Sunday, July 22

8:00 AM

Uveal Melanoma Fine Needle Aspiration Biopsy (FNAB) for Molecular Genomic Classification: Evaluation of Transscleral Versus Transvitreal Biopsy

- Timothy G. Murray, MD, MBA
- Victor M Villegas, MD
- Aaron S Gold, OD

OBJECTIVE To determine the efficacy and complications of FNAB in the molecular classification of uveal melanoma comparing trans-vitreal to trans-scleral biopsy.

PURPOSE To evaluate the efficacy of trans-vitreal and trans-scleral fine needle aspiration biopsy to obrain tumor tissue for molecular classification with gene expression profiling (GEP) of uveal melanoma.

METHODS Institutional review board approved, single surgeon, retrospective analysis of a consecutive case series of all patients undergoing fine aspiration needle biopsy (FNAB) utilizing a 25 gauge needle, multi-pass approach for GEP analysis of uveal melanoma between 2012 and 2016. All FNAB specimens were processed for uveal melanoma diagnostic testing using a standard processing approach and all testing was completed with a single laboratory (Castle Biosciences, Inc.).

RESULTS Three hundred and fifty three eyes (353 patients) with a mean follow-up of 36 months (minimum follow-up 3 months) were included. Trans-vitreal biopsies were

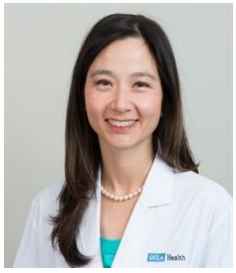
performed in 216 eyes (216/353, 61.2%), while trans-scleral biopsies were performed in 137 (137/353, 38.8%). Twenty biopsies exhibited multiple gene failure (20/353, 5.6%). Excessive fluid biopsy volume was the primary association with reported multiple gene failure occurring in 10 of 20 eyes (50%). FNAB performed via trans-vitreal approach was significantly more likely to have an excessive volume report as compared with trans-scleral biopsy (18/216, 8.3% vs 1/137, 0.7%, p<.001).

CONCLUSION Fine needle aspiration biopsy performed via a trans-scleral OR trans-vitreal multi-pass approach utilizing a 25-gauge needle achieves molecular classification in greater than 95% of all patients undergoing treatment for presumed uveal melanoma independent of tumor size. Complications related to FNAB using these techniques are rare but may be both anatomically and visually compromising.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

8:08 AM

Long-term Outcomes of 27-Gauge Vitrectomy-Assisted Biopsy for Molecular Prognostication in Very Small Uveal Melanoma



- Tara A. McCannel, MD, PhD
- Colin A. McCannel, MD
- Vidal Soberon, MD

OBJECTIVE To report the long term outcomes of patients with very small uveal melanoma who underwent 27-gauge vitrectomy-assisted biopsy for molecular prognostication.

PURPOSE Fine needle aspiration biopsy (FNAB) of uveal melanoma is a standard technique to obtain tumor sample for molecular prognostication. We have previously reported on our technique of 27-gauge vitreous cutter biopsy in melanomas less than 2 mm in thickness to improve yield for molecular prognostication. In this report we evaluated long-term outcomes of this technique.

METHODS A retrospective review of all patients with tumors less than 2.0 mm in height treated with brachytherapy and who underwent concomitant 27-gauge vitrectomy assisted biopsy for molecular prognostication, without laser retinopexy were included. Patients with less than 6 months of follow up were excluded. Gene expression profiling and multiplex ligation probe amplification were used to determine prognosis.

Postoperative outcomes including vitreous hemorrhage, epiretinal membrane, choroidal neovascular membrane and retinal detachment were evaluated.

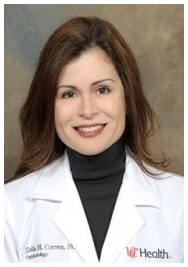
RESULTS A total of 42 patients were included. The mean follow-up was 19 months (range 6 to 35 months). An average of two passes with the vitreous cutter were made through the tumor for biopsy. A molecular test result was obtained in each case. Twenty-two (52%) patients had focal non-macular preretinal hemorrhage on post-operative day one. Three (7%) patients had diffuse vitreous hemorrhage requiring secondary vitrectomy. One patient developed an asymptomatic epiretinal membrane by 6 months. No patient developed a rhegmatogenous retinal detachment.

