# Adding the Cancer Genome Atlas Chromosome Classes to American Joint Committee on Cancer System Offers More Precise Prognostication in Uveal Melanoma

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# Adding the Cancer Genome Atlas Chromosome Classes to American Joint Committee on Cancer System Offers More Precise Prognostication in Uveal Melanoma

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***Purpose:*** Uveal melanoma (UM) is a rare disease and the most common primary intraocular malignancy in adults, with a high risk of metastases. Reliable prognostication systems are based on anatomic features, as in the tumor–node–metastasis staging of the American Joint Committee on Cancer (AJCC) system, or on genetic information, as in The Cancer Genome Atlas (TCGA) system. Prior evidence suggests that combining both systems may be beneficial. We evaluated the benefit of combining the TCGA and AJCC systems in a large cohort of patients.

***Design:*** Retrospective case series of patients with UM.

***Participants:*** Nine hundred seventy-nine patients with a choroidal or ciliary body melanoma treated at the Wills Eye Hospital between 1998 and 2020, 94% of whom received eye-sparing treatment.

***Methods:*** Tumors were classified into 4 TCGA groups based on chromosome copy number: A (disomy 3, normal 8q), B (disomy 3, any 8q gain), C (monosomy 3, 1 extra copy of 8q), and D (monosomy 3, multiple 8q gain). The eighth edition of the AJCC staging manual was used for AJCC staging. Cox regression and the log-rank test were used for survival analysis.

***Main Outcome Measure:*** Metastasis-free survival.

***Results:*** Combining information of the 2 systems improved prognostication in intermediate groups: in TCGA group C, we saw an increased rate of metastasis in AJCC stage III (28%) compared with stage II (8.9%); the same was seen in AJCC stage II, going from TCGA group C (8.9%) to group D (46%), and in AJCC stage III, going from group C (28%) to group D (49%). In patients with AJCC stage II or III disease, loss of chromosome 3 and gain of 8q (TCGA groups C and D) significantly worsened the prognosis, with multiple 8q gain (TCGA group D) having a greater impact.

***Conclusions:*** Combining information from AJCC stages and TCGA groups yields a better predictive power even in this set of relatively small tumors. We propose that physicians take both systems into account whenever possible, especially in moderate-risk groups. *Ophthalmology 2022;129:431-437 © 2021 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

*Supplemental material available at www.aaojournal.org.*

Uveal melanoma (UM) is a rare disease and the most common primary intraocular malignancy in adults.[1] This malignancy has a high rate of metastases, which usually involve the liver, and a grim prognosis after metastases have developed.[2–4] Improvements in diagnostic methods and the advent of successful eye-sparing treatment options have achieved good local tumor control; however, the rate of metastasis formation remains high, and over the past 5 decades, no improvement in UM-specific survival has been achieved.[1,5,6] Similar to the situation in cutaneous melanoma, adjuvant therapies are in development that can target high-risk patients. For this, it is vital to identify optimally which patients are at high risk of metastasis and of UM-related death.

Several prognostication tools exist, some focusing on clinical or histologic features and others on molecular factors, each with its own benefits and limitations. The tumor–node–metastasis staging of the American Joint Committee on Cancer (AJCC) focuses on tumor size (a combination of diameter and thickness), measured either indirectly by ultrasound or directly in a pathologic sample, and takes ciliary body involvement and extrascleral extension into account to calculate 17 different tumor stages. These stages as well as the presence of regional lymph node



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metastasis or tumor deposits in the orbit (node stage) and the presence of distant metastases (metastasis stage) then are used to calculate 4 AJCC stages.[7,8]

Not only the anatomic extent but also tumor-intrinsic features play a role in tumor dissemination.[9] The Cancer Genome Atlas (TCGA) study analyzed a wide range of tumor parameters, such as chromosome copy numbers; expression of mRNA, micro RNA, and long noncoding RNA; and methylation patterns and identified 4 subgroups of UM.[10] Earlier research showed that the most relevant chromosomal abnormalities that influence prognosis of UM are loss of heterozygosity of chromosome 3 and gain of extra copies of the long arm of chromosome 8q.[11–15] Jager et al[16] proposed to call these 4 groups A, B, C, and D. The 4 TCGA UM subgroups are characterized by their chromosome 3 and chromosome 8q status: group A shows disomy 3 and normal 8q, group B shows disomy 3 and any 8q gain, group C shows monosomy 3 and 1 extra 8q, and group D shows monosomy 3, with $>$ 1 extra copy of 8q. As described previously, the gene expression classes known as class I and class II as analyzed in the TCGA study usually followed the tumor's chromosome 3 status, with class I corresponding to disomy 3 (tumor types A and B) and class 2 corresponding to monosomy 3 (tumor types C and D).[16,17]

