intraocular production of inflammatory cytokines, which can be used to prognose the risk of metastatic disease.

The traditionally described liquid biopsy from cancer is the blood. One may analyze blood samples for prognostication or to identify metastases, studying circulating tumor cells (CTCs), protein levels, cell-free circulating tumor DNA, mRNA, or exosomes. No marker has as yet been shown to be an early indicator of metastasis development. The presence of CTCs has been confirmed by several studies but is not necessarily a predictor of a bad prognosis or risk of metastatic disease.

Using an immune-FISH technique, CTCs were identified in the peripheral blood of 91% of UM patients with primary UM.[11] Using the FISH analysis, 58% of samples were positive for monosomy 3, which in almost all cases corresponded with the tumor's intrinsic chromosome 3 status. Another study showed the presence of melanoma cells in the bone marrow of the majority of uveal melanoma patients, without a link to the later presence of metastases.[12]

With regard to circulating cell-free DNA, new techniques such as droplet digital PCR and next-generation sequencing may help to detect the presence of tumor DNA. One might expect that mutated DNA from the tumor with mutations in GNAQ and GNA11 would be found in the circulating cell-free DNA. Similar to the findings with proteins, these analyses have not yet provided a test for the early detection of metastases. Bidard et al[13] performed a study in 40 patients who already had metastases of uveal melanoma. They determined the presence of CTC and circulating tumor DNA (ctDNA), using a mutation-specific technique for GNAQ and GNA11 mutations. CTCs were found in 30% of patients, and ctDNA in 84%. CTC and ctDNA could be used to predict progression-free survival. Similarly, mRNA of Melan-A/Mart-1 was present in 2 of 3 patients with metastases, and expression in the blood was a negative risk factor for progression-free and overall survival.[14]

## Retinoblastoma

Unlike other uveal melanoma and ocular neoplasms, where direct tumor and/or liquid biopsy of the aqueous or vitreous humor is considered gold standard for disease management, any attempt to biopsy or extract fluid from retinoblastoma eyes has historically been contraindicated; this is due to the risk of extraocular spread.[15] Studies of the aqueous humor, obtained from enucleated eyes, has shown that it is a rich source of tumor biomarkers that may be used for diagnosis and to monitor treatment response. These include proteins such as lactate dehydrogenase (LDH),[16] neuron-specific enolase,[17] survivin,[18] and cytokines. These studies described characteristic differences between retinoblastoma and control eyes, as well as changes in biomarkers with treatment. Nonetheless, there was minimal clinical utility to these tests, given that all studies were done in enucleated eyes, and direct or liquid biopsy remained contraindicated.

The only study to date[19] evaluating a liquid biopsy from retinoblastoma eyes actively undergoing treatment sampled the

aqueous humor during a safety-enhanced procedure for injection of chemotherapy into the aqueous.[20] With safe, routine access to the aqueous humor, Berry et al[19] demonstrated that tumor-derived cfDNA is present in the aqueous in both primarily enucleated and treated eyes. Further, this cfDNA can be amplified and sequenced to identify chromosomal alterations (regions of gains and losses) that correspond to the intrinsic genomic changes in the tumor. This opens the door for the aqueous to serve as true liquid biopsy for retinoblastoma; however, further research is required to delineate the role of the aqueous in diagnosis, prognosis, and management of this ocular cancer.

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# Adjuvant Therapy for High-Risk Uveal Melanoma With Sunitinib

## (and New Exciting Information on Immunotherapies)

*Carol L Shields MD*

I. What Is High-Risk Uveal Melanoma?
   A. At high risk for metastatic disease
   B. Could benefit from adjuvant therapy
II. How Do We Identify High-Risk Patients?
   A. Genetics alone
      1. Cytogenetics: Ch 3 monosomy+8q amplification
      2. Gene expression: Class 2
      3. Genetics plus size: Ch 3 monosomy + AJCC T3/T4
III. What Is the Exact Risk?
   A. Kaplan-Meier 7-year risk for metastasis based on cytogenetics (see Figure 1)
   B. Kaplan-Meier risk for metastasis based on cytogenetics and AJCC staging (see Figure 2)
   C. Kaplan-Meier risk for metastasis based on gene expression (see Figure 3)

**Combined DNA defects**

| 3 | 6p | 6q | 8p | 8q | Hazard Ratio for metastasis |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 1 |
| 0 | 0 | gain | 0 | 0 | 4 |
| loss | 0 | gain | 0 | gain | 11 |
| loss | 0 | 0 | 0 | gain | 19 |
| loss | 0 | 0 | gain | gain | 18 |
| loss | 0 | 0 | loss | gain | 32 |
| loss | loss | gain | 0 | gain | 77 |
| loss | loss | gain | loss | gain | 113 |
| loss | loss | 0 | loss | gain | 123 |

Figure 1. Reprinted with permission from Shields CL, Say EAT, Hasanreisoglu M, et al. Personalized prognosis of uveal melanoma based on cytogenetic profile in 1059 patients over an 8-year period. *Ophthalmology* 2017; 124(10):1523-1531.

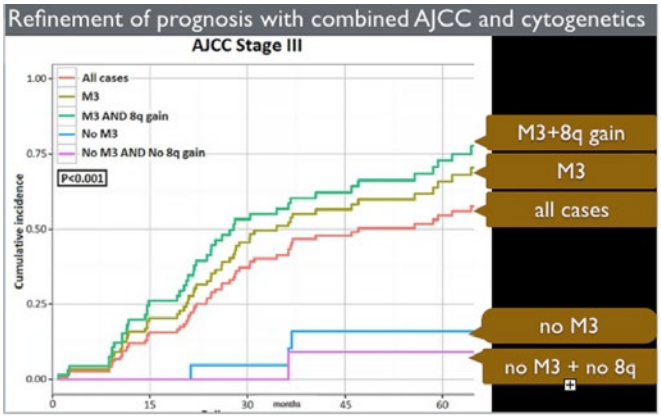


Figure 2. Reprinted with permission from Dogrusöz M, Bagger M, van Duinen SG, et al. The prognostic value of AJCC staging in uveal melanoma is enhanced by adding chromosome 3 and 8q status. *Invest Ophthalmol Vis Sci.* 2017; 58(2):833-842.

