Ocular Oncology and Pathology 2014
Saving Eyes and Saving Lives

Program Directors
Hans E Grossniklaus MD, Arun D Singh MD

In conjunction with the American Association of Ophthalmic Oncologists and Pathologists

McCormick Place
Chicago, Illinois
Saturday, Oct. 18, 2014

Presented by:
The American Academy of Ophthalmology
2014 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 2014: Saving Eyes and Saving Lives.

Hans E Grossniklaus MD  
Program Director
Aura Biosciences: S  
Clearside Biomedical: P  
Fight for Sight: S  
National Cancer Institute: S

Arun D Singh MD  
Program Director
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.

The American Medical Association has determined that non–U.S. licensed physicians who participate in this CME activity are eligible for AMA PRA Category 1 Credits™.

Attendees registered as exhibitors, spouses or guests are not eligible to receive CME credit.

2014 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 ocular melanoma, retinoblastoma, conjunctival tumors, and orbital tumors
■ Apply basic surgical and chemotherapeutic techniques to treat simple conjunctival and eyelid tumors
■ Recognize when to appropriately refer patients to an ocular oncology center

2014 Ocular Oncology and Pathology Subspecialty Day Meeting Target Audience

The intended target audience for this program is practicing ophthalmologists, residents in training and fellows.

2014 Ocular Oncology and Pathology Subspecialty Day CME Credit

The American Academy of Ophthalmology is accredited by the Accreditation Council for Continuing Medical Education to provide CME 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/cme/.

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. Please contact the AMA to obtain an application form 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.

Attendance Verification for CME Reporting

Before processing your requests for CME credit, the Academy must verify your attendance at Subspecialty Day and/or at AAO 2014. 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 Final Program and/or Subspecialty Day Syllabus exchange voucher(s) onsite;
■ Register in advance and pick up your badge onsite if materials did not arrive before you traveled to the meeting; or
■ Register onsite.

CME Credit Reporting

South, Level 2.5; Academy Resource Center, Booth 508

Attendees whose attendance has been verified (see above) at AAO 2014 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 2014 at the CME Credit Reporting booth.

Academy Members: The CME credit reporting receipt is not a CME transcript. CME transcripts that include AAO 2014 credits entered onsite will be available to Academy members on the Academy’s website beginning Nov. 13, 2014.

NOTE: CME credits must be reported by Jan. 15, 2015. After AAO 2014, credits can be claimed at www.aao.org.
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 2014.

Nonmembers: The Academy will provide nonmembers with verification of credits earned and reported for a single Academy-sponsored CME activity, but it does not provide CME credit transcripts. To obtain a printed record of your credits, you must report your CME credits onsite at the CME Credit Reporting booths.

Proof of Attendance

The following types of attendance verification will be available during AAO 2014 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 Form
- Instruction Course Verification Form

Visit the Academy’s website for detailed CME reporting information.
Faculty

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New York, NY  
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Memorial Sloan Kettering Cancer Center  
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Weill Cornell University

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Houston Methodist Hospital

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Miami, FL  
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Director, Uveitis Service  
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Director of Ocular Oncology
Bascom Palmer Eye Institute and Sylvester Comprehensive Cancer Center

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Massachusetts Eye and Ear Infirmary

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Washington University in St Louis

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Professor of Ophthalmology
Emory University

Ted H Wojno MD
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Director of Oculoplastic and Orbital Surgery
The Emory Clinic
Ocular Oncology and Pathology 2014
Saving Eyes and Saving Lives

In conjunction with the American Association of Ophthalmic Oncologists and Pathologists

SATURDAY, OCT. 18, 2014

Section I: Ocular Oncology/Pathology Update – Part I
Moderator: Patricia Chévez-Barrios MD

<table>
<thead>
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<td>Introduction and Self-assessment</td>
<td>Patricia Chévez-Barrios MD</td>
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<td>8:07 AM</td>
<td>Retinoblastoma: Clinical Aspects</td>
<td>Dan S Gombos MD*</td>
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<td>8:19 AM</td>
<td>Retinoblastoma: Pathology, Genetics</td>
<td>Hans E Grossniklaus MD*</td>
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<td>8:31 AM</td>
<td>Uveal Melanoma: Clinical Aspects</td>
<td>Arun D Singh MD</td>
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<td>8:43 AM</td>
<td>Uveal Melanoma: Pathology, Genetics</td>
<td>Ralph Eagle MD*</td>
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<td>Other Intraocular Tumors: Clinical Aspects</td>
<td>Carol L Shields MD</td>
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<td>Other Intraocular Tumors: Pathology, Genetics</td>
<td>David J Wilson MD*</td>
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<td>9:19 AM</td>
<td>Conjunctival (Nonpigmented) Tumors: Clinical Aspects</td>
<td>Jill R Wells MD</td>
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<td>9:31 AM</td>
<td>Conjunctival (Nonpigmented) Tumors: Pathology</td>
<td>Michele M Bloomer MD</td>
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<tr>
<td>9:43 AM</td>
<td>Conclusion and Self-assessment</td>
<td>Patricia Chévez-Barrios MD*</td>
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Section II: Ocular Oncology/Pathology Update – Part II
Moderator: J William Harbour MD*

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<td>J William Harbour MD*</td>
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<td>Conjunctival (Pigmented) Tumors: Clinical Aspects</td>
<td>Jerry A Shields MD</td>
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<td>10:39 AM</td>
<td>Conjunctival (Pigmented) Tumors: Pathology</td>
<td>George Harocopos MD</td>
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<td>10:51 AM</td>
<td>Eyelid Tumors: Clinical Aspects</td>
<td>Ted H Wojno MD*</td>
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<td>11:03 AM</td>
<td>Eyelid Tumors: Pathology</td>
<td>Curtis E Margo MD MPH</td>
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<td>11:15 AM</td>
<td>Orbital Tumors: Clinical Aspects</td>
<td>David T Tse MD FACS*</td>
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<td>11:27 AM</td>
<td>Orbital Tumors: Pathology</td>
<td>Victor M Elner PhD MD*</td>
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<td>11:39 AM</td>
<td>Challenging Cases: Clinico-Pathologic Correlations</td>
<td>Sander Dubovy MD</td>
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<td>11:51 AM</td>
<td>Advocating for Patients</td>
<td>Zelia M Correa MD</td>
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<td>11:56 AM</td>
<td>Conclusion and Self-assessment</td>
<td>J William Harbour MD*</td>
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* Indicates that the presenter has financial interest.
No asterisk indicates that the presenter has no financial interest.
**Section III: Controversies in Ocular Oncology/Pathology**

Moderator: Bertil E Damato MD PhD

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<td>Retinoblastoma: Intra-arterial Chemotherapy – Pro</td>
<td>David H Abramson MD FACS</td>
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<td>Retinoblastoma: Intra-arterial Chemotherapy – Con</td>
<td>Matthew W Wilson MD</td>
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<td>Uveal Melanoma: Systemic Surveillance – Pro</td>
<td>Chris S Bergstrom MD</td>
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<td>Uveal Melanoma: Systemic Surveillance – Con</td>
<td>Evangelos S Gragoudas MD*</td>
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<td>Iris Melanoma: Excision</td>
<td>Arun D Singh MD</td>
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<td>Iris Melanoma: Radiation Therapy</td>
<td>E Rand Simpson MD</td>
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<td>Primary Intraocular Lymphoma: Radiation</td>
<td>Janet Louise Davis MD*</td>
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<td>Primary Intraocular Lymphoma: Intraocular Chemotherapy</td>
<td>David J Wilson MD*</td>
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**Section IV: Frontiers in Ocular Oncology/Pathology**

Moderator: David J Wilson MD*

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<td>Retinoblastoma: Intravitreal Injections</td>
<td>Francis L Munier MD</td>
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<td>Retinoblastoma: Gene Therapy</td>
<td>Patricia Chévez-Barrios MD</td>
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<td>Retinoblastoma: Nanoparticle Therapy</td>
<td>Hans E Grossniklaus MD*</td>
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<td>Uveal Melanoma: Imaging Techniques</td>
<td>Stefan Seregard MD</td>
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<td>Uveal Melanoma: Novel Therapies</td>
<td>Bertil E Damato MD PhD</td>
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<td>Uveal Melanoma: Emerging Treatments for Metastases</td>
<td>J William Harbour MD*</td>
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<td>Conclusion and Self-assessment</td>
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<td>Closing Remarks</td>
<td>Hans E Grossniklaus MD*</td>
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* Indicates that the presenter has financial interest.
No asterisk indicates that the presenter has no financial interest.
Retinoblastoma: Clinical Aspects

Dan S Gombos MD

I. Epidemiology
   A. Incidence worldwide
   B. Geographic variation

II. Diagnostic Evaluation
   A. Detection of leukocoria
   B. Exam under anesthesia
   C. Echography: A/B scan, ultrasound biomicroscopy
   D. Neuroimaging CT vs. MRI
   E. OCT: a new tool
   F. Fine needle aspiration biopsy
   G. 13q deletion syndrome

III. Differential Diagnosis
   A. Persistent fetal vasculature
   B. Coats disease
   C. Trends in pseudo retinoblastomas

IV. Grouping and Staging Systems
   A. International Classification for Intraocular Retinoblastoma (ICIRB)
   B. Reese-Ellsworth Grouping
   C. American Joint Committee on Cancer (AJCC) Retinoblastoma TMN Staging
   D. Children’s Oncology Group (COG) high-risk histopathology assessment

V. Treatment Strategies: Intraocular disease
   A. Surgery
   B. Systemic: intravenous (IV) chemotherapy
      1. Traditional agents: carboplatin, vincristine, etoposide
      2. Newer approaches: topotecan
      3. Toxicities associated with IV chemotherapy
   C. Local chemotherapy
      1. Periocular carboplatin: Complications associated with periocular chemotherapy
      2. Intra-arterial melphalan: Toxicities associated with intra-arterial chemotherapy
      3. Intravitreal melphalan: Strategies to reduce risk of extraocular extension
   D. Focal therapies: Laser, cryotherapy
   E. Radiation therapy
      1. Current role for radiation therapy; risk of second non-ocular tumors
      2. Teletherapy: EBRT/IMRT/charged particle
      3. Brachytherapy

VI. Treatment Strategies: Extraocular disease
   A. Cut-end disease
   B. High-dose chemotherapy
   C. Bone marrow transplantation

VII. Second Non-ocular Tumors
   A. Rates of primitive neuroectodermal tumors (PNET)
   B. Reducing the risk of secondary tumors
   C. Morbidity of radiation-induced tumors

VIII. Genetic Testing
   A. Current methods of genetic testing and rates of detection
   B. Neonatal assessment
   C. Preimplantation genetic testing

IX. Collaborative Prospective Trials
   A. Children’s Oncology Group (COG)
   B. ARET-0332: A Study of Unilateral Retinoblastoma With and Without Histopathologic High-risk Features
   C. ARET-0331: Trial of Systemic Neoadjuvant Chemotherapy for Group B Retinoblastoma
   D. ARET-0231: A Single Arm Trial of Systemic and Subtenon Chemotherapy for Groups C and D Retinoblastoma
   E. ARET-0321: A Trial of Intensive Multimodality Therapy for Extraocular Retinoblastoma
   F. ARET-12P1: A Multi-institutional Feasibility Study of Intra-arterial Chemotherapy in Children with Retinoblastoma
   G. Observations made from COG trials

X. Areas of Controversy
   A. Role of intra-arterial chemotherapy: cost, technical expertise, choroidal ischemia, damage to vascular endothelium
   B. Risks and benefits of systemic intravenous chemotherapy: oto-toxicity, secondary leukemia, chemoprophylactic effect
C. Use of Reese-Ellsworth vs. ICIRB grouping: Role of the ICIRB in national trials
D. Prophylactic systemic chemotherapy for high-risk histopathology

XI. Novel Modalities
A. Gene therapy
B. Nanoparticle therapy
C. ICG-assisted laser therapy
D. Episcleral exoplant

XII. Conclusions

Selected Readings


Retinoblastoma: Pathology and Genetics

Hans E Grossniklaus MD

I. Pathology
A. Described in 1800s
1. Virchow cellular pathology
2. Rosettes
B. Small round blue cell tumor
1. Similar to leukemia, rhabdomyosarcoma, neuroblastoma
2. Grows in sleeves and cuffs around central vascular channels
C. Homer Wright and Flexner-Wintersteiner rosettes
1. Homer Wright with neuropil in lumen, nonspecific
2. Flexner-Wintersteiner with clear lumen, more specific
D. Growth patterns
1. Endophytic: Grows into vitreous from retina; vitreous seeds
2. Exophytic: Grows toward choroid from retina, subretinal seeds
3. Anterior diffuse growth pattern: Spreads into aqueous, pseudohypopyon
E. Vitreous seeds
1. Central necrosis/apoptosis
2. Difficult to treat

II. Retinocytoma
A. Benign variant of retinoblastoma
1. Small and fleshy
2. Calcifications
3. Clinically described by Gallie and co-workers
4. Pathologically described by Margo and co-workers
B. Pathology
1. Bland nuclei with abundant cytoplasm
2. Fleurettes

III. Trilateral retinoblastoma
A. Pineal tumor
B. Midbrain tumor

IV. Pathologic High-risk Features
A. Optic nerve invasion past lamina
1. Survival decreased by level of invasion
2. Direct spread to CNS
B. Choroidal invasion of 3 mm in contact with sclera
1. True invasion vs. artifact
2. Risk of hematogenous spread
C. Any optic nerve invasion or choroidal invasion

V. Genetics
A. Knudson’s two-hit hypothesis
1. Graphed age at diagnosis vs. percent undiagnosed cases
2. Linear and quadratic groups
B. Tumor suppressor gene
1. Presence of Rb protective against getting tumor
2. Mutations in both alleles needed for tumor progression
C. Heritable vs. sporadic retinoblastoma
1. Heritable: Germline mutation plus mutation in developing retina
2. Sporadic: Two mutations in developing retina
3. Heritable: Multiple, bilateral tumors, average age at diagnosis 1 year
4. Sporadic: Single, unilateral tumor, average age at diagnosis 2 years
D. Gene located at 13q14 (Dryja, et al.)
E. Cell cycle regulation-progression and exiting cell cycle
1. Phosphorylated Rb (pRb) leads to normal progression through cell cycle.
2. Dephosphorylated Rb leads to differentiation / senescence.
3. Hyperphosphorylation leads to apoptosis.
F. Events other than Rb mutation required for tumor progression
1. Two Rb mutations required for proliferation, retinocytoma
2. Other events: gene amplification, deletion, mutation, epigenetic silencing

VI. Molecular Pathology
A. Gene expression profiling: retinal precursor cell vs. cone cell of origin
1. Genes expressed in retinal precursor cells (RPCs)
2. Genes expressed in cone photoreceptors
B. Anaplasia and prognosis
   1. Anaplasia graded as mild, moderate, and severe
   2. Severe anaplasia correlates with increased risk of metastasis.