Vichitvejpaisal et al[18] analyzed the prognostic value of all 4 groups in a large set of patients. This study of a cohort of 658 patients with UM showed that the TCGA categories worked well to separate patients in different risk categories: patients in higher TCGA groups were older, had a larger and more anteriorly located tumor, and had a worse prognosis (higher rate of metastasis and UM-related death at 5 years, shorter time to metastasis and death). These findings were confirmed subsequently in a larger study including choroidal, ciliary, and iris melanomas by the same group involving 1001 patients with more robust 10-year follow-up.[19]

The TCGA system and the AJCC system recently were compared in a cohort of 642 patients with choroidal and ciliary melanoma enrolled from 2008 through 2018 in a study by Mazloumi et al.[20] The study showed that the 2 systems are correlated positively, with tumors of more advanced AJCC categories having a worse chromosome profile, and that the TCGA classification is superior to the AJCC in predicting the 5-year risk of distant metastases.

Several authors have explored the possibility of combining genetic and clinical features to achieve a better predictive value. Both Bagger et al[21] (n = 153 patients) and Dogrusöz et al[22] (n = 470 patients) showed that combining information from the AJCC classification and chromosome status achieved a greater prognostic accuracy than either system independently. Indeed, both studies showed that within each AJCC stage, the presence of both monosomy 3 and 8q gain led to a worse survival than either of these alone and, conversely, that within a chromosome group, the presence of a higher AJCC stage led to a worse prognosis. These findings were confirmed in a recent study by Negretti et al[23] in a small series (n = 155) that showed that patients with advanced AJCC stage and both chromosomal abnormalities (monosomy 3 and 8q gain) have the highest cumulative incidence of UM-related death. All patients in the study of Negretti et al had undergone an enucleation, whereas in the study of Dogrusöz et al, 156 of the 470 patients had not undergone enucleation. The conclusions from those studies therefore focus mainly on large tumors.

In the current study, we did not compare classification systems but rather aimed at evaluating the potential added benefit of combining the TCGA classification and the AJCC staging in a cohort of tumors in which genetic information had been obtained mainly by biopsy and in which most patients did not undergo enucleation. We performed a retrospective analysis of a cohort consisting of 979 patients with choroidal or ciliary body UM, or both, treated at the Wills Eye Hospital between 1998 and 2020, with only 60 patients having undergone enucleation. Hence, this cohort contains comparatively more tumors with good prognosis. We show that combining the information from AJCC stage and TCGA chromosome status still yields a more accurate predictive power than either system independently, especially in the moderate-risk groups.

## Methods

### Patients

The original cohort included 1001 patients with UM. We excluded patients with iris melanomas and carried out a retrospective observational analysis of the patient records. Details on data collection and patient management were published previously.[20] Patients with UM diagnosed from November 1998 through June 2020 were included in the study. Patients with iris melanoma were excluded because they have a different AJCC staging system. The study was carried out in accordance with the tenets of the Declaration of Helsinki and approved by the institutional review board of the Wills Eye Hospital, Philadelphia, Pennsylvania. Informed consent for research was signed by all patients at their first visit.

### AJCC Staging

American Joint Committee on Cancer staging was performed at the time of diagnosis. Largest basal diameter and thickness were measured by B-scan ultrasonography, and ciliary body involvement and extrascleral extension were evaluated clinically and through ultrasonography. Largest basal diameter and thickness were used to divide patients into 4 size categories (T1–T4), and subsequently, information on ciliary body involvement, extrascleral extension, and systemic metastasis was added to calculate the AJCC stages (I–IV), according to the AJCC Staging Manual, eighth edition.[7]

### TCGA Groups

Samples for molecular analyses were collected by fine-needle aspiration biopsy at the time of treatment. DNA extraction was performed with DNA Microkit (Qiagen), and Affymetrix Human 100K, SNP-5.0, or SNP-6.0 genotyping arrays (Affymetrix) was used to determine chromosome copy number, as detailed in previous articles.[20,24,25] In each sample, chromosome 3 status was classified as disomy or monosomy, whereas chromosome 8q status was classified as disomy, 8q gain, or multiple 8q gain. This information was used to classify patients into 4 TCGA Jager–Shields groups as follows: group A showed disomy 3 and

disomy 8q, group B showed disomy 3 and any 8q gain, group C showed monosomy 3 and 1 extra copy of 8q, and group D showed monosomy 3 with >1 extra copy of 8q.

