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ONCOLOGY

Metastatic patterns and metastatic sites in mucosal melanoma: a retrospective study

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Abstract

Objectives Melanomas arising from mucosa are rare and associated with a poor prognosis. This study aims to provide an analysis of metastatic pathways, time intervals, factors influencing metastatic spread and organs for distant metastases.

Methods A total of 116 patients with mucosal melanomas of different sites were included. The mean follow-up interval was 47±52 months. Patients were assigned to two different metastatic pathways, either presenting loco-regional lymph node metastases as first spread or direct distant metastases. The distribution of distant metastases was assessed.

Results Twenty-six patients presented with a pre-existing metastatic spread and were not assigned to pathways. Of the included patients, 44 developed metastases after treatment of the primary tumour; 25 patients directly developed distant metastases; 16 patients developed regional lymph node metastases prior to distant metastases. Location of the primary tumour in the upper airway or GI tract and advanced T stage were significant risk factors of direct distant metastases. Distant metastases are mainly located in the lung, the liver and non-regional lymph nodes.

Conclusions Mucosal melanomas show a high rate of direct distant metastases rather than regional lymph node metastases. Thus the follow-up should always include a whole-body cross-sectional imaging in high-risk tumours.

Key points

- *Mucosal melanomas show a high rate of direct distant metastases.*
- *T stage and primary location are predictors for direct distant metastases.*
- *Distant metastases were mainly found in lung, liver and lymph nodes.*
- *Follow-up of a high-risk mucosal melanoma should include whole-body imaging.*

Keywords Mucosal melanoma · Progression · Metastatic spread · Metastatic pathway · Imaging

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Introduction

Primary mucosal melanomas are a very rare subgroup of melanomas and account only for approximately 1 % of all primary malignancies arising from melanocytes [1]. On average they present one decade later than primary cutaneous melanomas (average of 67 years versus 55 years in cutaneous melanoma) [1]. The primary cutaneous melanoma is more common in light-skinned individuals; in contrast, mucosal melanomas are rather equally distributed among different races [1–3]. The most common primary site of mucosal melanoma is the head and neck region, which accounts for more than half of all mucosal melanomas. Among head and neck tumours, most are located in the nasal cavity (55 %) followed by the oral cavity (40 %).

Other common sites are the anal/rectal tract (23 %), the female genital tract (18 %) and the urinary tract [1]. Because of the high incidence of tumours affecting the female genital tract, mucosal melanomas are found more frequently in women (65 %) than in men [1]. The incidence of primary cutaneous melanoma has increased during the past decades because of increased exposure to ultraviolet light [4, 5]. In contrast the incidence of primary mucosal melanoma has remained stable [5]. Because their location is shielded from sunlight, UV irradiation is unlikely to be a risk factor, despite the origin of the tumour from melanocytes [6, 7]. In addition to a different epidemiologic pattern, an increasing number of reports suggest differences in tumour biology and molecular aberrations between primary cutaneous melanomas and primary mucosal melanoma [8]. For example the common BRAF mutations, commonly associated with cutaneous melanoma, are rarely seen in mucosal melanomas. In contrast mucosal melanomas show a high rate of c-KIT mutations (up to 50 %) [8, 9]. Because of the lack of obvious clinical signs during the early stages, mucosal melanomas are usually diagnosed at a locally advanced tumour stage. Its hidden primary location in combination with its aggressive tumour biology is supposed to account for the poorer prognosis of mucosal melanomas compared to the more common cutaneous melanoma [1]. Medical therapy usually consists of surgery, often combined with radiation of the tumour bed. In advanced stages of the disease, therapy regimes for cutaneous melanomas are usually applied [10, 11].

