Conditional survival of uveal melanoma using The Cancer Genome Atlas (TCGA) classification (Simplified Version) in 1001 cases

Carol L. Shields, Philip W. Dockery, Eileen L. Mayro, Zeynep Bas, Antonio Yaghy, Sara E. Lally, Marlana Orloff, Takami Sato, Jerry A. Shields

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Abstract:

PURPOSE: To understand conditional prognostic value of the Cancer Genome Atlas (TCGA) for uveal melanoma metastasis based on event-free survival at 1, 2, 3, 4, and 5 years.

METHODS: A retrospective study of eyes with uveal melanoma categorized according to TCGA and studied for nonconditional and conditional risks for metastasis at 5 and 10 years.

RESULTS: Of 1001 eyes with uveal melanoma, the nonconditional (standard, at presentation) 5-year/10-year metastatic rate was 18%/25%. The conditional 5-year/10-year metastatic rate (for those without metastasis at 2 years) revealed 10%/18% and the conditional 10-year metastatic rate (for those without metastasis at 5 years) revealed 9%. The TCGA categories included Group A (n = 486, 49%), B (n = 141, 14%), C (n = 260, 26%), and D (n = 114, 11%). The non-conditional 5-year/10-year metastatic rate revealed Group A (4%/6%), Group B (12%/20%), Group C (23%/49%), and Group D (60%/68%). The conditional 5-year/10-year metastatic rate (for those without metastasis at 2 years) revealed Group A (2%/5%), Group B (8%/18%), Group C (21%/40%), and Group D (38%/50%). The conditional 10-year metastatic rate (for those without metastasis at 5 years) revealed Group A (2%), Group B (10%), Group C (33%), and Group D (20%). The peak incidence of metastasis for Groups A and B occurred during years 5–6, C during years 4–6, and D during years 1–2.

CONCLUSION: Survival outcomes for uveal melanoma as non-conditional (at presentation) and conditional (event-free survival during follow-up) reveal reduction in metastatic rate over time. For those with 5-year metastasis-free survival, the 10-year conditional risk for metastasis was 9%.

Keywords:

Choroid, conditional, genetics, melanoma, survival, The Cancer Genome Atlas, Uvea

Introduction

There are different methods for estimating survival, including nonconditional (standard, estimated from date of diagnosis) and conditional survival (estimated from various event-free points during the patient's course).[1] Traditionally, most cancer reports focus on nonconditional survival analysis. Nonconditional survival analysis estimates survival probability from one point, at initial diagnosis, and is a static, nonchanging value. However, the reality is that patients survive for 1, 2, or 5 years without events, and the survival estimates change at each time point, known as conditional survival. Conditional survival is a dynamically evolving probability and is highly relevant to patients with treated uveal melanoma who seek survival risks at each point in time.

The Cancer Genome Atlas (TCGA) provides a genetic-based, 4-category prognostic classification of uveal melanoma into simplified cohorts of Group A (disomy 3, disomy 8), Group B (disomy 3, 8q gain), Group C (monosomy 3, 8q gain possible), and Group D (monosomy 3, 8q gain multiple [isochromosome for 8q]).[2-9] Analyses of TCGA in large-cohort series of uveal melanoma (n = 658 cases) revealed 5-year nonconditional cumulative rate of metastasis for Group A (4%), Group B (20%), Group C (33%), and Group D (63%) and additionally documented

Ocular Oncology Service (CLS, PWD, ELM, ZB, AY, SEL, JAS), Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA and Department of Medical Oncology (MO, TS), Thomas Jefferson University, Philadelphia, PA

Address for correspondence: Dr. Carol L. Shields, Ocular Oncology Service, Suite 1440, Wills Eye Hospital, 840 Walnut Street, Philadelphia, PA, USA. E-mail: carolshields@gmail.com

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that TCGA was more predictive of uveal melanoma prognosis compared to the American Joint Committee on Cancer (AJCC) 8th edition classification.[8,9] Recently, a larger cohort of 1001 eyes with uveal melanoma, classified according to TCGA, and with 10-year nonconditional rate of metastasis revealed Group A (6%), Group B (20%), Group C (49%), and Group D (not available).[10] These estimates revealed nonconditional risk for melanoma-related metastasis based on one point in time, at diagnosis. Herein, we explore conditional estimates for uveal melanoma-related metastasis using TCGA classification at event-free time points of 1, 2, 3, 4, and 5 years following diagnosis and treatment.

