Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Metastasis Risk After Biopsy for Posterior Uveal Melanoma

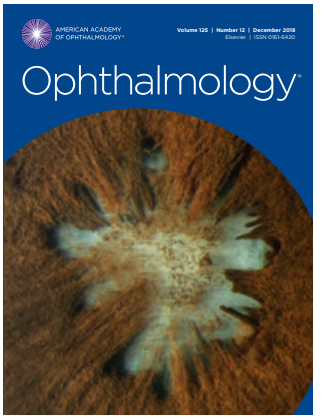
December 2018

Do the risks of biopsy in patients with uveal melanoma outweigh the benefits? Although some investigators have found a low frequency of ocular complications after such biopsies, the long-term risks have not been studied extensively. In a large longitudinal study spanning 32 years, **Bagger et al.** looked at the risk of metastasis after biopsy for posterior uveal melanoma. They found that rates of all-cause and melanoma-specific mortality were similar between biopsied and nonbiopsied patients.

This study included all patients with posterior uveal melanoma treated in Denmark between January 1985 and December 2016 (N = 1,637). Clinical and histopathologic findings for the study population were linked to pathology, cancer, and mortality registries. Patients had follow-up from diagnosis of choroidal or ciliary body melanoma until migration, death, or study conclusion (November 2017). Data included age, sex, tumor characteristics, and diagnostic and therapeutic measures.

The absolute risk of melanoma-specific death was denoted by cumulative incidence curves that accounted for competing risks. Cox regression models were applied to estimate crude and adjusted hazard ratios and 95% confidence intervals for all-cause mortality and melanoma-specific mortality among patients and to compare data between biopsied and nonbiopsied cohorts. Fine and Gray risk regression served as a sensitivity analysis of the effects of competing risks.

Of the 1,637 patients, 567 (35%) had a biopsy during primary treatment. At the time of diagnosis, those who received a biopsy had better prognostic factors, including smaller tumor size and younger age. Adjusted analyses showed no meaningful differences between the study groups in all-cause mortality or melanoma-specific mortality.



Combination of Imaging Modalities for Highly Asymmetric Keratoconus

December 2018

Hwang et al. assessed whether variables from Scheimpflug imaging and/or spectral-domain optical coherence tomography (SD-OCT) could help distinguish clinically unaffected eyes of patients with asymmetric keratoconus (AKC) from normal control eyes. They found that a combination of metrics from the 2 modalities was useful for this purpose and was superior to the metrics of either modality alone.

The authors reviewed medical records of 30 patients with AKC. In these patients, 1 eye had clinical evidence of keratoconus (based on slit-lamp, retinoscopic, and topographic findings) and corrected distance acuity worse than 20/20. The fellow eye was clinically unaffected, with corrected distance acuity of 20/20 or better. The control group consisted of 60 normal eyes of 60 patients who had uneventful LASIK and at least 2 years of follow-up. Scheimpflug imaging and SD-OCT were obtained for all study eyes, and receiver operating characteristic curves were generated to determine area under the curve (AUC), sensitivity, and specificity for each machine-derived variable and each combination of variables. The main outcome was the ability to distinguish clinically unaffected AKC eyes from controls.

According to the analyses, no individual machine-derived metric from Scheimpflug or SD-OCT technology was able to produce an AUC >0.75. With Scheimpflug imaging, the best results were achieved by combining 5 metrics: index height decentration, index vertical asymmetry, pachymetry apex, inferior-superior value, and Ambrosio's relational thickness maximum. Together, they produced AUC of 0.86 and sensitivity and specificity of 83%. For SD-OCT, an aggregate of 11 thickness-related parameters achieved the greatest accuracy, yielding AUC of 0.96 and sensitivity and specificity of 89%. However, the best results were

obtained with a mix of 13 metrics from the 2 modalities, which produced AUC of 1.0 and sensitivity and specificity of 100%. The most influential variables in combination models were epithelial thickness and total focal corneal thickness (from SD-OCT) and anterior curvature and topometric indices (from Scheimpflug). No posterior corneal metrics were helpful.

