Journal of Cranio-Maxillo-Facial Surgery 47 (2019) 1370–1377

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Primary head and neck mucosal melanoma: Predictors of survival and a case series on sentinel node biopsy☆

Tom Prinzen [a,*], Martin Klein [b,1], Christian Hallermann [c], Kai Wermker [d]

[a] Department of Otorhinolaryngology, Duesseldorf University Hospital (UKD), Moorenstrasse 5, 40225, Duesseldorf, Germany
[b] Department of Oral and Maxillofacial Surgery, Fachklinik Hornheide, Head and Neck Cancer Center, Dorbaumstraße 300, 48157, Muenster, Germany
[c] Department of Dermatology and Histopathology, Fachklinik Hornheide, Dorbaumstraße 300, 48157, Muenster, Germany
[d] Department of Oral and Maxillofacial Surgery, Klinikum Osnabrueck, Am Finkenhuegel 1, 49076, Osnabrueck, Germany

A R T I C L E I N F O

Article history:
Paper received 17 February 2019
Accepted 19 June 2019
Available online 25 June 2019

Keywords:
Malignant melanoma
Mucous membrane
Head and neck neoplasm
Prognosis
Sentinel lymph node biopsy

A B S T R A C T

Introduction: Head and neck mucosal melanoma (HNMM) is a rare tumor with a poor outcome. The objective of this study was to assess outcome and prognostic factors for a cohort of patients treated in a head and neck cancer center. In addition, a case series on sentinel lymph node biopsy (SLNB) was included to evaluate it as a method for staging the node-negative neck.

Methods: A retrospective study design was chosen, and 50 patients who were treated from 1973 to 2015 in our institution for primary HNMM were included. The Kaplan–Meier method was used to estimate survival rates. Uni- and multivariate analyses were used to study the influence of possible risk factors on the patients' outcome. These risk factors included patient demographics, tumor characteristics, and treatment modalities.

Results: All patients were treated surgically and 50% received adjuvant treatment. The median disease specific survival (DSS) was 38 months, with a 5-year survival rate of 44%. Positive surgical margin ($p = 0.004$) and distant failure ($p = 0.005$) were associated with a worse DSS. The median disease-free survival (DFS) was 27 months, with a 5-year disease-free rate of 12%. Only tumor depth >5 mm ($p = 0.002$) was associated with a worse DFS. Five clinically node-negative patients received SLNB and only the two SLN-positive individuals suffered from distant failure. Radiotherapy, chemotherapy, and AJCC/UICC stage had no influence on any outcome measure.

Conclusions: Positive surgical margin and distant failure are the only independent prognostic factors for DSS. Tumor depth can predict distant failure. SLNB may be a valuable staging tool for the node-negative neck.

1. Introduction

Mucosal melanoma is a rare malignancy that derives from melanocytes within the mucosal membrane. These melanocytes originate from the neural crest and are thought to play an immunomodulatory role at the entries to our body. Thus, a high concentration of mucosal melanocytes is found in the aerodigestive tract, genital organs, and the anus (Mackintosh, 2001). Mucosal melanoma (MM) accounts up to 1.3% of all melanomas and 55.4% of mucosal melanomas are found in the head and neck area. In the head and neck (HNMM), the most common primary sites are sinonasal (60–70%), followed by the oral cavity (20–30%) (Shuman et al., 2011; Jethanamest et al., 2011). Compared with its cutaneous counterpart (84.7% 10-year DSS), the prognosis for HNMM continues to be poor, with a 10-year disease specific survival rate of around 20% (Jethanamest et al., 2011; Lazarev et al., 2014; Tseng and Martinez, 2011). This is in part due to late symptoms such as epistaxis and nasal obstruction for sinonasal MM and a bleeding mass or poorly fitting dentures for oral MM. Another reason for survival not

☆ Preliminary results of this study were presented at the 2018 German Society of Otorhinolaryngology and Head & Neck Surgery (DGHNO) Annual Meeting (Luebeck, Germany).

* Corresponding author. Fax: +49 0 211 81 18880.
E-mail addresses: tom.prinzen@med.uni-duesseldorf.de (T. Prinzen), martin.klein@fachklinik-hornheide.de (M. Klein), christian.hallermann@fachklinik-hornheide.de (C. Hallermann), kaiwermker@web.de, kai.wermker@klinikum-os.de (K. Wermker).

