Review Article

# Prognostication of uveal melanoma is simple and highly predictive using The Cancer Genome Atlas (TCGA) classification: A review

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**Purpose:** The cancer genome atlas (TCGA) is a comprehensive project supported by the National Cancer Institute (NCI) in the United States to explore molecular alterations in cancer, including uveal melanoma (UM). This led to TCGA classification for UM. In this report, we review the American Joint Committee on Cancer (AJCC) classification and TCGA classification for UM from the NCI's Center for Cancer Genomics (NCI CCG) (based on enucleation specimens [$n$ = 80 eyes]) and from Wills Eye Hospital (WEH) (based on fine needle aspiration biopsy [FNAB] specimens [$n$ = 658 eyes]). We then compare accuracy and predictability of AJCC versus (vs.) TCGA. **Methods:** Review of published reports on AJCC and TCGA classification for UM was performed. Outcomes based on AJCC 7th and 8th editions were assessed. For TCGA, UM was classified based on chromosomes 3 and 8 findings including disomy 3 (D3), monosomy 3 (M3), disomy 8 (D8), 8q gain (8qG), or 8q gain multiple (8qGm) and combined into four classes including Class A (D3/D8), Class B (D3/8qG), Class C (M3/8qG), and Class D (M3/8qGm). Outcomes of metastasis and death were explored and a comparison (AJCC vs. TCGA) was performed. **Results:** In the NCI CCG study, there were 80 eyes with UM sampled by enucleation ($n$ = 77), resection ($n$ = 2), or orbitotomy ($n$ = 1) and analysis revealed four distinct genetic classes. Metastasis and death outcomes were subsequently evaluated per class in the WEH study. The WEH study reviewed 658 eyes with UM, sampled by FNAB, and found Class A ($n$ = 342, 52%), B ($n$ = 91, 14%), C ($n$ = 118, 18%), and D ($n$ = 107, 16%). Comparison by increasing class (A vs. B vs. C vs. D) revealed older mean patient age ($P$ < 0.001), worse entering visual acuity ($P$ < 0.001), greater distance from the optic disc ($P$ < 0.001), larger tumor diameter ($P$ < 0.001), and greater tumor thickness ($P$ < 0.001). Regarding outcomes, more advanced TCGA class demonstrated increased 5-year risk for metastasis (4% vs. 20% vs. 33% vs. 63%, $P$ < 0.001) with corresponding increasing hazard ratio (HR) (1.0 vs. 4.1, 10.1, 30.0, $P$ = 0.01 for B vs. A and $P$ < 0.001 for C vs. A and D vs. A) as well as increased 5-year estimated risk for death (1% vs. 0% vs. 9% vs. 23%, $P$ < 0.001) with corresponding increasing HR (1 vs. NA vs. 3.1 vs. 13.7, $P$ = 0.11 for C vs. A and $P$ < 0.001 for D vs. A). Comparison of AJCC to TCGA classification revealed TCGA was superior in prediction of metastasis and death from UM. **Conclusion:** TCGA classification for UM is simple, accurate, and highly predictive of melanoma-related metastasis and death, more so than the AJCC classification.

**Key words:** AJCC, American joint committee on cancer, classification, genetics, TCGA, the cancer genome atlas, uveal melanoma

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Prognostication is a valuable tool in the management of uveal melanoma (UM) in terms of understanding cancer biology, knowing the rate and impact of metastatic disease, providing management options for patients, and consideration of new therapeutic alternatives in clinical trials. There are several prognostic parameters that have been explored in the past including tumor location, basal dimension and thickness, histopathologic cell type, vascular mimicry patterns, infiltrating lymphocytes, and others. More recently, tumor categorization by the American Joint Committee on Cancer (AJCC) staging and by genetic analysis or gene expression profiling have become of utmost importance. Herein, we will review UM classification using AJCC and genetic testing, and will explore the *new* nationally sponsored, multicenter effort of TCGA project.

