Symposium

Uveal melanoma: Estimating prognosis

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Uveal melanoma is the most common primary malignant tumor of the eye in adults, predominantly found in Caucasians. Local tumor control of uveal melanoma is excellent, yet this malignancy is associated with relatively high mortality secondary to metastasis. Various clinical, histopathological, cytogenetic features and gene expression features help in estimating the prognosis of uveal melanoma. The clinical features associated with poor prognosis in patients with uveal melanoma include older age at presentation, male gender, larger tumor basal diameter and thickness, ciliary body location, diffuse tumor configuration, association with ocular/oculodermal melanocytosis, extraocular tumor extension, and advanced tumor staging by American Joint Committee on Cancer classification. Histopathological features suggestive of poor prognosis include epithelioid cell type, high mitotic activity, higher values of mean diameter of ten largest nucleoli, higher microvascular density, extravascular matrix patterns, tumor-infiltrating lymphocytes, tumor-infiltrating macrophages, higher expression of insulin-like growth factor-1 receptor, and higher expression of human leukocyte antigen Class I and II. Monosomy 3, 1p loss, 6q loss, and 8q and those classified as Class II by gene expression are predictive of poor prognosis of uveal melanoma. In this review, we discuss the prognostic factors of uveal melanoma. A database search was performed on PubMed, using the terms "uvea," "iris," "ciliary body," "choroid," "melanoma," "uveal melanoma" and "prognosis," "metastasis," "genetic testing," "gene expression profiling." Relevant English language articles were extracted, reviewed, and referenced appropriately.

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Uveal melanoma represents 79-81% of ocular melanomas and 3-5% of all melanomas.[1-3] In the United States, the incidence of uveal melanoma is 5/million population.[1] In Europe, the incidence of uveal melanoma follows a north-to-south decreasing gradient ranging from 2 to 8/million population.[2] Over the years, with advances in the treatment strategies, there is an improvement in the rate of local tumor control and globe salvage, but survival rate remains relatively unchanged.[1,4,5]

Uveal melanoma has a high tendency to metastasize resulting in high mortality.[1,5-10] The common sites of metastasis include liver (89%), lung (29%), and bone (17%).[8] Approximately, 50% of patients with uveal melanoma succumb to metastasis within 10 years of diagnosis, irrespective of the type of treatment.[1,5-10] Median survival after metastasis is 6 to 12 months, though long-term survival has been reported.[8,11] Though, the overall survival rate of patients with metastatic uveal melanoma is poor, median survival of patients receiving treatment for metastasis is better than those receiving no treatment.[8,12-16]

Various clinical, histopathological, and cytogenetic features of uveal melanoma can identify those patients who are at high risk of developing metastasis and probably benefit from appropriate prophylactic/therapeutic adjuvant and adjunctive treatments [Table 1]. In this review, we describe the features predictive of poor prognosis in patients with uveal melanoma. A database search was performed on PubMed, using the terms "uvea," "iris," "ciliary body," "choroid," "melanoma," "uveal melanoma" and "prognosis," "metastasis," "genetic testing," "gene expression profiling (GEP)". Relevant English language articles were extracted, reviewed, and referenced appropriately.

Clinical Features

The clinical features predicting prognosis in patients with uveal melanoma include age at presentation, gender, tumor size, tumor location, tumor configuration, presence or absence of ocular/oculodermal melanocytosis (OM), extraocular tumor extension (EOE), and American Joint Committee on Cancer (AJCC) classification.[17-65]

Age at presentation

A few studies have concluded that the age of presentation has no influence on the prognosis of uveal melanoma.[17-19] In contrast, other studies have indicated that the life prognosis is more favorable in children with uveal melanoma compared with adults.[21-26] The favorable prognosis of uveal melanoma in children is attributed to a bias secondary to confounding factors such as higher percentage of iris melanoma, smaller tumor size at diagnosis, lower incidence of EOE, and shorter follow-up duration in children compared to adults.[20-22] In an attempt to overcome these confounding factors, Kaliki *et al*. matched clinical predictive factors for metastasis such as gender, tumor location, tumor basal diameter, tumor thickness, extraocular extension, and follow-up duration in 122 patients in each age category (young [≤20 years], mid-adults [21-60 years], older adults [>60 years]) and found that younger patient age