[1] Martin Klein is Deceased at the 1st of December 2018.

https://doi.org/10.1016/j.jcms.2019.06.012
1010-5182/

improving over recent decades is the lack of evidence regarding risk factors, prognostic factors, and the best management. Promoted prognostic factors are certain head and neck subsites like the nasopharynx and sinus, high age, presence of distant metastasis, positive nodal status, tumor size, depth of invasion, and positive margins after surgical resection (Shuman et al., 2011; Jethanamest et al., 2011; Lawaetz et al., 2016; Patel et al., 2002). Distinguishable histological features like lymph or blood vessel invasion may also be of prognostic relevance (Wermker et al., 2015).

To strengthen the power of the existing data we analysed the patient data in our institution covering the last 42 years. Our aim was to find and evaluate predictors of survival and to analyse the administered therapies in order to contribute to the establishment of an optimized treatment strategy. In addition, we took a more detailed look at the patients who received sentinel node biopsy to evaluate the prognostic value of this diagnostic intervention.

2. Materials and methods

2.1. Study design

To analyse the outcomes and possible predictors of survival a retrospective study design was chosen. A comprehensive computer search was conducted to retrieve and analyse all suitable patients who were diagnosed and treated for primary mucosal melanoma of the head and neck from 1973 to 2015, at the Fachklinik Hornheide, a referral skin cancer center in Germany. The scientific use of the anonymised patient data was approved by the local ethics committee (Ethical Committee of the Westfalian Wilhelms-University Muenster, Approval No. 2006-088-f-S). Included patients had biopsy-proven primary mucosal melanoma of the head and neck, available survival data, and no metastatic cutaneous melanoma in their history. Of the 66 patients with HNMM, seven were excluded because of a follow-up time of less than 12 months, and nine because their histopathological sections were missing. The 50 remaining histopathological sections were reviewed by a pathologist. The sections were restrained with immunohistochemical markers to confirm the diagnosis (S-100, HMB45, Melan A) and to assess lymph vessel (S-100/Podoplanin) and blood vessel invasion (S100/CD31). R-status was confirmed by histopathological examination of the entire resection margin. Furthermore, all patients were staged or restaged according to the 7th edition of the *AJCC/UICC Staging Manual* (Sobin et al., 2011). In recognition of the aggressive behaviour of mucosal melanomas, the classification starts with the T3-tumor as the most limited form that does not exceed the mucosa. A T4a-tumor involves deep soft tissue, cartilage, bone, or overlying skin and a T4b-tumor invades another compartment, such as the brain, masticator space, or carotid artery. The subsite sinonasal (SNMM) was considered as mucosal melanoma arising from the mucosa of the nasal antrum; the sinus and nasopharynx and oral (OMM) as from the mucosa of the oral cavity.

Diagnostic workup for all of our patients consisted of a thorough examination by a maxillofacial surgeon and a complete endoscopic examination by an ENT specialist. For the patients treated after 1985 (46/50), imaging for assessment of local extent and regional and distant metastasis included CT scans of the head and neck, chest, and abdomen. For the evaluation of soft-tissue involvement, MRI was carried out in some cases over the last decade. The four patients treated between 1973 and 1981 received plain radiographs of the head and neck, chest, and abdomen, and ultrasound of the neck and abdomen. Sentinel node biopsy for HNMM had been performed since 2012 at Fachklinik Hornheide, and was conducted in the following manner. 2 h after injection of a 99m-technetium-labelled colloidal tracer into the surroundings of the primary tumor, a SPECT-CT was performed to show the drainage pattern and the presence of sentinel nodes. The radioactive lymph nodes were harvested intraoperatively with the use of a hand-held gamma-probe.

2.2. Variables

In addition to demographic features, the following clinical and histological variables were obtained and analysed: anatomic subsite, tumor depth in millimeters, lymph vessel invasion, blood vessel invasion, tumor stage according to the *AJCC/UICC Staging Manual* (7th edn), radicality of surgical excision, lymph node management, adjuvant therapy, date of local, regional, or distant failure, and cause of death. Besides overall and disease-specific survival, we calculated disease-free and distant-failure-free survival. The outcomes were calculated from the date of treatment initiation to the date of event. For disease-free survival (DFS) the event was any recurrence and death from any cause. For distant-failure-free survival (DFFS) it was metastatic tumor progression.

