Determinants of Long-Term Survival in Metastatic Choroidal and Ciliary Body Melanoma

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• PURPOSE: To build and validate a prognostic model that predicts long-term overall survival (OS) in metastatic choroidal and ciliary body melanoma (CCBM) to facilitate patient counseling and planning, reporting, and interpreting clinical trials.

• DESIGN: Retrospective cohort study with validation.

• METHODS: We analyzed predictors of intermediate (IMT; 25-<42 months) and long-term (LT; ≥42 months) OS in a Finnish nationwide cohort of 330 patients with metastatic CCBM. Short-term (<25 months), IMT, and LT survival were compared with pairwise and ordinal logistic regression. A single-center cohort of 259 patients from Italy was used for validation. Models were compared with a deviance test.

• RESULTS: Median OS was 12 and 17 months in the building and validation datasets, respectively; 40 (12%) and 31 (9%) compared with 44 (17%) and 32 (12%) patients were IMT and LT survivors, respectively. Alkaline phosphatase or lactate dehydrogenase level never exceeded 2 times the upper normal limit (UNL) in either LT cohort. Conditional to both being ≤2 times the UNL, distant metastasis-free interval (DMFI) >42 months (odds ratio [OR] 4.09-4.64; $P < .001$) paired with age <60 years (OR 3.23; $P = .002$), having no symptoms (OR 4.19; $P = .005$), and the largest diameter of the largest metastasis <30 mm (Tumor, Node, Metastasis stage M1a; OR 3.05; $P = .001$) independently predicted higher odds of surviving longer (IMT or LT) without model preference. These results were confirmed in the validation dataset.

• CONCLUSIONS: Alkaline phosphatase or lactate dehydrogenase >2 times the UNL essentially precluded LT survival. The most robust predictor otherwise was DMFI >42 months, followed by age <60 years, absence of symptoms, and Tumor, Node, Metastasis stage M1a. (Am J Ophthalmol 2023;246: 258–272.

PROFESSIONALS AND PATIENTS ALIKE SELDOM associate metastatic uveal melanoma with long-term (LT) survival. Historically, overall survival (OS) after the diagnosis of metastases from a primary uveal melanoma has been short—a median of 6 months—and even in meta-analyses that focus on more recent actively treated patients the median is 12 to 13 months.[1–4] Moreover, metastatic uveal melanoma remains the leading cause of death even 30 years after the diagnosis of the primary tumor.[5] Although the cure rate approaches nil over time, LT survival is possible, and about 2% of patients with metastases survive for 5 years.[2,6,7]

Indeed, both clinical practice and a few reports show that a subset of LT survivors exists with as yet uncertain clinical characteristics.[1,8–12] The number of LT survivors in these studies has ranged from 1-44, depending on sample size and the definition of LT survival, variably defined as ≥12-48 months. Seven clinical indicators emerge that have been proposed in these reports to be associated with LT survival: female sex,[10] younger age,[1,8,10,11] longer distant metastasis-free interval (DMFI),[10,11] normal level of serum or plasma lactate dehydrogenase (LD),[8,12] absence of hepatic metastases,[10] higher number of affected organ systems,[12] smaller size of the largest liver metastasis,[8] and surgical resection or liver-directed therapy.[10,11]

A systematic approach to predictors of LT survival in a larger series of patients that would build on previously published findings and validate the resulting model is unavailable. A validated model based on such an analysis would help identify patients with newly diagnosed metastases whose characteristics predict likely LT survival so that they can be counseled and managed accordingly. Among other benefits, the availability of such a model could prevent inadvertent overestimation of OS outcomes in non-randomized trials—a common setting in reports on this rare cancer. We hereby report systematic modeling of robust predictors of LT survival in patients with metastatic choroidal and ciliary body melanoma (CCBM) in a comprehensive

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national dataset, and validation of the model with a large external independent dataset.

METHODS

• **AIMS OF THE STUDY:** Our primary aims were to model and verify factors previously proposed to predict LT survival of patients with metastatic CCBM in a nationwide cohort and to validate a model built from the most robust independent predictors using a large independent cohort of patients from a tertiary referral center for eye cancer to support the reliability and applicability of the results.

• **MODEL BUILDING DATASET:** Eligible for the first stage of this retrospective observational cohort study were 338 patients treated for primary CCBM in the Ocular Oncology Service, Department of Ophthalmology, Helsinki University Hospital, Finland—a national referral center that manages >95% of patients with this type of cancer—and later diagnosed with metastases between January 1, 1999 and December 31, 2016. Less than 1% of patients had received any adjuvant treatment before metastases were diagnosed. The institutional review board and the National Institute for Health and Welfare approved the study. Informed consent was waived because of its retrospective, record-based nature. Exclusion criteria were diagnosis of metastases first at autopsy (2 patients), metastases not consistent with uveal melanoma upon review (1 patient), a concurrent active second cancer (3 patients), or lack of main details of metastases (2 dead patients whose medical records already had been destroyed according to local law; Supplemental Figure 1, A).

We obtained patient charts from all hospitals that participated in the management of metastases. The verification of metastases in the 330 consecutive enrolled patients has been described previously.[7] Sex, age, date of diagnosis of primary CCBM and its metastases, American Joint Committee on Cancer (AJCC) 8th edition Tumor, Node, Metastasis (TNM) staging,[13] and participation in annual (semiannual from 2014 onward for TNM stage III) review with liver function tests (LFTs) and upper abdominal ultrasonography (US) to detect metastases early, followed by staging computed tomography (CT), magnetic resonance imaging (MRI), or both, when metastases were suspected,[14] DMFI (time from the diagnosis of the primary tumor to the diagnosis of metastases), total serum or plasma levels of LD and alkaline phosphatase (AP), sites of metastases (hepatic, extrahepatic with or without hepatic), the largest diameter of the largest metastasis (LDLM), presence of symptoms from metastases, the Eastern Cooperative Oncology Group (ECOG) performance status (PS) at the time of treatment decision widely used to quantify the symptoms and functions in cancer patients,[15] treatment modality, and the number of treatment lines eventually given were considered. First-line treatment modalities—surgical resection, other active treatment, or best supportive care (BSC)—were categorized.[6,7] Follow-up ended on May 25, 2020. The date and cause of death were provided by Statistics Finland, and we verified them against patient records.

For the purpose of this study, the patients were divided into 3 cohorts according to their observed OS after diagnosis of metastases: <69 percentile (short-term [ST]), 69-84 percentile (intermediate-term [IMT]), and >84 percentile (LT), translating to <25 months, 25-42 months, and >42 months, respectively. These percentiles were chosen because in the normal distribution they would correspond to <0.5 standard deviation (SD), 0.5-1.0 SD, and >1.0 SD above the mean.

• **MODEL VALIDATION DATASET:** We validated the model by using an independent dataset from the University of Padova, Italy, a major tertiary referral center for eye cancer. The prospective melanoma database kept at the Melanoma Oncology Unit of the Istituto Oncologico Veneto was queried under institutional review board approval to expand a previously published dataset of 152 patients with patients diagnosed with metastases from CCBM between September 1990 and September 2020 (in the published series, October 2013). Of 273 identified patients, 14 were excluded because the date of diagnosis of metastatic CCBM and thus also the DMFI was unavailable (Supplemental Figure 1, B).[16]

The validation dataset of 259 patients was construed identically with the building dataset. Metastases were diagnosed by US or CT. Staging was completed with CT or MRI, if not previously performed as a screening procedure. Data from some variables from the earlier period could no longer be retrieved.

• **STATISTICAL ANALYSIS AND MODELING:** Statistical analysis was performed with Stata software (version 17, Stata Corp, College Station, Texas, USA). Significance was set at $P < .05$ unless otherwise stated. All P values are 2-tailed. We report median with range and interquartile range for continuous variables as descriptive statistics. We compared unordered and ordered variables across the 3 ordered categories of OS using the nonparametric test for trend and the Jonckheere-Terpstra test, respectively.[17,18] We estimated OS in the entire datasets and by cohort of OS using the Kaplan-Meier product-limit method and report the median OS with its 95% confidence interval (CI). We censored survivors at their last follow-up visit. Follow-up time was measured from the detection of likely or suspected metastases by imaging, subsequently confirmed typically through a biopsy specimen when treatment was active or through progression when the patient was not fit for active therapy, to the death or most recent clinical evaluation.

