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Validation of a Prognostic Staging for Metastatic Uveal Melanoma: A Collaborative Study of the European Ophthalmic Oncology Group

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- **PURPOSE:** To validate a staging system for metastatic uveal melanoma that will facilitate planning, reporting, and interpreting the results of clinical trials.
- **DESIGN:** Reliability and validity study.
- **METHODS:** The performance index, the largest diameter of the largest metastasis and alkaline phosphatase level at the time of diagnosis of metastases, and overall survival of 249 patients from 7 ocular oncology centers who died of dissemination were analyzed. Predicted median survival time calculated according to the Helsinki University Hospital Working Formulation was used to assign patients to stages IVa, IVb, and IVc, which correspond to predicted survival times of ≥ 12 , $< 12-6$, and < 6 months, respectively. The predictions were compared against observed survival.
- **RESULTS:** The 3 variables used to assign stage were independent predictors of survival in the validation dataset. Of the 249 patients, 110 (44%), 109 (44%), and 30 (12%) were classified to Working Formulation stages IVa, IVb, and IVc, respectively. Corresponding median observed survival times were 18.6, 10.7, and 4.6 months and worsened by increasing stage ($P < .001$). Of 201 patients managed without surgical resection of metastases,

83 (41%), 89 (44%), and 29 (15%) were classified to stages IVa, IVb, and IVc, respectively, and their median observed survival times were 17.2, 10.0, and 4.6 months ($P < .001$). Survival of 47 patients who underwent resection did not differ by working formulation stage ($P = .69$).

- **CONCLUSIONS:** This multicenter study confirms that the Working Formulation is a reliable and valid, repeatable system for dividing metastatic uveal melanoma into distinct prognostic subgroups, especially for stage-specific reporting of survival in prospective clinical trials. (Am J Ophthalmol 2016;168:217–226. © 2016 Elsevier Inc. All rights reserved.)

UVEAL MELANOMA IS THE SECOND MOST COMMON primary intraocular cancer after retinoblastoma, with an estimated annual incidence of 6679–7095 patients.¹ Half of them develop metastases over 3 decades.² Their life expectancy after detection of metastases is short, a median of 8 months for unselected patients,³ although median overall survival times ranging from 12 to 24 months are commonly reported in retrospective analyses of specific treatments.^{4–9} These patients typically participated in surveillance for early detection of asymptomatic metastases so that lead time bias likely contributed to their survival times.^{10,11} For example, patients reviewed annually with abdominal ultrasonography to detect hepatic metastases, the predominant type of metastasis from uveal melanoma,^{12–14} survived a median of 5 months longer than those who were not screened, but their survival times from diagnosis of the primary tumor to death did not differ.³

Because uveal melanoma is rare, few randomized clinical trials are performed.^{15–17} Thus, there is a need for validated staging systems to adjust for differences in case mix in nonrandomized phase II studies that would aid in selecting patients for trials, in stratifying the analysis, and in interpreting the results.^{10,18} Recently, a nomogram-based system for this purpose was developed and externally validated.¹⁹

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A previous multivariate analysis of the overall survival of 91 consecutive patients who died of metastatic uveal melanoma identified 3 variables—performance index, reflecting general health of the patient; largest diameter of the largest metastasis (LDLM), reflecting measurable metastases; and serum alkaline phosphatase (AP) level, reflecting both liver function and, indirectly, unmeasurable miliary metastases—as being independently associated with survival.³ A prognostic Helsinki University Hospital Working Formulation based on this multivariate model divides newly diagnosed metastatic (stage IV²⁰) uveal melanoma into 3 prognostic categories with a predicted median overall survival of either ≥ 12 months (IVa), <12 -6 months (IVb), or <6 months (IVc).^{3,21,22} It categorizes patients who would normally be eligible for chemotherapy into 3 groups based on predicted median overall survival. Such an effort to categorize is warranted because the resulting prognostic estimate would be useful in clinical practice. Knowing the prognostic category of each patient would help the ophthalmologist in counseling the patient, in selecting patients for enrollment in clinical trials together with an oncologist, in stratifying them in trials, and in interpreting the results of clinical trials.

Until now, this prognostic model has not been validated. For this purpose, we performed the present collaborative European Ophthalmic Oncology Group (OOG) study.

METHODS

• **STUDY DESIGN AND INCLUSION CRITERIA:** This reliability and validity study was approved by the institutional review boards of the 7 participating institutions and followed the tenets of the Declaration of Helsinki as well as all laws applicable in each participating country. Informed consent was not collected because of the study design, which was based on retrospective data and enrolled only deceased patients.