Identifying corneal ectasia at its earliest stages is a challenge and will likely remain so until it's possible to directly measure corneal biomechanics rather than corneal morphology alone. At present, a combination of metrics from the Scheimpflug and SD-OCT modalities appears to have excellent discriminative utility. *(Also see related commentary by Stephen D. Klyce, PhD, in the same issue.)*

Low-Dose Bevacizumab for ROP: Update on Outcomes

December 2018

Although intravitreal bevacizumab continues to gain popularity for treatment of severe retinopathy of prematurity (ROP), concerns remain regarding long-term sequelae. In an earlier publication, **Wallace et al.** reported short-term outcomes for 61 infants in a dose de-escalation study. The authors have updated their study. Although they observed good structural outcomes after low-dose bevacizumab treatment, many eyes needed further treatment.

This masked multicenter study included 61 infants with type 1 ROP in at least 1 eye. If the ROP was bilateral at enrollment, the study eye was chosen randomly. Study eyes received intravitreal injections of bevacizumab at de-escalating doses (0.25 mg, 0.125 mg, 0.063 mg, or 0.031 mg). If necessary, fellow eyes received 1 dose level higher (0.625 mg, 0.25 mg, 0.125 mg, or 0.063 mg, respectively). After 4 weeks, the decision to use additional treatment was made at the investigator's discretion. Main outcomes were early ROP recurrence, late ROP recurrence, additional treatment, and structural findings.

Of the 61 eyes, 25 (41%) had additional treatment: 3 for early failure (within 4 weeks), 11 for late recurrence of ROP (after 4 weeks), and 11 for persistent avascular retina. Retreatment for late recurrence or early failure occurred in 2 of the 11 eyes receiving 0.25 mg (18%), 4 of the 16 eyes receiving 0.125 mg (25%), 8 of the 24 eyes given 0.063 mg (33%), and none of the 10 eyes given 0.031 mg. By the 6-month corrected age, 56 of the 61 study eyes (92%) exhibited ROP regression and normal posterior poles. One eye developed stage 5 retinal detachment, and 4 patients died of preexisting conditions.

In this study, bevacizumab doses as low as 0.031 mg resulted in favorable outcomes. It has been estimated that the standard 0.625-mg dose for ROP may be 10,000 times that needed to neutralize intraocular vascular endothelial growth factor. Hence, it may be prudent to reduce the dosage as much as possible. *(Also see related commentary by Andreas Stahl, MD, in the same issue.)*

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Correlation of IOP and Anterior Segment Imaging

November/December 2018

Xu et al. set out to characterize the relationship between intraocular pressure (IOP) and angle configuration measured by anterior segment optical coherence tomography (AS-OCT). They found that there is an anatomic threshold for angle configuration below which IOP is strongly related to the degree of angle closure. Specifically, IOP tends to increase as angle width decreases in patients with untreated primary angle-closure disease (PACD).

The authors evaluated participants in the Chinese American Eye Study, a population-based epidemiologic study based in Los Angeles. The researchers examined 10 anterior segment parameters that directly measure the configuration of the angle, and the relationship between these AS-OCT measurements and IOP was assessed using locally weighted scatterplot smoothing regression and change-point analysis.

Mean IOP was 16.3 ± 3.9 mm Hg for angle-closure eyes (n = 382) and 15.3 ± 2.7 mm Hg for open-angle eyes (n = 320). In closed-angle eyes, the mean IOP increased as AS-OCT decreased for all parameters except the trabecular-iris angle measured at 750 µm from the scleral spur. The parameters that had the strongest correlation with IOP below their threshold values were angle recess area and trabecular-iris space area, both at 500 µm and 750 µm from the scleral spur. There was no correlation between AS-OCT measurements and IOP in open-angle eyes.

The authors suggested that their findings support the theory that PACD occurs along a disease continuum, and they recommended development of a classification system that would reflect that understanding. They also noted that this study supports an expanded role for AS-OCT in the management of angle-closure patients as a complement—or possibly even an alternative—to gonioscopy.

—Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Real-World Outcomes of Anti-VEGF for DME

December 2018

Ciulla et al. set out to assess visual acuity (VA) outcomes in patients treated with anti–vascular endothelial growth factor (VEGF) for diabetic macular edema (DME). They found that in the "real world," eyes with DME experienced worse visual outcomes and received slightly fewer anti-VEGF injections than did eyes enrolled in randomized controlled trials.

For this retrospective population-based analysis, the researchers evaluated electronic health records from a demographically diverse sample of U.S. retina specialists. The treatment period spanned from January 2011 to March 2017. Eyes included in the study were those that had received at least 3 intravitreal injections within 4 months of the first injection and that had follow-up data available up to March 2018.

Eyes (N = 15,608) were initially

classified into 3 groups based on choice of anti-VEGF agent and then subdivided into 3 cohorts depending on length of follow-up. Primary outcome measures were VA and the number of treatments. Results were compared to those achieved in several randomized controlled trials, including the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study.

For the entire study group at 12 months, eyes initiated on aflibercept, bevacizumab, and ranibizumab gained 5.5, 5.5, and 4.0 letters, respectively, compared with gains of 13.3, 9.7, and 11.2 letters for the same 3 agents in the Protocol T trial. With regard to the number of injections, the mean number of injections at 12 months was 7.5, 7.9, and 7.7 for aflibercept, bevacizumab, and ranibizumab versus 9.2, 9.7, and 9.4, respectively, in Protocol T.

When stratified by baseline VA, DME eyes with well-preserved VA (i.e., 20/40 or better at baseline) experienced some visual loss by month 12 despite treatment. Those initiated on aflibercept, bevacizumab, and ranibizumab lost 2.5, 2.0, and 2.7 letters, respectively. In contrast, eyes in the Protocol T trial with a baseline VA of 20/40 or better gained 7.4, 6.0, and 6.1 letters with the same 3 agents at the 12-month mark.

At 12 months, the real-world outcomes were inferior to those achieved in randomized controlled trials by approximately 1 line of VA for all eyes and 2 lines for eyes with a baseline VA of 20/40 or better. The results cannot be pinned entirely on undertreatment, as patient characteristics found outside of controlled trials—such as uncontrolled systemic comorbidities—will obviously play a role in real-world outcomes.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Neovascular AMD: Less-Frequent Dosing With Conbercept

December 2018

Monthly intravitreal injections of anti-vascular endothelial growth factor (VEGF) drugs are the standard treatment for choroidal neovascularization in age-related macular degeneration (AMD). However, the frequent visits can be burdensome. **Liu et al.** tested less-frequent treatment intervals for conbercept, a new anti-VEGF drug, and found the regimen to be effective and well tolerated.

This prospective, double-masked, sham-controlled, phase 3 PHOENIX trial was conducted at 9 sites in the People's Republic of China from 2011 to 2013. Participants (N = 124) were ≥50 years old with a best-corrected visual acuity (BCVA) ranging from 19 to 73 letters. They were assigned randomly (2:1) to receive either 3 monthly injections of 0.5-mg conbercept followed by quarterly injections until month 12 (n = 81) or 3 monthly sham injections plus 3 monthly doses of 0.5-mg conbercept followed by quarterly administration of the agent until month 12 (n = 43). The main outcome was mean change in BCVA score from baseline to month 3. Tolerability also was assessed.

Baseline demographics and ocular characteristics were similar for the study groups. Overall, 123 patients completed the initial 3 months of treatment, and 113 patients completed the full 12 months. The mean number of injections within 12 months was 5.8 in the conbercept group and 4.8 in the sham group. From baseline to 3 months, the mean change in BCVA score was +9.20 in the conbercept group and +2.02 in the sham groups. From 3 to 12 months, the mean additional changes were +0.78 and +6.76, respectively. In general, both treatments were well-tolerated. The most common adverse ocular events in both groups were injection-site hemorrhage, conjunctivitis, reduced VA, and elevated intraocular pressure.

Because no significant between-group differences in VA or central retinal thickness were noted at 12 months (once all patients had received 3 monthly injections of conbercept), the authors focused on the first 3 months, when improvement in VA occurred quickly for the conbercept group. They suggested that the long half-life and strong bioavailability of conbercept support a quarterly dosing schedule.