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Table 1: Features predictive of poor prognosis for uveal melanoma

Clinical features
Older age at presentation
Male gender
Larger tumor basal diameter
Thicker tumor
Ciliary body tumor location
Diffuse tumor configuration
Association with ocular/oculodermal melanocytosis
Extraocular tumor extension
Advanced AJCC category and staging
Histopathologic features
Epithelioid cytology
High mitotic activity/PC-10/Ki-67
High values of mean diameter of ten largest nucleoli
High microvascular density
Microvascular loops and patterns
Tumor-infiltrating lymphocytes
Tumor-infiltrating macrophages
High expression of insulin-like growth factor 1 receptor
High expression of HLA class I and II
Cytogenetic features
Chromosome 3 loss (monosomy 3)
Chromosome 8q gain or 8p loss
Chromosome 1p loss
Chromosome 6q loss
Transcriptomic feature
Gene expression profile class 2

AJCC: American Joint Committee on Cancer, HLA: Human leukocyte antigen

at the time of diagnosis of uveal melanoma is associated with lower rate of metastasis compared with mid-adults and older adults.[27] Evaluation by decade of presentation in 8,033 patients with uveal melanoma by Shields *et al*. showed similar gradual increase in risk for metastasis with increasing age.[26] At 10 years, metastasis was 10% in patients aged 11-20 years, 21% for 41-50 years, and 30% for 71-80 years.[26]

Gender

The Collaborative Ocular Melanoma Study (COMS) study group found no difference in uveal melanoma-related metastasis and death between men and women.[26] Other study groups made similar observations.[9,28] However, in a study of 723 uveal melanoma patients, Zloto *et al*. found significant gender differences in prognosis.[29] Male patients had worse prognosis with higher melanoma-related metastasis and death than female patients. Melanoma-related mortality in the first 10 years was two-fold higher in males compared with females.[29] By multivariable regression analysis, Rietschel *et al*. found that male gender was associated with significantly higher risk of melanoma-related mortality than female gender.[30] The lower metastatic rate in females could be related to hormonal factors.[29,31] Zloto *et al*. suggested that estrogen may indirectly influence the tissue through the regulation of other factors that directly affect the melanoma or could be related to inhibitory action of estrogen on the growth of micro-metastases within the liver.[29]

Tumor size

Tumor size (largest basal diameter and thickness) is one of the most important clinical prognostic feature of uveal melanoma.[6,7,9,30,32-37] In a meta-analysis of 8 articles by Diener-West *et al*., the combined weighted estimates of 5-year mortality rates associated with uveal melanoma were 16% for small tumors (<2 or 3 mm tumor thickness and <10 or 11 mm basal diameter), 32% for medium tumors (3-8 mm tumor thickness and <15 or 16 mm basal diameter), and 53% for large tumors (>8 mm tumor thickness and >15 mm basal diameter).[7] The medium sized tumor trial (2.5-10 mm tumor thickness and <16 mm basal diameter) by COMS group revealed 5, 10, and 12 years melanoma-related mortality at 10%, 18%, and 21%, respectively, for patients in the iodine - 125 brachytherapy treatment arm and 11%, 17%, and 17%, respectively, for those in the enucleation treatment arm.[6] In the large tumor trial (>10 mm tumor thickness or >2 mm tumor thickness and >16 mm basal diameter) by COMS group, melanoma-related mortality at 5 and 10 years was 28% and 40%, respectively, for patients in the enucleation treatment arm and 26% and 45% in the external beam radiotherapy preceding enucleation treatment arm.[32,33]

In a long-term study of 289 patients with uveal melanoma, Kujala *et al*. found significant association between largest basal diameter of the tumor and melanoma-related mortality.[9] By competing risks regression analysis, the Hazard ratio was 1.08 for each millimeter increase in tumor diameter. The cumulative incidence estimates of melanoma-related mortality increased with increasing tumor basal diameter at 18% for small tumors (<10 mm basal diameter), 52% for medium tumors (10-15 mm basal diameter), and 59% for large tumors (≥16 mm basal diameter) at 25 years.[7]