2.3. Statistics

The data were analysed with SPSS version 22.0 (SPSS, Inc. Chicago IL). The Kaplan–Meier method was used to estimate survival rates, and the log-rank test for univariate comparisons of survival. All significant factors with at least 10 events per covariate were assessed by multivariate analysis using the Cox proportional hazards model. This procedure is recommended by Bradbrun et al. to avoid biased regression coefficients (Bradburn et al., 2003).

3. Results

3.1. General

50 patients (25 women and 25 men) with head and neck mucosal melanoma were included in our study. The patients' age ranged from 24 to 93 years, with a median age of 65 years. As shown in Table 1, OMM was the most common subgroup with 29 patients (58%) followed by SNMM with 21 patients (42%). Within the OMM group, the majority of patients presented with a primary tumor arising from the palate and from the upper jaw, followed by buccal mucosa, lower jaw, and the mucosal part of the lip. In the SNMM group most had melanoma in the nasal cavity, followed by the maxillary and other paranasal sinuses, and the nasopharynx. Most patients presented with local disease only (45/50, 90%), followed by three with regional and two with distant disease. At first diagnosis, no patient presented with both regional and distant disease. SNMM patients were more likely (76%, $p = 0.1$) to be in an advanced local stage (T4a) than OMM (55%), and tumor depth exceeded 5 mm more frequently in SNMM than in OMM (57% vs 31%, $p = 0.06$). On the other hand, some patients with OMM (10%, $p = 0.128$) presented with regional disease, whereas no patient with SNMM did. Blood and lymph vessel invasion was present in 34% and 20% of the patients, respectively, and more frequent in SNMM than in OMM (48% vs 24%, $p = 0.08$; 33% vs 10%, $p = 0.04$).

3.2. Treatment

All patients underwent surgical resection and it was possible to obtain clear margins in 100% of stage III and 71% of stage IVA cases. OMM could be resected with clear margins in 83% of the cases, but SNMM in only 68% ($p = 0.189$). There is no strict policy for the administration of adjuvant treatment for HNMM in our institution, and the choice is based on the individual agreement between patient and surgeon. Patients from T4 and upwards were generally advised to receive adjuvant radiation of the primary site,

Table 1
Patient characteristics ($n = 50$).

Variable	n (%)
Age (years)	
median, range	65, 24–93
<70	30 (60%)
≥70	20 (40%)
Sex ratio (F:M)	1:1
Site	
Oral cavity	29 (58%)
Palate	16 (55%)
Upper jaw	6 (21%)
Buccal mucosa	4 (14%)
Lower jaw	2 (7%)
Lip	1 (3%)
Sinunasal	21 (42%)
Nasal cavity	15 (72%)
Sinus	4 (19%)
Nasopharynx	2 (10%)
Stage	
III	16 (32%)
IVA	31 (62%)
IVB	1 (2%)
IVC	2 (4%)
T	
T3	17 (34%)
T4a	32 (64%)
T4b	1 (2%)
cN	
N0	47 (94%)
N1	3 (6%)
M	
M0	48 (96%)
M1	2 (4%)

F=Female; M = Male; TNM according to the Seventh Edition of the Union for International Cancer Control (2009).

and all patients with positive lymph nodes were advised to receive adjuvant neck radiation. In total, 50% (25/50) of the patients received adjuvant treatment, consisting of radiotherapy, dacarbazine-based chemotherapy, and/or interferon. 64% (16/25) of the adjuvant-treated patients were treated with a single modality while 36% (9/25) received a combination of the above-mentioned therapies. In stage III most patients were treated by surgery alone (12/16, 75%), three (17%) received adjuvant chemotherapy, and two (11%) received adjuvant radiotherapy. In stage IVA, most patients received adjuvant treatment (17/31, 55%), six (21%) received chemotherapy, and 11 (38%) received radiotherapy. Interferon was administered in 19% (3/16) of the stage III cases and in 26% (8/31) of the stage IVA cases. The patient in stage IVB received adjuvant radiotherapy, and of the two patients in stage IVC one was treated just with just palliative surgery and one with adjuvant chemotherapy. All three patients with positive regional lymph nodes at first presentation were treated with a modified radical neck dissection. Seven patients without evidence of disease in the neck received selective neck dissection as a prophylactic procedure. Those patients were in stage III or IVA and did not differ from the rest of the study population regarding site and depth of invasion.