VII. Summary
   A. Pathology
      1. Small, round, blue cell tumor
      2. Homer Wright and Flexner-Wintersteiner rosettes
      3. Endophytic, exophytic, and diffuse anterior growth patterns
      4. Retinocytoma-fleurettes
      5. Optic nerve/choroid invasion, high risk for metastasis

   B. Genetics
      1. Knudson two-hit hypothesis
      2. Rb tumor suppressor protein
      3. Rb master regulator of cell cycle
      4. Other events needed for tumor progression
      5. Gene expression profiling
      6. Anaplasia

Selected Readings
Uveal Melanoma: Clinical Aspects

Arun D Singh MD

I. Introduction
II. Epidemiology and Risk Factors
III. Diagnostic Features
IV. Differential Diagnosis
   A. Benign
      1. Nevus
      2. Melanocytoma
      3. Bilateral diffuse uveal melanocytic proliferation
      4. Hemangioma
      5. Neural tumors (eg, Schwannoma)
      6. Leiomyoma
      7. Reactive lymphoid hyperplasia
   B. Malignant
      1. Lymphoma
      2. Metastasis
   C. Other entities
      1. Suprachoroidal hemorrhage
      2. Sclerochoroidal calcification
      3. Granuloma
      4. Scleritis
V. Diagnostic Techniques
   A. Color photography
   B. Fluorescein angiography
   C. Indocyanine green angiography
   D. Ultrasonography
   E. OCT
   F. Radiologic techniques
      1. CT scan
      2. MRI
      3. PET scan
   G. Biopsy
VI. Staging Systems
VII. Conclusions
Uveal Melanoma: Pathology, Genetics

Ralph C Eagle Jr MD

I. Uveal Malignant Melanoma

A. Most common primary intraocular tumor in white adults

B. Worldwide, retinoblastoma is the most common intraocular tumor.

C. Uveal metastases are thought to be the most common intraocular malignancy, but most cases are inapparent, or are not seen by ophthalmologists.

II. Risk Factors

A. Race

1. Uveal malignant melanoma is predominantly a tumor of blue-eyed Europeans.
2. Two-thirds of uveal melanomas arise in whites, who comprise 8% of the global population.
3. Incidence in U.S. whites is 8.5 times greater than that in blacks.

B. Age

1. Median age at diagnosis: 53 years (Armed Forces Institute of Pathology Study; AFIP), 59 (Collaborative Ocular Melanoma Study; COMS)
2. Tumor size increases, poorer survival with increasing age

C. No sex predilection: Male = female in COMS

III. Genetic Mutations and Predisposing Lesions

A. GNAQ/GNA11

1. GNAQ mutations present in 50% of uveal melanomas.
2. Also found in Nevus of Ota, blue nevus, ocular melanocytosis
3. An early or initiating event: present at all stages of malignant progression

B. BAP1- (very important prognostic marker)

1. 84% incidence of inactivating mutations in class II uveal melanomas. Association with monosomy 3
2. Chromosome 3 loss appears to uncover recessive mutations in chromosome 3.

C. Congenital ocular or oculodermal melanocytosis (Nevus of Ota). 1/400 lifetime risk of MM in whites.

IV. Gross Pathology

A. Choroidal melanoma: Most common location (90%)

1. Small tumors (Largest tumor diameter [LTD] ≤ 10 mm): almond shape, confined to choroid
2. Medium tumors (LTD 11-15 mm)
   a. Typical mushroom or collar button configuration (63%)
   b. Rupture through Bruch membrane, grow in subretinal space
   c. Dilated vessels in head of mushroom caused by cinch-like effect of Bruch membrane on waist of tumor
3. Large tumors (LTD > 15 mm)
   a. Tumor invades and destroys ocular tissues, may fill globe.
   b.Extrascleral extension more common
4. Diffuse infiltrating melanoma
   a. Uncommon, grows laterally with little choroidal thickening
   b. Extrascleral extension more common
   c. Poor prognosis

5. Ciliary body melanoma
   a. Poorer prognosis
   b. Diagnostic delay; may be asymptomatic, no RD
   c. Tend to be more spherical
   d. Can invade anterior chamber anterior (“tip of the iceberg”)
   e. Can cause cataract; sentinel vessels, cystoid macular edema

V. Cytology and Histopathology

A. Cell type (Callender classification [modified by McLean et al, 1978]).

1. Association between mortality and cytology of melanoma
2. Spindle cells
   a. Bipolar cells with spindle-shaped cytoplasm; arranged in parallel fascicles
   b. Grow as syncytium; cellular margins indistinct
c. Spindle A: slender cigar-shaped nuclei with finely dispersed chromatin and indistinct nucleolus. Longitudinal chromatin stripe or streak caused by fold in nuclear membrane (most benign)
d. Spindle B: plumper, oval nucleus with coarser chromatin and a more prominent nucleolus
e. Intermediate cells: nuclear characteristics intermediate between spindle B and epithelioid
f. Epithelioid melanoma cells: most malignant
   i. Polyhedral cells with abundant glassy cytoplasm
   ii. Large and pleomorphic, bizarre giant cells occasionally seen
   iii. Poorly cohesive with distinct cytoplasmic borders
   iv. Large round to oval nucleus with peripheral margination of coarse chromatin (chromatin clumped along interior of nuclear membrane)
   v. Prominent eosinophilic or purple nucleolus

B. Four subcategories of tumors based on cellular constituents
1. Spindle cell nevus: composed entirely of bland spindle A cells
2. Spindle cell melanoma
   a. Composed of malignant spindle A, spindle A and B, or spindle B cells
   b. 72% 15 year-survival
3. Mixed cell melanoma: mixture of spindle and epithelioid cells. 86% of medium and large posterior tumors in COMS study
4. Epithelioid cell melanoma: rare, poorest prognosis. Composed predominantly of epithelioid cells

C. Other pathologic features
1. Retinal pigment epithelium and outer retinal degeneration at tumor apex
2. Retinal invasion common, retinal perforation rare; epiretinal seeding
3. Most cases have secondary exudative retinal detachment.
4. 13% incidence of extrascleral extension (tumors extend extraocularly along scleral emissarial canals, vortex veins)
5. Optic nerve invasion rare (usually in cases with diffuse growth pattern)
6. Orange pigment: macrophages laden with lipo-fuscin; indicates actively growing lesion but is not pathognomonic for melanoma

VI. Prognostic Features
A. Prognostic features are detectable on clinical examination.
   Tumor size, ciliary body involvement, extraocular extension form a basis for American Joint Commission on Cancer TMN classification
B. Prognostic features detectable on routine histopathologic exam
   1. Cell type and tumor size are most important factors that can be assessed histopathologically.
   2. Cell type (modified Callender classification), see above
      a. Patients with spindle cell tumors have a better prognosis than patients whose tumors contain epithelioid cells (survival of 4728 patients at AFIP).
      b. No epithelioid cells: 28%, 15-year mortality; epithelioid cells present: 63%, 15-year mortality
      c. Tumor size is as important as cell type.
         i. LTD is best prognostic indicator:
            ii. 5-year-survival: small (< 11 mm) 86%, medium (11-15) 66%, large (>15) 56%
   3. Other prognostic factors assessable during routine pathologic exam
      a. Anterior location (ciliary body tumors have poorer prognosis)
      b. Extraocular extension
      c. Mitotic activity - more mitoses - worse prognosis
      d. Lymphocytic infiltration: associated with poorer prognosis
      e. Vascular mimicry patterns (formerly called extracellular matrix patterns; EMP) or vascular loops and networks (Folberg)
      f. Melanophagic infiltration: poorer prognosis
C. Prognostic factors disclosed by special testing
   1. Nonrandom chromosomal abnormalities: monosomy 3, trisomy 8q
      a. Monosomy 3: 50% die within 3 years
   2. Gene expression profile
      a. Proprietary commercial test: expensive
      b. Class IA melanomas: low-grade, do not metastasize
      c. Class IB melanomas: late metastasis
      d. Class 2 melanomas: high risk for early metastases (> 90%), primitive neural / ectodermal stem cell-like phenotype, contain epithelioid cells, vascular mimicry patterns. 84% have inactivating BAP1 mutations.
8 Section I: Ocular Oncology/Pathology Update – Part I

VIII. Iris Melanoma

A. Best prognosis: 4% overall mortality (actually may be higher)

B. Most pigmented tumors of the iris are benign nevi; only 6.5% grow when observed for 5 years.

C. Diffuse iris melanomas that cause heterochromia and secondary glaucoma usually (89%) contain epithelioid cells.

References and Selected Readings


Other Intraocular Tumors: Clinical Aspects

Carol L Shields MD

I. Retinal Tumors
   A. Vasoproliferative tumor
      1. Types
         a. Primary: 80%
         b. Secondary: 20%
            i. pars planitis: 30%
            ii. retinitis pigmentosa: 20%
            iii. toxoplasmosis: 7%
            iv. toxocariasis: 7%
            v. chronic RD: 3%
            vi. Coats disease: 3%
      2. Features
         a. Ill-defined
         b. Minimally dilated retinal vessels
         c. Periphery
         d. Exudation
         e. Subretinal fluid
      3. Nomenclature: Also known as “reactive retinal astrocytic tumors”
   B. Metastasis (rare)
      1. Primary cancer sites
         a. Skin melanoma: 50%
         b. Breast cancer: 25%
         c. Lung cancer: 13%
         d. Esophageal cancer: 13%
      2. Treatment
         a. External beam radiotherapy – if diffuse or multifocal
         b. Plaque radiotherapy – if localized

II. Retinal Pigment Epithelial (RPE) Tumors
   A. Congenital hypertrophy of RPE – solitary type
      1. Features
         a. Flat with crisp margin
         b. Enlargement in 83% over long period
         c. Adenoma develops < 1%
      2. Imaging with OCT
         a. Flat, slightly thicker RPE

III. Choroidal Tumors
   A. Metastasis
      1. Primary cancer sites breast or lung cancer in > 75%
      2. No history of cancer in 34%; proves to be lung cancer in 35% or breast cancer in 7%
      3. Treatment
         a. External beam radiotherapy – if diffuse or multifocal
         b. Plaque radiotherapy – if localized
B. Osteoma

1. Clinical features
   a. Young women
   b. Juxtapapillary or macular region
2. Imaging with OCT
   a. Tumor originates in choroid
   b. Horizontal lines and tubules
   c. Vertical lines and tubules
   d. Photoreceptor loss
3. Outcomes at 10 years
   a. Tumor growth in 50%
   b. Visual acuity < 20/200 in 50%
   c. Vision loss > 3 lines in 50%
   d. Related choroidal neovascular membrane in 30%

IV. Scleral Tumors

A. Sclerochoroidal calcification

1. Clinical features
   a. Older men and women
   b. Superotemporal arcade most common
2. Imaging with OCT
   a. Tumor originates in sclera
   b. Rock and rolling configuration

Selected Readings

Other Intraocular Tumors: Pathology, Genetics

David J Wilson MD

I. Vascular Tumors
   A. Vasoproliferative tumor
      1. Pathology
         a. Thick walled vessels
         b. Glial proliferation
         c. Inflammatory component
         d. Vascular endothelial growth factor
         e. Connection to choroidal circulation
      2. Genetics: no major role
   B. Retinal hemangioblastoma
      1. Pathology
         a. Interstitial cell: primary
         b. Vascular proliferation: secondary
         c. Exudative retinal detachment
      2. Genetics
         a. Von Hippel-Lindau (VHL)
         b. VHL gene – tumor suppressor gene
   C. Cavernous hemangioma
      1. Pathology
         a. Large caliber vessels in choroid
         b. Overlying cystoid edema and subretinal fluid
         c. Retinal pigment epithelial (RPE) hyperplasia may mimic melanoma.
      2. Genetics: no major role

II. Lymphoma
   A. Uveal
      1. Pathology
         a. Low grade lymphoma
         b. Diffuse infiltrate of the choroid
         c. Cell marker studies
         d. Genetic studies
         e. Biopsy techniques
      2. Genetics: no major role
   B. Vitreoretinal
      1. Pathology
         a. High grade lymphoma
         b. Infiltrate the sub-RPE space, retina, and vitreous
      2. Genetics: no major role

III. Other Uveal Tumors
   A. Melanocytoma
      1. Pathology
         a. Polyhedral cells with eccentric bland nucleus
         b. Location
            i. Optic nerve
            ii. Ciliary body
            iii. Choroid
         c. Invasion of other tissues
      2. Genetics: no major role
   B. Bilateral diffuse uveal melanocytic proliferation
      1. Pathology
         a. Spindle-shaped melanocytic cells
         b. Surface lipofuscin
         c. Location
            i. Iris
            ii. Ciliary body
            iii. Choroid
         d. Associated with systemic malignancies
      2. Genetics: no major role
   C. Leiomyoma
      1. Pathology
         a. Spindle-shaped cells with indistinct cell borders
         b. Immunohistochemistry: smooth muscle markers
         c. Location: Ciliary body
      2. Genetics: no major role
Conjunctival (Nonpigmented) Tumors: Clinical Aspects

Jill R Wells MD

I. Classification of Epithelial Tumors (Nonmelanocytic)
   A. Benign
      1. Squamous papilloma
      2. Inverted follicular keratosis
      3. Reactive epithelial hyperplasia
      4. Keratoacanthoma
      5. Hereditary benign intraepithelial dyskeratosis
      6. Epithelial cyst
      7. Dacryoadenoma
      8. Actinic keratosis
   B. Malignant
      1. Conjunctival intraepithelial neoplasia (CIN)
      2. Squamous cell carcinoma (SCC)

II. Classification of Stromal Tumors
   A. Vascular
      1. Pyogenic granuloma
      2. Capillary hemangioma
      3. Cavernous hemangioma
      4. Varix
      5. Kaposi sarcoma
      6. Cavernous hemangioma
      7. Racemose hemangioma
      8. Lymphangioma
      9. Hemangiopericytoma
   B. Fibrous
      1. Fibroma
      2. Fibrous histiocytoma
      3. Nodular fasciitis
   C. Neural
      1. Neurofibroma
      2. Schwannoma
      3. Granular cell tumor
   D. Histiocytic
      1. Xanthoma
      2. Juvenile xanthogranuloma
      3. Reticulohistiocytoma
   E. Myxoid (myxoma)
   F. Myogenic (rhabdomyosarcoma)
   G. Lipomatous
      1. Lipoma
      2. Liposarcoma
      3. Herniated orbital fat
   H. Lymphoproliferative
      1. Benign reactive lymphoid hyperplasia
      2. Lymphoma
      3. Leukemic infiltrates

III. Squamous Papilloma

Figure 1. Squamous papilloma.