Methods

The medical records on the Ocular Oncology Service at Wills Eye Hospital, Thomas Jefferson University, Philadelphia, Pennsylvania, USA, were retrospectively reviewed for patients with the clinical diagnosis of uveal melanoma between November 16, 1998, and June 2, 2020. All patients who underwent genetic evaluation by fine needle aspiration biopsy (FNAB) or open solid tissue sampling and subsequent genetic classification according to TCGA were included. This study was approved by the Institutional Review Board of Wills Eye Hospital, adhered to the tenets of the Declaration of Helsinki, and complied with the Health Insurance Portability and Accountability Act. Informed consent was obtained from each patient.

All patients were examined by a trained ocular oncologist for clinical confirmation of diagnosis of uveal melanoma based on indirect ophthalmoscopy with detailed fundus drawings and imaging. Ophthalmic imaging included fundus photography with wide-angle imaging, fundus autofluorescence, ultrasonography, optical coherence tomography (OCT), fluorescein angiography, indocyanine green angiography, and OCT angiography, as needed for documentation at the first examination and subsequent examinations. Patients were then classified according to TCGA as Group A, B, C, or D based on tumor DNA results and included in this study.

Data were recorded at each examination and documented on the patient's chart. The demographic data included age (years), sex (male, female), race (Caucasian, African American, Hispanic, Asian, others/unknown), affected eye (right, left), and visual acuity (20/20–20/50, 20/60–20/200, 20/400–no light perception). The tumor features at presentation included tumor location with distance to the optic disc (millimeters [mm]), distance to the foveola (mm), largest tumor basal diameter (mm), tumor thickness (mm), tumor epicenter (choroid, ciliary body, iris), anterior margin of the tumor, and posterior margin of the tumor.

Samples for genetic testing were obtained with FNAB, performed in the operating room at the time of uveal melanoma treatment, as described in the literature.[8,10] The samples were stored in Hanks balanced salt solution (Gibco, Life Technologies, Grand Island, NY) at 4°C, and DNA analysis was performed using DNA Micro Kit (Qiagen, Valencia, CA).[8]

Primary outcomes included event-free survival for uveal melanoma, specifically metastasis-free survival (MFS) and death-free (overall) survival (OS). Nonconditional MFS (ncMFS) and OS (ncOS) were assessed at presentation. Conditional MFS (cMFS) and conditional OS (cOS) were assessed after specific event-free points including 4 months, 8 months, 12 months, 16 months, 20 months, 2 years, 3 years, 4 years, and 5 years. Kaplan–Meier analysis was performed for ncMFS and ncOS as well as cMFS and cOS for the entire group and then stratified by TCGA Classification (Group A vs. Group B vs. Group C vs. Group D). Conditional survival was assessed primarily for 5-year and 10-year endpoints (9-year endpoint for Group D due to insufficient data at 10-year point). Annual likelihood for metastasis for each TCGA group was obtained through conditional Kaplan-Meier analysis. In addition, Cox regression analyses to assess for competing risks were performed but did not differ significantly from Kaplan–Meier analysis in this population.

Statistical analysis was performed using Statistical analysis was performed using SAS Software Suite (version 9.4; SAS Institute). Continuous variables were expressed as mean (median, range). The one-sample Shapiro–Wilk test was used to assess normality of distribution. Comparison between groups was performed using the one-way ANOVA test for continuous variables with normal distribution and Kruskal–Wallis test for continuous variables without normal distribution. Comparison of categorical variables was performed using the likelihood ratio Chi-square test and Fisher's exact test when indicated. Kaplan–Meier analysis was performed for cMFS and cOS for uveal melanoma, which also determined an annual likelihood of metastasis. Cox regression analysis for competing risks was performed with no significant discrepancies from Kaplan–Meier analysis. Assessment of Kendall's Tau correlation coefficient was performed to determine the significance of trends for the annual risk of metastasis. $P < 0.05$ was considered statistically significant for results of regression and Kaplan–Meier analyses.