3.3. Sentinel node biopsy

Since 2012, five (45%) of 11 node-negative patients underwent sentinel node biopsy, four with SNMM and one with OMM. As Table 2 shows, SPECT-CT showed ipsilateral uptake in Level II in 80% (4/5) and in Level IB in 75% (3/5), with no difference between anatomical subsites. Two of the patients turned out to have micrometasases in the histopathological sections, and therefore received subsequent modified radical neck dissection. In contrast to the SLN-negative patients, the SLN-positive patients carried additional risk factors, such as being in a higher T-stage, positive for blood- and lymph-vessel invasion, and having positive surgical margins.

3.4. Outcomes

The median and mean disease-specific survival values for the entire cohort were 38 and 88 months, and the median and mean overall survival values were 38 and 72 months (Fig. 1). The corresponding 5-year DSS and OS rates were 44.2% and 42% respectively. The median and mean disease-free survival values were 27 and 12 months, with a corresponding 5-year disease-free rate of 15.8%. Local recurrence occurred in 52% (26/50) of the patients (Fig. 2), with a 3-year local control rate of 47.6%. There were no statistical differences between AJCC/UICC stages regarding local recurrence, but OMM tended to have a higher local recurrence rate, when compared with SNMM (59% vs 43%, $p = 0.27$). 22% of all patients had isolated local and 14% had locoregional failure, which reduced their median DSS from 89 months following only local failure to 64 months following locoregional failure. Regional failure occurred in 36% (18/50) of all patients (Fig. 2), with a 3-year regional control rate of 62.6%. The effect of isolated regional failure on survival could not be examined because it occurred in only four patients. Of the eight patients who received elective neck dissection, three (37.5%) had regional recurrence. Of the five patients who received sentinel node biopsy, none had a regional recurrence (Table 2). Compared with SNMM, OMM had a significantly higher rate of regional failure (48% vs 19%, $p = 0.03$) and a significantly worse regional-recurrence-free survival (3 years; 45.2% vs 78.7%). Distant failure occurred in 34% of the patients, with a 3- and 5-year distant-failure-free survival of 69.1% and 58.5%, respectively. The median and mean distant-failure-free survival values were 71 and 36 months. Lymph vessel invasion and positive surgical margins turned out to be significant and independent prognostic factors for distant-failure-free survival (Table 4), increasing the chance for distant spread by 10-fold and 3.7-fold, respectively. There was no difference between OMM and SNMM in terms of distant failure rate. Disease-free survival was significantly influenced by tumor depth ($p = 0.002$, Table 5). A tumor depth of more than 5 mm increased the risk of disease recurrence by 2.7-fold. As Table 3 shows, distant failure ($p = 0.005$, Fig. 3) and the extent of surgical resection ($p = 0.004$, Fig. 4) were the only statistically significant and independent predictors for disease-specific survival. Regarding radiotherapy, we were not able to find a beneficial effect, either on local, regional, or distant failure, or on any other survival measure. Disease recurrence and survival rates did not change with time of first diagnosis when we compared outcomes for the four decades since 1980 ($p = 0.425$).

4. Discussion

The median age of the studied population was 65 years, with a range of 24–93 years. This wide range and high median age is consistent with the published literature (Jethanamest et al., 2011; Meleti et al., 2008), and reminds us that mucosal melanoma is a disease of the elderly but should not be ruled out in the young. Although some studies have shown a sex predominance (Patel et al., 2002; Meleti et al., 2008), large cohort studies have reported a similar incidence in both sexes (Nandapalan et al., 1998; DeMatos et al., 1998). Our study population was no exception in this regard, so in agreement with most of the existing literature we could not find a gender-related difference in survival (Chan et al., 2012). In contrast to most studies, the proportion of OMM in our

Table 2
SLN patient characteristics ($n = 5$).