A. Sessile or pedunculated pink/red fleshy frond of tissue with finger-like projections
B. Usually solitary, but may be bilateral, multiple, and can become confluent
C. Complete excision with “no-touch” technique and cryo
D. Interferon alpha 2b for recurrences
IV. Keratoacanthoma

Figure 2. Keratoacanthoma

A. Benign reactive inflammatory lesion
B. May spontaneously regress
C. May be difficult to clinically distinguish from SCC

V. Epithelial Cyst

A. Smooth, translucent benign lesion that contains fluid
B. May occur spontaneously or secondary to surgery or trauma
C. Observe or excise

VI. Ocular Surface Squamous Neoplasia (OSSN)

Figure 3. Ocular surface squamous neoplasia.

A. Term used for precancerous and cancerous epithelial lesions of the conjunctiva and includes dysplasia, carcinoma in situ, and SCC
B. Epidemiology
   1. 0.3 per million in the United States
   2. More common in adults
   3. More common in males
C. Etiology
   1. Sunlight exposure, higher incidence closer to equator
   2. HPV in conjunction with other factors may increase risk
   3. AIDS
   4. Xeroderma pigmentosa
D. Clinical features
   1. May be difficult to distinguish between dysplasia and invasive SCC
   2. Gelatinous, papilliform, leukoplakic, or nodular in appearance
E. Diagnosis
   1. Biopsy
   2. Ultrasound biomicroscopy to help estimate depth of invasion
   3. Anterior segment OCT to detect borders
   4. Diagnostic cytology – does not provide information about depth of invasion.
F. Treatment
   1. Surgery
      a. Complete excision with 2-3 mm margin
      b. If sclera is involved, partial sclerectomy
      c. If cornea is involved, ethanol debridement
      d. High risk of recurrence (up to 50%) with surgery alone, so cryotherapy at the time of surgery in double freeze thaw fashion to reduce risk
      e. Reconstruction with amniotic membrane graft may be necessary.
   2. Topical chemotherapeutic agents
      a. Interferon alpha 2b
         i. Protein molecules that act as the body’s defense against viral infections as well as combat tumors and regulate immunity
         ii. Cause a slow-down of tumor cell growth by increasing cell multiplication cycle length
         iii. Topical (1 million IU/cc) or intralesional (10 million IU/cc)
      iv. Advantageous for giant OSSN as opposed to surgery, which may deplete limbal stem cells
      v. Treatment may last for many months
      vi. May be used as primary treatment or to treat positive margins or recurrences after surgery
      vii. Drops typically well tolerated; injection may cause flu-like symptoms
b. Mitomycin C
   i. Alkylating agent in all phases of cell cycle
   ii. 0.02% to 0.04% q.i.d. (7 days on/7 days off)
   iii. Excellent results with recurrent CIN or SCC
   iv. Multiple side effects, including pain, hyperemia, punctate epithelial erosions, photosensitivity, limbal stem cell deficiency

c. 5-fluorouracil
   i. Inhibits DNA synthesis
   ii. 1% q.i.d., various dosing regimens
   iii. Used as adjunct to surgery and as primary treatment for primary and recurrent CIN and SCC
   iv. Side effects include conjunctival and corneal inflammation, corneal epithelial defects, irritation, discomfort.

3. Brachytherapy for recurrence, scleral or intraocular invasion

G. Metastasis
   1. Extremely rare
   2. Sites include preauricular, submandibular, and cervical lymph nodes, parotid gland, lungs, and bone.

VII. Pyogenic Granuloma
   A. Proliferative fibrovascular response to tissue insult by inflammation, surgery, or trauma
   B. Fleshy, red, elevated, vascular mass
   C. Corticosteroids or excision

VIII. Kaposi Sarcoma
   A. Reddish, vascular mass that may resemble hemorrhagic conjunctivitis
   B. Seen in patients with AIDS
   C. Treatment options include excision, chemotherapy, and low-dose radiotherapy.

IX. Lymphangiectasia
   A. Dilated and prominent lymphatic channels in the conjunctiva
   B. May fill with blood; hemorrhagic lymphangiectasia

Figure 5. Lymphangiectasia.

X. Lymphangioma
   A. Multiloculated lesion composed of dilated cystic spaces
   B. May represent superficial component of deeper orbital lymphangioma
   C. Difficult to completely remove tumor

XI. Lymphoma
   A. Diffuse, slightly elevated pink mass “salmon patch” in the bulbar conjunctiva or fornix
   B. Non-Hodgkin B-cell lymphoma
   C. Not possible to differentiate clinically between lymphoma and reactive lymphoid hyperplasia (benign)
   D. Systemic evaluation for systemic lymphoma

Figure 6. Lymphoma.
E. Treatment modalities include:
1. Excisional biopsy if small
2. External beam radiation (2000-4000 cGy)
3. Radioactive plaque
4. Local interferon
5. If systemic involvement, chemotherapy
6. Anti-CD20 monoclonal antibody (rituximab)

Select Readings
Conjunctival (Nonpigmented) Tumors: Pathology

Michele M Bloomer MD
Conjunctival (Pigmented) Tumors: Clinical Aspects
Melanocytic Tumors of the Conjunctiva

Jerry A Shields MD

I. Nevus
   A. Clinical
      1. Children and young adults
      2. Discrete
      3. Elevated
      4. Cysts
      5. Variably pigmented
      6. Stationary
   B. Pathology: May be junctional, compound, or deep, as in eyelid nevi
   C. Management: Observation; excision if growth occurs

II. Primary Acquired Melanosis
   A. Clinical
      1. Middle age
      2. Diffuse, patchy
      3. Flat
      4. No cysts
      5. Always pigmented
      6. Wax and wane
   B. Pathology
      1. Abnormal melanocytes in basal layer of the epithelium
      2. May show atypia
   C. Chances of evolution into melanoma (Armed Forces Institute of Pathology series)
      1. Overall: 32%
      2. Without atypia: 0%
      3. With atypia: 46%
      4. Severe atypia: 75%
   D. Most recent Wills Eye Institute series (Zimmerman Lecture 2008)
      1. Overall: 4%
      2. Without atypia: 0%
      3. With atypia: 3%
      4. Severe atypia: 13%
   E. Surgical management
      1. Varies with the clinical findings
      2. Good preoperative clinical evaluation
      3. Local retrobulbar anesthesia
      4. Superficial alcohol keratectomy
      5. Local excision of highly suspicious nodules
      6. Quadrantic map biopsies
      7. Limbal peritomy 360
      8. Cryotherapy from underside of conjunctiva
      9. Closure of conjunctiva with absorbable sutures
   F. Supplemental management: chemotherapy, mitomycin C or 5-fluorouracil

III. Malignant Melanoma
   A. Origin
      1. Primary acquired melanosis
      2. Pre-existing nevus
      3. De novo
   B. Clinical
      1. Variably pigmented mass
      2. Prominent conjunctival vessels
      3. Can involve cornea
      4. Can involve fornices
      5. Can invaded the orbit and globe
   C. Pathology: Malignant melanocytes; spindle or epithelioid cells
   D. Management
      1. Varies with the clinical findings
      2. Good preoperative clinical evaluation
      3. Local retrobulbar anesthesia
      4. Superficial alcohol partial epitheliection
      5. Excision by partial lamellar sclerokeratoconjunctivectomy
      6. A “no touch” approach should be employed
      7. Double freeze-thaw cryotherapy to conjunctival margins
      8. Closure of conjunctiva with absorbable sutures
9. Supplemental treatment
   a. Topical chemotherapy: mitomycin C
   b. Amnion or mucous membrane grafting
   c. Irradiation (plaque or external beam)

10. Orbital exenteration occasionally necessary

IV. Lesions Simulating Pigmented Conjunctival Tumors
    If time permits, short, rapid cases of lesion that simulate conjunctival melanoma will be presented, with audience participation.
Conjunctival (Pigmented) Tumors: Pathology
Histopathologic Aspects of Conjunctival Melanocytic Lesions

George J Harocopos MD

I. Specimen Submission

A. For optimal assessment of margins, it is helpful for the pathologist for the surgeon to specify the orientation by marking the specimen (eg, with differently colored sutures placed at 2 adjacent edges of the tissue). This is preferable to relying on markings placed on the filter paper, as the tissue may fall off the filter paper in the formalin jar. A diagram of the lesion should be included on the pathology requisition form, showing orientation of the specimen on the ocular surface and locations of orienting sutures.

B. Try to gently flatten the tissue as much as possible when placing it on the filter paper; minimizing any folding / scrolling of the tissue facilitates assessment of margins.

C. Allow the specimen to dry for about 1 minute on the filter paper (to help maintain the flattening of the tissue) before gently placing the paper in the formalin jar.

II. Gross Examination

A. It is important to send ocular surface neoplasm specimens directly to a pathologist with sufficient experience with conjunctiva, as optimal grossing examination / preparation technique is crucial to enabling reliable assessment of margins.

B. If the surgeon has specified the orientation on the requisition form, then the pathologist should preserve this orientation during grossing.

C. The pathologist should take care to embed the specimen on edge, to facilitate histologic assessment of the deep margin.

III. Histologic Features

A. Melanocytic nevus

1. May be confined to the stroma (intrastral melanocytic nevus) or be mostly in the stroma and in some areas across the stromal-epithelial junction (compound nevus) or, occasionally in pediatric cases, be confined to the junction (junctional nevus)

2. Oval, pear-shaped, and spindly cells, mostly with small nuclei, arranged in nests

3. Cells may or may not have melanin pigment in the cytoplasm. Lesions lacking pigment appear amelanotic clinically.

4. Epithelial cysts/nests are often present in the stroma interspersed among the melanocytes (and these cysts may generally be appreciated clinically at slit lamp)

5. There is generally no inflammatory reaction (correlating with the noninflamed clinical appearance), except in pediatric cases, which sometimes have inflammation.

B. Primary acquired melanosis (PAM) without atypia

1. Proliferation of melanocytes with small, bland nuclei (without prominent nucleoli), confined to the basal epithelial layer

2. Histologically similar to benign acquired melanosis (BAM), but the nomenclature is determined by clinical / demographic features (ie, “PAM without atypia” if the lesion is unilateral in a light-skinned patient, vs. “BAM” if there are bilateral patches of pigmentation in a dark-skinned patient)

BAM would generally not have any reason to be biopsied but may be seen incidentally in conjunctival biopsied for another reason (as can PAM without atypia); accordingly, it is helpful for the surgeon to specify the patient’s ethnicity on the pathology requisition form when submitting a conjunctival biopsy.

C. Primary acquired melanosis (PAM) with atypia

1. Generally unilateral in a light-skinned patient

2. Intraepithelial proliferation of melanocytes involving more than just the basal layer, with variable degrees of atypia (eg, epithelioid cells) and “discohesiveness,” and a variable amount of pigmentation

3. Variable degree of chronic inflammatory reaction in the subepithelial stroma

4. If involves > 75% of epithelial thickness, then may use the term “melanoma in situ”

5. Rule out invasion beneath the basement membrane and into the stroma (in which case the diagnosis is invasive melanoma rather than PAM with atypia): immunostaining with MART-1/tyrosinase-red or MelanA-red (or HMB45-red) may be helpful in ruling out invasion and in assessing lateral margins.

D. Invasive melanoma

1. Majority (~70%) of cases arise from PAM with atypia, fewer de novo or from nevus

2. Track of invasion of PAM into the stroma may be seen on histology, but may not be evident on every section.

3. Invasive portion may be amelanotic, even if arising from pigmented PAM.
4. A chronic inflammatory reaction is generally present in the stroma, correlating with the inflamed clinical appearance that is generally seen.

5. Thickness must be measured for staging purposes.

6. The surgeon should specify the location / extent of the lesion via a diagram on the requisition form, as this information is also required for staging purposes.

7. The deep and lateral margins must be assessed, as the status of the margins bears relevance for prognosis: immunostaining may be useful for margin assessment.

Selected Readings


Eyelid Tumors: Clinical Aspects

Ted H Wojno MD

I. Risk Factors for Malignancy
   A. History of prior skin cancer
   B. Excessive sun exposure, tanning bed
   C. Prior radiation history
   D. Smoking history
   E. Fair complexion

II. Signs of Malignancy
   A. Slow, painless growth
   B. Ulceration
   C. Irregular pigmentation
   D. Destruction of normal eyelid anatomy, lash loss (madarosis)
   E. Telangiectasis

III. Basal Cell Carcinoma (BCC)
   A. 90% of malignant eyelid lesions
   B. Location: lower lid (60%), medial canthus (20%), upper lid (15%), lateral canthus (5%)
   C. If seen in patients younger than 35 years old, suspect basal cell nevus syndrome (Gorlin syndrome) or xeroderma pigmentosum.
   D. Subtypes
      1. Nodular
         a. Most common
         b. Raised, pearly nodule with telangiectasia and central ulceration
      2. Morpheaform
         a. Slight elevation with indistinct margins
         b. More aggressive
      3. Subcutaneous; very uncommon

IV. Squamous Cell Carcinoma (SCC)
   A. More aggressive than BCC
   B. Arise spontaneously or from actinic keratosis
   C. More common in immunosuppressed patients
   D. May metastasize through the bloodstream, lymphatics, and via neurotrophic spread
   E. Clinical subtypes
      1. Erosive lesion is the most common and may simulate blepharitis.
      2. Nodular lesion is less common.

V. Sebaceous Cell Carcinoma
   A. Arises from meibomian glands, Zeis glands, or sebaceous glands in the caruncle.
   B. More common in women
   C. More common in the upper lid (more meibomian glands)
   D. May mimic blepharitis, conjunctivitis, or chalazion
   E. May be multicentric
   F. Pagetoid, intraepidermal spread is common.
   G. A full-thickness, wedge biopsy is often needed to confirm.
   H. A map biopsy is often needed to confirm multicentricity and pagetoid growth.

VI. Malignant Melanoma
   A. Incidence is increasing (sun exposure, tanning beds), and this is the fastest growing cancer in men.
   B. Arises spontaneously or from nevi or lentigo maligna
   C. Clinical subtypes
      1. Lentigo maligna melanoma is the most common form on the eyelid.
      2. Nodular melanoma
      3. Superficial spreading melanoma
      4. Amelanotic (nodular) melanoma

VII. Other Malignant Lesions

VIII. Treatment
   A. Surgery remains the mainstay of therapy.
   B. Mohs micrographic resection or resection with frozen section control for BCC, SCC, and some cases of sebaceous cell carcinoma. Otherwise, wide excision for sebaceous cell carcinoma.
   C. “Slow Mohs” can be used for melanoma vs. wide excision with histologic confirmation.
   D. Metastatic workup for melanoma over 1.5 mm thickness and should be considered for high-risk SCC and sebaceous cell carcinoma.
   E. Radiation therapy may be considered for BCC but is less effective than surgery. It is relatively ineffective for SCC, sebaceous cell carcinoma, and melanoma.
   F. Sentinel lymph node biopsy may be considered for sebaceous cell carcinoma, melanoma over 1 mm in thickness, or Merkel cell carcinoma.
G. Ipilimumab, a monoclonal antibody, is approved for advanced melanoma.

