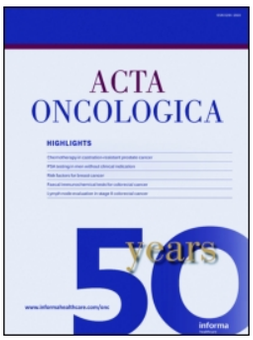

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LETTER TO THE EDITOR

Metastatic uveal melanoma managed with best supportive care

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Introduction

As long as 25 years after treatment of primary uveal melanoma (UM), metastases are the leading cause of death and, eventually, over 50% of patients die of metastatic disease [1,2]. The liver is the first site of metastases in 90% of patients and remains the only site in more than 50% of them [2,3]. Thereafter, the median overall survival (OS) has been 13 months with little difference between non-surgical treatments [4,5]. Neither advances in managing the primary tumour nor novel therapies for metastatic cutaneous melanoma have translated to survival benefit in metastatic UM [6,7]. In fact, no consensus exists on which first-line treatments for metastatic UM, if any, provide OS benefit.

There is no published survival data on consecutive patients managed with best supportive care (BSC) to allow historical comparison with those actively treated, although such data would be valuable for planning and analysing trials of metastatic UM, most of which continue to be non-randomised and non-comparative [8,9]. We report population-based OS according to previously validated prognostic stages [10] for patients with metastatic UM managed only with BSC.

Methods

Study design

Eligible to our retrospective observational cohort study were patients previously treated for primary UM in the Ocular Oncology Service, Department of Ophthalmology, Helsinki University Hospital, Finland, who developed metastases between January 1999 and December 2016, and received only BSC, although palliative radiotherapy to control pain was allowed for five patients [11,12]. The BSC decision was made by an oncologist in 96% of the patients and by a general practitioner in 4%. Our service is a national referral centre that manages over 95% of Finnish patients with UM. The institutional review board and the National Institute for Health and Welfare approved our study.

Data collection

We obtained patient charts from all hospitals managing metastatic UM. Because the Finnish law permits destroying patient records 12 years after death, data were incomplete for 21 patients. Of 338 patients with metastatic UM, 111 received no active treatment but two of them were diagnosed only at autopsy and excluded (Supplementary Figure S1).

We adapted definitions of the Collaborative Ocular Melanoma Study (COMS) [1,13] to ascertain whether metastatic UM was present, and obtained histopathologic specimens for review (Supplementary Text). Based on that, one patient was excluded, resulting in 108 enrolled patients.

We recorded the gender, age, date of diagnosis of the primary and metastases, Tumour, Node, Metastasis (TNM) stage [14,15], date of treatment decision (i.e. BSC), liver function tests (LFTs), Eastern Cooperative Oncology Group performance status (PS) [16], sites of metastases, the largest diameter of the largest metastasis (LDLM), symptoms, participation in regular follow-up to detect metastases [17], and the date and registered cause of death. The regular follow-up included annual LFTs and upper abdominal ultrasonography (US), followed by magnetic resonance imaging or computed tomography when metastases were suspected. Follow-up ended on December 31, 2018.

Outcomes

Our primary endpoint is OS from the date of treatment decision to death as most common in clinical trials [4,18]. A secondary endpoint is OS from the date of diagnosis of metastases to death that is less frequently reported in the literature [4].

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Supplemental data for this article can be accessed here.

In TNM staging, metastatic UM is currently divided in three categories (M1a to M1c) based on LDLM [14]. The PS and serum or plasma alkaline phosphatase (AP) level are additional independent predictors of OS [3,10]. The Helsinki University Hospital Working Formulation (WF) staging uses all three variables and has been validated by the European Ophthalmic Oncology Group (Supplementary Table S1) [10]. We assigned patients to the WF stages IVa, IVb, and IVc [10] by calculating their individual predicted median OS (online calculator available at http://www.prognomics.org/huhwf.aspx). As originally described, the WF stages correspond to median predicted OS of ≥12, <12–6, and <6 months, respectively, based on data at the time of diagnosis of metastases. For primary outcome assessment, we used the same data as available at the time of treatment decision.

The LDLM, PS, or AP level were missing for 16 patients, preventing calculation, but we could assign the WF stage for 13 of them using a published summary table [3].

Statistical analysis

Analysis was performed with Stata (version 15, Stata Corp., College Station, TX). All *p*-values are two-tailed, and $p<.05$ was considered significant. We report median with range and interquartile range (IQR) for continuous variables and compare gender distribution using binomial test. We estimated OS using Kaplan-Meier product-limit method, report the median OS with 95% confidence interval (CI), and compare unordered and ordered categories with the log-rank test and test for trend, respectively.

