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CLINICAL INVESTIGATION

Clinical predictors of survival in metastatic uveal melanoma

Daniel Lorenzo[1] · Josep Maria Piulats[2] · María Ochoa[2] · Luis Arias[1] · Cristina Gutiérrez[3] · Jaume Català[1] · Estefanía Cobos[1] · Pere Garcia-Bru[1] · Bruno Dias[1] · Noel Padrón-Pérez[1] · Josep Maria Caminal[1]

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Abstract

Purpose To determine the clinical factors that influence survival in patients with metastatic uveal melanoma.

Study design Single-center, retrospective review of patients' medical records.

Methods The following data of ninety-nine consecutive patients (49 men, 50 women) with metastatic uveal melanoma were registered: patient demographics; primary tumor characteristics; features of first melanoma-related metastasis; symptoms and patient status at distant disease debut and metastasis treatment. Overall survival was analyzed by Kaplan-Meier estimates. A Cox proportional hazards regression model was applied to identify independent predictors associated with survival.

Results Mean patient age at metastatic diagnosis was 60.7 years (standard deviation, 12.8). The liver was the first metastatic site in most (92.9%) cases. The median disease-free interval was 26 months (interquartile range, 34). Median overall survival after detection of the first metastasis was 8 months (interquartile range, 14). The baseline characteristics of the primary uveal melanoma were not associated with survival in patients with stage IV disease. In the multivariate analysis, the following factors at first metastatic diagnosis were associated with improved overall survival: disease-free interval > 36 months; better performance status; and normal serum lactate dehydrogenase and gamma glutamyl transpeptidase levels. Overall survival was not influenced by specific metastatic treatment.

Conclusion Although metastatic uveal melanoma has a poor prognosis, this study reveals the existence of several independent prognostic factors for prolonged overall survival. These findings may help improve survival estimates in patients with advanced disease.

Keywords Uveal melanoma · Metastasis · Survival · Prognostic factors · Clinical predictors

Introduction

Uveal melanoma is the most common primary intraocular tumor in adults, with an incidence in Europe and North America ranging from 2-8 cases per million per year, and a 5-year relative survival rate of 78%-90% [1–4]. The most common cause of death in these patients is distant metastasis, which occurs in 50% of patients with large uveal melanomas [5]. The most common site of metastatic spread is the liver (89% of cases) [6, 7]. There is currently no standard therapeutic approach to the treatment of metastatic uveal melanoma and prognosis is very poor, with a median survival of only 8 months [8, 9]. Notably, survival in patients with disseminated disease has not improved for several decades [10–12].

Despite the substantial recent progress in our understanding of genetic alterations in uveal melanoma, few molecular markers are available to predict prognosis in patients with metastatic diseases [13]. Due to the lack of full understanding of the intrinsic mechanisms involved in metastatic disease, clinicians still rely primarily on clinical factors to help estimate expected survival. Numerous variables – including various clinical, histopathological, and cytogenetic uveal melanoma features, have been investigated to determine their ability to predict progression and survival at diagnosis

Corresponding author: Daniel Lorenzo

✉ Daniel Lorenzo
dlorenzo@bellvitgehospital.cat

[1] Department of Ophthalmology, Bellvitge University Hospital, Feixa Llarga, s/n, 08907 L'Hospitalet de Llobregat, Barcelona, Spain

[2] Department of Oncology, Catalan Institute of Oncology, Barcelona, Spain

[3] Department of Brachytherapy, Catalan Institute of Oncology, Barcelona, Spain

of the primary tumor [14]. By contrast, less research has been performed to identify the prognostic factors for survival among patients with metastatic disease. In fact, the few available studies report highly heterogeneous results, probably due to the rarity of this disease together with the diverse data collection approaches used. Nevertheless, in recent years, an improved understanding of the molecular basis of uveal melanoma, together with the emergence of new therapeutic targets, have rekindled interest in understanding how metastatic disease develops. Clearly, it would be beneficial to identify the clinical features most closely associated with survival in patients with melanoma-related metastasis in order to offer patients a more accurate prognosis and to increase opportunities for patients to participate in clinical trials. In this sense, Valpione et al. and Kivelä et al. have independently developed clinical tools for prognostic staging of metastatic uveal melanoma [15, 16].

Given the limited data on predictors of survival in metastatic uveal melanoma, the aim of the present study was to comprehensively evaluate numerous variables thought to be associated with the course of the disease in order to identify potential predictors of survival. We retrospectively evaluated 95 potential ophthalmological and oncological clinical parameters in a single center cohort of 99 consecutive patients diagnosed with metastatic uveal melanoma. Multivariate analysis was performed to determine the variables associated with improved survival which would prove relevant to clinical practice.

Material and Methods

Patient and clinical assessments

This retrospective study included all patients diagnosed with metastatic uveal melanoma at the oncology unit of Bellvitge University Hospital (Barcelona, Spain) between January 1996 and January 2014. One-hundred and seven consecutive patients were initially identified; of these, 8 were excluded due to missing data. Thus, a total of 99 patients were finally included in the study. This study was approved by the Clinical Research Ethics Committee of Bellvitge University Hospital.

Diagnosis of melanoma-related metastasis was based on the usual clinical and imaging findings, presence of progression, and the absence of any additional cancer, in accordance with previous studies [17]. A fine-needle aspiration biopsy was performed in cases of diagnostic uncertainty. Patients underwent routine surveillance testing (liver ultrasound and blood liver function tests) every six months. If abnormal results were detected, confirmatory computed tomography, or magnetic resonance imaging were performed.

Clinical data

The ophthalmological and oncological features retrieved from the medical records included: demographic data; characteristics of the primary uveal melanoma; and other features – including the characteristics of the metastatic lesion(s); the patients' general health state, and treatment modalities – at metastatic diagnosis.

