Ocular Oncology and Pathology 2016
Breezing Along in Ocular Oncology and Pathology in the Windy City

Program Directors
Patricia Chevez-Barrios MD and Carol L Shields MD

In conjunction with the American Association of Ophthalmic Oncologists and Pathologists

McCormick Place
Chicago, Illinois
Saturday, Oct. 15, 2016

Presented by:
The American Academy of Ophthalmology
2016 Ocular Oncology and Pathology Planning Group

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 2016: Breezing Along in Ocular Oncology and Pathology in the Windy City.

Patricia Chevez-Barrios MD
Program Director
None

Carol L Shields MD
Program Director
Aura BioScience: C

2016 SUBSPECIALTY DAY ADVISORY COMMITTEE

Daniel S Durrie MD, Chair (Refractive Surgery)
Abbott Medical Optics: L,S
AcuFocus Inc.: C,L,O,S
Alcon Laboratories Inc.: S
Allergan: S
Alphaeon: C,L,O
Avedro: L,O,S
Hoopes Durrie Rivera Research Center: C
Strathspay Crown LLC: C,L,O
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Celgene: O
Janssen: C
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ThromboGenics Inc.: S

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Alcon Laboratories Inc.: L,S,C
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CoDa: C
ForeSight: C
NovaBay: C
Ocular Science: O,C
Ocular Therapeutix: C,S
PolyActiva: C
Shire: C
Slack Publishing: C
Sun Pharma: C
Syndexis: C
TearLab: C

R Michael Siatkowski MD (Pediatric Ophthalmology)
National Eye Institute: S

Kuldev Singh MD MPH (Glaucoma)
Abbott Medical Optics Inc.: C
Aerie: C
Alcon Laboratories Inc.: C
Allergan: C
Carl Zeiss Meditec: C
ForSight Vision 5: C
InnFocus: C
Ivanitis: C
Mynosys: C
National Eye Institute: S
National Space Biomedical Research Institute: C
Santen Inc.: C
Shire: C
Thieme Medical Publishers: C
Transcend: C
U.S. Food and Drug Administration: C

Nicholas J Volpe MD (Neuro-Ophthalmology)
Opticent Inc.: O

AAO STAFF

Ann L’Estrange
None

Melanie Rafaty
None

Lisa Romero
None

Debra Rosencrance
None

Beth Wilson
None
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CME Credit

Academy’s CME Mission Statement
The purpose of the American Academy of Ophthalmology’s Continuing Medical Education (CME) program is to present ophthalmologists with the highest quality lifelong learning opportunities that promote improvement and change in physician practices, performance, or competence, thus enabling such physicians to maintain or improve the competence and professional performance needed to provide the best possible eye care for their patients.

2016 Ocular Oncology and Pathology Subspecialty Day Meeting 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, conjunctival tumors, and orbital tumors
- Identify and manage treatment complications such as radiation retinopathy
- Recognize advances in biologic markers for ocular pathology
- Determine when a patient should be referred to an ocular oncology center

2016 Ocular Oncology and Pathology Subspecialty Day Meeting Target Audience
The intended target audience for this program is practicing ophthalmologists, residents in training, and fellows.

2016 Ocular Oncology and Pathology Subspecialty Day CME Credit
The American Academy of Ophthalmology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The American Academy of Ophthalmology 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.

Self-Assessment Credit
This activity meets the Self-Assessment CME requirements defined by the American Board of Ophthalmology (ABO). Please be advised that the ABO is not an accrediting body for purposes of any CME program. The ABO does not sponsor this or any outside activity, and the ABO does not endorse any particular CME activity. Complete information regarding the ABO Self-Assessment CME Maintenance of Certification requirements is available at http://abop.org/maintain-certification/part-2-lifelong-learning-self-assessment/sacme/.

NOTE: Credit designated as “self-assessment” is AMA PRA Category 1 Credit™ and is also preapproved by the ABO for the Maintenance of Certification (MOC) Part II CME requirements.

Teaching at a Live Activity
Teaching instruction courses or delivering a scientific paper or poster is not an AMA PRA Category 1 Credit™ activity and should not be included when calculating your total AMA PRA Category 1 Credits™. Presenters may claim AMA PRA Category 1 Credits™ through the American Medical Association. To obtain an application form please contact the AMA at www.ama-assn.org.

Scientific Integrity and Disclosure of Financial Interest
The American Academy of Ophthalmology is committed to ensuring that all CME information is based on the application of research findings and the implementation of evidence-based medicine. It seeks to promote balance, objectivity, and absence of commercial bias in its content. All persons in a position to control the content of this activity must disclose any and all financial interests. The Academy has mechanisms in place to resolve all conflicts of interest prior to an educational activity being delivered to the learners.

The Academy requires all presenters to disclose on their first slide whether they have any financial interests from the past 12 months. Presenters are required to verbally disclose any financial interests that specifically pertain to their presentation.

Control of Content
The Academy considers presenting authors, not co-authors, to be in control of the educational content. It is Academy policy and traditional scientific publishing and professional courtesy to acknowledge all people contributing to the research, regardless of CME control of the live presentation of that content. This acknowledgement is made in a similar way in other Academy CME activities. Though they are acknowledged, co-authors do not have control of the CME content and their disclosures are not published or resolved.

Attendance Verification for CME Reporting
Before processing your requests for CME credit, the Academy must verify your attendance at Subspecialty Day and/or AAO 2016. In order to be verified for CME or auditing purposes, you must either:

- Register in advance, receive materials in the mail, and turn in the Subspecialty Day Syllabi exchange voucher(s) onsite;
- Register in advance and pick up your badge onsite if materials did not arrive before you traveled to the meeting;
- Register onsite; or
- Scan the barcode on your badge as you enter an AAO 2016 course or session room.

**CME Credit Reporting**

**Academy Resource Center, Booth 508, and South Level 2.5**

Attendees whose attendance has been verified (see above) at AAO 2016 can claim their CME credit online during the meeting. Registrants will receive an email during the meeting with the link and instructions on how to claim credit.

Onsite, you may report credits earned during Subspecialty Day and/or AAO 2016 at the CME Credit Reporting booth.

**Academy Members:** The CME credit reporting receipt is not a CME transcript. CME transcripts that include AAO 2016 credits entered onsite will be available to Academy members on the Academy’s website beginning Nov. 10, 2016.

After AAO 2016, credits can be claimed at www.aao.org/cme.

The Academy transcript cannot list individual course attendance. It will list only the overall credits spent in educational activities at Subspecialty Day and/or AAO 2016.

**Nonmembers:** The Academy will provide nonmembers with verification of credits earned and reported for a single Academy-sponsored CME activity.

**Proof of Attendance**

The following types of attendance verification will be available during AAO 2016 and Subspecialty Day for those who need it for reimbursement or hospital privileges, or for nonmembers who need it to report CME credit:

- CME credit reporting/proof-of-attendance letters
- Onsite registration receipt
- Instruction course and session verification

Visit www.aao.org/cme for detailed CME reporting information.
Faculty

David H Abramson MD FACS
New York, NY
Chief, Ophthalmic Oncology Service
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# Ocular Oncology and Pathology 2016:  
**Breezing Along in Ocular Oncology and Pathology in the Windy City**

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

## SATURDAY, OCT. 15

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<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Presenter</th>
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<tbody>
<tr>
<td>7:00 AM</td>
<td>CONTINENTAL BREAKFAST</td>
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<tr>
<td>8:00 AM</td>
<td>Welcome, Introductions, and Audience Interaction</td>
<td>Patricia Chevez-Barrios MD</td>
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<tr>
<td></td>
<td><strong>Section I: Sunrise Over Lake Michigan—Top 5 Advancements Over the Past Decade</strong></td>
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<td>Moderators: Carol L Shields MD*, Amy C Schefler MD*</td>
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<tr>
<td>8:05 AM</td>
<td>Top 5 Advancements Over the Past Decade With Retinoblastoma</td>
<td>Jonathan W Kim MD*</td>
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<tr>
<td>8:12 AM</td>
<td>Top 5 Advancements Over the Past Decade With Choroidal Melanoma</td>
<td>Mary E Aronow MD</td>
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<td>8:19 AM</td>
<td>Top 5 Advancements Over the Past Decade With Choroidal Hemangioma</td>
<td>Amy C Schefler MD*</td>
</tr>
<tr>
<td>8:26 AM</td>
<td>Top 5 Advancements With Other Intraocular Tumors: What Should I Know?</td>
<td>Carol L Shields MD*</td>
</tr>
<tr>
<td>8:33 AM</td>
<td>Top 5 Current Approaches in Ophthalmic Pathology</td>
<td>Patricia Chevez-Barrios MD</td>
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<tr>
<td>8:40 AM</td>
<td>Can OCT Help in Diagnosis and Management?</td>
<td>David J Wilson MD</td>
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<tr>
<td>8:47 AM</td>
<td>Is Intravenous Fluorescein Angiography or OCT Angiography Better for Imaging Tumors?</td>
<td>Emil Anthony T Say MD</td>
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<tr>
<td>8:54 AM</td>
<td>How Well Does OCT Correlate With Histopathology?</td>
<td>Sander Dubovy MD</td>
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<tr>
<td>9:01 AM</td>
<td>Next Generation Sequencing of Vitreoretinal Lymphomas: New Routes to Targeted Therapies through Precision Medicine</td>
<td>Rajesh C Rao MD</td>
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<tr>
<td>9:08 AM</td>
<td>REFRESHMENT BREAK and AAO 2016 EXHIBITS</td>
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<td><strong>Section II: Blustery Debates in the Management of Intraocular Tumors</strong></td>
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<td>Moderators: Tara A McCannel MD*, Jose S Pulido MD MS</td>
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<tr>
<td>9:50 AM</td>
<td>Introduction and Audience Interaction</td>
<td>Patricia Chevez-Barrios MD</td>
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<tr>
<td>9:55 AM</td>
<td>Fine Needle Aspiration Biopsy for Genetic Information: Pro</td>
<td>Tara A McCannel MD*</td>
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<tr>
<td>10:00 AM</td>
<td>Fine Needle Aspiration Biopsy for Genetic Information: Con</td>
<td>Jose S Pulido MD MS</td>
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<tr>
<td>10:05 AM</td>
<td>Fine Needle Aspiration Biopsy for Genetic Information: Emotional Distress</td>
<td>Arun D Singh MD</td>
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<tr>
<td>10:10 AM</td>
<td>Cancer of Unknown Primary: From Immunohistochemistry to Gene Expression Profiling</td>
<td>Nora V Laver MD</td>
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<tr>
<td>10:17 AM</td>
<td>Bevacizumab for Prevention of Radiation Retinopathy: The Evidence</td>
<td>Timothy G Murray MD MBA*</td>
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<tr>
<td>10:22 AM</td>
<td>Bevacizumab for Prevention of Radiation Retinopathy: Hogwash</td>
<td>Brian P Marr MD*</td>
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<td>10:27 AM</td>
<td>Sector Panretinal Photocoagulation for Prevention of Radiation Retinopathy: The Evidence</td>
<td>Miguel A Materin MD*</td>
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<td>10:32 AM</td>
<td>How We Manage Radiation Retinopathy in the UK</td>
<td>Victoria M Cohen FRCOpth</td>
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<tr>
<td>10:37 AM</td>
<td>Retinoblastoma: Intra-arterial Chemotherapy All the Way</td>
<td>Jasmine H Francis MD</td>
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</tbody>
</table>

* Indicates that the presenter has financial interest.
No asterisk indicates that the presenter has no financial interest.
<table>
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<tr>
<th>Time</th>
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<tr>
<td>10:42 AM</td>
<td>Retinoblastoma: Intra-arterial Chemotherapy in Selected Cases</td>
<td>Mandeep S Sagoo MBBChir PhD</td>
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<td>10:47 AM</td>
<td>Retinoblastoma: Intra-arterial Chemotherapy—Never</td>
<td>Matthew W Wilson MD</td>
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<tr>
<td>10:52 AM</td>
<td>Retinoblastoma: Children's Oncology Group Update on Intra-arterial Chemotherapy</td>
<td>Murali Chintagumpala MD</td>
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<td>10:57 AM</td>
<td>Retinoblastoma: Documented Toxicities of Intra-arterial Chemotherapy</td>
<td>Dan S Gombos MD*</td>
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<tr>
<td>11:02 AM</td>
<td>Pathology: Evisceration and Enucleation Disasters</td>
<td>Ralph Eagle MD*</td>
<td>31</td>
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<td>11:09 AM</td>
<td>Advocating for Patients</td>
<td>Zelia M Correa MD*</td>
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<td>11:14 AM</td>
<td>LUNCH and AAO 2016 EXHIBITS</td>
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**Section III: Forecasting the Future**
Moderators: Prithvi Mruthyunjaya MD*, Diva R Salomao MD*

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<tr>
<td>12:40 PM</td>
<td>Introduction and Audience Interaction</td>
<td>Carol L Shields MD</td>
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<td>12:45 PM</td>
<td>Sildenafil Citrate (Viagra) for Lymphatic Malformations</td>
<td>Mary A O’Hara MD</td>
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<td>12:52 PM</td>
<td>Sclerosing Therapy for Lymphatic Malformations</td>
<td>Kenneth V Cahill MD FACS</td>
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<td>12:59 PM</td>
<td>Coats Disease: What Works</td>
<td>G Baker Hubbard MD</td>
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<td>1:06 PM</td>
<td>mTOR Inhibitors for Retinal Astrocytic Hamartomas</td>
<td>Prithvi Mruthyunjaya MD*</td>
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<tr>
<td>1:13 PM</td>
<td>Vismodegib for Basal Cell Carcinoma: Current Status and Future Promise</td>
<td>Bita Esmaeli MD FACS*</td>
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<tr>
<td>1:20 PM</td>
<td>Update on Orbital Xanthogranuloma Diseases: Role of BRAF Inhibition</td>
<td>Hakan Demirci MD</td>
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<tr>
<td>1:27 PM</td>
<td>What Pathology Biomarkers Should We Use for Conjunctival Tumors?</td>
<td>Victor M Elner PhD MD*</td>
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<tr>
<td>1:34 PM</td>
<td>What Pathology Biomarkers Should We Use for Skin and Orbital Tumors?</td>
<td>Tatyana Milman MD</td>
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<td>VEGF Receptors on Orbital Vascular Tumors</td>
<td>Diva R Salomão MD</td>
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<td>Is IgG4 Orbitopathy for Real?</td>
<td>James A Garrity MD</td>
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<tr>
<td>1:55 PM</td>
<td>Orbital Fine Needle Aspiration Biopsy: What Works</td>
<td>Richard C Allen MD PhD</td>
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<tr>
<td>2:02 PM</td>
<td>How Can We Improve Ocular Oncology Care in Developing Nations?</td>
<td>Fairozu Puthiyapurayil Manjandavida MD</td>
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<td>2:09 PM</td>
<td>Day by Day Ocular Oncology in India</td>
<td>Santosh G Honavar MD</td>
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<td>2:16 PM</td>
<td>The First Eye Cancer Working Day in Paris: Outcomes</td>
<td>Paul T Finger MD*</td>
<td>51</td>
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<tr>
<td>2:23 PM</td>
<td>REFRESHMENT BREAK and AAO 2016 EXHIBITS</td>
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**Section IV: Frosty Opinions in Ocular Oncology**
Moderators: G Baker Hubbard MD, Ivana K Kim MD*

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<th>Time</th>
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<tbody>
<tr>
<td>3:07 PM</td>
<td>Introduction and Audience Interaction</td>
<td>Carol L Shields MD</td>
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<tr>
<td>3:12 PM</td>
<td>Conjunctival Melanoma: How to Beat This Disease</td>
<td>Jill R Wells MD</td>
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<tr>
<td>3:19 PM</td>
<td>Conjunctival Squamous Cell Carcinoma: Which Topical Therapy and Why</td>
<td>Carol L Karp MD</td>
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<td>3:26 PM</td>
<td>Conjunctival Lymphoma: What Works</td>
<td>Sara E Lally MD</td>
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<td>Vitreoretinal Lymphoma: How Can We Improve Outcomes?</td>
<td>Tero T Kivela MD</td>
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<td>3:40 PM</td>
<td>BAP-1 Cancer Predisposition Syndrome</td>
<td>Colleen M Cebulla MD PhD</td>
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<td>3:47 PM</td>
<td>Future Applications of Uveal Melanoma Genetic Testing</td>
<td>J William Harbour MD*</td>
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<tr>
<td>3:54 PM</td>
<td>Systemic Melanoma Therapies That Work</td>
<td>Ivana K Kim MD*</td>
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<td>Do I Use the American Joint Commission on Cancer Classification?</td>
<td>Alison H Skalet MD PhD</td>
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* Indicates that the presenter has financial interest.
No asterisk indicates that the presenter has no financial interest.
### Program Schedule

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<td>Online Forum and Social Media: Communication Between Oncologist and Pathologist</td>
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<td>Telemedicine in Ocular Oncology and Pathology: What Works</td>
<td>Hans E Grossniklaus MD*</td>
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### Section V: Weathering the Storm

Moderators: G Baker Hubbard MD, Ivana K Kim MD*

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<td>Ocular Oncology: What I Like and Don’t Like</td>
<td>David H Abramson MD FACS</td>
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<td>Forty Years in Practice: I Will Tell You 5 Secrets</td>
<td>Evangelos S Gragoudas MD*</td>
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<td>Running an Ocular Oncology Practice: My Top 5 Lessons Learned</td>
<td>Jerry A Shields MD</td>
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<td>Closing Remarks</td>
<td>Carol L Shields MD*</td>
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* Indicates that the presenter has financial interest.
No asterisk indicates that the presenter has no financial interest.
Top 5 Advancements Over the Past Decade With Retinoblastoma