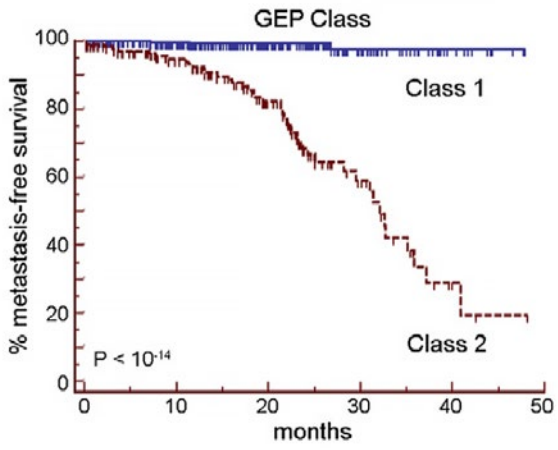


Figure 3. Reprinted with permission from Onken MD, Worley LA, Char DH, et al. Collaborative Ocular Oncology Group Report Number 1: Prospective validation of a multi-gene prognostic assay in uveal melanoma. *Ophthalmology* 2012; 119(8):1596-1603.

IV. What Can We Offer High-Risk Patients?

A. Sunitinib (Sutent)

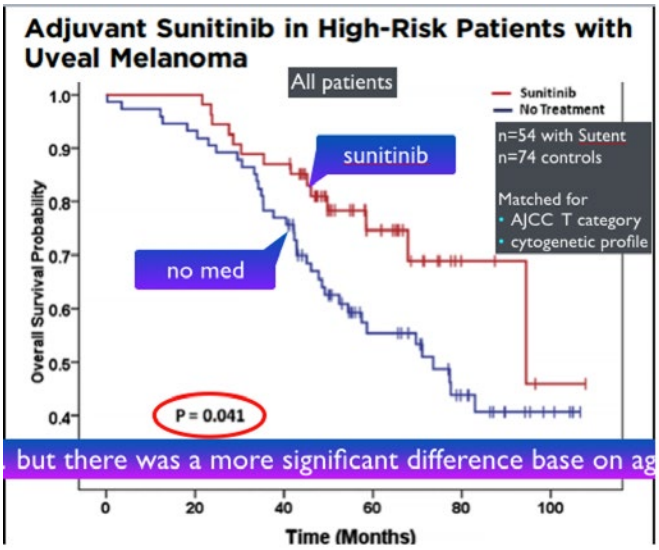


Figure 4. Reprinted with permission from Valsecchi ME, Orloff M, Sato R, et al. Adjuvant sunitinib in high-risk patients with uveal melanoma: comparison with institutional controls. *Ophthalmology* 2018; 125(2):210-217.

B. Valproic acid

C. Immunotherapies

1. Vaccine
2. Immunocore
3. Checkpoint inhibitors

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2. Dogrusöz M, Bagger M, van Duinen SG, et al. The prognostic value of AJCC staging in uveal melanoma is enhanced by adding chromosome 3 and 8q status. *Invest Ophthalmol Vis Sci*. 2017; 58(2):833-842.
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# AJCC 8th Edition Update on Uveal Melanoma

***Tero Kivelä MD***

I. The American Joint Committee on Cancer Tumour, Node, Metastasis (TNM) Classification

A. Is a cancer staging system in worldwide use across all specialties since 1977

B. Is based on the anatomic extent of each tumor as determined first clinically (cTNM) and then, although rare for uveal melanoma, histopathologically (pTNM)

C. An international Ophthalmic Oncology Task Force thoroughly revised the section of ophthalmic sites for the 7th edition in 2009; the staging of uveal melanoma became evidence-based for the first time.

D. Based on validation studies and other reports in the interim, minor refinements were incorporated in the 8th edition of the uveal melanoma TNM system in 2017.

II. T Categories

The T categories refer to the primary tumor and its contiguous extension, if any, and they range from T1 to T4, indicating increasing size, local extension, or both. Subcategories are used to extend and refine the system; they are indicated with a small letter postfix.

A. For iris melanoma, the several T subcategories changed in the 8th edition:

1. T1 is a tumor limited to the iris.
   a. T1a: ≤3 clock hours
   b. T1b: >3 clock hours
   c. T1c: with secondary glaucoma
2. T2 is a tumor confluent with or extending into the ciliary body or choroid.
   a. T2a: extending into the ciliary body, without secondary glaucoma
   b. T2b: extending also into the choroid, without secondary glaucoma
   c. T2c: with secondary glaucoma
3. T3 is a tumor otherwise corresponding to T2 but with scleral extension.
4. T4 is a tumor with extrascleral extension.
   a. T4a: extrascleral extension ≤ 5 mm in largest diameter
   b. T4b: extrascleral extension > 5 mm in largest diameter

B. For ciliary body and choroidal melanoma the categories have performed exceedingly well as prognosticators and did not change from the 7th edition:

1. T1 to T4 indicate increasing tumor thickness and largest basal diameter, divided in 3-mm increments (see Figure 1). These categories were designed to be as homogenous in survival as possible, and they derive from a collaborative data set of 7369 tumors (Kujala, et al. *J Clin Oncol*. 2013; 31(22): 2825-2831).
2. Subcategories a to d indicate the extent of contiguous extension:
   a: Choroidal tumor without ciliary body or extrascleral extension
   b: Ciliary body involvement without extrascleral extension
   c: Choroidal tumor with extrascleral extension ≤ 5 mm in diameter
   d: Ciliary body and extrascleral extension ≤ 5 mm in diameter
3. Subcategory T4e indicates a tumor of any size with extrascleral extension exceeding 5 mm in largest diameter.

