Editorial

Is Collaborative Ocular Melanoma Study (COMS) still relevant?

Enucleation was the standard of care for the management of uveal melanoma until the 1970s, while plaque brachytherapy was strongly emerging as a possible conservative alternative. Zimmerman, *et al*.'s hypothesis that "enucleation of eyes with uveal melanoma hastened metastatic death by disseminating the tumor cells" caused much concern when it was published 40 years ago.[1-3] The hypothesis was based on their astute observation of a peak in mortality in 2–3 years following enucleation.[1-3] Manschot and van Strik added to the confusion by emphasizing that radiotherapy of uveal melanoma was unjustifiable because histology frequently demonstrated viable melanoma cells in irradiated eyes.[4]

The "Zimmerman–Manschot debate" ignited a major controversy about both the available choices of treatment of uveal melanoma and the outcomes. Survival data of patients treated with plaque brachytherapy compared with historical series of patients treated with enucleation indicated that enucleation and plaque brachytherapy were equally effective.[5,6] However, due to the retrospective nature of the studies and differences in the baseline characteristics of patients included for comparison, the evidence was not readily accepted, the uncertainty remained, and the debate lingered on. Meanwhile, the tumor size came to be identified as the major prognostic factor for mortality in patients with choroidal melanoma. A meta-analysis of patients with choroidal melanoma treated by enucleation from 1966 to 1988 confirmed that tumor size correlated strongly with mortality – 16% for small tumors, 32% for medium tumors, and 53% for large tumors.[7]

A consensus gradually emerged in favor of conducting a prospective randomized clinical trial to settle the ongoing debate about the treatment of uveal melanoma. The Collaborative Ocular Melanoma Study (COMS) in its final shape consisted of two prospective randomized multicenter clinical trials designed to compare the outcome of therapies for large and medium choroidal melanomas and a third arm to assess the natural history of small choroidal melanomas.[8-10] Patients with large choroidal melanomas were randomized to enucleation alone or enucleation preceded by external-beam radiation (20 Gy).[8-10] Patients with medium choroidal melanomas were randomized to enucleation or iodine-125 plaque brachytherapy.[8-10] Patients with small choroidal melanomas were enrolled and observed.[8-10] The primary outcome measure was time to death from all-cause mortality. Secondary outcome measures included metastasis-free survival, cancer-free survival, and years of useful vision.[8-10]

COMS was the largest study ever to be performed in ocular oncology, initially funded by the National Eye Institute from 1985, and also by the National Cancer Institute from 1991. With 43 participating centers, more than 2000 patients, 28 numbered publications, and numerous collateral publications generated by its findings, the knowledge produced and disseminated by the COMS is immense.[8-10] The major derivates of COMS that have had significant impact on the management of choroidal melanoma are as follows:

1. The trial of enucleation alone versus pre-enucleation radiotherapy included 1003 patients with large choroidal melanoma (>10 mm in apical height and >16 mm in basal diameter) and concluded that there was no difference between the two treatment arms (the 5-year all-cause mortality was 43% and 38%; 5-year tumor-related mortality was 28% and 26%; and 10-year tumor-related mortality was 40% and 45% in the groups enucleation and enucleation with preoperative radiation, respectively), thus contradicting Zimmerman's hypothesis and reassuring that primary enucleation does not accelerate death from metastatic melanoma.[11,12]
2. In 1317 patients with medium-sized choroidal melanoma (2.5–10 mm in apical height and ≤16 mm in basal diameter), mortality with histopathologically confirmed melanoma metastasis after brachytherapy with iodine-125 was no worse than that following enucleation.[13] By 12 years, cumulative all-cause mortality was 43% in the brachytherapy arm and 41% in the enucleation arm.[14] The 5-, 10-, and 12-year mortality with histopathologically confirmed melanoma metastasis was 10%, 18%, and 21%, respectively, in the brachytherapy arm, and 11%, 17%, and 17%, respectively, in the enucleation arm.[13,14] These data provided reassurance that brachytherapy is at least as safe as enucleation.
3. COMS observational study of 204 small melanomas (1.5–2.4 mm in apical height and 5–16 mm in basal diameter) reported 2- and 5-year Kaplan–Meier estimates of tumor growth of 21% and 31%, respectively. The clinical risk factors associated with tumor growth included increased tumor thickness, presence of orange pigmentation, absence of drusen, absence of retinal pigment epithelial changes surrounding the tumor, and presence of pinpoint hyperfluorescence on fluorescent angiography. The 5-year all-cause mortality was 6% and tumor-related mortality was 1% in patients with small choroidal melanomas under observation.[15]

It is 12 years since the last official report of COMS was published. Some of the new knowledge about the biology and prognosis of uveal melanoma has raised pertinent questions about our understanding of and treatment implications based on COMS results. COMS used only the tumor size to categorize the treatment and assess the outcome. We now understand that the measures of prognosis are multifactorial. Damato *et al.* have developed an online neural network to generate personalized survival curves using demographic, clinical, histological, and genetic predictors (http://www.ocularmelanomaonline.com).[16] Such multifactorial analysis will possibly enhance the reliability of prognostication for metastasis in patients with uveal melanoma.

