7/15/2022 04:45 pm

Ocular Oncology Symposium

Early Targeted Treatment for Uveal Melanoma Markedly Reduces Mortality: Evaluation of a Large Cohort of Class 2 GEP-Treated Small Ocular Melanoma Patients

- Timothy Murray, MD, MBA, FASRS
- Aaron Gold, OD
- Azeema Latiff, RN, BSN, MBA

Objective:
To report the decreaswe in tumor related mortality for early treatment iof uveal melanoma patients with Class 2 Gene Expression Profiling (GEP)

Purpose:
To report the impact of early treatment in uveal melanoma patients with Class 2 Gene Expression Profiling (GEP). Previous reporting has noted a 78% melanoma metastatic rate for uveal melanoma patients treated with a Class 2 GEP. This study, for the first time, reports the largest cohort of patients treated with Class 2 GEP genetics with treatment targeted to a small melanoma.

Methods:
IRB approved consecutive case series of 21 patients with small malignant melanoma undergoing primary treatment with FNAB documented Class 2 GEP. Small tumors were treated with either primary 125-Iodine brachytherapy or direct endolaser surgical ablation. All patients were followed with serial comprehensive ophthalmic evaluations and medical oncology imaging/examination. Primary outcome was survival, development of metastatic disease, local tumor recurrence, and anatomic/visual function. Patients were serially evaluated with directed medical oncology screening/imaging every 3/4 months. Ocular oncology comprehensive evaluation utilized widefield imaging, sdOCT, and quantitative a/b scan ultrasound to confirm ocular tumor stability and to direct targeted anti-VEGF treatment for tumor related maculopathy.

Results:
20/21 patients are alive and well at a mean follow-up of 64 months (range 36 to 93). One patient died from melanoma metastatic disease. 21/21 eyes showed local tumor control. Mean VA was 20/40 (20/20 to 20/100). 12/21 eyes developed retinopathy and received anti-VEGF treatment.

Conclusion:
Early treatment of GEP class 2 tumors reduces 5 year mortality/metastases rates from a reported 78% to 4.8%. This is the largest series reporting a marked decrease in metastases/mortality for Uveal Melanoma.This data further supports the benefit of early tumor intervention for small ocular melanomas. Further, this report notes local tumor control of virtually 100% for both 125-Iodine brachytherapy and direct MIVS endolaser tumor ablation.

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Ocular Oncology Symposium

Likelihood of Germline Mutation With Solitary Unilateral Retinoblastoma Based on Patient Age at Presentation: Real-World Analysis of 482 Consecutive Patients.

- Carol Shields, MD
- Philip Dockery, MD, MPH
- Megan Ruben, BA
- Antonio Yaghy, MD
- Madalyne Sunday, BS
- Emily Duffner, BS
- Sara Lally, MD
- Jerry Shields, MD

Objective:
Study compares patients with solitary unilateral retinoblastoma who showed greatest likelihood of germline disease.

Purpose:
Patients with solitary unilateral retinoblastoma remain a mystery regarding genetic status as somatic or germline and this information is important for future care. In this analysis we evaluate the likelihood of germline retinoblastoma in patients who present with solitary unilateral retinoblastoma (one tumor in one eye).

Methods:
Retrospective case series of 482 consecutive patients presenting with solitary unilateral retinoblastoma.

Results:
By comparison, patients ≤1 year (vs. >1 year) demonstrated 3x odds ratio (OR) (p=0.001) for likelihood of germline retinoblastoma. For those classified as infants (≤1 year) (n=132 patients), the youngest patients (0-3 months vs. >3-6 months, vs. >6-9 months vs. >9-12 months) demonstrated greatest likelihood for germline mutation (61% vs. 20% vs 24% vs 22%, p=0.009) and greatest odds ratio (>5x, p=0.002) compared to >3-12 months old.

Conclusion:
The youngest patients with solitary unilateral retinoblastoma showed greatest likelihood of germline disease when evaluating all patients (≤1 year vs. >1 year of age) (OR 3) and sub-study of infants (≤3 months vs. >3-12 months of age) (OR >5).