H. There are many trials for melanoma involving immunotherapy, cytokines, vaccines, and targeted therapy.

I. Exenteration is usually necessary for orbital involvement.

IX. Topical Therapy

A. Imiquimod (Aldara, Zyclara) is a Toll-like receptor agonist that activates immune cells that can be used to treat actinic keratosis (2 times/week for 16 weeks) and superficial basal cell carcinoma < 2 cm (5 times/week for 6 weeks).

B. 5-fluorouracil (Carac, Efudex, Fluorplex) is an antimetabolite that can be used to treat actinic keratosis (2-4 weeks) and superficial basal cell carcinoma (3-12 weeks).

X. Vismodegib (Erivedge)

A. An oral medication (“hedgehog signaling pathway” inhibitor) approved for metastatic BCC and locally advanced BCC that has recurred following surgery or in patients who are not candidates for surgery or radiation therapy. It has relatively mild side effects.

B. The hedgehog signaling pathway

1. Increases angiogenesis factors, cell proliferation cyclins, and anti-apoptotic gene expression

2. Is active in > 90% of basal cell carcinomas

3. Probably leads to disease through transformation of adult stem cells into cancer stem cells

4. Inappropriate activation leads to a variety of cancers.

XI. Other Investigational Chemotherapy for BCC

Itraconazole (Sporanox) and sonidegib

Selected Readings


Eyelid Tumors: Pathology

Curtis E Margo MD MPH

I. Theme: Perspectives on the Subclassification of Eyelid Tumors
   A. The subclassification of malignant skin tumors
      1. Pathologists’ perspective
      2. Clinicians’ perspective
      3. Clinical scientists’ perspective
   B. The subclassification of cutaneous tumors is common and, while usually based on reasonable histological criteria, can result in confusion and misleading implications about biological behavior.
      This discussion will focus on two examples:
      1. Basal cell carcinoma, the most common eyelid malignancy
      2. Merkel cell carcinoma, the most lethal eyelid malignancy

II. Basal Cell Carcinoma (BCC)
   A. Locally aggressive tumor of fair-skinned persons
      1. Usually on sun-exposed skin
         a. Surprisingly poorly correlated with total UV light exposure
         b. Increased incidence in immunosuppressed individuals
      2. Cell of origin: Evidence for follicular matrix cell
         a. Cytokeratin pattern almost identical to that of trichoblastoma
         b. Similar expression of epithelial adhesion molecule
      3. BCCs are stromal-dependent tumors; cannot transplant BCC without its stroma
   B. Histopathology
      1. Basaloid cells, peripheral palisading, and stromal changes
      2. Depending on source, 20 or more histological subtypes of BCC are recognized or reported
         a. Nodular
         b. Micronodular
         c. Pigmented
         d. Adenoid
         e. Adenoidcystic
         f. Infiltrating
         g. Superficial
         h. Cystic
         i. Keratotic
         j. Sclerosing
         k. Metatypical
         l. Morpheaform
         m. Pleomorphic
         n. And the list goes on . . .
   3. Why are there so many histological subtypes of BCC?
      a. Pathologists’ perspective
         They help to distinguish BCC variants from other non-BCC tumors. (Examples of this utility)
      b. Clinicians’ perspective: Subgroups of BCC should signify differences in clinical behavior.
         i. This may not always the case, however. Example: Pleomorphic BCC behaves like a typical BCC despite its ominous name.
         ii. What BCCs behave aggressively?
            (a) The most likely to recur after treatment (as an index of aggressiveness)
               (i) infiltrative
               (ii) micronodular
               (iii) multifocal-superficial
               (iv) sclerosing
               (v) perhaps metatypical
            (b) Confusion arises when pathologists do not use terms consistently; for example: infiltrative vs. sclerosing vs. morpheaform vs. fibrosing BCC
      c. Clinical scientists’ perspective: Interest is finding evidence to support a biological reason for dividing tumors into subgroups.
         i. Is there clinical utility in recognizing subgroups?
            When differences in clinical prognosis exist
            This hypothesis must be tested and validated clinically.
         ii. Is there a more fundamental aspect of tumor biology that justifies subclassification?
            Perhaps. The answer to this question is the domain of the research scientist.
III. Merkel Cell Carcinoma

Dermal tumor first recognized in 1972 and called “trabecular carcinoma.”

A. The trabecular pattern noted histologically is not always present, so it was eventually subdivided into 3 histological subgroups:
   1. Trabecular
   2. Intermediate cell
   3. Small cell

B. Discovery of neurosecretory granules suggested the tumor’s origin as the neural crest, probably from the Merkel cell, a neurocrest cell inhabitant of the epidermis associated with sensory nerve axons.
   1. Merkel cells are usually found in the epidermis, yet the tumor usually arises in the dermis. The precise histogenesis is unclear, but the name “Merkel cell carcinoma” has gained popularity and is generally accepted.
   2. Merkel cell carcinoma during the age of immunohistochemistry developed a marker profile:
      Positive expression: pan-cytokeratin (92%-100%); cytokeratin 20 (92%-100%); CAM 5.2 (80%-98%); EMA (73%-93%); neuro-specific enolase (70%-88%); chromogranin A (46%-74%); neurofilament protein (30%-70%); synaptophysin (19%-48%); vimentin (0%-12%)

C. Most authorities consider Merkel cell carcinoma synonymous with primary neuroendocrine carcinoma of the skin.

D. Reports began to emerge describing tumors with Merkel cell carcinoma morphology by light microscopy but with negative CK20 staining and with negative chromogranin A or synaptophysin.
   These tumors were described as “primary neuroendocrine carcinomas of the skin” (including eyelid) and explicitly separated from Merkel cell carcinoma.

E. Too few cases have been reported to determine if they behave differently from “typical” Merkel cell carcinoma.

Clinicians now face a diagnosis of Merkel cell carcinoma and primary neuroendocrine carcinoma of the eyelid, in which the pathologist may or may not imply a distinct biological distinction. The clinical relevance of the distinction is unresolved.

IV. Summary

A. Pathologists tend to subclassify tumors based on light microscopic appearances to help them correctly distinguish tumors with similar histological features. This utility serves the pathologists but may not translate into differences in biological behavior; in other words, subclassification of tumors may not have clinical relevance.

This phenomenon varies according to tumor.
   1. Some subgroups of BCC behave more aggressively. Nodular BCC is the usually standard.
   2. Beware that not all pathologists use subclassification terminology of BCC the same way.
   3. Merkel cell carcinoma may differ from primary neuroendocrine carcinoma of eyelid, but additional clinical studies are needed to determine if the later diagnosis is a low-grade malignancy.

B. The era of immunohistochemistry has enhanced the pathologist’s ability to subclassify tumors based on patterns of marker expression. This may help pathologists to achieve greater diagnostic certainty but may not always translate into differences in clinical behavior.

C. The clinical scientist faces the challenge of correlating subgroups of tumors with clinical outcome.

Select Readings

Orbital Tumors: Clinical Aspects
Recent Advancements in the Management of Lacrimal Gland Adenoid Cystic Carcinoma

David T Tse MD FACS

I. Introduction

The grave prognosis for patients with adenoid cystic carcinoma of the lacrimal gland (LGACC) is well recognized. The difficulty in achieving a long-term disease-free survival in this disease is attributed to the complex regional orbital anatomy and the aggressive biological behavior of the tumor. The intent of this presentation is to review the clinical characteristics, pertinent diagnostic and pathologic features, biological behavior, conventional management options, and long-term survival outcomes of the intra-arterial cytoreductive chemotherapy protocol. Research efforts on tumor cell line development, elucidating molecular signature, and identifying new targets for potential therapeutic applications will also be explored.

II. Epidemiology

A. Adenoid cystic carcinoma constitutes the most common nonlymphoid malignant tumor of the lacrimal gland.

B. Accounts for 25%-30% of epithelial lacrimal gland tumors

C. A bimodal distribution, with a peak incidence in the second and fourth decades of life

D. No apparent sex predilection

E. This tumor tends not only to affect younger patients but also to confer the worst prognosis among the malignant tumors of the lacrimal gland.

III. Clinical Presentation

A. Patient usually complains of periocular pain, mild ptosis, and proptosis, along with downward and inward displacement of the globe.

B. Pain is a predominant symptom due to perineural invasion and bone infiltration of the tumor.

C. Other symptoms include brow numbness and diplopia.

D. Symptoms typically have been present for around 6 months and almost always less than 1 year.

IV. Biological Behavior

A. Tends to invade nerves and lymphatic channels, resulting in microscopic spread

B. Local recurrence is common, occurring in nearly half of patients within 2 years, with soft tissues or orbital bone as the most frequent sites.

C. Bone and lung are common foci of distant metastases.

D. A propensity for intracranial extension via the lacrimal nerve through the superior orbital fissure

E. Intracranial involvement is the principal cause of death.

V. Conventional Treatment Options

A. Orbital exenteration alone or exenteration combined with removal of the contiguous bone

B. A more aggressive multidisciplinary team approach includes resection of the orbital roof, the lateral wall, the lids, and the anterior portion of the temporalis muscle where the zygomaticofrontal and zygomaticotemporal nerves extend.

C. Adjunctive postoperative radiotherapy of 5000 to 6000 rads

VI. Prognosis

Despite extensive surgery and radiation therapy, the prognosis for LGACC patients remains grim, with survival of less than 50% at 5 years and a dismal 20% at 10 years regardless of the local treatment regimens.

VII. Rationales for a New Treatment Approach

A. Since adenoid cystic carcinomas have a proclivity for microscopic perineural, soft tissue, and bone infiltration, the bounds of surgical excision may have been breached.

B. Surgery alone does not routinely result in a high cure rate.

C. Radiation therapy may “mop up” residual cancer cells, but tissue penetration by radiation can be a limiting factor.

D. Exenterations, exenteration combined with radiation, and radical cranio-orbital resection have not resulted in improved survival.

VIII. Rationales for Neoadjuvant Intra-arterial Cytoreductive Chemotherapy (IACC)

Major advantages of intra-arterial drug infusion:

A. A very high dose of drug is delivered to the target area; enhancing tumor cell kills by increasing AUC (area under curve) concentration and shifting the dose response curve to the right.

B. Systemic toxicity may be limited if a high percentage of the drug is removed as it passes through the target capillary bed and the remainder is diluted in the systemic circulation.
C. Neoadjuvant chemotherapy, chemotherapy given prior to the primary or definitive treatment, induces tumor cell necrosis and potentially minimizes dissemination of any viable tumor cells during the subsequent surgical manipulation.

D. Induction chemotherapy may induce a reduction in tumor size, rendering the mass more amenable to surgery for tumor margin clearance.

IX. IACC Protocol

A. Two preoperative cycles of chemotherapy. Each cycle consists of a single intra-arterial cis-platinum infusion and intravenous doxorubicin (Adriamycin) push for 3 days.

B. Each neoadjuvant chemotherapy cycle is given at least 21 days apart, followed by serial orbital CT scans to assess “radiographic response.” A third cycle may be given.

C. Three to four weeks after the last cycle of chemotherapy and following hematologic recovery, patient undergoes orbital exenteration.

D. Four to six weeks after exenteration, radiation therapy to the orbit is given.

E. Two to 4 weeks after the completion of radiation, 4 cycles of adjuvant intravenous cis-platinum and Adriamycin chemotherapy are administered.

F. Rationale for the 6 cycles of chemotherapy is based upon the theoretic principle that at diagnosis, a tumor has a population of approximately $10^{12}$ cells. A highly effective (99%) chemotherapy regimen will kill $10^2$ or 2 log-unit cells with each application. Thus, 6 applications ($10^2 \times 10^2 \times 10^2 \times 10^2 = 10^{12}$) would theoretically be required to achieve a “cure.”

X. Outcomes of Neoadjuvant IACC Protocol

A. 19 consecutive patients

B. Group 1 ($n = 8$)
   1. Intact lacrimal artery
   2. Completed protocol
   3. Cumulative 10-year disease-free survival: 100%
   4. Complete local disease control and no metastatic disease
   5. Longest survivor is 25 years

C. Group 2 ($n = 11$)
   1. Absent lacrimal artery
   2. Did not complete or deviated from protocol
   3. Cumulative survival: 72%
   4. 8 patients disease-free
      a. Median survival of 7 years (range: 2-13 years)

b. 3 patients are not disease-free.
   i. 2 patients died as a direct result of ACC.
   ii. 1 patient is alive with no locoregional disease but has unresectable lung metastases.

D. Factors contributing to suboptimal response to the IACC protocol
   1. Extent of disease or breach of orbital boundaries at presentation
   2. Failure to obtain a preoperative incisional biopsy prior to surgical planning
   3. Surgical disruption of the lateral orbital wall, tumor manipulation, and incomplete excision
   4. Absence of a lacrimal artery to maximize drug delivery
   5. Failure to implement all components of the IACC protocol

E. Conclusions
   1. IACC appears to be effective in local disease control and overall disease-free survival.
   2. An intact lacrimal artery, no disruption of bone barrier or tumor manipulation, and protocol compliance are factors responsible for favorable outcomes.
   3. The chemotoxicity complication rate is limited and manageable.

XI. Future Directions

A. Globe-sparing strategy by incorporating IACC as the core element: Confirmation of IACC apoptotic effect on histologically viable cells at time of tumor resection

B. Exome sequencing to better understand tumor biology: Identify mutational profile
   1. Mutational clustering analysis as prognostic tool for survival, recurrence, and/or metastasis – toward personalized medicine
   2. Identify possible pathway dysregulation as therapeutic targets

C. Lacrimal gland ACC cell line from human samples
   1. In-vitro model for pharmaceutical library testing on cell proliferation, postmitotic commitment and differentiation
   2. Xenograft tumor animal model
      a. Identification of cellular phenotypes / genotypes capable of generating exogenous tumor masses – cancer stem cell theory – therapeutic target identification
      b. In-vivo model system for pharmaceutical testing based on in-vitro assays with cell line
References


Orbital Tumors: Pathology

Victor M Elner PhD MD

I. Epithelioid Hemangioma / Angiolymphoid Hyperplasia With Eosinophilia

A. Benign vascular proliferation with associated inflammation
   1. Proliferating arterioles, venules, and capillaries
      a. Vascular proliferations form lobular configurations.
      b. Endothelial cells show hobnail configurations and vacuolization.
   2. Benign inflammatory component
      a. Chronic inflammatory cells
      b. Eosinophils

B. Clinical findings and course
   1. Female preponderance; young and middle-aged
   2. Combined findings of inflammation and mass effect of eyelids and orbit
      a. Symptoms of blurred vision, eyelid swelling, and ptosis
      b. Proptosis if orbital involvement is present
   3. Often resolves with surgery
      a. Bevacizumab may be useful adjuvant.
      b. Lesions are usually corticosteroid resistant.