Data of consecutively registered patients who died of metastatic uveal melanoma (stage IV) were requested from members of the OOG; 90% of the patients had metastases diagnosed between 2000 and 2007. The diagnosis of metastases was based on autopsy, biopsy, or typical clinical course (progressive hepatic metastases in the absence of second cancer). The data requested were the date of diagnosis of metastases; the performance index, LDLM, and serum or plasma AP level when metastases were diagnosed; and the date of death. Patients without measurable metastases or recorded AP level were ineligible. No limitations regarding treatment for metastases were applied.

• **PATIENTS AND CLINICAL DATA:** Data on 249 patients were received from 7 medical and ocular oncology services: 90 patients from Institut Curie, Paris; 60 from Klinikum Benjamin Franklin, Berlin; 23 from University of Padua, Padua; 22 from Hopital Jules Gonin, Lausanne; 19 from Helsinki University Hospital, Helsinki; 18 from Croix-Rousse Hospital, Lyon; and 17 from Royal Liverpool University Hospital, Liverpool.

The Karnofsky index or the Eastern Cooperative Oncology Group (ECOG) score was taken from patient charts. The LDLM was the best estimate from ultrasonography (US), computed tomography (CT), or magnetic resonance imaging (MRI) reports. The serum or plasma AP level and the corresponding upper normal limit (UNL) were also taken from the charts.

Most patients participated in 6- to 12-monthly surveillance that included liver imaging and liver function tests (various combinations of US, CT, MRI, aspartate and alanine aminotransferase, AP, and lactate dehydrogenase), according to the preference of each center.

• **STAGING OF METASTATIC DISEASE:** We staged patients according to the Helsinki University Hospital Working Formulation by calculating their predicted median overall survival using the published final Cox proportional hazards regression model.³ AP and the LDLM were modeled as continuous variables. The performance index was divided into 3 categories: asymptomatic (Karnofsky 100-90; ECOG 0); symptomatic (Karnofsky 85-60; ECOG 1-2); and symptomatic, unfit for chemotherapy (Karnofsky <60 ; ECOG 3-4).

The original final model included time on chemotherapy as a confounder.³ This term helped in quantitating the contribution to prognosis of the other factors of interest when the model was built, irrespective of whether longer times on therapy were due to efficacy of the treatment or to less aggressive disease. When applying the model, the population mean of 5 months, taken from the building dataset,³ is used in all calculations as the likely time on chemotherapy or comparable medical treatment because it is not yet known how long such a therapy, if any, will continue.

• **STATISTICAL ANALYSIS:** All analyses were performed with Stata (v10.0; Stata, College Station, Texas, USA). The *stcurve* command was used to plot the estimated survival function from which we read the corresponding median predicted survival. We assigned each patient correspondingly to stage IVa (≥ 12 months), IVb (<12 -6 months), or IVc (<6 months).

We used Cox multivariate proportional hazards regression to confirm that the variables of the Working Formulation were independent predictors of survival. Regression coefficients and hazard ratios (HR) with

TABLE 1. Characteristics of 249 Patients With Newly Diagnosed Metastatic Uveal Melanoma, Primary Treatment and Survival