Glistening and Straylight in Hydrophobic-Acrylic IOLs

December 2018

Glistenings, or fluid-filled microvacuoles (MVs), have been reported for implanted intraocular lenses (IOLs). However, relationships between glistenings and glare symptoms (i.e., straylight) and their effects on visual acuity are subjects of debate. In a study of 6 IOL models, **Łabuz et al.** found that although glistening formation varied, higher quantities correlated with elevated levels of straylight, regardless of the type of IOL. In 20% of IOLs, the amount of light scatter was high enough to hinder vision.

The authors looked at 5 samples of all 6 hydrophobic-acrylic IOL models. (Each model has a unique composition of polymers.) All lenses were manufactured recently and had an expiration date of ≥3 years. To mimic accelerated aging, IOLs were incubated for 24 hours at 45 degrees C (113 degrees F) before placement into a water bath (37 C; 98.6 F) for 2.5 hours. Light microscopy and digital processing of images revealed the number of MVs per square millimeter and their size. A modified clinical meter depicted in vitro straylight originating from the IOL before and after the aging process. Results were compared with data from 20-, 70-, and 80-year-old crystalline lenses.

Glistenings were observed in all but a single IOL model. The number of glistenings ranged from 0-3,532 MV/mm^2, and their mean size varied from 5.2 µm to 10.2 µm. In 4 models, peak density occurred in the center of the lens; in another model, glistening appeared only in the periphery. Aging increased the mean straylight in IOLs from 0.6-5.0 degrees squared per steradian, and a strong correlation was observed between straylight parameters and the number of glistenings.

Although the importance of straylight remains debatable, such light has been associated with impaired visual function, especially during driving. In this study, light scattering was sufficient to compromise visual function in one-fifth of the IOLs. The relationship between MVs and straylight was main-

tained despite differences in glistening size and IOL material. Glistening variations were observed between, as well as within, the IOL models.

—Summaries by Lynda Seminara

JAMA Ophthalmology

Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

Can OCT Angiography Detect Preclinical Alzheimer Disease?

November 2018

Current methods to diagnose asymptomatic preclinical Alzheimer disease (AD) are costly and invasive. Optical coherence tomographic angiography (OCT-A) is a noninvasive technique for analyzing retinal and microvascular anatomy, which is altered in early-stage AD. **O'Bryhim et al.** used OCT-A in a case-control study and found that the foveal avascular zone (FAZ) was larger in participants with preclinical AD than in those without AD. Hence, OCT-A may have utility as a rapid, noninvasive method to identify preclinical AD.

For their study, the authors recruited 32 participants from an AD research center in St. Louis, Missouri. Results of extensive neuropsychometric testing determined that the enrollees were cognitively healthy. The participants received positron emission tomography and/or cerebral spinal fluid testing to determine biomarker status. Individuals with previous ophthalmic disease, media opacity, diabetes, or uncontrolled hypertension were excluded. Primary outcome measures were retinal nerve fiber layer thickness, ganglion cell layer thickness, inner and outer foveal thickness, vascular density, macular volume, and FAZ size. Measurements were obtained by OCT-A. Mixed-effects analysis of covariance was applied to evaluate individual outcomes.

Thirty participants (58 eyes) were included in the analysis (mean age, 74.5 years). Twenty-nine participants were white; 1 was African American. Fourteen had biomarkers positive for AD, denoting preclinical AD (mean age, 73.5 years). The 16 participants without biomarkers served as the control group (mean age, 75.4 years). The group with positive biomarkers had larger FAZs (mean, 0.364 vs. 0.275 mm^2; $p = .002$) and narrower inner foveae (mean, 66.0 vs. 75.4 μm; $p = .03$).