Cutaneous melanoma follows different metastatic pathways. In-transit metastases in the surrounding tissue, lymph node metastases or visceral metastases due to haematogenous dissemination bypassing the lymphatic system are manifestations of tumour progression. On the contrary to cutaneous melanoma, for which the patterns of metastatic pathways are well understood, there is a striking lack of data on metastatic behaviour of mucosal melanomas [12–14]. Furthermore, as a result of the low prevalence there is still no validated prognostic staging system. In addition there is still a lack of data about stage-adequate time intervals for follow-up and appropriate imaging modalities. To establish a stage-adjusted follow-up system, data is needed describing the orderly course of the disease including the stepwise progression and frequent sites of distant metastases. Therefore, the analysis of metastatic patterns and preferred sites for distant metastases are of high relevance for the assessment of treatment strategies and follow-up regimes.

In this retrospective study we analysed a cohort of 116 patients with mucosal melanoma as regards the site and time of metastatic progression.

Material and methods

Patients

The retrospective study included 116 patients diagnosed with primary mucosal melanoma. The patient data was retrieved from the databases of the Comprehensive Cancer Center Tübingen and of the Central Register of the German Dermatologic Society (Deutsche Dermatologische Gesellschaft) in Tübingen. Primary mucosal melanoma was defined as a malignant melanoma with the primary site being the mucosal epithelium of any anatomical region. Both databases contained patients treated from 1984 until 2011. All patients had a clinically and histologically confirmed diagnosis. The study protocol was approved by the institutional review board (IRB).

Follow-up

All patients had received a follow-up. In general, follow-up was carried out according to standards in cutaneous melanoma: during the first 5 years after diagnosis follow-up examinations were carried out every 3 months, thereafter every 6 months. However, as a result of the lack of specific guidelines for mucosal melanoma, time windows for follow-up were not always standardized. Examinations consisted of a clinical examination of the original location and a blood test including a full blood count, differential blood count, liver enzymes, creatinine and lactate dehydrogenase. Depending upon the extent of the primary tumour and the initial presentation, either ultrasound scans of the upper abdomen and a chest X-ray or whole-body CTs were performed every 6–12 months, depending on the initial stage of the tumour. A full body CT scan included imaging of the head, neck, thorax, abdomen and pelvis. If metastases were suspected, further diagnostic measures were carried out according to the clinician's decision. The mean follow-up interval of the cohort was 47±52 months, ranging from 8 month to 297 months.

Evaluated parameters

The files of all patients were analysed. The data set was checked and medical reports of the follow-up examinations were reviewed for the course of the disease, including radiological reports of imaging studies and clinical findings. We considered the initial staging at first presentation per patient. Time to metastasis was assessed using a time-to-event analysis. The time to metastasis was defined as the interval from the date of histological diagnosis of the primary tumour to the time of appearance of metastases. If regional lymph node metastasis was the first sign of tumour progression, the time from first appearance of regional lymph node metastasis until appearance of distant metastasis was also calculated. The site of any distant metastasis was reported. If visceral metastases appeared at more than one site, all described sites all were reported.

Two major patterns of dissemination were defined:

Pathway I: Dissemination from the primary tumour site to regional lymph nodes. Secondary dissemination to distant organs or distant lymph nodes.

Pathway II: Direct dissemination of the primary disease to distant organs or distant lymph nodes. In case of simultaneous dissemination to distant metastases and regional lymph nodes, the patients were also classified as pathway II (two patients).

Classification and influencing factors

Primary sites of mucosal melanoma were clustered as gastrointestinal (GI) tract, conjunctiva, upper airway, anus, penis, vagina and vulva.

The degree of tissue invasion was classified according to the system published by Clark et al. [15]. In 85 patients the T stage could be obtained. The degree of tumour invasion was classified according to the TNM classification system proposed by the American Joint Committee on Cancer (AJCC) [16]: pT1, no greater than 1.00 mm; pT2, 1.01–2.00 mm; pT3, 2.01–4.00 mm; and pT4, greater than 4.00 mm. The exact depth of the tumour invasion was obtained in 65 patients.

Statistical analysis

JMP 10.0 was used for statistical analysis. Differences in distributions were tested using the Chi^2 test for binary data and the Wilcoxon–Mann–Whitney test for continuous data. Statistical differences were considered significant if $p<0.05$. Competing risk analysis was performed with the cmprsk package for R and applying the method described by Scrucca et al. [17].