CONCLUSION 27-gauge vitrectomy-assisted biopsy is a safe and efficient technique to obtain molecular information from very small tumors. Secondary vitrectomy is effective for visual improvement in the infrequent event of non-clearing vitreous hemorrhage.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

8:16 AM

Comparative Survival of Patients With Posterior Uveal Melanoma Presenting Class 1A Versus Class 1B Gene Expression Profile



- Zelia M. Correa, MD, PhD
- James J Augsburger, MD

OBJECTIVE Determine whether patients with a Gene Expression Profile Class 1 posterior uveal melanoma aclassified as 1A versus 1B experienced substantially differential survival and higher rate of metastasis.

PURPOSE To determine whether patients with a Gene Expression Profile Class 1 posterior uveal melanoma assigned to subclass 1A versus 1B experienced substantially differential survival and higher rate of death from metastasis in the 1B subgroup.

METHODS Retrospective survival study of patient cohort of 565 consecutive patients with posterior uveal melanoma (PUM) evaluated at a single center between 9/2007 and 8/2015. Patients with an inconclusive or failed GEP test and non-melanoma cytology were excluded. The remaining cases were evaluated by fine needle aspiration biopsy (FNAB) for cytology and GEP prior to or in conjunction with treatment of PUM. Cases were divided into GEP class 1 (historical cases), class 1A, class 1B, and class 2 based on the GEP assignment. Kaplan-Meier (KM) actuarial curves for death from metastatic

melanoma were computed for each group. Survival between the different groups was compared using the log rank test.

RESULTS After exclusions, the 538 patients in this study ranged in age at FNAB from 4.4 years to 99.2 years (mean 62.4 years, std. dev. = 14.2). 286 (53.2%) were male and 252 (46.8%) were female. The tumors ranged in largest basal diameter from 3.7 to 24 mm (mean 12.1 mm, std. dev. = 3.8) and in maximal thickness from 1.0 mm to 18 mm (mean 5.7 mm, std. dev. = 3.2). Tumors were classified as Class 1 in 129 cases (24.0%), Class 1A in 153 cases (28.4%), Class 1B in 90 cases (16.7%), and Class 2 in 166 cases (30.9%). All patients were biopsied more than 12 months prior to this study. The mean follow-up among Class 1 patients was 98.3 months, Class 1A patients 53.3 months, Class 1B patients 75.6 months, and Class 2 patients was 67.0 months. During the available follow-up, 62 patients (11.5%) died of uveal melanoma metastasis, 10 of them had class 1 tumors, 10 had class 1A tumors, 2 had class 1B tumors, and 40 had class 2 tumors.

CONCLUSION The survival of patients with class 1 and class 1B tumors was similar. Patients with class 1A tumors had worse survival compared to the other 2 groups. Such difference can be related to lead time bias and other individual features such as patient age, health status, and tumor size that will be further analyzed.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Exempt from approval

8:24 AM

6-Month Results of a Phase 1b-2 Prospective Multicenter Clinical Trial of a Novel Targeted Therapy (AU-011) for the Treatment of Choroidal Melanoma

- Amy C. Schefler, MD
- Carol L. Shields, MD
- Ivana K. Kim, MD
- Peter G. Hovland, MD, PhD
- Antonio Capone, MD
- Cadmus Rich, MD, MBA
- Brian Marr, MD

OBJECTIVE To evaluate the safety and preliminary efficacy of AU-011, a potential first-in-class, light-activated, vision-sparing, tumor cell selective therapy for patients with choroidal melanoma.

PURPOSE To present the interim six-month results that demonstrate this first-in-class treatment is safe and well tolerated at the doses tested to date.