Table 1: Current adjuvant therapy clinical trials in uveal melanoma[29]

Mechanism	Trial	Phase
Chemotherapy	Dacarbazine + interferon-alfa	II
Chemotherapy	Cisplatin + tamoxifen + sunitinib	II
Chemotherapy	Fotemustine vs observation	III
Target therapy	Crizotinib	II
Target therapy	Sunitinib vs valproic acid	II
Immunotherapy	Ipilimumab + nivolumab	II
Immunotherapy	Dendritic cell vaccine	I/II

Following are some of the currently recognized prognostic factors for systemic metastasis:[17,18]

1. *Anatomic predictors:* Largest basal tumor diameter, tumor thickness, ciliary body involvement, and extraocular extension. American Joint Committee on Cancer uses all these anatomical factors to prognosticate and it may be more precise than just using the tumor dimensions.
2. *Histopathological predictors:* Epithelioid cells, closed loops vascular patterns, macrophages and lymphocytes, HLA expression, high microvascular density, high mitotic count, loss of nuclear immunostaining for BAP1, and so on.
3. *Genetic predictors:* Chromosome 3 deletion (partial or total), *BAP*1 loss, chromosome 8q gain, chromosome 1p loss, and chromosome 9q loss are associated with poor prognosis. Disomy 3 and chromosome 6p gain are associated with a good prognosis. Based on gene expression profiles (GEPs), uveal melanoma is now classified into three prognostic categories for metastasis – low risk (Class 1A), intermediate risk (Class 1B), or high risk (Class 2), with 2%, 21%, and 72% risk, respectively, for systemic metastasis at 5 years.[19-22]

Damato has postulated that there are three groups of uveal melanoma: (1) metastasizing melanomas, which have already metastasized by the time of ocular treatment even though the metastases may not be detectable; (2) pre-metastasizing melanomas, which develop metastatic capability and disseminate if treatment is delayed, and (3) non-metastasizing melanomas, which do not metastasize even if never treated.[18] With the currently available diagnostic techniques, it is difficult to precisely predict which melanoma might metastasize, but there may soon be a set of reliable molecular markers and their clinical surrogates to predict the same.

The current belief is that the risk for metastasis is governed by GEP and not by the treatment.[19-22] The correlation between tumor size and increased mortality is attributed to the higher prevalence of monosomy-3 in large tumors rather than to any therapeutic effect.[23,24] Genetic alteration within the tumor seems to be an ongoing evolutionary process, and the concept is supported by the demonstration of intratumoral genetic heterogeneity[25] – it is possible that melanoma may remain small and slowly growing over several years but may acquire Class 2 genetic changes over time (so-called "crescendo malignancy") that predisposes it to grow and metastasize.[18]

The new knowledge does not, however, imply that the ocular treatment of uveal melanoma is ineffective. Straatsma *et al*. compared 43 untreated patients with historical controls and reported a trend toward higher mortality in patients who were not immediately treated.[26,27] Estimates of tumor doubling time prompted the hypothesis that lethal melanomas metastasize when they are very small,[28] which supports the concept that small melanomas should be promptly treated at the point of detection, before they metastasize or acquire genetic changes that predispose to metastasis. Similarly, medium and large melanomas also deserve to be locally treated by an appropriate modality to minimize the risk of metastasis, preserve the eye, and optimize vision. Identification of patients at high risk of metastasis by multifactorial prognostication and GEP, personalized risk-based surveillance, and effective adjuvant therapy seems to be a logical approach beyond local treatment.[29] Fine needle aspiration biopsy to acquire sample for GEP in every case of conservatively treated uveal melanoma may soon become the standard of care. Patients with Class 2 risk profile need aggressive protocol-based surveillance for systemic metastasis. New knowledge has improved our ability to risk-stratify patients and identify distinct subsets for possible individualized adjuvant therapy.[29] Although several studies are in progress [Table 1], there is no agreement yet on the precise role and benefit of adjuvant therapy to minimize the risk of systemic metastasis.[29]

COMS was indeed the burning need of the hour when it was designed and conducted, and its results have had tremendous positive impact on the standardization and accuracy of diagnosis and the clinical care of uveal melanoma. The new knowledge is, however, groundbreaking in suggesting that it is the genetic profile that governs prognosis and not just the modality of treatment. Based on the evidence available currently, it would be logical to continue to locally treat uveal melanoma optimally to conserve the eye and vision when possible, risk-stratify patients based on the established clinical profile, histopathological characteristics, and GEP, and consider patients at high risk for systemic metastasis for adjuvant therapy when its beneficial role becomes well-established.

Santosh G Honavar

Editor, Indian Journal of Ophthalmology, Editorial Office: Centre for Sight,
Road No. 2, Banjara Hills, Hyderabad 500034, Telangana, India.
E-mail: editorjournal@aios.org

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