Continuous variables including DMFI were alternatively divided in tertiles. We also considered different previously applied ways to categorize DMFI.[19–22] Of note, pathogenic variants in *BAP1* are associated with frequent, generally

rapid metastasis whereas those in *SF3B1* and, especially, *EIF1AX* lead less frequently to metastases that usually seem to appear later.[19,21,23–26] This suggests that short, intermediate, and long DMFI might act as surrogates for the different driver genes.[27]

To choose robust independent prognostic factors associated with IMT (25-42 months) to LT (>42 months) OS, we first applied penalized likelihood-based Firth logistic regression (LR) to make 3 pairwise comparisons: ST vs LT, IMT vs LT, and ST-to-IMT vs LT survival. Firth LR was chosen because it reduces bias and also provides finite and consistent estimates in datasets like ours that are relatively small, imbalanced—ie, only a small proportion of patients survived LT—and include variables that exhibit complete or quasi-complete separation—ie, they predict perfectly or almost perfectly only because the dataset is relatively small and its distribution is rather extreme.[28,29]

In addition, we applied ordinal LR[30] that allows >2 response categories to estimate the influence of an independent variable on the probability of being at a given or higher level on an ordinal variable scale (here, IMT or LT survival cohort). To overcome the problem of complete separation when serum or plasma LD or AP level exceeded 2.0 times the upper normal limit (UNL), we run the ordinal LR conditional to these LFT levels being ≤2.0 times the UNL. As a bridge between Firth LR and ordinal LR we verified that the 3 pairwise comparisons, when conditional to LD and AP being ≤2.0 times the UNL, produced LR estimates comparable to those from Firth LR.

We considered a variable to be a robust predictor if it predicted longer OS in ≥2 of the 3 pairwise regressions (both in Firth LR and in the conditional LR) as well as in the conditional ordinal LR. Ordinal LR alone was used for subsequent bivariable regression based on the identified univariable robust predictors to avoid multiple binary comparisons. We allowed independent variables in models if $P < .10$. Effect sizes are expressed as odds ratios (ORs) with their 95% CIs. The model assumptions were tested with Maarten Buis's *oparallel* command in Stata.

Competing bivariate models obtained from analysis of OS in the building dataset were compared using the deviance test in a dataset collapsed listwise to comprise patients who had all available variables included in the competing models. Finally, the preferred models were tested in the independent external validation dataset. The tertile cutpoints from the building dataset were applied also to the validation dataset.

RESULTS

- **CLINICAL CHARACTERISTICS:**

Building dataset

The median OS after metastasis of the 330 patients (Table 1) was 12 months (range 0.1-171 months; Figure 1, A), and 259 (78%) patients survived <25 months (ST), 40 (12%) survived 25-42 months (IMT), and 31 (9%) survived >42 months (LT; Figure 1, B). In 12 patients, metastases were diagnosed before the primary CCBM (range 1-39 days); of these 8, 2, and 2 were in the ST, IMT, and LT cohorts, respectively. Surveillance for metastases was regular for 320 (97%) patients who had the LFTs and upper abdominal US taken within 4 weeks before their next scheduled surveillance visit. Eleven patients were alive with progressive metastases at the time of analysis, 2 and 9 of them in the IMT and LT cohorts of which they formed 5% and 29%, respectively.

The age at diagnosis of the primary CCBM (median 66 vs 59 vs 55 years, $P < .001$ nonparametric test for trend) and, to a lesser extent, its metastases (median 69 vs 63 vs 62 years, $P = .003$) decreased by OS cohort, whereas the age at death was comparable between the cohorts (median 70 vs 66 vs 68 years, $P = .36$; Table 1). The DMFI correspondingly increased across the OS cohorts, especially from the IMT to the LT cohort (median 25 vs 27 vs 54 months, $P < .001$). DMFI as a prognostic factor has been categorized in several ways in the published literature,[19–22] provided for comparison in Table 1 in addition to the tertiles that were primarily used in modeling ($P < .001$ Jonckheere-Terpstra test). We did not have evidence that sex ($P = .46$, nonparametric test for trend), tumor extension from the choroid to adjacent tissues ($P = .18$), or the distribution of TNM size categories and stages would have differed between the OS cohorts ($P = .99$ and $P = .95$, respectively, Jonckheere-Terpstra test). Of note, no IMT or LT cohort survivor represented the worst local TNM stage IIIC, but 4 (10%) and 2 (6%) patients in these cohorts, respectively, had synchronous metastases (stage IV disease).

The percentage of patients without symptoms from metastases increased by OS cohort from 57% to 97% ($P < .001$ nonparametric test for trend), and only 2 (5%) and 1 (3%) patients in the IMT and LT cohorts, respectively, had a PS worse than 1 compared with 100 (38%) patients in the ST cohort ($P < .001$, Jonckheere-Terpstra test; Table 1). The percentage of patients with AP and LD level within their UNL increased with OS cohort (50% vs 63% vs 81% and 22% vs 35% vs 48%, respectively, $P < .001$ for both), and neither LFT exceeded 2.0 times the UNL in the LT cohort, although 1 (3%) patient in the IMT cohort had LD >2.0 times the UNL, and the levels were not recorded for 4 (13%) and 12 (39%) patients, respectively. The median LDLM decreased with increasing OS cohort (35 vs 24 vs 20 mm, $P < .001$ nonparametric test for trend), and only 2 (5%) and 1 (3%) patient in the IMT and LT cohorts, respectively, had a metastasis >80 mm (M1c) compared with 37 (14%) of patients in the ST cohort ($P < .001$ across all 3 M1 categories, Jonckheere-Terpstra test).

The percentage of patients with only hepatic metastases was 69% overall and comparable between the OS cohorts ($P = .92$ nonparametric test for trend; Table 1). A larger percentage of patients in the LT cohort than in the other

TABLE 1. The building and validation datasets. Characteristics of patients diagnosed with metastatic choroidal and ciliary body melanoma. Characteristics for patients with newly diagnosed metastatic choroidal and ciliary body melanoma in the building and validation datasets.

Variable	Building dataset (N = 330)					Validation dataset (N = 259)				
	All patients N = 330 (100%)	Short-term survival <25 mo N = 259 (78%)	Intermediate-term survival 25–42 mo N = 40 (12%)	Long-term survival >42 mo N = 31 (9%)	*P*-value for trend	All patients N = 259 (100%)	Short-term survival <25 mo N = 183 (71%)	Intermediate-term survival 25–42 mo N = 44 (17%)	Long-term survival >42 mo N = 32 (12%)	*P*-value for trend
Sex, *n* (%)[a]					.46[b]					.37[b]
Female	161 (49)	123 (47)	22 (55)	16 (52)		127 (49)	86 (47)	24 (55)	17 (53)	
Male	169 (51)	136 (53)	18 (45)	15 (48)		132 (51)	97 (53)	20 (45)	15 (47)	
Status at last follow-up, *n* (%)					<.001[b]					.073[b]
Alive with metastases	11 (3)	0 (0)	2 (5)	9 (29)		32 (12)	18 (10)	8 (18)	6 (19)	
Dead of metastases	319 (97)	259 (100)	38 (95)	22 (71)		227 (88)	165 (90)	36 (82)	26 (81)	
Age, median (IQR, range), y										
Primary tumor	65, (56–74), (18–92)	66, (57–75), (18–92)	59, (54–71), (28–82)	55, (47–67), (27–86)	<.001[b]	61, (53–68), (19–88)	63, (55–69), (19–88)	60, (49–68), (33–81)	54, (44–65), (25–76)	.001[b]
Metastatic disease	68, (59–77), (20–95)	69, (59–78), (20–95)	63, (59–74), (31–94)	62, (54–70), (33–90)	.003[b]	65, (57–72), (28–91)	66, (59–72), (28–91)	64, (55–72), (34–84)	58, (49–69), (38–80)	.018[b]
Death	69, (61–78), (22–97)	70, (61–78), (22–96)	66, (61–76), (34–97)	68, (59–76), (39–94)	.36[b]	66, (59–73), (29–92)	67, (59–73), (29–92)	66, (58–75), (37–86)	65, (55–75), (42–85)	.83[b]
Primary tumor extent, *n* (%)					.18[b]					.88[b]
Limited to choroid	179 (54)	138 (53)	20 (50)	21 (68)		120 (46)	89 (49)	17 (39)	14 (44)	
Ciliary body involvement	129 (39)	101 (39)	19 (48)	9 (29)		45 (17)	30 (16)	10 (23)	5 (16)	
Extraocular extension	22 (7)	20 (8)	1 (3)	1 (3)		10 (4)	9 (5)	1 (2)	0 (0)	
Unknown	0 (0)	0 (0)	0 (0)	0 (0)		84 (32)	55 (30)	16 (36)	13 (41)	
TNM size category, *n* (%)					.99[c]					.99[c]
T1	29 (9)	22 (8)	3 (8)	4 (13)		14 (5)	5 (3)	4 (9)	5 (16)	
T2	70 (21)	52 (20)	11 (28)	7 (23)		55 (21)	38 (21)	10 (23)	7 (22)	
T3	124 (38)	91 (35)	19 (48)	14 (45)		69 (27)	56 (31)	8 (18)	5 (16)	
T4	107 (32)	94 (36)	7 (18)	6 (19)		29 (11)	23 (13)	4 (9)	2 (6)	
Not staged	0 (0)	0 (0)	0 (0)	0 (0)		92 (36)	61 (33)	18 (41)	13 (41)	