### Statistical Analysis

Statistical analysis was carried out using SPSS software version 25 (IBM Corp). Correlations between categorical variables (namely, TCGA groups and AJCC stages) were calculated with Pearson's chi-square test. Survival analysis was carried out with both Cox regression and the Kaplan−Meier log-rank test. For both tests, the event was considered the development of metastasis, and the follow-up was calculated until 48 months; patients with shorter follow-up were censored. Univariate Cox regression was computed independently in each group, correcting for age at treatment and sex. A $P$ value of $< 0.05$ was considered significant. Figure 1 was computed with R statistical software version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria), using the plot3D package.

## Results

### Patients

Of the 979 patients with choroidal and ciliary body melanoma, 60 patients (6%) underwent enucleation, and the remaining 919 patients (94%) received eye-sparing treatment. In this cohort, 52% of the patients were men, 48% were women, and the median age at diagnosis was 60 years (range, 10−94 years). The mean follow-up was 41.8 months, and the median follow-up was 32.7 months, with a range of 0 to 184 months. For this reason, we chose to evaluate the presence of metastases at 48 months. The time elapsed between diagnosis and treatment was a median of 3 days (interquartile range, 3−10 days).

All 979 patients had information on TCGA status and tumor size (largest basal diameter and thickness), which allowed us to calculate the AJCC tumor size categories that were used subsequently to calculate the AJCC stage. For TCGA grouping, group A included 477 patients (49%), group B included 136 patients (14%), group C included 252 patients (26%), and group D included 114 patients (12%).

The AJCC stage was classified as I, II, III and IV, without subclassifying stages II and III into substages. In this cohort, 265 patients (27%) showed ciliary body involvement, and 12 patients (1%) demonstrated extrascleral extension. For 1 patient with extrascleral extension, we do not have any information on the extent of the extension, but because we did not use substages, we were able to classify this patient reliably in stage III (tumor category: T2, with ciliary body involvement and extrascleral extension). No patient showed regional lymph node metastasis or orbital involvement at presentation, and only 1 patient demonstrated distant metastases at diagnosis. Looking at the different categories, 334 patients (34%) showed stage I disease, 427 patients (44%) showed stage II disease, 217 patients (22%) showed stage III disease, and 1 patient (0.1%) showed stage IV disease. Stage IV was excluded from the analysis because it included only 1 patient.

Because our aim was to test the combination of genetic and clinical information, we first tested each system independently. Table 1 shows the distribution of metastases at 48 months in 4 TCGA groups and 3 AJCC stages (Table 1). The percentage of metastases increased with the increase in TCGA group (from A to D) and AJCC stage (from I to III).

Table S1 (available at www.aaojournal.org) shows the distribution of patients with UM in categories calculated combining TCGA groups and AJCC stages. As expected, tumors with low AJCC stage more frequently showed a favorable chromosome profile (disomy 3 and disomy 8q, TCGA group A), whereas tumors with a high AJCC stage more frequently showed monosomy 3 and chromosome 8q gain (TCGA groups C and D).

Subsequently, we calculated the percentage of metastases at 48 months in 12 groups obtained from the combination of TCGA groups and AJCC stages I, II, and III (excluding stage IV; Table S2, available at www.aaojournal.org; Fig 1). The table shows that the combination of the 2 systems improves the prognostication of patients with UM: a progressive increase in the proportion of patients who demonstrated metastases appears from the top left corner of the table (TCGA group A, AJCC stage I) to the bottom right corner (TCGA group D, AJCC stage III). Moreover, a comparison with Table 1 shows that tumors of TCGA group A and AJCC stage I have a lower percentage of metastasis (0.4%) than the lowest-risk categories of each system independently (2% in both), and tumors of TCGA group D and AJCC stage III have a higher percentage of metastases (49%) than the highest-risk group of each system independently (44% in TCGA and 27% for AJCC stage).