	Participating Center							Total, N (%)
	Berlin, Germany, N (%)	Helsinki, Finland, N (%)	Lausanne, Switzerland, N (%)	Liverpool, UK, N (%)	Lyon, France, N (%)	Padua, Italy, N (%)	Paris, France, N (%)	
Performance index								
ECOG 0	43 (72)	13 (68)	16 (73)	11 (65)	16 (89)	16 (70)	39 (43)	154 (62)
ECOG 1-2	17 (28)	6 (32)	6 (27)	5 (29)	1 (6)	6 (26)	51 (57)	92 (37)
ECOG 3-4	–	–	–	1 (6)	1 (6)	1 (4)	–	3 (1)
LDLM (cm)								
≤3.0	12 (20)	14 (74)	10 (45)	6 (35)	14 (78)	10 (43)	50 (56)	116 (47)
3.1–8.0	34 (57)	5 (26)	10 (45)	9 (53)	4 (22)	13 (56)	37 (41)	112 (45)
>8.0	14 (23)	–	2 (9)	2 (12)	–	–	3 (3)	21 (8)
AP level, ×UNL								
1.0	31 (52)	16 (84)	17 (77)	8 (47)	7 (39)	17 (74)	83 (92)	179 (72)
1.1–2.0	21 (35)	1 (5)	3 (14)	5 (29)	8 (44)	5 (22)	5 (6)	48 (19)
>2.0	8 (13)	2 (10)	2 (9)	4 (24)	10 (56)	1 (4)	2 (2)	22 (9)
Primary treatment								
Chemotherapy								
Dacarbazine	–	16 (84)	–	1 (6)	–	–	35 (39)	52 (21)
Fotemustine	9 (15)	–	7 (32)	–	–	6 (22)	19 (21)	41 (16)
Treosulfan	51 (85)	–	–	–	–	–	–	51 (20)
Other	–	–	–	11 (65)	5 (28)	6 (22)	2 (2)	24 (10)
Chemoembolization	–	–	–	–	4 (22)	–	–	4 (2)
Interferon- tamoxifen	–	–	–	–	–	6 (22)	–	6 (2)
Tumor vaccine	–	–	–	–	–	–	9 (10)	9 (4)
Surgical resection								
No chemotherapy	–	–	–	–	1 (6)	1 (4)	9 (10)	11 (4)
Chemotherapy	–	–	15 (64)	1 (6)	8 (44)	1 (4)	11 (12)	36 (14)
Best supportive care		1 (5)	–	4 (24)	–	1 (4)	5 (6)	11 (4)
Other		2 (11)	–	–	–	2 (9)	–	4 (2)
Observed survival (y)								
≤1.0	40 (67)	7 (37)	6 (27)	14 (82)	2 (11)	10 (44)	38 (42)	117 (47)
1.1–2.0	15 (25)	5 (26)	2 (9)	2 (12)	5 (28)	9 (39)	38 (42)	76 (31)
2.1–3.0	4 (7)	5 (26)	9 (41)	–	2 (11)	1 (4)	9 (10)	30 (12)

Continued on next page

TABLE 1. Characteristics of 249 Patients With Newly Diagnosed Metastatic Uveal Melanoma, Primary Treatment and Survival (Continued)

	Participating Center							Total, N (%)
	Berlin, Germany, N (%)	Helsinki, Finland, N (%)	Lausanne, Switzerland, N (%)	Liverpool, UK, N (%)	Lyon, France, N (%)	Padua, Italy, N (%)	Paris, France, N (%)	
>3.0	1 (2)	2 (10)	5 (23)	1 (6)	9 (50)	3 (13)	5 (6)	26 (10)
Working formulation								
All patients								
Stage IVa	20 (33)	13 (68)	9 (41)	6 (35)	10 (56)	12 (52)	40 (44)	110 (44)
Stage IVb	23 (38)	5 (26)	12 (55)	8 (48)	5 (28)	9 (39)	47 (52)	109 (44)
Stage IVc	17 (28)	1 (5)	1 (5)	3 (18)	3 (17)	2 (9)	3 (3)	30 (12)
Excluding surgically treated patients								
Stage IVa	20 (33)	13 (68)	2 (29)	5 (31)	5 (56)	11 (55)	27 (39)	83 (41)
Stage IVb	23 (38)	5 (26)	4 (57)	8 (50)	2 (22)	7 (35)	40 (57)	40 (57)
Stage IVc	17 (28)	1 (5)	1 (14)	3 (19)	2 (22)	2 (10)	3 (4)	29 (14)

AP = serum or plasma alkaline phosphatase level; LDLM = largest diameter of the largest metastasis; UNL = upper normal limit.

95% confidence intervals (CI) were calculated. Assumption of proportional hazards was assessed with complementary log plots.

We generated Kaplan-Meier survival curves for each stage and compared unordered and ordered categories with log-rank test and test for trend, respectively. All *P* values were 2-sided (*P* < .05 was taken as significant). We adjusted *P* values in pairwise comparisons with Bonferroni correction. Primary analysis was based on all patients. Secondary analysis considered separately patients whose metastases had or had not been resected.

We compared predicted and observed survival visually using scatterplots and agreement between predicted and observed survival categories (≥12 months, <12-6 months, and <6 months) using weighted kappa (weighting matrix, 1 \ 0.50 1 \ 0 0.50 1).

RESULTS

• **PATIENT CHARACTERISTICS AT DIAGNOSIS OF METASTASES:** Of the 249 eligible patients, most had an ECOG score 0 (62%) and 1-2 (37%) or an equivalent Karnofsky index (Table 1). The distribution of performance indices was comparable in all participating centers except that ECOG 1-2 was the most common index in 1 center.

