

News in Review

COMMENTARY AND PERSPECTIVE

RETINA

RPE Deterioration Tracked With Adaptive Optics

A SPECIALIZED IMAGING SYSTEM developed at the NEI can directly visualize deterioration of the retinal pigment epithelium (RPE) over time—an achievement that is enabling the researchers to begin investigating the system’s utility for directly tracking the progression of blinding retinal diseases.

“We’ve only recently started to apply this technique to investigate diseases,” said study leader Johnny Tam, PhD, at the NEI. “Currently we’re interested in seeing how RPE cells are affected in diseases such as age-related macular degeneration as well as various inherited retinal degenerations.”

How it works. The imaging system combines adaptive optics (AO) with indocyanine green (ICG) angiography and scanning laser ophthalmoscopy to produce detailed structural images of the photoreceptor-RPE-choriocapillaris complex in living human eyes.¹ (See “News in Review,” February.)

Focusing on the RPE. In their most recent study, the researchers concentrated their attention on the RPE. They injected ICG dye in healthy subjects with visual acuity of 20/20 or better and in patients with two types of progressive hereditary degenerative retinal diseases—late-onset retinal degeneration (L-ORD) and Bietti crystalline dystrophy (BCD).

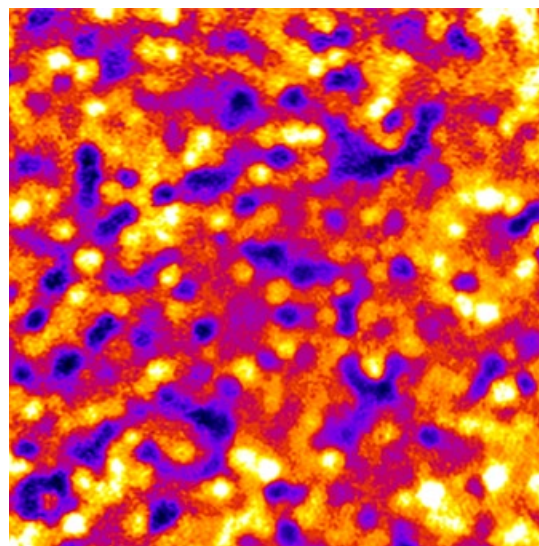
The images from ICG injections taken months apart showed that the system could track changes in the RPE, the researchers found.² The RPE cell mosaic was stable in the healthy eyes, was slightly less stable in L-ORD, and changed drastically in BCD.

“This study is a step toward functional imaging of RPE cells, in which we start to explore the dynamics of dye uptake and clearance across a large range of time—seconds to a year,” Dr. Tam said. “We believe that imaging the RPE, in combination with other clinical assessments, will allow us to identify patients who are at risk for losing their vision.”

Long-term goal. The research group’s long-term goal is to bring the lessons from its adaptive optics system into widespread clinical use, Dr. Tam said. As part of this, the researchers noted that they observed a characteristic AO-ICG fluorescence pattern in every healthy eye that they imaged, and they are using this information to create an in vivo database of human foveal RPE cell-to-cell spacing.²

“Translating this technique to a standardized clinical test is a tremendous endeavor, but we have achieved a critical first step by deploying our custom-built instrument in a clinical setting at the NEI’s Eye Clinic,” Dr. Tam said.

“In the past decade we’ve witnessed rapid advances in technology, and it would not be inconceivable to think



IN SITU. NEI scientists have visualized and tracked the mosaicism of RPE cells (shown here).

that we can simplify this technique over the coming decade and make it robust enough to be used in a conventional clinical setting,” he said. —*Linda Roach*

1 Jung H et al. *Commun Biol.* 2018;1:189.

2 Jung H et al. *JCI Insight.* 2019;4(6):e124904.

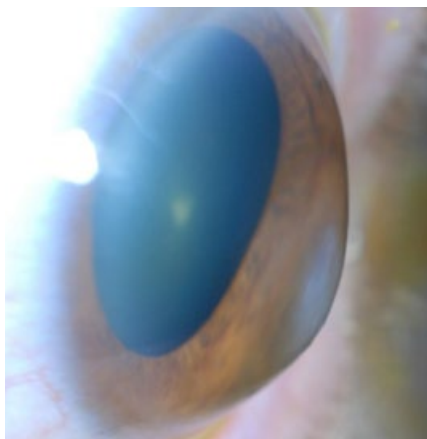
Relevant financial disclosures — Dr. Tam: None.

CORNEA

Keratoconus Progression: Assessing Risk

A REVIEW OF STUDIES ON THE natural history of keratoconus has found that children and those with a maximum keratometry (K_{max}) steeper than 55 D at presentation have a significantly higher risk of disease progression.¹ These patients need careful monitoring and a lower threshold for collagen cross-linking (CXL) to prevent further disease progression, the authors said.

