Application of Molecular Genomics in Radiation-Sparing Therapy

Pars plana vitrectomy, membrane peel, endolaser ablation, and transvitreal biopsy in the primary management of uveal malignant melanoma.

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Malignant melanoma is the most common primary cancer of the uveal tract and the most common primary intraocular malignant tumor in adults.[1,2] The pathologic mechanism and risk factors leading to uveal melanoma are poorly understood. The incidence of uveal malignant melanoma is reported to be 5 to 6 cases per million individuals per year.[1,2] Despite the relative rarity of this disease, it continues to cause significant morbidity and mortality.[3] Once metastasis is detected, no curative therapy is available. Early detection and treatment of biopsy-proven lesions are vital to decrease morbidity and mortality.

Historically, patients with suspected uveal malignant melanoma were routinely enucleated to eradicate the primary tumor. In 1978, Zimmerman et al reviewed data from the Armed Forces Institute of Pathology and concluded that enucleation might accelerate the dissemination of malignant cells into the systemic circulation and therefore accelerate death by metastatic disease.[4] Pre-enucleation irradiation was therefore proposed to minimize the possibility of tumor metastasis at the time of enucleation.

Concern among ophthalmologists at the time prompted the development of the multicenter Collaborative Ocular Melanoma Study (COMS) Group, the primary goal of which was to evaluate with sufficient power the survival outcomes in patients with uveal malignant melanoma.[5,6] The COMS was designed as a set of clinical trials funded by the National Eye Institute, National Institutes of Health, US Department of Health and Human Services, and the National Cancer Institute.

> "A pivotal study ... concluded that almost 50% of patients with choroidal melanoma die of metastatic disease despite successful eradication of the primary ocular tumor."

The primary interest of the COMS investigators was to compare enucleation alone with I-125 brachytherapy for the treatment of medium-size uveal melanomas. More than 1000 patients were enrolled in the COMS medium-size melanoma study in North America. The study concluded that I-125 brachytherapy was equally effective as enucleation alone in the prevention of metastasis.[6] However, there is still debate in the scientific community about the strength of the trial.[7]

METASTASIS OUTCOMES

A pivotal study performed at Helsinki University Central Hospital in Finland between 1962 and 1981 concluded that almost 50% of patients with choroidal melanoma die of metastatic disease despite successful eradication of the primary ocular tumor.[8] A 50% death rate despite treatment of the primary tumor emphasizes that uveal melanomas have often metastasized by the time of treatment. In the medium-sized melanoma

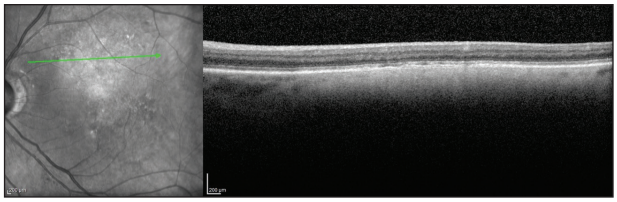

Figure 1. Spectral-domain optical coherence tomography scan over a small atypical macular lesion prior to treatment showing choroidal hyperreflectivity.

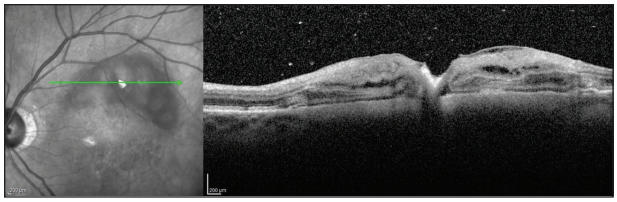

Figure 2. Spectral-domain optical coherence tomography scan after transvitreal biopsy.

COMS, the estimated all-cause 5-year survival rates with 95% confidence intervals were similar: 81% in the enucleation arm and 82% in the brachytherapy arm.[6] Ten-year all-cause survival rates were also the same in the 2 treatment arms: 65%.[6] No statistically significant differences between treatments were detected in either all-cause mortality rate or rates of death with histologically confirmed melanoma metastasis at both the 5-year and 10-year marks.[6]

Patients with recurrent disease after brachytherapy who underwent subsequent enucleation were not excluded from analysis in either arm. There may be an increased metastasis risk after failed primary brachytherapy, but this could not be determined in the COMS.