The median LDLM was 3.5 (range 0.8–19; interquartile range [IQR] 2.0–5.8) cm. The largest metastasis was small (≤3.0 cm) in 116 (47%) and large (>8.0 cm) in 21 patients (8%).²⁰ Small metastases predominated in 3 centers and medium-sized ones in 3; the remaining center had both in equal proportions (Table 1). The median AP level was 0.70× UNL (range 0.24–8.15; IQR 0.53–1.11). It was <1.0× UNL in 179 patients (72%) and >2.0× UNL in 22 (9%). Most patients had a normal level in all but 2 centers (Table 1).

• **TREATMENT OF METASTASES AND OBSERVED SURVIVAL:** The patients had been treated on an individual basis according to the prevailing practice in each participating center (Table 1). Of the entire cohort, 11 patients (4%) received best supportive care; 165 (66%) were given single-agent or combination chemotherapy with or without immunotherapy or vaccine, usually a regimen based on dacarbazine, fotemustine, or treosulfan; 4 (2%) underwent chemoembolization; 4 (2%) received interferon, usually with tamoxifen; 9 (4%) were immunized with a tumor vaccine; 47 (18%) had metastases surgically resected with or without chemotherapy, immunotherapy, or vaccine; and 4 (2%) underwent other treatments.

The observed median survival was 13.5 months (range, 0.2–129 months; IQR 6.7–22.6 months; Figure 1, Top left) for the entire cohort; 132 patients (53%) survived

FIGURE 1. Kaplan-Meier survival curves displaying overall survival after diagnosis of metastatic uveal melanoma in 249 patients in the entire validation dataset (Top left); according to the Helsinki University Hospital Working Formulation for all patients (Top right); and for patients managed without surgery (Bottom left) and with surgery (Bottom right). Numbers below graphs are patients at risk and shaded ranges are 95% confidence intervals. Note that the intervals completely overlap when surgery was part of treatment of metastases.

>1 year, 56 (22%) >2 years, 26 (10%) >3 years, and 8 (3%) >5 years (Table 1).

The observed median survival was comparable for the 3 main types of chemotherapy, based on dacarbazine, fotemustine, or treosulfan ($P = .23$, log-rank test). It was 10.9 months (95% CI 9.6–13.5) for the 202 patients managed without surgery, which was significantly shorter than 26.0 months (95% CI 17.4–32.1) for the 47 patients who underwent surgical resection of metastases as part of their treatment ($P < .001$). The surgically treated group had more favorable performance indices ($P = .048$, nonparametric test for trend) and more favorable largest diameters of the largest metastases ($P < .001$, Mann-Whitney U test), but their AP levels were comparable ($P = .24$).

• **VERIFICATION OF THE PROGNOSTIC PARAMETERS:** All 3 variables on which the Working Formulation is based were significantly and independently associated with overall survival, irrespective of whether AP level was treated as a continuous or a categorical variable relative to UNL (models 1 and 2; Table 2).

• **WORKING FORMULATION: ALL PATIENTS:** Of the 249 patients, 110 (44%) were assigned to stage IVa, 109 (44%) to IVb, and 30 (12%) to IVc (Table 1). Observed survival shortened with increasing stage ($P < .001$, log-rank test for trend; Figure 1, Top right). The observed median survival was 18.6 months (95% CI 16.3–21.1) for stage IVa, 10.7 months (95% CI 8.6–14.0) for IVb, and 4.6 months (95% CI 3.0–6.7) for IVc. Stage IVa predicted

TABLE 2. Cox Proportional Hazards Regression of Survival in 249 Patients With Newly Diagnosed Metastatic Uveal Melanoma

Variable	Beta Coefficient (SE)	Wald χ^2	P	Hazard Ratio (95% CI)
Model 1 (–2 log likelihood, 2216.1)				
Performance index ^a	0.440 (0.134)	10.8	.001	1.55 (1.19–2.02)
Serum or plasma alkaline phosphatase level ^b	0.195 (0.060)	10.4	.001	1.21 (1.08–1.37)
Largest diameter of the largest metastasis ^c	0.087 (0.022)	15.5	<.001	1.09 (1.04–1.14)
Model 2 (–2 log likelihood, 2219.6)				
Performance index ^a	0.445 (0.134)	11.1	.001	1.56 (1.20–2.03)
Serum or plasma alkaline phosphatase level ^d	0.239 (0.111)	4.6	.032	1.27 (1.02–1.58)
Largest diameter of the largest metastasis ^c	0.084 (0.224)	14.1	<.001	1.09 (1.04–1.14)
Model 3 (–2 log likelihood, 2214.4)				
Working formulation				Reference
Stage IVa				
Stage IVb	0.394 (0.137)	8.2	.004	1.48 (1.13–1.94)
Stage IVc	1.591 (0.216)	54.3	<.001	4.91 (3.22–7.50)

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; SE = standard error.