Results

There were 1001 consecutive eyes with uveal melanoma that were sampled for DNA analysis of chromosomes 3 and 8 immediately prior to tumor treatment over a 22-year period on the Ocular Oncology Service at Wills Eye Hospital of Thomas Jefferson University, Philadelphia, Pennsylvania, USA. Patients with sufficient genetic testing results and with follow-up information were included in this analysis.

Of the 1001 eyes with uveal melanoma, TCGA categories included Group A (n = 486, 49%), B (n = 141, 14%), C (n = 260, 26%), and D (n = 114, 11%). A portion of this cohort had been independently analyzed for 5-year[8] and 10-year[10] standard (nonconditional) estimates for melanoma-related metastasis and compared with prognostic outcomes from

the AJCC 8th edition.[9] In this current analysis, we further explored conditional survival. Demographic features are listed in eTable 1. Increasing category (A vs. B vs. C vs. D) was associated with initial features of older age (56.8 vs. 52.8 vs. 61.1 vs. 63.5 years, $P < 0.001$) and less often visual acuity of 20/20–20/50 (80% vs. 67% vs. 70% vs. 65%, $P = 0.001$). Tumor features are listed in eTable 2. Increasing category (A vs. B vs. C vs. D) was associated with more peripheral tumor location ($P < 0.001$) and increasing tumor basal diameter (10.5 mm vs. 12.7 mm vs. 13.6 mm vs. 15.3 mm, $P < 0.001$) and tumor thickness (4.4 mm vs. 6.2 mm vs. 6.7 mm vs. 7.6 mm, $P < 0.001$).

The nonconditional and conditional survival estimates are listed in Table 1 for the entire population and according to TCGA classification. The ncMFS for the entire population revealed 5-year/10-year metastatic rate at 18%/25%. The cMFS for the entire population revealed 5-year/10-year metastatic rate (for those without metastasis at 2 years) at 10%/18% and the conditional 10-year metastatic rate (for those without metastasis at 5 years) at 9%.

According to TCGA groups, the ncMFS revealed 5-year/10-year metastatic rate for Group A (4%/6%), Group B (12%/20%), Group C (33%/49%), and Group D (60%/68% [at 9 years]). The cMFS revealed 5-year/10-year metastatic rate (for those without metastasis at 2 years) for Group A (2%/5%), Group B (8%/18%), Group C (21%/40%), and Group D (38%/50% [at 9 years]) and the conditional 10-year metastatic rate (for those without metastasis at 5 years) for Group A (2%), Group B (10%), Group C (23%), and Group D (20% [at 9 years]).

The cMFS was listed for each timepoint with a history of a metastatic event, including 4, 8, 12, 16, and 20 months as well as 2, 3, 4, and 5 years for the entire population and each specific TCGA group, demonstrating decreasing risk for metastasis over time, particularly in Group D ($P = 0.012$) [Table 1]. Similar decreasing 5-year/10-year rate of ncOS and cOS were found for the entire population and with increasing TCGA group. For cOS, with increasing timepoint of event-free survival, there was concomitant improvement in cOS with reduction in melanoma-related death rate [Table 1].

Kaplan–Meier analyses for ncMFS and cMFS per TCGA group is illustrated in Figure 1. By comparison, increasing TCGA group (A vs. B vs. C vs. D) was associated with reduced ncMFS with greater risk for melanoma-related metastasis ($P < 0.001$) and reduced cMFS after surviving 1 year without metastasis ($P < 0.001$), after surviving 2 years without metastasis ($P < 0.001$), and after surviving 5 years without metastasis ($P = 0.001$). Patients with event-free survival at 2 and 5 years showed more favorable outcomes with greater cMFS than those surviving 1 year or those with ncMFS. Kaplan–Meier analysis for ncOS and cOS per TCGA group

Table 1: Nonconditional and conditional survival of uveal melanoma based on The Cancer Genome Atlas classification in 1001 patients analysis at initial presentation and specific event-free timepoints