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TABLE 1. (*continued*)

Variable	Building dataset (N = 330)					Validation dataset (N = 259)				
	All patients N = 330 (100%)	Short-term survival <25 mo N = 259 (78%)	Intermediate-term survival 25–42 mo N = 40 (12%)	Long-term survival >42 mo N = 31 (9%)	*P*-value for trend	All patients N = 259 (100%)	Short-term survival <25 mo N = 183 (71%)	Intermediate-term survival 25–42 mo N = 44 (17%)	Long-term survival >42 mo N = 32 (12%)	*P*-value for trend
TNM stage, *n* (%)					.95[c]					.97[c]
I	28 (8)	21 (8)	3 (8)	4 (13)		12 (5)	5 (3)	2 (5)	5 (16)	
IIA	60 (18)	46 (18)	8 (20)	6 (19)		47 (18)	30 (16)	11 (25)	6 (19)	
IIB	65 (20)	49 (19)	7 (18)	9 (29)		55 (21)	46 (25)	5 (11)	4 (13)	
IIIA	86 (26)	64 (25)	14 (35)	8 (26)		36 (14)	28 (15)	6 (14)	2 (6)	
IIIB	52 (16)	46 (18)	4 (10)	2 (6)		12 (5)	9 (5)	1 (2)	2 (6)	
IIIC	8 (2)	8 (3)	0 (0)	0 (0)		1 (0)	1 (1)	0 (0)	0 (0)	
IV	31 (9)	25 (10)	4 (10)	2 (6)		6 (2)	5 (3)	1 (2)	0 (0)	
Not staged	0 (0)	0 (0)	0 (0)	0 (0)		90 (35)	59 (32)	18 (41)	13 (41)	
DMFI, median (IQR, range), mo	27, (13–52), (-1–265)	25, (12–46), (-1–265)	27, (15–60), (-1–160)	54, (35–96), (-1–169)	<.001[b]	30, (14–60), (-2–338)	26, (13–49), (-2–287)	43, (16–86), (0–271)	50, (22–96), (1–338)	<.001[b]
DMFI tertiles, *n* (%)					<.001[c]					.001[c]
<19 mo	110 (33)	93 (36)	15 (38)	2 (6)		87 (34)	68 (37)	13 (30)	6 (19)	
≥19–<42 mo	110 (33)	92 (36)	11 (28)	7 (23)		77 (64)	60 (33)	9 (20)	8 (25)	
≥42 mo	110 (33)	74 (29)	14 (35)	22 (71)		94 (36)	54 (30)	22 (50)	18 (56)	
Unknown	0 (0)	0 (0)	0 (0)	0 (0)		1 (0)	1 (1)	0 (0)	0 (0)	
DMFI, *n* (%)[d]					.007[c]					.059[c]
0–6 mo	32 (10)	25 (10)	5 (13)	2 (6)		28 (11)	24 (13)	3 (7)	1 (3)	
6–12 mo	33 (10)	31 (12)	2 (5)	0 (0)		18 (7)	13 (7)	2 (5)	3 (9)	
12–24 mo	77 (23)	65 (25)	11 (28)	1 (3)		58 (22)	42 (23)	11 (25)	5 (16)	
>24 mo	188 (57)	138 (53)	22 (55)	28 (90)		154 (59)	103 (56)	28 (64)	23 (72)	
Unknown	0 (0)	0 (0)	0 (0)	0 (0)		1 (0)	1 (1)	0 (0)	0 (0)	
DMFI, *n* (%)[e]					<.001[c]					.007[c]
<24 mo	142 (43)	121 (47)	18 (45)	3 (10)		104 (40)	79 (43)	16 (36)	9 (28)	
24–42 mo	77 (23)	63 (24)	8 (20)	6 (19)		59 (23)	48 (26)	6 (14)	5 (16)	
>42 mo	111 (34)	75 (29)	14 (35)	22 (71)		95 (37)	55 (30)	22 (50)	18 (56)	
Unknown	0 (0)	0 (0)	0 (0)	0 (0)		1 (0)	1 (1)	0 (0)	0 (0)	

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TABLE 1. (*continued*)

Variable	Building dataset (N = 330)					Validation dataset (N = 259)				
	All patients N = 330 (100%)	Short-term survival <25 mo N = 259 (78%)	Intermediate-term survival 25–42 mo N = 40 (12%)	Long-term survival >42 mo N = 31 (9%)	*P*-value for trend	All patients N = 259 (100%)	Short-term survival <25 mo N = 183 (71%)	Intermediate-term survival 25–42 mo N = 44 (17%)	Long-term survival >42 mo N = 32 (12%)	*P*-value for trend
DMFI, *n* (%)[f]					<.001[c]					<.001[c]
<60 mo	262 (79)	216 (83)	30 (75)	16 (52)		195 (75)	150 (82)	27 (61)	18 (56)	
≥60 mo	68 (21)	43 (17)	10 (25)	15 (48)		63 (24)	32 (17)	17 (39)	14 (44)	
Unknown	0 (0)	0 (0)	0 (0)	0 (0)		1 (0)	1 (1)	0 (0)	0 (0)	
DMFI, *n* (%)[f]					.012[c]					<.001[c]
<69 mo	268 (81)	217 (84)	32 (80)	19 (61)		204 (79)	156 (85)	29 (66)	19 (59)	
≥69 mo	62 (19)	42 (16)	8 (20)	12 (39)		55 (21)	26 (14)	15 (34)	13 (41)	
Unknown	0 (0)	0 (0)	0 (0)	0 (0)		1 (0)	1 (1)	0 (0)	0 (0)	
Symptoms from metastases, *n* (%)					<.001[b]					.007[b]
No	212 (64)	147 (57)	35 (88)	30 (97)		160 (62)	104 (57)	31 (70)	25 (78)	
Yes	111 (34)	106 (41)	4 (10)	1 (3)		92 (36)	74 (40)	12 (27)	6 (19)	
Unknown	7 (2)	6 (2)	1 (3)	0 (0)		7 (3)	5 (3)	1 (2)	1 (3)	
ECOG performance status, *n* (%)					<.001[c]					.011[c]
0–1	221 (67)	154 (59)	37 (93)	30 (97)		160 (62)	104 (57)	31 (70)	25 (78)	
2	39 (12)	37 (14)	2 (5)	0 (0)		90 (35)	72 (39)	12 (27)	6 (19)	
3–4	64 (19)	63 (24)	0 (0)	1 (3)		2 (1)	2 (1)	0 (0)	0 (0)	
Unknown	6 (2)	5 (2)	1 (3)	0 (0)		7 (3)	5 (3)	1 (2)	1 (3)	
AP level, *n* (%)					<.001[c]					.17[c]
<1.0 x UNL	179 (54)	129 (50)	25 (63)	25 (81)		96 (37)	63 (34)	17 (39)	16 (50)	
1.0–2.0 x UNL	52 (16)	45 (17)	5 (13)	2 (6)		7 (3)	6 (3)	1 (2)	0 (0)	
>2.0 x UNL	64 (19)	64 (27)	0 (0)	0 (0)		5 (2)	4 (2)	1 (2)	0 (0)	
Unknown	35 (11)	21 (8)	10 (25)	4 (13)		151 (58)	110 (60)	25 (57)	16 (50)	
LD level, *n* (%)					<.001[c]					.001[c]
<1.0 x UNL	86 (26)	57 (22)	14 (35)	15 (48)		91 (35)	52 (28)	21 (48)	18 (56)	
1.0–2.0 x UNL	75 (23)	62 (24)	9 (23)	4 (13)		33 (13)	26 (14)	5 (11)	2 (6)	
>2.0 x UNL	48 (15)	47 (18)	1 (3)	0 (0)		14 (5)	13 (7)	1 (2)	0 (0)	
Unknown	121 (37)	93 (36)	16 (40)	12 (39)		121 (47)	92 (50)	17 (39)	12 (38)	
LDLM, median (IQR, range), mm	30, (20–55), (2–270)	35, (20–60), (7–270)	24, (16–34), (2–112)	20, (16–27), (2–84)	<.001[b]	28, (17–45), (8–150)	30, (20–53), (8–150)	25, (13–43), (8–60)	20, (15–27), (9–47)	<.001[b]