II. IgG4-Related Orbital Inflammation / Inflammatory Orbital Pseudotumor

A. Tumefactive lesions containing rich in IgG4+ plasma cells
   1. Lymphoplasmacytic infiltrates; eosinophils
   2. Storiform fibrosis
   3. Obliterative phlebitis

B. Clinical findings
   1. Almost always an orbital process, most often involving lacrimal gland
   2. Similar lesions involving salivary glands, sinuses, lymph nodes, or distant sites
   3. Elevated serum IgG4 (> 135 mg/dL)
   4. Peripheral eosinophilia
   5. Asthma

C. Pathogenesis
   1. Likely Th-2 and Treg responses to autoantigen that is host driven
   2. Elevated levels of Th-2 cytokines, TGF-beta, and CTGF cytokines
   3. Fibroblast proliferation and fibrosis due to cytokine response
   4. IgG4 secreted as a mitigating anti-inflammatory response to cytokines
      a. Inability to activate complement responses in contrast to other IgG
      b. Inability to activate Fc receptor in contrast to other IgG
      c. Promotes development of antigenic tolerance

D. IgG4-related inflammation: subtype of orbital inflammatory pseudotumor
   1. Responds to corticosteroids
   2. Rituximab

III. Necrotizing Granulomatous Myositis

A. Extraocular muscle showing diffuse granulomatous inflammation
   1. Many giant cells
   2. Geographic areas of necrosis with palisaded histiocytes
   3. Degenerating and necrotic muscle fibers
   4. Moderate numbers of lymphocytes; rare plasma cells

B. Immunohistochemical findings
   1. CD3+ T-lymphocytes >> CD20+ B-lymphocytes
   2. CD4+ T-lymphocytes >> CD8+ T-lymphocytes
   3. Many CD163+ histiocytes
   4. T-lymphocytes and histiocytes line degenerating myofibers
   5. Stains for bacteria, mycobacteria, and fungi are negative.

C. Clinical
   1. Abrupt onset of periocular edema, erythema, and pain
   2. Diplopia with impaired ocular motility
   3. May be a variant of focal myositis that usually involves large skeletal muscles
   4. Initial response to corticosteroids has been dramatic.
   5. Recurrence requires cytotoxic therapy
IV. Multiple Myeloma of the Orbit

A. Clinical findings
   1. Disease of middle-aged and elderly adults
   2. Almost every case of malignant plasma cell neoplasm in the orbit
      a. Radiographic evidence of destruction of bone
      b. Very rare to have only soft tissue involvement
      c. These cases are multiple myeloma of the orbit not plasmacytoma.
   3. May have effect on vision due to vascular compromise of retina or optic nerve

B. Pathological findings
   1. Plasma cells of varying degrees of differentiation
   2. Monoclonal restriction; immunoglobulin light chain restriction
   3. CD138, CD38, CD56, and CD79 immunopositivity
   4. Systemic evaluation
      a. SPEP, bone marrow biopsy, etc.
      b. Needed in cases where orbital lesion is initial manifestation
Challenging Cases: Clinico-Pathologic Correlations

Sander Dubovy MD
2014 Advocating for Patients

Zelia M Correa MD

Ophthalmology’s goal in protecting quality patient eye care remains a key priority for the American Academy of Ophthalmology (the Academy). All Eye M.D.s should consider their contributions to the following three funds as (a) part of their costs of doing business and (b) their individual responsibility in advocating for patients:

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

Your Eye M.D. colleagues serving on the Academy’s Secretariat for State Affairs commit many hours on your behalf while strategizing and collaborating with state ophthalmology society leaders to ensure the success of Surgery by Surgeons. Their ultimate goal—protecting quality patient eye care in the states—requires a robust Surgical Scope Fund, and we need every single Eye M.D. to step up to the plate and deliver with their checkbooks.

The Academy’s federal advocacy arm works to protect ophthalmology practices from payment cuts, burdensome regulations, and scope of practice threats, as well as to advance the profession by promoting funding for vision research and expanded inclusion of ophthalmology in public and private programs. It is critical for our OPHTHPAC Fund to also be strong.

Surgical Scope Fund

The Surgical Scope Fund (SSF) provides grants to state ophthalmology societies to support their legislative, regulatory and public education efforts. Since its inception, the Surgery by Surgeons campaign, in partnership with state ophthalmology societies and with support from the SSF, has helped 31 state/territorial ophthalmology societies reject optometric surgery proposals.

2014 has proved to be a challenging year, with several battleground states facing major optometric surgery initiatives. A number of state ophthalmic societies benefited from SSF disbursements and were able to successfully implement patient safety advocacy campaigns to defeat attempts by optometry to expand its scope of practice to include surgery. The Nebraska Academy of Eye Physicians and Surgeons was successful in its patient advocacy and public education efforts to derail legislation that would have granted optometrists the authority to perform eyelid surgery and injections. Additionally, the Arizona Ophthalmological Society succeeded in protecting patients by stopping legislation that would have allowed optometrists to gain authority to perform injections. The SSF is also at work assisting ophthalmic societies with their efforts to protect patients in California, Delaware and Massachusetts.

Proactively, the Georgia Society of Ophthalmology introduced a bill that would establish a formal definition of “surgery” into state law. While the legislative session expired before the bill could advance, Georgia ophthalmologists will be back in 2015 in an effort to pass this important safeguard for their patients.

2014 was certainly not without its challenges. Despite a vigorous battle for patient safety on the part of the Tennessee Academy of Ophthalmology, the Tennessee Medical Association and the Academy, the legislature passed a bill allowing optometrists to inject anesthesia into the eyelids. Previously, optometrists were authorized to perform only therapeutic injections and any surgical procedure that required no more than a topical anesthetic. And in Louisiana, the Academy, the Louisiana Ophthalmology Association, and the Louisiana State Medical Society vigorously opposed legislation that would authorize optometrists to perform certain scalpel and laser surgeries and injections.

On June 1, 2014, Louisiana Governor Bobby Jindal signed into law a laser surgery bill that will allow optometrists to perform scanning laser trabeculoplasty and argon laser trabeculoplasty glaucoma surgery procedures, as well as YAG capsulotomy surgery procedures, with the completion of as little as 32 hours coursework. The Academy’s Secretariat for State Affairs knows from past experience that with this success in Louisiana, organized optometry will push hard in 2015 to see if they can gain additional surgery states. This is why everyone must “advocate for patients,” engage in the state political process and aggressively support the SSF.

California, Delaware and Massachusetts remain “in play” and are still faced with active O.D. surgery legislation. When it comes to state legislation of any kind, California and Massachusetts are often considered bellwether states for the rest of the nation. Now more than ever, your contribution to the SSF is needed as a critical tool of the Surgery by Surgeons campaign to protect quality surgical care for our patients. The Academy relies not only on the financial contributions to the SSF from individual Eye M.D.s and their business practices, but also on the contributions made by ophthalmic state, subspecialty and specialized interest societies. The American Association of Ocular Oncology and Pathology (AAOOP) contributed to the Surgical Scope Fund in 2013, and the Academy counts on its contributions in 2014.

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, today OPHTHPAC is one of the largest and most successful political action committees in the physician community. In the past, Politico highlighted OPHTHPAC as one of the most successful health PACs in strategic giving. By making strategic election campaign contributions and independent expenditures, OPHTHPAC helps us elect friends of ophthalmology to federal leadership positions, ultimately resulting in beneficial outcomes for all Eye M.D.s. For example, in the 2012 election cycle, OPHTHPAC was able to help retain 20 physicians in Congress. Among the significant impacts of OPHTHPAC are the following:

- Prevented onerous national patient prescription requirements for compounded drugs and preserved access to most ophthalmic compounded drugs for office use
- Averted significant cuts to Medicare payments due to the Sustainable Growth Rate (SGR) formula
Advocating for Patients

2014 Subspecialty Day | Ocular Oncology/Pathology

Protected practice expense increases for ophthalmology when other specialties sought legislative carve-outs

Protected ophthalmologists’ ability to provide in-office diagnostic testing without triggering self-referral violation

Prompted congressional action that helped reduce ophthalmology’s multiple procedure payment reduction

Secured appointment of full-time ophthalmology national program director in the U.S. Department of Veterans Affairs

Provided further exemptions from both the Electronic Prescribing and Meaningful Use EHR penalties

Leaders of the AAOOP are part of the Academy’s Ophthalmic Advocacy Leadership Group (OALG), which has met for the past seven years in January in the Washington, D.C., area to provide critical input and to discuss and collaborate on the Academy’s advocacy agenda. The topics discussed at the 2014 OALG meeting included a focus on the collaboration needed among the Academy and its OALG partners on the issue of compounding. As a 2014 Congressional Advocacy Day (CAD) partner, the AAOOP ensured a strong presence of ocular oncology and pathology specialists to support ophthalmology’s priorities as nearly 400 Eye M.D.s had scheduled CAD visits to members of Congress in conjunction with the Academy’s 2014 Mid-Year Forum in Washington, D.C. The AAOOP remains a crucial partner with the Academy in its ongoing federal and state advocacy initiatives.

State Eye PAC

We all must also support our respective State Eye PACs, because state ophthalmology societies cannot count on the Academy’s SSF alone. 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 also critical. The Secretariat for State Affairs strategizes with state ophthalmology societies on target goals for state eye PAC levels.

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 three funds are necessary and should be considered the costs of doing business. 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 who are volunteering their time on your behalf to serve on the OPHTHPAC* and Surgical Scope Fund** Committees, as well as your state ophthalmology society leaders, when they call on you and your subspecialty society to contribute. Advocate for your patients now!

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Retinoblastoma: Intra-arterial Chemotherapy – Pro

David H Abramson MD FACS

Although intra-arterial chemotherapy for retinoblastoma (now called ophthalmic artery chemosurgery; OAC) was first performed for retinoblastoma more than 50 years ago, by Reese, it has been the over 25-year experience from Japan in more than 1000 infusions and the over 1000 infusions done in New York since 2006 (and replicated in 40 countries worldwide since then), followed by over 40 peer-reviewed publications, that have confirmed the efficacy, reproducibility, and safety of this approach. No other technique can match its ability to cure eyes with extensive subretinal seeds, and its use has dramatically affected the need for primary enucleation of Group D, E, and Reese-Ellsworth V eyes. It remains as the only choice for management of eyes that fail primary systemic chemotherapy. Success rates appear similar in all published reports, but ocular side effects are clearly related to experience; as with all surgery, the largest number of complications occur in the centers with the least experience.

Selected Reading

Retinoblastoma: Intra-arterial Chemotherapy – Con
Or, The Importance of Preclinical Models

Matthew W Wilson MD

I. Super-selective Intra-arterial Chemotherapy (SSIOAC)
   A. Why?
      1. Targeted local delivery of drug
      2. Minimize total dose exposure of chemotherapy
      3. Great results
         a. Ocular salvage
         b. Electroretinogram data
   B. Why not?
      1. SSIOAC is an evolution of Kaneko’s intra-carotid chemotherapy, but not the same.
         a. Different delivery site
         b. Different dilution of drug
         c. Same amount of drug (5 mg melphalan)
      2. No preclinical modeling
      3. Retrospective complications have been reported, principally vascular.
      4. SSIOAC does not provide patient-centric care.
         a. High-risk eyes have high-risk pathology.
         b. Undertreating the entire patient poses risk of metastases.
         c. Neoadjuvant therapies alter pathology going forward.

II. Preclinical Model
   A. In vitro: Melphalan 4 μg/ml kills retinal endothelial cells (RECs).
      1. p38 mediated REC apoptosis
      2. NFκB mediated ICAM-1 upregulation in RECs with leukostasis
   B. In vivo: Nonhuman primate (NHP) model of SSIOAC
      1. 6 NHPs were treated with SSIOAC x 3 per published protocols.
      2. Real-time fundus photography and post-treatment intravenous fluorescein angiography were performed.
         a. Pulsatile pallor of the optic nerve
         b. Retinal arteriole precipitates
         c. Choroidal and retinal capillary drop out
         d. Vascular sheathing
         e. Leakage
   3. Pathology
      a. Retinal arteriole leukostasis and occlusion
      b. Occlusion of the short posterior ciliary arter-ies
      c. Intraluminal birefringent foreign bodies
      d. Choroidal inflammation
      e. Central retinal artery thrombosis
      f. Loss of the ganglion cell layers
      g. Ophthalmic artery dissection
      h. Intimal hyperplasia
      i. Central retinal dissection
      j. Orbital vessel thrombosis

III. Case Report: Progressive Enophthalmos and Choroidal Atrophy Following SSIOAC

A 9-month-old with unilateral retinoblastoma of the right eye (Reese Ellsworth Group E and International Classification Group E) was treated with 4 cycles of SSIOAC with melphalan and topotecan at an outside institution. The tumor responded to therapy, regressing to a calcified mass. Upon follow-up evaluations, both the iris and choroid were observed to atrophy, enophthalmos was noted, and the eye became painful. Vision declined from normals to light to no reaction to light. The eye was enucleated at the parents’ request. Pathology showed iris and choroidal atrophy with an existing iritis, cyclitis, and scleritis. Occlusion of uveal and retinal vessels was noted. Review of serial MRIs from diagnosis to prior to enucleation showed proportional decreases in the rate of ocular and orbital growth.

