

## 67.2. Uvea: Choroidal and Ciliary Body Melanomas

---

### Authors

Tero Kivelä, E. Rand Simpson, Hans E. Grossniklaus, Martine J. Jager, Arun D. Singh, José M. Caminal, Anna C. Pavlick, Emma Kujala, Sarah E. Coupland, Paul T. Finger

### Emerging Prognostic Factors for Clinical Care

#### Mutational Analysis

Preliminary results suggest that identification of mutations in *BAP1*, *EIF1AX*, and *SF3B1* may further enhance prognostication in uveal melanoma, especially if the *BAP1* gene is not mutated and the tumor has disomy 3 (AJCC Level of Evidence: III).<sup>1-5</sup> Mutations in these genes may be assessed from either a biopsy sample of the tumor or a resection specimen using sequencing (e.g., Sanger sequencing). Expression of BAP1 protein also may be assessed immunohistochemically.<sup>6-8</sup> Mutation leads to the absence of normally occurring nuclear immunoreaction. Currently, it is estimated that *BAP1* is mutated in 45–55%, *EIF1AX* in 10–20%, and *SF3B1* in 10–20% of all primary uveal melanomas, the first predominantly in those with monosomy 3 and the second two in those with disomy 3. *EIF1AX* is mutated in about 6% and 48% of monosomy 3 and disomy 3 primary uveal melanomas, and *SF3B1* (usually in codon 625) in 3–7% and 27–29% of tumors, respectively. Mutations in *BAP1* have been found in 80–85% and those in *SF3B1* in about 5% of metastatic uveal melanomas, according to preliminary studies.<sup>9</sup> *BAP1* mutations also may occur in the germline, and these inherited mutations predispose to familial uveal melanoma and other cancers, especially cutaneous melanoma, mesothelioma, and renal cell cancer.<sup>10</sup> If *EIF1AX* is mutated in a disomy 3 melanoma (typically with wild-type *BAP1*), the risk of metastasis is preliminarily estimated to be 6 to 10 times lower than if *EIF1AX* is wild type.<sup>4</sup> When it rarely is mutated in a monosomy 3 melanoma (typically with mutated *BAP1*), the risk of metastasis is estimated to be three or four times lower than if *EIF1AX* is wild type. Patients with *SF3B1* mutations also carry a lower risk of metastasis than those with wild-type *SF3B1* in their tumor.<sup>2,3</sup>

Mutations in *GNAQ* are found in 40–45% and those in *QNA11* in 30–35% of primary uveal melanomas, usually in codon 626, and are considered early or initiating events.<sup>11-13</sup> These mutations may be assessed from a biopsy sample, from a resection specimen, or potentially, from circulating DNA by using sequencing (e.g., Sanger sequencing) or related techniques. *GNA11* mutations are more frequent than *GNAQ* mutations in uveal melanomas with *BAP1* mutations, and the former may mark a higher risk of metastasis and, in metastatic uveal melanoma, shorter survival (AJCC Level of Evidence: III).<sup>9,14</sup>

#### Tumor-infiltrating Lymphocytes

The number of tumor-infiltrating lymphocytes is associated with metastatic risk and may be relevant with regard to immunotherapy (AJCC Level of Evidence: III).<sup>15-18</sup> The presence of lymphocytes may be

## 67.2. Uvea: Choroidal and Ciliary Body Melanomas

---

assessed semiquantitatively or quantitatively—for example, by confocal imaging of cells stained by immunohistochemistry or immunofluorescence. Higher numbers are associated with shorter survival.

### Human Leucocyte Antigen Expression

The level of expression of human leukocyte antigen (HLA) molecules is associated with metastatic risk and may be relevant with regard to immunotherapy (AJCC Level of Evidence: III).<sup>19,20</sup> The level of expression is determined by assessing the percentage of immunopositive tumor cells. Higher expression is related to shorter survival.

### Risk Assessment Models

The AJCC recently established guidelines that will be used to evaluate published statistical prediction models for the purpose of granting endorsement for clinical use.<sup>21</sup> Although this is a monumental step toward the goal of precision medicine, this work was published only very recently. Therefore, the existing models that have been published or may be in clinical use have not yet been evaluated for this cancer site by the Precision Medicine Core of the AJCC. In the future, the statistical prediction models for this cancer site will be evaluated, and those that meet all AJCC criteria will be endorsed.

### Recommendations for Clinical Trial Stratification

Clinical trials addressing treatments for metastatic uveal melanoma are recommended to stratify patients on the basis of the M categories (M1a-c).