Results

Patients and location of primary tumour

Of the 116 patients, 85 (73.3 %) were female. The median age at diagnosis was 64 years, with a range from 20 to 89 years. The anatomical sites of the primary tumour were vulva (41 patients, 35.3 % of total), upper airway (36 patients, 31.0 %), GI tract (20 patients, 17.2 %), penis (8 patients, 6.9 %), vagina (6 patients, 5.2 %) and conjunctiva (5 patients, 4.3 %). The highest mean tumour depth was found in tumours of the GI tract (11.5 mm), whereas conjunctival melanomas were the most superficial (0.7 mm). The exact distribution of tumour invasion is given in Table 1.

Initial tumour spread

Of the 116 patients, 18 (15.5 %) initially presented with metastatic regional lymph nodes and 5 patients (4.3 %) had solely distant metastases. Three patients presented with disseminated disease. In the rest of the patients initial staging indicated no evidence for metastases. Of 18 patients with initial lymph node metastases, 11 developed distant metastases during follow-up. All patients with initial metastatic disease in local lymph nodes or distant organs were excluded from classification in pathways.

Metastatic pathways

During the follow-up period 49 patients did not develop local lymph node metastases or distant metastases. Forty-four patients developed metastases during the follow-up period. Three of these patients were not included in one of the pathways as regional lymph node metastases and distant metastases were detected at the same time. Accordingly a total of 41 patients were assigned to metastatic pathways (Figs. 1, 2 and 3, Tables 1 and 2).

Pathway I

During follow-up, 16 of 44 (36 %) patients developed regional lymph node metastases (Table 2). The mean (±standard deviation) time to develop regional lymph node metastases was 20.1 (±17.3)months. The longest time to regional progression was found for tumours located in the paranasal sinus. However there were no significant differences according to localization of the primary tumour. Of 16 patients with lymph node metastases, 11 developed distant metastases in the following months. The mean time interval from regional metastases to distant metastases was 10.2 (±8.5)months. In those 11 patients following pathway I, 33.4 (±8.5)months elapsed between primary diagnosis and diagnosis of distant metastasis. Nine of these 11 patients died during follow-up. All nine

Table 1 Patient characteristics at initial presentation and distribution of metastatic pathways according to different locations of the primary tumour

Location	All patients (n=116[a])	GI tract (n=20[a])	Conjunctiva (n=5[a])	Upper airway (n=36[a])	Penis (n=8[a])	Vagina (n=6[a])	Vulva (n=41[a])
Tumour thickness (mm), n=65							
Mean	4.9	11.5	0.7	7.3	2.1	6.3	2.9
Std deviation	6.1	11.6	0.6	6.7	1.4	4.5	2.5
Min–Max	0.1–30	2.1–30	0.3–1.1	0.1–21	0.36–4	1.2–12	0.2–9
Regional lymph nodes at presentation							
Nx	17	4	0	8	0	0	5
N0	81 (81.81 %)[a]	10 (62.5 %)	5 (100 %)	25 (89.29 %)	6 (75 %)	5 (83.33 %)	30 (83.33 %)
N1–3	18 (18.18 %)	6 (37.5 %)	0 (0 %)	3 (10.71 %)	2 (25 %)	1 (16.67 %)	6 (16.67 %)
Distant metastases at presentation							
Mx	9	1	0	5	0	0	3
M0	102 (95.33 %)[a]	18 (94.74 %)	5 (100 %)	27 (87.1 %)	8 (100 %)	6 (100 %)	38 (100 %)
M1	5 (4.67 %)	1 (5.26 %)	0 (0 %)	4 (12.9 %)	0 (0 %)	0 (0 %)	0 (0 %)
Distribution of metastatic pathways							
Pathway I	16 (17.8 %)	2 (15.4 %)	3 (60 %)	5 (18.5 %)	1 (16.7 %)	1 (20.0 %)	4 (11.8 %)
Pathway II	25 (27.8 %)	6 (46.1 %)	0 (0 %)	11 (40.7 %)	0 (0 %)	2 (40.0 %)	6 (17.6 %)
Ratio (PI/PII)	0.64	0.33	–	0.45	–	0.5	0.66
No metastasis	49 (54.4 %)	5 (38.3 %)	2 (40 %)	11 (40.7 %)	5 (83.3 %)	2 (40.0 %)	24 (70.6 %)