## Prognostication of UM by American Joint Committee on Cancer (AJCC)

The AJCC staging manual is designed to provide a detailed classification for numerous solid cancers, including UM.[1] The intent of this classification is to allow clinicians to assess tumor extent with a uniform language and ultimately improve

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understanding and prognostication of cancer. This classification scheme is based on tumor (T), node (N), and metastasis (M), and is sometimes referred to as the "TNM classification". The tumor is graded according to size category based on a combination of basal diameter and thickness and labeled as T1, T2, T3, and T4 with increasing category. Subclassification of each T category is judged by (a) the absence of ciliary body (CB) involvement and extraocular extension, (b) the presence of CB involvement, (c) the presence of extraocular extension ≤5 mm, (d) the presence of both CB involvement and extraocular extension ≤5 mm, and (e) any tumor size category with extraocular extension >5 mm diameter.[2] The node and metastasis are graded as present or absent with tumor invasion and metastasis additionally is graded by nodule size of (a) ≤3 cm, (b) 3.1–8.0 cm, and (c) ≥8.1 cm. This is further refined into prognostic staging based on the T, N, and M findings. The AJCC classification includes histopathologic grade (G) as (1) spindle melanoma, (2) mixed melanoma, and (3) epithelioid melanoma.

Several studies have explored the AJCC classification regarding prognostic capability for UM. Most studies[3-5] have focused on AJCC 7th edition as the 8th edition was only recently released. Shields *et al*. released two reports on a single center AJCC classification 7th edition in 7731 patients with posterior UM based on T category and, subsequently, based on anatomic stage.[3,4] Regarding T category, they found UM was categorized as T1 in 3557 (46%), T2 in 2082 (27%), T3 in 1599 (21%), and T4 in 493 (6%).[3] There were clinical features that increased per T category (T1, T2, T3, T4) including patient age (57, 58, 58, 61 years, $P < 0.001$), tumor base (8, 12, 15, 20 mm, $P < 0.001$), tumor thickness (3.5, 5.2, 8.9, 11.4 mm, $P < 0.001$), mushroom configuration (8%, 20%, 38%, 39%, $P < 0.001$), associated subretinal fluid (64%, 80%, 82%, 83%, $P < 0.001$), Bruch's membrane rupture (9%, 24%, 40%, 40%, $P < 0.001$), and extraocular extension (1%, <1%, 4%, 12%, $P < 0.001$).

These authors found that T category was strongly predictive of metastatic disease. Using Kaplan–Meier estimates of metastasis (at 5, 10, 20 years) following therapy they found increasing rate of metástasis per category, including category T1 (8%, 15%, 25%), T2 (14%, 25%, 40%), T3 (31%, 49%, 62%), and T4 (51%, 63%, 69%) ($P < 0.001$ at all time points).[3] Compared to category T1, the HR for metastasis for T2 was 1.8, T3 was 4.5, and T4 was 8.2. Similar increasing risk was noted for death by Kaplan–Meier analysis.

Subsequent analysis on this cohort of 7731 patients with posterior UM was performed based on anatomic stage, revealing stage I in 2767 (36%), stage II in 3735 (48%), stage III in 1220 (16%), and stage IV in 9 (<1%).[4] By specific tumor stage (I, II, III, IV), some clinical features demonstrated significant increase per stage, including age at diagnosis (57, 58, 60, 60 years, $P < 0.001$), tumor base (8, 12, 17, 17 mm, $P < 0.001$), tumor thickness (2.9, 6.0, 10.1, 10.2 mm, $P < 0.001$), distance to optic disc (3, 5, 5, 5 mm, $P < 0.001$), distance to foveola (3, 5, 5, 5 mm, $P < 0.001$), mushroom configuration (6%, 24%, 34%, 33%, $P < 0.001$), and extraocular extension (0%, 1%, 11%, 22%, $P < 0.001$). The tumor stage was highly predictive of risk for metastasis (at 5, 10 years), including stage I (5%, 12%), stage II (17%, 29%), stage III (44%, 61%), and stage IV (100% by 1 year)[4] [Table 1]. They concluded that the rate of metastasis was 3.1 times greater for stage II, 9.3 times greater for stage III, and greater yet for stage IV, compared to stage I.