Demographic data included age at diagnosis of the primary uveal melanoma, gender, and systemic and ocular comorbidities. We evaluated the following clinical characteristics of the primary tumor: laterality; presenting symptoms; location of tumor epicenter (ciliary body or choroid); largest tumor thickness and largest basal diameter I in millimeters (mm); distance to optic disc margin and foveola (mm); Bruch's membrane rupture; presence of subretinal fluid; orange pigment over tumor surface; and acoustic hollowness on B-scan ultrasonography. Tumor size was assessed according to the 7th edition of the American Joint Committee on Cancer (AJCC) tumor staging criteria and the Collaborative Ocular Melanoma Study (COMS) criteria [18, 19]. The treatment administered for the initial uveal melanoma and local recurrences, if any, was recorded. Wherever available, histopathological data were obtained.

The following factors determined diagnosis of metastatic spread: metastatic location; number of lesions per site; largest dimension of the largest metastasis (mm); AJCC M-stage; surveillance testing versus symptom-prompted evaluation; and diagnostic method (radiology imaging tests: liver ultrasonography, computed tomography, magnetic resonance imaging; biochemical analysis; biopsy; or physical exam). When available, histopathologic confirmation and metabolic activity of the metastasis measured by combined positron-emission tomography/computed tomographic imaging (PET/CT) were recorded.

Baseline patient characteristics at onset of metastatic disease included: age; disease-free interval (DFI), defined as the time elapsed from the initial uveal melanoma diagnosis to date of first metastasis; Eastern Cooperative Oncology Group (ECOG) performance status; and presenting symptoms. Clinical laboratory values at metastatic diagnosis were categorized relative to the upper normal limit according to the reference ranges at our institution, and included the following variables: aspartate aminotransferase (AST); alanine aminotransferase (ALT); gamma glutamyl transpeptidase (GGT); lactate dehydrogenase (LDH); alkaline phosphatase (AP); total bilirubin and hemoglobin. The treatment parameters of the metastatic lesions (surgery, radiotherapy, and the types of first-line and second-line chemotherapy) and clinical outcomes were recorded. The specific treatment approach was selected according to the location of the metastatic lesion(s) and the availability of clinical trials.

Statistics

The patient data and characteristics of the metastatic lesions were tabulated and reported as descriptive variables. Categorical variables are reported as frequencies and percentages. For continuous variables, measures of the central tendency (mean, median) and dispersion (standard deviation [SD], interquartile range [IQR]) were determined depending on the distribution of the variable. A receiver operating characteristic (ROC) curve was calculated for clinical laboratory values. Areas under the ROC curves were measured to compare their overall diagnostic performance.

Overall survival (OS) was calculated from date of the first metastasis to death or to the date of last follow-up for incomplete observations (censored). OS curves were estimated using the Kaplan-Meier method. The initial univariate analysis was performed using the log-rank test to determine differences between cohorts. Patient age at diagnosis of uveal melanoma and at metastasis, as well as DFI values, were categorized using optimal cut-off points obtained on univariate analysis. The variables found to be significant on univariate analysis were entered into a multivariate analysis to identify the independent predictors of survival using the Cox proportional hazard regression model. The final multivariate model was constructed using a backward stepwise regression with manual selection of variables and $P \geq 0.05$ as the removal criterion. Effect estimates were expressed as hazard ratios with 95% confidence intervals. The level of statistical significance was set at $P < 0.05$. All statistical analyses were performed with the IBM-SPSS software, version 20.0 (IBM, Inc.).

Results

Patient characteristics from the 99 eligible patients (50 men and 49 women) are shown in Tables 1 and 2. At the final follow-up, 94 of the 99 subjects had died. All deaths were considered secondary to metastatic disease.

Initial uveal melanoma

The mean age at diagnosis of the primary uveal melanoma was 57.5 years (SD, 13.5). The size of the primary tumor was available in 97 of the 99 patients, with Tumor, Node, Metastasis (TNM) staging size distributed as follows: T1, 2 patients (2.1%); T2, 25 patients (25.8%); T3, 44 patients (45.4%); and T4, 26 patients (26.8%). Histological features were available for 47 patients; the most common feature being the epithelioid pattern (present in 46.8% of cases). A cytogenetic analysis was performed in 14 patients, 8 of whom presented monosomy 3. Primary tumors were treated in most cases by brachytherapy (54%) followed by enucleation (35%). Local recurrences were observed in 15% of cases with a median interval of 21 months (IQR, 40).

Metastatic disease

The mean age at first metastatic diagnosis was 60.7 years (SD, 12.8), and the median DFI was 26 months (IQR, 34). The liver was the first metastatic site in 92 patients (92.9%); of these, the liver was the only organ with metastasis in 78 subjects (78.8%), while 15 patients (15.2%) presented with multiple metastatic sites at detection of distant disease. A median number of four liver lesions was found (IQR, 5), and the diameter of the largest liver metastasis was 22 mm (median value; IQR, 22). Other common sites of metastasis included the bones (11.1%), lungs (5.1%), skin (3%), and central nervous system (2%).

In most cases (70.8%), the metastasis was detected by surveillance methods in patients with good performance status (ECOG 0-1); in the other patients (29.2%), the symptoms led to diagnosis. The majority (84.4%) of patients were diagnosed by radiological imaging. Histopathological confirmation of the metastasis was obtained in 39.6% of cases. The metabolic activity of the liver metastases was measured by PET/CT in 38 patients and considered positive (higher metabolic activity in liver metastases than in normal liver parenchyma) in 71.1% of those patients. The percentages of patients at metastatic diagnosis with laboratory results above the upper limit were as follow: LDH (47.6%); GGT (42.2%); AP (24.4%); AST (31.3%); ALT (27.4%); and bilirubin (8.3%). The overall performances of LDH, GGT, and AP were compared by ROC analysis curves (Fig. 1), which suggested that AP serum levels provided the greatest discriminative ability.