We used Cox proportional hazards regression to check whether gender, age at the time of treatment decision (categorized as <80 and ≥80, based on the age criterion for referral to a geriatric oncologist), relapse-free interval (RFI) (from the primary tumour to the diagnosis of metastases), symptoms from metastases, LDLM (TNM categories M1a, <30 mm; M1b, 31–80 mm; M1c, >80 mm) [14], AP level (categories <1.0 x, 1.0–2.0 x, >2.0 x upper normal limit [UNL]), and PS (categories 0–1, 2, 3–4 according to the WF) retained residual predictive power, given the WF stage, and might thus help predict OS. We allowed independent variables in models if $p<.10$, tested the assumption of proportional hazards using scaled adjustment of Schoenfeld residuals [19], and compared models using the deviance test.

Results

Patient characteristics

The median age of the 108 patients with metastatic UM managed only with BSC was 78 (range, 48–95) at the time of treatment decision (Table 1). The median RFI was 32 months (range, 0–194; IQR 2–150; Supplementary Figure S2). The characteristics of the primary UM are summarised in Supplementary Table S2.

Ninety-four percent of patients attended regular follow-up, 41% were asymptomatic, and 94% had liver metastases with or without other sites of metastases (Table 1). The median LDLM was 33 mm (range, 2–270). The AP exceeded UNL in 50% of 94 patients with available data. The PS was 0–2 and 3–4 for 44% and 52% of patients, respectively.

The median interval from diagnosis of metastases to treatment decision (i.e. BSC) was 29 days (range, 0–758; IQR, 7.5–63). The median OS after treatment decision was 1.6 months (range, 0–83; Figure 1(A)). One patient was alive with progressive metastases at the time of analysis. The audited cause of death was metastatic UM for others.

Overall survival by stage

Of the 105 patients who could be staged according to the WF, 24% represented stage IVa, 19% IVb, and 55% IVc. The median OS from treatment decision shortened with increasing stage. It was 12 (range, 1.6–83), 5.7 (range, 0.5–40), and 0.6 (range, 0–8.0) months for stage IVa, IVb, and IVc, respectively ($p<.001$, log-rank test for trend, Figure 1(B)). By univariable Cox regression, WF predicted shorter OS: stage IVb versus IVa ($p=.038$, HR 1.9), IVc versus IVb ($p<.001$, HR 4.2), and IVc versus IVa ($p<.001$, HR 11.9; Supplementary Table S3).

In stage IVa, 50% of patients survived with BSC for ≥12 months (Supplementary Figure S3). In stage IVb, 50% and 25% of patients survived ≥6 and ≥12 months, respectively. In stage IVc, 97% of them died within 6 months.

The weighted kappa for agreement between observed and predicted OS category was 0.614 and 0.615 (agreement 84% versus 59% expected, $p<.001$ and 83% versus 57% expected, $p<.001$, Supplementary Table S4), calculated from the treatment decision and diagnosis of metastases, respectively [10].

The historical benchmarks for OS from treatment decision, stratified by WF stage, and an Excel file with the corresponding data to calculate the historical survival curve are provided (Appendix C, D, and https://doi.org/10.5281/zenodo.3369090).

Verification of and search for further prognosticators

Regarding the components of the WF, the median OS from treatment decision was 9.7 months (range, 0.5–83) for PS 0–1, 6.1 months (range, 0.2–40) for PS 2, and 0.6 months (range, 0–27) for PS 3–4 ($p<.001$, log-rank test for trend). A higher AP level and a larger LDLM (by TNM M1 category) also associated with shorter OS ($p<.001$), verifying their validity as predictors when analysing OS with BSC.

The median OS was 1.1, 1.0, and 1.9 months for RFI <2.0, 2.0–3.5, and >3.5 years, respectively ($p=.033$, log-rank test for trend; Supplementary Figure S4 for different variables); and 8.3 months for absence of symptoms from metastases versus 0.6 months for presence of symptoms ($p<.001$, log-rank test).

In bivariable Cox regression models with WF stage, presence of symptoms independently predicted survival ($p<.001$), and this model fitted better with the data (–2 log likelihood = 332.59 versus 348.27, $p<.001$, $df=1$; Supplementary Table S3).