These findings suggest that people with biomarker-positive preclinical AD may experience retinal vascular and architectural changes before their cognitive symptoms manifest clinically. According to the authors, this may imply that the retina undergoes neuronal loss and vascular modifications much earlier in the disease process than previously thought. However, they cautioned, confounding factors (unrelated to FAZ enlargement) may have contributed to the results. *(Also see related commentary by Christine A. Curcio, PhD, in the same issue.)*

Differences in Tertiary Glaucoma Care Among VA Health System Models

November 2018

In a retrospective review, **Lee et al.** compared rates of tertiary glaucoma management among the 4 care delivery models of the Veterans Affair (VA) health system. They noted substantial disparity in the use of glaucoma surgery: Rates of laser and filtering surgery were much lower in optometry-only clinics than in those with an ophthalmology component or specialty.

The eye care models in the health system are 1) ophthalmology-only clinics, 2) optometry-only clinics, 3) centers with optometry and ophthalmology functioning as an integrated unit with ophthalmology at the helm, and 4) centers with optometry and ophthalmology functioning separately. Data were extracted from a large VA database, which included the medical records of 490,926 veterans with a glaucoma-related diagnosis who received care at a VA medical center in 2016.

Documented data included demographics, baseline clinical factors, ICD-10 and CPT codes, and rates of glaucoma surgery procedures. Also noted was the organizational structure of each facility. Univariate and multivariate regression analyses were applied to discern log percent associations with laser peripheral iridotomy (LPI), laser trabeculoplasty (LTP), and filtering surgery. The main outcomes were rates of LPI, LTP, and filtering surgery. (Treatment outcomes were not addressed.)

Most patients were male (95%); more than half were white (63%); and 41% were 65 to 74 years of age. The rates of LPI were 0.30%, 0.28%, 0.67%, and 0.69% for optometry-only clinics, ophthalmology-only clinics, integrated centers, and nonintegrated centers, respectively ($p < .001$). The corresponding rates of LTP were 0.31%, 1.06%, 0.93%, and 0.92% ($p < .001$). The rates of filtering surgery were 0.32%, 0.51%, 0.69%, and 0.60%, respectively ($p < .001$). In multivariate regression analyses, these differences remained significant even with adjustment for potential confounders.

Overall, rates of laser and filtering surgery were 3.39-fold to 19.11-fold higher in care delivery models that included ophthalmologists. Further research is needed to identify factors responsible for this disparity and to determine whether the discrepancy in rates is associated with differences in clinical outcomes. *(Also see related commentary by Alan L. Robin, MD, in the same issue.)*

Optimal Time to Intervene for Nasolacrimal Duct Obstruction

November 2018

Congenital nasolacrimal duct obstruction occurs in 1 of 9 newborns and will spontaneously resolve in most. However, 25% of affected children require mechanical probing of the duct. Some investigators have proposed delaying such treatment until the child is about 1 year old. In a retrospective review, **Sathiamoorthi et al.** aimed to define the optimal time to probe nasolacrimal duct obstructions. They noted that spontaneous resolution appeared to plateau after 9 months of age, whereas the success rate for initial probing declined after 15 months of age. Hence, the ideal window for successful surgical intervention may be earlier and smaller than that used in clinical practice.

The study cohort comprised 1,998 infants in Olmstead County, Minnesota, who received follow-up for 10 years

after diagnosis. The median age at diagnosis was 1.2 months. All told, 1,669 of the infants experienced spontaneous resolution, 289 required surgical intervention, and 40 were lost to follow-up. The rate of resolution was 35% faster at <1 month than at 3 months of age, 43% faster at 3 months than at 6 months, 39% faster at 6 months than at 9 months, and 1% slower at 9 months than at 12 months. Probing after 15 months of age was linked to lower likelihood of success. Success rates for initial probing, by ascending age group, were 90.2% (6-12 months), 83.1% (12-18 months), 71.4% (18-24 months), and 64.7% (24+ months).