No	Age, sex	Site	Stage	TD (mm)	LVI	BVI	Therapy	Surgical margin	SLN level	SLN result	Follow-up (months)	Outcome
1	48, F	oral	III	3.6	no	no	S, RT, I	R0	Ib + II	neg.	9.8	dead, non-cancer related
2	86, M	nasal cavity	IVA	23	no	no	S	R0	II	neg.	26.8	alive, local recurrence
3	44, M	maxillary sinus	IVA	20	yes	yes	S, RT, I	R1	II	pos.	10.9	alive, distant failure
4	56, M	maxillary sinus	IVA	12	yes	yes	S, RT, I	R1	Ib	pos.	11.4	dead, cancer-related
5	49, M	nasal cavity	IVA	1.8	no	no	S, RT, I	R0	Ib + II	neg.	40.9	alive, NED

F = female; M = male; TD = tumor depth; LVI = lymph vessel invasion; BVI = blood vessel invasion; SLN = sentinel lymph node; S = surgery; RT = radiation; I = interferone; R0 = clear margin; R1 = no clear margin; NED = no evidence of disease.

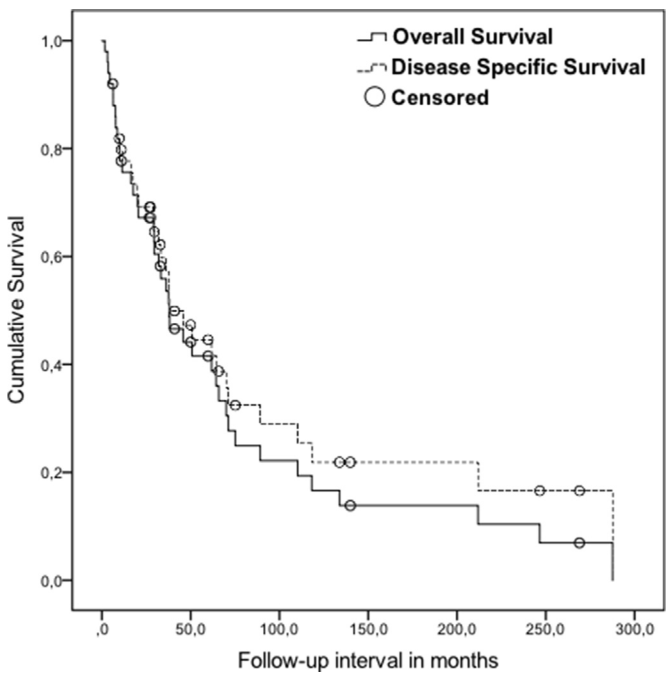

Fig. 1. Overall and disease specific survival.

study population exceeded that of SNMM (58% vs 42%), which may be due to the fact that our institution has a historic focus on oral, maxillary, and facial surgery. However, comprehensive studies based on national cancer registries have shown that OMM is seen in about 20% and SNMM in 80% of patients with HNMM (Jethanamest et al., 2011; Lawaetz et al., 2016).

Although SNMM and OMM have been mostly found in anatomical regions related to maxillary bone (palate, nasal cavity, maxillary sinus), connected by a common embryogenetic origin, they show different morphological and clinical behaviours. Like us, McLean et al. and Prasad et al. found that SNMMs were in a more advanced local stage at initial diagnosis. They are generally thicker and show necrosis and surface ulceration more frequently than OMM (McLean et al., 2008; Prasad et al., 2003). According to Prasad et al., this seems to be in part due to the loose and richly vascular subepithelial connective tissue in the respiratory mucosa (Prasad et al., 2003). Another reason for the lower local stage of OMM may be that the oral cavity is examined more often, especially by the patients themselves, hence making an early detection more likely. For OMM, on the other hand, a higher proportion of nodal disease at initial diagnosis is found in our study and in the literature (Prasad et al., 2003).

Besides the morphological differences, SNMM and OMM show different clinical behaviours. Our own data showed a higher local and regional recurrence rate for OMM, but like most study groups we found that both subsites shared a similar overall and disease-specific survival (Jethanamest et al., 2011; Lawaetz et al., 2016; Patel et al., 2002; McLean et al., 2008; Prasad et al., 2003). In contrast, Meleti et al. found that OMM had a significantly better 5-year disease specific survival than SNMM, a finding that could only partly be explained by a higher percentage of deep tissue infiltration in the SNMM group (Meleti et al., 2008). Due to a very large sample size, Jethanamest at el. were able to conduct a subsite analysis and found that nasal cavity and oral cavity indeed share the same prognosis, but that the nasopharynx, oropharynx, and paranasal sinus do each have a significantly shorter survival value. Late onset of symptoms and a challenging examination are thought to be the reason for the poorer survival.