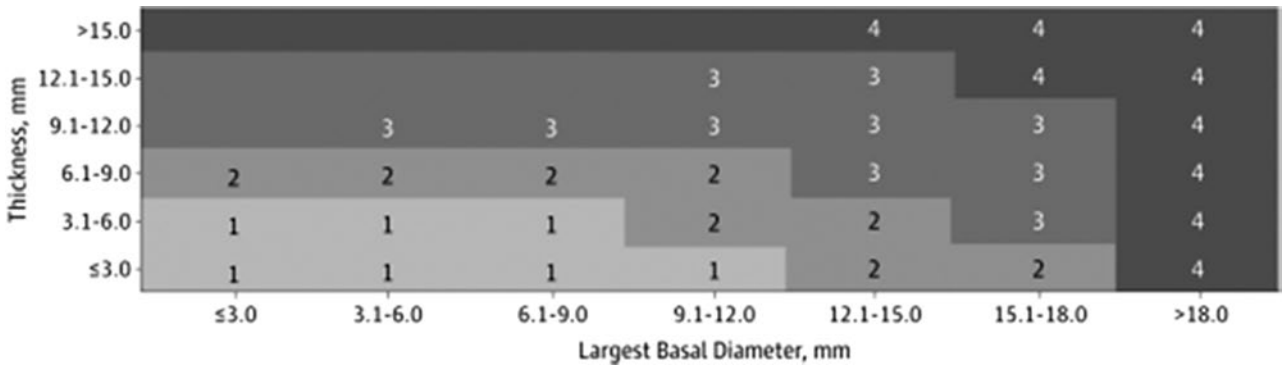


Figure 1.

III. N Categories

The N categories refer to regional lymph node or other regional metastases and were updated in the 8th edition.

A. N0 indicates no lymph node metastases.

B. N1a indicates 1 or more regional lymph node metastases, a rare occurrence seen only occasionally after extraocular extension to the conjunctival lymphatics.

C. N1b indicates satellite growth in the orbit not contiguous to the primary tumor; this is a new category in the 8th edition and follows other TNM systems in which nonnodal regional metastasis is categorized along with regional lymph node metastases (eg, satellites from Merkel cell carcinoma or cutaneous melanoma).

IV. M Categories

The M categories refer to systemic metastasis and remain unchanged in the 8th edition:

A. M0 indicates no metastases.

B. M1 indicates systemic metastasis and is subdivided according to the largest diameter of the largest metastasis:

1. M1a: ≤3 cm
2. M1b: from 3.1 to 8.0 cm
3. M1c: ≥8 cm

V. Important Note About Staging

Ciliary body and choroidal melanomas have a staging system. Each stage aims to be homogeneous with respect to survival and as different from the other stages as possible. Survival should primarily be analyzed according to the stages rather than by the underlying anatomic categories. No stages are defined for iris melanomas. The stages did not change in the 8th edition.

A. Stages I to III correspond to progressively higher mortality from localized or regional cancer; stages II and III have subcategories (see Table 1).

B. Stage IV is synonymous with systemic metastasis.

C. The staging system has performed well in all validation studies and special groups:

1. Shields et al. Iris melanoma outcomes based on the American Joint Committee on Cancer Classification (eighth edition) in 432 patients. *Ophthalmology* 2018; 125(6):913-923.
2. Shields et al. American Joint Committee on Cancer classification of uveal melanoma (anatomic stage) predicts prognosis in 7,731 patients: the 2013 Zimmerman lecture. *Ophthalmology* 2015; 122(6):1180-1186.
3. AJCC Ophthalmic Oncology Task Force. International validation of the American Joint Committee on Cancer's 7th edition classification of uveal melanoma. *JAMA Ophthalmol.* 2015; 133(4):376-383 (table 3).
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**Table 1.**

| | No Extension | Ciliary Body Only | Extraocular Only, ≤ 5 mm | Ciliary Body and Extraocular, ≤ 5 mm | Any Extraocular ≥ 5 mm |
|---|---|---|---|---|---|
| T1 | T1a (stage I) | T1b (stage IIA) | T1c (stage IIA) | T1d (stage IIA) | |
| T2 | T2a (stage IIA) | T2b (stage IIB) | T2c (stage IIIA) | T2d (stage IIIA) | |
| T3 | T3a (stage IIB) | T3b (stage IIIA) | T3c (stage IIIA) | T3d (stage IIIB) | |
| T4 | T4a (stage IIIA) | T4b (stage IIIB) | T4c (stage IIIB) | T4d (stage III C) | T4e (stage IIIC) |

If N1 or M1, stage if IV regardless of size category.

**Table 2. Five- and 10-Year Survival Rates**

| Five-Year Survival Rate (%) | | | Ten-Year Survival Rate (%) | |
|---|---|---|---|---|
| Stage | Original study | Validation study | Original study | Validation study |
| I | 96 (94-97) | 97 (95-98) | 88 (84-91) | 94 (91-96) |
| IIA | 89 (87-91) | 89 (86-91) | 80 (76-83) | 84 (80-88) |
| IIB | 81 (78-84) | 79 (75-83) | 67 (62-71) | 70 (62-76) |
| IIIA | 66 (62-70) | 67 (59-73) | 45 (39-51) | 60 (51-68) |
| IIIB | 45 (39-52) | 50 (33-65) | 27 (19-36) | 50 (33-65) |
| IIIC | 26 (13-40) | 25 (4-53) | not available | not available |

Note: 95% confidence interval.

VI. If the tumor is treated surgically, a histologic grade can be assigned:

A. G1 is spindle cell melanoma, >90% of spindle cells.

B. G2 is mixed cell melanoma.

C. G3 is epithelioid cell melanoma, >90% of spindle cells.

VII. Additional Data to Be Collected by Cancer Registrars, As Available

A. Chromosome 3 and 8 loss or gain

B. Gene expression profile (GEP; 1A, 1B or 2)

C. Mitotic count per 40 high power fields

D. Extravascular matrix patterns

E. Microvascular density

VIII. Future Directions

A. Although the anatomic extent has lost some of its significance as an indicator of prognosis, it remains crucial in planning treatment, evaluating complications, and estimating prognosis when genetic testing was not performed.

B. Not enough data collected in a uniform manner with a sufficient follow-up were yet available to incorporate genetic data to the 8th edition:

1. One would need a minimum of 100 and ideally 200 or more patients in each substage IA to IIIB and several dozen in IIIC.