Most earlier studies showing spontaneous resolution in >90% of conservatively treated infants involved fewer than 200 patients, with associated biases that may have skewed results. In this study, the authors corroborated the tendency for congenital nasolacrimal duct obstructions to resolve without surgical treatment, and they affirmed that the rate of spontaneous resolution declines with age and eventually plateaus. A narrower-than-typical time frame for intervention (between 9 and 15 months of age) may capitalize on variations in resolution and the declining success rate for initial probing. *(Also see related commentary by Michael X. Repka, MD, MBA, in the same issue.)*

—Summaries by Lynda Seminara

Other Journals

Selected by Deepak P. Edward, MD

Use of OCT-A to Evaluate Acute Coronary Syndrome

Investigative Ophthalmology & Visual Science
2018;59(10):4299-4306

Microcirculation abnormalities contribute to processes that induce ischemic coronary heart disease. Although various devices can quantify microvascular perfusion, most entail invasive techniques. **Arnould et al.** conducted a pilot study of retinal examination with optical coherence tomography angiography (OCT-A) to see whether this noninvasive technology could provide information about the cardiovascular profile of patients with acute coronary syndrome (ACS). Their findings showed that inner vascular density measured by OCT-A coincides with cardiovascular risk profile and left ventricular ejection fraction (LVEF).

This prospective study was performed at Dijon University Hospital in France. Within 2 days of hospital admission, each patient underwent OCT-A, during which the vascular density of the superficial retinal capillary plexus was measured. Patients were grouped into tertiles, from lowest to highest retinal vascular density (RVD).

Overall, 237 cases were analyzed. Patients in the first (lowest) RVD tertile were older and were more likely to have diabetes and systemic hypertension than were patients in the third tertile. The first tertile also had greater American Heart Association (AHA) risk, higher Global Registry of Acute Coronary Events (GRACE) scores, and lower LVEF. Multivariate analysis showed that, among the first tertile, associations between AHA risk score and LVEF were significant. A link between RVD and a high-risk cardiovascular profile was confirmed by the moderate correlation with GRACE scores.

To the authors' knowledge, this is the first study of the potential utility of retinal examination with OCT-A to gauge cardiovascular risk in patients with ACS. Results suggest that retinal vascular density may be a biomarker of overall microvascular status and cardiovascular risk. Larger studies are needed for validation.

Spironolactone or Observation for Acute CSC?

British Journal of Ophthalmology
2018;102(8):1060-1065

Central serous chorioretinopathy (CSC) usually is benign and self-limiting, and most cases resolve spontaneously within 3 months of onset. Therefore, observation is indicated initially. However, cases that don't resolve on their own may become chronic.

Corticosteroids have been implicated in the development of CSC, but their pathogenic mechanism is unclear. Research in rats showed expression of the mineralocorticoid receptor in ganglion cells, retinal Müller glial cells (RMGs), and cells of the inner nuclear layer. Aldosterone maintains homeostasis of retinal fluid by upregulating the ion and water channel, which is expressed in the apical region of RMGs. Subsequently, aldosterone was shown to increase expression of the KCa2.3 channel. Since then, a novel pathogenesis was proposed: Excessive activation of the mineralocorticoid receptor signaling pathway induces dilation and leakage of choroid vessels, resulting in choroidal thickening and leading to CSC. Clinical evidence indicates that mineralocorticoid receptor antagonism is effective in patients with chronic or recurrent CSC, leading **Sun et al.** to test spironolactone in acute CSC. They found that the treatment led to faster absorption of subretinal fluid.

For this randomized study, the researchers included 30 patients (30 eyes) with acute CSC. Eighteen patients received oral spironolactone (40 mg twice daily) for 2 months, and 12 had observation (control group) for the same period. Outcomes of interest were complete resolution of subretinal fluid and changes in central macular thickness (CMT), subretinal fluid height, best-corrected visual acuity (BCVA), and subfoveal choroidal thickness.

By 2 months, complete resolution of subretinal fluid had occurred in 10 patients (55.6%) of the spironolactone group and 1 patient (8.3%) of the control group. Mean CMT and subretinal fluid height declined significantly in both groups, and the between-group differences at 2 months were significant. By 2 months, BCVA had improved in both groups. The reduction in mean subfoveal choroidal thickness from baseline to month 2 was significant in the spironolactone group but not in the control group. Between-group differences in actual BCVA and subfoveal choroidal thickness were not significant.

The authors concluded that oral spironolactone is a promising treatment for acute CSC. They emphasized that, because the condition is multifactorial, the mineralocorticoid receptor may not play a major role in all cases.

—Summaries by Lynda Seminara