Guidelines (National Comprehensive Cancer Network, 2019; Leitlinienprogramm Onkolo, 2018) on the management of HNMM agree on the importance of a primary surgical treatment for patients in stage III and IVA. Unfortunately, the close relationship with critical anatomical structures in the head and neck can make a wide surgical resection difficult to achieve. The concomitant morbidity from excessive resection has to be in balance with the benefit for survival. Our data support complete surgical resection as the mainstay of an effective treatment. We were able to show significantly superior disease-specific survival for patients with clear margins, but as all our patients received surgical resection we could not make a comparison with non-surgical management. Jethanamest et al. were able to show in this manner that surgical treatment is indeed superior to conventional radiation alone,

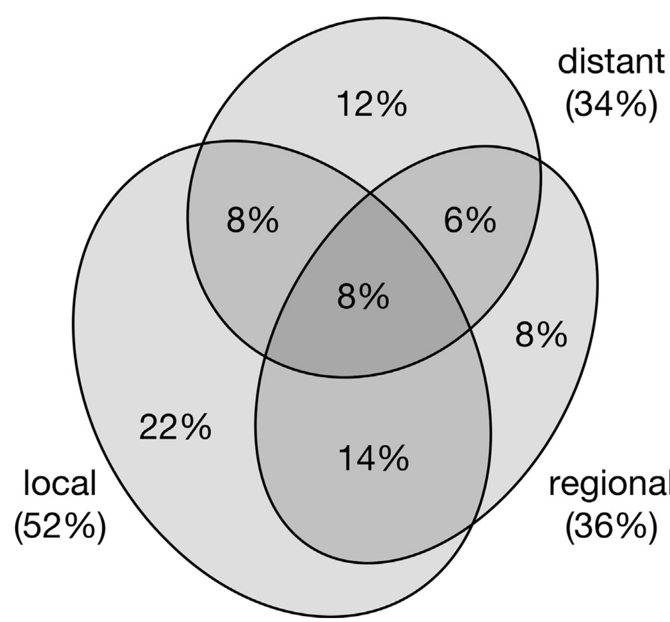

Fig. 2. Pattern of recurrence in study population. Disease recurrence occurred in 39 of 50 patients (78%).

Table 3
Prognostic factors for disease-specific survival.

Factor	Variable	*n*	Disease-specific survival			
			5-year survival (%)	Univariate (log-rank)	Multivariate (Cox)	Relative risk (94% CI)
Age (years)	<70	30	53.6	$p = 0.253$		
	≥70	20	30.6			
Sex	female	25	56.1	$p = 0.688$		
	male	25	34.0			
Site	oral	29	42.2	$p = 0.815$		
	sinonasal	21	47.5			
Stage	III	16	52.4	$p = 0.081$		
	IVA	31	45.6			
T	T3	17	51.3	$p = 0.098$		
	T4a	32	43.5			
Tumor depth	<5 mm	29	61.6	**$p = 0.030$**	NS	
	≥5 mm	21	19.2			
Surgical margin	R0	38	55.0	**$p < 0.001$**	**$p = 0.004$**	3.84 (1.6–10)
	R1	12	10.4			
BVI	yes	17	22.5	**$p = 0.044$**	NS	
	no	33	55.6			
LVI	yes	10	23.3	**$p = 0.018$**	NS	
	no	40	50.0			
RT	yes	13	38.5	$p = 0.383$		
	no	37	46.3			
CT	yes	10	22.9	$p = 0.419$		
	no	40	50.1			
Local failure	yes	26	57.6	**$p = 0.031$**	NS	
	no	24	28.1			
Regional failure	yes	18	43.1	$p = 0.717$		
	no	32	44.4			
Distant failure	yes	17	17.0	**$p = 0.007$**	**$p = 0.005$**	2.94 (1.4–5)
	no	33	58.8			

T = T-stage; LVI = lymph vessel invasion; BVI = blood vessel invasion; RT = radiation; CT = chemotherapy.
A p-value of p≤0.05 was considered significant.

Table 4
Prognostic factors for distant-failure-free-survival.