Very few metastases develop when the tumor lacks monosomy 3 (TCGA groups A and B) and belong to stage I or II. Among the TCGA groups, group C, and group B to a lower extent, seems to be the one that is most influenced by the increase in the AJCC stage, whereas among the AJCC stages, the influence of TCGA status seems to be strongest in patients with AJCC stage II and III tumors.

Cox regression and the Kaplan−Meier curves (log-rank test) confirmed these findings. Table 2 and Figure 2B show that in tumors with TCGA group C, the presence of AJCC stage III significantly worsens the prognosis (Wald statistic, 7.675; $P = 0.006$), whereas in TCGA group B, no significant difference was found (Table 2; Fig 2A). In TCGA group D, patients with AJCC stage II and III tumors have a significantly worse prognosis than patients with AJCC stage I disease (Table 2; Fig 2C), but because the reference category (TCGA group D, AJCC stage I) contains only 11 patients, we should be careful in interpreting these findings. Conversely, as shown in Table 2 and Figure 3A, loss of 1 chromosome 3 (TCGA groups C and D) significantly decreases the prognosis of patients with UM of AJCC stage II, with a greater effect when combined with multiple 8q gain, identified by TCGA group D (TCGA group C vs. TCGA group A: Wald statistic, 8.066; $P = 0.005$; TCGA group D vs. TCGA group A: Wald statistic, 40.589; $P < 0.001$). In patients with UM of AJCC stage III, the influence of chromosome 3 loss and 8q gain on survival shows a similar pattern, but with a lower significance and strength (TCGA group C vs. TCGA group A: Wald statistic, 4.200; $P = 0.04$; TCGA group D vs. TCGA group A: Wald statistic, 8.907; $P = 0.003$).

## Discussion

As outlined above, the prognosis of patients with UM can be predicted with several methods, some focused on clinical or pathologic tumor features[7] and others focused on genetic features, which may be based on mutation or chromosome status or mRNA expression patterns.[10,16,17,26,27] All these methods have been validated in large cohort studies[18] and currently are used in clinics in different centers.

The original TCGA project that led to the identification of 4 categories of UM (1−4) analyzed primary UM tissues at many levels, not only chromosome copy number variation but also expression of mRNA. This showed that the categories with chromosome 3 loss corresponded with the mRNA expression profile known as gene expression profile class 2.[17]

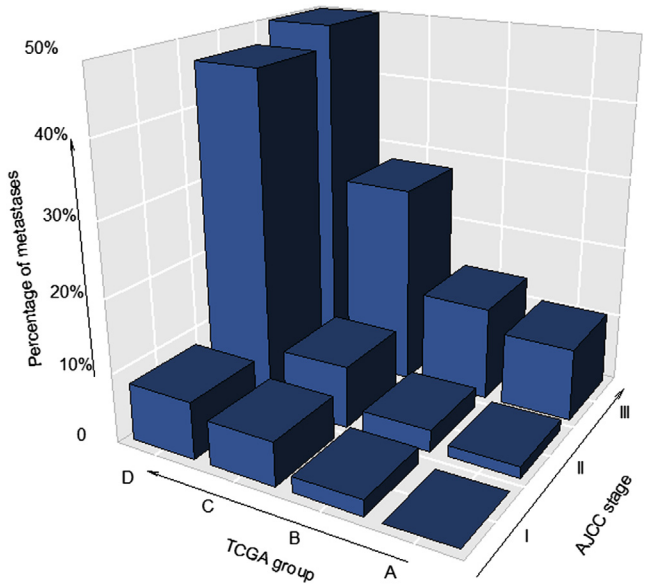



**Figure 1.** Three-dimensional bar graph showing the percentage of patients with uveal melanoma in whom metastasis developed at 48 months. Twelve groups were analyzed, based on the combination of The Cancer Genome Atlas (TCGA) and American Joint Committee on Cancer (AJCC) stages, in a total group of 979 patients.