Exact tumour thickness was known in 65 of 116 patients

[a] Total number of patients for each group

patients died from their metastatic disease. No non-tumour-related deaths were observed. The mean overall survival time of the nine patients following and "completing" pathway I was 55 months.

Pathway II

During follow-up 25 of 44 (57 %) patients developed primary distant metastases without evidence of prior regional lymph

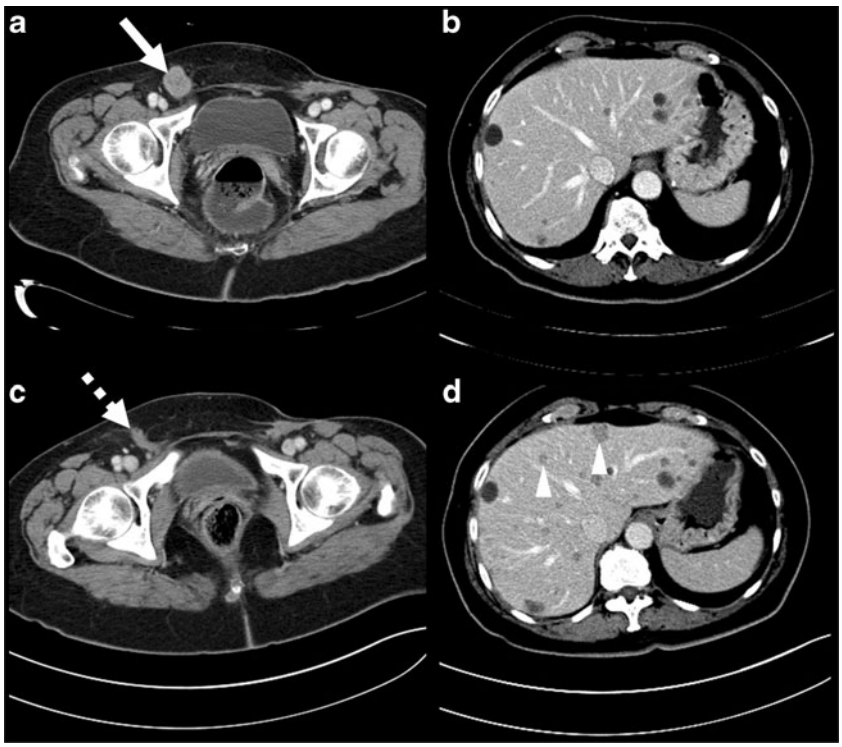

Fig. 1 68-year-old female patient with mucosal melanoma of the vulva indicative of pathway I: The initial tumour was located at the internal portion of the right labia minora and had a thickness of 7 mm. **a**, **b** CT scan 11 months after initial surgery of the primary tumour showing a lymph node metastasis in the right groin and a tumour-free liver. **c**, **d** 17 months after the initial tumour diagnosis the metastatic lymph node in the right groin has been removed (*dashed arrow*) but distant metastases were detected in the liver (*arrowheads* in **d**)