2. One would need a follow-up of 10 years for most cases surviving without metastases to reliably estimate 10-year survival.

C. Once sufficient evidence has accumulated, cytogenetic and gene expression data can easily be incorporated in the staging table.

D. Until that time, preliminary data suggest that combining TNM with genetic data will enhance both. Patients with disomy 3/GEP 1 melanomas survive similar to stage I, irrespective of T size category, whereas the survival of monosomy 3/GEP 2 patients progressively worsens from stage I to stage III.

1. Dogrusöz M, et al. The prognostic value of AJCC staging in uveal melanoma Is enhanced by adding chromosome 3 and 8q status. *Invest Ophthalmol Vis Sci.* 2017; 58(2):833-842.

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# Cytopathology Improves Prognostic Testing in Uveal Melanoma

*Nora V Laver MD*

## Introduction

Accurate diagnosis of most intraocular tumors depends primarily on clinical evaluation in conjunction with noninvasive ancillary tests. However, in rare situations, these noninvasive diagnostic tests may fail to give an accurate diagnosis. Moreover, fine needle aspiration biopsy (FNAB) allows for further genetic testing to characterize uveal melanoma grading, prognosis, and treatment decisions. Survival and risk of distant metastasis in uveal melanoma are believed to be independent of the method selected for primary tumor management. Some have suggested that micrometastatic disease precedes local therapy.

Uveal melanoma shows characteristic chromosomal aberrations. Monosomy 3, the most frequent karyotypic abnormality, is present in 50%-60% of patients. Monosomy and additional copies of 8q have been correlated with reduced survival. The combination of monosomy 3 with cell type analyses or greatest tumor dimension have greater prognostic impact than monosomy 3 alone. Accurate detection of the chromosome aberrations used to predict the risk of metastasis and death from uveal melanoma is important for patient management and may also impact follow-up recommendations and future treatments.

## Background Observations

FNAB used in conjunction with genetic testing in uveal melanoma is a safe and reliable method in 88%-95% of cases. False negative rates are around 3%-7%. The fine needle used for the procedure shows a decreased risk of local tumor spread and creates a smaller surface wound than an incisional biopsy.

Access to an experienced cytopathologist and appropriate use of direct smears and liquid-based cytology and other ancillary techniques increase the yield of histopathological diagnosis. The presence of malignant melanoma cells and tumor cell type increase the diagnosis certainty. In a series of 45 fine needle biopsies performed at the New England Eye Center over the span of 10 years, 3 of the fine needle aspirations showed diagnoses different than uveal melanoma. In 1 of the cases a retinal pigment epithelial adenocarcinoma was diagnosed, and in the 2 other cases inflammatory conditions were found (granulomatous inflammation).

FNAB with cytopathology interpretation and tumor confirmation and further genetic testing is useful in the diagnosis and treatment of uveal melanoma.

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# Cytopathology Does Not Contribute to Prognostication in Uveal Melanoma

*Evangelos S Gragoudas MD*

## Introduction

Despite high rates of local control achieved in treating uveal melanoma, no progress has been made in treating metastasis.[1] There are no effective treatments for metastatic melanoma, and survival does not appear to be affected by early detection of metastasis.[2]

## Prognostic Tools

Predictors of metastasis include clinical characteristics (largest basal diameter, ciliary body involvement of tumor) and cytopathological findings.

### Cytopathology

Cytogenetic testing using samples obtained from fine needle aspiration biopsies has been successful in predicting metastatic disease. Available techniques include fluorescence in situ hybridization (FISH), single nucleotide polymorphism (SNP) arrays, multiplex ligation-dependent probe amplification (MLPA), and genetic expression profiling (GEP). Aberrations that are associated with poor prognosis can be identified with each of these methods, but the GEP assay has proven to be the best test for accurately predicting a patient's risk of dying from uveal melanoma. Patients classified as Class 2 are at high risk of developing metastasis, while those with Class 1 tumors are at low risk of metastasis.[3]

### Improvements to Prognostic Power

Despite the impressive predictive power of this assay, some patients with Class 1 tumors develop metastasis, and this finding led to modification of the classification. Patients are now assigned to a Class 1a or a Class 1b subgroup. With data continuing to accumulate, further modifications may become necessary in the future. More recently, the addition of PRAME to the assay has increased its predictive power, particularly in Class 1 tumors,[4] and largest basal diameter has also been found to enhance prognostication independent of GEP.[5,6]

## Value of Prognostic Information

Cytopathology has certainly improved our ability to determine risk of metastasis. However, since the results do not affect the management of the disease, the question remains as to whether cytopathological analysis should be done routinely.

### Pros

1. Patients may wish to know their risk of developing metastasis.
2. Increased surveillance in high-risk patients can be implemented.
3. High-risk patients may be eligible for clinical trials of experimental therapies for metastasis.
4. Patients may derive psychological benefits from knowing their risk:
   a. Low-risk patients have peace of mind.
   b. High-risk patients can "arrange their affairs."

### Cons

1. Cytopathology contributes to prognostication but does not affect the clinical management of the patient.
2. Patients may have an unfounded expectation that action can be taken based on these results.
3. Early diagnosis of metastasis does not improve survival, and increased surveillance of high-risk patients is not beneficial.
4. Patients may suffer psychological harm if they find out they are at high risk of metastasis.

## Recommendation

I do not perform tests, especially invasive ones, if I cannot use the results to benefit the patient.

Cytopathological testing should be done if:

1. The patient understands that his or her care will not be affected in any way based on the results of such tests, and
2. The patient is going to participate in therapeutic clinical trials that require test results to determine study eligibility.

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# We Are Improving Survival in Patients With Uveal Melanoma

*Sapna Patel MD*

NOTES

# We Have Done Nothing to Improve Survival of Patients With Uveal Melanoma

***Arun D Singh MD***

Treatment options for metastatic liver lesions include systemic therapy (chemotherapy and immunotherapy) and local therapy to the liver. Immunotherapy regimens are adopted from cutaneous melanoma treatments with checkpoint inhibitors, including anti-CTLA-4 blocking antibodies such as ipilimumab and anti-PD-1 blocking antibodies such as pembrolizumab and nivolumab. Local therapies directly targeting the liver include surgical resection of the tumor(s) and radiofrequency ablation (RFA) using localized thermal treatment to destroy tumor tissue. High-dose chemotherapeutic agents can also be directly infused after temporarily isolating the hepatic circulation (isolated hepatic perfusion) to achieve local control. This method can also be combined with an embolic agent to reduce blood flow to the tumor, as in transarterial chemoembolization (TACE).