In a study of 8,033 uveal melanoma patients by Shields *et al*., increasing tumor thickness of uveal melanoma was found to be associated with increasing risk for metastasis.[34] Kaplan–Meier estimates of metastasis at 5, 10, and 20 years was 6%, 12%, and 20% for small melanoma (<3 mm tumor thickness), 14%, 26%, and 37% for medium melanoma (3.1-8 mm), and 35%, 49%, and 67% for large melanoma (>8 mm) respectively. Each millimeter increase in tumor thickness was associated with approximately 5% increased risk for metastasis at 10 years and a hazard ratio of 1.08.[34]

Tumor location

Uveal melanoma can arise in the iris, ciliary body, or choroid. Iris melanoma has a better prognosis and ciliary body melanoma has the worst prognosis.[34-45] In a study of 8,033 patients with uveal melanoma, metastasis at 5 and 10 years was 4% and 7% for iris melanoma, 19% and 33% for ciliary body melanoma, and 15% and 25% for choroidal melanoma, respectively.[34]

The lower metastasis rate of iris melanoma is related to lower biologic activity or smaller tumor size of iris melanoma.[34,37,42] In a study of 3432 cases of uveal melanoma, iris melanoma was reported to have 10 times lower mortality compared with ciliary body and choroidal melanoma.[37] In another study of 8033 patients with uveal melanoma, the 10-year metastatic rate from iris melanoma was approximately 5 times less than ciliary body melanoma and 4 times less than choroidal melanoma.[34,38]

Patients with ciliary body melanoma greater than 7 mm in thickness are at 2.5 times greater risk than patients with

thinner tumors for metastatic disease and melanoma-related death.[43] According to Li *et al*., there is a significant relation between degree of ciliary body involvement (% of tumor base within the ciliary body) and melanoma-related metastasis.[44] According to this study, a melanoma of presumed ciliary body origin (>50% of the tumor base within the ciliary body) had 1.6-2.3 times higher chance of metastasis than a choroidal (<50% of the tumor base within the ciliary body) tumor. Tumors with 100% ciliary body involvement had 3.6 times higher chance of metastasis than choroidal melanoma.[44] The poor prognosis of ciliary body melanoma has been related to larger tumor size, predilection for monosomy 3 and 8q gain, and tumor microvascular patterns.[35,37,39,41,45] However, ciliary body involvement has been an independent predictor of survival in several multivariate models.[36,40,45]

Tumor configuration

Diffuse configuration of uveal melanoma is associated with poor prognosis.[46-50] Diffuse uveal melanoma represents horizontal, flat growth pattern of uveal melanoma, including diffuse iris melanoma, ring melanoma of ciliary body, and diffuse choroidal melanoma.[51]

Diffuse iris melanoma is a rare variant of iris melanoma representing 11% cases.[47,48] Diffuse iris melanoma is associated with greater metastatic potential compared with non-diffuse iris melanoma. In an analysis of 25 cases of diffuse iris melanoma, metastasis occurred in 13% cases at 6 years follow-up,[48] compared to 2-4% metastasis in cases with nondiffuse iris melanoma.[34,38,52] The higher metastatic rate in diffuse iris melanoma is associated with high incidence of epithelioid cells, elevated intraocular pressure, posterior tumor margin at iris root or angle, and extraocular extension.[48,53]

Ring melanoma of the ciliary body is a rare variant of uveal melanoma occurring in <1% cases.[49] Metastasis in these cases is as high as 52% at 5-year follow-up,[49] compared to 19% in cases with nondiffuse variant.[34] Poor prognosis in cases with ring melanoma of ciliary body is attributed to difficult and delayed diagnosis and treatment.