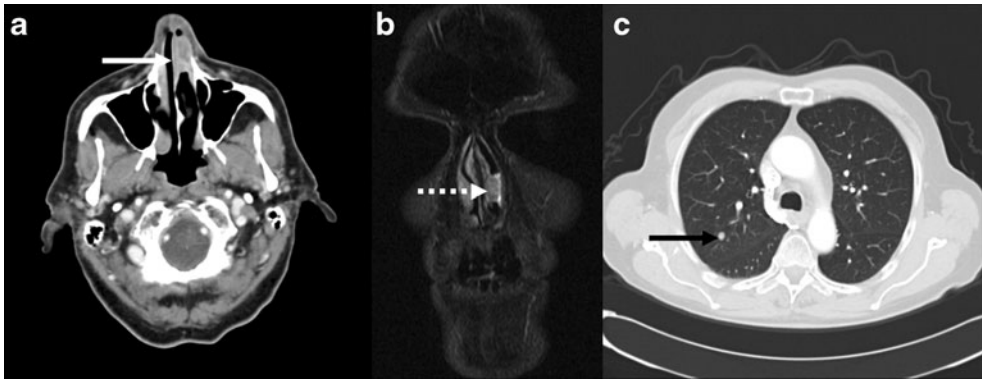

Fig. 2 Pathway II illustrated on a patient with melanoma of the nasal septum. The initial tumour thickness was 20 mm. **a** The primary tumour in an axial slice of a contrast-enhanced CT image (*white arrow*). For the local staging an additive MRI was performed depicting the primary tumour in coronal STIR image (*dashed arrow* in **b**). 20 months after initial diagnosis the first pulmonary metastasis was detected (*black arrow* in **c**)

node metastases (Table 2). In this subgroup time to distant metastases was 21.0 (±21.5)months. Five of the 25 patients developed regional lymph node metastases in the following months (average 4.9±1.6 months). All 25 patients died of their metastatic disease during follow-up. The mean time from first diagnosis to death was 56 months.

The time to develop distant metastases is shorter for patients with direct distant metastases (pathway II) (21 vs. 33 months, $p<0.05$) compared with patients developing local lymph node metastases (pathway I) as the first step of progression.

Excluded patients with initial metastases

It can be assumed that the 18 patients with regional lymph node metastases upon presentation also tend to follow pathway I. In addition it can be assumed that patients with initial distant metastases followed pathway II. Taking this into account the number of patients progressing via a regional lymph node pattern increases to 34 and the number of patients with a direct–distant pattern increases to 30. Hence the proportion of patients following a "regional lymph node pattern" rises to 51 % (34 of 67 patients) and the proportion following a "direct–distant pattern" drops to 44 %.

Determinants of different pathways

In order to identify factors that could potentially influence the metastatic pathway we analysed the location of the primary tumour as well as the T stage (Tables 1 and 3).

For all primary sites with the exception of conjunctiva and penis, spread from the primary tumour site to regional lymph nodes (pathway I) was less common than direct spread to distant organs or distant lymph nodes (pathway II). The location of the primary tumour in the upper airway or in the GI tract was associated with an increased tendency to develop

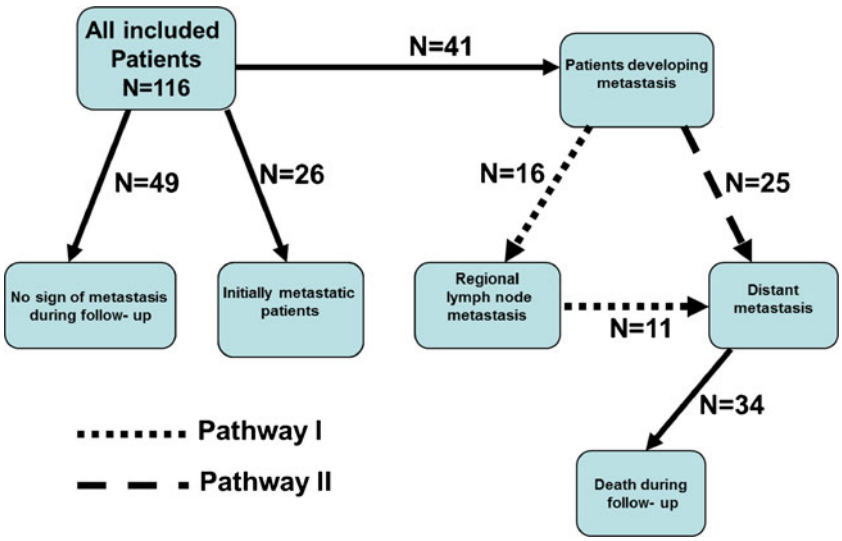

Fig. 3 Orderly course of the disease in $n=116$ included patients. The different metastatic pathways are indicated. Three patients without initial metastases were not included in one of the pathways as regional lymph node metastases and distant metastases were detected at the same time. These patients are not shown the diagram