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TABLE 1. (*continued*)

Variable	Building dataset (N = 330)					Validation dataset (N = 259)				
	All patients N = 330 (100%)	Short-term survival <25 mo N = 259 (78%)	Intermediate-term survival 25–42 mo N = 40 (12%)	Long-term survival >42 mo N = 31 (9%)	*P*-value for trend	All patients N = 259 (100%)	Short-term survival <25 mo N = 183 (71%)	Intermediate-term survival 25–42 mo N = 44 (17%)	Long-term survival >42 mo N = 32 (12%)	*P*-value for trend
TNM M-category, *n* (%)					<.001[c]					<.001[c]
M1a (<30 mm)	158 (48)	106 (41)	27 (68)	25 (81)		86 (33)	49 (27)	18 (41)	19 (59)	
M1b (30–80 mm)	102 (31)	89 (34)	9 (23)	4 (13)		46 (18)	3 (20)	9 (20)	1 (3)	
M1c (>80 mm)	40 (12)	37 (14)	2 (5)	1 (3)		11 (4)	11 (6)	0 (0)	0 (0)	
Unknown	30 (9)	27 (10)	2 (5)	1 (3)		116 (45)	87 (48)	17 (39)	12 (38)	
Limited to the liver, *n* (%)					.92[b]					.73[b]
No	102 (31)	81 (31)	11 (28)	10 (32)		53 (20)	37 (20)	9 (20)	7 (22)	
Yes	228 (69)	178 (69)	29 (73)	21 (68)		122 (47)	82 (45)	22 (50)	18 (56)	
Unknown	0 (0)	0 (0)	0 (0)	0 (0)		84 (32)	64 (35)	13 (30)	7 (22)	
1st line treatment, *n* (%)					.023[b]					.22[b]
BSC	107 (32)	97 (37)	6 (15)	4 (13)		9 (3)	9 (5)	0 (0)	0 (0)	
Surgery	20 (6)	10 (4)	3 (8)	7 (23)		17 (7)	6 (3)	5 (11)	6 (19)	
Other active	203 (62)	152 (59)	31 (78)	20 (65)		145 (56)	102 (56)	25 (57)	18 (56)	
Unknown	0 (0)	0 (0)	0 (0)	0 (0)		88 (34)	66 (36)	14 (32)	8 (25)	
Lines of treatment, *n* (%)					<.001[c]					.10[c]
1	204 (62)	182 (70)	10 (25)	12 (39)		33 (13)	21 (11)	6 (14)	6 (19)	
2	60 (18)	45 (17)	7 (18)	8 (26)		67 (26)	51 (28)	9 (20)	7 (22)	
≥3	66 (20)	32 (12)	23 (58)	11 (35)		49 (19)	24 (13)	15 (34)	10 (31)	
Unknown	0 (0)	0 (0)	0 (0)	0 (0)		110 (42)	87 (48)	14 (32)	9 (28)	

AP = alkaline phosphatase; BSC = best supportive care; DMFI = distant metastasis-free interval; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; LD = lactate dehydrogenase; LDLM = largest diameter of the largest metastasis; mo = months; N/A = not applicable; TNM = tumor, node, metastasis; UNL = upper normal limit; y = years.

[a] Binomial test, p=.49 in both datasets. The expected gender ratios were retrieved from.[46]

[b] Nonparametric test for trend

[c] Jonckheere–Terpstra test

[d] Categorized as applied in Mariani and associates.[20]

[e] Categorized as applied in Eskelin and associates.[22]

[f] Categorized by assumed genetic changes as in Yavuzyigitoglu and associates.[19]

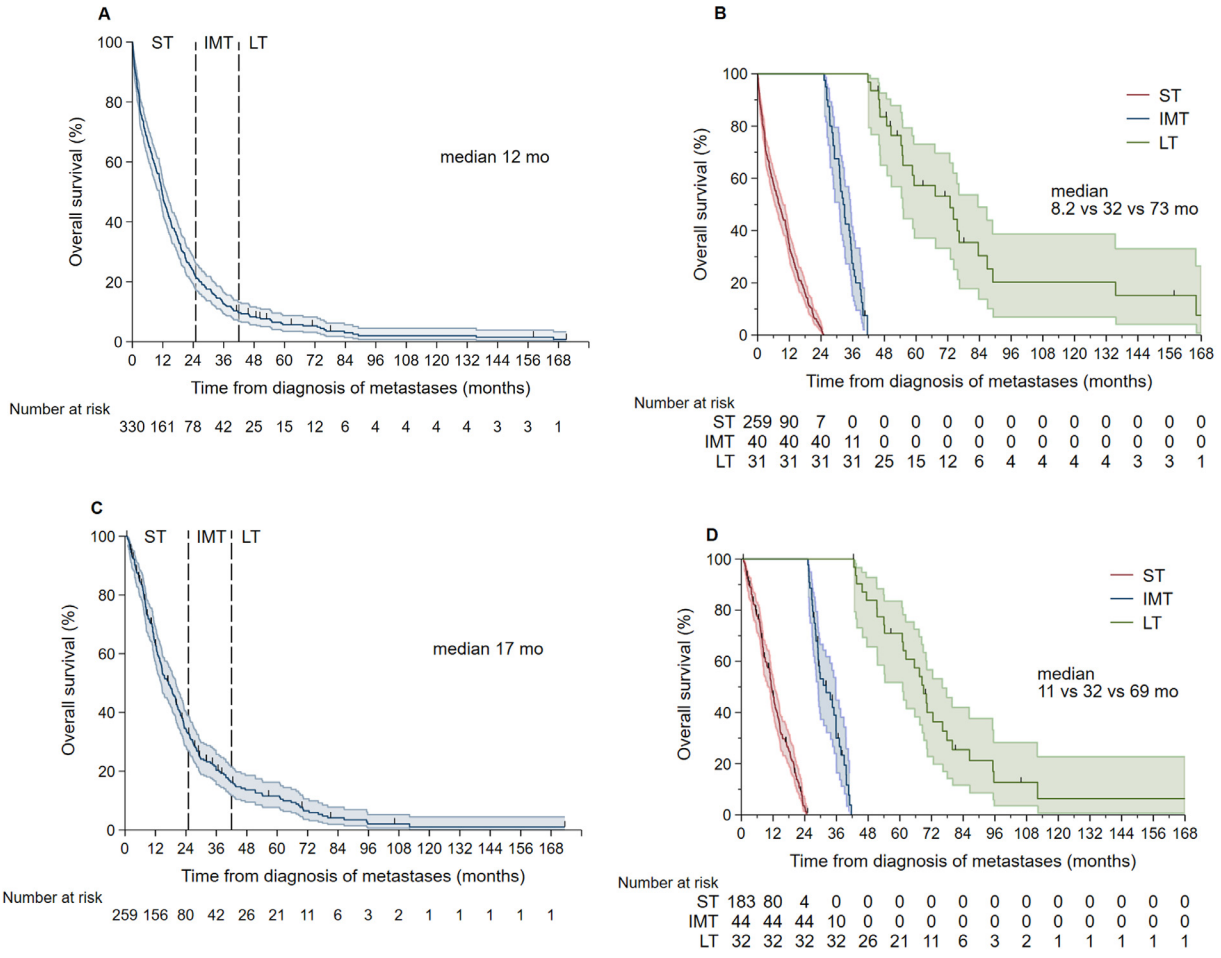

FIGURE 1. Kaplan-Meier estimates of overall survival (OS) for patients with newly diagnosed metastatic choroidal and ciliary body melanoma. A. OS for the entire model building cohort. B. OS for the short-term (ST), intermediate term (IMT; conditional to surviving ≥25 months), and long-term (LT; conditional to surviving ≥42 months) survival cohorts. C. OS for the entire validation cohort. D. OS for the 3 subcohorts. Median OS is given. Shaded areas indicate 95% confidence intervals and ticks show censored observations.

cohorts (4% vs 8% vs 23%, respectively) underwent surgical first-line treatment of metastases. Six (15%) and 4 (13%) patients in the IMT and LT cohorts received only BSC. In the LT cohort, 11 (35%) patients received ≥3 lines of treatment, and a median of 1, 3, and 2 lines were administered in the ST, IMT, and LT cohorts, respectively.

