Editorial

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Prognostication for Uveal Melanoma: Are Two Tests Better than One?

Claudine Bellerive[a] Hans E. Grossniklaus[b] Arun D. Singh[a]

[a]Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, and
[b]Department of Ophthalmology and Pathology, Emory University, Atlanta, GA, USA

Over the last 2 decades, several prognostic tests have been developed for assisting clinicians to predict the metastatic potential of uveal melanoma, including fluorescence in situ hybridization (FISH), comparative genomic hybridization, microsatellite analysis, single-nucleotide polymorphism array (SNP), multiplex ligation-dependent probe amplification (MLPA), and gene expression profiling (GEP) [1].

Naturally, the questions regarding concordance between the tests and superiority of one test over the other become relevant. There are only a few reports wherein 2 prognostic tests have been performed on a given tumor sample and results evaluated for concordance (SNP/FISH [2], MLPA/FISH [3], and GEP/SNP) [4].

At present, only 2 prognostication tests – MLPA (Impact Genetics, Toronto, Canada) and GEP (DecisionDx-UM; Castle Biosciences, Inc., Pheonix, Arizona, USA) – are commercially available. Therefore, any comparison of these 2 tests has important implications for clinical usage. In the MLPA test, chromosome 3 loss (monosomy 3) and chromosome 8q gain are cytogenetic markers predictive of poor prognosis, and the presence of chromosome 6p gain is suggestive of good prognosis [5, 6]. On the other hand, GEP testing categorizes uveal melanoma as class 1 or class 2, corresponding to a low and a high metastatic risk, respectively [4, 7].

Is the risk of metastasis equivalent between a class 2 tumor (GEP) and monosomy 3 tumor as determined by MLPA? The concordance between these tests in patients with uveal melanoma undergoing a prognostic fine-needle aspiration biopsy (FNAB) has not been studied until recently. In a retrospective study, GEP and FISH (44 patients) or GEP and MLPA (49 patients – 6 technical failures GEP [3] and MLPA [3]) prognostication was performed on consecutive patients with posterior uveal melanoma (iris melanoma excluded) over a period of 2 years (2012–2014) [8]. In 43 patients, with available results of both GEP and MLPA, the GEP classification was discordant with monosomy 3 in 16% (7/43 tumors). More specifically, 19% (6/31) of the tumors categorized as class 1 (GEP) had monosomy 3, and disomy 3 was observed in 8% (1/12) of the tumors categorized as class 2.

In simple terms, in 6 (19%) patients, a contradictory prognosis would have been rendered; good prognosis by GEP and bad prognosis by MLPA. Similarly, but to a lesser extent, in 1 (8%) patient, a contradictory prognosis would have been rendered; bad prognosis by GEP and good prognosis by MLPA.

Several explanations have been put forward to elucidate the observed external discordance between 2 validated commercial prognostication tests. The first is the evidence of tumor heterogeneity and of internal discor-

E-Mail karger@karger.com
www.karger.com/oop

Arun D. Singh, MD
Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic
9500 Euclid Avenue, Desk i32
Cleveland, OH 44195 (USA)
E-Mail singha@ccf.org

dance; i.e., discordance within the same test performed from 2 or more biopsy sites of a tumor either by FISH (17%) [9], MLPA (50%) [10], or GEP (11%) [11]. The tumor size did not have any impact on tumor heterogeneity as detected either by FISH or MLPA but was less likely by GEP in tumors more than 7 mm in height [11].

Second is the possibility that class 1 GEP and monosomy 3 tumors may represent a subset of class 1 tumors with a tendency for late metastases (class 1B) as compared to class 1A with no risk of metastases [12]. Similarly, class 2 GEP disomic tumors may represent tumors associated with *SF3B1* mutations with a risk for late metastases [13, 14].

Third is the possibility of the sampling error of obtaining nonuveal melanoma tissue in a FNAB aspirate. This is a likely contributory factor as there is no inherent diagnostic cytological confirmation of the prognostic FNAB sample, unless separate cytological assessment is performed. Several non-melanoma tumors have been classified to have GEP class 1 or class 2 profiles [15, 16]. Within the MLPA test, attempt is made to identify GNAQ/11 mutations as surrogate for uveal melanoma tissue because these mutations are present in over 85% of the uveal melanoma tumor samples [17–19].

Fourth, any technical advantage of each test can only be speculated because prognostic superiority of either test (GEP or MLPA) cannot be ascertained by this study as the prognostic prediction was not correlated with patient survival. In fact, none of the patients in the study cohort developed metastases because of the short follow-up period (mean 8.9 months, range 5.4–11.4). The authors are encouraged to provide long-term outcomes of their study. In short, the superiority of one test versus another is unknown at this time due to a lack of survival data in the discordant cases.

The study findings have major implications for the management of patients. Even for patients with good prognosis, periodic systemic surveillance should be offered as they are not necessarily free from risk of metastases and conversely, one should not take a fatalistic view of a patient with poor prognosis. With availability of adjuvant therapy trials, strict enrollment criteria based upon one type of prognostic test rather than any prognostic test may be prudent [20]. Although currently available prognostic tests offer significant improvement upon traditional histopathologic prognostic factors, one must consider all of the available data when making recommendations [21].

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Statement of Ethics

Not applicable as this paper is an invited editorial.

Disclosure Statement

C.B. and H.E.G. have no conflicts of interest to disclose. A.D.S. is a consultant for IsoAid and Iconic Therapeutics, has a pending patent for the vision prediction calculator, and is a member of the Advisory Board of Aura Biosciences and Castle Biosciences.

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