Table 2 Time intervals during the course of the metastatic spread (pathway I and II)

Pathway I			
Time interval in months	Mean	Std error	Std deviation
Diagnosis until regional lymph node metastasis (n=16)	20.1	4.3	17.3
Regional lymph node metastasis until distant metastasis (n=11)	10.2	2.4	8.0
Diagnosis until distant metastasis (n=11)	33.5	6.7	22.3
Distant metastasis until death (n=11)	14.6	6.1	–[a]
Diagnosis until death (n=9)	55	9.5	–[a]
Pathway II			
Diagnosis until distant metastasis (n=25)	21.0	4.3	21.5
Diagnosis until death (n=25)	56	11.2	–[a]

[a] Censored value. No standard deviation calculated

distant metastases directly without prior regional lymph node metastasis (40.7 and 46.1 % of all the included cases of the initial cohort) compared with primary location in the vulva (17.6 %, p=0.013/p=0.02). Interestingly, direct distant metastases were not observed in any of the conjunctival melanomas.

In the patients with known T stage (79 of 116), T stage was associated with the incidence of pathway II. Patients with T4 tumours had the highest incidence of pathway II (42.3 %). In T1 tumours or a carcinoma in situ, no metastasis were observed during the follow-up time.

Locations of distant metastases

Fifty-four patients of the study group either presented with distant metastases or developed distant metastases during the course of the disease. In 42 of these patients exact localization of the distant metastases is known. In most cases (12 of 42, 28.6 %) the lung was the first organ in which distant metastases were detected, followed by disseminated metastases (8/42, 19.0 %), liver (6/42, 14.3 %) and distant lymph nodes (5/42). In total 92 sites of distant metastases were reported. All locations where distant metastases were found are listed in Fig. 4. There was no association between primary tumour site and site of distant metastases. In 12 patients the exact localization of the distant metastases could not be assessed retrospectively (anus, n=1; internal organs, n=2; conjunctiva, n=1; upper airway, n=7; vulva, n=1).

Discussion

In this study we assessed the course of the disease in patients with primary mucosal melanoma. A particular aim was to examine the orderly progression of the disease including time windows and to describe the localization of appearing distant metastases with regard to different primary tumour localizations. Until now literature describing the orderly progression of this rare disease is sparse. To our knowledge, this study represents one of the largest cohorts comprising patients with mucosal melanomas and is the first study to examine metastatic patterns, time intervals and distribution of distant metastases in this rare neoplastic entity [12, 14, 18, 19].

However, there are some methodical limitations to our study and conclusions from the comparison of time intervals or probabilities of metastatic pathways should be drawn cautiously. It is possible that patients without metastases stopped follow-up before occurrence of metastases. It is also possible that within these patients without further follow-up, a tumour-related or non-tumour-related death occurred or will occur in the future. However within these dropouts a further analysis is unfortunately not possible. Therefore a possible bias for the temporal development of metastases due to these dropouts cannot be excluded. However this bias is expected to be small as the probability of metastatic progression decreases with time after treatment of the primary tumour and patients without metastatic progression (mainly T_{is} and T1 tumours) had the longest average follow-up time (Table 3).