Data on the first metastatic treatment were available for 91 subjects; of these, 52.7% received first-line chemotherapy (fotemustine, 39.6%; dacarbazine, 37.5%; ipilimumab, 16.7%; and temozolomide in combination with interferon-alpha, 6.2%), with initial stable disease in 26.1%. Clinical response was determined after several cycles of chemotherapy by clinician assessment of changes in tumor size evaluated by conventional imaging procedures. Fewer patients underwent surgical resection (19.8%) or palliative radiotherapy (12.1%).

Overall survival

The median OS was 8 months (IQR, 14) (Fig. 2). Note that the slope of the survival curve flattened out after month 12. As a result, 34% of patients were alive at 1 year and 7% at 4 years. On the univariate analysis, none of the features related to the primary uveal melanoma were associated with survival. By contrast, several characteristics related to the first metastasis were associated with improved OS: age ≤ 65

Table 1 Demographic data and uveal melanoma characteristics of the study population and univariate survival analysis

	number (%) (n = 99)	Median survival (95% confidence interval)	*P* value
DEMOGRAPHIC DATA			
Age at diagnosis of UM			***0.014***
≤ 65 years	*71 (71.7)*	11 (4.98 - 17.02)	
> 65 years	*28 (28.3)*	8 (5.43 - 10.57)	
Sex			0.340
Male	*49 (49.5)*	8 (4.65 - 11.35)	
Female	*50 (50.5)*	8 (3.75 - 12.25)	
Other lifetime primary cancer			0.807
Yes	*12 (12.1)*	5 (1.61 - 8.40)	
No	*87 (87.9)*	9 (5.57 - 12.43)	
UVEAL MELANOMA CHARACTERISTICS			
Eye			0.547
right	*51 (51.1)*	11 (6.09 - 15.91)	
left	*48 (48.5)*	8 (3.63 - 12.37)	
Type of UM			0.718
choroid	*90 (90.9)*	8 (4.98 - 11.02)	
ciliary body	*9 (9.1)*	12 (0 - 28.63)	
T, tumor size category (n=97)			0.243
T1	*2 (2.1)*	-	
T2	*25 (25.8)*	7 (4.06 - 9.94)	
T3	*44 (45.4)*	8 (5.94 - 10.06)	
T4	*26 (26.8)*	10 (5.00 - 14.99)	
Anatomic staging, TNM (n=97)			0.235
I	*2 (2.1)*	57 (-)	
IIa	*24 (24.7)*	7 (1.40 - 12.60)	
IIb	*35 (36.1)*	8 (5.81 - 10.19)	
IIIa	*31 (32)*	8 (3.93 - 12.07)	
IIIb	*2 (2.1)*	12 (-)	
IV	*3 (3.1)*	38 (-)	
COMS (n=99)			0.234
small	*2 (2)*	57 (-)	
medium	*35 (35.4)*	8 (2.21 - 13.79)	
large	*62 (62.6)*	8 (3.81 - 12.19)	
Diagnosis			0.654
symptomatic	*9 (9.1)*	8 (4.33 - 11.67)	
incidental finding	*90 (90.9)*	8 (5.54 - 10.46)	
Rupture of Bruch's membrane			0.669
No	*68 (71.6)*	8 (4.02 - 11.97)	
Yes	*27 (28.4)*	10 (5.12 - 14.88)	
Orange pigment (n=95)			0.187
No	*75 (78.9)*	7 (5.36 - 8.64)	
Yes	*20 (21.1)*	14 (6.96 - 21.04)	
Subretinal fluid			0.914
No	*28 (28.3)*	7 (0 - 16.19)	
Yes	*71 (71.7)*	9 (5.38 - 12.62)	
Ultrasound acoustic hollowness (n=89)			0.731
No	*3 (3.4)*	8 (3.20 - 12.80)	
Yes	*86 (96.6)*	9 (5.60 - 12.41)	
Histopathology (cell type) (n=47)			0.960
spindle cell	*5 (10.6)*	8 (5.85 - 10.15)	

Table 1 (continued)

	number (%) (n = 99)	Median survival (95% confidence interval)	*P* value
epithelioid	*22 (46.8)*	12 (10.23 - 13.80)	
mixed	*20 (42.6)*	8 (5.35 - 10.65)	
Chromosome 3 monosomy (n=14)			0.226
No	*6 (42.9)*	4 (1.60 - 6.40)	
Yes	*8 (57.1)*	18 (11.91 - 24.08)	
Primary treatment			0.807
brachytherapy	*53 (53.5)*	8 (4.49 - 11.51)	
transscleral	*5 (5)*	13 (0 - 29.47)	
endoresection	*4 (4)*	4 (0 - 21.64)	
enucleation	*35 (35.4)*	8 (4.52 - 11.48)	
*no treatment**	*2 (2)*	1 (-)	
Local recurrence			0.816
No	*84 (84.8)*	8 (5.05 - 10.95)	
Yes	*15 (15.2)*	12 (6.04 - 17.96)	

Significant values ($P < 0.05$) are bolded

*These patients were not initially treated because of metastasis was detected concurrently with the primary tumor diagnosis

Abbreviations: UM = uveal melanoma; TNM = tumor, node and metastasis; COMS = Collaborative Ocular Melanoma Study

years at metastatic diagnosis; DFI > 36 months; ≤ 5 liver metastases; and absence of symptoms. The following clinical parameters at first metastatic diagnosis were correlated with prolonged survival: better ECOG (0-1) performance status; initial M-stage; and normal levels of LDH, GGT, AP, AST, ALT, and bilirubin (Fig. 3). In terms of metastatic treatment, only surgery and complete response to first-line chemotherapy were associated with improved survival.