The findings emerged from a sys-



EVALUATION. Keratoconus patients who have steeper corneas and those who are younger at presentation may need more frequent follow-up.

tematic review of 41 publications. Of these, 23 studies with 12-month outcomes were included in a meta-analysis. “It was surprising how few modern studies have investigated the natural progression of keratoconus,” said Alex C. Ferdi, MD, at the University of Sydney in New South Wales, Australia. “Yet knowledge of the natural history is crucial to understanding progression and hence the need for interventions such as CXL.”

At greatest risk. The results indicate that young patients progress more aggressively than adults; those younger than 17 years were more likely to have more than 1.5 D of K_{max} progression at 12 months. With regard to the severe progression noted among all patients with steeper K_{max} at initial assessment, those with greater than 55 D K_{max} at presentation were likely to progress by at least 1.5 D K_{max} at the one-year mark.

In addition, Middle Eastern patients experienced more progression over 12 months than did European and East Asian patients, the researchers found. They called for further studies to clarify the influence of ethnicity on keratoconus progression.

A note on topography. Earlier studies demonstrated that progression was associated with significant changes in visual acuity and refraction.^{2,3} In contrast, this meta-analysis found no significant progression related to changes in these factors. In addition, the rate of thinnest pachymetry change was not

clinically significant. While these are important aspects of progression, they may be less sensitive measures of progression than topography, the researchers suggested.

In the clinic. Dr. Ferdi advised clinicians to consider age and corneal parameters when evaluating the risk of progression and the risks and benefits of CXL. His institute has increased the frequency of follow-up visits for patients with keratoconus who have steeper corneas and are at younger age at presentation. In addition, they now have a lower threshold for recommending CXL in such patients.

Dr. Ferdi also urged clinicians to report patient data to the Save Sight Keratoconus Registry (<https://frb.research.org>). “Our study highlighted an urgent need to collect data on keratoconus to add to our knowledge of disease natural history and to understand treatment outcomes and how individual patients respond to CXL,” he said. —Miriam Karmel

1 Ferdi AC et al. *Ophthalmology*. Published online March 8, 2019.

2 Tuft SJ et al. *Ophthalmology*. 1994;101(3):439-447.

3 Wagner H et al. *Cont Lens Anterior Eye*. 2007; 30(4):223-232.

Relevant financial disclosures—Dr. Ferdi: None.

GLAUCOMA

Following CRVO, Who’s at Risk of Developing NVG?

WHEN DOCTORS IN MIAMI OBSERVED high rates of neovascular glaucoma (NVG) in patients who had experienced a central retinal vein occlusion (CRVO), they set out to identify risk factors that could predict the blinding complication. Three risk factors were associated with that progression—and affected patients should be followed at closer intervals and informed of the greater risk of neovascularization, the researchers said.

Risk of progression. In a five-year retrospective review of medical records, the researchers found that 13 of the 98

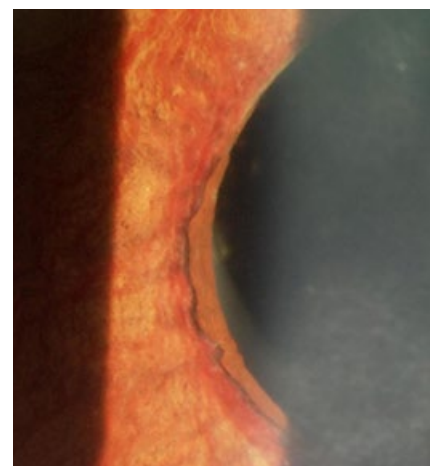
CRVO patients in their series (13%) progressed to NVG.¹ The mean adjusted time from CRVO-related symptoms to diagnosis of NVG was 212 days.

Three key risk factors emerged.

- History of systemic hypertension. This factor has not previously been reported.
- Relative afferent pupillary defect (RAPD). Patients with a RAPD had a relative risk increase of 2.15, at least doubling the probability that the eye will develop NVG. The researchers suggested that a simple pupil exam at each visit should identify the presence of RAPD and determine the course of follow-up care.
- Poorer visual acuity. For every 0.5 logMAR visual acuity worse on presentation, the risk of NVG increased 1.7 times.

No association. Age, body mass index, history of diabetes, and degree of diabetic retinopathy were not associated with NVG. In addition, history of glaucoma did not significantly differ among patients who did and did not develop NVG.