Based on chromosome copy number variation and mRNA expression, the TCGA then split the group with monosomy 3 into 2 groups. Jager et al[16] proposed to call these categories C and D. Jager et al also proposed to call the 2 groups with disomy 3 groups A and B to prevent confusion with classes 1 and 2. The prior study by Vichitvejpaisal et al[18] showed that using information on the chromosome 3 and 8q status helps to make a clinically practical evaluation.

Previous comparative studies have shown that some overlap exists between these methods.[20–22] Tumors with a less favorable chromosomal profile tend to be larger and have more frequent ciliary body involvement and extrascleral extension (hence, a higher AJCC tumor size category and stage). When the TCGA tumor categories and the AJCC system were compared, the TCGA system was reported to have a better predictive power than the AJCC system in a large cohort of 642 patients.[20] As Bagger et al,[21] Dogrusöz et al,[22] and Negretti et al[23] showed in their studies, combining physical tumor features and the genetic profiles of tumors allowed for a better prognostication when compared with the use of each system independently. Those studies mainly used information from patients who had undergone enucleation. They concluded that combining information from multiple systems provides valuable information for prognostication for relatively large UM tumors.

Unlike the cohort published by Dogrusöz et al[22] and Negretti et al,[23] our cohort contained only a small proportion of patients who had undergone enucleation (6%), whereas the remaining 94% of patients received eye-sparing treatment. This allowed us to include smaller and more benign tumors in our analysis. Moreover, because we had measured the number of additional 8q chromosomes, we were able to evaluate separately TCGA Jager–Shields group C (monosomy 3, 8q gain) and TCGA Jager–Shields group D (monosomy 3, multiple 8q gain). Our analyses showed that the combination of the TCGA and AJCC systems allowed for more precise prognostication of all categories of patients with UM. In tumors with a normal chromosome 3 status and stage I or II status, hardly any metastases were seen at 48 months of follow-up. Approximately 10% of patients with stage III tumors and good chromosome constitution demonstrated metastases. It may be that tumor heterogeneity plays a role here, with the biopsy sample having been obtained in a tumor area with a normal chromosome 3 status. When a tumor showed AJCC stage I status, a worse chromosomal profile did not have much influence on metastasis formation. Importantly, metastasis formation was influenced significantly by combining the 2 systems in the moderate-risk categories (TCGA group C and AJCC stages II and III). The difference between TCGA groups C and D illustrates the effect of chromosome 8q copy number.

One potential limitation of this study is that tumor size (largest basal diameter and thickness), ciliary body

Table 1. Presence of Metastases in Patients with UM at 48 Months According to the Characteristics of the Primary Tumor Divided into 4 Cancer Genome Atlas Groups or 3 American Joint Committee on Cancer Stages

| | Group or Stage | | | | |
|---|---|---|---|---|---|
| | *The Cancer Genome Atlas Groups* | | | | |
| **Variable** | *A (n = 477)* | *B (n = 136)* | *C (n = 252)* | *D (n = 114)* | ***P* Value** |
| Metastases | | | | | <0.001* |
| No | 468 (98%) | 128 (94%) | 213 (84%) | 64 (56%) | |
| Yes | 9 (2%) | 8 (6%) | 39 (15%) | 50 (44%) | |
| | **American Joint Committee on Cancer Tumor Stages** | | | | ***P* Value** |
| | **I (n = 334)** | **II (n = 427)** | **III (n = 216)** | **IV†** | |
| Metastases | | | | | |
| No | 328 (98%) | 387 (91%) | 158 (73%) | † | <0.001* |
| Yes | 6 (2%) | 40 (9%) | 59 (27%) | † | |