The multicenter AJCC Ophthalmic Oncology Task Force provided a similar analysis on the predictive value of the AJCC classification 7th edition in 2015.[5] They investigated 3127 patients with posterior UM and found categories of T1 (35%), T2 (35%), T3 (24%), and T4 (6%). They evaluated the Kaplan–Meier metastasis-free estimates (5, 10 years) and result revealed T1 (97%, 94%), T2 (85%, 80%), T3 (77%, 68%), and T4 (61%, 5-year only)). Increasing category was associated with increasing risk for metastasis ($P < 0.001$).[5] They also explored AJCC anatomic stage and found the Kaplan–Meier metastasis-free point (5, 10 years) revealed stage 1 (97%, 94%), stage IIA (89%, 84%), stage IIB (79%, 70%), stage IIIA (67%, 60%), stage IIIB (50%, 50%), and stage IIIC (25%, 5-year only). They indicated that this multicenter, internet-based data sharing was able to study a heterogeneous patient population from around the world and demonstrate the facility of the AJCC 7th edition classification.[5]

## Prognostication of UM by Genetic Analysis

There have been several centers interested in prognostication of UM by genetic alterations.[6-15] Genetic testing has become the standard of care for modern UM management. Most ocular oncologists employ fine needle aspiration biopsy (FNAB) to sample melanoma for genetic profile immediately preceding the time of plaque radiotherapy or proton beam radiotherapy. The sample is sent for a DNA-based or RNA-based evaluation. Our team prefers DNA-based evaluation as it is highly predictive of prognosis and is quite affordable for the patient. Once the genetic profile is received, then stratification of the patient, based on genetic results, into low or high risk for metastatic disease is performed and patient management is adjusted. This affects surveillance decisions regarding frequency of systemic monitoring, enrollment into adjuvant systemic therapy for reduction of metastatic potential and consideration of patient psychologic concerns.

**Table 1: American Joint Committee on Cancer (AJCC) classification (anatomic stage) can predict uveal melanoma-related metastasis in 7731 patients**

| AJCC | Metastasis | | | | | |
|---|---|---|---|---|---|---|
| | @ 1 year | @ 3 years | @ 5 years | @ 10 years | @ 15 years | @ 20 years |
| Stage I | <1% | 2% | 5% | 12% | 15% | 20% |
| Stage II | 2% | 10% | 17% | 29% | 36% | 44% |
| Stage III | 6% | 26% | 44% | 61% | 73% | 73% |
| Stage IV | 100% | - | - | - | - | - |

[4]Data from Shields CL, Kaliki S, Furuta M, Fulco E, Alarcon C, Shields JA, *et al.* American Joint Committee on Cancer classification of uveal melanoma (anatomic stage) predicts prognosis in 7731 patients. The 2013 Zimmerman Lecture. Ophthalmology 2015;122:1180-6

In 2017, Shields *et al*. provided a large cohort assessment on FNAB genetic testing in 1059 consecutive patients with UM, with specific focus on abnormalities in chromosomes 3, 6, and 8.[10] By combination of cytogenetic abnormalities, Kaplan–Meier risk estimates (3, 5 years) for melanoma-related metastasis for 3, 6, and 8 disomy (1%, 4%) were low compared with higher-risk combinations of monosomy 3, 6p gain, and 8q gain (29%, 29%), monosomy 3, disomy 6, 8q gain, and 8p gain (14%, (not evaluable)), monosomy 3, disomy 6, and 8q gain (27%, 39%), and monosomy 3, disomy 6, 8q gain, and 8p loss (28%, (not evaluable)) [Table 2].[10] Later, they correlated melanoma cytogenetics with clinical features and found those with any mutation in chromosomes 3, 6, or 8 (vs. no mutation) showed significant differences in mean age (58 vs. 55 years, $P$ = 0.02), ocular melanocytosis (5% vs. 1%, $P$ = 0.03), mean visual acuity (VA) (20/50 vs. 20/30, $P$ = 0.01), poor VA ≤20/200) (15% vs. 9%, $P$ = 0.04), ciliary body location (11% vs. 5%, $P$ < 0.001), increased mean distance to optic disc (5.0 vs. 3.3 mm, $P$ < 0.001), and foveola (4.7 vs. 3.1 mm, $P$ < 0.001), and increased mean basal diameter (12.6 vs. 9.8 mm, $P$ < 0.001) and thickness (5.9 vs. 3.8 mm, $P$ < 0.001).[11] Damato and Coupland emphasized the importance of prognostication with combination of tumor basal dimension with genetic tumor type and melanoma cell type.[9] Since then, others have corroborated the importance of tumor size with gene expression profiling and other genetic factors.[12,13]