^aCategories: 0 = ECOG 0 or Karnofsky 100–90; 1 = ECOG 1–2 or Karnofsky 85–60; 2 = ECOG 3–4 or Karnofsky <60.

^bContinuous variable, $\times$ upper normal limit.

^cContinuous variable, cm.

^dCategories: 0 = $1.0 \times$ upper normal limit; 1 = $1.1\text{--}2.0 \times$ upper normal limit; 2 = $>2.0 \times$ upper normal limit.

longer survival than stage IVb ($P = .009$, log-rank test with Bonferroni correction for 3 comparisons), as did stage IVb as compared with IVc ($P < .001$). The Working Formulation stage was also strongly associated with observed survival by Cox regression (model 3; HR 1.48 for IVb vs IVa, and HR 4.91 for IVc vs IVa, $P = .004$ and $P < .001$, respectively, Table 2; HR 2.77 [95% CI 1.82–4.24] for IVb vs IVc, $P < .001$).

In stage IVa, 74% of patients survived ≥ 12 months (Figure 2, Table 3). In stage IVb, 76% of patients survived ≥ 6 months and 44% survived ≥ 12 months, and in stage IVc, 63% and 90% died within <6 and <12 months, respectively. The weighted kappa for agreement between observed and predicted survival category was 0.364 (agreement 75% vs 61% expected, $P < .001$).

• **WORKING FORMULATION: STRATIFIED BY SURGICAL TREATMENT:** Of the 201 patients managed without surgical resection of metastases, 83 (41%) were assigned to stage IVa, 89 (44%) to IVb, and 29 (15%) to IVc (Table 1). Observed survival worsened significantly with increasing stage ($P < .001$, log-rank test for trend; Figure 1, Bottom left). The observed median survival was 17.2 months (95% CI 14.7–19.4) for stage IVa, 10.0 months (95% CI 7.9–11.7) for IVb, and 4.6 months (95% CI 2.6–6.0) for IVc. Stage IVa and IVb ($P = .003$) and stage IVb and

IVc ($P < .001$, log-rank test with Bonferroni correction for 3 comparisons) differed significantly from one another in survival.

Of patients representing stage IVa, 70% survived ≥ 12 months; 74% and 38% of patients representing stage IVb survived ≥ 6 and ≥ 12 months, respectively; and 66% and 93% of patients representing stage IVc died in <6 and <12 months, respectively (Table 3). The weighted kappa for agreement between the observed and predicted survival categories was 0.388 (agreement 75% vs 60% expected, $P < .001$).

Of the 47 patients managed with surgical resection of metastases as part of their treatment, 27 (57%) were assigned to stage IVa, 19 (40%) to IVb, and 1 patient to IVc. The Working Formulation stages did not differ significantly from each other in survival ($P = .69$, log-rank test for trend; Figure 1, Bottom right). The observed median survival was 26.7 months (95% CI 17.3–38.3) for stage IVa and 26.0 months (95% CI 9.9–32.1) for stage IVb, and the only patient of stage IVc survived 17.0 months. The surgically treated group did not have more favorable performance indices than other patients when stratified by stage ($P = .61$ and $P = .46$ within stage IVa and IVb, respectively, nonparametric test for trend), whereas they had more favorable largest diameters of the largest metastases within stage

FIGURE 2. Scatterplot of the predicted median survival time derived from the Helsinki University Hospital Working Formulation against observed overall survival by stages IVa (predicted median survival ≥ 12 months), IVb (predicted survival < 12 -6 months), and IVc (predicted survival < 6 months).

IVa but not within stage IVb (median $P = .023$ and $P = .33$, respectively, Mann-Whitney U test). Their AP levels were comparable ($P = .24$ and $P = .91$, respectively). Correspondingly, largest diameter of the largest metastasis was associated with longer survival within stage IVa (HR 1.23; 95% CI 1.04–1.45 for each cm increase) but not within stage IVb (HR 1.02; 95% CI 0.94–1.12) by Cox regression ($P = .016$ and $P = .63$, respectively).