Selected Readings


Uveal Melanoma: Systemic Surveillance – Pro

Chris Bergstrom MD

I. How do we screen patients for metastatic disease?
   A. Liver function testing (LFT)
      1. Advantages
      2. Disadvantages
   B. Imaging
      1. Chest x-ray (CXR)
         a. Advantages
         b. Disadvantages
      2. Abdominal ultrasound
         a. Advantages
         b. Disadvantages
      3. Computerized tomography (CT)
         a. Advantages
         b. Disadvantages
      4. Positron emission tomography (PET) scanning
         a. Advantages
         b. Disadvantages
      5. Magnetic resonance imaging (MRI)
         a. Advantages
         b. Disadvantages

II. Why screen patients with uveal melanoma for metastasis?
   A. Earlier detection may prolong survival by offering treatment of metastatic disease.
      1. Partial hepatectomy
      2. Intrahepatic chemotherapy
      3. Ipilimumab treatment
      4. Selective internal radiation therapy (SIRT)
      5. Selumetinib treatment
   B. Enhanced quality of life
      1. Most patients want screening.
      2. Normal screening is reassuring for the patient.
   C. Life planning: Allows patients more time for life planning with earlier detection of metastasis

III. Survey of Ocular Oncologist Screening Recommendations and Practice Patterns
   A. What tests do you recommend for metastatic screening?
      1. LFTs/CXR: 22.22%
      2. Abdominal ultrasound: 27.78%
      3. CT/PET CT: 16.67%
      4. MRI: 22.22%
      5. Other: 11.11%
   B. Do you recommend screening prior to treatment?
      1. Yes: 94.12%
      2. No: 0%
      3. Sometimes: 5.88%
   C. Do you recommend screening after treatment?
      1. Yes: 88.24%
      2. No: 0%
      3. Sometimes: 11.76%
   D. At what frequency do you recommend screening?
      1. Annually: 23.53%
      2. Biannually: 17.65%
      3. More than twice a year: 5.88%
      4. Depends on tumor size / genetics / age of patient: 52.94%
   E. Do you biopsy the tumor for genetic testing?
      1. Yes: 64.71%
      2. No: 5.88%
      3. Sometimes: 29.41%
   F. Do adjust your screening based on the biopsy results?
      1. Yes, I adjust the frequency and/or modality: 47.06%
      2. No change: 5.88%
      3. I refer high-risk patients to a medical oncologist for screening: 41.18%
      4. I don’t do biopsies: 5.88%
   G. Is it your perception that patients want metastatic screening?
      1. Yes, they want screening: 47.06%
      2. No, they don’t care: 5.88%
      3. Depends on the patient: 47.06%
   H. Do you adjust your screening protocol based on patient desires?
      1. Yes: 76.47%
      2. No: 23.53%
I. How long do you recommend screening after treatment of the primary tumor?
   1. 5 years: 20%
   2. For life: 53.33%
   3. Depends on the size or genetics of the tumor: 26.67%

Selected Readings
Uveal Melanoma: Systemic Surveillance – Con

Evangelos S Gragoudas MD

Background

Up to 50% of patients diagnosed with uveal melanoma eventually die from metastasis, most commonly developing in the liver (approximately 90% of cases\textsuperscript{1,2}). Effective therapies for treating hepatic metastasis are currently unavailable, and this raises questions about the value of early diagnosis and treatment of metastasis to reduce mortality.

Metastasis Surveillance

Methods

The standard surveillance protocol followed by the Collaborative Ocular Melanoma Study (COMS)\textsuperscript{3} sites included annual liver function tests and chest x-ray, to monitor for metastasis. If indicated (eg, if liver enzymes were elevated), this was followed by imaging (ultrasound, abdominal CT scan, MRI) and other diagnostic tests (eg, liver biopsy) to confirm the presence of metastasis. Although annual chest x-rays were performed in the past, there is evidence that very few cases of metastatic disease are identified with this procedure.\textsuperscript{3}

Recently, newer diagnostic imaging tools (eg, positron emission tomography / computed tomography) have begun to be evaluated,\textsuperscript{3} but thus far the use of these more sophisticated imaging tools does not appear to have been adopted as a standard diagnostic procedure. Depending on the frequency of use for surveillance purposes, CAT scans may place some patients at increased risk of other cancers due to radiation exposure.\textsuperscript{3}

Impact on mortality

Investigators in the COMS Trials found no differences in survival between patients who received treatment for metastatic disease and those who did not.\textsuperscript{1} Patients in a Finnish registry 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.\textsuperscript{6} Similar results were found by our group at Massachusetts Eye and Ear Infirmary. A comparison of patients who were diagnosed with metastasis at the time of routine metastatic examination (“asymptomatic” group) and those who were diagnosed after developing symptoms (“symptomatic” group) revealed longer median survival time from diagnosis of metastasis to death in the asymptomatic group than the symptomatic group (6 months vs. 3 months; \( P < .001 \)). Similar median survival times between initial diagnosis of the tumor and death were observed in the 2 groups (45 months for symptomatic patients and 41 months for asymptomatic patients; \( P = .61 \)).\textsuperscript{7} These findings suggest that the apparent increase in survival time after metastasis diagnosis in asymptomatic patients is due to lead time bias.

Of note, patients in the 2 groups were similar with regard to known prognostic factors for melanoma-related death (tumor diameter \( P = .12 \), tumor location \( P = .39 \), and age \( P = .21 \)), and the proportion of patients undergoing any treatment for metastasis was similar between the 2 groups (67% of the asymptomatic group and 60% of the symptomatic patients).

Treatment for Metastatic Uveal Melanoma

Currently there are no effective treatments for hepatic metastasis, with median survival ranging from 2 to 12 months.\textsuperscript{7-9} A meta-analysis of studies completed through mid-2008, which included 25 Phase 1 and 2 clinical trials, provided no evidence that any treatments for liver metastases prolong life or that aggressive invasive interventions confer a survival benefit.\textsuperscript{9}

Many studies have evaluated treatments that have been shown to be beneficial for cutaneous melanoma, but efficacy has not been demonstrated in patients with uveal melanoma, perhaps due to differences in molecular pathogenesis.

Molecurally targeted therapy and immunotherapy are promising approaches currently under evaluation for metastatic uveal melanoma, but data are not yet available to confirm efficacy.

Until more effective treatments can be found, aggressive systemic surveillance seems unnecessary. However, reasonable surveillance measures (ie, in terms of costs, risks, and benefits to the patient), may be worthwhile to identify patients who may benefit from investigational treatments in clinical trials.

Summary

The present data suggest the following:

1. Systemic surveillance does not confer a survival benefit.
2. There are currently no effective treatments for hepatic metastases, which are fatal soon after diagnosis.
3. Close monitoring for and treatment of metastasis is associated with high, unnecessary expenses and occasional morbidities (eg, hemorrhage from liver biopsy).

Nevertheless, annual liver function tests and imaging with ultrasound in high-risk patients may be worthwhile. Patients diagnosed with metastasis may choose to participate in ongoing clinical trials evaluating therapies that could prove to be efficacious.

Evolving evidence of the value of mammography to reduce deaths from breast cancer may serve to illustrate the careful consideration that must be made when making decisions about surveillance procedures. Recent findings from a 25-year follow-up study of women enrolled in a randomized trial of mammography screening revealed no survival advantage associated with annual mammogram screening.\textsuperscript{10} Based on these and other similar studies, the Swiss Medical Board recommended that mammography screening programs be discontinued, a controversial recommendation among cancer experts.\textsuperscript{11}
References


Iris Melanoma: Excision

Arun D Singh MD

Iris melanoma and its simulating entities are managed by observation, incisional biopsy, excisional biopsy, or radiation therapy, depending upon the size, extent, and suspected clinical diagnosis. Where indicated, surgical excision for localized iris melanoma has the advantage of providing diagnosis, prognosis, and treatment in a single surgical procedure. However, traditional methods of iris melanoma resection via sector iridectomy require a single, large corneoscleral incision with or without conjunctival flap. In order to obtain clear surgical margins for a potentially malignant tumor, sector iridectomy may involve excision of 25%-50% of the iris. Correspondingly, the corneoscleral incision can involve 25%-50% of the limbus circumference. Repair of such a large corneoscleral incision has the potential for wound leak, hypotony, hyphema, cataract, corneal edema, and astigmatism, with visual recovery requiring up to 6 weeks or longer, reminiscent of recovery after extracapsular cataract surgery. Limited outcome data have been reported for iridectomy performed for iris, in part because of the rarity of such indication.
Iris Melanoma: Radiation Therapy

E Rand Simpson MD

Uveal melanoma involving the iris is typically visible to the patient and during routine ophthalmic examinations. These tumors are usually small in size and owing to their limited metastatic potential, can often be observed for growth before treatment. A significant majority of iris tumors extend into the ciliary body or are themselves extensions from primary ciliary body tumors.

When indicated, melanomas that involve the iris can be treated by iridectomy, iridocyclectomy, or enucleation based on whether the tumor is thought to be resectable and contributing to the presence of glaucoma. Radiotherapy, employing brachytherapy or charged particle radiation, has provided an option for management without requiring intraocular surgery with its attendant risks.

Our present series includes 35 patients with melanoma confined to the iris or melanoma in the iris with extension to or from the ciliary body, treated with iodine-125 brachytherapy. A full ophthalmic evaluation, including assessment of visual acuity, tonometry, slitlamp examination, and ophthalmoscopy, was completed in all cases. Low- and high-frequency ultrasound with or without stand-off techniques was performed in all cases, and ultrasound biomicroscopy was particularly helpful in determining tumor margins and apical height for brachytherapy planning purposes. This examination was critical in establishing the presence and degree of ciliary body involvement in cases of melanoma primarily thought to be located in the iris exclusively.

Episceral plaques containing iodine-125 are fixed to the eye over the tumor base, and ionizing radiation penetrates the sclera and cornea, sterilizing the tumor as well as supplying a safety factor to include tumor margins. All iodine-125 seeds were calculated as point sources, according to Collaborative Ocular Melanoma Study calculations. All tumor margins were estimated with transillumination and/or ultrasound microscopy, together with immersion ultrasound as required.

Corneal integrity in all patients and local tumor control were achieved in > 90% of patients. Thirty-three of 35 patients were alive at 2 years following treatment.

Conclusions

Plaque radiotherapy employing iodine-125 is a successful management option for treating melanoma involving the iris. Methods and outcomes as well as advantages and disadvantages to this therapy will be discussed.
Primary Intraocular Lymphoma: Radiation

Janet L Davis MD

I. Reports of Ocular Irradiation for Intraocular Lymphoma (after Jahnke, et al.)1

<table>
<thead>
<tr>
<th>Author(s), Year of Publication</th>
<th>Treatment Modalitya</th>
<th>Chemotherapeutic Agentsb</th>
<th>No. of PIOL Patients</th>
<th>Ocular Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valluri, 1995</td>
<td>High-dose IV chemo, IT chemo, WBRT, ORT</td>
<td>MTX, cytarabine</td>
<td>3</td>
<td>3/3 (3 CR)</td>
</tr>
<tr>
<td>Cassoux, 2000</td>
<td>Retrospective series with various modalities</td>
<td>Retrospective series with various regimens</td>
<td>44</td>
<td>Not reported on an individual basis</td>
</tr>
<tr>
<td>Ferreri, 2001</td>
<td>High-dose IV chemo, PO chemo, WBRT</td>
<td>Vincristine, MTX, procarbazine</td>
<td>2</td>
<td>2/2 (2 CR)</td>
</tr>
<tr>
<td>Ferreri, 2002</td>
<td>High-dose IV chemo, IT chemo, WBRT, ORT</td>
<td>MTX, cytarabine, CHOP</td>
<td>22</td>
<td>15/22 (13 CR, 2 PR)</td>
</tr>
<tr>
<td>Hoffman, 2003</td>
<td>Retrospective series with various modalities</td>
<td>Retrospective series with various regimens</td>
<td>10</td>
<td>Not reported on an individual basis</td>
</tr>
<tr>
<td>Hormigo, 2004</td>
<td>High-dose IV chemo, IT chemo, PO chemo, WBRT, ORT</td>
<td>MTX, cytarabine, vincristine, procarbazine, thiopeta, CHOP, rituximab</td>
<td>31</td>
<td>29/31 (24 CR, 5 PR)</td>
</tr>
<tr>
<td>Isobe, 2006</td>
<td>Chemo, WBRT, ORT</td>
<td>Retrospective series with various regimens</td>
<td>15</td>
<td>13/15 CR or CRu</td>
</tr>
<tr>
<td>Jahnke, Korfel, 2006</td>
<td>Retrospective series with various modalities</td>
<td>Retrospective series with various regimens</td>
<td>19</td>
<td>17/19 (13 CR, 4 PR)</td>
</tr>
</tbody>
</table>

Abbreviations: PIOL indicates primary intraocular lymphoma; IT, intrathecal; WBRT, whole brain radiotherapy; ORT, ocular radiotherapy; MTX, methotrexate; CR, complete remission; PR, partial remission; CRu, complete remission/unconfirmed

A. 158 patients across all studies, up to 2006.2-9
B. Outcomes not correlated with specific treatments in all cases. Complete remission in 68/92 patients (74%) with individual results reports.
C. Not all patients in each series received all treatments.