Given the wide range of the inclusion period (from 1996 to 2014), we performed a subgroup survival analysis to check for differences in survival according to the date of diagnosis of metastasis: 1996-2004 versus 2004-2014. However, no significant differences were found between these two groups.

Multivariate analysis

The following factors were significantly associated with improved survival on multivariate analysis (Table 3): DFI > 36 months; better ECOG (0-1) performance status; normal LDH and GGT levels. Age ≤ 65 years at first metastatic diagnosis was nearly significant ($P = 0.064$).

Discussion

The main treatment aim in uveal melanoma is to prevent metastatic dissemination. Several effective treatments, ranging from enucleation to eye-conserving therapies, are currently available to prevent and eradicate local melanoma recurrences. All of these methods yield comparable survival outcomes [20–24]. Given the very poor prognosis in cases with disseminated disease, prevention of metastatic disease in uveal melanoma is crucial [8, 9]. The main objective of this study was to identify the clinical factors present at metastatic diagnosis that were significant predictors of survival. We retrospectively analyzed 95 potential prognostic factors in 99 patients with metastatic uveal melanoma. The following clinical factors were independent predictors of prolonged survival: age ≤ 65 years; lower ECOG (0-1) performance status; DFI ≥ 36 months; and normal LDH and GGT serum levels. These findings are important because they help to better establish the prognosis, thus facilitating future care. In addition, such data may be useful for patient stratification in clinical trials.

Previous studies have evaluated the relationship between certain clinical features and survival in patients with metastatic malignant uveal melanoma. However, these studies vary substantially in the methodologies used; moreover, in most cases, the number of factors analyzed was limited. Due to this heterogeneity, it is difficult to directly compare the findings of those studies. As Table 4 shows, the main clinical factors that have been found to be independently associated with OS after metastatic diagnosis include age; gender; performance status; DFI; altered liver function tests (especially LDH and AP serum levels); organ involvement (site, number and diameter of the metastasis); and surgical treatment [10, 11, 15, 25–31]. Compared to most previous studies, we included many more variables in our analysis, including: the characteristics of the primary tumor, the patient's

Table 2 Baseline characteristics of the study population at first metastasis diagnosis and univariate survival analysis

	number (%) (n = 99)	Median survival (95% confidence interval)	*P* value
CHARACTERISTICS OF THE FIRST METASTASTIC UVEAL MELANOMA LESION			
Age at metastatic diagnosis			**0.006**
≤ 65 years	*60 (60.6)*	12 (5.47 - 18.54)	
> 65 years	*39 (39.4)*	8 (5.66 - 10.34)	
Disease-free interval			**0.021**
> 36 months	*35 (35.4)*	14 (0 - 29.15)	
≤ 36 months	*64 (64.6)*	8 (4.88 - 11.12)	
Site of first metastasis			0.960
liver	*92 (92.9)*	8 (5.38 - 10.62)	
other sites*	*7 (7.1)*	14 (0 - 29.40)	
Number of liver metastases, (n=84)			**0.001**
> 5 metastases	*29 (34.5)*	5 (3.25 -6.75)	
≤ 5 metastases	*55 (65.5)*	12 (9.36 - 14.64)	
Diagnosis of metastasis (n=96)			**0.002**
surveillance	*68 (70.8)*	12 (9.05 - 14.95)	
symptoms	*28 (29.2)*	5 (2.41 - 7.59)	
Diagnostic method (n=96)			0.184
imaging testing	*81 (84.4)*	*8 (4.78 - 11.22)*	
biopsy	*11 (11.5)*	*12 (7.47 – 16.53)*	
blood liver function test	*3 (3.1)*	*3 (-)*	
physical examination	*1 (1)*	*10 (-)*	
PET/CT (n=38)			0.452
negative	*11 (28.9)*	18 (5.05 - 30.95)	
positive	*27 (71.1)*	12 (9.56 - 14.44)	
PATIENT CHARACTERISTICS AT FIRST METASTASTIC DIAGNOSIS			
Performance status, ECOG (n=94)			**< 0.001**
0	*59 (62.8)*	13 (9.74 - 16.26)	
1	*25 (26.6)*	7 (4.60 - 9.40)	
2	*9 (9.6)*	1 (0.27 - 1.73)	
3	*1 (1.1)*	3 (-)	
M-stage (TNM) (n=91)			**0.047**
1a	*60 (65.9)*	12 (7.80 - 16.20)	
1b	*25 (27.5)*	7 (3.33 - 10.67)	
1c	*6 (6.6)*	5 (0.20 - 9.80)	
Lactate dehydrogenase (n=82)			**0.003**
elevated	*39 (47.6)*	7 (4.66 - 9.34)	
unaltered	*43 (52.4)*	15 (10.48 - 19.52)	
Aspartate transaminase (n=83)			**< 0.001**
elevated	*26 (31.3)*	4 (2.33 - 5.67)	
unaltered	*57 (68.7)*	14 (9.87 - 18.13)	
Alanine transaminase (n=84)			**0.001**
elevated	*23 (27.4)*	4 (2.12 - 5.88)	
unaltered	*61 (72.6)*	14 (11.29 - 16.71)	
Gamma glutamyl transpeptidase (n=83)			**< 0.001**
elevated	*35 (42.2)*	5 (3.30 - 6.70)	
unaltered	*48 (57.8)*	16 (11.86 - 20.14)	
Bilirubin (n=84)			**0.001**
elevated	*7 (8.3)*	2 (0 - 4.66)	
unaltered	*77 (91.7)*	14 (11.29 - 16.71)	
Alkaline phosphatase (n=82)			**< 0.001**