No therapy has been consistently proven to be superior to others in the treatment of metastatic liver lesions. Retrospective study data suggest that local therapy targeting the liver metastases may offer greater improvement in survival than systemic therapy. However, not all patients are candidates for local therapy; some must be excluded because of their overall performance status or diffuse disease burden. The advent of immunotherapy in recent years has provided promising results in the survival of cancer patients, including those with cutaneous melanoma. As yet, however, it is unclear if this benefit clearly translates to improved survival in uveal melanoma patients with liver metastasis.

Future studies with larger cohorts and randomized controls are needed to elucidate treatment regimens with the best outcomes for patients with uveal melanoma metastatic to the liver.

# Children's Oncology Group: Unilateral Adjuvant Chemotherapy Update

***Murali Chintagumpala MD***

**NOTES**

# Children's Oncology Group: Group B Retinoblastoma

***Debra L Friedman MD***

NOTES

# Children's Oncology Group: Group C/D Retinoblastoma

*Murali Chintagumpala MD*

NOTES

# Children's Oncology Group: Metastatic Retinoblastoma

## Intensive Multi-modality Therapy for Extraocular Retinoblastoma: A Children's Oncology Group Trial (COG ARET0321)

***Ira J Dunkel MD for the COG ARET0321 Study Committee (Mark Krailo, Guillermo Chantada, Anuradha Banerjee, Sherif Abouelnaga, Jeff Buchsbaum, Thomas Merchant, Meaghan Granger, Rima Jubran, Michael Kellick, Joanna Weinstein, David Abramson, Carlos Rodriguez-Galindo, and Murali Chintagumpala)***

### Introduction

Extraocular retinoblastoma has historically been associated with a poor prognosis. Previous small series suggested that intensified systemic chemotherapy with or without radiation therapy (RT) may improve outcomes in this population. The Children's Oncology Group (COG) opened this prospective, multi-institutional, international trial to study the effectiveness of this approach.

### Methods

Patients with regional extraocular retinoblastoma (stage 2 or 3) were treated with 4 cycles of intensive conventional chemotherapy (vincristine 0.05 mg/kg/day, cisplatin 3.5 mg/kg/day, cyclophosphamide 65 mg/kg x 2 days, etoposide 4 mg/kg x 2 days) followed by involved-field radiation therapy (4500 cGy). Two strata of patients with metastatic retinoblastoma—stage 4a: distant metastases not involving the CNS, and stage 4b (CNS metastases) / trilateral retinoblastoma—were treated with 4 cycles of the same chemotherapy. Patients who achieved at least a partial response then received 1 cycle of high-dose carboplatin (Calvert formula with AUC = 7/day, maximum 16.7 mg/kg/day) on Days –8 to –6, thiotepa (10 mg/kg/day) and etoposide (8.3 mg/kg/day) on Days –5 to –3, with autologous hematopoietic stem cell rescue on Day 0. Patients with metastatic retinoblastoma who did not achieve an adequate response to chemotherapy also received radiation therapy.

### Results

Sixty subjects (20 in each stratum) were enrolled; 57 were eligible and included in the analyses (based on data current to June 30, 2016). Toxicity was significant as expected and there were 2 therapy-related deaths. Event-free survival at 36 months was 87.7% (90% CI, 65.4%-96.0%) for subjects with stage 2 or 3 disease, 79.3% (90% CI, 54.2%-91.6%) for subjects with stage 4a disease, and 8.0% (90% CI, 1.0%-25.1%) for subjects with stage 4b / trilateral disease. The observed results significantly improved the event-free survival in each stratum compared with historical results used for planning the study.

### Conclusions

This is the first prospective, multi-institutional, international study to show that intensive multimodality therapy is highly effective for patients with regional extraocular retinoblastoma and metastatic retinoblastoma not involving the CNS. More effective therapy is required for patients with CNS retinoblastoma.

### Selected Readings

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# Ranibizumab for Radiation Retinopathy Clinical Trial: One-Year Results

*Amy C Schefler MD, Cassandra Cone, Dwain Fuller MD, Maru Bretana, Rajiv Anand MD, Chelsey Moore, Timothy Fuller MD, Richard Vestewig PhD, and Ryan S Kim MD*

## Background

Radiation retinopathy is a common and devastating visual side effect of brachytherapy or external beam radiotherapy for uveal melanoma and other ocular cancers. Treatment methods for visual stabilization or improvement in these patients are sorely needed. Although local tumor control rates in the Collaborative Ocular Melanoma Study (COMS) and other reports are excellent for small to medium-sized choroidal melanoma,[1] long-term visual acuity outcomes have been poor for many patients. In the COMS report examining visual outcomes at 3 years, 43% of patients had a visual acuity of 20/200 or worse and 49% had a loss of 6 or more lines from the pretreatment level at 3 years post-treatment.[2] Furthermore, in the COMS, as soon as poor visual outcome was observed, improvement in vision to a level that no longer met the definition of poor vision was rare. The most common reason for irreversible vision loss is radiation retinopathy. In Kaplan-Meier analysis, rates of nonproliferative and proliferative disease at 5 years after plaque therapy are 42% and 8%, respectively.[3]

Anti-VEGF injections have been used on label in millions of patients worldwide for diseases as diverse as diabetic macular edema, AMD, and myopic choroidal neovascular membranes. These medications have also been used off label at many centers for patients with radiation retinopathy. Several large retrospective reviews of these patients have been published with some success, mostly utilizing an approach in which initiation of treatment occurs immediately at the time of radiation.[4-6] However, there has been only 1 prospective randomized trial examining the use of an anti-VEGF agent for this condition.[7] This study was designed to assess the efficacy of intravitreal ranibizumab with and without the addition of laser for radiation retinopathy-related cystoid macular edema when initiated at the time of clinically detectable disease.