II. International Primary Central Nervous System Lymphoma Collaborative Report10

A. 83 patients in 16 centers in 7 countries
B. Patients with systemic lymphoma were excluded; 11% with positive lumbar puncture
C. Focal therapy to the eyes in 23 patients
   1. Ocular radiation (median 36 Gy) in 16 patients
   2. Intraocular methotrexate in 6 patients
   3. Both in 1 patient
D. Extensive therapy defined as:
   1. Chemotherapy alone or with whole brain irradiation in 22 patients
   2. Ocular irradiation with any other modality in 28 patients
   3. Intraocular methotrexate in 4 patients
E. No difference in progression-free survival whether treated by focal ocular therapy alone or with extensive therapy (see Figure 1):

![Figure 1. Kaplan-Meier curve showing progression-free survival for primary intraocular lymphoma patients treated with dedicated ocular therapy (dashed line) and WBRT and/or systemic chemotherapy (solid line). Grimm SA, Pulido JS, Jahnke K, et al., 2007.10](image)

F. Ocular complications were reported in 32% of patients who received ocular radiation.
III. Small Series Promoting Benefits of Ocular Radiation Therapy

A. Berenbom, 2006\textsuperscript{11}
1. 7 patients with external beam radiotherapy (EBRT) and chemotherapy or EBRT alone: no ocular relapses
2. 5 patients with no EBRT: ocular relapses in 2

B. Stefanovic, 2010\textsuperscript{12}
1. 6 patients with ocular radiation and chemotherapy with 80% survival at 5 years (95% CI, 42-100)
2. Radiation performed first in 5/6 patients
3. No adverse ocular effects

IV. Conclusion

A. Ocular radiation is effective and tolerated in intraocular lymphoma.
B. Local therapy alone in isolated ocular disease did not influence symptom-free survival in the largest retrospective series to date.
C. Advantages include one treatment course rather than repeated injections.
D. Radiation retinopathy, if it occurs, may be effectively treated with anti-VEGF agents.\textsuperscript{13}

References

Primary Intraocular Lymphoma: Intraocular Chemotherapy

David J Wilson MD

I. Presentation of a Typical Case of Intraocular lymphoma
A. Initial presentation: February 2007
   1. History: decreased vision
   2. Examination: subretinal infiltrate, CNS involvement
   3. Treatment
      a. Intravitreal methotrexate and rituximab monthly for 1 year
      b. Systemic chemotherapy by blood-brain barrier disruption
B. Recurrent disease: July 2009
   1. Subretinal infiltrate
   2. Complete remission with methotrexate and rituximab
C. Recurrent disease: May 2014
   1. Retinal infiltrate
   2. Complete remission with methotrexate and rituximab

II. Important Considerations in Treating Intraocular Lymphoma
A. Disease characteristics
   1. Diffuse large B cell lymphoma
   2. Extended survival with current treatment regimens
B. Ocular considerations
   1. Preserve vision for expected survival
   2. Chemotherapy complications
      a. Infection
      b. Vitreous hemorrhage
      c. Cataract
C. Chemotherapy agents
   1. Methotrexate 400 micrograms/0.1 ml
   2. Rituximab 1 mg/0.1 ml
   3. Others

III. Future Considerations
A. Maintenance therapy
B. Additional agents

References
Retinoblastoma: Intravitreal Injections

Intravitreal Chemotherapy for Vitreous Seeding in Retinoblastoma

Francis L Munier MD

Definition

“Retinoblastoma seeding” refers to any type of tumor dispersion into an adjacent liquid or semi-liquid compartment. Seeding is typically seen in advanced intraocular retinoblastoma and represents a major determinant for eye grouping at presentation (see International Classification of Retinoblastoma: group C, D, and E). It can also be a feature observed in extraocular retinoblastoma (see Retinoblastoma Staging System stage II N3 and IV b3).2

The Seeding Anatomic Sites

Intraocular retinoblastoma may seed into 4 distinct anatomic sites: (1) tumor dispersion into the vitreous gel following endophytic disruption of the internal limiting membrane (ILM) and hyaloid at tumor apex, (2) tumor suspension spreading into the retrohyaloidal aqueous space secondary to endophytic disruption of the ILM at tumor base alone, and partial or complete posterior vitreous detachment, (3) tumor suspension into the subretinal aqueous space created by exophytic retinal detachment, and (4) tumor suspension into the aqueous fluid of the posterior and anterior chambers secondary to disruption of the anterior hyaloid.

Extraocular retinoblastoma may seed in 2 different anatomic sites: (1) anteriorly into the amniotic fluid in the case of fetal fungating retinoblastoma1,4 and (2) posteriorly in the case of retrolaminar invasion, with seeding into the circulating subarachnoidal fluid and progress from localized micrometastasis (stage IIN3) with negative lumbar puncture cytology5 to diffuse CNS disease with leptomeningeal carcinomatosis (stage IV b3). Alternatively, direct seeding into the CSF can occur from a pinealoblastoma (see Retinoblastoma Staging System stage II N3 and IV b3).2

The Therapeutic Challenge of Seeding

While solid vascularized retinal tumors are easily accessible to various treatment modalities, the tumor avascular counterpart involving the other ocular sites are either poorly controlled by conventional therapies or beyond any conservative treatment, as in the case of anterior segment invasion (absolute criteria for enucleation). The high drug resistance of these avascular tumors may be explained by the inability of the present routes of antimitic administration to achieve tumoricidal concentrations in the corresponding eye compartments. In addition, these tumors are virtually inaccessible to focal treatments and are highly radio-resistant due to their hypoxic nature.

Historically, the best salvage rates reported with first-line external beam radiotherapy barely exceeded 50% for group Vb eyes.7 The shift to first-line systemic (IVC) chemotherapy (with or without prechemo cryorupture of the external hematoo-retinal barrier to increase the vitreous drug concentration) failed to improve eye survival of advanced retinoblastoma, with only 47% avoiding enucleation and external beam radiotherapy (EBR) at 5 years follow-up. The probability of ocular salvage without EBR in eyes with vitreous seeding significantly increased to 64% at 2 years follow-up after the introduction of first-line intra-arterial chemotherapy.9

Despite tremendous advances in the conservative management of advanced retinoblastoma, the major cause of failure remains the persistence or recurrence of resistant vitreous seeding. Pharmacokinetic studies in the preclinical model have recently shown that if the novel routes of administration, such as intra-arterial chemotherapy, have greatly improved the ocular penetration of the drugs compared to systemic chemotherapy, the achieved vitreous concentration is barely tumoricidal and does not last long enough for tumor control. The Cmax obtained in the vitreous following intra-arterial infusion of melphalan remains more than 10 times lower than the 50% inhibiting concentration (IC50).10

To circumvent this concentration problem, intravitreal delivery of chemotherapy would offer the highest drug bioavailability in the vitreous. Despite the obvious risk of tumor spread, this invasive approach was first explored by Ericson and Rosengren in 1960, but the literature owes to Kaneko and Suzuki the pioneering role in IVc, for publishing the largest series of IVc treatments in eyes with retinoblastoma.11 These authors performed intravitreal injections of 8 μg of melphalan combined with ocular hyperthermia for vitreous tumor, and claimed an eye-preservation rate of 51% at 50 months follow-up.

Conditional Rehabilitation of Intravitreal Chemotherapy

Until recently, the intravitreal approach remained virtually banished from the therapeutic armamentarium against retinoblastoma, due to the risk of loco-regional and systemic tumor spread. This risk results from two distinct underlying mechanisms, the one active postoperative and the other passive per-operative. Active postoperative exteriorization may occur via tumor growth along a contaminated surgical wound, or in consequence to co-localization of the entry site with a parietal tumor. Passive per-operative tumor spread may occur due to vitreous incarceration or spilling of tumor cells adherent to surgical instruments when removed from the eye, or to the reflux of contaminated humors secondary to variations of IOP.

In the light of these data, we decided to revisit the feasibility of injecting the chemotherapeutic agent directly into the vitreous cavity through the pars plana as the best way to achieve the appropriate drug concentration. As intravitreal injection constitutes a violation of the “metastatic grace period” typically operated during conservative management of intraocular retinoblastoma, reappraisal of this route of administration was subjected to 3 prerequisites susceptible to prevent tumor spread: (1) to validate a method reliably assessing the anterior extension of retinoblastoma, hidden in the dead angle of ophthalmoscopy (anterior hyaloid and posterior chamber), in order to secure the needle entry site, (2) to delineate eligibility criteria for the procedure, and (3) to describe a safety-enhanced injection technique.

In order to meet these prerequisites, we first tested the value of ultrasonic biomicroscopic (UBM) imaging of the anterior
segment, using a 35-mHz transducer, to predict the safety of a pars plana route of administration. This allowed us to show that tumoral contamination of the posterior chamber can be assessed by UBM with high sensitivity and specificity even in the absence of anterior chamber involvement.12 Our next step was to profile eligibility criteria for intravitreal injection by parameterizing all risk factors for tumor spread and then by designing an injection technique minimizing the addressed risks.13

Present Management of Vitreous and Retrohyaloid Seeding

Using the above-mentioned technique, we reported the first case series showing the efficacy and safety of intravitreal chemotherapy (IViC) in retinoblastoma patients presenting with vitreous disease.14 Overall success with control of vitreous seeds was achieved in 21 of 23 eyes (91%) after a mean number of 4 injections. Globe retention was achieved in 87% of cases, with only 2 eyes enucleated for progressive disease and 1 for phthisis bulbi unrelated to IViC. All retained eyes were in complete remission, and there were no cases of orbital or systemic retinoblastoma recurrence over a mean 22 months of follow-up. The Kaplan-Meier estimate of ocular survival rates at 2 years was 84% (95% CI, 62.5%-95.3%). All patients were alive without evidence of extraocular spread (95% CI, 82.19%-100%).

For the first time the eye retention rate of the worst retinoblastoma eye group (group D and all cases with recurrent or refractory vitreous seeding) appeared to parallel that of groups A to C without external beam radiotherapy.

Clinical Guidelines and Rules Conditioning the Prescription of IViC for Vitreous and/or Retrohyaloid Seeding

- The tumoral nature of the seeding is unequivocal and differentiated from other mimicking conditions, such as old vitreous hemorrhage or vitritis.
- The tumoral viability of the seeding is obvious, which can sometimes require an observation period to document the vitreous growth.
- All UBM-based contraindications have been ruled out.
- Finally, the retinal source of the seeding must be identified and, if still active and accessible to focal treatments, must be concomitantly eradicated. If the retinal source is not amenable to focal treatment, combined intra-arterial and intravitreal chemotherapy may be considered.

References

Retinoblastoma: Gene Therapy

Patricia Chévez-Barrios MD

I. Overview and Background: Gene Delivery to the Eye and in Retinoblastoma

A. Preclinical studies
   1. Vitreous seeding of retinoblastoma, xenograph model
   2. Vector and gene delivered
      Adenovirus (AdV) + herpes simplex thymidine kinase gene (TK) delivery followed by ganciclovir (after AdV-TK)
   3. Gene delivery route: intravitreal
   4. Results and efficacy
      a. 70% of the animals showed a complete response of tumor.
      b. Treated animals had significant prolongation of progression-free survival as compared with untreated controls.

B. Clinical studies in children with retinoblastoma using ADV-TK followed by ganciclovir (suicide gene therapy)
   1. Phase 1 (safety) study
      a. Surgical injection technique was designed to avoid tumor seeding of needle tract.
      b. Toxicity criteria were developed for:
         i. cornea and conjunctiva
         ii. anterior chamber
         iii. uvea
         iv. vitreous
         v. retina
   2. Intrapatient dose escalation
   3. Bilateral retinoblastoma with vitreous tumor seeding refractory to all standard therapies
   4. Vitreous tumor seeds were treated by intravitreous injection of AdV-TK adjacent to disease sites.
      a. Transcorneal approach to vitreous injection
      b. Previous anterior chamber tap with aqueous sent to cytology
      c. Injection of vector adjacent to tumor seeds
      d. Retrieval of needle with concomitant cryo to the site of entry
      e. Copious washing of the site of cryo with saline solution
   5. Each injection was followed by ganciclovir delivered intravenously every 12 hours for 7 days.
   6. Eight patients with vitreous tumor seeds were enrolled. Total of 21 injections were performed.
   7. One patient was free of active vitreous tumor seeds for more than 38 months after therapy.
   8. No dose-limiting toxicities were observed.
   9. No patient had tumor in injection needle tract.
   10. Results suggest that gene therapy may be a useful adjuvant to other standard therapies for the treatment of children with retinoblastoma and vitreous seeds.

C. Lack of systemic inflammatory / immune response
   1. Ocular environment
   2. Immunology study
      a. Local ocular response
      b. Systemic response

D. Reopening trial
   1. Unambiguous clinical diagnosis of bilateral retinoblastoma complicated with vitreous seeds in at least 1 eye substantiated by examination under anesthesia, ultrasound and/or enhanced MRI in which enucleation would be indicated.
   2. Patients will be treated with systemic chemotherapy concomitant with the intraocular injections to treat the retinal tumors.

Selected Readings


Retinoblastoma: Nanoparticle Therapy

Hans E Grossniklaus MD

I. Current Treatment for Retinoblastoma
   A. Unilateral cases
      1. Chemoreduction/consolidation for Groups A-C
      2. Enucleation for most Group D and E cases
   B. Bilateral cases
      1. Chemoreduction: vincristine, etoposide, carboplatin (VEC)
      2. Local consolidation
         a. Laser therapy
         b. Cryotherapy
         c. Thermotherapy
         d. Radiotherapy
      3. Enucleation for many Group D and E cases
   C. Failures
      1. Aggressive tumor
      2. Vitreous seeds
      3. Well-differentiated tumors
      4. Intra-retinal tumor
   D. Alternative treatments
      1. Periocular injections
      2. Intra-arterial chemotherapy
      3. Intravitreal injections

II. Nanoparticles
   A. 1 to 10\(^2\) nanometers
   B. Types
      1. Micelle
      2. Liposome
      3. Dendrimer
      4. Gold nanoshell
      5. Quantum dot
      6. Polymers
   C. Advantages
      1. Improves solubility
      2. Prolongs half-life
      3. Sustained drug release
      4. Lowers frequency of administration
      5. Targeted delivery with minimal systemic effects
      6. Delivers 2 or more drugs simultaneously
   D. Already in use
      1. Liposomes: Bengham, Gregoriadis
      2. Antibodies: Celltech
      3. Gene therapy: Seymour
      4. Nanoparticles: Florence, Davis, Illum
      5. Unimolecular polymer: Duncan

III. Examples for Retinoblastoma
      1. Transgenic mouse model of retinoblastoma
      2. Periocular carboplatin nanoparticle significantly reduced size of tumor.
   B. Intravitreal injections
      1. Needle size: smaller needle, less tumor seeding in wound
      2. Topotecan concentrations in retina and vitreous using small needle
      3. Topotecan sustained release with liposomes
      4. Intravitreal topotecan in rabbit model of retinoblastoma
   C. Suprachoroidal injections
      1. Avoids entering vitreous
      2. Drug spreads posteriorly
      3. In development (Clearside Pharmaceuticals)

IV. Laser Targeted Release of Nanoparticles
   A. IV or local administration
   B. Laser activation in tumor
   C. Example: pseudovirions (Aura Biosciences)
      1. Viral particle capsomeres (no live virus)
      2. Binds to glycosaminoglycans in tumor
      3. May be bound with infrared absorbing dye
      4. Laser activation with 700-nm laser results in cell death
      5. Currently in preclinical trials

V. Summary
   A. Nanoparticles are currently used in medicine.
   B. Nanoparticles offer alternative for targeted, sustained drug release.
C. Nanoparticles may be locally delivered by intravitreal or suprachoroidal injection in experimental retinoblastoma.

D. Laser active nanoparticles are in development for targeted therapy of retinoblastoma.

Selected Readings


Uveal Melanoma: Imaging Techniques

Stefan Seregard MD

A wide range of imaging techniques is available for primary and secondary (metastatic) uveal melanoma. Although most primary uveal melanoma can be diagnosed by a trained clinician using binocular ophthalmoscopy, many imaging techniques provide important adjuncts. These are particularly helpful in some settings, like when monitoring small, indeterminate lesions for growth using serial fundus photography and when the ocular media are opaque using ultrasonography or MRI. Because of the significant risk for patients with uveal melanoma to develop metastatic disease, often first noticed in the liver, many ocular oncology centers now advise periodic imaging of the liver. It is important for the ophthalmologist to be updated on recent advances in uveal melanoma imaging primarily for the diagnosis of primary disease, but also when performing screening for metastatic disease.

Primary Uveal Melanoma

Imaging of primary uveal melanoma using one or more of a range of techniques is largely performed for diagnostic purposes, delineating the extent of a lesion or as part of the management, including the follow-up of indeterminate melanocytic lesions.