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Impact of PRAME Status on Gene Expression Profile to Predict Metastasis in Uveal Melanoma: Interim Analysis of the Collaborative Ocular Oncology Group Study Number 2 (COOG2)

- Prithvi Mruthyunjaya, MD, MHS
- Amy Schefler, MD FACS FASRS
- Zelia Correa, MD, PhD
- Christina Decatur
- Thomas Aaberg, MD
- Miguel Materin, MD
- Alison Skalet, MD, PhD
- Brian Marr, MD
- William Harbour, MD

Objective:
Preferentially expressed antigen in melanoma (PRAME) was recently implicated as a risk modifier in UM and this report describes the interaction of both GEP and PRAME status on prediction of metastasis rate in the COOG Study Number 2 (COOG2) study.

Purpose:
Gene expression profiling (GEP) separates uveal melanoma (UM) tumors into Class 1 and Class 2, with low and high metastatic risk, respectively, which was prospectively validated by the first Collaborative Ocular Oncology Group (COOG) Study. Preferentially expressed antigen in melanoma (PRAME) was recently implicated as a risk modifier in UM. The purpose of this report is to describe the interaction of both GEP and PRAME status on prediction of metastasis rate in the COOG Study Number 2 (COOG2) study.

Methods:
COOG2 is an NCI-sponsored 25-center prospective study to evaluate the role of new prognostic biomarkers for patients with UM. The study is evaluating the prognostic value of the expression status of PRAME, and deep targeted sequencing for UM mutations. Patient baseline and follow-up data are recorded in a REDCap database. Metastasis incidence was calculated and impact of clinical and molecular features was assessed by multivariate analysis. Hazard ratios (95%CI) were calculated.

Results:
1586 patients with posterior UM met inclusion criteria; the mean age was 61 years and 49% were women. Mean follow up was 34.3 months (95%CI 32.7-35.8). Median UM thickness was 5.4mm (rang e0.5-18mm) and basal size was 12mm (1.9-32mm). Plaque brachytherapy was the most common treatment (80%) and tumor biopsy was obtained via fine needle aspiration in 85% of patients. GEP was designated as Class 1 and Class 2 in 1077 (68%) and 496 (32%), respectively, and PRAME – and PRAME + in 1103 (70%) and 470 (30%), respectively. Metastasis incidence for Class 1 PRAME – patients was 3.1% (1.9-4.9%) compared to Class 2 PRAME + in 45.3% (37.7-52.7%) ($p<0.001$). Risk of metastasis was significantly increased in tumors with ciliary body involvement ($p=0.009$). Multivariate analysis identified a 21.49 (12.67-36.43)

fold increase in metastasis risk in Class2 PRAME + patients.

Conclusion:
This is the first prospective multicenter study to validate PRAME as a significant risk modifier to GEP in predicting metastatic risk in UM. As longer follow up becomes available, new strategies for metastasis screening, clinical trial enrollment, and targeted therapy will emerge. The inclusion of patients from a diverse multi-center population enhances the applicability of these results.

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Ocular Oncology Symposium

Clinical Features in Advanced Retinoblastoma: High-Risk Pathology and Metastatic Death

- Paul Finger, MD, FACS
- Ankit Singh Tomar, MD
- Brenda Gallie, MD
- Tero Kivelä, MD
- Ashwin Mallipatna, MBBS, MS

Objective:
What clinical risk factors at presentation predict the risk of metastatic death as well as the presence of high-risk pathology in advanced retinoblastoma?

Purpose:
Clinical features of retinoblastoma are widely used to decide between globe-salvage versus primary enucleation. This study investigates whether clinical features and tumor size in advanced intraocular retinoblastoma (RB) can provide statistically significant medical evidence for high-risk pathological features (HRPF) and thus risk of metastatic death.

Methods:
It is an international, multicenter, internet-enabled, registry-based retrospective data analysis of 2190 patients from 18 ophthalmic oncology centers across 13 countries on 6 continents (enrolled between January 2001 and December 2013). Clinical features associated with advanced RB were defined by the 8th edition AJCC categories cT2 and cT3. In addition, new AJCC-Ophthalmic Oncology Task Force(OOTF) Tumor Size Groups were defined as Group 1:<50% of globe volume involved, Group 2:>50% but<2/3, Group 3:>2/3, and Group 4: diffuse infiltrating retinoblastoma.