Diffuse choroidal melanoma represents 3-17% of all choroidal melanomas.[50] Diffuse choroidal melanoma carries a substantial risk for metastasis despite its flat appearance.[54] In a comparative study of diffuse versus nondiffuse choroidal melanoma in 2121 patients, Kaplan–Meier estimates of melanoma-related metastasis (diffuse vs. nondiffuse) was 8% versus 4% at 5 years and 17% versus 10% at 10 years.[50] The poor prognosis in diffuse choroidal melanoma may be related to delayed diagnosis, a greater proportion of epithelioid cells, and its tendency for extraocular extension.[46,50]

Ocular/oculodermal melanocytosis

Ocular/OM is associated with increased risk of development of uveal melanoma, estimated at 1 in 400 affected patients.[54] The influence of ocular/OM on the prognosis of uveal melanoma has been recently explored.[55,56]

In a study of 7872 patients with uveal melanoma, patients with associated OM had double the risk for metastasis compared with those with no OM.[55] By Kaplan–Meier estimates, metastasis in patients with OM versus no OM was 27% versus 15% at 5 years, and 48% versus 24% at 10 years.[55] Similar findings were recorded in a matched study where each patient with uveal melanoma associated with OM was matched for factors age, gender, tumor thickness, tumor basal diameter, location of tumor epicenter, and location of anterior tumor margin.[56] In that analysis, Kaplan–Meier estimates for systemic metastasis in the melanocytosis group at 5 and 15 years were 27% and 59% (respectively) compared with 15% and 33% in the no melanocytosis group.[56]

Extraocular tumor extension

Extraocular tumor extension is a poor prognostic factor for uveal melanoma, occurring in 8-15% cases.[57-61] EOE is more commonly associated with larger tumors, anterior tumor extension, large basal tumor diameter, diffuse uveal melanoma, epithelioid cellularity, closed vascular loops, high mitotic rate, and monosomy 3, resulting in poor prognosis.[50,54,57-61]

The overall survival could be related to the characteristics of the intraocular portion of the tumor rather than the EOE, except when the size of the EOE is large (>5 mm).[58] In a study of 610 patients with uveal melanoma, the 5-year mortality rate for patients with a microscopic extension and small EOE (1-4 mm) were 37% and 24%, respectively.[58] These numbers were markedly higher for patients with large EOE with 5-year mortality rate of 78%.[58]

American Joint Committee on Cancer classification

The AJCC (7th edition) is an attempt to unify the clinical prognostic factors into a single classification system.[62] In this classification, iris melanoma is graded according to tumor extent, associated secondary glaucoma, and EOE. Posterior uveal (ciliary body and choroid) melanoma is graded according to tumor basal diameter and thickness, ciliary body involvement, and extraocular extension.[62] The patients with advanced AJCC tumor staging exhibit poor prognosis.[63]

In a study of 452 patients with iris melanoma based on AJCC classification, the 10-year metastatic rate was 2% for stage I tumors, 6% for stage II, and 41% for stage III.[63] In a study of 7731 patients with posterior uveal melanoma based on T category of AJCC classification, the 10-year metastatic rate was 15% for T1 tumors, 25% for T2, and 49% for T3, and 63% for T4.[63] The risk for metastasis and death increased two-fold with each increasing tumor category.[64] Based on AJCC staging for posterior uveal melanoma, 10-year metastatic rate was 12% for stage I tumors, 29% for stage II, and 61% for stage III. The risk for metastasis and death increased three-fold with each increasing melanoma staging.[64]

Histopathological Features

The histopathologic features predicting prognosis of uveal melanoma include tumor cell type, mitotic activity, mean diameter of ten largest nucleoli, microvascular density (MVD), extravascular matrix patterns, tumor-infiltrating lymphocytes, tumor-infiltrating macrophages, insulin-like growth factor-1 receptor (IGF-1R), and human leukocyte antigen (HLA) Class I expression.[65-113]

Tumor cell type

Tumor cell type is an important prognostic factor. Callender initially proposed a classification system for uveal melanoma including spindle A, spindle B, epithelioid, mixed, fascicular, and necrotic types.[65] This was later modified to include spindle A, spindle B, epithelioid, and mixed tumors.[66] The modified

Callender classification showed an improved correlation between the cell type and the mortality.[66]