Ultrasonography is the most widely spread imaging technique for primary uveal melanoma and is used for nearly all patients with uveal melanoma at an ocular oncology referral center. This modality is helpful in outlining tumor extension and provides an excellent estimate of tumor thickness, and it also detects the presence of any associated retinal detachment and possible extraocular growth. Ultrasonography is particularly useful when opaque media obscures the clinical details. Standardized A-scan ultrasonography provides more information on tissue characteristics and may further enhance diagnostic accuracy. Uveal melanoma confined to the ciliary body and/or iris is often better imaged by high-frequency ultrasound biomicroscopy. Additional information may be obtained from MRI, which greatly improves the spatial resolution compared to that offered by computerized tomography (CT) imaging.

Trans-scleral or transpupillary transillumination may be used to delineate the extent of a lesion and is helpful to distinguish (e.g., choroidal detachment from a uveal melanoma). Specificity is, however, often lacking, and it is often impossible to reliably distinguish a hemorrhage from a uveal melanoma using transillumination of the globe. Fluorescein angiography was once included in the standard trio of imaging techniques used at many ocular oncology centers, jointly with fundus photography and ultrasonography. This technique may detect tumor vessels and document vessel leakage, but typically these features are not very specific for uveal melanoma and the role of fluorescein angiography has been much reduced in recent years, though it is still used on a regular basis at some centers. Wide-angle fundus photography and wide-angle fluorescein angiography are readily available and may be helpful to fully assess the extent of a lesion. Doppler imaging highlights the vascular flow of a tumor but is less often used in clinical practice. When lesions are amelanotic, or small, or when ocular media are opaque, clinical diagnosis may become more of a challenge. Unfortunately, the accuracy of most imaging techniques is similarly reduced for small lesions. Serial fundus photography may be used to monitor treated lesions or untreated lesions of indeterminate origin for growth. OCT is frequently used to detect and quantify subretinal fluid in association with a presumed uveal melanoma, but less often to image the actual tumor. This may well change in the future as the recent advance of enhanced depth OCT imaging now allows for improved imaging of choroidal tumors.

Metastatic Uveal Melanoma

Typically, metastases from uveal melanoma are first detected in the liver. Liver lesions of the same size as a readily detectable primary uveal melanoma (≤ 1 cm in diameter) are often obscured and may remain undetected for a long period of time. This necessitates serial examinations through a period of many years. The standard choice of monitoring is typically by contrast-enhanced liver ultrasonography or CT imaging. Recently, there have been indications that serial MRI may improve the detection rate of smaller metastatic lesions. Functional imaging using positron emission tomography (PET) combined with CT imaging (PET-CT) further improves specificity. This modality is currently the most sensitive technique available, though spatial resolution is still not better than that of conventional CT imaging. Cost and limited access usually confines PET-CT imaging to exploring lesions initially detected by another technique. Recently, PET specificity has been combined with the enhanced resolution of MRI (PET-MRI) and shows promising results. Although now available at a few selected centers, this technique is still emerging. It is likely that PET-MRI will improve detection rate of metastases to the liver, but the cost of PET-MRI when screening for metastatic disease may be prohibitively expensive in many settings.

Frontiers

Further improvements in MRI of the eye using techniques based on multiple-channel radiocoils at 7T or more may further enhance spatial resolution. This may be combined with PET to allow for functional imaging that improves specificity for ocular lesions. The potential role of enhanced depth OCT imaging of primary uveal melanoma needs to be further explored. Liver imaging or whole body imaging using PET-MRI for high-resolution functional imaging has recently become available, but the effectiveness when screening for metastases from uveal melanoma is still unclear.
Uveal Melanoma: Novel Therapies

Bertil E Damato MD PhD

Introduction

The treatment of uveal melanoma varies so widely between centers that it would be possible to give only a very superficial account if I attempted to summarize all methods and attitudes around the world. The aim of this presentation, therefore, is to describe my personal experience over the past 30 years, which I hope will show how much uveal melanoma treatment has advanced during this time.

Objectives of Treatment

When I joined ocular oncology in 1984, there was a heated debate regarding the impact of ocular treatment on survival, with some authors advocating enucleation for all patients and others suggesting that this treatment actually accelerated metastatic death. In 1996, Prescher et al found that metastasis occurs exclusively in patients with chromosome 3 deletion, almost all of whom died of their disease. My colleagues and I confirmed these findings. The concept arose that uveal melanomas were either lethal or nonlethal from their inception and that the patient’s fate was already sealed by the time the tumor was detected. The implication of this hypothesis was that ocular treatment was only palliative and therefore neither necessary nor urgent, except to conserve the eye and vision. Recent data suggest that delayed ocular treatment is associated with increased metastatic mortality, but randomized trials are needed to confirm these tentative findings.

Treatment Modalities

In 1984, there had to be very good justification for not enucleating an eye with melanoma; today, the converse is true and enucleation is performed only as a last resort.

Most of my experience with brachytherapy has been with ruthenium applicators. Initially, I administered 85 Gy to the tumor apex, with the plaque physically overlapping the tumor margins by at least 2 mm. Over the years, my dosimetry evolved so that minimum scleral and apex doses of 350 Gy and 80 Gy respectively were delivered, without any posterior safety margin. I developed various tools and techniques to ensure accurate plaque placement, thereby reducing collateral damage to optic disc and fovea without increasing the rate of local treatment failure. In the meantime, others reported much progress in iodine plaque design and in palladium plaque radiotherapy.

Protocols for administering proton beam radiotherapy have changed relatively little over the years and there is more uniformity than with brachytherapy. Soon after adopting this modality, however, I became concerned about the painful keratopathy I was seeing in my patients as a result of collateral damage to the superior eyelid margin. My colleagues at Clatterbridge and I therefore started administering transpupillary proton beam radiotherapy to patients with a superior choroidal melanoma, with an immediate improvement in the results. After radiotherapy, many patients develop macular exudates, serous retinal detachment and neovascular glaucoma, which I termed ‘toxic tumor syndrome.’ In 1987, I started treating these complications by excision of the irradiated tumor in selected cases, with dramatic improvement in some patients. In 1994, a patient with an iris melanoma declined iridectomy because she worked in Antarctica and was concerned about photophobia. I therefore administered proton beam radiotherapy, which was successful, so that this became the preferred choice of treatment for such tumors, not only in Liverpool but also in several other centers. In the meantime, others successfully developed plaque radiotherapy for iris melamomas.

I still perform resection for peripheral iris tumors involving the angle and for small ciliary body tumors, but my techniques have changed. Previously, I performed the dissection in an antero-posterior direction (iridocyclectomy) after dilating the pupil; today, I prefer to perform the excision postero-anteriorly (cycloiridectomy) or circumferentially, after administering miotics, to conserve more of the iris and to avoid damaging the iris sphincter.

My initial techniques for trans-scleral choroidectomy, which I learned from Foulds, have since evolved considerably. The most important developments have been (1) adjunctive brachytherapy, obviating the need for wide surgical margins, (2) conserving the ciliary epithelium over pars plana by commencing the tumor excision posterior to ora, to prevent retinal dialysis, (3) separating tumor from any adherent retina with a scalpel instead of scissors, thereby reducing the incidence of retinal breaks, and (4) applying bipolar cautery to short posterior ciliary arteries in the quadrant of the tumor, reducing hemorrhage.

In 1989, I started treating juxtapapillary melanomas by en-doresection, to avoid radiation-induced optic neuropathy, using silicone oil to prevent postoperative hemorrhage and retinal detachment. Until recently, air was used to flatten the retina intraoperatively, but there have been reports of fatal air embolism. Heavy liquid is now used instead. Some authors have advocated en-doresection only after sterilization by neoadjuvant radiotherapy, because of intuitive concerns about disseminating the tumor around the eye and systemically. Long-term studies indicate local tumor recurrence rates of under 5% after en-doresection alone, which suggests that the large majority of patients undergoing neoadjuvant radiotherapy are experiencing iatrogenic morbidity unnecessarily.

In 1984, some small uveal melanomas were treated by photocoagulation, delivering brief, high-intensity flashes of light. Because of local tumor recurrence and other complications, Foulds and I developed low-energy, long-duration photoresection, administering 60-second diode laser applications, with improved outcomes. Transpupillary thermotherapy using a diode laser soon followed, with even better results. Photodynamic therapy has also been developed for small tumors and is still under investigation. Phototherapy is not as reliable as radiotherapy and is therefore not used as widely, but it can give good results in selected cases. Both transpulmonary phototherapy and photodynamic therapy can reduce or arrest exudation from irradiated tumors.

Previously, there was much debate as to which therapeutic modality was “best”; today, treatment tends to be selected...
according to multiple factors, combining different modalities to optimize outcomes.\textsuperscript{23,24}

Conclusions
Despite recent advances, most patients suffer loss of vision, loss of the eye, and/or untimely death. The best hopes for improving outcomes are with early detection and treatment, when the tumor is still small. However, many patients experience delays in tumor detection and treatment.\textsuperscript{25} Soon, uveal melanomas will hopefully be treated with targeted therapy, administered intra-arterially and/or systemically, deploying focal therapy only for consolidation, as with retinoblastoma.

References
Uveal Melanoma: Emerging Treatments for Metastases

J William Harbour MD

I. Survival
No documented improvement in survival rates despite better diagnosis and treatment

II. Micrometastasis Occurs Prior to Primary Diagnosis.
A. Metastasis approaches 50% by 10 years.
B. Initial metastatic sites
   1. Liver (93%)
   2. Lungs (24%)
   3. Bone (16%)
C. Resistant to traditional systemic chemotherapy and immunotherapy

III. Gene Expression Profiling of Primary Uveal Melanomas

IV. Standardized Clinical Prognostic Test Using 15-Gene Microfluidics Platform

V. Gene Expression Profiling of Primary Uveal Melanomas
A. 15 gene profile
   1. Class 1: Low metastatic risk
   2. Class 2: High metastatic risk
B. Prospectively validated in a 12-center study

VI. Drivers Mutations
A. Until the late 2000s no driver mutations had been discovered in uveal melanoma.
B. MAPK activated in most uveal melanomas
C. Mutations in KIT, RAS, and RAF members are rare.
D. Systemic interrogation of 21 other MAPK pathway candidates identified no mutations.

VII. GNAQ/GNA11
A. G-coupled protein receptor subunit alpha
B. Point mutation inactivates GTPase activity.
   1. Constitutive activation of the G-alpha-q subunit
   2. Constitutive activation of MAPK and other mitogenic pathways

VIII. Selumetinib is the first effective drug for advanced melanoma of the eye.

IX. New Pathways = New Therapeutic Opportunities

X. Combination Therapy for GNAQ/11 Mutations

XI. GNAQ/11 Are Early or Initiating Events.
A. Q/11 mutations
   1. Do not transform normal melanocytes
   2. Only transform immortalized melanocytes if p53 and Rb pathways are inactivated
   3. Are present in nevi and melanomas of all stages
   4. Are not strongly linked to metastasis
B. Consistent with early or initiating mutation

XII. BAP1 Mutations Identified by Exome Sequencing
A. BRCA1-associated protein 1 (BAP1): Located at chr 3p21
B. Mutations almost exclusively in class 2 tumors
C. Loss of other copy of chromosome 3 leads to complete loss of BAP1 function.
D. Likely explains the association between monosomy 3 and metastasis

XIII. BAP1 Protein
A. Interacts with many proteins, mostly involved with transcriptional and epigenetic regulation
   1. HCF1
   2. KDM1B (AOF1)
   3. ASXL1 & ASXL2
B. Is an enzyme that removes mono-ubiquitin molecules from substrates
   1. BAP1 (auto-deubiquitination)
   2. BRCA1
   3. Histone H2A
   4. Host cell factor-1 (HCF1)
   5. O-linked N-acetylglucosamine transferase (OGT)

XIV. BAP1 Function
A. BAP1 loss reverts class 1 uveal melanoma cells to undifferentiated, stem-like class 2 cells.
B. BAP1 mutant cells grow like stem cells.
C. HDAC inhibitors reverse the effects of BAP1 loss.

XV. HDAC Inhibitors in Clinical Trials
A. Are current HDAC inhibitors targeting the right HDACs?
B. HDAC4 (and to a lesser extent HDAC5) are the only HDACs that are upregulated in class 2 (BAP1-deficient) uveal melanomas.
C. Most HDAC inhibitors are derivatives of benzamide or hydroxamic acid.
XVI. SF3B1 Mutations Identified by Exome Sequencing
   A. Exome sequencing in 18 BAP-wildtype uveal melanomas
   B. Sanger sequencing in 102 uveal melanomas
   C. Somatic mutations in SF3B1 in 20% of primary uveal melanomas
   D. Almost all were class 1 tumors.
   E. Mutually exclusive with BAP1 mutations
   F. Associated with better prognosis

XVII. Splicing Factor 3B, Subunit 1 (SF3B1)
   A. Located at chr 2q33.1
   B. Component of splicing factor 3b complex
   C. Point mutations aggregate at R625
   D. Results in altered mRNA splicing of selected genes
   E. How this contributes to uveal melanoma is unknown.

XVIII. EIF1AX mutations
   A. Somatic mutations in EIF1AX in 20% of primary uveal melanomas
   B. Eukaryotic translation initiation factor 1A
   C. Located at Xp22
   D. Almost all class 1 tumors
   E. Mutually exclusive with BAP1 and SF3B1 mutations
   F. Associated with better prognosis

XIX. Mutual Exclusivity of Late Mutations

XX. Low Mutation Burden in Uveal Melanoma

XXI. Immunotherapy for Selected Uveal Melanomas

XXII. Mutational Landscape of Primary Uveal Melanoma

XXIII. Mutation Landscape in Uveal Melanoma

XXIV. New Treatments for Metastatic Uveal Melanoma

XV. Future Directions
   A. Identify key therapeutic targets of Gq/11 pathway
   B. Combination therapy
      1. Gq/11 pathway
      2. BAP1 pathway
      3. Immunotherapy
      4. Other?
   C. Selective Class Ia HDAC Inhibitors?
   D. Other Therapeutic Targets in BAP1 Pathway?
   E. Predictors of Response to Immunotherapy?

XXXII. Conclusions
   A. Molecular prognostic testing is of significant clinical value and should be offered to all patients.
   B. Early detection of metastasis provides patients with more treatment options that may extend survival.
   C. Therefore, metastatic surveillance testing customized to the patients risk level should be offered to all patients.
   D. An increasing number of clinical trials of adjuvant therapy are becoming available and these should be offered to all high-risk patients.
   E. Therapeutic agents with demonstrated benefit in the metastatic setting are now available, and patients should be offered access to such agents through enrollment in clinical trials.
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