Table 2 (continued)

	number (%) (n = 99)	Median survival (95% confidence interval)	*P* value
elevated	*20 (24.4)*	4 (2.25 - 5.75)	
unaltered	*62 (75.6)*	13 (9.95 - 16.05)	
Hemoglobin (n=85)			0.123
< 120 g/L	*9 (10.6)*	3 (0.08 - 5.92)	
120-160 g/L	*73 (85.9)*	12 (8.38 - 15.66)	
> 160 g/L	*3 (3.5)*	10 (7.06 - 12.94)	
FIRST METASTASIS TREATMENT			
Surgery (n=91)			**0.015**
No	*73 (80.2)*	7 (4.80 - 9.20)	
Yes	*18 (19.8)*	18 (5.53 - 30.47)	
Radiotherapy (n=91)			0.568
No	*80 (87.9)*	9 (5.58 - 12.41)	
Yes	*11 (12.1)*	13 (3.29 - 22.71)	
First-line chemotherapy (n=91)			0.241
No	*43 (47.3)*	7 (4.45 - 9.55)	
Yes	*48 (52.7)*	12 (8.25 - 15.75)	
First-line response (n=46)			**0.005**
stable disease	*12 (26.1)*	25 (10.27 - 39.73)	
partial response	*2 (4.3)*	5 (-)	
progression	*32 (69.6)*	8 (4.83 - 11.17)	
Second-line chemotherapy (n=91)			0.156
No	*75 (82.4)*	8 (6.10 - 9.90)	
Yes	*16 (17.6)*	18 (10.16 - 25.84)	
Second-line response (n=16)			0.526
stable disease	*2 (12.5)*	34 (-)	
progression	*14 (87.5)*	13 (2.00 - 24.00)	

Significant values ($P < 0.05$) are bolded

*Other non-liver sites included: lung (n=2), bone (n=1), skin (n=1), brain (n=1), and other locations (n=2)

Abbreviations: TNM = tumor, node and metastasis; PET/CT = combined positron emission tomography/computed tomographic imaging; ECOG = Eastern Cooperative Oncology Group

general condition upon detection of the first metastasis and the main characteristics of the first metastatic lesion and the treatment thereof. In general, our results are consistent with previous reports. However, we did find some notable differences, probably because we assessed a much wider range of potential predictors. Additionally, it is worth emphasizing that these findings are consistent with the prognostic systems developed by Valpione et al. [15] and Eskelin et al. (Helsinki staging model) [11]. Notably, the Helsinki model was recently validated by the European Ophthalmic Oncology Group [16]. Both of those studies take a slightly different approach to categorizing survival outcomes of metastatic patients. By contrast, the aim of our study was not to create prognostic groups, but rather to identify independent prognostic factors. To our knowledge, none of the aforementioned studies assessed all of the prognostic factors that had been previously identified in other studies. Another key difference between the present study and previous studies is that we performed a multivariate analysis to determine the relative value of those factors.

Diverse clinical, histopathological, cytogenetic, and transcriptomic parameters related to the primary uveal melanoma can predict the development of metastasis at earlier stages of disease and for that reason these variables have been particularly useful in patient management [14]. Nevertheless, despite the undisputed clinical value of factors related to the primary tumor, it is important to underscore our findings – which are consistent with previous studies – showing that the characteristics of the primary tumor had no influence on survival in patients with metastatic disease: the only values predictive of survival were those related to the metastatic disease. For this reason, although the AJCC staging system has been validated for use as a prognostic parameter for the risk of metastasis in uveal melanoma patients, once metastatic disease develops, this system does not correlate with overall survival in this patient subset.