Table 3 Pathways according to T stage (n=79 included patients)

Pathway	Tis	T1	T2	T3	T4	Sum
I	0	0	4 (23.5 %)	10 (41.7 %)	9 (34.6 %)	23
II	0	0	1 (5.9 %)	4 (16.7 %)	11 (42.3 %)	16
No metastasis	2 (100 %)	10 (100 %)	12 (70.6)	10 (41.7 %)	6 (23.1 %)	40
Sum	2	10	17	24	26	79
Average follow-up time in months	123±172	82±81	62±60	44±40	27±27	

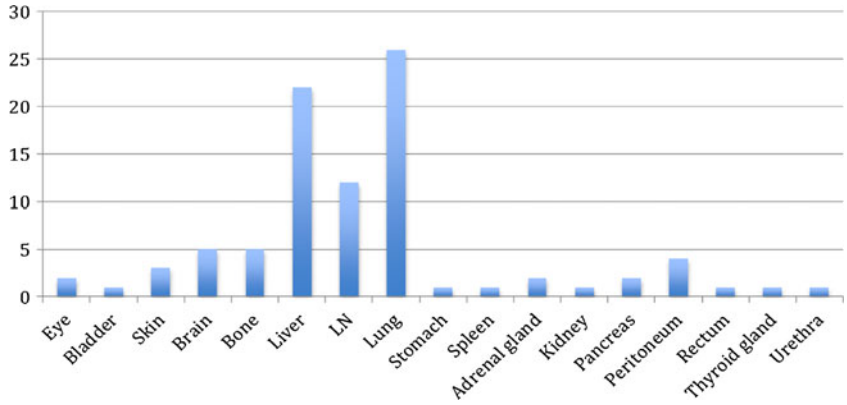

Fig. 4 Number of organs where distant metastases were found in $n=54$ patients with distant metastases. *LN* distant lymph nodes

A further limitation is the selection of our study subpopulation: indeed, when considering the entire population of 116 cases, eight died before developing metastasis. This could in theory bias the recommendations for follow-up time spans. However, when performing a competing risk analysis for metastasis and death before metastasis as the two competing events, we could see that the cohort in which death occurred prior to the appearance of distant metastasis had a significantly lower cumulative incidence rate than those developing distant metastasis at 5 and 10 years (5.8 % [2.4–11.6 %] and 9.0 % [3.2–18.4 %] for the cohort in which death occurred before occurrence of distant metastasis as well as 50.9 % [40.0–60.8 %] and 59.5 % [46.7–70.2 %], respectively). We therefore conclude that the rate of bias due to competing risks is low.

We found a high number of patients that already were diagnosed with metastatic disease by the time of the initial presentation (19.8 % of all patients). Until now it was not certain if this was a feature of intrinsic tumour aggressiveness derived from different tumour biology or a result of a delayed diagnosis of the primary disease. The hypothesis of an influence of a delayed diagnosis is supported by the finding of a high average tumour depth of invasion at the internal locations. Our results are consistent with previous studies describing rates between 27.7 and 32 % of metastatic patients on admission [19, 20]. Hence, mucosal melanomas show much higher ratios of initial metastatic spread than cutaneous (approximately 12 %) or ocular melanomas (3 %) [20]. In our study 67 of the 116 patients (approx. 58 %) were affected by disease progression during the follow-up period compared with 15.5 % of patients in a cohort with cutaneous melanoma from the same centre [21].

For cutaneous melanoma, patterns of spread and time courses of the orderly progression are well documented [21]. In primary cutaneous melanoma around 50 % of the patients who suffer from disease progression start with loco-regional lymph node metastases [21, 22]. Our results indicate that mucosal melanomas are more likely to directly develop distant metastases compared with cutaneous melanomas (pathway II in our study, 57 % of all patients who suffer from disease progression compared to 28.1 % in the study by Meier et al. [21]). However this result of our study is biased by an initially high number of regional lymph node metastases at the time of diagnosis (15.5 %) which is most likely due to the delayed diagnosis of the primary tumour. This is a common feature in mucosal melanomas as confirmed by a recent study of 41 patients with mucosal melanoma of the upper airway, 10 % of whom had regional lymph node metastases by the time of admission [23]. However, even if patients with initial regional lymph node metastases are assigned to a "lymphonodal pattern" the percentage of patients developing direct distant metastases remains higher for mucosal melanomas compared with the cohort of cutaneous melanomas reported by Meier et al. (44 vs. 28.1 %). The time to development of distant metastases is shorter for patients with direct distant metastases (21 vs. 34 months) compared with patients developing local lymph node metastases as the first step of progression. In both pathways patients died after approximately 55 months irrespective of the metastatic pathway. This finding contrasts literature reports of cutaneous melanoma in which distant metastases were observed between 24 and 30 months after the detection of the primary tumour, irrespective of whether lymph node metastases or distant metastases were detected first [21, 24]. However the presented time intervals seem to be in the same range for mucosal and cutaneous melanomas.