Jonathan W Kim MD

Top 5 Advancements 2006-2016

1. Intra-arterial chemotherapy
2. Intravitreal chemotherapy
3. Gene testing for retinoblastoma
4. Optical coherence tomography
5. Treatment for extraocular retinoblastoma


A. Protocol
   1. Microcatheter at ophthalmic artery (500 μm)
   2. Melphalan 3-7.5 mg diluted in 30 cc, infused over 30 minutes

B. Clinical results
   1. First 9 patients treated (mean follow-up 9 months)
   2. 7 of 9 eyes with advanced retinoblastoma (RB) salvaged
   3. 2 eyes enucleated (no active tumor seen)

C. Systemic toxicity: No vascular complications

II. Clinical Experience at Memorial Sloan-Kettering Cancer Center (MSKCC)

A. 4-year experience at MSKCC (2011)
   1. 95 eyes in 78 patients, 289 infusions
   2. Median: 3 infusions per patient (1-7), 2-7.5 mg (mean: 4 mg)
   3. Catheterization successful in 98.5%

B. Results in Group D eyes (MSKCC 2015):
   1. Treatment naïve: 85%
   2. < 6 months of age: 85%
   3. Secondary treatment: 72%

C. No catheterization complications

D. Grade 3 neutropenia: 29% (> 0.5 mg/kg)

E. No deaths

III. Intravitreal Melphalan: Munier Technique

A. Mark the injection site 3.25-3.5 mm posterior the limbus.

B. Paracentesis (0.1 cc of aqueous humor)

C. An injection is done with a 32-gauge needle in a quadrant of the eye free of tumor.

D. The needle is visualized behind the lens.

E. Cryotherapy is applied as the needle is withdrawn.

F. The eye is then shaken to distribute the chemotherapy.


A. 10 published studies on IVC for RB

B. 295 patients, 1287 injections, mean follow-up: 74 months

C. 38 patients with ocular side effects
   1. 17 major (2 with retinal detachment)
   2. 21 minor (IOP, cataract)

D. 1 patient with extraocular spread in Japan

E. 395 injections in 71 patients outside Japan with no extraocular spread

V. Overview of Clinical Results in Published Series of IVC

A. Munier, 2012
   1. 23 eyes, 122 injections, 20-30 μg

B. Abramson, 2014
   1. 107 eyes: 30 μg, median 6.5 injections per eye
   2. Decreased ERG responses at 30 μg (5.8 uV per injection)

C. Shields, 2015
   1. 12 eyes, 8-50 μg, 83% salvage rate

VI. Next-Generation Sequencing (NGS) for RB

A. Ion semiconductor sequencing

B. Sequences the entire RB1 gene including promoter, exons, and introns with an average coverage above 500x, MYCN copy number

C. Mosaicism detected to 5% level

D. Cannot detect RB1 promoter hypermethylation

VII. MCYN and Retinoblastoma

A. 2.7% of unilateral RB tumors demonstrate no RB1 mutations. 50% of these tumors demonstrate MCYN oncogene amplification (28-121 copies), functional RB protein.
B. MCYN: encodes N-Myc, transcription factor that controls expression of cell cycle genes that promote proliferation. Often amplified in neuroblastoma, retinoblastoma, glioblastoma, medulloblastoma, rhabdomyosarcoma.

C. Subset of unilateral RB patients who have wild type RB1 gene and functional RB protein. Median age: 4.5 months, aggressive histology.

D. Up to 18% of unilateral RB < 6 months of age may be due to MYCN.

E. Enucleation recommended

VIII. OCT and RB

A. Identify retinal anatomy adjacent tumor/seeding

B. Monitor treatment (distinguish scar vs. tumor)

C. Identify small tumors

D. Elucidating tumorigenesis

IX. Top 5 Advancements 2006-2016: Summary

A. IAC rivals systemic chemoreduction as a primary modality for retinoblastoma in 2016.

B. IVC has replaced external beam radiation as a salvage therapy for vitreous seeding.

C. Gene testing for RB is becoming faster, cheaper, and more widely used in clinical practice.

D. OCT is currently an important diagnostic tool to detect early RB lesions.

E. Treatment for extraocular RB: Radiation and surgery are becoming less important in treatment regimens, as survival rates improve.
**Top 5 Advancements Over the Past Decade With Choroidal Melanoma**

*Mary E Aronow MD*

I. Introduction

Uveal melanoma is the most common primary intraocular malignancy in adults. The incidence, which has remained stable over the past several decades, is estimated to be 5.1 per million population in the United States. Approximately half of individuals with uveal melanoma ultimately develop metastatic disease. While present therapies for metastatic uveal melanoma are minimally effective, recent discoveries are changing the landscape of ophthalmic oncology. This presentation focuses on several of the most influential areas of progress.

II. Advancements

A. Improvements in ancillary imaging technology
   1. OCT
   2. Color fundus photography (ultrawide-field systems)
   3. Angiography

B. Universal language for tumor staging; tumor-node-metastasis staging system

C. Tumor prognostication: DNA- and RNA-based techniques

D. Adjuvant treatments; multiple clinical trials worldwide

E. Collaboration

III. Summary

Recent developments have furthered our ability to characterize and document uveal melanoma, to classify these tumors, to understand the underlying mechanisms governing metastatic behavior, and to explore potential adjuvant therapies. These advances, combined with a collaborative effort, create an ideal environment for study of emerging therapies.

**Selected Readings**


Top 5 Advancements Over the Past Decade With Choroidal Hemangioma

Amy C Schefler MD

I. Introduction

II. Choroidal Hemangioma: Anatomy and Recently Described Clinical Associations
   A. Circumscribed
   B. Diffuse

III. Choroidal Hemangioma: New Diagnostics and Clinical Observations
   A. Spectral domain OCT
   B. Swept source OCT
   C. OCT angiography
   D. 20 MHz ultrasound

IV. Reviews of New Treatment Strategies
   A. Photodynamic therapy / other forms of laser
   B. Anti-VEGF and steroid injections
   C. Beta blockers
   D. Radiation: plaques, intensity modulated radiation therapy, proton beam

V. Conclusions
Top 5 Advancements With Other Intraocular Tumors: What Should I Know?

Carol L. Shields MD

I. Choroid Nevus

A. Prevalence of nevus in two 45-degree fundus photographs from National Health and Nutrition Examination Survey (NHANES); see Table 1.

B. Risk for transformation to melanoma: 1/8845 but varies with age

C. Risk factors predictive of growth to melanoma (see Table 2)

Table 1. Prevalence of Choroidal Nevus in NHANES: Stratified by Age, Gender, and Race

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Gender</th>
<th>Male n = 2785</th>
<th>Female n = 2790</th>
<th>P-value</th>
<th>Total</th>
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<td>5.0%</td>
<td>4.4%</td>
<td>0.7</td>
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<tr>
<td>50-60</td>
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<td>3.3%</td>
<td>2.9%</td>
<td>0.7</td>
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<td>60-70</td>
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<td>6.5%</td>
<td>4.4%</td>
<td>0.2</td>
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<td>70-80</td>
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<td>6.8%</td>
<td>6.5%</td>
<td>0.9</td>
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<tr>
<td>80+</td>
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<td>7.5%</td>
<td>7.5%</td>
<td>0.9</td>
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<tr>
<td>P-value</td>
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<td>0.1</td>
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Table information adapted from Qiu M, Shields CL. Choroidal nevus in the United States adult population: racial disparities and associated factors in the national health and nutrition examination survey. Ophthalmology 2015; 122(10):2071-2083.

Table 2.

<table>
<thead>
<tr>
<th>Initials</th>
<th>Mnemonic</th>
<th>Features</th>
<th>Hazard Ratio</th>
<th>Nevus Growth Into Melanoma if Feature Present (%)</th>
<th>Nevus Growth Into Melanoma if Feature Absent (%)</th>
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<tbody>
<tr>
<td>T</td>
<td>To</td>
<td>Thickness &gt; 2 mm</td>
<td>2</td>
<td>19%</td>
<td>5%</td>
</tr>
<tr>
<td>F</td>
<td>Find</td>
<td>Fluid</td>
<td>3</td>
<td>27%</td>
<td>5%</td>
</tr>
<tr>
<td>S</td>
<td>Small</td>
<td>Symptoms</td>
<td>2</td>
<td>23%</td>
<td>5%</td>
</tr>
<tr>
<td>O</td>
<td>Ocular</td>
<td>Orange pigment</td>
<td>3</td>
<td>30%</td>
<td>5%</td>
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<tr>
<td>M</td>
<td>Melanoma</td>
<td>Margin ≤ 3 mm to disc</td>
<td>2</td>
<td>13%</td>
<td>4%</td>
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<tr>
<td>UH</td>
<td>Using Helpful</td>
<td>Ultrasound hollow</td>
<td>3</td>
<td>25%</td>
<td>4%</td>
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<tr>
<td>H</td>
<td>Hints</td>
<td>Halo</td>
<td>6</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>D</td>
<td>Daily</td>
<td>Drusen absent</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
</tbody>
</table>

na: The risk factor of drusen absent was identified in other studies to be significant so it was included in this mnemonic for risk factors.

II. Choroid Lymphoma
A. Clinical features: Patchy orange-yellow choroidal infiltration
B. Systemic outcome: Depends on whether lymphoma is primary or secondary (see Table 3)

III. Retinal Astrocytic Hamartoma
A. Clinical features: Yellow-white inner retinal tumor with/without intrinsic calcification
B. Systemic implications: If a patient with tuberous sclerosis complex has astrocytic hamartoma, risk for:
   1. Subependymal giant cell astrocytoma: 37%
   2. Renal angiomylipoma: 60%
   3. Cognitive impairment: 77%
   4. Seizure: 91%
C. Imaging: OCT has documented astrocytic hamartoma is in the nerve fiber layer in all cases and many show optically empty “moth-eaten” cavities, representing calcification or cavitation.

IV. Retinal Hemangioblastoma
A. Clinical features: Red-orange retinal tumor with surrounding exudation and subretinal fluid
B. Visual outcomes: Depends on number and location of tumors. Risk for poor vision of 20/160 or worse:
   1. Juxtapapillary tumor (vs. peripheral tumor[s] only): odds ratio (OR) = 2.88
   2. Juxtapapillary and peripheral tumors (vs. peripheral tumor[s] only): OR = 6.38
   3. ≥ 3 (vs. < 3) peripheral tumors: OR = 4.18
   4. ≥ 5 (vs. < 5) peripheral tumors: OR = 8.27
   5. ≥ 1 (vs. < 1) quadrant of peripheral involvement: OR = 26.58

V. Sclerochoroidal Calcification
A. Clinical features: Yellow-white mass deep to choroid, generally superotemporally and calcified
B. Relationship with serum metabolic abnormalities:
   1. Calcium high 21%
   2. Potassium low 7%
   3. Magnesium low 24%
   4. Parathyroid hormone high 27%
   5. Parathyroid adenoma 15%
C. Imaging: OCT shows mountain-like topography with rocky, rolling, or table mountain configuration.

References & Selected Readings
Top 5 Current Approaches in Ophthalmic Pathology

Patricia Chévez-Barrios MD

Advancements in ophthalmic pathology are tied to technological advancements, as many tests depend on faster and more precise ways of detecting proteins, antigens, and molecular messages. The following are 5 current approaches used in ophthalmic pathology that exemplify these advancements.

I. Retinoblastoma Assessment of Genetics and Prognostic Factors

A. Guidelines for handling eyes with retinoblastoma
   1. Fresh retrieval of tumor (opening with blade vs. trephine or by needle aspiration biopsy [FNABx])
   2. Assessment of genetics: Recognition of small cohort of patients with N-MYC amplification with different histopathologic and clinical features
   3. Adequate fixation and sampling of optic nerve margin
   4. Entire eye submitted for examination: Pupil optic nerve (PO) and calottes (in anterior posterior segments for maximum choroidal examination) sections
   5. Adequate sampling of each block with histologic examination of complete optic nerve in the PO section (central vessels present in lamina cribrosa and optic nerve head)
   6. Definition of massive choroidal invasion (equal or more than 3 mm in any diameter) and focal choroidal invasion (less than 3 mm)

B. New staging for retinoblastoma: American Joint Commission on Cancer, 8th edition, incorporating “H” for hereditary and assessing a stage

C. Use of “liquid biopsy” for assessment of recurrence of disease at extraocular sites using blood and CSF (ie, cone-rod homeobox [CRX] mRNA as a marker for retinoblastoma)

II. Ocular Melanoma Diagnosis and Assessment of Metastatic Potential

FNABx prior to plaque implantation for uveal melanoma to obtain material for molecular analysis

A. Gene expression profile
B. Monosomy of chromosome 3 assessment
C. Assessment of other chromosomes by other molecular techniques
D. Cytopathology for confirmation of diagnosis
   1. With or without adequacy check
   2. Immunohistochemistry (double stain – melanoma marker + proliferation rate marker)
E. Biomarkers for skin, conjunctiva, and uveal melanomas (BRAF, BAP1)

III. Infectious Ocular Diseases (Atypical Keratitis, Uveitis and Retinitis)

Aqueous and vitreous and corneal scrapings, tap / biopsy

A. Polymerase chain reaction single or multiplex to detect most common viral pathogens
B. Whole genome sequencing of nonhuman message
C. Cultures and cytology

IV. Lymphoma, Conjunctiva, Orbit, and Intraocular

A. Flow cytometry
B. Molecular
   1. Gene rearrangement
   2. Other markers
C. Immunohistochemistry

V. Other Tumors and Lesions With Biomarkers and Specific Antigen Expression

A. Rhabdomyosarcoma: Mutations for alveolar vs. embryonal
B. Sebaceous gland adenoma / carcinoma
   1. Microsatellite instability associated with Muir-Torre syndrome (association with internal malignancies)
   2. Androgen receptor
C. Other orbital tumors
Can OCT Help in Diagnosis and Management of Ocular Neoplasia?

David J Wilson MD

I. Ocular Surface Disease
   A. Diagnosis
      1. Thickened epithelium
      2. Abrupt transition between normal and abnormal epithelium
      3. Distinction from benign surface disease
   B. Monitoring treatment

II. Anterior Intraocular Tumors
   A. OCT vs. ultrasound biomicroscopy
   B. OCT angiography of iris tumors

III. Posterior Segment
   A. Melanoma
      1. Detection of subretinal fluid
      2. Differential diagnosis
   B. Retinoblastoma
      1. Defining foveal anatomy
      2. Optic nerve evaluation
   C. Lymphoma: Monitoring subclinical disease

IV. Enhanced Depth OCT
   A. Metastatic lesions
   B. Choroidal nevi

V. OCT Angiography for Radiation Retinopathy
   A. Early detection
   B. Quantitative evaluation
Is Intravenous Fluorescein Angiography or OCT Angiography Better for Imaging Tumors?

Emil Anthony T Say MD

I. Background on Angiography Use in Ophthalmology
   A. Intravenous fluorescein angiography (IVFA)
      1. Real-time perfusion through intravenous dye injection
      2. Dependent on actual flow of blood
      3. Detects patterns of flow (leakage, staining, pooling) and areas of nonperfusion
      4. Detects microvascular anomalies based on leakage (CNV and neovascularization of the disc [NVD] and elsewhere [NVE])
      5. Takes 15-20 minutes
   B. OCT angiography (OCT-A)
      1. Analyzes relative perfusion noninvasively
      2. Dependent on movement of red blood cells
      3. Cannot detect patterns of flow but can detect areas of nonperfusion
      4. Takes less than 10 seconds

II. Clinical Use of Angiography in Ocular Oncology
   A. Differentiate tumors from pseudotumors
      1. Check for patterns associated with tumors or pseudotumors, such as smoke stack (central serous chorioretinopathy) and double circulation (choroidal melanoma)
      2. IVFA: Wide-field and increased depth of field allow visualization of all regions of interest.
      3. OCT-A: Limited field of view and limited depth of field do not allow visualization of the entire tumor due to artifacts (cut edge, mirror, etc.).
      4. Advantage: IVFA
   B. Assess etiology of vision loss
      1. Macular etiologies of vision loss
         a. Macular nonperfusion
         b. Foveal avascular zone (FAZ) enlargement and irregularity
         c. Loss of capillary density
      2. IVFA: Detects nonperfusion and FAZ at the superficial plexus only, cannot analyze capillary density due to limited axial resolution
      3. OCT-A: Detects all possible macular etiologies of vision loss, at both the superficial and deep plexus in less than 10 seconds
      4. Advantage: OCT-A
   C. Assess peripheral vascular abnormalities
      1. Assessment of peripheral vascular anomalies required for assessment of treatment complications (after intra-arterial chemotherapy or radiation) and diagnosis (Coats disease, familial exudative vitreoretinopathy), particularly in children
      2. IVFA: Field of view up to 200° in both nonsteering and steering machines
      3. OCT-A: Nonsteerable 3-, 6-, and 8-mm en face views with current machines and loss of detail with increasing scan lengths
      4. Advantage: OCT-A
   D. Check for neovascularization
      1. CNV is sometimes associated with treatment (laser scars) or associated with tumors (choroidal osteoma and choroidal nevus).
      2. Surface neovascularization (NVD and NVE) is sometimes associated with radiation and rarely seen in treatment-naïve tumors.
      3. IVFA: Poorly delineates neovascularization but detects all NV regardless of velocity of flow (not flow limited)
      4. OCT-A: Excellent delineation of neovascularization but is flow limited
      5. Advantage: IVFA = OCT-A
   E. Laser treatment planning
      1. Focal/grid laser and photodynamic therapy require visualization of areas with active leakage, such as focal leaks in choroidal nevi with subretinal fluid.
      2. Panretinal photocoagulation requires visualization of all areas of nonperfusion for complete therapy.
      3. IVFA: Detects actual flow and can analyze leakage; wide-field allows visualization of all areas of nonperfusion.
      4. OCT-A: Cannot determine leakage or lesion activity with correlation with IVFA and OCT; limited field of view to check for all areas of nonperfusion
      5. Advantage: IVFA
III. Conclusion
   A. Intravenous fluorescein angiography
      1. Can differentiate tumors from pseudotumors
      2. Assesses peripheral vascular abnormalities
      3. Laser treatment planning
      4. Assesses neovascular activity for diagnosis and treatment planning
   B. OCT angiography
      1. Assesses etiology of vision loss efficiently
      2. Assesses size of neovascular tissue for treatment monitoring
How Well Does OCT Correlate With Histopathology?

