DOI: 10.1111/jdv.16306 JEADV

ORIGINAL ARTICLE

Prognostic factors in 161 patients with mucosal melanoma: a study of German Central Malignant Melanoma Registry

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Abstract

Background Mucosal melanoma is a rare malignancy which represents approximately 1% of all melanomas. It is shown that mucosal melanomas have a different biology and less favourable prognosis than its cutaneous counterpart.

Objectives Predictive and prognostic factors of survival for mucosal melanoma have not yet been elucidated. The aim of this study was to investigate risk factors affecting the course of mucosal melanoma patients followed in our clinic.

Methods One hundred and sixty-one patients with mucosal melanoma prospectively documented in the German Central Malignant Melanoma Registry (CMMR) were included in this study. Gender, age, localization, stage at first medical examination, tumour thickness and mutational status were documented. The American Joint Committee on Cancer (AJCC), 7th edition was used to define tumour stage. Kaplan–Meier survival curves were evaluated compared with the log-rank test. Multivariate Cox proportional hazard models were used to identify significant independent prognostic factors.

Results According to the localization, patients were categorized in 44.7% oral–nasal, 28.6% genital, 20.5% anorectal and 6.2% visceral. Genital mucosal melanomas had the most favourable 5-year OS rate (58.6%) followed by visceral (58.3%) and oral–nasal (39.3%). Anorectal melanomas had the worst OS time (median: 21 ± 4.8 months) and 5-year survival rate (22.7%). Patients <60 years had a better survival than the older group ($P = 0.013$). Tumour stage at the time of the first medical examination was also a significant factor for survival ($P = 0.001$). Gender and mutational status were found to have no effect on survival. Age (<60 years vs. ≥60 years; HR = 2.1) and stage at first medical examination (Stage I vs. Stage IV; HR = 8.2) are shown to be significant independent prognostic factors on multivariate Cox regression analysis, but not localization.

Conclusion In this study, we observed that older age and advanced stage have significant negative effects on the survival of mucosal melanoma. Thus, the AJCC staging system is applicable for mucosal melanoma.

Received: 6 October 2019; Accepted: 29 January 2020

Conflicts of interest

ES and UK have no conflicts of interest. TA reports other from Novartis, personal fees and other from BMS, personal fees from Klinik für Dermatologie und Allergologie Universitätsklinikum Gießen und Marburg GmbH, outside the submitted work. UL reports personal fees from MSD, personal fees from Roche, personal fees from Novartis, personal fees from Pierre Fabre, personal fees from Sanofi, outside the submitted work. AF reports other from Roche, other from Novartis, other from BMS, other from MSD, other from Cegat, other from Pierre Fabre, outside the submitted work. TKE reports personal fees from Amgen, personal fees from BMS, personal fees from MSD, personal fees from Roche, personal fees from Novartis, personal fees from Pierre Fabre, personal fees from Sanofi, personal fees from Leo Pharma, outside the submitted work. CG reports personal fees from Amgen, grants and personal fees from BMS, personal fees from MSD, personal fees from Philogen, grants and personal fees from Roche, grants and personal fees from Novartis, personal fees from Pierre Fabre, personal fees from Sanofi, outside the submitted work.

Funding sources

None declared.

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Introduction

Melanomas are highly malignant tumours that originate from melanocytes. After embryogenic migration and differentiation, melanocytes can settle in the skin, as well as the mucous membranes, eyes, cochlea, leptomeninges, brain, heart and adipose tissue.[1] Mucosal melanomas represent approximately 1% of all melanomas. They can arise from any mucosal anatomical site, including the oral, nasal, respiratory, genitourinary, anorectal, gastrointestinal and cervical areas.[2] The most common site is head/neck area considering approximately 50% of all mucosal melanomas.[3]

Mucosal melanomas have different mutation profiles than cutaneous melanomas; although BRAF mutations are infrequent, there is an increased rate of c-KIT overexpression.[4–6] This comparatively higher proportion of c-KIT mutations and lower proportion of BRAF mutations indicate that mucosal melanoma has a different biology than cutaneous melanoma.[7] The frequency of the BRAF, NRAS and c-KIT oncogenic mutations for mucosal melanoma is reported to be 5%, 14% and 14%, respectively.[8]

Due to the low incidence, the predictive and prognostic factors for mucosal melanoma have not yet been clarified. Diagnosis is often delayed due to the hidden localization of mucosal melanomas, and their rich lymphatic and hematogenic vascularization further contribute to the relatively poor prognosis.[7,9] This study aimed to investigate the clinical factors that affect the survival of mucosal melanoma.