We could identify two important predictors for the development of direct distant metastases (pathway II). The local stage is a decisive risk factor for the development of direct distant metastases. In T4 tumours 41.7 % of the patients directly developed distant metastases without prior local lymph node metastases compared to 16.7 % in T3 and 5.6 % in T2, in contrast to cutaneous melanomas where T stage is not associated with a trend to primary distant metastases [21]. The most likely explanation for the finding is that the level of invasion in mucosa and the underlying tissue determines the metastatic behaviour. T4 tumours infiltrate deep into surrounding tissues gaining direct access to systemic circulation, bypassing the surveillance of the loco-regional lymphatic system. This

finding has to be recorded for follow-up strategies. As in our study none of the T1 tumours developed direct distant metastases, a whole-body cross-sectional imaging is probably not necessary and follow-up may be reduced to loco-regional surveillance with ultrasound and clinical examination. In the unlikely case of the detection of local lymph node metastasis, a cross-sectional whole-body imaging can be applied.

The second important determinant of the metastatic pathway is the site of the primary tumour. Tumours located in the upper airway and GI tract are associated with increased trend to follow pathway II (40.7 % and 46.1 %, respectively) and accordingly developed distant metastases without prior regional lymph node metastases compared with primary location in the vulva (17.6 %). In both locations the rate of patients which followed pathway I and developed local lymph node metastases was not significantly different. Primary localization of the tumour in the GI tract or upper airway suggests a less favourable prognosis. This could be explained by the fact that the average depth of tumour invasion of the GI tract and upper airway is already rather high at diagnosis, most likely because of the hidden location. Accordingly, follow-up examinations for mucosal melanomas with a primary located in this region should always include whole-body cross-sectional imaging and a close clinical monitoring.

Metastases of cutaneous melanoma have been found in most organs or tissues, including some sites rarely seen in other solid tumours [16]. Lung metastases are the most frequent single location of distant metastases (approx. 25 %) followed by the brain (14 %), the liver (5 %) and distant lymph nodes (approx. 10 %), whereas disseminated disease was found in 33 % of cases [25]. These findings are supported by autopsy studies were the lung was found to be the organ with the most frequent localization of distant metastases, followed by the liver and the brain [26].

In our study we could confirm that similarly to cutaneous melanoma, lung and liver were the most frequently involved sites of visceral metastasis. This finding is consistent with a recently published observational study [19]. Similar to cutaneous melanoma, most of the patients develop a disseminated disease once distant metastases have been diagnosed. However the number of brain metastases was surprisingly low in our study.

In primary cutaneous melanoma with distant metastatic disease, patients have a better prognosis with lung metastasis compared to other single locations or disseminated disease [25]. Our sample size was too small to check this hypothesis in mucosal melanomas.

Conclusion

In mucosal melanoma the pathway of metastatic progression is associated with the T stage and the location of the primary tumour. Sentinel lymph node biopsy and extensive lymph node dissection may be of little value because of the high proportion of direct haematogenous dissemination. Patient follow-up of a high-risk primary tumour (T2 tumour or higher, location in the GI tract, upper airway location) would probably benefit from whole-body cross-sectional imaging with a high sensitivity for soft tissue metastases, in the lung or the liver and distant lymph node metastases such as contrast-enhanced CT, PET-CT or MRI.

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