Sander Dubovy MD
Next Generation Sequencing of Vitreoretinal Lymphomas: New Routes to Targeted Therapies through Precision Medicine

Rajesh C Rao MD
In 2016, the modern approach to the treatment of a patient with choroidal melanoma includes determining metastatic risk with fine needle aspiration biopsy for molecular prognosis at time of brachytherapy. Although we are highly successful at treating the primary tumor, choroidal melanoma has at least a 50% risk of developing metastatic disease and death due to liver metastases. People want to receive all possible information regarding their cancer, including metastatic prognosis, whether or not it will alter their present medical therapy. Knowledge of metastatic risk may empower patients and reduce anxiety caused by uncertainty. Since 1993, monosomy 3, or loss of one copy of chromosome 3 in the tumor tissue, was demonstrated to be highly associated with the development of metastases. It wasn’t until 2006 that the first publication demonstrating the feasibility of in vivo fine needle aspiration biopsy for molecular prognostication in North American was reported. Since then a number of publications have demonstrated feasibility, success rates, and safety of performing in vivo fine needle biopsy during brachytherapy treatment of the primary tumor. Major ophthalmic oncology centers have demonstrated that needle biopsy does not alter the risk of metastasis and that this technique is safe in experienced hands. Furthermore, evolving techniques for fine needle biopsy, such as transvitreal and vitrectomy-assisted methods, have allowed clinicians to obtain tissue from patients with very small tumors in whom future targeted therapies may benefit most. Finally, fine needle aspiration biopsy of choroidal melanoma is critical to obtain tissue for research to better understand the biology of choroidal melanoma so that new targeted treatments for metastasis can be developed.

References

Fine Needle Aspiration Biopsy for Genetic Information: Con
Evolution of Decisions, Species, Tumors, and Tests

Jose S Pulido MD MS

I. Evolution of Decisions
   A. Decision making: science showed that decisions are formed by a surprisingly rapid combination of emotion (“gut,” “instinct”) and reason (“facts,” “rationality,” “science”).
   B. Some patients are dead-set on having a biopsy.
   C. Some of you are dead-set on doing biopsies.
   D. I will still have the talk.
   E. Descartes’ Error: Emotion, Reason, and the Human Brain

II. Cancer Selection vs. Darwinian Selection

III. Evolution of a Test

IV. Original: Nice Binary! Failure Rate 3%

V. Next Iteration: Report Sent, 3 Classes

VI. Most Recent Publication: 4 Classes

VII. Class 2 <12 mm vs. Website Class 1a (98%) and 1b (79%)

   Results: better to be Class 2 (90%)

VIII. Comparing size equivalent to size equivalent, it’s still better to be class 2!

IX. Truly an Evolution From the Original Binary Result

X. Evolution of Tumors: Clonality

XI. Is there heterogeneity in uveal melanomas like other tumors?

   16% discordance if biopsied at 2 sites, and discordant cases have a greater chance of mortality similar to class 2.

XII. So how is discordance/heterogeneity handled?

   A. So some are suggesting biopsying more than 1 site.
   B. But we know that for other melanomas, incisional biopsies are associated with a worse prognosis.
   C. Do uveal melanomas have exceptionalism in this regard? Or should we take care, and if we do a biopsy limit ourselves to 1 site?

XIII. Other Concerns That We Do Not Have Time to Discuss

   A. 20% incidence of regret following biopsy
   B. No prophylactic therapy, and if prophylactic therapy will be tried, it should be in a clinical trial.
   C. No data that early treatment makes a difference in the vast majority of cases

XIV. Final Questions

   A. So should one biopsy a melanoma <12 mm lbd since if it is Class 2, the prognosis is about the same as Class 1 tumors?
   B. For those >12 mm, if it is Class 2 the patient needs to be aware that 20% will have regret after doing the biopsy.
   C. In addition, if it is Class 1, there is still a 16% chance that it is Class 2.
Fine Needle Aspiration Biopsy for Genetic Information: Emotional Distress

Arun D Singh MD

Given that prognostication fine needle aspiration biopsy is routinely performed as management of uveal melanoma and would be eventually used to identify patients eligible for enrollment into adjuvant treatment trials, psychosocial assessment, including anxiety, depression, and decision regret, should be integrated into clinical trials, ideally prior to any testing. Decline in depression, anxiety, and decision regret appears to lessen or dissipate with time; study on larger numbers of patients is necessary to elucidate factors that may be addressed to mitigate decision regret.
Introduction
Carcinoma of unknown primary (CUP), although uncommon, is usually a challenging clinical problem. Approximately 15% of all cancers first present with metastasis; in approximately two-thirds of those cases the primary is found early in the course of the disease. However, in up to one-third of the cases the primary remains unknown or is found out over a longer period of time. The use of sophisticated imaging, immunohistochemical testing, and molecular-profiling tools has influenced the approach to CUP diagnosis. In most patients with CUP, pathological findings supersede the interpretations of radiologic testing. Adequate tissue sampling is essential, as is communication between the treating oncologist and the pathologist. Diagnostic biopsies classify tumors based on anatomic location and tumor morphology to guide patient care. Immunohistochemistry panels aid in establishing cancer type, subtype, and site of origin. Molecular tissue profiling can aid not only in determining the tumor origin in CUP but also in uncovering therapeutic targets and key mutational signatures of certain cancers. A growing number now believe that CUP may retain the signature of the primary origin and that extending the management of known cancers to subtypes of unknown primary cancer can contribute to advancements in therapies for this disease.

Background Observations
Since the 1990s immunohistochemistry (IHC) has revolutionized the way we make diagnoses, with large numbers of validated panels available for pathology interpretation. IHC antibodies are used singly or in panels, and the results depend on the tissue fixation, staining technique, and microscopic interpretation. Table 1 presents the usual algorithm used to make a histological diagnosis and lists the common immunohistochemical markers to determine tumor type, subtype, and site of origin. Although individual immunohistochemical tests have modest specificity and sensitivity, their predictive value may improve with grouping and recognition of patterns that are strongly indicative of specific tumors. Diagnostic dilemmas arise when few specific immunohistochemical markers stain or when the staining is hard to interpret due to insufficient tissue, necrosis, or poor staining or when the results conflict with the morphology or clinical scenario.

Molecular tissue differentiation is based on the differences in gene expression profiles. The human genome contains approximately 25,000 protein encoding genes; of these, 12,000 genes are active and expressed at the mRNA and protein levels in tissues. Of the 12,000 active genes, 8000 are expressed widely and are involved in basic cellular functions. A subset of active genes is specific to one or a few tissue types related to its differentiation. Tissue-specific or -restrictive genes are often regulatory genes or protein products. Regulatory genes include transcription factors, like thyroid transcription factor in lung and thyroid tissues. Protein products may be secreted or expressed in the cell—for example, cytokeratins in carcinomas. Tissues tend to resemble morphologically the tissue of origin and also express some tissue-specific genes, not only in primary cancers but also in metastasis.

Tissue-of-origin molecular profiling assays large numbers of genes from known cancers examined with tools such as DNA microarray and quantitative real-time polymerase chain reaction (rt-PCR) assay, using formalin-fixed tissue samples. Both techniques exploit the preferential binding or “base pairing” of complementary nucleic acid sequences. Metastatic CUP tumors have molecular signatures that match their primary origin (see Table 2). The performance of tissue-of-origin molecular-profiling assays in known cancers has been validated with the use of independent, blinded evaluation of sets of tumor samples, with an accuracy of approximately 90%. Molecular profiling performs well in already worked-up, poorly differentiated metastatic tumors, including CUP, with sensitivities of 72%-95%. For CUP patients, molecular profiling may change the diagnosis in around 50% of cases, and it affects management in most cases. There are numerous commercially available molecular profile panels (see Table 3). The use of IHC and molecular profiling in CUP is gradually aiding in finding the unknown tumor primary and will continue to improve with advances in treatments for patients with CUP.
### Table 1. Diagnostic Pathology Approaches Using Immunohistochemical Stains

<table>
<thead>
<tr>
<th>CUP Morphologic Workup</th>
<th>Useful Immunohistochemical Panels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Identify cancer type</strong></td>
<td></td>
</tr>
<tr>
<td>Carcinoma</td>
<td>Pancytokeratin AE1/3, EMA, CK7, CK20, CK5 (and other), p16, p63, HPV, etc.</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Melan-A, S100, HMB45, TIFT-1</td>
</tr>
<tr>
<td>Lymphoma/leukemia</td>
<td>LCA, CD20, CD3, CD138, CD30, CD5, CD10, kappa, lambda, EBV, etc.</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>Vimentin, desmin, actin, c-kit, S100, myogenin-D</td>
</tr>
<tr>
<td>Neuro-glial tumors</td>
<td>GFAP, EMA, CD34, CD99, synaptophysin, HMB-45, S100, vimentin, pancytokeratin</td>
</tr>
<tr>
<td><strong>2. Identify subtype (for example if carcinoma)</strong></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>CK7, CK20, PSA, etc.</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>CK5, p63, p16, HPV</td>
</tr>
<tr>
<td>Neuroendocrine carcinoma</td>
<td>Chromogranin, synaptophysin, CD56, TTF-1</td>
</tr>
<tr>
<td>Transitional cell carcinoma</td>
<td>TCC, CK7, urothelin</td>
</tr>
<tr>
<td>Renal carcinoma</td>
<td>RCC, CD10, PAX8, Napsin A</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Hepar-1, glypican 3, CD10</td>
</tr>
<tr>
<td>Thyroid carcinoma</td>
<td>TTF-1, thyroglobulin, PAX8</td>
</tr>
<tr>
<td>Adrenal carcinoma</td>
<td>Melan-A, inhibin</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>OCT4, PLAP, HCC, AFP</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>Calretinin, mesothelin, WT1, D2-40</td>
</tr>
<tr>
<td><strong>3. Identify possible primary site</strong></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>TTF-1, Napsin A, CK7</td>
</tr>
<tr>
<td>Breast</td>
<td>GCDFP-15, mammmaglobin, CK7, ER, PR</td>
</tr>
<tr>
<td>Colon</td>
<td>CDX2, CK7</td>
</tr>
<tr>
<td>Pancreas</td>
<td>CK7, CA125, CDX2</td>
</tr>
<tr>
<td>Stomach</td>
<td>CK7, CK20, CDX2</td>
</tr>
<tr>
<td>Prostate</td>
<td>PSA, NKX3.1</td>
</tr>
<tr>
<td>Ovary</td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>PAX8, WT1, ER, CA125, CK7</td>
</tr>
<tr>
<td>Mucinous</td>
<td>PAX8, WT1, ER, CA125, CK7, CDX2</td>
</tr>
</tbody>
</table>

### Table 2. Example of Genetic Panels Used in the Diagnosis of CUP

<table>
<thead>
<tr>
<th>Solid Tumors Panel</th>
<th>Breast Cancer Panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKT1, ALK, BRAF, CTNNB1, DDR2, EGFR, EPHA2, ERBB2,</td>
<td>Ki67, STK15, Survivin, CCNB1, MYTBL2, ACTB, GAPDH, RPLPO,</td>
</tr>
<tr>
<td>ESR1, FGFR1, FGFR2, FGFR3, GNA11, GNAQ, HRAS, IDH1,</td>
<td>MMP11, GUS, CTL2, TFRC, GRB2, Her2, ER, PGB, BCL2, SCUBE2</td>
</tr>
<tr>
<td>IDH2, IDH5, KIT, KRAS, MAP2K1, MET, MTOR, NOTCH1,</td>
<td></td>
</tr>
<tr>
<td>NRAS, PDGFRα, PIK3CA, PTEN, RAC1, RET, ROS1, TP53</td>
<td></td>
</tr>
<tr>
<td>Melanoma Panel</td>
<td>Lung Cancer Panel</td>
</tr>
<tr>
<td>BRAF, CTNNB1, GNA11, GNAQ, KIT, MAP2K1, NRAS</td>
<td>AKT1, ALK, BRAF, DDR2, EGFR, EPHA2, ERBB2, FGFR1, FGFR2,</td>
</tr>
<tr>
<td></td>
<td>FGFR3, KRAS, MAP2K1, MET, NRAS, PIK3CA, RET, ROS1, TR53</td>
</tr>
</tbody>
</table>
### Table 3. Commercially Available Molecular Profile Panels

<table>
<thead>
<tr>
<th>Company Name</th>
<th>City</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foundation One (Foundation Medicine)</td>
<td>Cambridge, MA</td>
</tr>
<tr>
<td>Molecular Intelligence™ Service or Target now™ Molecular Profiling Service</td>
<td>Irving, TX</td>
</tr>
<tr>
<td>(Caris Life Sciences)</td>
<td></td>
</tr>
<tr>
<td>GeneTrails® Solid Tumor Panel (Knight Diagnostic Lab)</td>
<td>Portland, OR</td>
</tr>
<tr>
<td>GeneKey (GeneKey Corp.)</td>
<td>Boston, MA</td>
</tr>
<tr>
<td>Guardant 360® Panel (Guardant Health)</td>
<td>Redwood City, CA</td>
</tr>
<tr>
<td>OncInsights™ (Intervention Insights)</td>
<td>Grand Rapids, MI</td>
</tr>
<tr>
<td>OnkoMatch™ (GenPath Diagnostics)</td>
<td>Elmwood Park, NJ</td>
</tr>
<tr>
<td>Pathwork Tissue of Origin – Cancer Genetics Incorporated-Gentrics</td>
<td>Raleigh NC; Hyderabad, India</td>
</tr>
<tr>
<td>BioTheranostics Cancer Type ID (CTID)</td>
<td>San Diego, CA</td>
</tr>
<tr>
<td>MiRview mets2 – Rosetta, Precision Therapeutics</td>
<td>Redwood, CA</td>
</tr>
</tbody>
</table>

### Selected Readings


Bevacizumab for Prevention of Radiation Retinopathy: The Evidence

Timothy G Murray MD MBA

Introduction

Radiation therapy for uveal melanoma, either brachytherapy or proton beam therapy, is the current “gold standard” for treatment. The largest prospective randomized clinical trial, the Collaborative Ocular Melanoma Study (COMS), has shown excellent survival outcomes that are influenced by tumor size. Recently, understanding of tumor biology and access to tumor genetics has shifted treatment away from enucleation and, in many instances, toward earlier treatments to minimize or avoid radiation treatment complications. In the COMS, approximately 12.5% of iodine-125 brachytherapy-treated medium-sized uveal melanoma patients were enucleated within the first 5 years after treatment. Radiation treatment complications, either radiation maculopathy, optic neuropathy, or secondary neovascular glaucoma, limited BCVA in the remaining eyes to approximately 20/200, occurring in 43% of eyes, while 49% of eyes lost greater than 6 lines of VA, all occurring within the first 36 months of treatment. Foundational work by Finger et al, Mieler et al, Shields et al, and others utilized treatment approaches to minimize radiation complications while maximizing visual acuity outcomes utilizing anti-VEGF, steroid, and/or laser therapies. Multiple investigators have now documented significant short- and long-term benefits of anti-VEGF treatments in decreasing enucleation rates, stabilizing IOP, enhancing macular anatomy, and ultimately improving visual acuity and function.

Data Review

Anti-VEGF treatment strategies evolved around the recognition of vascular damage secondary to direct, and indirect, vascular damage. Documentation of elevated VEGF levels in primary uveal melanoma along with significantly elevated post-radiation therapy levels led many investigators to utilize anti-VEGF therapies in clinical practice and in small clinical studies. A confluence of understanding of tumor biology, advances in imaging technologies (spectral domain OCT [SD-OCT]/ widefield fluorescein angiography / indocyanine green angiography), and intravitreal pharmacotherapies, including multiple anti-VEGF agents / steroids, enabled clinicians to enhance the early detection of radiation retinopathy, establish grading schemas, and personalize treatment approaches targeted at reducing retinal edema and improving VA.

Finger et al first reported anti-VEGF use for radiation maculopathy. Shields et al then developed an SD-OCT targeted grading schema for radiation maculopathy. Since 2008, over 70 peer-reviewed articles have discussed the use of anti-VEGF in the treatment of radiation complications associated with treated uveal melanoma. In 2012, Shah et al reported serial SD-OCT follow-up for detection and targeted treatment of radiation maculopathy. In this series of 159 patients, the mean VA at 36 months was 20/50 (compared to COMS VA at 20/200). Additionally, targeted use of anti-VEGF was found to decrease enucleation rates at 5 years from 12.5% in the COMS to < 1%. A subset of eyes showed severe radiation maculopathy and were subsequently treated with combination anti-VEGF and triamcinolone acetonide. Several recent long-term follow-up studies by Murray et al and Finger et al have documented the ability to preserve VA and anatomic function over treatment periods greater than 10 years.

Key take-home points for enhanced VA and anatomic outcomes include:

1. Early detection and treatment, with typical onset of radiation retinopathy at 9 months following radiation therapy
2. Need for close follow-up and targeted treatment often requiring anti-VEGF treatment at 4-6 week intervals
3. The benefit of early recognition of peripheral ischemia and tractional changes of the retina that may be amenable to surgical intervention via laser and/or vitrectomy.