DISCUSSION

OUR STUDY VALIDATES THE HELSINKI UNIVERSITY HOSPITAL Working Formulation for staging metastatic uveal melanoma. The original single-institution building dataset and the present 7-center validation dataset were comparable with respect to all variables needed for staging.³ The performance index corresponded to ECOG score 0, 1-2, and 3-4 in 67%, 29%, and 4% in the original dataset as compared to 62%, 37%, and 1% in the validation set. The median

LDLM of patients with measurable lesions in the original dataset was 4.8 cm, exceeding the median of 3.5 cm in the validation set, possibly because surveillance was more frequent in some of the validating centers. The AP level exceeded the UNL in 30% of the original dataset as compared to 28% in the validation set. All variables remained independent, significant predictors of survival, confirming their statistical validity in the Working Formulation.

In the original building dataset, LDLM outperformed other measures of the extent of metastasis, such as total and hepatic metastatic burden.³ This was serendipitous, as LDLM is easily measured in clinical practice. LDLM also showed the strongest association with survival,³ also a finding confirmed in the present validation dataset. In a recent study, data of 152 patients were used to build, and data from an additional 102 patients were used to validate, a new nomogram-based prognostic system for metastatic uveal melanoma.¹⁹ The nomogram includes performance status, percentage of liver involvement, lactate dehydrogenase level, and disease-free interval. The authors measured the largest diameter of liver metastases but elected not to analyze this variable because, on theoretical grounds, they considered the percentage of liver substitution to be the best indicator of the effective volume of hepatic disease. They also concluded, contrary to findings in our building and validation data,³ that liver function tests other than lactate dehydrogenase were not associated with survival. However, data on AP were not reported.¹⁹ We did not record the disease-free interval in the present validation study, but it was not an independent prognostic factor in our building dataset.³ A potential explanation for these differences is that the eventual true survival was not yet known for 29% of patients in the building and for 69% of patients in the validation datasets used to construct the nomogram who were either alive or lost to follow-up at the time of analysis,¹⁹ whereas we followed all patients until they had died and their exact survival time was known.³

Percentages of patients assigned to stages IVa, IVb, and IVc—43%, 40%, and 17% in the original dataset³ and 44%, 44%, and 12% in the validation set, respectively—were similar. The median observed overall survival after diagnosis of metastases in the original dataset was 8.4 months, vs 10.9 months in the validation set. This potentially reflects lead time bias from more intensive surveillance^{23–25} of patients in the present validation set that was enrolled about a decade later.^{3,13} The median observed survival for each stage likewise was longer than that in the original dataset: 17.2 vs 14.9 months for stage IVa, 10.0 vs 8.9 months for IVb, and 4.2 vs 2.0 months for IVc. Observed median survival times differed significantly by stage in the validation dataset, and they all fell within the corresponding predicted interval (≥ 12 months, < 12 -6 months, and < 6 months), validating the Working Formulation. The investigators who described the recent

TABLE 3. Agreement Between Observed and Predicted Survival of 249 Patients With Newly Diagnosed Metastatic Uveal Melanoma

Variable	Observed Survival			Weighted Kappa
	≥12 Months, N (%)	<12-6 months, N (%)	<6 months N (%)	
Working formulation				.364
All patients				
Stage IVa	81 (74)	22 (20)	7 (6)	
Stage IVb	48 (44)	35 (32)	26 (24)	
Stage IVc	3 (10)	8 (27)	19 (63)	
Excluding surgically treated patients				.388
Stage IVa	58 (70)	20 (24)	5 (6)	
Stage IVb	34 (38)	32 (36)	23 (26)	
Stage IVc	2 (7)	8 (28)	19 (66)	

prognostic nomogram for metastatic uveal melanoma have not yet provided a comparison of predicted with observed survival times.¹⁹

In the building dataset, 73% of patients received chemotherapy or chemioimmunotherapy, and 10% underwent surgical resection.³ In the validation set, these percentages were 67% and 18%, which reflects the participation of 2 OOG centers in which surgery is the preferred approach to metastatic uveal melanoma. The Working Formulation predicted survival well when metastases were not resected. The observed survival was not associated with stage if they were resected. This observation lends further support to the hypothesis that the largest metastases, which typically are resected, often strongly influence survival, especially in oligometastatic disease.