In a study of 2652 enucleated eyes with uveal melanoma by Paul *et al*., the 15-year mortality for spindle A tumor was 19%, spindle B was 26%, mixed spindle B and epithelioid was 59%, and epithelioid tumor was 72%.[67] The 15-year mortality of patients with melanomas of mixed cell type is three times that of patients with tumors of pure spindle cell type.[37] Various studies have established that the spindle cell uveal melanoma has the best prognosis, mixed cell melanoma an intermediate, and epithelioid cell melanoma has the worst prognosis.[37,40,61,67-70] The prognosis worsens with increasing number of epithelioid cells per high power field (HPF).[69] In a study of 232 enucleated eyes from patients with uveal melanoma, the 10-year survival was 82% in patients with <0.5 epithelioid cells/HPF, 55% for 0.5 to 4.9 epithelioid cells/HPF, and 33% in patients with >5 epithelioid cells/HPF.[69]

Mitotic activity

Tumors with high cellular proliferation have a poor prognosis. Cellular proliferation in uveal melanoma can be determined by counting number of mitoses per 40 HPFs. Tumors with a low mitotic activity have a relatively good prognosis compared to those showing high mitotic activity.[71] In a study of 217 small malignant melanomas by McLean *et al*., increase in the number of mitoses/40 HPFs was significantly associated with increasing mortality rate. Six-year mortality was 16% for 0 mitosis/40 HPSs, 23% for 1mitosis/40 HPFs, 40% for 2-4, 47% for 5–8, and 56% for 9-48 mitoses/40 HPFs.[71]

In recent years immunohistochemical markers, PC-10 for proliferating cell nuclear antigen and MIB-1 for Ki-67 are used to examine cellular proliferation in conventionally processed histological preparations.[72-77] These markers seem to be reliable and easy tools for evaluating cellular activity. A high fraction of PC-10 and Ki-67 in uveal melanoma cells is associated with decreased melanoma-specific survival.[77,78]

Mean diameter of ten largest nucleoli

A large mean diameter of ten largest nucleoli (MLN) is associated with poor prognosis.[37,79-85] MLN can be measured on silver or hematoxylin-eosin stained sections. Larger MLN is found in tumors with epithelioid cells and in those with increasing MVD, which could influence poor prognosis.[79,81,85] However, studies have shown that larger MLN is an independent predictor of melanoma-related mortality.[79,83,84] There is a 0.58-1.27 times increase in melanoma-related mortality for each 1-um increase in MLN.[79-84]

In a study of 167 specimens for MLN, the median MLN was 4.05um (range, 2.60-6.18sum).[79] The 10-year Kaplan–Meier estimate for melanoma-specific survival was 74% for small, 60% for medium, and 42% for large MLN.[79] MLN remained an independent predictor of prognosis, when adjusted in turn for the effect of ciliary body involvement, largest tumor basal diameter, presence of epithelioid cells, and microvascular loops and networks. When adjusted for MVD, it was of borderline significance. However, combined MLN with cell type and MVD best predicted melanoma-specific survival.[79]

Microvascular density

MVD is a quantitative measurement of tumor vascularity. Microvessels are more distinct and easier to count from sections immunolabeled for CD34 epitope or FVIII-Rag.[86,87] Noninvasive methods of detection of MVD by ultrasound parameter imaging and confocal microscopy are also described.[88-90] High MVD is associated with a shortened survival of patients with uveal melanoma.[79,86,87,91] There is a significant association between high MVD and presence of microvascular loops and networks, epithelioid cells, and largest basal tumor diameter, thus influencing poor prognosis.[86,87] High MVD alone can also serve as an independent risk factor for melanoma-related metastasis and death.[79,87]

In a study of 162 consecutive enucleation specimens by Mäkitie *et al*., the median MVD was 40 vessels/0.313 mm^2 (range, 5-121).[87] The 10-year melanoma-specific mortality increased from quartile to quartile with increasing MVD, at 9%, 29%, 59%, and 64% according to quartiles.[87] Similar results were shown by Foss *et al*., with estimated 9-year cumulative probabilities of survival for the four quartiles at 85%, 55%, 44%, and 27%, respectively.[86]

Extravascular matrix patterns

The concept of microvascular patterns was introduced by Folberg *et al*., who suggested that microvessel architecture has a strong association with prognosis of uveal melanoma.[92] In addition to normal vessels incorporated into the tumor stroma and focal avascular zones, the tumors contain straight vessels, parallel straight vessels, parallel vessels that cross-link, vascular arcs (incomplete loops), arcs with branching, closed vascular loops that encircle small clusters of tumor cells, and microvascular networks composed of back-to-back loops.[92] The patterns are assessed with light microscopy on periodic-acid-schiff stained tissues.