## Methods

### Study Design

- Phase 2, multicenter, randomized, controlled clinical trial
- Patients were randomized 1:2:2 to 3 cohorts:
  - Monthly 0.5-mg intravitreal (IVT) ranibizumab for 1 year
  - Monthly IVT ranibizumab with targeted PRP (PRP to ischemic areas identified on wide-field fluorescein angiography) for 1 year
  - PRN IVT ranibizumab with targeted PRP (PRP to ischemic areas identified on wide-field fluorescein angiography) for 1 year
  - For the second year of the study, all 3 cohorts were treated with a standardized treat-and-extend protocol

### Inclusion Criteria

- Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA from 20/25 to 20/400 (Snellen equivalent)
- Clinically evident radiation retinopathy-related cystoid macular edema assessable on standard spectral domain OCT by standardized criteria
- History of plaque radiotherapy, external beam radiotherapy, or proton beam therapy

### Exclusion Criteria

- Anti-VEGF within 60 days
- Intravitreal steroid within 90 days
- Macular ischemia >7 DD on FA
- History of vitreous hemorrhage, panretinal photocoagulation
- History of retinal detachment, pars plana vitrectomy
- History of uncontrolled glaucoma or glaucoma surgery

## Results

### Baseline Features of Enrolled Patients

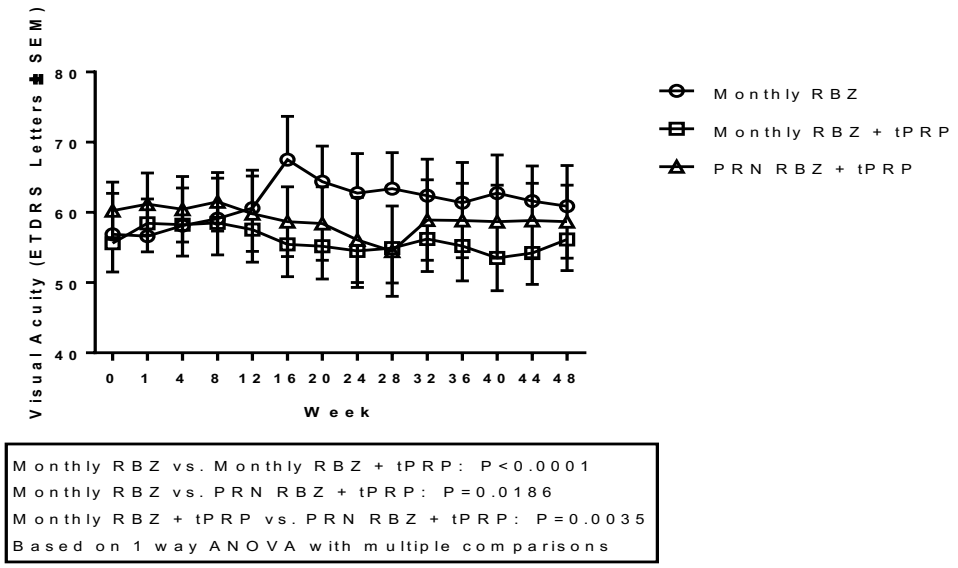
- Mean age: 57 years (range: 22-80)
- BCVA: Snellen equivalent 20/62.5
- Patients with visual acuity ≥20/40 Snellen equivalent distributed equally among groups
- Central retinal thickness: 385 µm
- Median number of years since radiation: 2.5
- Range: 6 months to 45 years
- 36/40 patients had radiation <10 years prior

## Visual Acuity Results: See Figures 1-3

Additional results will be presented at AAO 2018.

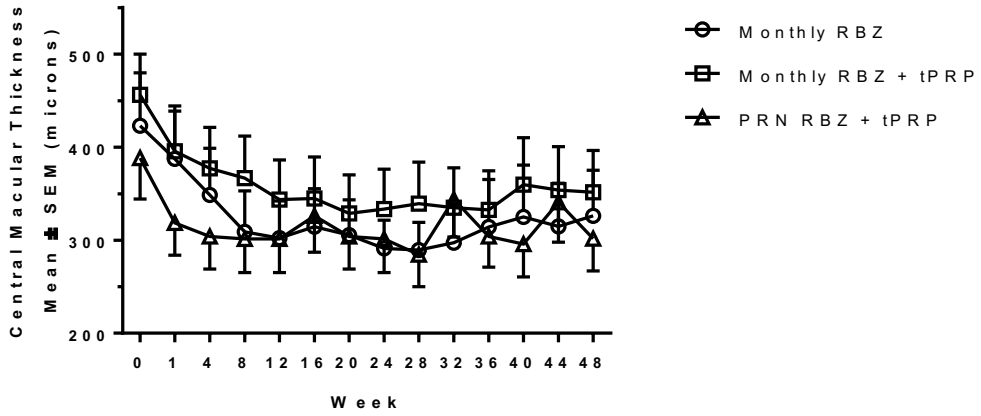
## Discussion

- All 3 groups treated with 0.5-mg IVT ranibizumab had significantly better visual outcomes than historical controls.
- Patients treated with monthly ranibizumab had significant visual gains compared to patients treated with a PRN approach.
- The addition of targeted PRP to monthly ranibizumab did not result in visual gain over monthly ranibizumab at the 12-month time point.
- Large scale, randomized, controlled trials of a monthly approach for clinically evident edema should be undertaken.
- Two-year results will be available in 1Q 2019.