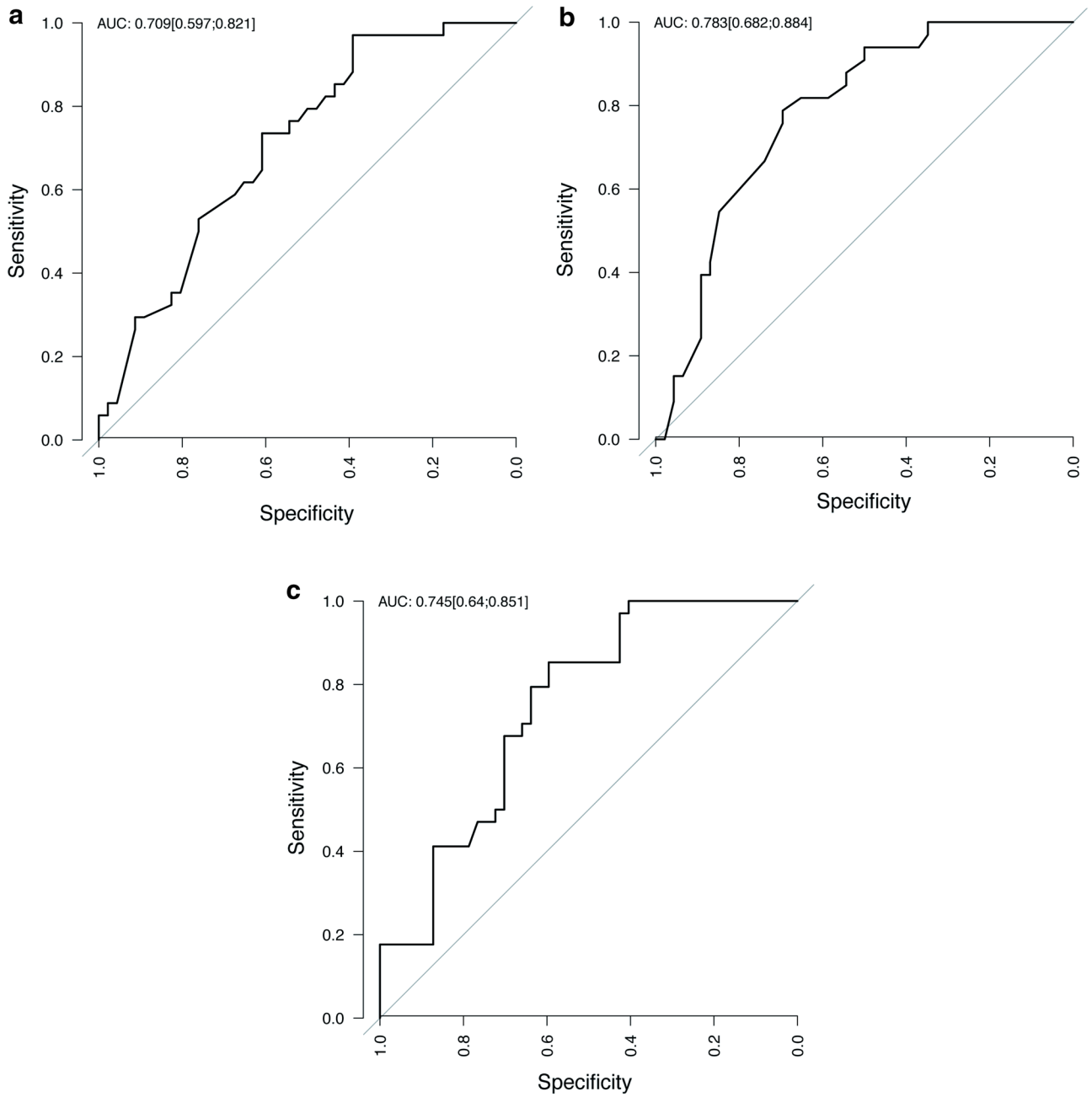

Fig. 1 Receiver operating characteristic (ROC) curve analysis of analytical parameters. (a) lactate dehydrogenase (LDH) (n=82), (b) alkaline phosphatase (AP) (n=83), and (c) gamma glutamyl transpeptidase (GGT) (n=83). AP serum levels showed the best overall diagnostic performance with an area under the ROC curve (AUC) of 78.3% (95% confidence interval [CI], 68.2%-88.4%), which was larger than the AUC observed with GGT (74.5%; 95% CI, 64%-85.1%), and LDH (70.9%; 95% CI, 59.7%-82.1%)

Clinically, distant metastases are rarely found when the primary uveal melanoma is diagnosed [31]. The COMS data show that, in most cases, disseminated disease occurs approximately 32 to 42 months after the primary diagnosis [17]. Our data are in line with these figures: in our series, metastases manifested a mean of 37.7 months after diagnosis of the primary tumor. Importantly, late development of metastatic disease (DFI of > 36 months) was associated with improved survival in our series. As in many cancers, it is assumed that metastasis is present (but not usually detectable) at the time of the primary diagnosis of uveal melanoma [32, 33]. Malignant cells, presumably present at primary diagnosis, remain quiescent for an extended time until some eventually manifest as a clinically-evident metastatic lesion; even so, some malignant cells remain dormant as residual disease [34]. We hypothesize that patients with

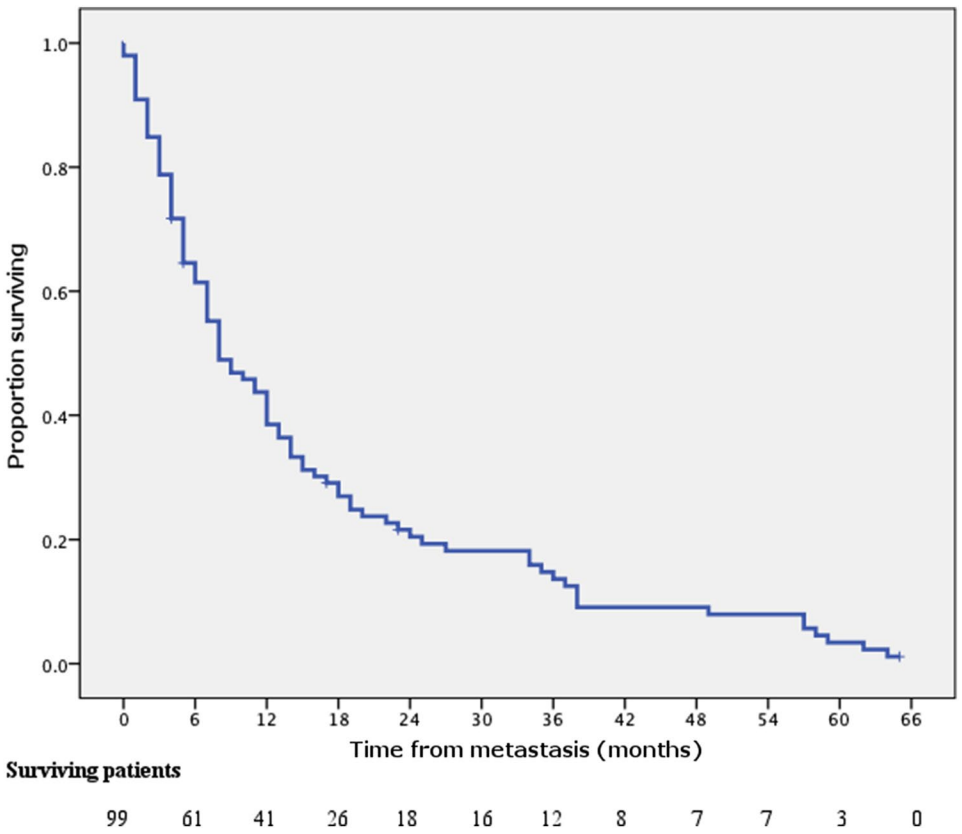

Fig. 2 Kaplan-Meier estimates of overall survival in the 99 patients with metastatic uveal melanoma

late recurrences may have less-aggressive disseminated dormant tumor cells with a lower proliferative capacity than observed in cases with early recurrences. Consequently, the presence of less-aggressive cells would result in a clinical increase in survival. This line of investigation could be of interest for further research into the use of new therapies to delay cancer progression.