### Bibliography

1. Harbour JW, Onken MD, Roberson ED, et al. Frequent mutation of BAP1 in metastasizing uveal melanomas. *Science*. 2010;330(6009):1410-1413.
2. Martin M, Masshofer L, Temming P, et al. Exome sequencing identifies recurrent somatic mutations in EIF1AX and SF3B1 in uveal melanoma with disomy 3. *Nature genetics*. 2013;45(8):933-936.
3. Harbour JW, Roberson ED, Anbunathan H, Onken MD, Worley LA, Bowcock AM. Recurrent mutations at codon 625 of the splicing factor SF3B1 in uveal melanoma. *Nature genetics*. 2013;45(2):133-135.
4. Ewens KG, Kanetsky PA, Richards-Yutz J, et al. Chromosome 3 status combined with BAP1 and EIF1AX mutation profiles are associated with metastasis in uveal melanoma. *Invest Ophthalmol Vis Sci*. 2014;55(8):5160-5167.
5. Dono M, Angelini G, Cecconi M, et al. Mutation frequencies of GNAQ, GNA11, BAP1, SF3B1, EIF1AX and TERT in uveal melanoma: detection of an activating

## 67.2. Uvea: Choroidal and Ciliary Body Melanomas

---

- mutation in the TERT gene promoter in a single case of uveal melanoma. *Br J Cancer*. 2014;110(4):1058-1065.
6. Koopmans AE, Verdijk RM, Brouwer RW, et al. Clinical significance of immunohistochemistry for detection of BAP1 mutations in uveal melanoma. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc*. 2014;27(10):1321-1330.
  7. Shah AA, Bourne TD, Murali R. BAP1 protein loss by immunohistochemistry: a potentially useful tool for prognostic prediction in patients with uveal melanoma. *Pathology*. 2013;45(7):651-656.
  8. Kalirai H, Dodson A, Faqir S, Damato BE, Coupland SE. Lack of BAP1 protein expression in uveal melanoma is associated with increased metastatic risk and has utility in routine prognostic testing. *Br J Cancer*. 2014;111(7):1373-1380.
  9. Griewank KG, van de Nes J, Schilling B, et al. Genetic and clinico-pathologic analysis of metastatic uveal melanoma. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc*. 2014;27(2):175-183.
  10. Rai K, Pilarski R, Cebulla CM, Abdel-Rahman MH. Comprehensive review of BAP1 tumor predisposition syndrome with report of two new cases. *Clin Genet*. 2016;89(3):285-294.
  11. Van Raamsdonk CD, Griewank KG, Crosby MB, et al. Mutations in GNA11 in uveal melanoma. *N Engl J Med*. 2010;363(23):2191-2199.
  12. Van Raamsdonk CD, Bezrookove V, Green G, et al. Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. *Nature*. 2009;457(7229):599-602.
  13. Onken MD, Worley LA, Long MD, et al. Oncogenic mutations in GNAQ occur early in uveal melanoma. *Invest Ophthalmol Vis Sci*. 2008;49(12):5230-5234.
  14. Bidard FC, Madic J, Mariani P, et al. Detection rate and prognostic value of circulating tumor cells and circulating tumor DNA in metastatic uveal melanoma. *Int J Cancer*. 2014;134(5):1207-1213.
  15. Maat W, Ly LV, Jordanova ES, de Wolff-Rouendaal D, Schalijs-Delfos NE, Jager MJ. Monosomy of chromosome 3 and an inflammatory phenotype occur together in uveal melanoma. *Invest Ophthalmol Vis Sci*. 2008;49(2):505-510.
  16. de la Cruz PO, Jr., Specht CS, McLean IW. Lymphocytic infiltration in uveal malignant melanoma. *Cancer*. 1990;65(1):112-115.
  17. Whelchel JC, Farah SE, McLean IW, Burnier MN. Immunohistochemistry of infiltrating lymphocytes in uveal malignant melanoma. *Invest Ophthalmol Vis Sci*. 1993;34(8):2603-2606.

## 67.2. Uvea: Choroidal and Ciliary Body Melanomas

---

18. Lagouros E, Salomao D, Thorland E, Hodge DO, Vile R, Pulido JS. Infiltrative T regulatory cells in enucleated uveal melanomas. *Trans Am Ophthalmol Soc.* 2009;107:223-228.
19. Ericsson C, Seregard S, Bartolazzi A, et al. Association of HLA class I and class II antigen expression and mortality in uveal melanoma. *Invest Ophthalmol Vis Sci.* 2001;42(10):2153-2156.
20. Blom DJ, Luyten GP, Mooy C, Kerkvliet S, Zwinderman AH, Jager MJ. Human leukocyte antigen class I expression. Marker of poor prognosis in uveal melanoma. *Invest Ophthalmol Vis Sci.* 1997;38(9):1865-1872.
21. Kattan MW, Hess KR, Amin MB, et al. American Joint Committee on Cancer acceptance criteria for inclusion of risk models for individualized prognosis in the practice of precision medicine. *CA: a cancer journal for clinicians.* 2016.