Type of survival	Duration of achieved event-free survival	TCGA Classification								Total population ($n=1001$), *n* (%)	
		Group A ($n=486$), *n* (%)		Group B ($n=141$), *n* (%)		Group C ($n=260$), *n* (%)		Group D ($n=114$), *n* (%)			
		5 years	10 years	5 years	10 years	5 years	10 years	5 years	9 years*	5 years	10 years
Metastasis-free survival from uveal melanoma											
ncMFS	At presentation ($n=1001$)	161 (96)	16 (94)	40 (88)	6 (80)	41 (67)	5 (51)	12 (40)	4 (32)	254 (82)	27 (75)
cMFS	4 months ($n=950$)	161 (96)	16 (94)	40 (89)	6 (80)	41 (68)	5 (52)	12 (43)	4 (34)	254 (83)	27 (76)
	8 months ($n=845$)	161 (97)	16 (94)	40 (90)	6 (81)	41 (70)	5 (54)	12 (45)	4 (36)	254 (84)	27 (77)
	12 months ($n=785$)	161 (97)	16 (94)	40 (90)	6 (81)	41 (72)	5 (55)	12 (47)	4 (38)	254 (85)	27 (78)
	16 months ($n=713$)	161 (97)	16 (95)	40 (90)	6 (81)	41 (75)	5 (58)	12 (49)	4 (39)	254 (87)	27 (79)
	20 months ($n=639$)	161 (97)	16 (95)	40 (91)	6 (82)	41 (78)	5 (59)	12 (59)	4 (47)	254 (89)	27 (81)
	2 years ($n=577$)	161 (98)	16 (95)	40 (92)	6 (82)	41 (79)	5 (60)	12 (62)	4 (50)	254 (90)	27 (82)
	3 years ($n=438$)	161 (98)	16 (96)	40 (93)	6 (83)	41 (83)	5 (64)	12 (83)	4 (67)	254 (94)	27 (86)
	4 years ($n=339$)	161 (99)	16 (96)	40 (98)	6 (88)	41 (88)	5 (68)	12 (94)	4 (75)	254 (97)	27 (88)
	5 years ($n=254$)	NA	16 (98)	NA	6 (90)	NA	5 (77)	NA	4 (80)	NA	27 (91)
Death-free survival from uveal melanoma											
NCOS	At presentation ($n=1001$)	162 (>99)	17 (99)	41 (100)	6 (100)	42 (93)	5 (93)	14 (85)	4 (85)	259 (97)	28 (97)
COS	4 months ($n=958$)	162 (>99)	17 (99)	41 (100)	6 (100)	42 (93)	5 (93)	14 (85)	4 (85)	259 (97)	28 (97)
	8 months ($n=861$)	162 (>99)	17 (99)	41 (100)	6 (100)	42 (93)	5 (93)	14 (85)	4 (85)	259 (97)	28 (97)
	12 months ($n=802$)	162 (>99)	17 (99)	41 (100)	6 (100)	42 (93)	5 (93)	14 (85)	4 (85)	259 (97)	28 (97)
	16 months ($n=731$)	162 (>99)	17 (99)	41 (100)	6 (100)	42 (93)	5 (93)	14 (87)	4 (87)	259 (98)	28 (97)
	20 months ($n=665$)	162 (>99)	17 (99)	41 (100)	6 (100)	42 (93)	5 (93)	14 (87)	4 (87)	259 (98)	28 (97)
	2 years ($n=604$)	162 (>99)	17 (99)	41 (100)	6 (100)	42 (93)	5 (93)	14 (89)	4 (89)	259 (98)	28 (97)
	3 years ($n=452$)	162 (100)	17 (99)	41 (100)	6 (100)	42 (93)	5 (93)	14 (90)	4 (90)	259 (98)	28 (98)
	4 years ($n=350$)	162 (100)	17 (99)	41 (100)	6 (100)	42 (96)	5 (96)	14 (96)	4 (96)	259 (99)	28 (99)
	5 years ($n=259$)	NA	17 (99)	NA	6 (100)	NA	5 (100)	NA	4 (100)	NA	28 (>99)

*Group D employed 9 years because there was insufficient follow-up data at 10 years. TCGA: The Cancer Genome Atlas, NA: Not available, cMFS: Conditional metastasis-free survival, ncMFS: Non-cMFS, COS: Conditional death-free (overall) survival, NCOS: Non-COS

eTable 1: Conditional survival of uveal melanoma using The Cancer Genome Atlas classification in 1001 cases patient demographics