Data from these studies created a paradigm shift, with a new trend of treating uveal malignant melanoma with globe-salvaging techniques. However, could metastasis have been prevented if tumors were discovered and treated earlier? In a disease that has seen significant diagnostic and treatment advances, metastasis rates are the same now as they were 2 or 3 decades ago.

RISK FACTORS

The risk factors associated with melanoma progression are incompletely understood. Multiple studies have reported a median age at diagnosis of 55 to 65 years.[1-3] However, malignant melanoma can also affect the pediatric population, and the incidence may be increasing in young adults.[9,10]

Race appears to be an independent risk factor for uveal melanoma. White individuals have a statistically significant increased risk of developing uveal melanoma compared with nonwhites.[2,11] Uveal melanoma prevalence does not appear to be increased in patients with albinism based on the limited case reports available, suggesting that melanin pigment in the eye might not be a key factor in the pathogenesis of uveal melanoma.

Sunlight exposure as a risk factor for uveal melanoma remains a topic of debate.[12] Current data are conflicting at best; however, sunlight exposure as a factor in the pathogenesis of uveal melanoma cannot be excluded.[13]

A study evaluating 946 patients with uveal melanoma who provided a smoking history found that metastasis-free survival rates 3 years after brachytherapy were similar regardless of never, past, or current cigarette smoking status.[14] A study in Germany investigating social and environmental risk factors found that smoking and alcohol consumption did not increase the likelihood of developing uveal melanoma.[15]

The COMS investigators and other authors found that increased basal diameter and increasing age were associated with increased risk of metastasis-associated death.[1-4,6]

GENETICS

An understanding of the genetics of uveal melanoma is emerging. Multiple studies have shown that nonrandom abnormalities of chromosomes 3, 6, and 8 are associated with posterior uveal melanoma.[16-18] Studies have also reported that inactivation of the BAP1 gene was associated with increased risk of metastasis in patients with uveal melanoma.[19]

Prescher et al analyzed 180 eyes enucleated due to malignant melanoma and reported a 50% survival rate associated with monosomy 3 in the tumor.[20] However, not all patients with tumors that retained both copies of chromosome 3 developed metastasis after 3-years of follow up.[20] It was concluded that monosomy 3 was a significant predictor for early metastasis and death.

Onken et al clustered uveal melanoma into 2 distinct molecular classes based on a gene expression profile (GEP) that strongly predicted metastatic death.[21] Further research and validation of this technology allows clinicians to stratify uveal melanoma patients based on genetic risk.[22] A uveal biopsy can be used to analyze the GEP of uveal melanoma tumors with as few as 6 viable cells. GEP classification is currently used for patients' education, screening protocols, enrollment into clinical trials, and prophylactic therapy (eg, valproic acid oral treatment).

APPLICATION OF GEP IN UVEAL MELANOMA THERAPY

Until recently, GEP and chromosomal analysis have been used only for prognostic and research purposes.

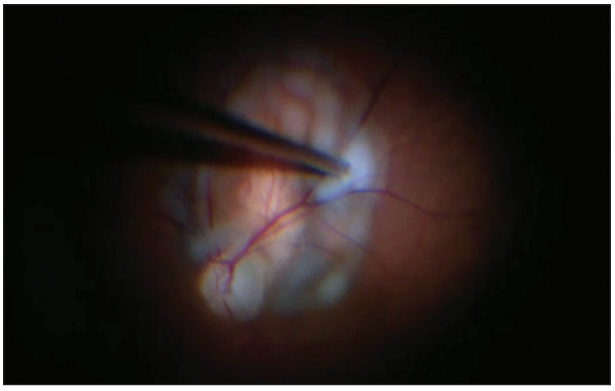

Figure 3. Transvitreal biopsy after complete endolaser ablation of the tumor surface.

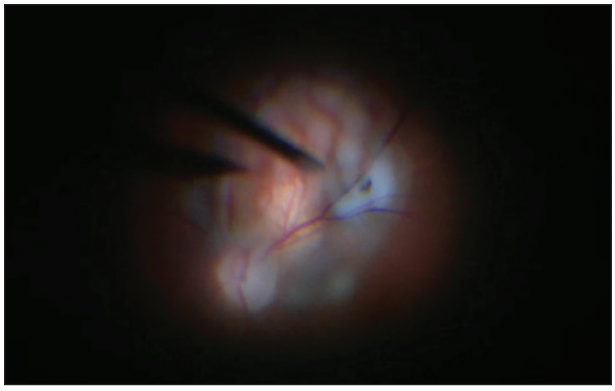

Figure 4. Full thickness retinal hole after transvitreal biopsy.