The liver is typically the first site of spread (92.9% patients in our series) [6]. Our finding in this regard is consistent with other reports, providing support for a surveillance strategy focused on the liver. An important strength of this study was the administration of hepatic ultrasound and liver function testing every 6 months as part of the standard surveillance process to check for metastasis. This routine surveillance program detected 70.8% of asymptomatic metastatic patients, a finding consistent with other reports showing that most patients are asymptomatic when metastasis is detected by surveillance techniques. Abdominal imaging tests (ultrasound, CT, and MRI) were the main tools used to diagnose distant metastases in this subset of patients [35]. Specifically, 84.4% of patients were diagnosed by radiological imaging. It is worth noting that physical examination and blood tests were not effective in detecting asymptomatic metastases. Survival was significantly better in asymptomatic versus symptomatic patients when the metastatic disease was detected early through surveillance testing, a finding that underscores the value of close surveillance in these patients. Notwithstanding this finding, we note that – similar to previous studies – the multivariate analysis failed to show any evidence of survival benefit due to lead time bias [27, 36, 37]. Lower ECOG performance status and younger age at diagnosis of the first metastasis both influenced OS; these two characteristics may reflect the patient's general good health and nutritional status, minimal tumor burden, and preserved organ function – all of which are characteristics of asymptomatic patients.

The use of routine liver function testing as a surveillance tool for the early detection of metastasis remains controversial because such tests are not sufficiently sensitive when there are only a few lesions or these are small [38, 39]. For this reason, better serological markers are needed [30, 40]. In our study, LDH, GGT, and AP yielded the highest detection rates (ROC analysis) for metastatic disease. Nevertheless, it is important to note that these values were within normal limits in a large proportion of patients at the time metastatic spread was diagnosed: LDH, GGT, and AP were normal in 52%, 58%, and 76% of patients, respectively. On the other hand, these variables seem to play an important prognostic role once the metastasis has been diagnosed: the multivariate analysis showed that both LDH and GGT were predictors of improved survival when serum values were normal. The status of these

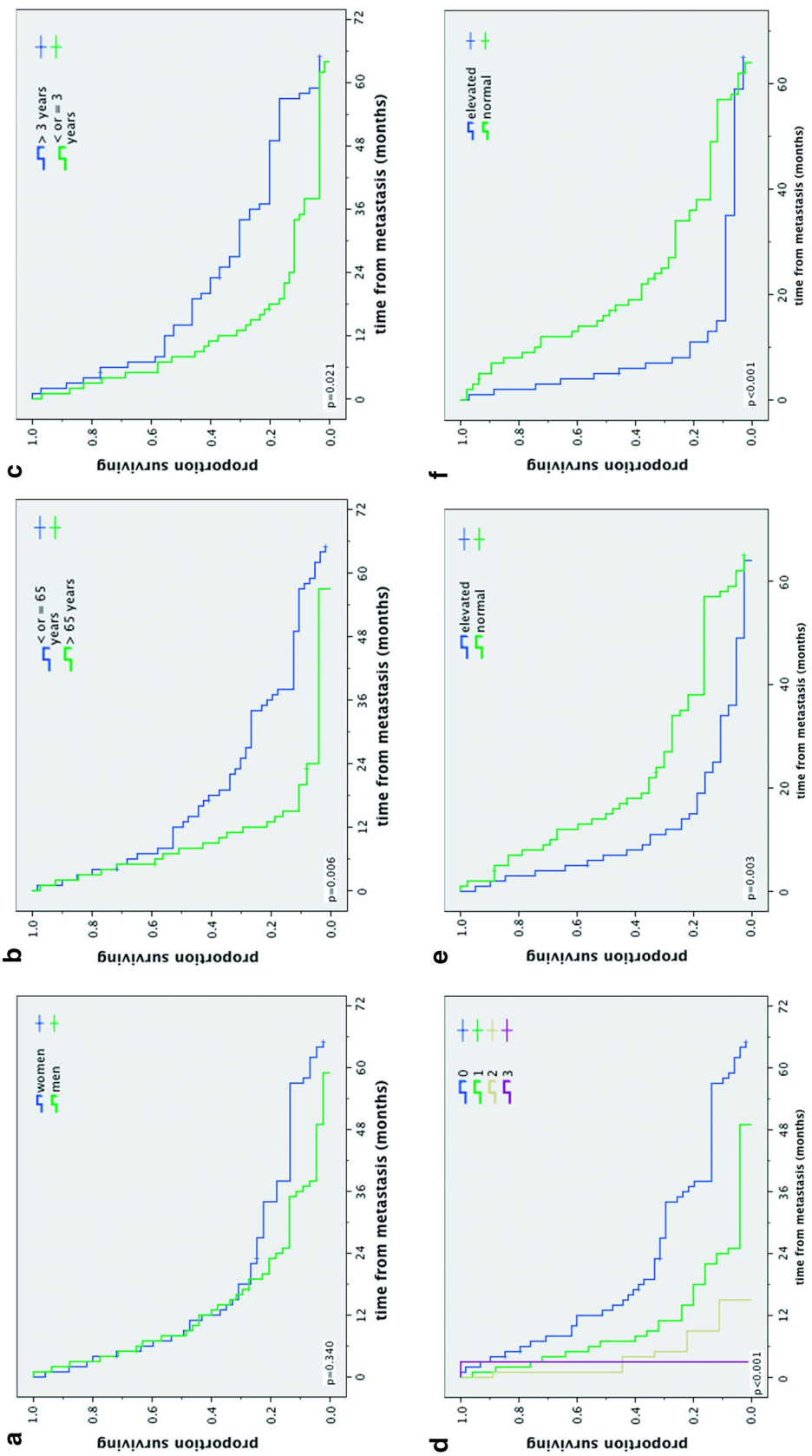

Fig. 3 Kaplan-Meier estimates of survival after diagnosis of metastatic uveal melanoma. Among the 99 patients according to (a) gender (n=99), (b) age at first metastasis diagnosis (n=99), (c) metastasis-free interval (n=99), (d) performance status (n=94), (e) lactate dehydrogenase levels (n=82), and (f) gamma glutamyl transpeptidase levels (n=83). Ticks show censored observations; (a-f) *P* values from log-rank test