Validation dataset

The median OS after metastasis of the 259 patients (Table 1) was 17 months (range 0.7-173 months; Figure 1, C), and 183 (71%), 44 (17%), and 32 (12%) patients fell into the ST, IMT, and LT cohorts, respectively (Figure 1, D). In 3 patients, metastases were diagnosed before the primary CCBM (range 5-22 days); all of them were in the ST cohort. Thirty-two patients were alive with metastases, 8 and 6 of them in the LT cohort, of which they formed 18% and 19%, respectively.

Like in the building dataset, the age at diagnosis of the primary CCBM (median 63 vs 60 vs 54 years; $P = .001$ nonparametric test for trend) and its metastases (median 66 vs 64 vs 58 years, $P = .018$) decreased and the DMFI correspondingly increased (median 26 vs 43 vs 50 months, $P < .001$) by OS cohort (Table 1). No IMT or LT cohort survivor represented TNM stage IIIC, but 1 survivor in the IMT cohort had stage IV disease. However, 35% of the patients had not been staged.

The percentage of asymptomatic patients likewise increased by OS cohort from 57% to 78% ($P = .007$ nonparametric test for trend), but 12 (27%) and 6 (19%) patients in the IMT and LT cohorts, respectively, represented PS 2 ($P = .011$ across all categories, nonparametric test for trend; Table 1). Also identical with the building dataset, neither AP nor LD level exceeded 2.0 times the UNL in the LT cohort, but both did so in 1 (2%) patient in the

TABLE 2. Bivariable ordinal logistic regression of overall survival in newly diagnosed metastatic choroidal and ciliary body melanoma in a listwise deleted model building dataset.
Final ordinal bivariable logistic regression over short-, intermediate-, and long-term overall survival cohorts (<25, 25–<42, and ≥42 months, respectively), restricted to 226 patients with complete data for all variables included in all three models and conditional to the serum and plasma alkaline phosphatase and lactate dehydrogenase levels being ≤2 x upper normal limit. *P* values <.10 are highlighted in bold.

Variable	Odds ratio	Standard Error	χ^2	*P* value	95% confidence interval
Bivariable analysis					
Model 1: –2 log likelihood = 168.84; LR chi2(4) = 29.22; n=226					
DMFI, tertiles					
<19 mo	Reference				
≥19–<42 mo	1.59	0.65	1.32	.25	0.72–3.52
≥42 mo	4.64	1.76	16.5	**<.001**	2.21–9.74
Age at diagnosis of metastases, tertiles					
>72 y	Reference				
≥60– ≤72 y	1.66	0.61	1.93	.17	0.81–3.42
<60 y	3.23	1.20	10.0	**.002**	1.57–6.68
Model 2: – 2 log likelihood = 168.78; LR chi2(3) = 29.34; n=226					
DMFI, tertiles					
<19 mo	Reference				
≥19–<42 mo	1.46	0.59	0.90	.35	0.66–3.23
≥42 mo	4.09	1.54	14.0	**<.001**	1.96–8.54
Symptoms from metastases					
Yes	Reference				
No	4.19	2.12	8.00	**.005**	1.55–11.3
Model 3: –2 log likelihood = 168.06; LR chi2(3) = 30.77; n=226					
DMFI, tertiles					
<19 mo	Reference				
≥19–<42 mo	1.61	0.65	1.37	.24	0.73–3.56
≥42 mo	4.29	1.62	14.9	**<.001**	2.05–8.99
TNM M1-category					
M1b–c	Reference				
M1a	3.05	1.04	10.8	**.001**	1.57–5.95
Univariable analysis; for comparison					
Model 4: –2 log likelihood = 173.95; LR chi2(2) = 19.00; n=226					
DMFI, tertiles					
<19 mo	Reference				
≥19–<42 mo	1.49	.59	1.02	.31	0.69–3.26
≥42 mo	4.37	1.62	15.8	**<.001**	2.11–9.03

IMT cohort, and the levels were unknown for 50% and 38% of patients, respectively. The median LDLM also decreased with increasing OS (30 vs 25 vs 20 mm, $P < .001$, Jonckheere-Terpstra test), and no patients in the IMT and LT cohorts had a metastasis >80 mm (M1c; $P < .001$ across all 3 M1 categories, Jonckheere-Terpstra test); LDLM was not recorded in 45% of patients.

The percentage of patients with only hepatic metastases was comparable by OS cohort (45% vs 50% vs 56%, $P = .73$; unknown for 32% overall). A larger percentage of patients in the LT cohort was managed with first-line surgery (3% vs 11% vs 19%; not recorded for 34% of patients) and none received only BSC. The median number of treatment lines was 2 in each cohort, but unknown for 42% of patients.

• **PREDICTORS OF LT SURVIVAL:** Characteristics that precluded inclusion in the LT cohort in the building and validation datasets were AP or LD level >2.0 times the UNL. Consequently, we modeled LT OS after metastasis conditional to not being in these subgroups. Because no patients in the validation dataset had a M1c metastasis, we dichotomized to M1a vs. M1b-c. For similar reasons, PS was dichotomized to 3-4 vs 0-2. We did not consider lines of treatment as an explanatory variable because it depends on

TABLE 3. Bivariable ordinal logistic regression of overall survival in newly diagnosed metastatic choroidal and ciliary body melanoma in the full model validation dataset.
Final ordinal bivariable logistic regression models over short-, intermediate-, and long-term overall survival cohorts (<25, 25–<42, and ≥42 months, respectively), conditional to the serum and plasma alkaline phosphatase and lactate dehydrogenase levels being ≤2 x upper normal limit. *P* values <.10 are highlighted in bold.

Variable	Odds ratio	Standard Error	χ^2	*P* value	95% confidence interval
Bivariable analysis					
Model 1: –2 log likelihood = 189.16; LR chi2(4) = 20.14; n=234					
DMFI, tertiles					
<19 mo	Reference				
≥19–<42 mo	1.06	0.41	0.02	.89	0.49–2.25
≥42 mo	2.94	1.00	10.0	**.002**	1.51–5.74
Age at diagnosis of metastases, tertiles					
>72 y	Reference				
≥60– ≤72 y	1.04	0.39	0.01	.92	0.50–2.19
<60 y	2.18	0.83	4.24	**.040**	1.04–4.60
Model 2: – 2 log likelihood = 183.87; LR chi2(3) = 19.55; n=241					
DMFI, tertiles					
<19 mo	Reference				
≥19–<42 mo	1.28	0.50	0.41	.52	0.60–2.76
≥42 mo	3.28	1.14	11.7	**.001**	1.66–6.49
Symptoms from metastases					
Yes	Reference				
No	2.08	0.68	5.02	**.025**	1.10–3.93
Model 3: –2 log likelihood = 104.65; LR chi2(3) = 17.64; n=127					
DMFI, tertiles					
<19 mo	Reference				
≥19–<42 mo	1.64	0.84	0.92	.34	0.60–4.48
≥42 mo	3.31	1.52	6.76	**.009**	1.34–8.15
TNM M1-category					
M1b–c	Reference				
M1a	4.29	1.96	10.1	**.001**	1.75–10.50

DMFI = distant metastasis-free interval; mo = months; TNM = tumor, node, metastasis; y = years.

the length of survival and is not known when treatment begins.