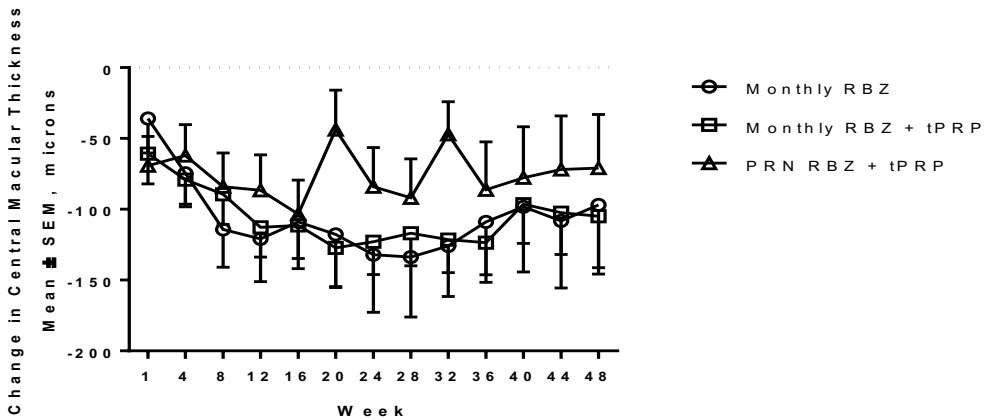

Monthly RBZ vs. Monthly RBZ + tPRP: P<0.0001
Monthly RBZ vs. PRN RBZ + tPRP: P=0.0186
Monthly RBZ + tPRP vs. PRN RBZ + tPRP: P=0.0035
Based on 1 way ANOVA with multiple comparisons

Figure 1. Mean visual acuity in 3 cohorts over time.




Monthly RBZ vs. Monthly RBZ + tPRP: P=0.0287
Monthly RBZ vs. PRN RBZ + tPRP: P=0.7324
Monthly RBZ + tPRP vs. PRN RBZ + tPRP: P=0.0040
Based on 1 way ANOVA wit multiple comparison

Figure 2. Mean central macular thickness.




Monthly RBZ vs. Monthly RBZ + tPRP: P=0.9974
Monthly RBZ vs. PRN RBZ + tPRP: P=0.0024
Monthly RBZ + tPRP vs. PRN RBZ + tPRP: P=0.0029
Based on 1 way ANOVA with multiple comparisons.

Figure 3. Mean change in central macular thickness.

## References


1. Jampol LM, Moy CS, Murray TG, 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. COMS Report no. 19. *Ophthalmology* 2002; 109:2197-2206.
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# Aura Trial: Uveal Melanoma

***Brian P Marr MD***

**NOTES**

# Latest Advances in Systemic Therapy for Uveal Melanoma: IMCgp100, TIL, and Selumetinib

***Richard D Carvajal MD***

I. Targeting the Molecular Mechanisms of Uveal Melanoma Growth
   A. Overview of the rationale for MAPK targeting in uveal melanoma
   B. Updates on targeting MEK in metastatic uveal melanoma
      1. SUMIT (Carvajal et al. *Journal of Clinical Oncology* 2018; 36(12):1232-1239)
      2. SelPac (CRUK/13/033)
      3. Novel dosing strategy for selumetinib (NCT02768766)

II. Updates on Immunological Treatment Strategies for Uveal Melanoma
   A. Differential efficacy of immunological checkpoint blockade in cutaneous and uveal melanoma
   B. Novel immunological treatment strategies for uveal melanoma
      1. Adoptive T-cell therapy (Chandran et al. *Lancet Oncol*. 2017; 18(6):792-802.)
      2. T-cell redirection therapy with IMCgp100 (NCT02570308, NCT03070392)

III. Future Directions

# Late Breaking Topic: Uveal Melanoma Clusters in the United States

***Miguel A Materin MD***

I. Cancer Cluster

A. Greater than expected number of cancer cases within a group of people in a geographic area over a limited period of time

B. More likely to be a true cancer cluster if:

1. A rare type of cancer

2. An age group not usually affected by that cancer

II. Incidence

A. In epidemiology, incidence is a measure of the probability of occurrence of a given medical condition in a population within a specified period of time.

B. Incidence proportion (also known as cumulative incidence) is the number of new cases within a specified time period divided by the size of the population initially at risk.

C. The incidence rate is the number of new cases per population at risk in a given time period.

D. Incidence of uveal melanoma in general population per year

III. Prevalence

Prevalence is the proportion of cases in the population at a given time rather than rate of occurrence of new cases.

A. Potential uveal melanoma cluster in Huntersville, North Carolina.

B. Potential uveal melanoma cluster in Auburn, Alabama.

C. Number of uveal melanoma patients in young females in Huntersville, NC, and Auburn, AL, in recent years

IV. Uveal Melanoma Tumor Registry: Benefits and Challenges

V. Risks and Benefits of Media Involvement in Medicine

# Retinoblastoma: Gender Differences in Second Cancers

***Ruth A Kleinerman PhD***

I. Second Cancer Incidence in Hereditary Retinoblastoma
   A. Bone tumors: Location of tumors differs by gender/age
   B. Soft tissue tumors: Location of leiomyosarcomas differs by gender.

II. Second Cancer Mortality in Hereditary Retinoblastoma
   A. Gender difference for total second cancer mortality
   B. Melanoma rates higher in females
   C. Brain tumor rates higher in females
   D. Lung tumors rates higher in females

III. Exposure Factors That May Explain Gender Differences
   A. Different baseline rates in general population
   B. Lifestyle or behavioral differences (smoking, sun exposure, reproductive, etc.)
   C. Tumor subtype differences

IV. Implications for Future Clinical Surveillance of Survivors

## Selected Readings

1. Yu CL, Tucker MA, Abramson DH, et al. Cause-specific mortality in long-term survivors of retinoblastoma. *J Natl Cancer Ins*t. 2009; 101(8):581-591.
2. Bright CJ, Hawkins MM, Winter DL, et al. Risk of soft-tissue sarcoma among 69 460 five-year survivors of childhood cancer in Europe. *J Natl Cancer Inst*. 2017; 10.1093/jnci/djx235.
3. Cook MB, McGlynn KA, Devesa SS, et al. Sex disparities in cancer mortality and survival. *Cancer Epidemiol Biomarkers Prev*. 2011; 20(8):1629-1637.
4. Francis JH, Kleinerman RA, Seddon JM, et al. Increased risk of secondary uterine leiomyosarcoma in hereditary retinoblastoma. *Gynecol Oncol*. 2012; 124(2):254-259.