Patient demographics	TCGA classification					Total population (*n*=1,001), *n* (%)
	Group A (*n*=486), *n* (%)	Group B (*n*=141), *n* (%)	Group C (*n*=260), *n* (%)	Group D (*n*=114), *n* (%)	*P*	
Age						
Mean (years) (median, range)	56.8 (58.0, 10.0-90.0)	52.8 (54.0, 13.0-83.0)	61.1 (62.5, 12.0-88.0)	63.5 (64.0, 28.0-94.0)	**<0.001**	58.1 (59.0, 10.0-94.0)
Sex						
Male	266 (55)	72 (51)	121 (47)	57 (50)	0.194	516 (52)
Female	220 (45)	69 (49)	139 (53)	57 (50)		485 (48)
Race						
Caucasian	472 (97)	130 (92)	251 (97)	112 (98)	0.088	965 (96)
African American	0	2 (1)	0	0		2 (<1)
Hispanic	10 (2)	3 (2)	5 (2)	2 (2)		20 (2)
Asian	1 (<1)	3 (2)	1 (<1)	0		5 (<1)
Other/unknown	3 (1)	3 (2)	3 (1)	0		9 (1)
Affected eye						
Right	249 (51)	77 (55)	143 (55)	60 (53)	0.760	529 (53)
Left	237 (49)	64 (45)	117 (45)	54 (47)		472 (47)
Visual acuity						
20/20-20/50	389 (80)	94 (67)	182 (70)	74 (65)	**0.001**	739 (74)
20/60-20/200	55 (11)	29 (21)	53 (20)	28 (25)		165 (16)
20/400-NLP	42 (9)	18 (13)	25 (10)	12 (11)		97 (10)

Bold values indicate significant *P* value. TCGA: The Cancer Genome Atlas, NLP: No light perception

eTable 2: Conditional survival of uveal melanoma using The Cancer Genome Atlas classification in 1001 cases tumor features

Tumor features	TCGA classification					Total population (*n*=1001), *n* (%)
	Group A (*n*=486), *n* (%)	Group B (*n*=141), *n* (%)	Group C (*n*=260), *n* (%)	Group D (*n*=114), *n* (%)	*P*	
Distance to optic disc (mm), mean (median, range)	3.9 (3.0, 0.0-20.0)	4.7 (4.0, 0.0-18.0)	5.5 (5.0, 0.0-17.0)	4.9 (5.0, 0.0-18.0)	**<0.001**	4.5 (3.5, 0.0-20.0)
Distance to foveola (mm), mean (median, range)	3.6 (2.3, 0.0-18.4)	4.1 (3.3, 0.0-15.0)	5.4 (4.0, 0.0-18.0)	4.7 (3.0, 0.0-17.0)	**<0.001**	4.3 (3.0, 0.0-18.4)
Largest basal diameter (mm), mean (median, range)	10.5 (10.0, 1.0-22.0)	12.7 (13.0, 2.0-22.0)	13.6 (14.0, 2.0-24.0)	15.3 (16.0, 6.0-24.0)	**<0.001**	12.1 (12.0, 1.0-24.0)
Thickness (mm), mean (median, range)	4.4 (3.5, 1.0-14.0)	6.2 (5.2, 1.3-15.0)	6.7 (6.0, 0.7-16.0)	7.6 (7.1, 2.1-20.4)	**<0.001**	5.6 (4.7, 0.7-20.4)
Tumor epicenter						
Choroid	457 (94)	126 (89)	227 (87)	103 (90)	**0.008**	913 (91)
Ciliary body	20 (4)	11 (8)	26 (10)	11 (10)		68 (7)
Iris	9 (2)	4 (3)	7 (3)	0		20 (2)
Anterior margin						
Macula	32 (7)	9 (6)	6 (2)	4 (4)	**<0.001**	51 (5)
Macula to equator	245 (50)	40 (28)	64 (25)	22 (19)		371 (37)
Equator to ora	131 (27)	44 (31)	81 (31)	38 (33)		294 (29)
Ciliary body	62 (13)	40 (28)	82 (32)	47 (41)		231 (23)
Iris	16 (3)	8 (6)	27 (10)	3 (3)		54 (5)
Posterior margin						
Macula	305 (63)	79 (56)	124 (48)	63 (55)	**<0.001**	571 (57)
Macula to equator	156 (32)	54 (38)	115 (44)	48 (42)		373 (37)
Equator to ora	10 (2)	2 (1)	12 (5)	3 (3)		27 (3)
Ciliary body	7 (1)	2 (1)	5 (2)	0		14 (1)
Iris	8 (2)	4 (3)	4 (2)	0		16 (2)

Bold values indicate significant *P* value. TCGA: The Cancer Genome Atlas

is illustrated in Figure 2. A similar comparison demonstrated increasing category of TCGA group (A vs. B vs. C vs. D) was associated with reduction in ncOS at presentation ($P < 0.001$), and cOS after surviving 1 year ($P < 0.001$), and after surviving 2 years ($P = 0.002$). After surviving 5 years, there was no association between TCGA group and cOS ($P = 0.895$).