METHODS The trial is a 2 year, prospective, multicenter, open label design. Six patients with choroidal melanoma with an apical height between 2.0 mm and 3.4 mm and a basal dimension of less than 16 mm received a single intravitreal administration of a viral nanoparticle conjugate at one of two sub-therapeutic dose levels (20 µg and 40 µg) followed by light-activation with a 689 nm laser at a fluence of 50 J/cm2. Subjects were then evaluated with ETDRS best corrected visual acuity, fundus examination, standardized ultrasound, digital fundus photography, and EDI-OCT at Day 1, 8, 15, 29

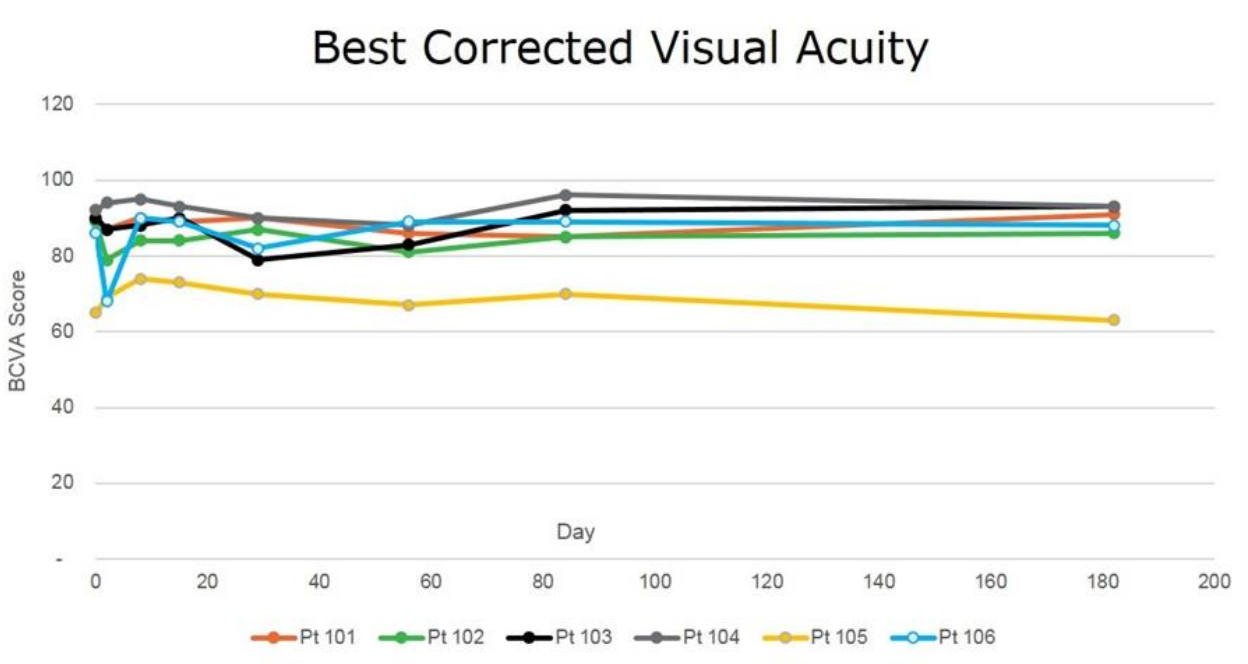
and week 6, 8, 12, 26, 39 after treatment with further planned follow up through week 102.

RESULTS All patients tolerated the procedure. Adverse events were mild/moderate and included anterior and posterior inflammation and increased intraocular pressure, all of which were transient. There were no serious adverse events. Visual acuities were unchanged in all patients. Five of six patients had stable disease as measured by tumor height and/or diameter. One subject demonstrated the pre-defined definition for disease progression and received rescue brachytherapy. Safety and preliminary efficacy assessments of all patients in the single ascending dose phase of the study through month 6 will be presented.

CONCLUSION AU-011 was safe and well-tolerated with no visual loss at the doses tested. Multiple dose treatment schemes are under investigation. AU-011 may offer a future alternative to radiotherapy as a first line option for the treatment of primary choroidal melanoma.