Patients and method

Data on primary mucosal melanoma patients diagnosed at or referred to the Department of Dermatology at the University Hospital of Tuebingen between January 1984 and December 2018 were obtained from the German Central Malignant Melanoma Registry (CMMR). Localization was categorized as oral–nasal, genital, anorectal and visceral mucosa. Ocular melanoma and mucosal metastases from cutaneous melanomas were excluded. We documented patient characteristics (gender, age, localization of primary tumour, tumour thickness, stage at first medical examination in Tuebingen, mutational status) and calculated survival rates and overall survival (OS) time. The American Joint Committee on Cancer (AJCC), 7th edition, was used to define tumour stage.[10] Time from the first medical examination or diagnosis to the last contact or death was defined as the follow-up time. The minimum follow-up time was 3 months.

Statistical analysis

The statistical analyses were performed using IBM SPSS Statistics Version 26.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA) and STATA (StataCorp LP, College Station, TX, USA).

Patients' characteristics as categorical variables were compared using Pearson's chi-squared test. Survival curves were evaluated using the Kaplan–Meier and compared with the log-rank test. Proportions were presented with 95% confidence intervals (95% CI). Multivariate Cox proportional hazard models were used to identify significant independent prognostic factors for survival. Results of Cox proportional hazards modelling were described as hazard ratios (HRs) together with 95% CIs. Throughout the analyses, P-values <0.05 were considered statistically significant.

Results

We identified 161 mucosal melanoma patients at the Department of Dermatology of the University Hospital of Tuebingen. Patients' characteristics and 5-year OS rates are summarized in Table 1. Our cohort had a female predominance (65.8% female vs. 34.2% male). Patients were categorized into two age groups defined as <60 years and ≥60 years; the younger group had a better survival ($P = 0.013$) than the older group (Fig. 1a). Localization of the tumour was distributed as 44.7% oral–nasal, 28.6% genital, 20.5% anorectal and 6.2% visceral. Visceral mucosal melanomas were anatomically located in cervix ($n = 3$), jejunum ($n = 2$), ileum ($n = 2$), oesophagus,[1] gastric cardia ($n = 1$) and gallbladder ($n = 1$). The most commonly affected localization in male patients was oral–nasal region (60%), while it was genital area (43.7%) in female. Tumours localized in the genital mucosa had the best OS followed by visceral and oral–nasal mucosal melanomas (Fig. 1b). Anorectal melanomas had the worst survival; median OS time was 21 months (95% CI: 11–30). It was observed that tumour thickness and disease stage correlated inversely with 5-year survival rate and median OS (Fig. 1c).

Mutational analyses had been performed in the routine clinical care in 57 patients (Table 2). Alterations were identified in *BRAF* for five patients, *NRAS* for seven patients and *c-KIT* for five patients. There was no statistically significant difference between the OS time of the patients with these mutations and that of the patients without these mutations ($P = 0.426$).

Age ($P = 0.013$), localization ($P = 0.014$), tumour thickness ($P = 0.017$) and the tumour stage at the first medical examination in Tuebingen ($P = 0.001$) were found to be significant OS prognostic factors in the univariate Kaplan–Meier analyses. Multivariate regression analyses were also performed to identify the independent OS prognostic factors. Tumour thickness was excluded from the Cox regression hazards modelling because of the large number of unknown cases. The multivariate Cox regression analysis showed that age ($P = 0.006$) and tumour stage at the first medical examination ($P = 0.011$) were significant independent prognostic factors for survival (Table 3).

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Table 1 Patient characteristics and survival rate

	n	5-year OS rate	*P* value*
Gender			0.416
Female	106	41.7%	
Male	55	41.6%	
Age group			0.013
<60	46	57.2%	
≥60	115	34.9%	
Localization			0.014
Oral–nasal	72	39.3%	
Genital	46	58.6%	
Anorectal	33	22.7%	
Visceral	10	58.3%	
Tumour thickness			0.017
≤1.0 mm	8	All alive	
1.01–2.0 mm	11	77.8%	
2.01–4.0 mm	15	54.2%	
>4 mm	33	30.7%	
Unknown	94	35.3%	
Stage at first medical examination			0.001
I	15	92.9%	
II	36	44.2%	
III	24	29.8%	
IV	67	28.6%	
Unknown	19	73.1%	