Recently, next-generation anti-VEGF agents have been investigated in the treatment of radiation maculopathy. In a prospective, randomized treatment cohort reported at the ASRS 2016, aflibercept was delivered for complications of radiation maculopathy using an every 6-week vs. treat-and-extend approach that documented improvement in radiation maculopathy grading classification, decreasing SD-OCT retinal thickness (CPT), lowered IOP, and improved VA.

Conclusions

Radiation complications are the most common treatment-related morbidity for patients with uveal melanoma. Currently, anti-VEGF treatments using SD-OCT targeted therapy and employing active short-interval screening are associated with marked improvements in all outcome measures, including VA, macular thickening, vitreous hemorrhage, and neovascular glaucoma. The use of anti-VEGF with iodine-125 brachytherapy has virtually eliminated the need for post-brachytherapy enucleation. These existing studies clearly document the impact of anti-VEGF therapy in managing the complications of radiation treatment for uveal melanoma. Ongoing and future studies will further identify eyes that may benefit from strategies incorporating anti-VEGF treatment to impact the development of radiation maculopathy, to evaluate combined therapies with ocular steroids, particularly sustained-release modalities, and to describe the impact of surgical management targeted to decrease tumor treatment-related ischemia and traction-related complications.
Bevacizumab for Prevention of Radiation Retinopathy: Hogwash

Brian Marr MD

Radiation has been used in the field of oncology for more than 8 decades as a means to cause irreversible damage to DNA in tumor cells to prevent replication. Unfortunately, healthy cells in the treatment field receive the same damage and can suffer the same fate, depending on the dose they receive and type of cell or rate of replication of that cell. Such damage in the retina, which we term “radiation retinopathy,” can be seen months to many years after treatment. This results in progressive visual loss.

Treatment with bevacizumab (Avastin) following radiation does not reverse the DNA damage to cells and thus cannot reverse the radiation effects. Treatment may delay the clinical appearance of radiation retinopathy but does not prevent it long term.

Selected Readings


Sector Panretinal Photocoagulation for Prevention of Radiation Retinopathy: The Evidence

Miguel A Materin MD

Radiation retinopathy represents the most common ocular side effect after brachytherapy for uveal melanoma. Different options of treatment have been used for this condition, including intraocular injections of anti-VGEF medications or corticosteroids, periocular injections of corticosteroids, sector retinal photocoagulation, and others, with variable results. Early microvascular damage has been demonstrated by OCT angiography.

The current treatments might improve the radiation retinopathy (cystoid macular edema) with a variable improvement in visual acuity loss.

Selected Readings


How We Manage Radiation Retinopathy in the UK

Victoria M L Cohen FRCOphth

Introduction

Most uveal melanomas are treated by radiotherapy, which can consist of various forms of brachytherapy, proton beam radiotherapy, and stereotactic radiotherapy. The therapeutic effects and the ocular morbidity differ according to the choice of radiotherapy treatment. The benefits of administering an effective tumoricidal dose must be balanced against the possible consequences of ocular morbidity from radiation retinopathy, radiation maculopathy, optic neuropathy, cataract, neovascular glaucoma, and scleral necrosis.

Prevention is better than cure.

Strategies to minimize the radiation dose to the macula have included reducing the overall tumor treatment dose, the use of collimating and “custom-designed” plaques, and the eccentric placement of plaques and delivery of a notched proton beam. We now use intravitreal anti-VEGF injections prior to brachytherapy and after proton beam therapy to reduce subretinal fluid and risk of the retinal ischemia that precipitates radiation retinopathy.

Treatment of Radiation Retinopathy

Different treatment modalities have been used to treat radiation retinopathy. These include laser photocoagulation, photodynamic therapy, corticosteroids, and anti-VEGF agents. Vitrectomy, endolaser, and argon laser photocoagulation are still used to treat retinal neovascularization. However, due to the limited success experienced with grid argon laser photocoagulation for radiation-induced macular edema, this complication has changed.

In London, laser and intravitreal steroid injection for macular edema have been superseded by the use of off-license intravitreal bevacizumab. Several studies have reported promising results with the use of anti-VEGF agents in the treatment of radiation-induced macular edema. Mason et al evaluated the effect of a single intravitreal injection of bevacizumab in 10 consecutive patients. The mean visual acuity improved from 20/100 to 20/86 at 6 weeks and to 20/95 at 4 months. The mean foveal thickness was 482 μm before injection, 284 μm at 6 weeks, and 449 μm at 4 months after injection. Finger reported the results of intravitreal injections of bevacizumab (1.25 mg in 0.05 mL) repeated every 6-12 weeks in 21 patients with radiation retinopathy. They noted reduction in retinal hemorrhage and exudation, while visual acuity was maintained in 86% of patients and 14% gained vision. Gupta and Muecke suggested that following ruthenium plaque brachytherapy, younger patients with shorter duration of macular edema benefit the most after intravitreal injections of bevacizumab.

In summary, most published studies suggest that anti-VEGF agents reduce radiation-induced macular edema and retinal neovascularization, although not all studies demonstrate improvement in visual acuity. The optimal treatment regime has yet to be defined.

References


Retinoblastoma: Intra-arterial Chemotherapy All the Way

Jasmine H Francis MD

In many centers worldwide, intra-arterial chemotherapy has become first-line treatment for retinoblastoma. Reportedly, three-quarters of retinoblastoma centers worldwide use intra-arterial chemotherapy as first-line treatment for advanced unilateral disease. Intra-arterial chemotherapy can also be useful for cases beyond those that are advanced unilateral disease, including bilateral, less advanced, and very advanced disease. With first-line use of intra-arterial chemotherapy and a decade of follow-up, our group demonstrates ocular survival rates that exceed all historical data without compromising patient survival.
Retinoblastoma: Intra-arterial Chemotherapy in Selected Cases

Mandeep S Sagoo MBChir PhD

I. Range of Options for Treating Intraocular Retinoblastoma (Rb)

A. Depends on the International Classification of Retinoblastoma (ICRB) group

1. Local treatments
   a. Diode thermotherapy laser (TTT)
   b. Cryotherapy
   c. Plaque brachytherapy

2. Chemotherapy
   a. Systemic chemotherapy
      i. Vincristine, etoposide, and carboplatin
      ii. 6 cycles, given intravenously
      iii. Some centers vary this regimen.
      iv. Cyclosporine added by some centers
      v. Primary treatment
   b. Intra-ophthalmic artery chemotherapy
      i. Initial reports with melphalan
      ii. Many centers now add in topotecan.
      iii. 2-6 cycles
      iv. Primary or secondary treatment
   c. Intravitreal chemotherapy
      i. Specific technique to avoid seeding
      ii. Melphalan ± topotecan
      iii. Main indication is vitreous disease.

3. Radiotherapy
   a. Plaque brachytherapy
   b. Proton beam radiotherapy
   c. External beam radiotherapy: Now considered equal to conservative treatment failure

4. Surgery: Enucleation with orbital implant insertion

B. Specialist Rb centers choose treatment according to:

1. ICRB group
2. Age of patient
3. Status of fellow eye
4. Treatment availability and expertise of the multidisciplinary team
5. Complication profile
6. Risk / benefit ratio
7. Parental wishes

II. The Pros and Cons of Systemic Chemotherapy

A. Advantages

1. Controls Rb according to ICRB group
2. Resolves retinal detachment
3. Prevents new tumors
4. Prevents pineoblastoma
5. Preserves visual acuity

B. Disadvantages

1. Recurrences or treatment failure
2. Failure related to tumor, vitreous, or subretinal seeds
3. Most recurrences year
4. Toxicities
   a. Short term: cytopenia, infection, fever
   b. Long term: hearing loss, kidney failure, leukemia

III. The Pros and Cons of Intra-arterial Chemotherapy (IAC)

A. Advantages

1. Selective local treatment
2. Controls Rb

B. Disadvantages

1. Highly specialized team to deliver IAC
2. Risks
   a. Severe visual loss: 42%
      i. Retinal detachment
      ii. Choroidal ischemia involving the foveola
   b. Third cranial nerve palsy: 40%
   c. Orbital edema: 20%
   d. Vitreous hemorrhage: 27%
   e. Retinal pigment epithelium changes: 47%
3. Failure related to vitreous seeds or anterior segment involvement
4. Toxicity – vagal response possible
5. Metastatic Rb reported
IV. Selected Cases for IAC

A. Relapse after primary systemic chemotherapy as a salvage treatment
   1. Burden of disease is retinal or subretinal.
   2. Multiple relapse in 1 eye
   3. Relapse has failed other local therapy.
   4. Area of relapse is too broad for other local therapy.
   5. Replaces external beam radiotherapy for salvage
   6. Poor for control of vitreous disease

B. Primary treatment
   1. ICRB Group C
   2. Possible role in ICRB Group D, but hard to predict cases with high-risk histopathology features from clinical presentation
   3. Unilateral vs. bilateral
**Retinoblastoma: Intra-arterial Chemotherapy—Never Super-Selective Intra-arterial Chemotherapy (SSIOAC) or Chemosurgery**

**Matthew W Wilson MD**

I. Why?
   A. Targeted local delivery of drug
   B. Minimize total dose exposure of chemotherapy
   C. Great results
      1. Ocular salvage
      2. Electroretinography data

II. Why Not?
   A. SSIOAC is an evolution of Kaneko’s intracarotid chemotherapy.
      1. Different delivery site
      2. Different dilution of drug
      3. Same amount of drug 5-mg melphalan
   B. Preclinical modeling with vascular toxicity
   C. Clinical vascular complications
      1. Ocular
      2. Cerebral
   D. Systemic dosing through the ophthalmic artery: Neutropenia
   E. SSIOAC does not provide patient-centric care.
      1. High-risk eyes have high-risk pathology.
      2. Undertreating the entire patient poses risk of metastases.
      3. Neoadjuvant therapies alter pathology going forward.
   F. No prospective clinical trial; Children’s Oncology Group trial ongoing

III. What Is the Value of the Eye Being Saved?

**Selected Readings**


Retinoblastoma: Children’s Oncology Group Update on Intra-arterial Chemotherapy

Murali Chintagumpala MD

Introduction
Systemic chemotherapy in combination with local ophthalmic therapies is successful in salvaging globes and avoiding radiation therapy. However, this approach is associated with systemic toxicity, sometimes requiring hospitalizations, decreased success in eyes with advanced disease, and the treatment course uniformly lasting approximately 6 months or longer. In an effort to overcome these limitations, efforts are under way to deliver chemotherapy directly to the tumor via the ophthalmic artery (intra-arterial chemotherapy) or into the vitreous.

Background
Single-institution experiences showed promising results with chemotherapy delivered through the ophthalmic artery of the affected eye. However, the data from these experiences were difficult to interpret in the absence of protocol-driven guidelines for treatment, number and course of chemotherapy agents, and the monitoring and grading of toxicities, either short term or cumulative. Evaluating the feasibility and efficacy of this procedure in the context of a multi-institutional study is a critical next step toward the goal of establishing guidelines for the safe implementation of the intra-arterial technique across Children’s Oncology Group (COG) sites.

COG Study
The primary objective of this study is to study the feasibility of delivering melphalan directly into the ophthalmic artery in children with newly diagnosed unilateral Group D retinoblastoma, who would otherwise be considered for enucleation. The secondary objectives are (1) to estimate the ocular salvage rate after treatment with intra-arterial melphalan in children with newly diagnosed unilateral retinoblastoma with Group D disease, (2) to evaluate the toxicities and adverse events associated with delivering multiple doses of intra-arterial chemotherapy, (3) to evaluate vision outcomes in children treated with intra-arterial chemotherapy, and (4) to monitor the rate of the development of metastatic disease while on protocol therapy.

Central review panels were established to confirm the diagnosis of “D” disease before study entry and confirm progression while on therapy, and to confirm the validity of the intra-arterial procedure. A patient will be considered to have experienced intra-arterial therapy feasibility failure if (1) the interventional radiologist is not able to access the ophthalmic artery for chemotherapy administrations during the first 3 cycles of therapy, (2) the patient develops central retinal artery occlusion after the first or second cycle that does not reopen by the time the next injection is due, or (3) the patient cannot receive all 3 treatments with intra-arterial therapy because of CTC adverse event complications Grade III or IV that are considered possibly, probably, or likely related to treatment.

This is the first attempt to conduct a multi-institutional study using intra-arterial therapy for retinoblastoma with well-established guidelines for the conduct of the study.
Retinoblastoma: Documented Toxicities of Intra-arterial Chemotherapy

Dan S Gombos MD

Introduction

The management of retinoblastoma is not limited in modalities associated with excellent tumor control. The malignancy is associated with a 98%-99% cure rate in developed countries. Surgery (enucleation), external beam radiation therapy, systemic chemotherapy, and local chemotherapy (intra-arterial and intravitreal chemotherapy) differ primarily in their toxicity profile. The side-effects associated with external beam radiation therapy and intravenous chemotherapy have played a significant role in advocating for local treatment strategies. A full understanding of the toxicity profile associated with intra-arterial chemotherapy (IAC) is critical as the acceptance and utilization of this modality increase among centers worldwide.

As with any new therapy, the learning curve associated with its application has the potential to impact reported and observed complication rates. Retrospective studies have been limited in their ability to report specific complication rates. Nonetheless, excellent review articles have attempted to collate and estimate the toxicity profile associated with IAC in the management of retinoblastoma.

Overall, the toxicities associated with this modality are best classified as local (globe and periocular structures) versus systemic (CNS and distant) effects.

Local Toxicity

Ocular (globe) toxicity

Vascular complications, including vascular occlusion and choroidal ischemia, are among the most common findings in eyes treated with IAC. Optic atrophy and vitreous hemorrhage have also been described. Careful attention by the interventional radiologist to avoid wedge flow and to ensure uniform pulsatile administration of chemotherapy is thought to reduce these complications. The presence of birefringent material in enucleated specimens is a new pathologic feature not seen prior to application of IAC. There is debate among experts whether this represents cotton fibers or crystalline deposits of the administered agents. Regardless, filtering the drugs and administering them in a timely fashion after compounding appears to mitigate this toxicity. Retinal detachment and phthisis are serious complications with increased likelihood of poor visual outcome and secondary enucleation. One group has suggested reduced axial length in eyes treated with IAC. Animal primate models have also demonstrated toxicity to the vascular endothelium following the administration of melphalan. The long-term implications of these findings in children remains unclear. Of note, few studies have looked at long-term visual outcomes and secondary related risks of amblyopia and strabismus.

Periocular/orbital toxicity

Significant periocular edema and cellulitis can occur following IAC administration. These cases can be treated with steroids. Some centers use periocular vasoconstrictors to reduce this risk. Secondary lash loss, ptosis, and motility abnormalities have all been described as well. Accessory lacrimal vasculature is likely to play a role in the amount of chemotherapy administered to the periocular structures, including the orbit and lid. Specific chemotherapeutic agents (such as high-dose carboplatin) may have a greater likelihood of causing these complications.

Distant (Non-ocular) Toxicity

CNS toxicity

Vasospasm is a common occurrence and one that should be anticipated by the interventional radiologist. Strokes and transient neurologic deficits have now been described by multiple centers and are fortunately a rare occurrence. Some experts have advocated screening patients at high risk for embolic phenomena, including sickle cell and hypercoagulable states. At present it is unclear how transient hypoxia associated with vasospasm or downstream administration of chemotherapy to the CNS impacts these patients neuro-developmentally.

IAC necessitates the use of fluoroscopy and thereby exposes all children to radiation. Although studies suggest that the amount of radiation exposure is low, patients with atypical vascularization requiring nontraditional approaches are more likely to be exposed to longer fluoroscopy times and increased radiation doses. It is unclear how even low-dose radiation will impact second tumor risk in this cohort, particularly children less than 1 year of age. Historically, most experts advocated against any radiation exposure during this critical developmental period, including avoidance of CT scans.

Systemic and distant toxicity

Although IAC is locally administered, it is well recognized that this approach is associated with fever and neutropenia in a small but considerable cohort. These findings demonstrate that despite local administration these agents are absorbed systemically and impact the bone marrow. Melphalan in particular is a highly toxic drug with significant impact on bone marrow myelosuppression.

While not a toxicity per se, many experts have raised the concern that locally administered chemotherapy does not provide systemic prophylaxis against metastasis to patients with eyes harboring high-risk histopathologic features. Data from limited studies demonstrate that a small number of children treated with IAC developed distant metastases, some of whom were cured with high-dose chemotherapy.

Conclusions

IAC is increasingly recognized as an effective modality in treating various stages of retinoblastoma. One of the main drivers in advancing this technique was to avoid enucleation and minimize toxicities associated with other treatment strategies. A thorough understanding of the toxicities and complications associated with this approach is critical if we are to integrate this treatment strategy with others that are long established. As with external
beam radiation and intravenous chemotherapy, long-term toxicity, particularly in high-risk cohorts, will ultimately impact the continued use of this technique in the future.

**Selected Readings**


Pathology: Evisceration and Enucleation Disasters

Ralph C Eagle Jr MD

Inadvertent Evisceration of Eyes With Unrecognized Intraocular Tumors

Today, an increasing number of blind painful eyes are being eviscerated instead of enucleated. Major reasons for this therapeutic modification include better cosmesis after evisceration and a reassessment of the risk of a sympathetic uveitis after evisceration. In many instances, patients with blind painful eyes are referred to oculoplastic surgeons who may perform evisceration without working-up the patient to exclude an occult tumor. It must be remembered that prior to the availability of modern imaging techniques, pathologic examination disclosed intraocular tumors, usually malignant melanomas, in approximately 10% of enucleated blind painful eyes with opaque media. This incidence has remarkably decreased in recent years, but neoplastic surprises are still encountered. Admittedly, most ophthalmic pathologists have never seen a case of sympathetic uveitis following evisceration, but many have seen one or more eyes with unsuspected uveal melanomas that have been inadvertently eviscerated.