# Ocular Tumor Changes During Pregnancy

***Colleen M Cebulla MD PhD, Lynn Schoenfield MD, Manisha Gamage BS***

This talk will focus on the topic of uveal melanoma (UM) in pregnancy, reviewing the following questions:

1. Is UM a potentially hormonally sensitive cancer?
2. What are risks of pregnancy on development of UM?
3. What is the influence of pregnancy on UM prognosis?
4. What are treatment strategies for pregnant patients with UM?

# Trends in Radiation Practices Among Women Ocular Oncologists in North America

***Mary E Aronow MD***

I. Introduction
   A. Plaque brachytherapy is widely used to treat ocular tumors.
   B. Considered safe by National Council on Radiation Protection and Measurements (NCRP)
   C. Description of current exposure guidelines
   D. Recognition of special circumstances: pregnancy
   E. Objective: To explore attitudes and practice patterns among female ocular oncologists

II. Methods
   A. Inclusion criteria
   B. Description of Qualtrics software (Provo, UT), 17-question survey

III. Results
   A. Response rate: 92%
   B. Demographic description of survey participants
   C. Review of survey responses
      1. Variation in institutional requirements for radiation safety training
      2. Frequency / type of radiation protective devices
      3. Annual radiation dose among female ocular oncologists
      4. Attitudes / practice patterns specifically related to pregnancy

IV. Conclusions
   A. The radiation exposure from plaque brachytherapy is minimal.
   B. Variability in safety training, protective devices, annual exposure, and practice patterns
   C. Opportunity for improving education and offering more consistent guidelines
   D. Expansion of survey to include international participants and male colleagues

# Trends in Practices for Women in Ocular Oncology

***Zelia M Correa MD***

**NOTES**

# Five Secrets From an Ocular Pathologist

*Ralph C Eagle Jr MD*

## 1. Communication

- If information is lacking, speak with the contributing ophthalmologist. (Talking is friendlier and takes less effort than email or texting!)
- If a consultation is sent by a general pathologist, you probably will get more pertinent information by speaking to the contributing ophthalmic surgeon.
- You usually can get the ophthalmologist's phone number by Googling his or her name.

## 2. Get Deeper Sections

- If pathology is not present in your initial sections, get deeper sections!!

## 3. Take Advantage of Your Photo Opportunities (and Document Your Good Cases)

- Prospectively collect photogenic microslides and make a list of retrievable "good cases."

## Photography Tips

**Gross Photography**

- Photograph gross specimens immersed in alcohol to minimize reflections.
- Blue background; rest dish on blue plexiglass, couple dish with ROH.
- Use malleable rings made from "bird bands" to support globes.
- Adjust lighting carefully to highlight pathology.
- Focus at highest magnification; then reduce to take lower mag photos.
- See video on grossing technique: "The Dissection and Processing of Human Eyes" at https://www.youtube.com/watch?v=FgGtw6oyHl8

**Photomicrography**

- High quality, artifact-free microslides are mandatory.
- Clean slides with grain alcohol and velvet; use dusters.
- Maximize microscope resolution with Koehler illumination.
- Use flat-bed scanner to "photograph" whole globes and other large specimens.
- Photoshop images: make background white, remove vignetting.

## 4. Use a Dissecting Microscope

- Carefully examine gross specimens with a dissecting microscope.
- With experience, you can make most of your diagnoses macroscopically.
- Magnification can disclose features (eg, sutures) that are invisible to the naked eye.

## 5. Examine the Calottes!

- The pathology may be more apparent or photogenic in the calottes. (Two of my most important papers used tissue from the calottes of cases initially worked-up by others—eg, ICE syndrome, fundus flavimaculatus.)

# Five Pearls From a Surgeon Scientist

## Lessons From My Patients

***Joan O'Brien MD***

### 1. Live in the Moment

For doctors, giving bad news and dealing with sadness during the work day is normal. We cannot let this seep into our home lives and the lives we share with our loved ones. Live in the moment, and learn how to leave those difficult moments in your driveway, before you go into your house.

### 2. Follow Your Passion, and Be Purposeful in Your Life

A young patient of mine, who was once told he would need both eyes enucleated, is now a successful Stanford swimmer. He saw those suffering around him and used gaming as a way to fundraise with his friends, hoping to benefit those who were worse off than he was during his illness.

### 3. Have Hope, and Give Hope

When my patients entered the round waiting room with the sign that said "Oncology" for the very first time, they were terrified. Patients and families with more experience with all that this room represents reached out to the new families, offering hope and comfort.

### 4. Decide to Be Happy

One of the early mistakes I made as a doctor has stuck with me forever. I was never taught how to give bad news, and I used to tell the parents of a patient all of the details of their child's disease. Then I would tell them, "I believe everything happens for a reason."

Once a father became furious when I said this. He was outraged that I could suggest that his young baby girl with retinoblastoma was made so sick for any reason. I immediately apologized and never said that again. Years later, after his daughter recovered, the father came back and told me about the good that came out of her illness. The awful experience of her sickness taught him that there are good people, and that the world is not as cold a place as we are sometimes taught.

### 5. Find a Way for Difficulties to Give You Strength, Compassion, Insight, Wisdom, and Courage

One of my patients, who had retinoblastoma and enucleation of one eye, has not let it stop him in his pursuits of becoming a stronger individual. He has excelled and is now the captain of his sports teams, and he and his mother have become voices for this disease and advocates for those dealing with it. I have seen countless patients take these tremendously difficult experiences and find ways to gain strength, compassion, insight, wisdom, and courage from them.

# Techniques in Ocular Oncology That Did Not Last

***Jerry A Shields MD***

This presentation includes some of the techniques that have been employed in ocular oncology in the past and have been replaced by newer techniques. The speaker will discuss the following:

1. p32 test
2. Zimmerman hypothesis
3. No-touch enucleation
4. Enucleation with vortex vein ligation
5. Prolonged observation of uveal melanoma
6. Water bath ultrasound
7. Prompt enucleation retinoblastoma
8. External beam radiation for retinoblastoma
9. Leech application to prevent pain at time of treatment with radiotherapy for melanoma (Can you believe this?)

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