Note on macular edema. Of the 98 CRVO patients, 67 (68%) had macular edema (ME) on initial presentation. Of these, 54 were imaged with optical coherence tomography. When these 54 patients were subdivided according to their NVG status, mean central retinal thickness was $632 \pm 221 \mu\text{m}$ in patients with NVG and $632 \pm 335 \mu\text{m}$ in those without NVG. This corroborates



ADVANCED CASE. Iris ectropion and prominent iris neovascularization are evident in this case of NVG.

earlier findings that ME and NVG are independent, unrelated sequelae of CRVOs. “Thus, the clinician should not be lulled into a false sense of security after resolution of macular edema,” as improved ME is not a surrogate for decreased neovascular risk, said Andrew J. Rong, MD, at Bascom Palmer Eye Institute in Miami.

Note on anti-VEGF treatment. As anti-VEGF therapy is used to treat CRVO-related ME, the researchers hypothesized that an anti-VEGF injection given on presentation could “decrease the acute ischemic burden in CRVO and provide a long-lasting protective effect against NVG development,” said Dr. Rong. “Instead, we saw that

anti-VEGF therapy merely delayed the onset of NVG.” Despite this finding, the researchers advised injecting patients when following CRVO patients.

—Miriam Karmel

1 Rong AJ et al. *Am J Ophthalmol*. Published online March 9, 2019.

Relevant financial disclosures—Dr. Rong: None.

ONCOLOGY

Assessment of Cancer Staging System

RESEARCHERS HAVE CONDUCTED

a validation study of the recently published *AJCC Cancer Staging Manual*, eighth edition (*AJCC 8*) and have found significant changes in definitions of tumor (T) and lymph node (N) categories. Whereas the T category definitions in *AJCC 7* included perineural invasion and subjective terms, these criteria were removed in *AJCC 8*.

“T category distribution in *AJCC 7* differed significantly from T category distribution in *AJCC 8*,” said lead investigator Bitá Esmaeli, MD, at MD Anderson Cancer Center in Houston.

“In our study, we found that *AJCC 8* allows for a more precise designation of T category and a more homogeneous distribution of eyelid squamous cell carcinomas across the T categories.”¹

Comparison of classifications.

In this single-center cohort study of 109 patients with eyelid and periorcular squamous cell carcinoma, T category differed in 33 patients.

Twenty patients with T3 disease per *AJCC 7* had T4 disease per *AJCC 8*. Local recurrence-free survival seemed better for patients with T4 than for those with T3 tumors, and the proportion of patients with local recurrence was higher among those with T3 tumors. Similarly, six patients with

histologic perineural invasion, classified as T3a disease in *AJCC 7*, had T2a or T2b disease when classified by *AJCC 8*.

Main outcomes and measures.

Main outcomes measured in this study were local recurrence, nodal metastasis (NM), distant metastasis, and disease-specific survival (DSS).

Forty-three patients presented with recurrent eyelid or periorcular squamous cell carcinoma, and 11 patients developed local recurrence during follow-up. NM was significantly associated with T category at presentation and was more common in patients with T2c, T3a, and T3b or more advanced tumors. NM at presentation and follow-up was associated with increased risk of distant metastasis. For patients with T4 disease, the two-year DSS rate was 92.6% and the five-year DSS rate was 87.7%. DSS was significantly worse in patients with T2c, T3a, and T3b or more advanced tumors. T4 disease was associated with worse DSS, but NM at presentation was not.

Limitations. This study was retrospective, and the univariate factors could be associated with one another. Due to the small number of events in each category, a multivariate analysis was not possible.

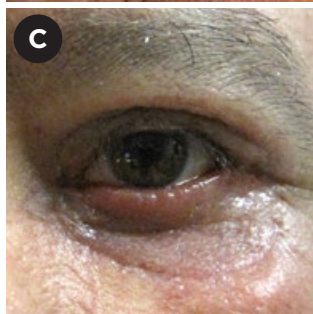
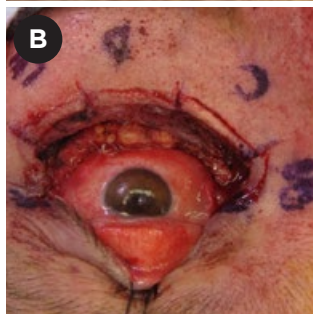
Conclusions. The bottom line: *AJCC 8* shows better predictive value in terms of local recurrence and DSS. Immunosuppression and presentation with recurrent disease are associated with increased risk of future local recurrence.

Patients with tumors of clinical stage of T2c or worse at presentation in the *AJCC 8* are at higher risk of NM and worse DSS and should undergo surveillance for NM, the authors said.

—Arthur Stone

1 Xu S et al. *JAMA Ophthalmol*. Published online March 14, 2019.

Relevant financial disclosures—Dr. Esmaeli: None.



SQUAMOUS CELL. This patient's lesion was at least a T2c (A). The margins were clear on frozen section (B). The immediate reconstructive outcome after a tarsal conjunctival flap and a full-thickness skin graft (C).