In 2017, Dogrusoz *et al*. reported that the AJCC staging can be improved by adding chromosomal status.[15] They studied 522 patients treated for UM and found stage I (17%), stage II (59%), stage III (23%), and stage IV (1%). They noted 5-year cumulative rate of melanoma-related death differed from those with AJCC stage I and no monosomy 3 or 8q gain (0%) to those with AJCC stage III and monosomy 3 and 8 q gain (73%) [Table 3]. By multivariable Cox regression analysis, the largest HRs identified AJCC stage III tumors (HR 8.8 $P$ < 0.001) and tumors with monosomy 3 plus 8q gain (HR 7.95, $P$ < 0.001).

## TCGA Project

TCGA is a project that was initiated in 2005 to comprehensively explore genetic mutations found in human cancer.[16-18] TCGA was funded by the United States government and directed by the National Cancer Institute's Center for Cancer Genomics and the National Human Genome Research Institute. The first three projects concerned glioblastoma multiforme, lung cancer, and ovarian cancer. In 2009, the project expanded to include 33 different solid cancers, including ten rare cancers.[17] Evaluation techniques comprised gene expression profiling, copy number variation profiling, SNP genotyping, genome-wide DNA methylation profiling, microRNA profiling, and exon sequencing. Later, whole exome and whole transcriptome sequencing were performed in all cases.

## TCGA from the National Cancer Institute's Center for Cancer Genomics (NIH CCG) for Uveal Melanoma (Based on Enucleation Specimens in 80 Cases)

TCGA researchers from the National Cancer Institute's Center for Cancer Genomics (NIH CCG) studied 80 cases with histopathologically proven UM, confirmed following enucleation ($n$ = 77), resection ($n$ = 2), or orbitotomy ($n$ = 1).[19] This research confirmed previous data documenting the importance of chromosome 3 monosomy (M3) and chromosome 3 disomy (D3).[6-11] Furthermore, it was noted that most M3 tumors demonstrated BAP1 alteration and BAP1 mutated tumors revealed unique global DNA methylation profile. Importantly, these researchers documented some differences between uveal and cutaneous melanoma, noting that UM has lower somatic mutational density, no ultraviolet radiation mutational signature, and a unique set of mutated genes, compared to cutaneous melanoma.[19]

TCGA used a comprehensive multiplatform assessment of this cohort of UM and found four molecularly distinct and clinically relevant subgroups based on alterations in chromosomes 3 and 8 (disomy 3 (D3), monosomy 3 (M3), disomy 8 (D8), 8q gain (8qG), or 8q gain multiple (8qGm)). Jager *et al*. recognized and labeled these 4 classes as Class A (D3/D8), Class B (D3/8qG), Class C (M3/8qG), and Class D (M3/8qGm).[20] Based on estimation, the best prognosis was with classes A and B and worst with classes C and D tumors.[20]

## TCGA Validation from Wills Eye Hospital (WEH) (Based on Fine Needle Aspiration Biopsy [FNAB] Specimens in 658 Cases)

In 2019, Vichitvejpaisal *et al*. analyzed 658 eyes with UM at WEH sampled by FNAB for genetic analysis over a 10-year