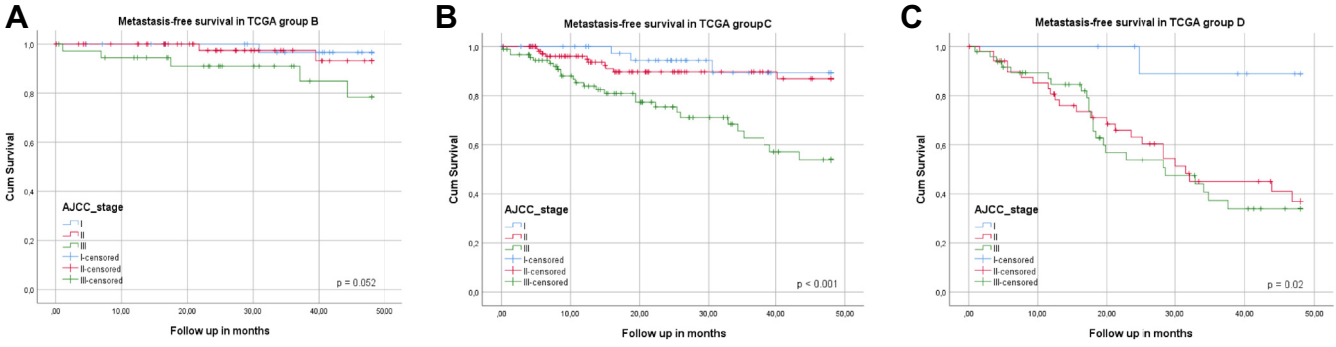
*Chi-square test.
†American Joint Committee on Cancer stage IV excluded from analyses.

Table 2. Combination of TCGA Groups and AJCC Stages with an End Point of Metastasis at 48 Months

| Classification System | Wald Statistic | Hazard Ratio (95% Confidence Interval) | P Value |
|---|---|---|---|
| TCGA group* | | | |
| B | | | |
| AJCC stage† | 4.821 | | 0.09 |
| II vs. I | 0.198 | 1.745 (0.151–20.226) | 0.66 |
| III vs. I | 3.058 | 7.091 (0.789–63.703) | 0.08 |
| C | | | |
| AJCC stage† | 16.513 | | <0.001 |
| II vs. I | 0.399 | 1.517 (0.417–5.523) | 0.53 |
| III vs. I | 7.675 | 5.421 (1.640–17.925) | 0.006 |
| D‡ | | | |
| AJCC stage† | 4.840 | | 0.09 |
| II vs. I | 4.442 | 8.588 (1.157–63.735) | 0.035 |
| III vs. I | 4.839 | 9.481 (1.278–70.340) | 0.028 |
| AJCC stage II§ | | | |
| TCGA group† | 59.092 | | <0.001 |
| B vs. A | 0.533 | 1.888 (0.343–10.399) | 0.47 |
| C vs. A | 8.066 | 5.385 (1.685–17.212) | 0.005 |
| D vs. A | 40.589 | 32.203 (11.066–93.710) | <0.001 |
| AJCC stage III§ | | | |
| TCGA group† | 15.703 | | 0.001 |
| B vs. A | 0.009 | 1.066 (0.283–4.012) | 0.92 |
| C vs. A | 4.200 | 3.015 (1.048–8.663) | 0.04 |
| D vs. A | 8.907 | 5.068 (1.746–14.711) | 0.003 |

AJCC = American Joint Committee on Cancer; TCGA = The Cancer Genome Atlas.
*Cox regression in TCGA groups B, C and D according to AJCC stage.
†Adjusted for age and sex.
‡Only 11 patients in TCGA group D and AJCC stage I.
§Cox regression in AJCC stages II and III according to TCGA group.

involvement, and extrascleral extension were evaluated clinically in most patients because most patients received eye-sparing treatment. This may lead to differences in AJCC classification when compared with studies that include only enucleated eyes. One further element that might have biased our analyses is the fact that, despite the very large sample size of this cohort, some of the categories contained comparatively few patients. This is

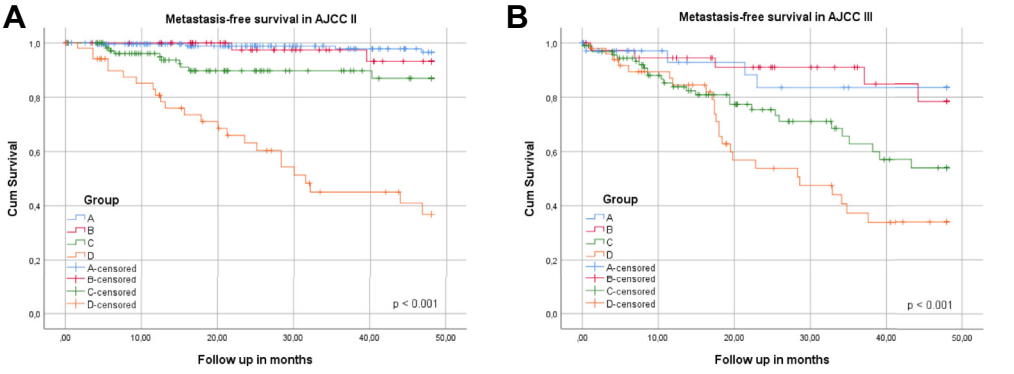



| Time (months) | 0 | 10 | 20 | 30 | 40 |
|---|---|---|---|---|---|
| AJCC stage | At risk | | | | |
| I | 38 | 32 | 30 | 28 | 13 |
| II | 61 | 47 | 35 | 26 | 11 |
| III | 37 | 30 | 23 | 17 | 7 |