Univariable analysis

Considering the 3 pairwise comparisons (ST vs LT, IMT vs LT, and ST-to-IMT vs LT) both from Firth LR and from LR conditional to AP and LD being ≤2 times the UNL, and the similarly conditional ordinal LR, only DMFI consistently predicted LT survival in all of them (OR 1.06-1.09 for each 6-month increase; $P < .001$-.018; Supplemental Tables 1-3). When divided in tertiles (<19 vs 19-<42 vs ≥42 months), the second tertile (ORs 3.03, 4.04, and 3.14, $P = .091$-.14 Firth LR) and the third tertile (ORs 11.3, 9.62, and 11.0, $P < .001$-.003 Firth LR) estimates remained consistent in all 3 binary analyses (Supplemental Tables 1 and 2). As mentioned, we also considered 4 previously applied cutpoints to categorize DMFI.[19–22] Our analysis supported dichotomizing at 42 months (OR 6.70-9.23, $P < .001$-.004 in the 6 pairwise comparisons), which serendipitously coincided with the third tertile, compared with a DMFI cutpoint at 60 or 69 months (OR 2.45-4.68). We could not properly evaluate published cutpoints earlier than 24 months, because only 3 patients in the LT cohort had a shorter DMFI than 3 months.

In all pairwise regressions except for IMT vs LT, and also in ordinal LR, 4 additional variables were associated with LT survival and were considered robust predictors (Supplemental Tables 1-3): age at diagnosis of metastases, whether modeled as a continuous variable or divided in tertiles (IMT vs LT, OR 1.20-1.80, $P = .30$-.40; other pairwise comparisons, OR 1.36-4.06, $P = .006$-.093; ordinal, OR 1.42-2.99, $P = .001$-.069), absence of symptoms from metastases (IMT vs LT, OR 2.58-3.43, $P = .28$-.33; other pairwise comparisons, OR 9.87-14.7, $P = .001$-.026; ordinal, OR 5.20, $P = .001$), normal LD level (IMT vs LT, OR 2.41-2.49, $P = .17$-.21; other pairwise comparisons, OR 3.43-6.68,

TABLE 4. Bivariable ordinal logistic regression of overall survival in newly diagnosed metastatic choroidal and ciliary body melanoma in a listwise deleted model validation dataset. Final ordinal bivariable logistic regression models over short-, intermediate-, and long-term overall survival cohorts (<25, 25–<42, and ≥42 months, respectively), restricted to 125 patients with complete data for all variables included in all three models and conditional to serum and plasma alkaline phosphatase and lactate dehydrogenase levels being ≤2 x upper normal limit. *P* values <.10 are highlighted in bold.

Variable	Odds ratio	Standard Error	χ^2	*P* value	95% confidence interval
Bivariable analysis					
Model 1: –2 log likelihood = 106.48; LR chi2(4) = 9.38; n=125					
DMFI, tertiles					
<19 mo	Reference				
≥19–<42 mo	1.58	0.81	0.79	.38	0.58–4.34
≥42 mo	3.45	1.60	7.13	**.008**	1.39–8.54
Age at diagnosis of metastases, tertiles					
>72 y	Reference				
≥60– ≤72 y	0.68	0.34	0.58	.45	0.26–1.83
<60 y	1.24	0.62	0.18	.67	0.46–3.31
Model 2: – 2 log likelihood = 106.09; LR chi2(3) = 10.17; n=125					
DMFI, tertiles					
<19 mo	Reference				
≥19–<42 mo	1.63	0.83	0.92	.34	0.60–4.44
≥42 mo	3.39	1.55	7.08	**.008**	1.38–8.32
Symptoms from metastases					
Yes	Reference				
No	2.01	0.87	2.62	.11	0.86–4.69
Model 3: –2 log likelihood = 102.17; LR chi2(3) = 18.01; n=125					
DMFI, tertiles					
<19 mo	Reference				
≥19–<42 mo	1.83	0.96	1.35	.25	0.66–5.09
≥42 mo	3.80	1.79	8.01	**.005**	1.51–9.55
TNM M1-category					
M1b–c	Reference				
M1a	4.05	1.86	9.24	**.002**	1.64–9.97

DMFI = distant metastasis-free interval; mo = months; TNM = tumor, node, metastasis; y = years.

P = .001-.036; ordinal, OR 2.30, *P* = .028), and LDLM either modeled as a continuous variable (IMT vs LT, OR 1.04-1.07, *P* = .55-.75; other pairwise comparisons, OR 1.33-1.41, *P* < .004-.033; ordinal, OR 1.30, *P* = .001) or dichotomized according to TNM M1a vs M1b-c (IMT vs LT, OR 1.85-1.94, *P* = .26-.32; other pairwise comparisons, OR 3.76-5.51, *P* < .004-.009; ordinal, OR 3.09, *P* = .001).

Bivariable analysis

We next built ordinal LR models in which our most robust predictor, DMFI, modeled in tertiles and alternatively as dichotomized to ≤42 vs >42 months, was paired with the additional 4 variables considered robust based on our univariable regressions (Supplemental Table 4). Any one of the latter independently predicted higher odds of being more likely to survive longer (IMT or LT): age <60 years (OR 3.33 and 3.60, *P* = .001 and < .001, respectively), no symptoms from metastases (OR 4.82 and 4.97, *P* = .002 and .001, respectively), normal LD level (OR 2.76 and 2.25, *P* = .012 and < .036, respectively), and TNM M1a (OR 2.94 and 3.25; *P* = .001 and < .001, respectively). In all these models, DMFI ≥42 months remained a robust predictor of being more likely to survive longer especially when modeled in tertiles (OR 3.90-5.12, *P* < .001) compared with the dichotomized model (OR 2.55-3.20, *P* < .001-.014).

None of these 3 models, limited listwise to patients who had DMFI and the 3 additional variables available (Table 2), was preferred to the other 2 (difference in −2 log likelihood 0.06 and 0.78, *P* = .94, and .46, deviance test, model 1 vs 2 and model 1 vs 3, respectively, df = 2), whereas each of them should be preferred to the simpler model with DMFI only (difference in −2 log likelihood 11.7-10.22, *P* < .003-.017).

• **MODEL VALIDATION:** DMFI ≥42 months (OR 2.94-3.31, *P* = .001-.009) in all 3 final bivariable models based

on the building dataset predicted higher odds of being more likely to survive longer (IMT or LT) independently with age <60 years (OR 2.18; $P = .040$), experiencing no symptoms from metastases (OR 2.08; $P = .025$), and TNM M1a (OR 4.29; $P = .001$) also in the validation dataset (Table 3). When limited only to patients who had DMFI and the 3 additional variables available (Table 4), the model with TNM M1a (OR 4.05; $P = .002$) retained its relevance better than the other 2 models (difference in −2 log likelihood 4.31, and 3.92, $P = .013$ and .005, model 1 vs 3 and model 2 vs 3, respectively, df = 2, and 1, respectively).

DISCUSSION

None of the patients with metastatic uveal melanoma who survived LT (≥42 months) had a serum or plasma AP or LD >2.0 times the UNL in either our building or validation dataset. A level exceeding >2.0 times the UNL thus appears to predict a very small likelihood of LT survival. Our comprehensive study was based on retrospective data like previous analyses (Supplemental Table 5) but differed in being nationwide in Finland. Even in the IMT cohort (25-<42 months), only in 1 patient in the validation dataset and 0 patients in the building dataset did AP or LD exceed 2 times the UNL. We presume, however, that in the long run this rule is unlikely to hold true in every patient and, indeed, 11% and 37% of patients in the building and 58% and 47% of patients in the validation dataset did not have their AP or LD level recorded, respectively. Nevertheless, AP or LD >2 times the UNL seems to make LT survival unlikely and even IMT survival rare. The ensuing perfect separation forced us to model other determinants conditional to AP and LD being ≤2 times the UNL, and to analyze AP and LD only as being either normal or exceeding their UNL.