Results:
Kaplan-Meier cumulative survival estimates showed that the risk of metastatic mortality increased with increasing cT subcategory and AJCC-OOTF Size Group ($P < 0.001$ for both). Cox-proportional hazards regression analysis confirmed a higher risk of metastatic mortality in categories cT3c, cT3d, and cT3e compared with category cT2a, and patients with AJCC-OOTF Group 3 and Group 4 compared to Group 1. Of 942 advanced RB eyes treated by primary enucleation, 282 (30%) had HRPF. Both cT subcategories and AJCC-OOTF Size Groups ($p<0.001$ for both) were associated with HRPF.

Conclusion:
Both AJCC RB staging clinical cT3 subcategories and AJCC-OOTF Size Groups can be used to predict the presence of HRPF and therefore the risk of metastatic death.

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Ocular Oncology Symposium

Application of a Novel Semi-Supervised Machine Learning Approach to Identify Choroidal Tumors From Fundus Photographs

- Armin Afshar, MD, MBA, MAS
- Bertil Damato, MD, PhD, FRCOphth
- Luay Abdeljaber
- Latifur Khan
- Mahmoud Zamani
- Musa Abdelaziz, MD

Objective:
To explore feasibility and accuracy of computer vision artificial intelligence for automated detection of different choroidal lesions from fundus photographs

Purpose:
To develop and apply a novel semi-supervised machine learning approach to prospectively collected fundus photographs to distinguish among choroidal melanomas and common simulating lesions (nevus, congenital hypertrophy of the retinal pigment epithelium [CHRPE], hemangioma, and metastatic lesion, etc.)

Methods:
Using a prospectively-collected dataset of 664 fundus photographs of choroidal lesions including melanoma, nevus, hemangioma, CHRPE and choroidal metastatic lesions, we applied supervised and semi-supervised learning approaches to classify images. Images were obtained from different fundus cameras. Supervised learning methods included traditional decision tree, multilayer perception [MLP], support vector machine [SVM], and k-nearest neighbors [k-NN]. Our semi-supervised learning approach utilized multicontrastive learning (Multicon), with stochastic data augmentation, pseudolabeling, and multicontrastive loss combining two loss functions: consistency regularization loss and unsupervised multicontrastive loss to optimize the relationship between pairwise samples. We iteratively assessed model performance with increasing numbers of labeled images. Model performance was assessed via accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC).

Results:
Best model performance was achieved using the Multicon approach on our augmented dataset. Choroidal melanoma was detected with high sensitivity (95.33%) and specificity (97.76%). Nevi, hemangioma, CHRPE, metastatic and indeterminate lesions were identified with high sensitivity (range 92.91-100%) and specificity (98.35-100%) [Table 1]. Model performance improved with increasing numbers of labeled images (84.14% accuracy, AUC 0.96 with 300 labeled images; 97.23% accuracy, AUC 1.00 with 1800 labeled images post-augmentation) [Fig. 1]. Multicon performance surpassed traditional supervised machine learning (which had accuracy 75-88%, AUC 0.75-0.87 on the augmented dataset; accuracy 57-68%, AUC 0.58-0.66 on the original dataset).

Conclusion:
Semi-supervised machine learning is able to accurately identify choroidal lesions from fundus photographs, with up to 97.23% overall accuracy. Our Multicon approach achieves better performance compared to standard supervised machine learning via data augmentation and application of a unique multicontrastive loss function to address data scarcity and dataset imbalance for rare lesions. Future work may improve sensitivity and specificity, including via increased numbers of labeled images in underrepresented classes and image enhancement, inclusion of additional data points, and model refinement.