Figure 1. Main Adverse Events Observed During the 6 Month Follow Up.

Event Name	Number of Events (n)	Severity
Anterior Chamber Inflammation	n=2	1 grade 1 (mild) 1 grade 2 (moderate)
Posterior Inflammation	n=5	2 grade 1 (mild) 3 grade 2 (moderate)
Increased Intraocular Pressure	n=3	3 grade 1 (mild)
Keratic Precipitates	n=3	3 grade 1 (mild)
Decreased vision (transient)	n=2	2 grade 1 (mild)
Linear Scotoma	n=1	1 grade 1 (mild)



HUMAN RESEARCH This study involves human research.

IRB Approval Status: Approved by institutional review board

8:39 AM

Ranibizumab for Radiation Retinopathy (RRR) A Prospective, Multicenter Trial of Monthly Versus PRN Dosing for Radiation Retinopathy-Related Macular Edema

- Rajiv Anand, MD, FRCS
- Amy C. Schefler, MD
- Dwain G. Fuller, MD, JD
- Timothy S Fuller, MD

OBJECTIVE The objective of this study was to assess the efficacy of ranibizumab for cystoid macular edema (CME) due to radiation retinopathy (RR).

PURPOSE This was a Phase II, multicenter, randomized, controlled clinical trial. Patients with CME due to radiation retinopathy were randomized 1:2:2 to monthly management with intravitreal ranibizumab versus monthly ranibizumab with targeted PRP versus a PRN ranibizumab approach with standardized retreatment criteria.

METHODS Forty patients (40 eyes) were enrolled with clinical evidence of RR and CME defined by strict spectral domain OCT (SD-OCT) criteria and ETDRS vision ranging from 20/25-20/400 best corrected visual acuity (BCVA) (Snellen equivalent). Patients were randomized to three groups: intravitreal ranibizumab injections every 4 weeks; intravitreal ranibizumab with targeted PRP (T-PRP) to areas of ischemia; intravitreal ranibizumab injections administered PRN based on defined SD-OCT criteria. Monthly follow up exams included ETDRS refraction, dilated fundus exam, SD-OCT and fluorescein angiograms at specified visits for two years.

RESULTS Mean patient age was 57 years (range 22-80 years) with mean BCVA 20/62 (Snellen equivalent) and mean central retinal thickness (CRT) 385 mm. 37 patients

(93%) had completed follow up at 6 months with a 6 letter improvement in eyes with monthly injections, 2 letter improvement in eyes with T-PRP+monthly injections and 1 letter worsening in eyes with PRN treatment ($p<0.001$). CRT at month 6 had decreased by 152 mm in monthly cohort, 123 mm in the T-PRP/monthly cohort and 73 mm in the PRN cohort ($p<0.001$).

CONCLUSION All patients had significant improvement in vision compared to controls. Patients treated with monthly dosing of ranibizumab had a statistically significant improvement in vision at month six compared to baseline. This is the first prospective trial of ranibizumab for radiation retinopathy utilizing a treatment initiated at the time of clinically significant CME in patients with RR.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

8:44 AM

Optical Coherence Tomography Angiographic (OCTA) Changes in Retinal Vasculature After Episcleral Plaque Brachytherapy (EPB) for Choroidal Melanoma

- Brian Toy, MD
- Jesse L Berry, MD
- Amir H Kashani, MD PhD
- Debarshi Mustafi, MD, PhD

OBJECTIVE This study aims to quantify analysis of OCTA imaging features associated with early, pre-clinical retinal vascular changes in radiation retinopathy not yet apparent with other imaging modalities.

PURPOSE EPB is a globe-sparing treatment for choroidal melanoma. Nevertheless, rates of visual morbidity remain high, often due to sequelae of radiation retinopathy. Understanding the development of early retinal vascular changes seen on OCTA may elucidate risk factors and impact the management of preclinical radiation retinopathy.