DMFI was in our building dataset the most robust predictor of IMT and LT survival, being the only one that was significant in every pairwise and ordinal regression strategy, and the only one that was able to predict IMT vs LT survival. Moreover, it returned a meaningfully large OR estimate in all pairwise cohort comparisons. This also held true when we applied nonconditional Firth LR that can lessen bias in small imbalanced datasets: OR was 3.03-4.04 when DMFI was 19-<42 months compared with <19 months, and 9.62-11.0 when DMFI was ≥42 months. DMFI is included in 2 nomograms that are available for staging of newly diagnosed metastatic uveal melanoma.[4,16,20]

It is intriguing to compare age at diagnosis of the primary CCBM and its metastases, DMFI, and the OS after metastasis. In the LT cohort, the intervals from the primary tumor, at a relatively young age (median 55 years), to metastasis (median 54 months; at the median age 62 years) and from metastasis to death (≥42 months, by definition) are both the longest, suggesting an early-onset, slowly growing tumor over time. This could be because of favorable tumor genetics and biology, maintained in the metastases, more vigorous host defenses in younger patients, or both. Indeed, *SF3B1* pathogenic variants have been found in relatively younger patients[31] and they have been associated with longer DMFI and slower growing metastases.[32] In the ST cohort, age both at diagnosis of the primary tumor (median 66 years) and metastases (median 69 years) is the oldest and both DMFI (median 25 months) and survival are the shortest (<25 months, by definition), in effect a late-onset, rapidly progressing tumor, suggesting *BAP1* pathogenic variants.[32]

The IMT cohort does not suggest an equally simple hypothesis. The age at diagnosis of the primary is intermediate (median 59 years) but at the time of metastasis (median age 63 years) comparable to that in the LT cohort, and despite the DMFI (median 27 months) being instead comparable to that in the ST cohort, the patients still survive longer (25-<42 months, by definition). One possibility is that the primary CCBM in the IMT cohort could, at least in part, correspond to a subset of recently identified *SF3B1*-mutated tumors that have a shorter than average DMFI and are larger than average.[33] A later diagnosis of the primary and, therefore, a relatively larger tumor with an apparently shorter subsequent DMFI, but a similar age than in the LT cohort when metastases are diagnosed, combined with relatively slowly progressing metastases and relatively longer OS because the driver gene is *SF3B1* could explain our observations in the IMT cohort. Of course, other molecular genetic differences could also underlie these observations.[33]

We believe that our results support the hypothesis that a long DMFI could reflect *SF3B1* driver mutations,[19] but they also support the observation that a shorter DMFI would not necessarily exclude one.[33] This could explain why DMFI dichotomized at 60 or 69 months did not provide a working surrogate for driver genes in LT survivors.[27] It should also be appreciated that DMFI is influenced by lead time bias (smaller primary tumors can be serendipitously diagnosed early) and by surveillance strategy (earlier detection of metastases) irrespectively of the underlying driver mutation,[6,8,11,16,20,34,35] and that not only *SF3B*1 but also *EIF1AX* pathogenic variants lead to less frequent, later metastases from uveal melanoma.[19,21,23–26] Finally, we were intrigued by the observation that in all 3 cohorts the median age at death converged to within 4 years of each other.

DMFI paired with 4 additional variables with approximately equally large ORs—age at the time of metastasis <60 years (OR 3.23), no symptoms from metastases (OR 4.19), TNM M1a equal to LMLD <30 mm (OR 3.05), and normal serum or plasma LD level (OR 2.94)—independently predicted higher odds of being more likely to survive longer (IMT or LT—both of which might reflect presence of *SF3B1* driver mutation as reasoned above). The first 3 bivariable models fitted the data equally well, but we had incomplete information regarding LD and could not test the fourth model. Moreover, our dataset did not have enough IMT and LT survivors to proceed to trivari-

able modeling. Age is quite likely another surrogate for *SF3B1* pathogenic variants as they occur in younger patients.[31] The other 3 predictors are obviously interrelated: smaller metastases are less likely to elevate LD and to cause symptoms. Of them, LDLM likely most directly reflects the metastatic process, although it might also in part be yet another surrogate for more favorable driver mutations. LDLM or an equivalent criterion for the extent of metastases is already in some form part of all staging systems for newly diagnosed uveal melanoma.[4,16,20,36]

The 3 final models also predicted LT survival in the external validation dataset, in which the percentage of IMT (12% and 17%) and LT (9% vs 12%) survivors also were comparable. The datasets also differed somewhat from one another, however, because the validation set was more referral-based than population-based. Thus, no patients in the validation set were managed with BSC compared with 32% in the building dataset—a percentage that is comparable to other nationwide series[37]—whereas surgery was more often offered for metastases. This was reflected in the longer than average median OS of 17 months in the validation dataset compared with comprehensive meta-analyses.[2,3] It is reassuring that our model also fitted data that reflected the experience in a single center, because this suggests wider applicability. On the other hand, the national building dataset allowed some interesting observations, such that LT survival was compatible with metastases at the time of diagnosis of the primary CCBM in 2 patients as well as with receiving no active cancer treatment in 4 patients.

Our results confirm several observations made in a recent single-center analysis of a series of 99 Spanish patients of whom 8 (8%) survived ≥42 months.[8] Multivariable logistic regression identified age <65 years (OR 5.14), normal LD (OR 4.38), and a smaller LDLM (OR 1.04 for each 1-mm decrease) as predictors of LT survival, defined as OS >12 months (Supplemental Table 5). The notable exception was that DMFI did not enter their multivariable model. The reason for this may be the different cutpoint used for LT survival (12 months), which is the median OS in comprehensive meta-analyses.[2,3] Indeed, DMFI was not an independent significant predictor of OS in a general multivariable analysis of our national dataset either.[6,7] Age <60 years was also associated with survival in 1 study in which an unusually large percentage, 22% of patients, were alive at 4 years.[10] PS, which is included in all 3 staging systems for newly diagnosed metastatic uveal melanoma, did not quite fulfill our criterion for robustness.[4,16,20,36] It also did not enter the multivariable model in the Spanish series,[8] despite a univariable OR of 2.94, and was not significant in a German multicenter study.[12] On the other hand, our analysis provided no evidence that sex would be associated with LT survival.[10] Interestingly, the TNM stages of the primary tumors in our 3 OS cohorts also were comparable.

No LFT is a sensitive criterion for early detection of metastases during surveillance of patients with uveal melanoma—their sensitivity ranges from 7%-19%[38,39]—but they tend to become abnormal soon when metastatic burden has reached a sufficiently advanced stage.[38,40] Elevated AP and LD can derive from other causes than metastases, especially from bone disorder, muscle injury, and liver disease.[41] The 2 former ones were not observed, and although a few patients had preexisting liver disease, the LFT levels typically increased further upon metastasis. The fact that in both our building and validation dataset, LD and AP >2.0 times the UNL never occurred in LT survivors suggests that irrespective of other characteristics, metastases are then too far advanced to allow LT survival. This could be either because the primary tumor had an unfavorable driver mutation (the ST cohort) or because the tumor has progressed after metastasis to acquire a *BAP1* pathogenic variant and loss of heterozygosity, or other additional driver mutations to allow faster growth, perhaps in only some of the metastases (the IMT and LT cohorts).[24,42] LD is an independent prognostic variable even in patients with metastatic cutaneous melanoma that far less frequently affects the liver.[43] LD is part of 2 of the 3 staging tools for metastatic uveal melanoma,[4,16,20] and AP is included in the third tool.[22,36] Recently, elevated LD was identified as a prognostic factor for LT survival in a German multicenter study, defined as OS >24 months.[12]

The limitations of our study include its small size especially regarding the cohorts of IMT and LT survivors, limiting our possibilities of categorizing and analyzing some interesting variables or proceeding beyond bivariable analysis. Moreover, the definition of LT survival is not universally defined.[44] Although our patients had progressive metastatic disease, resulting typically in hepatomegaly, wasting, jaundice, and other signs of advanced malignant disease, it is reasonable to presume that any chronic diseases, when present, may have to some extent contributed to the speed of their demise. We were unable to model this effect, which interacts with sex and age, in our retrospective setting. The most important limitation is that we did not have genetic data on the metastases. The genetic landscape of metastatic uveal melanoma is still incompletely defined, but consistent with primary uveal melanoma, the mutational burden of metastases can be low—a median of 2 driver mutations may be observed.[23] Genetic profiling of not only the primary tumor but also of its metastases is likely to become a powerful prognostic and predictive biomarker to be implemented in staging systems and treatment planning for metastatic uveal melanoma.[4] A further reason is that genetic analysis of metastases can reveal not only prognostic but also predictive markers.[45] Strong aspects of our study are that the building dataset was comprehensive, nationwide, and unselected, 97% of patients adhered to a standard surveillance program, and the results were verified using an external independent dataset.

Paying attention to the validated determinants of LT survival in clinical practice has potential to improve counseling of patients with newly diagnosed metastases from uveal

melanoma, guided by our OR estimates. The validated predictors also facilitate preventing overestimation of survival outcomes in nonrandomized trials by helping identify the patients whose baseline characteristics already predict LT survival. International and collaborative biobanking on a large scale would be highly desirable to facilitate research in genetic alterations of prognostic importance in metastatic uveal melanoma.