Table 3 Final step model of multivariate survival analysis of patients with metastatic uveal melanoma. The model is adjusted by age and sex, and shows the clinically-significant features predictive of poor prognosis

	Hazard ratio	95% confidence interval	*P* value
Male gender	1.566	0.960-2.555	0.073
Age > 65 years at first metastatic diagnosis	1.676	0.969-2.898	0.064
Disease-free interval ≤ 36 months	1.744	1.014-2.999	0.045
Performance status (ECOG scale)	1.527	1.032-2.258	0.034
Elevated lactate dehydrogenase levels	1.898	1.180-3.052	0.008
Elevated gamma glutamyl transpeptidase levels	2.269	1.376-3.741	0.001

Table 4 Summary of published studies of survival in patients with metastatic uveal melanoma

Study	n	Median survival from diagnosis of metastasis (months)	Liver involvement (%)	Independent prognostic factors for survival	Survival benefit
Rajpal et al. (1983) [25]	35	8.2	71.4	Metastatic site, age, sex.	Non-liver, < 50 years, female.
Gragoudas et al. (1991) [10]	145	3.7	94	Age, diagnostic approach, treatment.	< 55 years, screening-detected, treated metastasis.
Bedikian et al. (1995) [26]	201	7	100 (only included liver metastasis)	DFI, AP.	Delayed recurrence, normal AP levels at diagnosis.
Eskelin et al. (2003) [11]	91	8.4	92	Performance status, largest diameter of the largest metastasis, AP.	Higher Karnofsky index, small size of the largest metastasis, normal AP at diagnosis.
Diener-West et al. (2004) [30]	714	< 6	91	not calculated	not calculated
Rietschel et al. (2005) [27]	119	12,5	60.5	Metastatic site, age, sex, DFI, treatment.	Lung/soft tissue, < 60 years, female, delayed recurrence, surgery/ intrahepatic treatment.
Kodjikian et al. (2005) [28]	63	15	100 (only included liver metastasis)	Number of liver metastases, location of uveal melanoma	< 10 liver metastases, not involving ciliary body
Pons et al. (2011) [29]	58	8.9	96	Performance status, number of liver metastases	Lower ECOG score, < 5 liver metastases
Valpione et al.* (2015) [15]	152 102	17.2 19.7	94 86.3	Performance status, percentage of liver involvement, DFI, LDH	Lower ECOG score, diminished liver substitution, delayed recurrence, normal LDH at diagnosis
Current study	99	8	92.9	Age, performance status, DFI, LDH, GGT	≤ 65 years, lower ECOG score, recurrence > 36 months, normal LDH & GGT at diagnosis

* In this study two independent cohorts were analyzed

** Pembrolizumab-treated patients

*** Nivolumab-treated patients

Abbreviations: DFI = disease-free interval; AP = alkaline phosphatase; LDH = lactate dehydrogenase; GGT = gamma glutamyl transpeptidase; ECOG = Eastern Cooperative Oncology Group; CRP = C-reactive protein; REC = relative eosinophil count

enzymes likely reflects the combined effect of liver function and overall tumor burden [11, 41]. Thus, it seems reasonable to expect that elevated levels of these markers at metastasis is indicative of more advanced disease and, consequently, worse survival. Based on our findings and previous reports, both LDH and GGT appear to be the

most sensitive liver function tests for uveal melanoma and are often elevated in patients with advanced liver disease [38]. These factors may be more useful to correlate the severity of the metastatic burden with survival than other factors (such as the number of metastases) described in previous studies.

Median survival was greater in patients with surgically-treated metastases compared to patients who underwent non-surgical treatment. This is consistent with non-randomized studies that report an association between surgical resection of the liver metastasis and prolonged survival in selected patient subsets [42, 43]. However, in the multivariate analysis in our study, this variable showed no significant effect on OS, a finding that seems to be consistent with the fact that to date, no treatment for metastatic uveal melanoma has been proven to change survival outcomes. Consequently, surgery may be a confounder because the patients who are eligible for surgery present the characteristics associated with longer survival: younger age, better performance status, and less bulky and more localized hepatic disease. Accordingly, it seems logical to assume that the improved outcomes associated with surgery are the results of a patient selection bias.

The present study has several limitations, the most important being its retrospective design. Another limitation is that this was a single-center study and thus the sample size was limited. In addition, despite the important role of molecular biology in uveal melanoma, we did not comprehensively assess genetic factors, which would have been valuable given that recent reports correlate conventional clinical prognostic factors for metastasis with the gene expression profile class of the tumor cells [44, 45]. For these reasons, future studies should explore the association between uveal melanoma molecular subgroups and survival in metastatic disease.

In conclusion, we evaluated overall survival in a cohort of patients with metastatic uveal melanoma to identify independent prognostic factors present at diagnosis of the first metastatic lesion. We found several significant predictors of improved survival including good performance status, younger age, longer disease-free interval, normal LDH levels, and normal GGT levels. These finding are highly relevant to ophthalmologists and oncologists alike because of their value in patient management and counseling. In addition, the data presented here may be useful in patient selection for clinical trial enrollment.

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