Factor	Variable	*n*	Distant-failure-free-survival			
			5-year survival (%)	Univariate (log-rank)	Multivariate (Cox)	Relative risk (94% CI)
Age (years)	<70	30	58.8	$p = 0.881$		
	≥70	20	58.9			
Sex	female	25	78.7	$p = 0.143$		
	male	25	42.3			
Site	oral	29	60.9	$p = 0.616$		
	sinonasal	21	55.1			
Stage	III	16	74.3	$p = 0.212$		
	IVA	31	51.2			
T	T3	17	73.1	$p = 0.214$		
	T4a	32	52.9			
Tumor depth	<5 mm	29	69.9	$p = 0.070$		
	≥5 mm	21	41.1			
Surgical margin	R0	38	64.2	**$p = 0.005$**	**$p = 0.027$**	3.7 (1.2–11.1)
	R1	12	36.0			
BVI	yes	17	41.7	$p = 0.058$		
	no	33	66.9			
LVI	yes	10	0	**$p < 0.001$**	**$p < 0.001$**	0.1 (0.03–0.3)
	no	40	72.0			
RT	yes	13	51.9	$p = 0.220$		
	no	37	61.4			
CT	yes	10	48.0	$p = 0.342$		
	no	40	62.2			
Local failure	yes	26	66.7	$p = 0.051$		
	no	24	50.3			
Regional failure	yes	18	51.8	$p = 0.896$		
	no	32	60.4			
Distant failure	yes	17				
	no	33				

T = T-stage; LVI = lymph vessel invasion; BVI = blood vessel invasion; RT = radiation; CT = chemotherapy.
A p-value of p≤0.05 was considered significant.

although the difference was only significant in univariant analysis. Mucosal melanoma, due to its high damage repair capacity (Smith et al., 1978; Bentzen et al., 1989), is thought to be resistant to conventional radiation. A recent meta-analysis by Li et al. concluded after reviewing 12 eligible studies that postoperative radiotherapy is effective in reducing the reduce risk of local

Table 5
Prognostic factors for disease-free survival.

Factor	Variable	*n*	Disease-free survival			
			5-year survival (%)	Univariate (log-rank)	Multivariate (Cox)	Relative risk (94% CI)
Age (years)	<70	30	16.2	$p = 0.212$		
	≥70	20	15.0			
Sex	female	25	17.0	$p = 0.561$		
	male	25	15.0			
Site	oral	29	18.1	$p = 1$		
	sinonasal	21	12.7			
Stage	III	16	21.6	$p = 0.132$		
	IVA	31	13.4			
T	T3	17	18.9	$p = 0.109$		
	T4a	32	15.5.			
Tumor depth	<5 mm	29	23.9	**$p < 0.001$**	**$p = 0.002$**	2.7 (1.5–5.1)
	≥5 mm	21	4.8			
Surgical margin	R0	38	18.1	**$p = 0.002$**	NS	
	R1	12	8.3			
BVI	yes	17	0	**$p = 0.004$**	NS	
	no	33	24.5			
LVI	yes	10	0	**$p = 0.02$**	NS	
	no	40	19.9			
RT	yes	13	0	$p = 0.113$		
	no	37	19.6			
CT	yes	10	10.0	$p = 0.204$		
	no	40	17.2			
Local failure	yes	26				
	no	24				
Regional failure	yes	18				
	no	32				
Distant failure	yes	17				
	no	33				

T = T-stage; LVI = lymph vessel invasion; BVI = blood vessel invasion; RT = radiation; CT = chemotherapy.
A p-value of p≤0.05 was considered significant.

recurrence, but does not reduce the risk of distant metastasis and death (Li et al., 2015). The German national guidelines for the management of mucosal melanoma also recommend radiotherapy for local control, acknowledging the missing evidence of a benefit for overall survival (Leitlinienprogramm Onkolo, 2018). We could not find a reduced risk for any recurrence or outcome measure in our cohort, but this was probably due to selection bias.