Table 1. Baseline characteristics of 108 patients with metastatic uveal melanoma managed with best supportive care, and stratification by the Helsinki University Hospital Working Formulation stage.[a]

Variable	All patients $N = 108$	Stage IVa $N = 26$ (24%)	Stage IVb $N = 20$ (19%)	Stage IVc $N = 59$ (55%)
Gender, *N* (%)[b]				
Female	53 (49)	14 (54)	11 (55)	27 (46)
Male	55 (51)	12 (46)	9 (45)	32 (54)
Age at treatment decision, median (range, IQR), years	78 (48–95, 55–93)	83 (64–95, 72–91)	79 (48–90, 70–85)	77 (48–94, 57–87)
Relapse-free interval, *N* (%)[c]				
<2.0 years	44 (41)	7 (27)	10 (50)	25 (42)
2.0–3.5 years	27 (25)	7 (27)	4 (20)	16 (27)
>3.5 years	37 (34)	12 (46)	6 (30)	18 (31)
Symptoms from metastasis, *N* (%)				
No	44 (41)	20 (77)	14 (70)	10 (17)
Yes	60 (56)	6 (23)	6 (30)	47 (80)
Unknown	4 (4)	0 (0)	0 (0)	2 (3)
Histologic confirmation, *N* (%)[d]				
Available	62 (57)	14 (54)	8 (40)	40 (68)
Not available	46 (43)	12 (46)	12 (60)	19 (32)
Location of metastases at the time of diagnosis, *N* (%)				
Liver only	75 (69)	19 (73)	10 (50)	44 (75)
Liver and other sites	27 (25)	6 (23)	8 (40)	13 (22)
Only other sites	6 (6)	1 (4)	2 (10)	2 (3)
TNM M1 category				
≤30 mm (M1a)	43 (40)	22 (85)	9 (45)	11 (19)
31–80 mm (M1b)	32 (30)	3 (12)	10 (50)	19 (32)
>80 mm (M1c)	16 (15)	0 (0)	1 (5)	14 (24)
Unknown	17 (16)	1 (4)	1 (5)	15 (25)
Serum or plasma alkaline phosphatase level, *N* (%)				
<1.0 x UNL	47 (44)	17 (65)	13 (65)	16 (27)
1.0–2.0 x UNL	18 (17)	0 (0)	1 (5)	16 (27)
>2.0 x UNL	29 (27)	1 (4)	4 (20)	24 (41)
Unknown	14 (13)	8 (31)	2 (10)	3 (5)
Performance status, *N* (%)[e]				
0–1	35 (32)	25 (96)	8 (40)	2 (3)
2	13 (12)	0 (0)	8 (40)	5 (8)
3–4	56 (52)	1 (4)	4 (20)	50 (85)
Unknown	4 (4)	0 (0)	0 (0)	2 (3)

IQR: interquartile range; UNL: upper normal limit.
[a]Stage IVa corresponds to predicted overall survival of ≥12 months, IVb <12–6 months, and IVc <6 months; three patients could not be staged.
[b]Binomial test, $p = .51$.
[c]Relapse-free interval is defined as the time from the primary tumour to the diagnosis of metastases.
[d]Please see Supplementary Text in Appendix A for details.
[e]Eastern Cooperative Oncology Group performance status.

Stratified by WF stage, none of the other variables was significant in all three strata of WF stage (Supplementary Table S5).

Discussion

Our nation-wide study with BSC for metastatic UM shows that the WF staging, previously validated by the OOG for mainly actively treated patients [10], differentiates also patients receiving BSC by OS. The agreement between predicted and observed OS, evaluated by weighted kappa, was even stronger in our dataset than in the OOG validation study (0.388), irrespective of whether we based staging on data at the time of treatment decision or diagnosis of metastases (0.614 and 0.615, respectively) [10].

Also, to the best of our knowledge, our cohort is the second largest one of patients receiving BSC for metastatic UM, and we are the first to stage them. We are aware of seven previous reports that included 11 to 191 patients with BSC [9,20–25]. One of these studies also analysed prognostic factors and found, in line with us, that patients who received BSC had worse PS than actively treated [23]. Correspondingly, the PS, but also the AP level and LDLM, the two other components of the WF, were independent predictors of OS in our dataset.

The median OS of 1.6 months in our BSC cohort was substantially shorter than 13 months in our recent meta-analysis of 2,494 actively treated patients and 10 months in another meta-analysis of 921 patients [4,5], but the stage distribution in the latter studies probably was very different [23]. The WF stage was available in 3 of 78 studies [26–28] included in the first meta-analysis, but none of them reported on BSC.