The Working Formulation has 4 major limitations. First, it is based on data at the time of diagnosis of first metastasis.³ It cannot predict survival of patients considered for second-line treatment. Second, the mode of imaging was not standardized, and this may have affected measuring of the LDLM and, thus, assignment to stages IVa–IVc. Third, another model is clearly needed to predict survival of patients who undergo resection of metastases. The Working Formulation will suggest, however, what their survival might be should metastases be managed without surgery. Fourth, the Working Formulation categorizes a cohort of patients by predicted survival but it does not precisely predict the fate of a single patient, in particular as regards stage IVb, and it should thus not be used for such a purpose.

The Working Formulation also needs further development. For example, the survival of patients who have miliary metastases may not be modeled optimally. Preliminary data suggest that histopathologic and genetic factors

determined from metastases—for example, microvascular density²⁶ and *GNA11*, *GNAQ*, and *BAP1* mutation status²⁷—also influence survival after metastasis and should be considered for refined prognostication in addition to clinical data.

Although the paper describing the Working Formulation³ has been cited over 60 times, according to Thomson Reuters' Web of Science (<http://apps.whoftknowledge.com>, accessed October 1, 2015), this staging has rarely been applied in reporting.^{21,22,28–30} Adoption of either of the 2 now validated systems for staging metastatic uveal melanoma^{3,19} would largely solve 3 prevalent problems. First, investigators fit *ad hoc* multivariate models, typically by a data-driven, stepwise approach. Such models often fit a typically small sample but may not be repeatable. Models built from established and validated prognostic factors are preferable. Second, investigators plot survival according to single predictors. Bias from other factors makes comparisons difficult. Third, investigators use no consistent reference categories such as the Working Formulation stages against which to compare survival. Many reports on treatment of metastatic uveal melanoma describe patients undergoing regular surveillance and thus likely include predominantly Working Formulation stage IVa metastatic melanomas. A median survival exceeding 12 months is then expected rather than suggestive of any therapeutic superiority.

We recommend that the validated Working Formulation³ or the recent prognostic nomogram,¹⁹ both of which share performance index, extent of measurable metastases, and liver function tests as their basis for staging, be used for evidence-based, stage-specific reporting of survival of patients with metastatic uveal melanoma in prospective studies.