| Time (months) | 0 | 10 | 20 | 30 | 40 |
|---|---|---|---|---|---|
| AJCC stage | At risk | | | | |
| I | 47 | 37 | 25 | 16 | 6 |
| II | 112 | 72 | 48 | 36 | 17 |
| III | 93 | 58 | 38 | 27 | 10 |

| Time (months) | 0 | 10 | 20 | 30 | 40 |
|---|---|---|---|---|---|
| AJCC stage | At risk | | | | |
| I | 11 | 10 | 9 | 7 | 3 |
| II | 52 | 36 | 26 | 17 | 7 |
| III | 49 | 34 | 18 | 15 | 5 |

**Figure 2.** Graphs and tables showing metastasis-free survival in patients with uveal melanoma in The Cancer Genome Atlas (TCGA) categories B, C, and D divided into 3 groups based on the American Joint Committee on Cancer (AJCC) stage. **A**, Metastasis-free survival in TCGA group B. **B**, Metastasis-free survival in TCGA group C. **C**, Metastasis-free survival in TCGA group D. Cum = cumulative.




| Time (months) | 0 | 10 | 20 | 30 | 40 |
|---|---|---|---|---|---|
| TCGA group | At risk | | | | |
| A | 202 | 153 | 121 | 98 | 45 |
| B | 61 | 47 | 35 | 26 | 11 |
| C | 112 | 72 | 48 | 36 | 17 |
| D | 52 | 36 | 26 | 17 | 7 |

| Time (months) | 0 | 10 | 20 | 30 | 40 |
|---|---|---|---|---|---|
| TCGA group | At risk | | | | |
| A | 38 | 22 | 19 | 16 | 7 |
| B | 37 | 30 | 23 | 17 | 7 |
| C | 93 | 58 | 38 | 27 | 10 |
| D | 49 | 34 | 18 | 14 | 5 |

**Figure 3.** Graphs and tables showing metastasis-free survival in patients with uveal melanoma of American Joint Committee on Cancer (AJCC) stages II and III, respectively, divided into 4 groups based on The Cancer Genome Atlas (TCGA) category. **A**, Metastasis-free survival in AJCC stage II. **B**, Metastasis-free survival in AJCC stage III. Cum = cumulative.

because of the already-explained correlation between the different prognostication systems. One last limitation is the relatively short follow-up, which may bias the analyses especially in patients with low-risk tumors, which are known to metastasize later than high-risk tumors.[28] For this reason, it would be interesting to repeat the analysis in the future, with longer follow-up and in other populations; however, the large sample size of this cohort and the inclusion of patients who received local treatment and those who underwent enucleation allowed us to draw meaningful conclusions.

Based on our findings, we can conclude that the combination of multiple systems benefits UM prognostication. In particular, clinicians should pay attention to tumor size and the presence of ciliary body involvement and extrascleral extension, especially in monosomy 3 UM with single 8q gain. Conversely, in UM classified as AJCC stages II and III, clinicians should evaluate carefully the chromosome status of patients with UM, possibly distinguishing simple 8q gain (TCGA Jager−Shields group C) from multiple 8q gains (TCGA Jager−Shields group D).

## Footnotes and Disclosures

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No animal subjects were included in this study.

Author Contributions:

Conception and design: Gelmi, Jager

Analysis and interpretation: Gelmi, Bas, Malkani, Ganguly, Shields, Jager

Data collection: Gelmi, Bas, Malkani, Ganguly, Shields, Jager

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Overall responsibility: Gelmi, Bas, Malkani, Ganguly, Shields, Jager

Abbreviations and Acronyms:
**AJCC** = American Joint Committee on Cancer; **TCGA** = The Cancer Genome Atlas; **UM** = uveal melanoma.

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