The presence of microvascular loops and networks surrounding nests of tumor cells can independently predict melanoma-related tumor death.[92-94] In a matched case control study by Folberg *et al*., it was shown that the presence of at least one closed vascular loop in a uveal melanoma is the most significant vascular pattern associated with death from metastatic melanoma.[92] The detection of at least one closed loop within a tumor is associated with the presence of epithelioid cells and at least one mitotic figure.[92] In a study by Al-Jamal *et al*., the Kaplan-Meier estimate for 10-year melanoma-specific survival was estimated at 80% if no loops, 48% if loops were present without networks, and 40% if loops forming networks were present.[79]

Tumor infiltrating lymphocytes

Increased infiltration of uveal melanoma by lymphocytes suggests poor prognosis.[95-98] An association between monosomy 3 and influx of tumor-infiltrating lymphocytes has been established.[97] Uveal melanoma cells which have lost one copy of chromosome 3 may produce inflammatory mediators, which recruit and activate $CD8^+$, $CD4^+$, and $Foxp3^+$ T cells, as well as $CD68^+$, and $CD68^+$ and $CD163^+$ macrophages. Activation of these infiltrating cells will result in production of more inflammatory mediators generating a tumor-promoting inflammatory microenvironment, resulting in poor prognosis.[98]

In a study of 1193 cases by de la Cruz *et al*., 134 (12%) tumors contained 100 or more lymphocytes per 20 HPF and were classified as high lymphocytic group.[95] An equivalent number of cases with fewer lymphocytes comprised the low lymphocytic group. The survival rate at 15 years was 37% for

patients in the high lymphocytic group and 70% for patients in the low lymphocytic group. Despite control of other risk factors, there was a significant association between increased number of lymphocytes per 20 HPF and survival.[95]

Tumor infiltrating macrophages

High numbers of tumor-infiltrating macrophages in uveal melanoma are associated with an unfavorable prognosis.[99-104] These tumors are associated with the presence of epithelioid cells, increased MVD, and monosomy 3.[99-103] Macrophages of the M2 phenotype promotes phagocytic activity, tissue remodeling, tumor progression, and angiogenesis.[104]

In a study of 43 uveal melanomas by immunohistochemistry, the infiltrating macrophages were predominantly $CD68^+$ $CD163^+$ (M2 phenotype).[104] Kaplan–Meier survival analysis revealed that a low $CD68^+$ or $CD68^+$ $CD163^+$ macrophages were associated with a significantly better survival. However, the significance of tumor-infiltrating macrophages as a predictor of melanoma-related mortality could not be established on multivariable analysis.[104]

Insulin-like growth factor-1 receptor

High expression levels of IGF-1R in primary tumors correlates significantly with lower survival rates.[105] The significant association between high IGF-1R expression and death due to metastatic disease may be related to the fact that IGF-1 is mainly produced in the liver, which is the preferential site for uveal melanoma metastases.[105] Based on this finding, IGF-1R blockage is a possible new treatment modality for metastases that may also play a role as adjuvant therapy in preventing the development of metastatic disease;[106] and serum IGF-1 level may be used as a predictive biomarker for metastatic uveal melanoma when measured repeatedly.[107]

In a study of 36 cases of uveal melanoma with more than 15 years follow-up, Kaplan-Meier analysis showed a significant association between a high IGF-1R (expression in >50% melanoma cells) and melanoma-related mortality.[105] Over a period of 15 years follow-up, 56% of patients with high IGF-1R, and 42% with low IGF-1R (expression in 15 to 50% cells), and 0% with very low IGF-1R (expression in <15% cells) died due to metastasis.[105]