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REFERENCES

1. Kivelä T. The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. *Br J Ophthalmol* 2009;93(9):1129–1131.
2. Kujala E, Mäkitie T, Kivelä T. Very long-term prognosis of patients with malignant uveal melanoma. *Invest Ophthalmol Vis Sci* 2003;44(11):4651–4659.
3. Eskelin S, Pyrhönen S, Hahka-Kemppinen M, Tuomaala S, Kivelä T. A prognostic model and staging for metastatic uveal melanoma. *Cancer* 2003;97(2):465–475.
4. Edelhauser G, Schicher N, Berzaczky D, et al. Fotemustine chemoembolization of hepatic metastases from uveal melanoma: a retrospective single-center analysis. *Am J Roentgenol* 2012;199(6):1387–1392.
5. Farolfi A, Ridolfi L, Guidoboni M, et al. Liver metastases from melanoma: hepatic intra-arterial chemotherapy. A retrospective study. *J Chemother* 2011;23(5):300–305.
6. Mariani P, Piperno-Neumann S, Servois V, et al. Surgical management of liver metastases from uveal melanoma: 16 years' experience at the Institut Curie. *Eur J Surg Oncol* 2009;35(11):1192–1197.
7. Yamamoto A, Chervoneva I, Sullivan KL, et al. High-dose immunoembolization: survival benefit in patients with hepatic metastases from uveal melanoma. *Radiology* 2009;252(1):290–298.
8. Peters S, Voelter V, Zografos L, et al. Intra-arterial hepatic fotemustine for the treatment of liver metastases from uveal melanoma: experience in 101 patients. *Ann Oncol* 2006;17(4):578–583.
9. Pföhler C, Cree IA, Ugurel S, et al. Treosulfan and gemcitabine in metastatic uveal melanoma patients: results of a multicenter feasibility study. *Anticancer Drugs* 2003;14(5):337–340.
10. Kivelä T, Eskelin S, Kujala E. Metastatic uveal melanoma. *Int Ophthalmol Clin* 2006;46(1):133–149.
11. Kim IK, Lane AM, Gragoudas ES. Survival in patients with presymptomatic diagnosis of metastatic uveal melanoma. *Arch Ophthalmol* 2010;128(7):871–875.
12. Collaborative Ocular Melanoma Study. Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the Collaborative Ocular Melanoma Study (COMS): COMS report no. 15. *Arch Ophthalmol* 2001;119(5):670–676.
13. Eskelin S, Pyrhönen S, Summanen P, Prause JU, Kivelä T. Screening for metastatic malignant melanoma of the uvea revisited. *Cancer* 1999;85(5):1151–1159.
14. Lorigan JG, Wallace S, Mavligit GM. The prevalence and location of metastases from ocular melanoma: imaging study in 110 patients. *Am J Roentgenol* 1991;157(6):1279–1281.
15. Schmittl A, Schmidt-Hieber M, Martus P, et al. A randomized phase II trial of gemcitabine plus treosulfan versus treosulfan alone in patients with metastatic uveal melanoma. *Ann Oncol* 2006;17(12):1826–1829.
16. Leyvraz S, Piperno-Neumann S, Suci S, et al. Hepatic intra-arterial versus intravenous fotemustine in patients with liver metastases from uveal melanoma (EORTC 18021): a multicentric randomized trial. *Ann Oncol* 2014;25(3):742–746.
17. Carvajal RD, Schwartz GK, Mann H, Smith I, Nathan PD. Study design and rationale for a randomised, placebo-controlled, double-blind study to assess the efficacy of selumetinib (AZD6244; ARRY-142886) in combination with dacarbazine in patients with metastatic uveal melanoma (SUMIT). *BMC Cancer* 2015;15:467.
18. Buzzacco DM, Abdel-Rahman MH, Park S, Davidorf F, Olencki T, Cebulla CM. Long-term survivors with metastatic uveal melanoma. *Open Ophthalmol J* 2012;6:49–53.
19. Valpione S, Moser JC, Parrozzani R, et al. Development and external validation of a prognostic nomogram for metastatic uveal melanoma. *PLoS One* 2015;10(3):e0120181.
20. Malignant melanoma of the uvea. In: Edge SE, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti AJ, eds. *AJCC Cancer Staging Manual*. 7th ed. New York: Springer; 2010:547–559.
21. Pyrhönen S, Hahka-Kemppinen M, Muhonen T, et al. Chemoimmunotherapy with bleomycin, vincristine, lomustine, dacarbazine (BOLD), and human leukocyte interferon for metastatic uveal melanoma. *Cancer* 2002;95(11):2366–2372.
22. Kivelä T, Suci S, Hansson J, et al. Bleomycin, vincristine, lomustine and dacarbazine (BOLD) in combination with recombinant interferon alpha-2b for metastatic uveal melanoma. *Eur J Cancer* 2003;39(8):1115–1120.
23. Piperno-Neumann S, Servois V, Mariani P, et al. Prospective study of surveillance testing for metastasis in 100 high-risk uveal melanoma patients. *J Fr Ophtalmol* 2015;38(6):526–534.
24. Nathan P, Cohen V, Coupland S, et al. Uveal Melanoma UK National Guidelines. *Eur J Cancer* 2015;51(16):2404–2412.
25. Gomez D, Wetherill C, Cheong J, et al. The Liverpool uveal melanoma liver metastases pathway: outcome following liver resection. *J Surg Oncol* 2014;109(6):542–547.
26. Toivonen P, Mäkitie T, Kujala E, Kivelä T. Microcirculation and tumor-infiltrating macrophages in choroidal and ciliary body melanoma and corresponding metastases. *Invest Ophthalmol Vis Sci* 2004;45(1):1–6.
27. Griewank KG, van de Nes J, Schilling B, et al. Genetic and clinico-pathologic analysis of metastatic uveal melanoma. *Mod Pathol* 2014;27(2):175–183.

28. Terheyden P, Brocker EB, Becker JC. Clinical evaluation of in vitro chemosensitivity testing: the example of uveal melanoma. *J Cancer Res Clin Oncol* 2004; 130(7):395–399.
29. Al-Jamal RT, Eskelin S, Pyrhönen S, Kivelä T. Long-term progression-free survival in metastatic uveal melanoma after chemoimmunotherapy and consolidation thermoablation. *Acta Oncol* 2009;48(3):476–479.
30. Vihinen PP, Hernberg M, Vuoristo MS, et al. A phase II trial of bevacizumab with dacarbazine and daily low-dose interferon-alpha2a as first line treatment in metastatic melanoma. *Melanoma Res* 2010;20(4):318–325.