Necrosis-related inflammation can confound the clinical diagnosis of occult lesions; patients with necrotic tumors have been misdiagnosed as having endophthalmitis, orbital cellulitis, or orbital pseudotumor. The failure of largely necrotic tumors to enhance on imaging studies may be a factor in misdiagnosis. The presence of a malignant intraocular neoplasm should be excluded prior to evisceration of a blind or blind painful eye. B-scan ultrasonography is recommended for screening. Evisceration of an eye with retinoblastoma usually has fatal consequences, but the effect on the prognosis of patients with melanoma is less clear since many cases are thought to have metastasized before they are evaluated by ophthalmologists. Despite this, physicians who inadvertently eviscerate an eye containing a uveal melanoma, a neoplasm that carries a 50% lifetime risk of metastasis, are at risk to be found liable medicolegally for failure to diagnose or offer effective treatment options if the patient subsequently develops metastasis.

Inadvertent Implantation of Tube Shunts in Glaucomatous Eyes With Unrecognized Intraocular Tumors

Intraocular tumors are well-recognized causes of secondary glaucoma. Common mechanisms of tumor-related glaucoma include infiltration and blockage of aqueous outflow pathways by tumor cells, neovascular glaucoma, anterior displacement of the lens-iris diaphragm in eyes with total retinal detachments, and blockage of the trabecular meshwork by macrophages that have ingested necrotic tumor. Cases of inadvertent tube shunt implantation in glaucomatous eyes with occult neoplasms have been reported in adults with ciliochoroidal or diffuse iris melanomas and children with unsuspected ciliary body medulloepitheliomas who developed neovascular glaucoma. In some instances, tumor cells were found in the tube shunt’s extraocular reservoir.

The possibility of an intraocular tumor should always be considered in an eye with unilateral glaucoma. Such glaucomatous eyes should be carefully evaluated for an occult intraocular tumor, particularly medulloepithelioma or uveal melanoma, before proceeding with tube shunt surgery. In suspicious cases, surgery may be deferred until an ocular oncology consultation is obtained and an intraocular tumor is excluded. Aqueous tube shunts can provide an avenue for extraocular tumor extension. A child with neovascular glaucoma has an intraocular tumor until proven otherwise. The incidence of neovascular glaucoma in eyes with ciliary body medulloepitheliomas and retinoblastoma are 47% and 26%, respectively.

Selected Readings

2016 Advocating for Patients

Zelia M Correa MD PhD

Ophthalmology’s goal to protect sight and empower lives requires active participation with and commitment to advocacy efforts. Contributions to the following three critical funds by all ophthalmologists is part of that commitment:

1. OPHTHPAC® Fund
2. Surgical Scope Fund (SSF)
3. State Eye PAC

Your ophthalmologist colleagues serving on Academy committees—the Surgical Scope Fund Committee, the Secretariat for State Affairs, and the OPHTHPAC Committee—are dedicating significant time to advocating for patients and the profession. 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. The Secretariat for State Affairs is collaborating closely with state ophthalmology society leaders to protect Surgery by Surgeons at the state level. Both groups require robust funds from both the Surgical Scope Fund and the OPHTHPAC Fund in order to protect quality patient care.

These committed ophthalmologists serving on your behalf have a simple message to convey: “It takes the entire community of ophthalmologists” to be effective.

- We need each member of the ophthalmology community to contribute to each of these 3 funds.
- We need each member of the ophthalmology community to establish relationships with state and federal legislators.
- We need each member of the ophthalmology community to make a commitment to protect quality patient eye care and the profession.

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 as well as 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. As one election cycle ends, a new one starts. OPHTHPAC is always under financial pressure to support our incumbent friends as well as to make new friends with candidates. These relationships allow us to have a seat at the table and legislators willing to work on issues important to us and our patients.

For the past year, the media and the country have focused on the U.S. presidential primaries. But the races most important to ophthalmology involve seats in Congress. The entire House of Representatives and one-third of the Senate is up for election. Several physicians need our help—and we have many new friends to make.

In order for ophthalmology to remain seated at the table, we need to be heavily invested in this year’s election. That takes investment by each member of the ophthalmology community, whether with time or money. Currently, only a minority of ophthalmologists have realized the vital importance of contributing to OPHTHPAC and the other funds. Right now, major transformations are taking place in health care and we need participation from the majority of ophthalmologists so that we have the resources to better our profession and ensure quality eye care for our patients.

Among the significant impacts made by OPHTHPAC are the following:

- Repealed the flawed Sustainable Growth Rate (SGR) formula
- Blocked the unbundling of Medicare global surgery payments
- Removed a provision in Medicare fraud and abuse legislation that targeted eyelid surgery
- Working to reduce the burdens from Medicare’s existing quality improvement programs, such as the EHR Meaningful Use program
- Working in collaboration with subspecialty societies to preserve access to compounded and repackaged drugs such as Avastin
- Working to get the Centers for Medicare and Medicaid Services to revisit drastic Medicare fee cuts to glaucoma and retinal detachment surgeries
- Working to protect your ability to perform in-office ancillary services in your office

Contributions to OPHTHPAC can be made here at AAO 2016 or online at www.aao.org/ophthpac.

 Leaders of the American Association of Ophthalmic Oncologists (AAOOP) are part of the American Academy of Ophthalmology’s Ophthalmic Advocacy Leadership Group (OALG), which has met for the past nine years in January in the Washington, DC, area to provide critical input and to discuss and collaborate on the Academy’s advocacy agenda. The topics discussed in the 2016 OALG agenda included the impact of the Medicare Access and the CHIP Reauthorization Act (MACRA); the IRIS Registry and quality reporting under Medicare; data transparency and public reporting, and a roundtable to discuss challenges for surgical specialties. At Mid-Year Forum 2016, the Academy and AAOOP ensured a strong presence of ophthalmic oncologists and pathologists to support our priorities, and a record number of 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 (SSF)

The Surgical Scope Fund (SSF) provides grants to state ophthalmology societies to support their legislative, regulatory, and public education efforts to derail optometric surgery proposals that pose a threat to patient safety, quality of surgical care, and surgical standards. Since its inception, the Surgery by Surgeons campaign—in partnership with state ophthalmology societies
Advocating for Patients

and with support from the SSF—has helped 32 state / territorial ophthalmology societies reject optometric scope of practice expansion into surgery.

In 2016, thanks to Surgical Scope Fund support by Academy members and tireless advocacy by state ophthalmology society leaders, ophthalmology continues to champion surgical safety at state capitols across the country. State ophthalmological societies and the Academy’s Secretariat for State Affairs faced eight concurrent Surgery by Surgeons battles, in Alaska, California, Delaware, Illinois, Iowa, Massachusetts, Pennsylvania, and Puerto Rico.

In each of these legislative battles, the benefits from Surgical Scope Fund distributions are crystal clear. The fund has allowed for successful implementation of patient safety advocacy campaigns, which result in defeating attempts by optometry to expand their scope of practice to include surgery.

The Academy relies not only on the financial contributions to the Surgical Scope Fund from individual ophthalmologists and their practices, but also on the contributions made by ophthalmic state, subspecialty, and specialized interest societies. The Academy counts on AAOOP’s contribution in 2016.

Contributions to the SSF can be made here at AAO 2016 or online at www.aao.org/ssf.

State Eye PAC

It is also important for all ophthalmologists to support their respective State Eye PACs because PAC contributions to legislators at the state level must come from individual ophthalmologists and cannot come from the Academy, OPHTHPAC, or the Surgical Scope Fund. 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 PATIENTS

Academy Surgical Scope Fund contributions are used to support the infrastructure necessary in state legislative / regulatory battles and for public education. PAC contributions are necessary at the state and federal level to help elect officials who will support the interests of our patients. Contributions to each of these funds are necessary and help us protect sight and empower lives. Surgical Scope Fund 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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Sildenafil Citrate (Viagra) for Lymphatic Malformations

Mary O’Hara MD

I. Types of Lymphatic Malformations (LM)
   A. Macrocystic
   B. Microcystic
   C. Mixed

II. Proposed Mechanism of Action of Sildenafil on LM
    Phosphodiesterase E selective inhibitor
    A. Smooth muscle relaxation
    B. Cyst decompression

III. Treatment Results to Date
    A. Not uniformly effective
    B. More effective on mixed or macrocystic LM
    C. Effect may be related to duration of treatment.
    D. Treatment with other interventions such as sclerotherapy does not diminish effect.

IV. Presentation of Long-term Follow-up on 2 Orbital LM Treated With Viagra

Selected Readings

Sclerosing Therapy for Lymphatic Malformations

Kenneth Cahill MD FACS, James Murakami MD, William Shiels DO (1954–2015), Jill Foster MD, Cameron Nabavi MD, Daniel Straka MD

This paper is presented regarding an institutional review entity–approved study of intralesional treatment of venolymphatic malformations at Nationwide Children’s Hospital in Columbus, Ohio.

The diagnosis of venolymphatic malformations is usually based upon clinical and radiological characteristics. Histopathology is only infrequently obtained. Affected patients usually have the onset of symptoms before the age of 20 years. There is typically an acute expansion(s). In this presentation, we are particularly interested in the periocular involvement of eyelids, conjunctiva, orbit, and face. CNS and other body parts can also be affected. Radiologically, there are typically thin-walled fluid-filled cysts ranging from micro (4 mm) to macro (> 1 cm) in size. They can be solitary or numerous. Frequently, they will exhibit layers associated with blood degradation products. Thick fibrotic tissue can occur, especially with chronic lesions.

The treatment can consist of observation or emergent aspiration when vision and/or the cornea are at risk. Intralesional sclerotherapy has been shown to be effective. Some systemic medications show promise and are being actively studied.

For sclerotherapy, there is no single agent or single treatment protocol that works for all lesions. Bleomycin in concentrations of 1-2 mg/mL is the most frequently used sclerosing agent. Of the agents that we use, it seems to cause the least amount of swelling and inflammation. When used in relatively low doses, its risks of pulmonary fibrosis and skin hyperpigmentation are diminished. It is used as a foam prepared with 25% human serum albumin (HAS) and administered with real-time ultrasound. Direct observation is used for the conjunctival lesions. This is not used for macrocysts.

Doxycycline can be used in concentrations of 10 mg/mL mixed with 25% HAS. More concentrated doses are not used because of the increased tissue inflammation. Despite this, doxycycline still causes more inflammation and swelling than bleomycin. For this reason, it is typically not chosen for deeper orbital lesions or subconjunctival cysts. It is primarily used for small to medium-sized cysts in the eyelids, especially if bleomycin has not been effective. Doxycycline has been shown to disrupt the VEGF pathway.

Dehydrated ethanol is used following the instillation of sodium tetradecyl sulfate (STS). The ethanol is very caustic, so we use it only in macrocysts in which an indwelling flexible pigtail catheter can be placed to facilitate steps of the treatment and to provide post-treatment drainage of the effusion fluids for 48 hours. Due to the potential for severe tissue damage caused by ethanol, the procedure is performed under fluoroscopy to make sure that no leakage occurs.

The review of our first 20 patients showed efficacy, low incidence of complications, frequent need for multiple treatments to minimize treatment swelling and to maximize the obliteration of cysts, and an apparent decrease in the risk of recurrent “rebleeds.” We are now reviewing our first 80 treated patients, who all have follow-up over 1 year, up to 13 years.

Systemic treatment with sildenafil and sirolimus as systemic or as medical treatments is being studied. Both of these medications do have side effects and need to be monitored. Their beneficial effect may be partially lost upon discontinuation. Hopefully, treatment trials of these medications will result in more treatment options, either as independent agents or as adjunct to sclerotherapy. Hopefully, these trials will also enable us to learn more about the nature of lymphangiomas so that future treatments can more specifically control their specific properties.

Selected Readings


Coats Disease: What Works

G Baker Hubbard MD

Coats disease is an idiopathic retinal vascular disease that typically affects young males. Characteristic retinal lesions include vascular telangiectasias and dilated aneurysmal vessels along with patches of avascular retina. These lesions are visible with indirect ophthalmoscopy, but the full extent of vascular abnormality is best seen by wide-angle fluorescein angiography (FA). The vascular lesions cause exudation that leads to progressive accumulation of yellow deposits, exudative retinal detachment, and fibrosis, which in turn cause vision loss or blindness. The goal of treatment is to reduce leakage by ablating the retinal vascular lesions or by pharmacologically modulating leakage from these lesions. Various techniques and agents have been described to achieve this goal.

Cryotherapy has been used for decades as an effective means of ablating the retinal vascular lesions of Coats disease. Cryotherapy has the advantage of being effective even when there is shallow subretinal fluid under the vascular lesions because the ice ball from the cryo probe can traverse shallow fluid and still freeze the vascular lesions. After a double freeze-thaw, vascular lesions reliably respond and stop leaking over a period of 1-2 months.

There are 2 main disadvantages of cryotherapy. One is that sometimes the vascular lesions are not accessible with a cryo probe. This is true when there is bullous subretinal fluid present or when the vascular lesions are located on top of subretinal fibrosis or thick accumulations of exudate. A second disadvantage is that the requisite heavy freezing can be inflammatory and can cause significant discomfort. As a result of the inflammatory effects, temporary worsening of exudation immediately after cryotherapy is common.

Laser has also been used to ablate retinal vascular lesions in Coats, and laser indirect ophthalmoscopes (LIOs) are now widely available in operating rooms. Wavelength of laser matters for Coats disease. Infrared 810-nm lasers commonly used to treat retinoblastoma and ROP in pediatric operating rooms are not effective for Coats because there is virtually no uptake of infrared energy by vascular lesions. The lack of uptake by vascularized structures is a major advantage for infrared lasers in treating ROP because there is no uptake by the perfused tunica vasculosa lentis and the risk of cataract is minimized. For Coats, however, uptake in the vascular lesions is the goal. Optimum uptake in vascular tissue is achieved with wavelengths in the yellow spectrum and yellow wavelength 577-nm LIOs are now available.

Intravitreal injections of steroids and more recently anti-VEGF agents have been reported to pharmacologically modulate the leakage associated with Coats disease. The rationale has been to reduce leakage to facilitate ablative treatment with cryotherapy or laser. Extensive experience with other exudative retinal vascular diseases (AMD, branch and central retinal vein occlusion, diabetic macular edema) has proven these agents to be effective. In Coats, however, results are mixed in comparison to the other diseases. Intravitreal steroids when used with cryotherapy may induce a “crunch” phenomenon with resulting rhegmatogenous detachment. Anti-VEGF results in Coats have been generally good but not as strikingly beneficial as with other retinal vascular diseases.

Advanced vitreoretinal techniques have been reported for Coats disease to drain subretinal fluid and to alleviate traction caused by organized vitreous and subretinal fibrosis. Techniques have included scleral buckling, vitrectomy, membrane peeling, internal or external drainage, and tamponade using oil or gas. Some have advocated for multimodal treatment using anti-VEGF, laser ablation, and vitreoretinal surgery for advanced cases.

We recently reported good results of treating Coats disease with FA-guided yellow (577-nm) LIO as monotherapy. Our protocol uses yellow LIO to “paint” all visible telangiectasias. Uptake with yellow laser can be achieved in the vascular lesion even when bullously detached. After resolution of exudative retinal detachment, we treat areas of nonperfusion with scatter laser treatment. The procedure is repeated every 3-4 months until all vascular lesions are ablated. Mild cases are treated in 1-2 sessions, and severe cases are treated in 3-4 sessions. In our series, even patients with bullous retinal detachment and highly detached vascular lesions were successfully treated with laser alone. Similar results have also been achieved with green 532-nm laser for Coats.

Laser monotherapy offers several advantages over treatment protocols that employ multiple treatment modalities. One, fewer examinations under anesthesia (EUAs) are required, and the patient is thereby spared of additional risk and expense associated with the EUAs required to deliver monthly injections of anti-VEGF in young children. Two, the technique is noninvasive, and risk of inadvertent injection or incision in a patient who may harbor occult retinoblastoma is avoided. Three, the noninvasive nature of the treatment is also preferable because of the limited visual potential for most eyes with Coats. The majority of eyes with advanced Coats, for which invasive vitreoretinal surgical techniques may be considered, have dense amblyopia that would severely limit vision even if normal anatomy could be promptly restored. Such cases generally have long-standing exudative retinal detachment with substantial accumulation of yellow exudate or fibrosis in the macula. As a result, the recovery time, expense, risk, and emotional investment of family members associated with major vitreoretinal surgery are not likely to be rewarded with outcomes that match expectation in most cases. This is especially true when there is a noninvasive treatment option available that can yield equivalent results.

To summarize, multiple modalities have been described to treat Coats disease. Advanced cases with bullous retinal detachment have a limited prognosis for good vision regardless of treatment. Our approach of laser monotherapy has achieved excellent results even with bullous retinal detachment. Laser monotherapy offers a noninvasive, low-risk, and cost-effective option for most cases of Coats disease. Rare cases may benefit from anti-VEGF injections or intervention with advanced vitreoretinal techniques.
References


Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by hamartomas in multiple organ systems caused by mutations in the TSC1 or TSC2 genes.\(^1\) The TSC1 and TSC2 genes are involved in integration of growth signals and nutrient inputs to downregulate mammalian target of rapamycin (mTOR), which controls cell growth and cell survival.\(^2\)

Aside from debilitating systemic manifestations (commonly in the CNS, kidney, heart, and lung), retinal astrocytic hamartomas (RAHs) are the most commonly noted ocular findings in TSC, occurring in approximately 50% of patients with TSC. When seen in association with TSC, RAHs are typically relatively stationary.