Human leukocyte antigen expression

Unlike the general rule of higher mortality with lower expression of HLA Class I determinants,[108] uveal melanoma exhibits an opposite association. This could be related to natural killer cells playing an essential role in immune responses directed against uveal melanoma metastases rather than cytotoxic T-lymphocytes.[109,110] Higher HLA Class I and II expression is associated with higher melanoma-related mortality.[109-111] However, some studies have found no association between HLA expression and melanoma-related mortality.[112]

In a study by Ericsson *et al*., a significant correlation between the expression of HLA Class I antigens, β_2-microglobulin, and HLA Class II antigens and the development of metastases was noted.[111] Jager *et al*. demonstrated that the tumors expressing HLA-A exhibited higher melanoma-related mortality (75%) as compared to those not staining for HLA-A (20%).[113] HLA-A was found to be the strongest independent predictor of tumor-related mortality, whereas HLA-B expression was not an independent predictor of survival.[113] Blom *et al*. have reported that a high expression of HLA-B significantly correlated with the presence of epitheloid cells, a cell type that carries a bad prognosis.[110]

Cytogenetic Features

Recent studies underscore the importance of cytogenetic features in the prognosis of uveal melanoma. Tumor sample for genetic testing is either obtained from enucleation specimen or intraoperatively by fine needle aspiration biopsy. Aberrations in chromosome 1, 3, 6, and 8 determine the survival in patients with uveal melanoma.[39,114-116] Chromosome 3 loss, 8q gain, 1p loss, and 6q loss are associated with poor prognosis.[39,41,114-133]

Chromosome 3

In majority of cases with chromosome 3 aberrations in uveal melanoma, monosomy 3 (complete loss of one copy of chromosome 3) is more common and is the most important prognostic factor.[39,41,118,119,122] Partial aberrations on chromosome 3 (partial deletion of one copy of chromosome 3) and isodisomy (loss of one copy of chromosome 3 and then duplication of the remaining defective copy) have also been reported, both of which have a metastatic potential.[123-125] A variation of monosomy 3 status can occur within the same tumor. In a study of uveal melanomas by Schoenfield *et al*., monosomy 3 was noted at the base and disomy 3 at apex of the tumor.[124]

In a landmark publication by Prescher *et al*., monosomy 3 was established as a significant prognostic factor for uveal melanoma.[39] Of 54 patients with uveal melanoma, monosomy 3 was identified in 30 (56%) patients. Three-year mortality rate in patients with tumors harboring monosomy 3 was 50%, and those with no monosomy 3 was 0%.[39] Subsequent studies have shown that monosomy 3 occurs in 21 to 56% cases and is associated with melanoma-related mortality in 42-54% over a follow-up period ranging from 2 to 8 years.[39,41,118,120,122] Presence of monosomy 3 indicates high-risk melanoma, with an increased risk for metastasis. Monosomy 3 is associated with clinical and histopathological risk factors including larger tumor diameter, ciliary body tumor location, epithelioid cell type, high mitotic rate, vascular loops, and extraocular extension.[39,41,118,120] Recently, the tumor suppressor gene BRCA1-associated protein 1 (BAP1) has been mapped on chromosome 3p21.1. Its somatic mutation has been associated with metastatic uveal melanoma.[127]

Chromosome 8

In majority of cases with aberrations in chromosome 8, 8q gain is more common occurring in 41 to 53% cases of uveal melanoma, while 8p loss occurs rarely.[128-130] The most common forms of 8q gain are trisomy 8, isochromosome 8q, and amplification of the c-myc gene.[123]

Chromosome 8q gain is an important prognostic factor for uveal melanoma either when it presents alone or co-exists with monosomy 3.[117,119] Chromosome 8q gain most commonly co-exists with monosomy 3 and is associated with poor prognosis than 8q gain alone or monosomy 3 alone. In a study of 356 patients with uveal melanoma by Damato *et al*., the tumors showed no cytogenetic abnormalities of chromosomes 3 or 8 in 42%, 8q gain in 11%, monosomy 3 in 21%, and combined 8q gain and monosomy 3 in 27%.[118] Five-year disease specific mortality rates were 6% in the absence of chromosomal

abnormality, 31% with only 8q gain, 40% with only monosomy 3, and 66% with combined 8q gain and monosomy 3.[118] 8q gain was associated with clinical and histopathologic risk factors, including larger tumor diameter, ciliary body tumor location, epithelioid cell type, high mitotic rate, and vascular loops.[118]