There is growing evidence that uveal malignant melanoma metastasis occurs early in the disease process and that treatment of small tumors represents the key to preventing metastasis and death.

Historically, treatment of small uveal malignant melanoma has been controversial. Small (< 2.5 mm in apical height) melanomas and atypical nevi were observed until clear evidence of growth was seen. However, by the time tumors exhibited growth, metastasis may have already occurred. GEP now allows validated risk stratification for small lesions with minimal surgical risk (Figures 1 and 2).

This technology gives the trained ocular oncologist the opportunity to treat ocular melanomas earlier, potentially killing tumor cells before they can leave the primary tumor focus, thus minimizing the likelihood of metastasis and death. These technological advancements have allowed surgeons to change their approach to treatment of uveal melanoma, particularly with regard to small atypical lesions.

For small atypical lesions, we [the authors] currently perform pars plana vitrectomy, transvitreal GEP biopsy, and membrane peel with endolaser over the entire tumor surface (Figures 3 and 4). Although endolaser penetration may be somewhat dependent on the pigmentation density of choroidal lesions, we have found sufficient laser penetration in all tumors up to 2.0 mm in thickness. Thus, this method treats small lesions and provides a stratification of metastasis risk.

GEP class 2 tumors subsequently undergo I-125 brachytherapy with a cumulative dose of 85 Gy to the tumor apex. GEP class 1 tumors do not undergo additional plaque brachytherapy.

We have performed more than 50 treatments using this protocol. This surgery has been combined with phacoemulsification and intraocular lens implantation in more than 90% of cases. In our experience, the risk of retinal detachment is less than 3%. However, retinal detachment risk assessment for an individual surgeon may vary depending on the surgeon's experience level.

> "We have performed more than 50 treatments using this protocol. ... The incidence of uveal melanoma recurrence is less than 1% thus far."

Retinal detachment risks are likely similar to those for transvitreal fine needle aspiration biopsy (FNAB) techniques. The advantages of laser ablation in combination with FNAB over FNAB alone include ablation of the tumor, resolution of subretinal fluid, and less theoretical risk of retinal detachment following biopsy.

Previous studies have reported an incidence of retinal detachment in 1% to 3% of eyes following cataract surgery.[23] Tumors that receive higher classification appear to have a higher likelihood of associated retinal detachment. Intravitreal steroids at the time of surgery lower the associated inflammatory response after endolaser treatment and may lower the risk of epiretinal membrane formation and subsequent combined tractional or rhegmatogenous retinal detachment. The incidence of uveal melanoma recurrence is less than 1% thus far with this treatment protocol.

CONCLUSIONS

GEP evaluation via transvitreal biopsy combined with vitrectomy and laser ablation provides a 2-pronged technique, allowing definitive tumor ablation of small lesions while also providing risk stratification. This management protocol significantly reduces radiation-associated visual

loss secondary to neovascular glaucoma, radiation maculopathy, and radiation optic neuropathy. It also reduces the patient's lifelong need for intravitreal injections with antiangiogenic and corticosteroid agents for the treatment of radiation complications.[24]

Studies comparing immediate treatment of medium uveal melanomas versus delayed treatment found increased mortality in patients with delayed therapy.[25] This finding has been corroborated in other studies.[26]

Observation of small uveal melanomas and atypical nevi may be associated with some risk of metastasis. At this time, clinical examination cannot reliably predict when a tumor will exhibit micrometastasis. In other fields of medicine, patients' survival and outcomes are heavily dependent on early identification and treatment of small neoplastic lesions. Larger tumors are more invasive and present a higher risk of metastasis. Once tumor cells have left the primary focus, prognosis declines significantly. Patients should be made aware of the risk of observing small lesions.

High-risk clinical features include thickness greater than 2.0 mm, presence of subretinal fluid, patient symptoms, orange pigment, margins close to the optic nerve, hollowness on ultrasound, and absence of a halo or drusen.[27] The morbidity associated with biopsy might be lower than the risk of mortality associated with observation.

Because increasing thickness and basal diameter of melanomas are strong predictors of metastatic death, earlier treatment with radiation-sparing surgery is recommended in these cases. Patients with small, suspicious lesions who exhibit high-risk clinical features may be offered GEP analysis to guide early, targeted treatment. ■

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