Treatments have been directed toward reducing growth and fluid exudation in RAH with numerous local therapies including photodynamic therapy, transpupillary thermotherapy (TTT), intravitreal anti-VEGF medications, and intravitreal steroids. However, a subset of patients with TSC has been described in whom aggressive behavior of RAHs leads to severe ocular complications, including vitreous tumor seeding, macular edema, exudative retinal detachment, and neovascular glaucoma. These patients tend to be young children, with onset often before the age of 5 years, ultimately requiring enucleation for a blind, painful eye.\(^3\)

TSC presents a unique opportunity to apply targeted drug therapies to a complex systemic disease. The TSC1 and TSC2 gene products form a complex, sensing the presence of nutrients, growth factors, and energy. The TSC1 / TSC2 complex down-regulates mTOR complex activation (mTORC1 and mTORC2) through the intermediary RHEB (Ras homolog enriched in brain). In the absence of TSC1 / TSC2 complex function, constitutive activation of mTORC1 occurs, leading to increased protein synthesis and decreased catabolic processes, such as autophagy. This imbalance of anabolic and catabolic processes results in a cell-growth advantage over surrounding cells, leading to development of hamartomatous lesions.

Further understanding of TOR-driven development of hamartomatous lesions in TSC has led to the study of rapamycin (sirolimus) and its analogs (everolimus, temsirolimus, and ridaforolimus) for the systemic treatment of TSC. Everolimus use has meaningfully reduced subependymal giant-cell astrocystoma volume in children with TSC in the Phase 3 EXIST-1 trial with secondary modification of other disease sites.\(^4\)

It may be inferred that systemic mTOR inhibition may impact ocular manifestations of TSC, including RAH. Zhang et al from Peking Union Medical College Hospital studied the impact of systemic oral sirolimus on RAH in a cohort of 7 TSC patients already being treated for systemic complications of the disease. All lesions improved in thickness, and there was no increase in lesion size. There was an average reduction of 13.9% after a mean treatment duration of 7.9 months.\(^5\)

An interventional case report presentation will outline impact of systemic mTOR inhibition with everolimus on an aggressive RAH and future therapeutic directions in this disease.

References


Vismodegib is sonic hedgehog pathway inhibitor that was first studied in humans in 2008 and was approved by the U.S. Food and Drug Administration (FDA) for treatment of metastatic and locally advanced basal cell carcinoma in January 2012. Since the identification of vismodegib, multiple small molecule inhibitors of the hedgehog pathway have been developed, and one additional drug, sonidegib, has also been approved by the FDA with indications similar to those of vismodegib.

Several small series have demonstrated promising results with the use of vismodegib in patients with large tumors of the orbit and periorbital region. Of particular interest is the use of vismodegib as a method of chemoreduction in the neoadjuvant setting prior to surgical resection, although this latter indication is considered off-label use. Several recent cases of locally advanced periorbital and orbital lesions not amenable to eye-preserving surgery or radiation that have been successfully managed with sonic hedgehog pathway inhibition using vismodegib will be highlighted in this presentation. The usual side-effect profile, as well as timing of surgery and typical duration of treatment prior to surgery, will also be discussed through illustrative cases and review of published literature.
Update on Orbital Xanthogranuloma Diseases: Role of BRAF Inhibition

Hakan Demirci MD

This heterogeneous group of rare orbital and ocular adnexal disorders are classified as class II non-Langerhans histiocytic proliferations. Classified into 4 subtypes:

1. Adult-onset xanthogranuloma: Any age from 17 to 85 years
   - No gender preference
   - Bilateral, yellow-orange, elevated, indurated, and nonulcerated xanthomatous eyelids and anterior orbit lesions
   - Good prognosis without systemic findings

2. Necrobiotic xanthogranuloma: Any age from 20 to 85 years
   - No gender preference
   - Indurated papule, nodule, or plaque that is violaceous, red-orange, or xanthgranulomatous in color
   - Involves periocular region (bilateral or unilateral), with other parts of the face, trunk, and extremities

3. Erdheim-Chester disease: Any age from 7 to 84 years
   - Male to female: 2:1
   - Xanthoma-like lesions of eyelids, orbital disease with exophthalmos, involvement of internal organs, including heart, lungs, retroperitoneum, and bone
   - Bone pain and associated systemic symptoms including fever, weakness, weight loss, and night sweats

4. Adult-onset asthma and periocular xanthogranuloma: Any age from 22 to 74 years
   - No gender preference
   - Bilateral, yellow-orange, elevated, indurated eyelid and orbital lesions
   - Associated asthma in patients with sinus histiocytosis and massive lymphadenopathy

Systemic Associations

- Necrobiotic xanthogranuloma is associated with plasma cell dyscrasias (paraproteinemia, monoclonal gammopathy, Waldenstrom macroglobulenia, plasmacytoma, multiple myeloma).
- In Erdheim-Chester disease, bony lesions including bilateral symmetric osteosclerosis involving metaphyseal and diaphyseal regions, with sparing epiphyses, are pathognomonic. Obstructive renal impairment, neurologic manifestations due to CNS involvement, and cardiac, pulmonary, liver, spleen, and skin involvement are the other signs.
- Adult-onset asthma and periocular xanthogranuloma are frequently associated with lymphadenopathy, paraproteinemica, and rarely hematologic malignancies including chronic lymphocytic leukemia, multiple myeloma, and small lymphocytic lymphoma.

Ethiopathogenesis

The ethiopathogenesis of xanthogranulomatous disorders is unknown. In the literature, 2 cases with juvenile xanthogranuloma have been reported to be associated with cytomegalovirus. Reported chromosomal instabilities in juvenile xanthogranuloma suggest a basic genetic defect or evidence of a cellular response to an environmental agent such as cytomegalovirus. Similarly, the association of necrobiotic xanthogranuloma and paraproteinemia suggests that paraproteinemia could be the primary inciting factor or a cofactor that facilitates in eliciting the characteristic giant cell granulomatous reaction.

Recent studies uncovered a complex network of cytokines that are involved in the disease process of Erdheim-Chester disease. A unique inflammatory cytokine signature is characterized by elevated levels of interferon-α, interleukin-12, and monocyte chemotactic protein-1 and decreased levels of interleukin-4 and interleukin-7. Interleukin-1 and interleukin-6 were also strongly expressed in biopsies obtained from patients with Erdheim-Chester disease. It is proposed that the production of cytokines by histiocytes and associated lymphoid infiltrate contribute to an inflammatory milieu with resultant tissue damage and organ dysfunction. The question of whether the Erdheim-Chester disease process is clonally driven or a reactive phenomenon was previously debated. In a study from France, 13 of 24 Erdheim-Chester disease patients (57%) showed the pathogenic gain-of-function V600E mutation in the BRAF proto-oncogene. The V600E mutation ratio varies from 13% to 100% of patients in different series. As the sensitive techniques are applied, BRAFV600E mutation is constantly detected in biopsies and in circulating monocytes from Erdheim-Chester disease, demonstrating that Erdheim-Chester disease is a clonal disease. BRAFV600E mutation has been associated with oncogene-induced senescence, a major protective mechanism against oncogenic events. In oncogene-induced senescence, the activating mutation of a specific oncogene without additional cooperating mutations leads to cell cycle arrest and induction of proinflammatory molecules. Oncogene-induced senescence has been linked to the induction of the senescence-associated secretory phenotype, a proinflammatory pattern characterized by the same chemokines and cytokines expressed by Erdheim-Chester disease histiocytes. So, oncogene-induced senescence seems to play a central role in Erdheim-Chester pathogenesis, as it is able to integrate the oncogene mutation and the observed inflammatory activation. However, this mutation was not observed in the other xanthogranulomas. V600E mutations in BRAF proto-oncogene was observed in 40% of patients with Langerhans cell histiocytosis, suggesting a common origin of these diseases.

Treatment

In adult-onset xanthogranulomatosis, systemic corticosteroid can be started with 1 mg/kg per day with tapering as the lesions abate. Local steroid injections have been used successfully for eyelid and orbital lesions. Methotrexate was used as corticosteroid-sparing therapy; however, it is not certain that it can be a
first-line therapy. The role of low-dose radiotherapy in the treatment of xanthogranulomatous disorder is controversial.

In Erdheim-Chester disease, systemic corticosteroid, low-dose radiotherapy, and chemotherapy, including cyclophosphamide, doxorubicin, and vincristine, and autologous hematopoietic stem cells were treatment choices used with limited clinical efficacy. Since the first report of its efficacy in 2005, interferon-α became the first line during the management of Erdheim-Chester disease. Depending on the severity of the disease, a dose of 3 million units to 9 million units 3 times/week was used with a significant overall survival compared to the other therapies. The optimal dose and schedule have not been established yet. After the identification of a complex chemokine-cytokine network, IL-1R antagonist anakinra, infliximab, an anti-TNFα monoclonal antibody, and monoclonal antibody against the IL-6 receptor has been used. With the recent discovery of BRAF^V600E^ mutation, BRAF inhibitor vemurafenib has been used in the management of Erdheim-Chester disease. So far, all patients have had an extremely positive and persistent response. The duration of therapy and the long-term outcome are still unclear.

References


What Pathology Biomarkers Should We Use for Conjunctival Tumors?

Victor M Elner PhD MD
What Pathology Biomarkers Should We Use for Skin and Orbital Tumors?

Tatyana Milman MD

I. Vascular and Lymphatic Lesions
   A. Infantile hemangioma, cavernous hemangioma (encapsulated cavernous venous lesion, cavernous venous malformation), lymphangioma (lymphatic venous malformation), and other vascular malformations
   B. The role of GLUT-1, ERG, CD31, FXIII, and D2-40

II. Fibrocytic Lesions
   A. Solitary fibrous tumor: the role of STAT-6
   B. Nodular fasciitis: the role of USP6
   C. Dermatofibrosarcoma protuberans: the role of COL1A/PDGFB rearrangement studies

III. Tumors With Muscle Differentiation
   A. Rhabdomyosarcoma: the role of desmin, myogenin, and t(2;13)(q35;q14): PAX3-FOXO1, PAX7-FOXO1

IV. Tumors With Adipocytic Differentiation
   A. Spindle cell/pleomorphic lipoma: the role of CD34 and RB1
   B. Liposarcoma: the role of MDM2 and CDK4

V. Epithelial Tumors of Lacrimal Gland
   A. Pleomorphic adenoma / adenocarcinoma ex pleomorphic adenoma: the role of 8q12 / PLAG1 studies
   B. Adenoid cystic carcinoma: the role of MYB-NFIB studies
   C. Mucoepidermoid carcinoma: the role of MECT-MAML studies

VI. Lymphoproliferative Orbital Lesions
   A. DLBCL: The role of MYD88, MYC, EBER, and CD30

VII. Metastases
   A. The role of GATA-3, PSMA, NKX3.1, and napsin A in metastatic carcinomas
VEGF Receptors on Orbital Vascular Tumors

Expression of Vascular Endothelial Growth Factors in Benign Vascular Lesions of the Orbit

Diva Regina Salomão MD, Elizabeth A Atchison MD, and James A Garrity MD

Introduction

Benign vascular lesions comprise a large number of mass-forming lesions in the orbit, varying from 9.5% to 24% of all orbital masses in large published case series. Although these lesions have no malignant potential, they can cause significant morbidity through compression and infiltration of crucial structures and interference with functional anatomy. Treatment has been usually observation or surgical excision. In this presentation, I will discuss the expression of the various vascular endothelial growth factor (VEGF) receptors in a series of these lesions, and the potential use of anti-VEGF agents as a nonsurgical alternative treatment for such lesions.

Results

A total of 55 specimens from 52 patients (38 female and 14 male; average age 40 years; range: 75 days – 90 years), all resected by a single surgeon, were included in our study. The lesions consisted of venous malformation (38), lymphatic malformation (7), lymphaticovenous malformation (6), and capillary hemangioma (4). Immunohistochemical stains were performed in all specimens for VEGF receptor (VEGFR; non-specific), VEGFR-1, VEGFR-2, and VEGFR-3. All lesions expressed VEGFR (27% focal and 73% diffuse). The majority of the lesions (94%) showed diffuse VEGFR-2 expression. Most lesions expressed VEGFR-3 (20% focal and 76% diffuse). However, the expression of VEGFR-1 was quite variable, with 45% of all lesions lacking expression for this receptor.

Conclusions

Most benign vascular lesions in the orbit in this series expressed VEGF receptors, particularly VEGFR2, suggesting that there may be a role for treatment of these lesions with anti-VEGF agents. Future prospective studies including larger numbers of cases are necessary to define the effectiveness of anti-VEGF agents in such patients.

Selected Readings

IgG4-related sclerosing disease is a recently recognized fibroinflammatory disease syndrome characterized by lymphocytolytic mass forming lesions in one or more tissues (usually exocrine organs), raised serum IgG4 levels, and increased IgG4 positive plasma cells in the involved tissues. The pancreas (autoimmune sclerosing pancreatitis) was the index organ described, but since then other sites including biliary tract, liver, lungs, retroperitoneum / mediastinum, kidney, breast, thyroid, prostate, lymph nodes, salivary gland, and lacrimal gland have all been reported. Histologically, a chronic inflammatory lymphocytolyticplasmic infiltrate includes numerous IgG4-positive plasma cells associated with CD4- or CD8-positive T-lymphocytes producing atrophy of normal tissue and sclerosis. Reactive lymphoid follicles are frequently present, and lymphomas have been seen. An obliterative phlebitis may also be present. A more recent consensus statement on the pathology of IgG4-related sclerosing disease emphasized that there are organ-specific diagnostic criteria in which histology is a key component. The two critical diagnostic features are a characteristic histopathological appearance (dense lymphocytolyticplasmic infiltrate, fibrosis often arranged in a storiform pattern, and obliterative fibrosis [not seen commonly in ophthalmic specimens]), along with an elevated number of IgG4 staining cells in the tissue, in terms of both absolute numbers and ratio of IgG4 to IgG staining cells.

The first reports of ocular adnexal involvement described lacrimal gland enlargement (dacryoadenitis), and one paper noted an association with lymphoma. Since then numerous reports have appeared in the literature with ocular adnexal disease. The clinical presentation typically resembles that of a lymphoma—namely, few symptoms and signs other than that of swelling or protrusion. Pain or an inflammatory presentation is unusual. Associated asthma is common. Radiographic features of 27 biopsy-proven cases revealed that extraocular muscle enlargement was the most frequent feature (24/27), which was typically bilateral (21/24), most commonly involved the lateral rectus muscle (41/54 orbits), and spared the tendon (26/27). The next most common feature was lacrimal gland enlargement, which was seen in 21/27 patients and was bilateral in 11/19. Enlargement of a lacrimal gland plus an extraocular muscle was seen in 16/27 patients. Orbital infiltrates were present in 12/27; infraorbital nerve enlargement, in 8/27; and 3/27 had intracranial (cavernous sinus) disease. Paranasal sinus disease was present in 24/27 patients. One important finding in patients with enlarged infraorbital nerves is retention of function in contradistinction to infraorbital nerves infiltrated with lymphoma or carcinoma that do lose their function. Biopsy specimens of the infraorbital nerve show infiltration of the peri- and epineurium with sparing of the endoneuron. Orbital biopsies are often reported as “reactive lymphoid hyperplasia” with fibrosis as described above. IgG4 staining in and of itself is not diagnostic, as other conditions are associated with IgG4 tissue staining, such as Castleman disease, granulomatosis with polyangiitis (formerly Wegener disease), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss), to name just a few. This emphasizes the critical appearance of the histologic picture as more important than the IgG4 staining of the tissue. Our evaluation of any patient with IgG4 disease includes an examination by a hematologist with imaging of the chest / abdomen / pelvis. Serum IgG4 levels are checked and are helpful if elevated but not diagnostic. Further investigation is directed by results of this evaluation.

In general, for any medical condition, treatment should be influenced by the natural history, which in IgG4-related disease is not known. Treatment is directed by the organs involved and the extent to which they are involved, with a goal of retaining function of the involved organ before it is replaced by fibrosis. Corticosteroids are first-line therapy, but relapses with dosage reductions or steroid dependency are common. Azathioprine and mycophenolate mofetil are effective steroid-sparing agents, but lymphocyte depletion with rituximab has been shown to be effective when other treatments fail. Asthma responds favorably to treatment with rituximab.

In summary, IgG4 related disease is a real phenomenon, but questions remain about its etiology, pathogenesis, and ultimate prognosis. What does this mean?

Selected Readings


Fine-Needle Aspiration Biopsy of the Orbit: What Works?
Richard C Allen MD PhD

I. History of Fine-Needle Aspiration Biopsy (FNAB) of the Orbit
A. Enthusiasm in the 1970s and early 80s
   1. Kennerdell et al, 1979
   2. Dubois et al, 1979
   3. Tarkkanen et al, 1982
   4. Dresner et al, 1983
B. Disparaging reports in the mid-80s
   2. Liu, 1985. Complications of fine-needle aspiration biopsy of the orbit
C. Enthusiasm persists in Europe and Asia
   2. Tijl and Koornneef, 1991
   4. Rastogi and Jain, 2001
   5. 75%-88% diagnostic accuracy reported.
D. FNAB in Stockholm
   1. Seregard and Tani
   2. Up to 99% successful diagnosis with the use of immunohistochemistry and flow cytometry

II. Concerns
A. Lymphoproliferative lesions
B. Inflammatory lesions
C. Cavernous hemangioma
D. Meningioma
E. Needle tract seeding

III. Advantage
   Less invasive

IV. Disadvantages
A. Less material
B. Need for an experience cytopathologist

V. Recent Study From Stockholm
A. 210 orbits from 2005 to 2013
   1. Diagnosis obtained in 176/210 orbits.
   2. FNA is more successful in anterior and palpable lesions.