Chromosome 1

Loss of part or all of chromosome 1p is associated with poor prognosis either when it presents alone or co-exists with monosomy 3.[120,121] Chromosome 1p loss occurs more frequently in tumors with monosomy 3 (40%) than those with disomy 3 (10%).[121]

Concomitant loss of chromosomes 1p and 3 has a stronger correlation with melanoma-related metastasis than either one of them separately. In a study 0f 120 patients with uveal melanoma by Kilic *et al*., it was noted that the effect of monosomy 3 on survival was largely modified by changes in 1p36.[120] After correcting for confounding variables, it was found that patients harboring tumors with concurrent loss of chromosomes 1p36 and 3 have 7.8 times higher chance of developing metastases than do those without these losses or with loss of either chromosomes 1p36 or 3.[120]

Chromosome 6

Chromosome 6 gain has an inverse relationship with melanoma-related metastasis, and is a strong indicator of good prognosis of uveal melanoma.[114,119] Chromosome 6p gain is usually mutually exclusive with monosomy 3.[114,131] These tumors with chromosome 6p gain have been proposed to represent a separate group of uveal melanomas with an alternative genetic pathway in carcinogenesis compared with those with monosomy 3.[131,132] The coexistence of 6p gain and monosomy 3 occurs in only 4% cases of uveal melanoma.[132]

Chromosome 6q loss is associated with poor prognosis. In a study of 35 tumors by Aalto *et al*., 6q loss was noted in 40% metastasizing tumors when compared to 7% non-metastasizing tumors.[133]

Transcriptomic Features

Based on analysis of mRNA by GEP of all chromosomes, 2 tumor classes of uveal melanoma were described by Tschentscher *et al*.[134] All tumors in Class I had disomy 3, and all tumors in Class II had monosomy 3.[134] Subsequently, a relationship between GEP and melanoma-related survival in patients with uveal melanoma was studied by Onken *et al*.[135] Based on the comparison of molecular classification to cytogenetic changes in 10 tumor samples, Class I tumors were considered as low-risk tumors and Class II tumors as high-risk tumors.[135] Chromosome 6p gain occurred in 80% Class I tumors, and monosomy 3 was noted in 80% Class II tumors and no Class I tumors.[135] Survival analysis of 50 patients revealed 95% survival probability in Class I versus 31% in class 2 at 7.7 years follow-up.[135] Subsequent studies noted similar findings. Class I lesions were unlikely to undergo metastasis, whereas Class II lesions predicted a greater rate of metastasis and melanoma-related mortality.[135-140] Patients with Class II tumors tend to be older, and are associated with thicker tumors, epithelioid cytology, higher proliferative rate (higher Ki-67 positivity), and mutations in BAP1 tumor suppressor gene.[127,138,139]

A recent study of 459 patients with uveal melanoma by a multicenter trial from 12 oncology centers, revealed a strong association between GEP and prognosis of uveal melanoma.[140] At a median of 17 months follow-up, metastasis was detected in 1% Class I cases and 26% Class II cases.[140] GEP class had a strong independent association with metastasis and chromosome 3 status did not provide additional prognostic information that was independent of GEP.[140]

Conclusion

The long-term prognosis of uveal melanoma is poor with death occurring in more than 50% cases. The prognosis of uveal melanoma can be estimated by clinical, histopathological, cytogenetic, and transcriptomic markers. Improved prognostication for uveal melanoma allows identification of patients at high risk for metastasis, thereby facilitating targeted screening, and probable adjunctive/adjuvant systemic treatment. Currently, the most effective measure to minimize poor prognosis is early detection of melanoma at a time when the tumor is small and at least risk for metastatic disease.

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