The annual likelihood of metastasis based on Kaplan–Meier analysis, stratified by TCGA group, is depicted in Figure 3. The annual likelihood of metastasis for Group A throughout the first 7 years was 0.4%–1.3%; for Group B, the first 3 years was <2% and the next 4 years between 2.2% and 5.0%; for Group C, the first 6 years was 4.6%–9.4% and the following 2 years at 2.5% and 4.0%; and for Group D, the first 3 years was 15.3%–20.5%, and thereafter dropped to 5.3% and 2.7%. The peak for metastasis for Group A was 5–6 years, Group B was 5–6 years, Group C was 4–6 years, and Group D was 1–2 years ($P = 0.012$). The peak incidence of metastasis for Group A occurred during years 5–6, B during years 5–6, C during years 4–6, and D during years 1–2. There was no incidence of metastasis after 7 years for Groups A or B, after 8 years for Group C, and only one episode of metastasis after 5 years for Group D.

Discussion

In 2018, Thomas commented in an editorial that cancer-related population-based survival data is readily available to provide outcomes for patients at 5 and 10 years following de novo diagnosis. 1 He noted, however, that this might not be sufficient for understanding global patients' concerns as patients seek a more dynamic approach to survival, for example, how outcomes might change with longer event-free survival. Patients who have survived 2, 5, or 10 years without metastatic disease often ask the clinician for their updated prognosis at each time point, and this is known as "conditional survival."[1] Conditional survival is an often-overlooked, yet pragmatic resource for cancer survivors.[1] Conditional survival provides outcomes predictions for event-free surviving patients at specific time points, allowing for a more fluid assessment of risks.

Swords *et al*. investigated conditional survival estimates for survivors of pancreatic ductal adenocarcinoma, a malignancy commonly leading to death within 5 years.[11] Using the Surveillance, Epidemiology, and End Results (SEER) database on 10,988 affected patients, they found approximately 85% were dead by 5 years, but they further calculated conditional estimates and for those that survived for 6 years without metastasis, the probability of surviving for 15 more years was 62%. They and others have concluded that conditional survival is useful for patients throughout their course, as prognosis tends to improve with time.[11,12]

Zabor *et al*. commented that nonconditional prognosis becomes less relevant to the patient as time interval from diagnosis increases.[13] For cutaneous melanoma (stage III), the 5-year survival (nonconditional vs. conditional at 4 years) increased with subsets IIIA (72% vs. 78%), IIIB (48% vs. 59%), and IIIC (29% vs. 40%).[13] Conditional survival was noted to be important for both patients and clinicians but has not been widely applied.