3. Successful diagnosis is not dependent on the size, quadrant, or imaging appearance of the lesion.
4. In patients who underwent additional biopsy, the FNA diagnosis and excisional/incisional biopsy diagnosis corresponded in 87%.
5. Complications, none of which were significant, occurred in 6 patients.
B. Lymphoproliferative lesions: 23% underwent additional biopsy to aid in classification.
C. Inflammatory lesions: 48% underwent additional biopsy to aid in diagnosis.
D. Recommendations from the study
   1. Patients with anterior lesions that are thought to be inflammatory or lymphoproliferative should undergo an incisional biopsy with the patient awake.
   2. If the lesion is radiographically suggestive of a lesion that would best be treated with complete excision, FNA does not need to be performed.
   3. If the lesion is the in the posterior third of the orbit, FNA should not be done.
   4. All other lesions should be considered for FNA. Patients with suspected posterior inflammatory or lymphoproliferative lesions may need an additional biopsy.
   5. If the FNA gives normal cytology, an open biopsy should be considered.

References


How Can We Improve Ocular Oncology Care in Developing Nations?

Fairooz Puthiyapurayil Manjandavida MD
Day by Day Ocular Oncology in India

Santosh G Honavar MD

Introduction

The practice of ocular oncology involves diagnosis and management of tumors of the eyelid, ocular surface, intraocular structures, and orbit. The spectrum of clinical cases and the severity (and thus prognosis) varies from one geographic region to another. While basal cell carcinoma is the most common malignant eyelid tumor and melanoma is the predominant ocular surface and intraocular tumor in the West, these are relatively rare in the East. While Group D and E retinoblastoma comprise 20%-30% of new cases in the developed countries, over 75% of retinoblastoma in India present at an advanced stage. This presentation aims to highlight the clinical spectrum of cases that one encounters in India.

Observations

Among malignant tumors of the eyelid, sebaceous gland carcinoma is most common (50%-70%), followed by squamous cell carcinoma and basal cell carcinoma, and very rarely melanoma. Prognosis is excellent with excision with 4-mm clinically clear margins, intraoperative frozen section margin control, and conjunctival map biopsy when indicated. Sebaceous gland carcinoma often presents at an advanced stage, with primary orbital invasion and regional lymph node metastasis. We use chemoreduction in such situations to reduce the tumor bulk, following which local tumor excision often becomes feasible in cases that otherwise would have needed primary orbital exenteration.

Ocular surface squamous neoplasia is the most common malignant conjunctival tumor in India. Standard management includes surgical excision with 4-mm clinically clear margins with alcohol-assisted keratectomy for the corneal epithelial component and excision edge cryotherapy. The use of topical chemotherapy (mitomycin C) and topical or injectable immunotherapy (interferon alpha-2b) has now replaced surgery in several patients or has resulted in minimally invasive surgery for the residual tumor following optimal chemoreduction. The use of anterior segment imaging to evaluate the tumor base and plaque brachytherapy for tumors with scleral infiltration has helped improve the prognosis for eye salvage.

Retinoblastoma is the most common primary malignant intraocular tumor in India. A majority of patients present at an advanced stage, thus precluding the use of standard intravenous chemotherapy. We extensively use high-dose intravenous chemotherapy, intra-arterial chemotherapy, periocular chemotherapy, and intravitreal chemotherapy to optimize eye and vision salvage. Standardized enucleation with a long optic nerve stump, assessment of histopathological high-risk features, and adjuvant therapy as appropriate has become the standard of care. Successful use of multimodal treatment for orbital retinoblastoma has brought in a paradigm change. With these recent advances, we are able to save over 90% of the eyes overall, and to salvage life in 95% of children with retinoblastoma using cost-effective treatment protocols.

The prognosis has improved in certain difficult malignant tumors of the orbit, such as rhabdomyosarcoma and adenoid cystic carcinoma of the lacrimal gland, with the use of multimodal treatment protocol.

Day-by-day practice of ocular oncology in India is challenging yet interesting and provides scope for lateral thinking and customization of treatment modalities to improve life, eye, and vision salvage.
The First Eye Cancer Working Day in Paris: Outcomes

Paul T Finger MD for the Ophthalmic Oncology Task Force

I. Multicenter Tumor Registries
   A. Toronto: Uveal melanoma, retinoblastoma, vitreoretinal lymphoma, and conjunctival melanoma
   B. Houston: eyelid, orbital carcinoma
   C. Copenhagen: ocular adnexal lymphoma
   D. Mainstream ophthalmic oncology: American Joint Commission on Cancer (AJCC) / Union for International Cancer Control (UICC) staging
   E. Evidence-Based medicine, recurrence-based mortality. What is TNMH!

II. Retinoblastoma Specialists for Unserved Countries
   A. The Eye Cancer Foundation
   B. Princess Margaret Cancer Center
   C. Children’s Eye Cancer Foundation Germany KAKS
   D. International Council of Ophthalmology
   E. IRB World

III. Doctor-Reported Outcomes
   A. Literature-based self-reporting
   B. Web-based self-reporting
   C. Clinical guidelines
   D. EMR crawlers
   E. E-Cancer Care

IV. Open Access Surgical Textbook
   A. Best practice recommendations for:
      1. Generalists providing oncology care
      2. Specialists without access
   B. Opens dialog for sharing techniques that are not typically published

V. The Second International Working Day at the ISOO 2017
   A. Organizing Committee
   B. Outline
   C. What we need to do!

Selected Readings

Conjunctival Melanoma: How to Beat This Disease

Jill Razor Wells MD

I. Epidemiology
   A. Incidence is between 0.24 to 0.8 per million.
   B. Represents 2%-4% of ocular melanomas
   C. More common in fourth to seventh decades of life
   D. White to black ratio: 13.6 : 1

II. Risk Factors and Associated Diseases
   A. No clear evidence that ultraviolet radiation is a causative factor
   B. Two main precursors to melanoma are nevus and primary acquired melanosis (PAM) with atypia
      1. 17% of conjunctival melanomas associated with conjunctival nevus
      2. 71% of conjunctival melanomas associated with PAM with atypia
         a. Up to 50% of PAM with atypia cases can progress to melanoma, so this condition must be treated (see Figure 1).
         b. PAM without atypia is unlikely to progress to melanoma.
      3. Racial- or complexion-associated melanosis has no malignant potential.

III. Clinical Features
   A. Typically unilateral
   B. Thickened, raised, smooth pigmented lesion with dilated feeder vessels and surrounding areas of pigment (see Figure 2)
   C. May be amelanotic (see Figure 3)
   D. Most develop in the bulbar conjunctiva at the limbus but can be found in caruncle, plica, and palpebral conjunctiva. Worse prognosis if not on the bulbar conjunctiva.
IV. Diagnosis
A. Definitive diagnosis is made by histopathologic examination.
B. If conjunctival melanoma is suspected, do not perform an incisional biopsy.

V. Treatment
A. Standard of care is surgical excision with wide margins (at least 3 mm) using a “no touch” technique.
   1. Double freeze thaw cryotherapy to the margins and base at the time of surgery
   2. When deep limbal or scleral involvement is suspected, partial sclerectomy should be considered.
   3. If corneal involvement, alcohol epithelectomy should be performed.
B. PAM must be treated with excision and/or cryo as it can be the origin of recurrent melanoma.
C. Adjuvant therapy after excision
   1. Mitomycin C typically used by ocular oncologists for melanoma
      a. Never use as primary treatment
      b. Occlude punctum prior to starting drops
      c. Can cause limbal stem cell deficiency
   2. Interferon alpha-2b
      a. Drops are tolerated well.
      b. Only few reports in the literature
   3. Sentinel lymph node biopsy to detect metastases and provide opportunity to treat systemic disease
      a. Controversial with no consensus
      b. May be indicated for patients with ≥ 2 high-risk clinical and/or pathological features for nodal metastasis, including tumor thickness > 2 mm, nonlimbal location, histopathologic ulceration, and presence of > 1 mitotic figure
   4. Possibility of new biological therapies
      a. Genetic mutations identified in conjunctival melanoma include BRAF, KIT, and NRAS.
      b. Clinical studies may help identify medications targeting these pathways.

VI. Prognosis
A. Local recurrence
   1. Reported in 56%-65% of cases
2. Mean interval between treatment and recurrence is 2.5 years.
3. Risk factors for recurrence include treatment with excision alone and no adjuvant therapy, location other than limbus, positive surgical margins, and multifocal disease.
B. Metastatic disease and mortality
   1. Systemic metastases following surgical excision range from 11%-16% to 18-26% at 5 and 10 years.
   2. Metastatic disease can be found in the liver, lung, brain, and skin.
   3. According to the American Joint Commission on Cancer classification of conjunctival melanoma, 5- and 10-year estimates of melanoma-related death were 5%-23% and 14%-20%, respectively.
   4. Risk factors for mortality include thickness greater than 2 mm, de novo origin, nodular growth pattern, caruncular involvement, recurrence, and involvement of nonbulbar conjunctiva.

Selected Readings
Conjunctival Squamous Cell Carcinoma: Which Topical Therapy and Why?

Carol L Karp MD


Ocular surface squamous neoplasia (OSSN) encompasses a spectrum of epithelial squamous malignancies, ranging from dysplasia to invasive carcinoma. It represents the most common nonpigmented tumor of the ocular surface. Risk factors for this disease include human immunodeficiency virus (HIV),1,2 ultraviolet light exposure,3,4 exposure to petroleum products,5 heavy cigarette smoking,6 age,6 and male gender.6 Human papilloma virus (HPV) has also been implicated in the pathogenesis of OSSN, although its role remains controversial.7-11

Traditional treatment for OSSN involves excision alone with a no-touch technique, described by Shields.12 Despite the surgeon’s best efforts, there is likely microscopic disease beyond the edge of the clinically identified lesion, and the frequency of recurrence with excision alone has been reported to be as high as 56%.13 Even with clear margins on pathology specimens, recurrence with excision alone has been reported to be as high as 33%.13 As a result, adjuvant therapies are often performed with excision, including cryotherapy or topical chemotherapy, with reduction in the rates of recurrence.14-16

Extensive tumor excision can carry risks of limbal stem cell deficiency and symblephara formation. In order to potentially avoid these risks and treat the entire ocular surface, medical treatment alone has increased in popularity.15 This has allowed for treatment of the entire ocular surface, treating subclinical tumor load.

Chemotherapeutic agents used for treatment of OSSN include mitomycin C, 5-fluorouracil, and interferon-alpha 2b (IFNα2b), all of which have been shown to be effective.16-26

Our discussion today will evaluate the pros and cons of surgery vs. interferon, 5-fluorouracil, and mitomycin as therapy for OSSN.

References


Conjunctival Lymphoma: What Works

Sara E Lally MD

I. Lymphoid Tumors
   A. Range from benign reactive lymphoid hyperplasia to malignant lymphoma
   B. Difficult to differentiate them clinically
   C. Can occur in intraocular and periocular structures
   D. Conjunctiva is the area most commonly involved.

II. Etiology
   A. Infectious
   B. Autoimmune

III. Clinical Features
   “Salmon patch”: pink fleshy mass
   A. Likes to hide out in the fornices, must look carefully
   B. Incidence on the rise

IV. Diagnosing: Biopsy
   A. Incisional
   B. Excisional

V. Pathology: How to Send Specimen and What Study
   A. Mucosa-associated lymphoid tissue (MALT)
   B. Follicular
   C. Diffuse

VI. Workup
   A. American Joint Commission on Cancer classification / staging
   B. Systemic monitoring: unilateral vs. bilateral involvement

VII. Treatment
   A. Observation: Why not?
   B. Oral antibiotics: Does it work?
   C. Cryotherapy: Viable option?
   D. Complete excision: If possible?
   E. Radiation
      1. Types
      2. Doses
   F. Systemic therapy
      1. Immunotherapy: cd20 antibody
      2. Chemotherapy
   G. Intraluesional injection
      1. Interferon alpha-2b
      2. Rituximab

VIII. Pseudolymphoma
   A. Benign reactive lymphoid hyperplasia
   B. Amyloidosis
   C. Follicular conjunctivitis
   D. Drug induced
   E. Others
Vitreoretinal Lymphoma: How Can We Improve Outcomes?

Tero T Kivela MD
BAP-I Cancer Predisposition Syndrome

Colleen M Cebulla MD PhD

I. BAP1 Germline Mutation / BAP1-TPDS (OMIM 614327)

A. 2010: Uveal melanoma somatic mutation
   1. One germline case reported
   2. Harbour, et al. (Science, 2010)

B. 2011: Hereditary predisposition syndrome
   1. Uveal melanoma (UM) and other cancers: Abdel-Rahman, et al. (J Med Genet.)
   2. Cutaneous melanoma and atypical spitz tumors: Wiesner, et al. (Nat Genet.)
   3. Mesothelioma: Testa, et al. (Nat Genet.)

C. 2013
   1. Renal carcinoma: Popova, et al. (Am J Human Genet.)

II. Purpose
To provide an update on the hereditary BAP1-TPDS (OMIM 614327)

III. Comprehensive BAP1-TPDS Review

A. 57 families with 174 individuals with germline BAP1 mutation
B. Autosomal dominant with high penetrance (148/174, 88%)
C. 67 male (39%), 95 female (55%), 12 not reported
D. Younger median age cancer diagnosis; UM most common cancer

IV. Other Possible Cancers

V. 8 Major Cancer BAP1 Families

A. 56/57 families presented with 1 or more of 4 main cancers.
B. 1/57 with atypical spitz nevi and another cancer

VI. Tumor Aggressiveness

A. Increased for:
   1. Uveal melanoma
   2. Cutaneous melanoma
   3. Renal carcinoma
B. Decreased for: Mesothelioma

VII. Germline BAP1 in Young Patients with UM

VIII. Germline BAP1 in Familial UM

IX. Proposed Counseling Recommendations
Consider genetics referral / germline testing for BAP1 in patients who are or have:

A. Family members of germline mutation carriers
B. 2 or more BAP1 tumors in the patient / family
C. Exception for 2 cases of cutaneous melanoma—high-frequency gen population

X. Our Recommendations for GERMLINE BAP1-Positive Individuals and Families

A. Annual eye examination: age, 11 years (5 years younger than the earliest reported case of UM (Hoio, et al., 2013)
B. Referral pigmented ocular lesions to an ocular oncologist
C. Annual dermatological examination: age, 20 years (5 years younger than the earliest reported CM in BAP1 families; see Abdel-Rahman et al., 2011)
D. Consider VHL renal protocol imaging (MRI q2y) for renal disease and mesothelioma.

XI. Conclusions
A. Important hereditary cancer syndrome
B. Risk of UM and other tumors/cancers
C. Need for ocular oncology monitoring

XII. OSU Uveal Melanoma Genetics Study

A. Rob Pilarski: study coordinator
   1. Phone: 614.293.7774
   2. Robert.pilarski@osumc.edu
B. Dr. Cebulla: colleen.cebulla@osumc.edu

XIII. Uveal Melanoma Team at OSU

A. Ocular Oncology
   1. Colleen Cebulla
   2. Frederick Davidorf
B. Radiation Oncology
   1. Doug Martin
   2. Karl Haglund
   3. Allison Quick
C. Pathology
   1. Lynn Schoenfield
D. Cancer Genetics
   1. Robert Pilarski
   2. Mohamed Abdel-Rahman
   3. Karan Rai

E. Medical Oncology
   1. Thomas Olencki
   2. Kari Kendra
   3. Joanne Jeter

F. Surgical Oncology
   1. Hepatic perfusion/resection: Carl Schmidt

XIV. Acknowledgments
   A. Melanoma Know More Foundation
   B. American Cancer Society, IRG-67-003-47
   C. National Eye Institute, K08EY022672
   D. National Cancer Institute, R21CA191943
   E. Ohio Lions Eye Research Foundation
   F. Patti Blow Research Fund in Ophthalmology
   G. Ocular Melanoma Foundation
Future Applications of Uveal Melanoma Genetic Testing

J William Harbour MD
Systemic Melanoma Therapies that Work

Ivana K Kim MD

I. Unique Molecular Biology of Uveal Melanoma
   A. Frequent mutations in GNAQ and GNA11; resulting activation of downstream signaling pathways
      1. MAP kinase pathway
      2. PI3K / AKT / mTOR pathway
      3. YAP pathway
   B. Few other recurring mutations
      1. BAP1
      2. SF3B1
      3. EIF1AX

II. Targeted Therapies
   A. MEK inhibition
      1. Selumetinib
         a. Phase 2 study: selumetinib vs. chemotherapy
            i. Longer progression-free survival in selumetinib group (15.9 weeks vs. 7 weeks, HR = 0.46, \( P < .001 \))
            ii. No benefit for overall survival (11.8 months vs. 9.1 months, HR = 0.66, \( P = .09 \))
         b. Phase 3 study (SUMIT): selumetinib + dacarbazine vs. placebo + dacarbazine
            i. No benefit in progression-free survival (2.8 months vs. 1.8 months, HR = 0.78, \( P = .32 \))
      2. Others
   B. Other targets: PKC, PI3K, MET, mTOR, HDAC
   C. Combination strategies

III. Immunotherapies
   A. Checkpoint blockade
      1. CTLA-4
         a. Ipilimumab
            i. Median progression-free survival: 2.8-3.6 months
            ii. Median overall survival: 5.2-10.3 months
            iii. Responses + stable disease: 46% at 12 weeks, 28% at 23 weeks
         b. Tremelimumab
            i. Median progression-free survival: 2.9 months
            ii. Median overall survival: 12.8 months
            iii. No responses
      2. PD-1
         a. Pembrolizumab
            i. Single report: 8/10 patients evaluated for response; all patients previously treated with ipilimumab
            ii. Median progression-free survival: 18 weeks
            iii. Responses + stable disease: 50%
   B. Dendritic cell vaccination
      1. 14 patients
      2. Median overall survival: 19.2 months
      3. Stable disease in 10/14 at 3 months, 3/14 at 6 months

IV. Adjuvant Therapy
   A. No proven agent
   B. Both targeted agents and immunotherapy under investigation

References

Do I Use the American Joint Committee on Cancer Classification?