METHODS This is a retrospective consecutive series of 29 eyes in 29 adult patients treated with Iodine-125 EPB for choroidal melanoma. As part of standard clinical care, OCTA was performed in both treated and fellow non-irradiated eyes. Semi-automated, quantitative analyses of microvascular abnormalities were performed on images of sufficient quality to grade. Patients who had other pre-existing retinal vascular disease were excluded from analysis. Comparison of OCTA metrics in treated and untreated fellow eyes was performed employing the Wilcoxon-Mann-Whitney U-test. Available

longitudinal data from patients were analyzed using generalized estimating equation regression.

RESULTS 14 (48%) participants were female. Median treatment values were: age (68y), time from plaque placement to first OCTA (1.9y), follow-up time (0.7y); radiation dose to tumor apex (85Gy), optic nerve head (27Gy), and fovea (27Gy). Median VA was 20/40 in treated eyes, compared to 20/25 in fellow untreated eyes ($p<0.0001$). Median values for OCTA measures in irradiated and untreated eyes, respectively, were: FAZ area (0.75mm2 vs 0.44mm2, $p=0.14$), vascular density (39% vs 45%, $p<0.0001$), branching index (117/mm2 vs 149/mm2, $p<0.0001$), total vessel length (144mm vs 162mm, $p<0.0001$), and lacunarity (0.09 vs 0.06, $p<0.0001$). Employing multivariate regression by generalized estimating equation to adjust for age, sex, and foveal radiation dose, the mean rate of change of the following indices in treated eyes was: VA (-2 letters/year), FAZ area (0.004mm2/year), vessel density (-0.11%/year), branching index (-0.6/[mm2*year]), total vessel length (-0.8mm/year), and lacunarity (0.005/year).

CONCLUSION Quantitative OCTA analyses demonstrated changes in retinal microvasculature after EPB. Thus, it may have a useful role elucidating the mechanism of and screening for early pathologic changes in preclinical radiation retinopathy.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

8:49 AM

3D Dosimetry Simulation for Plaque Selection in Uveal Melanoma: Comparison of COMS Versus Eye Physics Plaques

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- Matthew T. Studenski, PhD
- Manuel Paez-Escamilla, MD, FICO
- Mary Dean
- Stuart E. Samuels, MD, PhD, MD, PhD
- Arnold M Markoe, MD, ScD
- J. William Harbour, MD

OBJECTIVE To compare dosimetry simulations of Collaborative Ocular Melanoma Study (COMS) and EyePhysics (EP) plaques and determine whether differences in toxicity might influence brachytherapy plaque selection.