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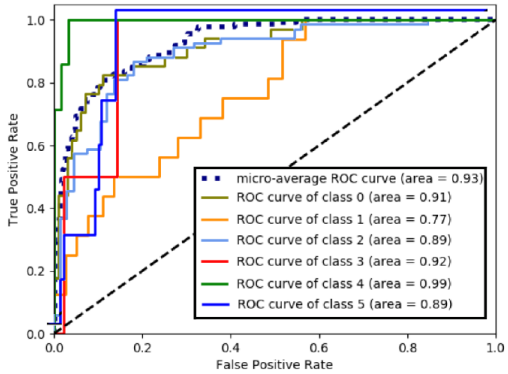
Table 1: Sensitivity and Specificity of Multicontrastive-Based Semi-supervised Learning Algorithm on Augmented Fundus Photograph Dataset for Choroidal Lesions

Lesion Type	Sensitivity	Specificity
Choroidal Melanoma	95.33%	97.76%
Indeterminate	92.91%	98.35%
Choroidal Nevus	93.08%	99.67%
Hemangioma	100.00%	100.00%
Metastatic Lesion	97.60%	100.00%
CHRPE	100.00%	100.00%

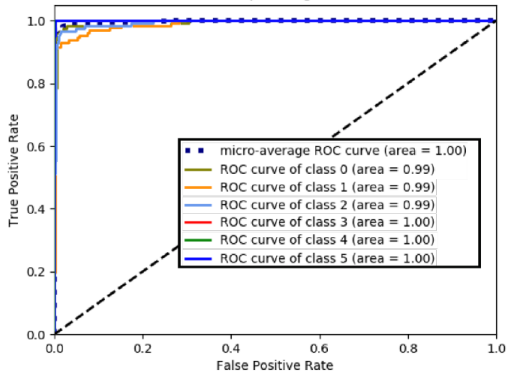
Sensitivity and Specificity

Figure 1: Receiver Operating Characteristic Curve for Multicontrastive-Based Semi-Supervised Learning Algorithm applied to Augmented Fundus Photograph Dataset for Choroidal Lesions

A. Original Labeled Dataset (360 Labeled Images)



B. Augmented Dataset (1800 Labeled Images)



Legend: Class 0 = Melanoma; Class 1 = Indeterminate Lesion; Class 2 = Nevus; Class 3= Hemangioma; Class 4 = Metastatic Lesion; Class 5 = Congenital Hypertrophy of the Retinal Pigment Epithelium (CHRPE)

Receiver Operating Characteristic Curves

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Ocular Oncology Symposium

Gene Expression Profile and Local Tumor Recurrence of Irradiated Uveal Melanomas

- Basil Williams, MD
- Jared Ebert, MD
- Maura Di Nicola

Objective:
To determine the relationship between gene expression profile class and local recurrence in uveal melanoma.

Purpose:
Gene expression profile accurately predicts risk of metastasis in uveal melanoma, but little is known regarding its association with local tumor recurrence.

Methods:
Retrospective case series of 480 patients who underwent primary plaque brachytherapy for uveal melanoma at a single institution. Fine-needle aspiration biopsy (FNAB) and gene expression profile (GEP) was obtained in all patients between December 2009 and April 2020. Demographic, clinical and treatment features were collected. Only patients with follow-up of at least 6 months were included.

Results:
Mean follow up was 50 months (range 6-248), and 460 patients achieved follow-up ≥6 months. Local recurrence occurred in 31 patients. GEP class was available in 433 patients, while it could not be determined in 27 patients (quantity not sufficient [QNS]). Of the 31 patients with recurrence, GEP was class 1 in 5 (16%), class 1A in 9 (29%), class 1B in 6 (19%), class 2 in 9 (29%), and QNS in 2 (6%) patients. Of the 429 patients without recurrence, GEP was class 1 in 24 (6%), class 1A in 172 (40%), class 1B in 103 (24%), class 2 in 105 (24%), and QNS in 25 (6%) patients. GEP class was not significantly associated with local recurrence, both when comparing class 1 and 2, and class 1A, 1B and 2 ($p=0.52$ and $p=0.58$, respectively).

Conclusion:
Gene expression profile class does not seem to affect local recurrence in uveal melanoma.

IRB APPROVAL No - exempt