Alison Skalet MD PhD

The short answer: No, not routinely for clinical care. But I do think staging is important.

Staging is a basic tenet of cancer care designed to serve several purposes:

1. Document the extent of disease and facilitate clinical communication
2. Assist in determining appropriate treatment
3. Provide a measurement tool for gauging therapeutic response
4. Provide prognostic information
5. Facilitate exchange of data / research

Currently, staging using the American Joint Committee on Cancer (AJCC) system rarely dictates clinical care for uveal melanoma patients. The AJCC system is defined by the primary tumor (T), lymph node (N), and distant metastasis (M). Based upon these factors, a disease stage (0-IV) is determined. For uveal melanoma, tumor classification is based upon tumor size, location, and presence of extrascleral extension. Nodal involvement is exceedingly rare in uveal melanoma, and the vast majority of patients do not have overt metastatic disease at the time of diagnosis. Therefore, stratification for uveal melanoma patients based upon the seventh edition AJCC system is limited primarily to tumor features, but the system does not include information pertinent to ocular morbidity and ophthalmic treatment decisions. Similarly, therapeutic response to local treatment is not easily documented using the AJCC system. While presence of metastatic disease (stage IV) necessarily changes care, more aggressive therapy is not typically offered to patients with higher stage disease (ie, stage III). This may change in the future, with better therapeutic options and emerging adjuvant therapies.

Prognostication is an important consideration. The AJCC system has been validated in a large multicenter study to have prognostic value for metastasis-free survival. However, my preference is to use molecular prognostication when possible. For patients who decline biopsy but desire prognostic information, I do discuss the AJCC Ocular Oncology Task Force data.

The most compelling reason to use a standardized staging system is to facilitate research. While the AJCC system is not perfect, it does provide a language to efficiently communicate the information most pertinent to survival outcomes, with the exception of molecular prognostic testing. With the promise of novel therapeutics on the horizon, staging will become more relevant. Improvements in coding specificity as well as disease staging, together with more widespread adoption of a staging system, will allow us to better study uveal melanoma and will provide a foundation for the type of collaborative research necessary for improving survival and vision outcomes.

Reference

Why You Should Use the American Joint Commission on Cancer Classification

Stefan Seregard MD

The key issue for the development of all cancer treatment is to be able to compare, and the appropriate comparison is made prospectively in the setting of a clinical trial. For this we need to make sure we compare cancers with a similar prognosis.

Cancer is a heterogeneous group of diseases, with any entity typically arranged in groups defined by their prognosis—so-called staging. This makes comparison easier and less prone to bias. Anatomy, like size, location, and histopathologic features, and presence or absence of metastases are important in assessing prognosis, but we are increasingly aware that a number of other factors, so-called biomarkers, also come into play. In the future, such biomarkers will increasingly be incorporated into cancer staging.

The American Joint Commission on Cancer (AJCC) classification was first published in 1977, and for many years there has been a collaborative effort with the International Union for Cancer Control (UICC). The present AJCC classification is the result of the combined efforts of workers from many countries and as such is a product of the ocular oncology community. The present AJCC classification is certainly not perfect; in fact, as more knowledge is gained there will always be a need to further refine the classification. Work is in progress to replace the current seventh edition with an updated version.

The editors of most ophthalmic journals now require that cancer data published in any one of their journals are presented uniformly according to the AJCC classification. Therefore, if cancer data are not classified according to AJCC, you are less likely to get your work published. Ocular cancer is rare, and improvement in treatment requires multicenter collaboration. Such collaboration should be based on the common ground provided by the AJCC classification. There is no alternative classification of a similar international standing.

In conclusion, the only reason for you not to use the seventh edition AJCC would be that the eighth edition has already become available.
Online Forum and Social Media: Communication Between Oncologist and Pathologist

Heather A D Potter MD

The need for a forum in which to collaborate comes from 4 main features common to ophthalmic pathology and oncology.

1. Small total number and widely spread geographically
2. Absence of local colleagues
3. Case complexity
4. Innovative specialty

Currently we have regional and national meetings, we have excellent journals, and we have friends and colleagues with whom we can consult.

And we have a forum built by the Academy. The forum is a HIPPA-compliant way to communicate with each other regarding:

- Complex cases where help/input would be appreciated
- Interesting cases for teaching medical students, residents, and fellows
- Polls of existing labs with regard to new technology/techniques
- New changes to technology/reimbursement
- Updates to our educational materials

One email is sent when there is an update to the forum, and this contains a link to take the user there. The current use of and membership to our forum will be discussed, and individuals will be present to help American Association of Ophthalmic Oncologists and Pathologists members subscribe to the forum.
Telemedicine in Ocular Oncology and Pathology: What Works

Hans E Grossniklaus MD

I. Telemedicine
   A. Branch of telehealth
   B. Remote transfer of clinical information via electronic communication
   C. Internet, video conferencing, store & forward imaging, streaming media, wireless communication, teleconferencing
   D. Subdivided: teleoncology, telepathology, teleophthalmology, etc.

II. Teleoncology
   A. Models: face to face, oral medications, chemotherapy infusion, multidisciplinary teams (MDTs)
   B. Examples: Townsville Teleoncology Network (TTN), Kansas Telemedicine Network
   C. Existing model: Medical oncologists consult to rural doctors and/or nurses
   D. MDTs
   E. Concerns: physical examination, remote supervision of chemotherapy
   F. Patient satisfaction: 80% to 90%
   G. Physicians less satisfied

III. Telepathology
   A. Historical milestones: See Table 1
   B. Advantages/disadvantages: See Table 2
   C. Types of telepathology: See Table 3

Table 1.

<table>
<thead>
<tr>
<th>Date</th>
<th>Historical Milestones</th>
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<tbody>
<tr>
<td>1968</td>
<td>Black-and-white photos sent via video</td>
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<tr>
<td>1980</td>
<td>Remote telepathology broadcasting</td>
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<tr>
<td>1986</td>
<td>Video robotic telepathology</td>
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<tr>
<td>1989</td>
<td>Norway nationwide telepathology</td>
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<tr>
<td>1990</td>
<td>Published VA experience</td>
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<tr>
<td>1994</td>
<td>Hardware becomes available</td>
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<td>1995</td>
<td>AFIP static image consult service</td>
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<tr>
<td>2000</td>
<td>WSI comes to market</td>
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<td>2001</td>
<td>Dynamic telepathology U.S. Army Telemedicine Program</td>
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<tr>
<td>2005</td>
<td>U.S. Army converts to WSI platform</td>
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<td>2011</td>
<td>WSI dynamic robotic / static imaging systems</td>
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<tr>
<td>2013</td>
<td>Telepathology guidelines Royal College of Pathologists</td>
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Abbreviations: AFIP indicates Armed Forces Institute of Pathology; WSI, whole slide imaging; ATA, American Telemedicine Association.

Table 2.

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<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Rapid diagnosis</td>
<td>Some cases difficult to handle</td>
</tr>
<tr>
<td>Cost-effective</td>
<td>Deferral to glass slide in some cases</td>
</tr>
<tr>
<td>Remote sites</td>
<td>May take longer than slide review</td>
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<tr>
<td>Remote frozen sections</td>
<td>Technology errors and down time</td>
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<tr>
<td>FNAB</td>
<td>System maintenance required</td>
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<td>Potential to improve care</td>
<td>State limited licensure</td>
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Abbreviation: FNAB indicates fine needle aspiration biopsy.

Table 3.

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<th>Technology Method</th>
<th>Image System</th>
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<th>Images per Case</th>
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<td>No</td>
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<td>Host</td>
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<td>Dynamic</td>
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<td>Hybrid</td>
<td>Still and live</td>
<td>Yes</td>
<td>Unlimited</td>
<td>Telepathologist</td>
<td>High</td>
<td>High</td>
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D. Eye pathology examples
   1. Internet Based Eye Pathology Teaching Initiative (IBETI)
   2. American Association of Ophthalmic Oncologists and Pathologists Virtual Eye Path Slides

IV. Teleophthalmology
   A. Widely accepted
   B. Worldwide adoption: UK, Canada, India
   C. Care extenders
      1. Store & forward
      2. Live contact
   D. Examples
      1. PHOTO ED (nonmydriatic emergency department fundus photos)
      2. TECS (Technology-based Eye Care Services)
      3. Proposed: Uveal Nevus Teleimaging Project

V. What Works?
   A. Static images for teaching and clinical impressions
   B. Equipment for static images inexpensive and available
   C. Dynamic images for teaching and more in-depth pathology assessment
   D. Equipment for dynamic images (Aperio, etc.) expensive; institutional purchase

Selected Readings
Comparative Eye Pathology:
The Third Dimension in Eye Pathology

Daniel M Albert MD MS

I. Background
A. Comparative pathology: An old discipline (Ham-murabi, 2100 BC; Aristotle, 350 BC)
B. Specimens collected at Armed Forces Institute of Pathology since 1862

II. My Introduction to the Subject
A. Whale eye specimen
B. Elk eye episode
C. Melanocytoma and snake eyes

III. Differences Exist
Dog melanomas and asteroid hyalosis

IV. Lens Tumors: Humans vs. Animals
A. Ida Mann’s dictum
B. Trout lens tumors
C. Induced lens tumors in hamsters
D. Spontaneous lens tumors in cats and other animals
E. No occurrence in humans
F. Hypothesis and ongoing research

Selected Readings
Ocular Oncology: What I Like and Don’t Like

David H Abramson MD FACS

- Assigned topic: What I like and don’t like
- My topic: Mistaken ideas, hypotheses, and misinterpretation of results in ocular oncology that led to major advances in the field

I. Gerd Myer-Schwickerath MD¹
   A. Hypothesis: Photocoagulation of macula holes would prevent peripheral retinal detachment.
   B. 103 cases of macula hole photocoagulated in macula (and no retinal detachments)
   C. Misinterpretation: Untreated macula holes rarely (?never) lead to rhegmatogenous detachments.
   D. Led to successful development of photocoagulation of ocular tumors (benign and malignant)

II. Algernon B Reese MD²
   A. Hypothesis: Adding systemic chemotherapy to external beam radiation allowed him to reduce the dose of 15,000 rads to 7500 rads and still be successful.
   B. Misinterpretation: Chemotherapy not needed to decrease the dose: Success with only 7500 rads would have been attained without chemotherapy.

III. Robert M Ellsworth MD
   A. Hypothesis: Late metastases of retinoblastoma may occur (even 30 years later).
   B. Sent me to the Armed Forces Institute of Pathology
   C. Recognition that bilateral patients had a cancer predilection and that this predilection was altered by exposure to external beam irradiation³

IV. David H Abramson MD
   A. Hypothesis: Periocular chemotherapy can cure retinoblastoma.⁴
   B. Pharmacokinetics / importance of dose
   C. Recognition that retinoblastoma can be cured with chemotherapy alone, but doses with periocular delivery are not high enough; doses attained with intra-arterial or intravitreal are curative.

V. Lorenz E Zimmerman MD
   A. Hypothesis: Enucleation causes release of cells and explains peak of metastases in uveal melanoma within 2.5 years after procedure.⁵
   B. Mathematical modeling demonstrating metastases within 2.5 years after enucleation.
   C. Led to recognition that uveal melanoma is more than one disease. One such group (class II tumors) present with metastases within a few years of diagnosis or treatment by any means.

VI. Carol Shields MD
   A. Hypothesis: Systemic chemotherapy decreases the incidence of pineal tumors in children with bilateral retinoblastoma.
   B. Based on two papers: First on 1 patient, second on 4 patients. Published conclusion says “no statistical evidence… but I still believe it.”
   C. Based on incorrect assumption for incidence of pineal. Subsequent meticulous meta-analysis showed incidence of trilateral to be not 10% but closer to 2%.⁶

VII. Ophthalmic Community
   A. CCSG (Children’s Cancer Study Group) protocol 961
   B. Randomized trial of systemic chemotherapy for unilateral retinoblastoma enucleated. Result: Excellent and equal survival in both chemotherapy group and no chemotherapy group. Recommendation: no systemic chemotherapy for unilateral retinoblastoma unless outside the eye.
   C. But many centers still expose children to systemic chemotherapy for so called “high-risk factors.” Survival excellent and similar to centers that use no systemic chemotherapy.

References
Forty Years in Practice: I Will Tell You 5 Secrets

Evangelos S Gragoudas MD

Introduction
Forty years ago almost all eyes with malignant melanoma were enucleated. The management of uveal melanoma (UM) has changed, and most eyes are treated with conservative therapies. Some unanswered questions still exist. I will share “secrets” about 5 issues that remain controversial.

1. Management of Suspicious Lesions
Rates of malignant transformation depend on the presence of several risk factors. Presence of orange pigment, subretinal fluid, and symptoms are some of the predictors. Growth of the lesion is the most reliable but not the most certain predictor. Rates of growth vary between 4% and 56%, depending on the number of risk factors present.

In my experience, follow-up of these lesions before definite and significant growth does not increase the risk of dying from UM and avoids treatments that are associated with morbidity in many patients. Of 334 suspicious lesions followed at Massachusetts Eye and Ear (MEE), 39 showed signs of tumor growth or other changes and were subsequently treated with proton irradiation. Two of these patients, treated 10 and 20 months after initial presentation at MEE, developed metastasis and died from UM 4.7 years and 10.3 years after receiving treatment.

There is no evidence to indicate that earlier treatment of these cases would have prevented metastasis.

2. Management of Iris Melanomas
The natural history of iris “melanomas” is different than that of choroidal melanomas, raising the question of their malignant potential. In one study of iris and iridociliary melanomas, 87% were reclassified as benign lesions after pathological evaluation. Iris melanoma dimensions are usually small, and these tumors rarely metastasize. Treatment should be restricted to “large” iris melanomas that show definitive and significant growth.

3. Treatment of Tumor Recurrences
The management of recurrences after conservative treatment has not been established. Reasonable results after proton irradiation of patients with recurrences have been demonstrated in our group and suggest that enucleation is unnecessary in many cases. In a recent review of 51 patients with tumor recurrences treated with proton beam irradiation at MEE, median visual acuity at last follow-up examination was 20/800, with 39.5% of patients retaining vision of at least 20/200. Four patients underwent enucleation due to complications. Approximately one-third of patients (n = 18) developed metastasis. In another study of treatment for recurrences, 32% who had proton irradiation died of UM, compared to 59% who underwent enucleation.

4. Treatment of Collaborative Ocular Melanoma Study (COMS) Ineligible Tumors
Conservative treatments can be used to treat patients with large tumors (largest tumor diameter > 16 mm or height > 10 mm) and tumors near the optic nerve (≤ 1 disc diameter) that were excluded from the COMS. Reasonably good results can be achieved in patients with these tumors using proton beam irradiation: vision loss is not inevitable, particularly for patients with small–medium tumors near the optic nerve, and long-term eye conservation is possible. Visual acuity of 20/200 or better was observed in 54.9% of patients at 2 years after irradiation, but this diminished to 20.3% by 5 years after irradiation.

5. Metastatic Surveillance
The optimal timing and battery of tests to use for diagnosis of metastasis remains unclear. The COMS found no differences in survival between patients who received treatment for metastatic disease and those who did not. In a Finnish registry, patients diagnosed with metastatic melanoma at an annual examination experienced longer survival than those diagnosed after developing symptoms (8.9 months vs. 4.3 months; P = .08), but there was no difference in survival from the time of initial tumor diagnosis (P = .25) to death.

At MEE, we evaluated the incidence of metastasis in asymptomatic (early diagnosis) vs. symptomatic (late diagnosis) patients and found the following:

a. Longer median survival time from diagnosis of metastasis to death was observed in asymptomatic patients.
b. Similar median survival time from diagnosis of primary tumor to death was observed in asymptomatic patients and symptomatic patients.

These data suggest lead-time bias. Regardless of the surveillance protocols that are followed, until effective treatments for hepatic metastasis are found, the benefit of surveillance is limited. Our data demonstrate that no progress has been made during the last 2 decades in improving survival after diagnosis of metastasis. The 1-year survival rate in 614 patients with metastasis was 20%, and after 3 years, only 4% of patients were alive. Over half of these patients (n = 323) received treatment, which included chemotherapy (44%) and treatment with more than one modality—eg, radiation, surgery (35%). Median survival was 6 months for patients who received treatment compared to 1.5 months for patients who did not receive treatment. Consistent with our findings, a meta-analysis of 25 clinical trials provided no evidence that any treatments for liver metastases prolong life. More recently, in a randomized Phase 2 clinical trial of selumetinib vs. chemotherapy for patients with metastatic uveal melanoma, no improvement in overall survival and a high rate of adverse events were observed.
### References


Running an Ocular Oncology Practice:
My Top 5 Lessons Learned

Jerry A Shields MD

1. Patients come first.
2. Take care of your office staff.
3. Teach your colleagues and students.
4. Try to be academic.
   a. Be organized.
   b. Keep track of good cases.
   c. Set up coding system so that you can retrieve large series of disease.
   d. Document with excellent images and know your technology.
5. Learn the business of running a business.
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* Indicates that the presenter has financial interest.
No asterisk indicates that the presenter has no financial interest.