**P* value of Kaplan–Meier log-rank test for survival analysis.

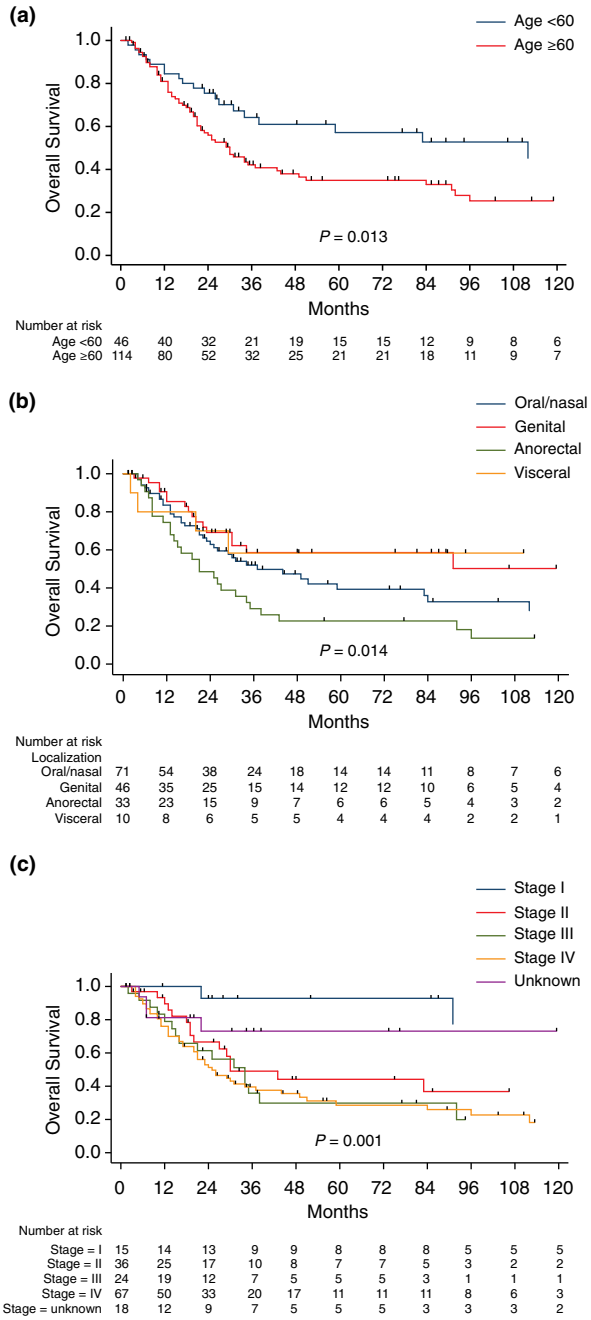


Figure 1 Kaplan–Meier overall survival analyses. (a) Comparing age groups. (b) Comparing localization. (c) Comparing stage.

Discussion

Mucosal melanomas have an aggressive behaviour, and population-based studies have demonstrated that the prognosis for mucosal melanomas is worse than that for cutaneous melanomas.[11–13] In a recent meta-analysis, mucosal melanomas are shown to be 2.25 times more lethal than cutaneous melanomas.[14] The reported survival rates for mucosal melanoma vary depending on the anatomical localization. The overall 5-year survival rate for mucosal melanoma is calculated to be 0–45%.[9]

In contrast to its cutaneous counterpart, the epidemiological data and prognostic factors for mucosal melanoma have not been clearly identified. Because the tumour localization is often not easily visible or accessible, most mucosal melanoma cases have reached an advanced stage by the time that they are diagnosed.[9] Nevertheless, it is known that mucosal melanomas have a worse prognosis than cutaneous melanomas regardless of the stage.[15] Male gender, tumour thickness, age, ulceration and advanced tumour stage at initial diagnosis are linked to a less favourable prognosis for mucosal melanoma.[14–21] In the current study, age ≥60, anorectal localization, thickness and advanced tumour stage were identified as significant negative prognostic factors for survival according to the univariate analysis. In the multivariate analysis, older age and advanced tumour stage remained independent significant influence factors for survival. Gender had no significant effect on survival in our analysis.