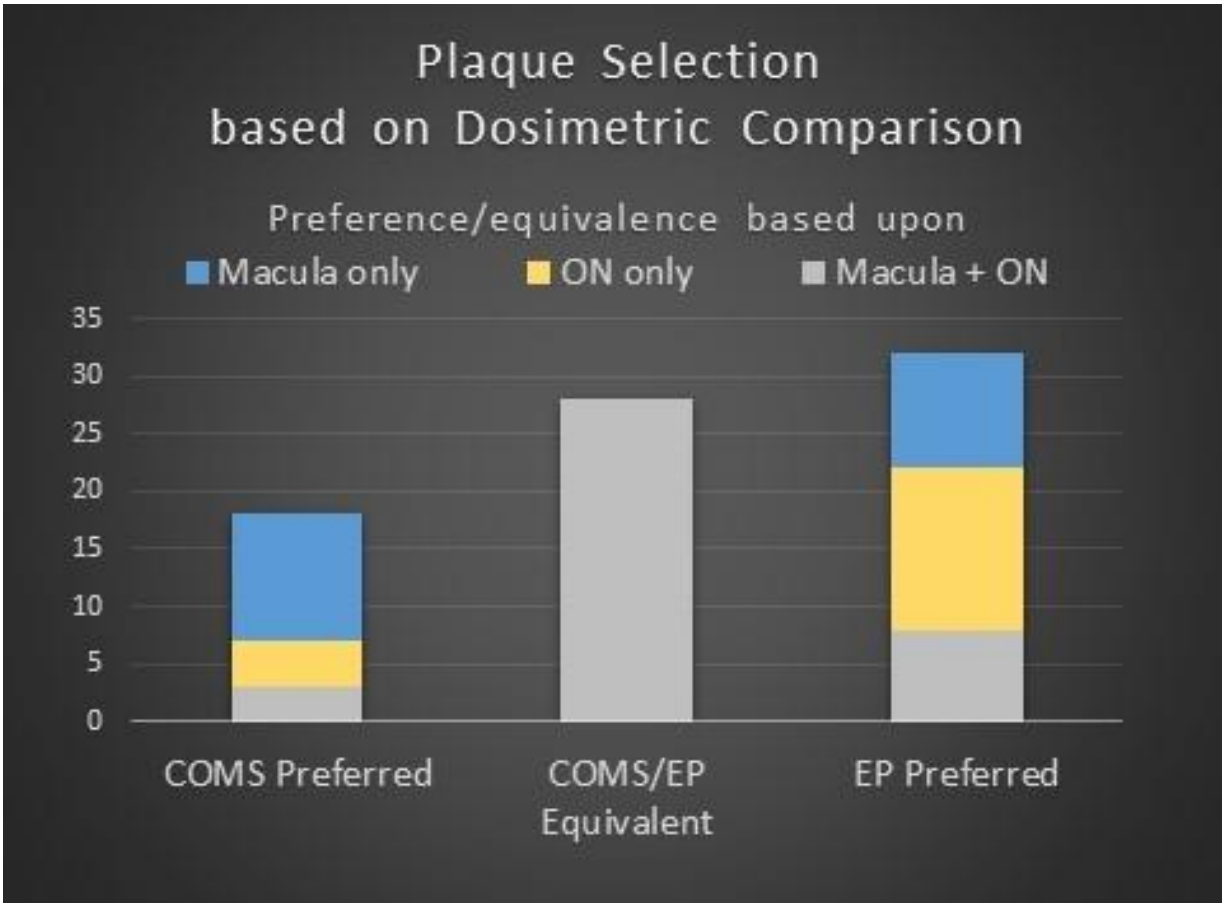
PURPOSE Dosimetry simulation software can be used to mitigate the competing risks of local treatment failure, radiation maculopathy, and radiation optic neuropathy. We used 3-dimensional simulation software to test the hypothesis that COMS and EP plaques are equivalent in terms of radiation dose to the macula and optic nerve (ON), given adequate dose to the tumor.

METHODS We analyzed a retrospective consecutive case series of patients diagnosed with uveal melanoma and treated with plaque brachytherapy at the Bascom Palmer Eye Institute by a single ocular oncologist (JWH). Each patient underwent simulation for both COMS and EP plaques using Plaque Simulator software (IsoAid; Port Richey, FL). Each plaque was calculated to deliver a dose of >85 Gy to the tumor apex and >95% coverage of the tumor margins. The primary outcome measures were macular and ON areas exposed to ≥35 Gy, which is generally agreed to be the threshold for radiation

maculopathy and optic neuropathy, respectively. COMS and EP were considered equivalent when the difference in area was <5%.

RESULTS The study included 78 cases with mean tumor height of 4.8 mm (range 1.4-14.4) and mean largest basal diameter of 12.7 mm (range 6.5-20.0). COMS and EP plaques were equivalent in the risk of ON toxicity in 48 cases (62%), macular toxicity in 44 cases (56%), and ON and macular toxicity in 28 cases (34%). Based on comparative dosimetry, COMS was preferred in 18 (23%) and EP was preferred in 32 (41%) cases (Figure 1).

CONCLUSION In most patients, COMS and EP plaques provide equivalent radiation dose to the macula and ON, given the same minimum tumor coverage. Each of these plaque designs was preferred in selected cases, but neither was consistently superior. Other variables such as plaque availability and surgical considerations may also influence which plaque is selected.



HUMAN RESEARCH This study involves human research.

IRB Approval Status: Approved by institutional review board