To best match our results with clinical research practice, we chose as our primary outcome the OS from treatment decision, as required of trials by the European Medicines Agency and the U.S. Food and Drug Administration [29,30]. The median interval between diagnosis of metastases and BSC decision was only 29 days in our cohort, and the agreement with observed OS was equivalent for both of these endpoints.

The median OS in the OOG validation study was 11 months, expectedly much longer than 1.6 months with BSC [10]. However, the median OS for stage IVa and, especially, stage IVb was more similar — 17 versus 14 months and 10 versus 8.6 months, respectively. The vast majority of patients with PS 0–1 in our study fell in these two stages.

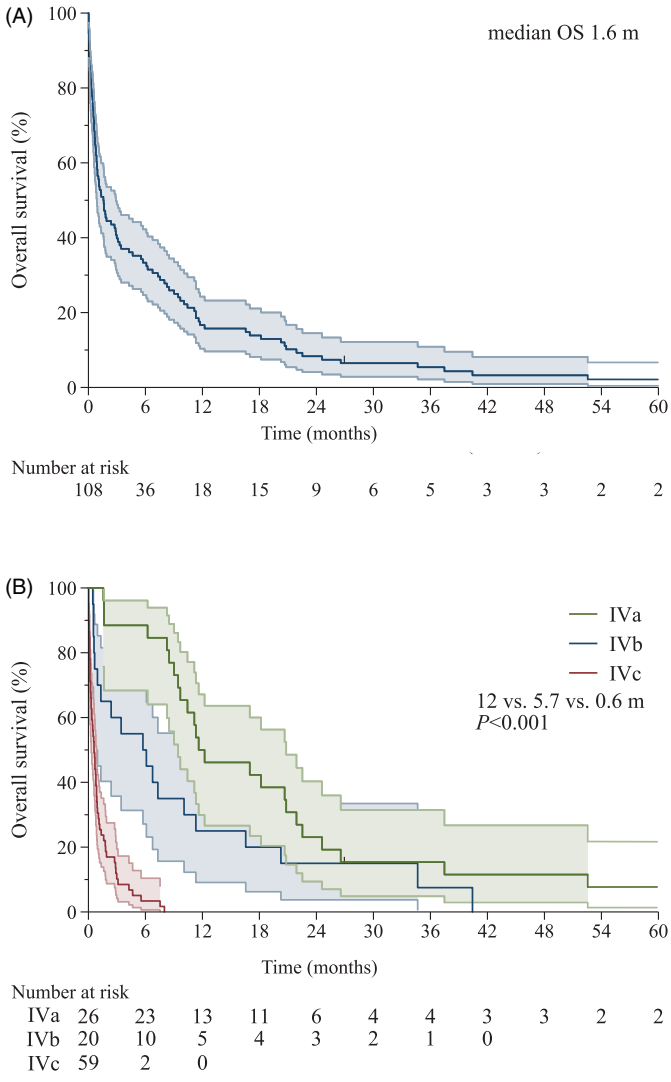

Figure 1. Kaplan-Meier graph of overall survival (OS) from decision to treat with best supportive care for metastatic uveal melanoma. (A) Entire cohort. (B) According to the Helsinki University Hospital Working Formulation. Three patients of 108 patients could not be staged and are omitted. Shaded areas show the 95% confidence intervals.

These observations are in line with a previous study that compared OS with systemic chemotherapy and BSC, and found no difference by multivariate analysis [23]. The OS for stage IVc in the OOG cohort was 4 times as long, 4.6 months versus 1.1 months, as with BSC [10]. Of our patients with stage IVc, 85% had a poor PS and they were thus probably excluded from active systemic treatment unlike in the OOG study.

Our overall and WF stage-specific benchmarks remain provisional until verified and refined with independent datasets. Limitations of our study include, in addition to the retrospective data collection, lack of genetic prognosticators and lack of a universal definition of BSC [12]. To improve understanding of the natural course of metastatic UM, we encourage collaboration to enrol patients who receive BSC in order to collect their WF stage and additional prognostic factors, especially genetic ones [31–33]. We strongly advocate using a validated system, such as the WF stage, for evidence-based, stage-specific reporting of outcomes.

Disclosure statement

ESR reports personal fees from Théa Nordic, MMH personal fees from BMS, MSD, Novartis, Roche, Sanofi, and Varian, and TTK personal fees from Santen Finland; all outside the submitted work. ML and JL have no conflicts of interests.

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