Consistent with the results of Schaefer[20] and Heppt,[21] we found that anorectal melanomas have the worst (median: 21 ± 4.8 months) survival time. Unexpectedly, melanomas that were located at the visceral mucosa (mean: 87.1 ± 20 months, median not reached) had a survival time that was as favourable

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Table 2 Mutational status

Genes analysed	Total number of analysed patients	Number of patients with mutation
BRAF	53	5 (9.4%)
NRAS	39	7 (17.9%)
c-KIT	44	5 (11.9)

Table 3 Significant risk factors for MSS on multivariate analysis

	Hazard ratio (95% CI)	*P* value
Age (<60 vs. ≥60)	2.1 (1.2–3.6)	0.006
Localization		0.374
Genital	Reference	
Oral–nasal	1.2 (0.6–2.2)	
Anorectal	1.5 (0.7–2.9)	
Visceral	0.6 (0.1–2)	
Stage		0.011
I	Reference	
II	6.3 (1.4–28.4)	
III	8.6 (1.8–40.8)	
IV	8.2 (1.8–36.5)	
Unknown	0.4 (0.4–13.3)	

as genital mucosal melanomas (mean: 91.3 ± 11.3 months, median not reached). One possible explanation for this result is that the patients in the visceral mucosal melanoma group were younger (mean 56.7 ± 9.6 years) than the rest of the collective (mean 66.4 ± 12.2 years). In addition, the sample size for visceral mucosal melanoma was comparatively small. Only 3 (30%) of the visceral mucosal melanoma patients died from melanoma, and six patients were still alive at the time of the last medical contact. Few case studies have evaluated the clinical course of visceral mucosal melanomas, and little is known about their prognosis.[22–25] To our knowledge, no studies have compared primary visceral mucosal melanomas by anatomical regions.

As most mucosal melanomas are metastatic and at an advanced tumour stage at the time of their diagnosis, it is challenging to histopathologically identify the precise tumour thickness [9,15] and ulceration status. There is no clear consensus on the staging definitions for mucosal melanoma. The classification of TNM is only used for head-and-neck-localized mucosal melanomas.[26] Once the melanomas have metastasize, the disease is at least in Stage III or Stage IV. In this study, patients with an unknown tumour stage at their first medical examination were assumed to be in the early stages of melanoma, but the exact tumour stage could not be determined due to the inadequate data about the tumour's thickness and ulceration. This assumption was supported by the fact that the survival of patients with an unknown tumour stage was similar to that of Stage I patients. In addition, the survival of the patients with unknown tumour thickness was closer to that of the thickest tumour group (>4 mm), suggesting that the tumours of this patients were too thick or extensive to be calculated.

Mucosal melanomas are known to carry less mutational burden than their cutaneous counterparts.[27] In addition, genetic aberrations identified for cutaneous melanoma are also reported to be fewer in mucosal melanomas. In a recent study, Newell *et al.* performed whole-genome sequencing in 67 mucosal melanomas from different geographic locations: Asia, Australia and Europe. Significantly mutated genes were presented as *NRAS* (17.9%), *BRAF* (16.4%), *NF1* (16.4%), *KIT* (14.9%), *SF3B1* (11.9%), *TP53* (8.9%), *SPRED1* (7.5%), *ATRX* (5.9%), *HLA-A* (5.9%) and *CHD8* (4.5%). The authors observed that mucosal melanoma has a heterogeneous nature related to the underlying mutagenic processes, body site-specific driver mutations and genetic origin of the patients. Mutation profiles of the majority of the mucosal melanomas indicated potential sensitivity to CDK4/6 and MEK inhibitors.[28] We searched mutation analyses in 57 patients which resulted *BRAF* positive for five patients (9.4%), *NRAS* positive for seven patients (17.9%) and *c-KIT* positive for five patients (11.9%). To date, only a few studies have evaluated the effect of mutations on mucosal melanoma survival, and the results have been inconsistent.[17,29,30] In our cohort, no statistically significant difference in OS time was detected between the patients with mutations and without mutations.

Our study has some limitations. We had a limited number of patients from one single centre. In addition, mutational genetic analyses were performed on only approximately one-third of the whole cohort. We also could not provide information about the treatments being given to patients due to inadequate data.

Conclusion

There is an unmet need for the explanation of the etiopathogenesis and prognosis of mucosal melanoma. Consistent with several previous studies, the current study found that older age and advanced disease stage have a significant negative effect on survival of mucosal melanoma. Although genetic alterations are less common in mucosal melanomas than cutaneous melanomas, we suggest that additional mutational analysis should be performed to elucidate the pathogenesis of the disease and to accelerate the optimal treatment selection for these aggressive tumours. Multicentre prospective clinical trials are required to illuminate the unique biology of mucosal melanoma.

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