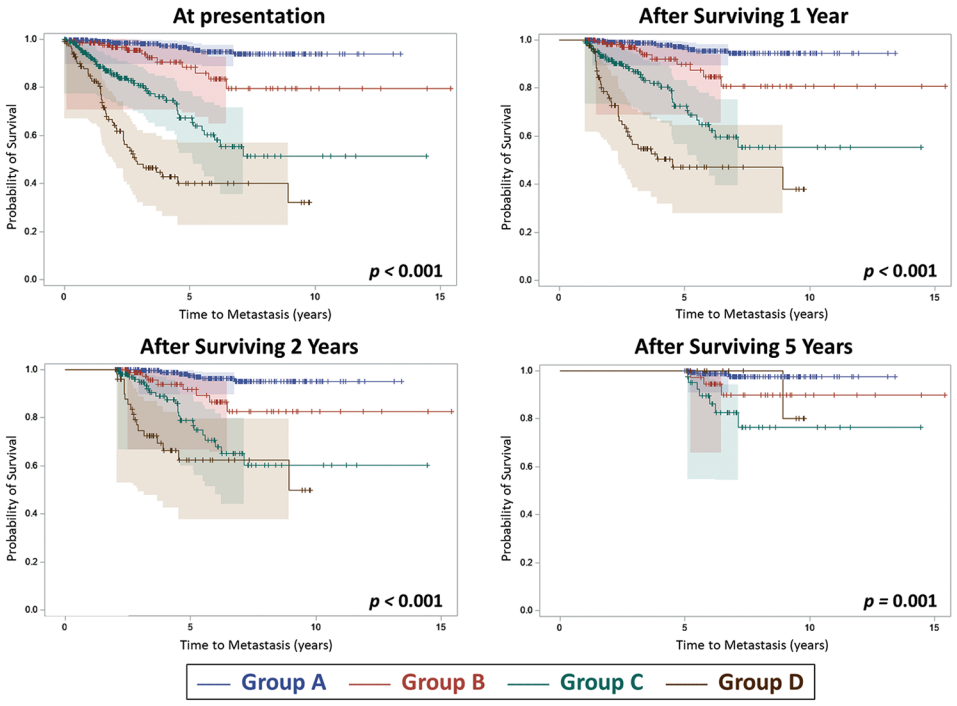

Figure 1: Kaplan-Meier analysis stratified per The Cancer Genome Atlas for nonconditional metastasis-free survival, calculated from presentation (upper left), and for conditional metastasis-free survival, after surviving for 1 (upper right), 2 (bottom left), and 5 years (bottom right) without metastasis. By comparison, increasing The Cancer Genome Atlas group (A vs. B vs. C vs. D) was associated with reduced nonconditional metastasis-free survival with greater risk for melanoma-related metastasis ($P < 0.001$) and reduced conditional metastasis-free survival after surviving 1 year without metastasis ($P < 0.001$), after surviving 2 years without metastasis ($P < 0.001$), and after surviving 5 years without metastasis ($P = 0.001$). The longer the timepoint of event-free survival, the fewer the metastatic events

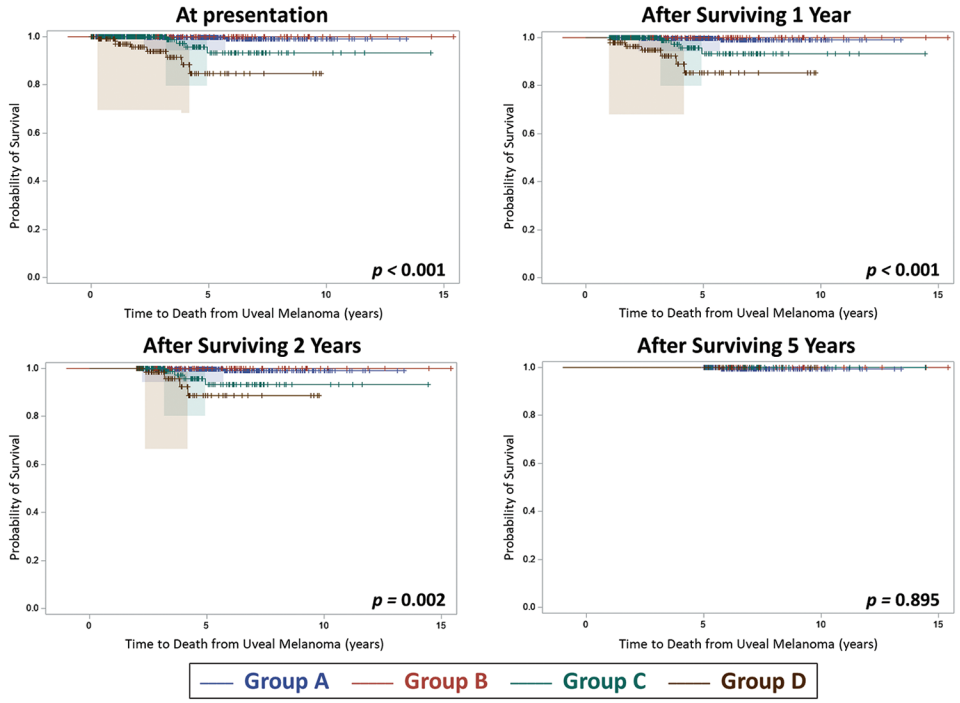

Figure 2: Kaplan-Meier analysis stratified per The Cancer Genome Atlas for non-conditional death-free (overall) survival, calculated from presentation (upper left), and for cOS, after surviving for 1 (upper right), 2 (bottom left), and 5 years (bottom right) without death. By comparison, increasing The Cancer Genome Atlas group (A vs. B vs. C vs. D) was associated with reduced ncOS with greater risk for melanoma-related death ($P < 0.001$) and reduced cOS after surviving 1 year without death ($P < 0.001$) and after surviving 2 years without death ($P = 0.002$). Those who survived 5 years without death showed no difference in conditional overall survival per TCGA group ($P = 0.895$)