**Table 2: Uveal melanoma prognosis based on cytogenetic testing of three chromosomes in 534 cases**

| Chromosomal abnormality | | | | | Kaplan-Meier estimate for metastasis | | | *P* |
|---|---|---|---|---|---|---|---|---|
| 3 | 6q | 6p | 8q | 8p | @1 year | @3 years | @5 years | |
| 0 | 0 | 0 | 0 | 0 | 1% | 1% | 4% | ns |
| 0 | 0 | Gain | 0 | 0 | 3% | 3% | 15% | ns |
| 0 | Loss | Gain | Gain | 0 | 0% | 0% | 33% | ns |
| Monosomy | 0 | 0 | 0 | 0 | 0% | 8% | 8% | ns |
| Monosomy | 0 | 0 | Gain | 0 | 8% | 27% | 39% | *P*<0.001 |
| Monosomy | 0 | 0 | Gain | Loss | 3% | 28% | NE | *P*<0.001 |
| Monosomy | Loss | 0 | Gain | Loss | 20 | 60 | NE | *P*<0.001 |
| Monosomy | Loss | Gain | Gain | 0 | 50 | 50 | NE | *P*<0.001 |
| Monosomy | Loss | Gain | Gain | Loss | 25 | NE | NE | *P*<0.001 |

0=normal, NE=not evaluable. Data adapted from [10]Shields CL, Say EAT, Hasanreisoglu M, Saktanasate J, Lawson BM, Landy JE, *et al.* Personalized prognosis of uveal melanoma based on cytogenetic profile in 1059 patients over an 8-year period: The 2017 Harry S. Gradle Lecture. Ophthalmology 2017;124:1523-31

period.[21] They subsequently classified the eyes based on TCGA and found the following distribution: class A ($n$ = 342, 52%), B ($n$ = 91, 14%), C ($n$ = 118, 18%), and D ($n$ = 107, 16%) [Table 4].

Based on tumor class, there were differences in demographics and clinical features. By demographics, TCGA class (A vs. B vs. C vs. D) showed more advanced tumor class with older age (56 vs. 53 vs. 60 vs. 63 years, $P < 0.001$) and poorer visual acuity (Snellen visual acuity 20/20-20/50 in 81% vs. 67% vs. 71% vs. 66%, $P < 0.001$).[21] There was no difference in sex ($P = 0.38$), Caucasian race ($P = 0.28$), or affected eye ($P = 0.62$). By clinical features, more advanced tumor class was located more anteriorly in the ciliary body (4% vs. 8% vs. 16% vs. 11%, $P < 0.001$), with greater distance from the optic disc (3.5 vs. 4.9 vs. 5.7 vs. 5.3 mm, $P < 0.001$) and foveola (3.2 vs. 4.3 vs. 5.3 vs. 5.1 mm, $P < 0.001$) and with larger tumor diameter (10.3 vs. 12.9 vs. 13.9 vs. 15.3 mm, $P < 0.001$) and thickness (4.3 vs. 6.1 vs. 6.6 vs. 7.5 mm, $P < 0.001$).[21]

This report demonstrated that patient outcomes paralleled increasing tumor class.[21] By comparison of TCGA class (A vs. B vs. C vs. D), there was significant increase in the 5-year cumulative percentage of distant metastasis (4% vs. 20% vs. 33% vs. 63%, $P < 0.001$), the 5-year cumulative percentage of liver metastasis (2% vs. 14% vs. 32% vs. 61%, $P < 0.001$), and the 5-year cumulative percentage of death (1% vs 0% vs. 9% vs. 23%, $P < 0.001$) as well as corresponding HRs for metastasis and death [Table 4].[21] These authors concluded that categorizing UM by TCGA classification can reliably predict risk for melanoma-related metastasis and death.[21] This classification scheme could prove useful for future studies targeted at treatment of high-risk tumor.

**Table 3: Combination of American Joint Committee on Cancer (AJCC) classification and tumor genetics can improve prognostication of uveal melanoma metastatic risk**

| AJCC Stage | 5-year cumulative rate of melanoma-related death (%) | | |
|---|---|---|---|
| | Chromosome status | | |
| | No monosomy 3 and no 8q gain | Monosomy 3 or 8q gain | Monosomy 3 and 8q gain |
| I | 0% | 0% | 25% |
| II | 11% | 17% | 50% |
| III | 9% | 32% | 73% |

Data adapted from [15]Dogrusoz M, Bagger M, van Duinen SG, Kroes WG, Ruivenkamp CA, Böhringer S, *et al*. The prognostic value of AJCC staging in uveal melanoma is enhanced by adding chromosome 3 and 8q status. Invest Ophthalmol Vis Sci 2017;58:833-42