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REFERENCES

1. Gragoudas ES, Egan KM, Seddon JM, et al. Survival of patients with metastases from uveal melanoma. *Ophthalmology*. 1991;98(3):383–389.
2. Rantala ES, Hernberg M, Kivelä TT. Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis. *Melanoma Res*. 2019;29(6):561–568.
3. Khoja L, Atenafu EG, Suciu S, et al. Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an International Rare Cancers Initiative (IRCI) ocular melanoma study. *Ann Oncol*. 2019;30(8):1370–1380.
4. Rantala ES, Hernberg MM, Piperno-Neumann S, et al. Metastatic uveal melanoma: the final frontier. *Prog Retin Eye Res*. 2022;90:101041.
5. 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.
6. Rantala ES, Kivelä TT, Hernberg MM. Impact of staging on survival outcomes: a nationwide real-world cohort study of metastatic uveal melanoma. *Melanoma Res*. 2021;31(3):224–231.
7. Rantala ES, Hernberg MM, Lundin M, et al. Metastatic uveal melanoma managed with best supportive care. *Acta Oncol*. 2021;60(1):135–139.
8. Lorenzo D, Ochoa M, Piulats JM, et al. Prognostic factors and decision tree for long-term survival in metastatic uveal melanoma. *Cancer Res Treat*. 2018;50(4):1130–1139.
9. Duh EJ, Schachat AP, Albert DM, et al. Long-term survival in a patient with uveal melanoma and liver metastasis. *Arch Ophthalmol*. 2004;122(2):285–287.
10. Rietschel P, Panageas KS, Hanlon C, et al. Variates of survival in metastatic uveal melanoma. *J Clin Oncol*. 2005;23(31):8076–8080.
11. Buzzacco DM, Abdel-Rahman MH, Park S, et al. Long-term survivors with metastatic uveal melanoma. *Open Ophthalmol J*. 2012;6:49–53.
12. Koch EAT, Petzold A, Wessely A, et al. Clinical determinants of long-term survival in metastatic uveal melanoma. *Cancer Immunol Immunother*. 2021;71(6):1467–1477.
13. Kivelä TT, Simpson ER, Grossniklaus HE, et al. Uveal melanoma. In: Amin MB, Edge S, Greene F, et al., eds. *AJCC Cancer Staging Manual* Springer International Publishing; 2017:813–826.
14. Rantala ES, Peltola E, Helminen H, et al. Hepatic ultrasonography compared with computed tomography and magnetic resonance imaging at diagnosis of metastatic uveal melanoma. *Am J Ophthalmol*. 2020;216:156–164.
15. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649–655.
16. 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.
17. Terpstra TJ. The asymptotic normality and consistency of Kendall's test against trend, when ties are present in one ranking. *Indagationes Mathematicae*. 1952;14(3):327–333.
18. Jonckheere AR. A distribution-free k-sample test against ordered alternatives. *Biometrika*. 1954;41(1/2):133–145.
19. Yavuzyigitoglu S, Koopmans AE, Verdijk RM, et al. Uveal melanomas with *SF3B1* mutations: a distinct subclass associated with late-onset metastases. *Ophthalmology*. 2016;123(5):1118–1128.
20. Mariani P, Dureau S, Savignoni A, et al. Development of a prognostic nomogram for liver metastasis of uveal melanoma patients selected by liver MRI. *Cancers (Basel)*. 2019;11(6):863.
21. Grimes J, Shoushtari AN, Orloff M, et al. Clinical characteristics of *SF3B1* mutant (mut) uveal melanoma (UM) and response to immune checkpoint inhibition (ICI). *J Clin Oncol*. 2021;39(15 suppl):9535.
22. Eskelin S, Pyrhönen S, Hahka-Kemppinen M, et al. A prognostic model and staging for metastatic uveal melanoma. *Cancer*. 2003;97(2):465–475.
23. Piperno-Neumann S, Larkin J, Carvajal RD, et al. Genomic profiling of metastatic uveal melanoma and clinical results of a phase I study of the protein kinase C inhibitor AEB071. *Mol Cancer Ther*. 2020;19(4):1031–1039.
24. Shain AH, Bagger MM, Yu R, et al. The genetic evolution of metastatic uveal melanoma. *Nat Genet*. 2019;51(7):1123–1130.
25. Robertson AG, Shih J, Yau C, et al. Integrative analysis identifies four molecular and clinical subsets in uveal melanoma. *Cancer Cell*. 2018;33(1):151.

26. Smit KN, Jager MJ, de Klein A, et al. Uveal melanoma: towards a molecular understanding. *Prog Retin Eye Res*. 2020;75:100800.
27. Szalai E, Jiang Y, van Poppelen NM, et al. Association of uveal melanoma metastatic rate with stochastic mutation rate and type of mutation. *JAMA Ophthalmol*. 2018;136(10):1115.
28. Firth D. Bias reduction of maximum likelihood estimates. *Biometrika*. 1993;80(1):27–38.
29. Heinze G, Schemper M. A solution to the problem of separation in logistic regression. *Stat Med*. 2002;21(16):2409–2419.
30. Hosmer Jr DW, Lemeshow S, Sturdivant RX. *Applied Logistic Regression* John Wiley & Sons; 2013:269–311.
31. Decatur CL, Ong E, Garg N, et al. Driver mutations in uveal melanoma: associations with gene expression profile and patient outcomes. *JAMA Ophthalmol*. 2016;134(7):728–733.
32. Isaacson AL, Sompallae RR, Guseva NV, et al. Genomic profiling of metastatic uveal melanoma shows frequent coexisting *BAP1* or *SF3B1* and *GNAQ/GNA11* mutations and correlation with prognosis. *Am J Clin Pathol*. 2022;158(2):177–186.
33. Drabarek W, van Riet J, Nguyen JQN, et al. Identification of early-onset metastasis in *SF3B1* mutated uveal melanoma. *Cancers (Basel)*. 2022;14(3):846.
34. Lorenzo D, Piulats JM, Ochoa M, et al. Clinical predictors of survival in metastatic uveal melanoma. *Jpn J Ophthalmol*. 2019;63(2):197–209.
35. 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.
36. Kivelä TT, Piperno-Neumann S, Desjardins L, et al. Validation of a prognostic staging for metastatic uveal melanoma: a collaborative study of the European Ophthalmic Oncology Group. *Am J Ophthalmol*. 2016;168:217–226.
37. Jochems A, van der Kooij MK, Fiocco M, et al. Metastatic uveal melanoma: treatment strategies and survival-results from the Dutch melanoma treatment registry. *Cancers (Basel)*. 2019;11(7):1007.
38. Diener-West M, Reynolds SM, Agugliaro DJ, et al. Screening for metastasis from choroidal melanoma: the Collaborative Ocular Melanoma Study Group Report 23. *J Clin Oncol*. 2004;22(12):2438–2444.
39. Hicks C, Foss AJ, Hungerford JL. Predictive power of screening tests for metastasis in uveal melanoma. *Eye*. 1998;12:945–948.
40. Patel M, Winston CB, Marr BP, et al. Characterization of computed tomography scan abnormalities in patients with biopsy-proven hepatic metastases from uveal melanoma. *Arch Ophthalmol*. 2011;129(12):1576–1582.
41. Wallach JB. *Interpretation of Diagnostic Tests* Lippincott Williams & Wilkins; 2007:34–63.
42. Rodriguez DA, Yang J, Durante MA, et al. Multiregional genetic evolution of metastatic uveal melanoma. *NPJ Genom Med*. 2021;6(1):70.
43. Long GV, Grob JJ, Nathan P, et al. Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomised trials. *Lancet Oncol*. 2016;17(12):1743–1754.
44. Servois V, Bouhadiba T, Dureau S, et al. Iterative treatment with surgery and radiofrequency ablation of uveal melanoma liver metastasis: retrospective analysis of a series of very long-term survivors. *Eur J Surg Oncol*. 2019;45(9):1717–1722.
45. Rodrigues M, Mobuchon L, Houy A, et al. Outlier response to anti-PD1 in uveal melanoma reveals germline *MBD4* mutations in hypermutated tumors. *Nat Commun*. 2018;9(1):1866.
46. United Nations Department of Economic and Social Affairs, Population Division (2019). World Population Prospects 2019, Online Edition. Rev 1. https://www.un.org/development/desa/pd/news/world-population-prospects-2019-0.