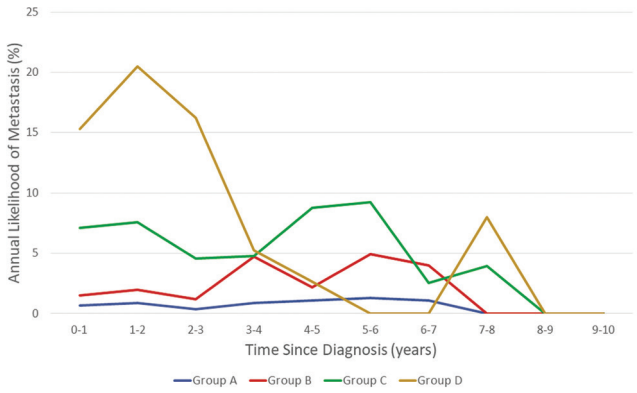

Figure 3: Kaplan-Meier analysis for annual likelihood of melanoma-related metastasis based on The Cancer Genome Atlas. The peak time point for incidence of metastasis for Group A was 5–6 years, B was 5–6 years, C was 4–6 years, and D was 1–2 years. Group D demonstrated a dramatic decline in risk for metastasis after the first 3 years

Regarding uveal melanoma, a PubMed search for <conditional survival uveal melanoma >yielded 1 report by Zabor *et al*., who used the SEER database on 6863 cases of uveal melanoma.[14] They found 5-year MFS (nonconditional vs. conditional at 3 years) at (80% vs. 92%) and the 10-year MFS (nonconditional vs. conditional at 5 years) at (69% vs. 87%). They concluded that conditional survival with uveal melanoma improves over time and plays a role in patient counseling.

In our analysis, we explored conditional survival for 1001 patients in our practice. Paralleling the findings of Zabor *et al*., we found 5-year MFS (non-conditional vs. conditional at 3 years) at (82% vs. 94%) and the 10-year MFS (nonconditional vs. conditional at 5 years) at (75% vs. 91%). In this cohort, we investigated deeper into cMFS based on tumor genetics using TCGA (A vs. B vs. C vs. D) and found 5-year ncMFS (96% vs. 88%. vs. 67% vs. 40%) compared to 5-year cMFS with 3-year event-free survival (98% vs. 93% vs. 83% vs. 83%). Similar improvement was noted with 10-year cMFS and cOS at specific time points. Importantly, we noted the peak incidence of metastasis for Group A occurred during years 5–6, B during years 5–6, C during years 4–6, and D during years 1–2. The dreadfully high rate of metastasis in Group D precipitously dropped after the first 3 years. However, the ncMFS and cMFS differed significantly per TCGA group at 1, 2, and 5 years, and Group C seemed to overtake Group D as the most at-risk group for metastasis for those who survive at least 5 years. The ncOS and cOS differed significantly per TCGA group at 1-and 2-year survival, but not at 5 years.

There are limitations to this study including the rarity of uveal melanoma and the retrospective data collection. However, this is a unique cohort of patients that have been sampled for genetic information over 22 years for chromosomes 3 and 8 and have robust outcomes regarding MFS and OS on a conditional year-to-year basis up to 10 years. In this analysis, we emphasized MFS more so than OS as MFS data is

readily available per patient examination or correspondence, whereas death data is available only per correspondence. Additionally, TCGA project explored further molecular aberrations including histopathologic features, genetic mutations, RNA expression, DNA methylation, and other features that were not included in this analysis due to cost and practicality.

Conclusion

We have provided nonconditional and conditional survival estimates for uveal melanoma as an entire group and based on TCGA classification. We have observed that over time, the risk for uveal melanoma metastasis decreases, particularly for TCGA Group D.

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Conflicts of interest

There are no conflicts of interest.

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