## Comparison of TCGA versus AJCC Classification

In 2019, Mazloumi *et al*. compared the AJCC 8th edition with TCGA for simplicity, accuracy, and robustness in prediction of UM metastasis.[22] They reviewed the clinical features and genetic results of 643 patients that were sampled by FNAB preceding plaque radiotherapy. Using univariate Cox-regression analysis, TCGA classification demonstrated greater prognostic acumen for prediction of melanoma-related metastasis (TCGA vs. AJCC 4 T categories vs. AJCC 17 T subcategories vs. AJCC 4 stages) (Wald: 94.8 vs. 67.5 vs. 74.3 vs. 67.0, $P < 0.001$ for all). By multivariate model, TCGA classification continued to demonstrate greater prognostic value (TCGA vs. AJCC) for metastatic disease (Wald: 61.5 vs. 35.5, $P < 0.001$ for both). The authors indicated that TCGA is superior to AJCC for prediction of UM-related metastasis.[22]

**Table 4: Genetic features and outcome of uveal melanoma in 658 patients based on The Cancer Genome Atlas (TCGA) Classification of A, B, C, & D**

| | The Cancer Genome Atlas (TCGA) Class | | | | |
|---|---|---|---|---|---|
| | A | B | C | D | *P* |
| Mutational profile | | | | | |
| Chromosome 3 | Disomy 3 | Disomy 3 | Monosomy 3 | Monosomy 3 | NA |
| Chromosome 8 | Disomy 8q | 8q gain | 8q gain | 8q gains (multiple) | NA |
| Prognosis per TCGA[19,20] | | | | | |
| Estimated outcome | Favorable | Late metastases | Unfavorable | Unfavorable | NA |
| Prognosis per Wills Eye Hospital series[21] ($n$=658) | | | | | |
| Number of patients (%) | 342 (52%) | 91 (14%) | 118 (18%) | 107 (16%) | |
| 5-year cumulative rate for distant metastasis | 4% | 20% | 33% | 63% | $P$<0.001 |
| 5-year odds ratio for distant metastasis* | 1.0 | 3.5 | 11.4 | 26.4 | $P$<0.001 |
| 5-year cumulative rate for liver metastasis | 2% | 14% | 32% | 61% | $P$<0.001 |
| 5-year odds ratio for liver metastasis* | 1.0 | 5.9 | 18.4 | 42.9 | $P$<0.001 |
| 5-year cumulative rate for death | 1% | 0% | 9% | 23% | $P$<0.001 |
| 5-year odds ratio for death* | 1.0 | NA | 2.1 | 5.9 | $P$=0.09 |

TCGA - The Cancer Genome Atlas, NA – not applicable. [19]Data from Robertson AG, Shih J, Yau C, Gibb EA, Oba J, Mungall KL, *et al*. Integrative analysis identifies four molecular and clinical subsets in uveal melanoma. Cancer Cell 2017;32:204-20 e215 and Jager MJ, Brouwer NJ, Esmaeli B. The cancer genome atlas project: An integrated molecular view of uveal melanoma. Ophthalmology 2018;125:1139-42. [20]From Jager MJ, Brouwer NJ, Esmaeli B. The cancer genome atlas project: An integrated molecular view of uveal melanoma. Ophthalmology 2018;125:1139-42. [21]Data from Vichitvejpaisal P, Dalvin LA, Mazloumi M, Ewens KG, Ganguly A, Shields CL, *et al*. Genetic analysis of uveal melanoma in 658 patients using The Cancer Genome Atlas (TCGA) classification of uveal melanoma as A, B, C & D. Ophthalmology 2019;126:1445-53. *Compared to Class A

## Conclusion

Prognostication of UM has gradually evolved over the past decades from tumor clinical and histopathologic features to more recently AJCC classification, cytogenetic and gene expression profiling, to now TCGA classification. The accuracy, simplicity, and superior prognostication of TCGA allows for better understanding of UM behavior with hope for improvement in adjuvant therapies to reduce the risk of metastasis in clinical care at a personalized level.

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### Conflicts of interest

There are no conflicts of interest.

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