There was a significantly higher percentage of patients with positive margins and blood vessel invasion in our RT group — both harbingers for worse survival. Unfortunately, the groups were too small for comparison when we controlled for these factors. There is

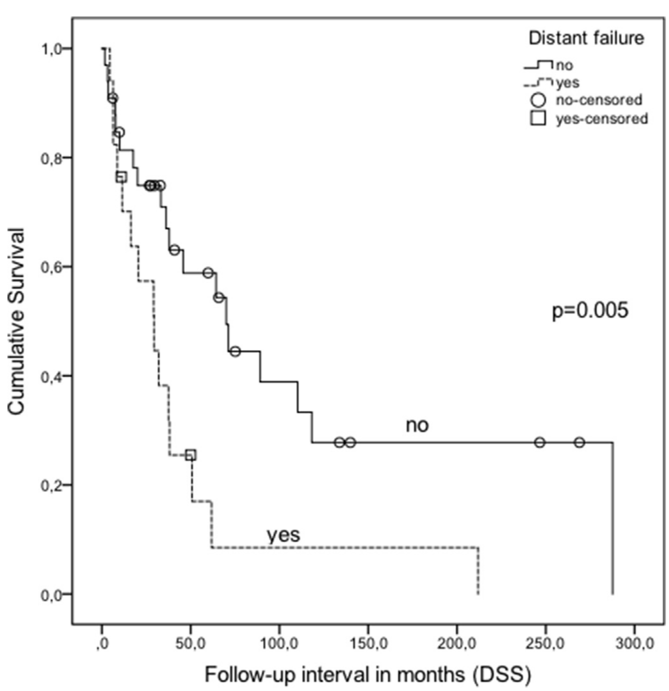

Fig. 3. Influence of distant failure on disease specific survival.

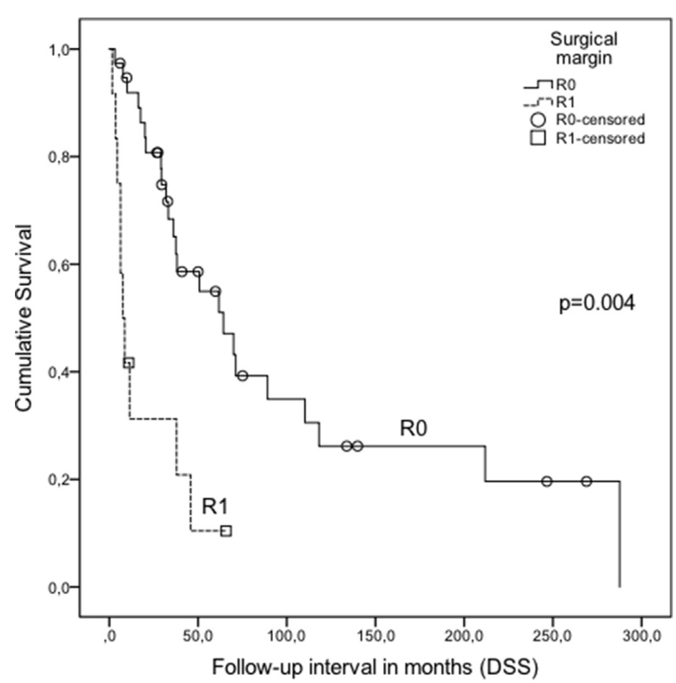

Fig. 4. Influence of surgical margins on disease specific survival.

growing evidence that newer radiation techniques — such as particle therapy using protons (PB) or carbon ions (CIT) — as primary treatment for unresectable tumors are able to generate similar outcomes to surgery (Yanagi et al., 2009). Yanagi et al. treated patients with inoperable or recurrent HNMM with CIT and found a 5-year DSS of 39.6% alongside a good 5-year local control of 84.1%. Demizu et al. confirmed the good local control that PB and CIT could accomplish and saw no difference between the two techniques (Demizu et al., 2014). Further studies are necessary to determine long-term efficacy, but studies on radiotherapy often underlie a selection bias, because they mostly examine cohorts with late-stage cases after surgery, with positive margins and/or local recurrence. Although surgery and adjuvant radiation are able to control the primary tumor, distant failure is the main problem, so early implementation of chemotherapy, targeted therapy, or immunotherapy may be useful for high-risk patients. Unfortunately, in HNMM low rates of mutation have been found for targeted therapies, so for most patients KIT or BRAF inhibitors will most likely not be beneficial (Öztürk Sari et al., 2017; Lyu et al., 2016). Immunotherapy is a rapidly evolving and promising field of research, which has led to a profound change in the management of various neoplasms, for example cutaneous melanoma. PD-L1 overexpression, as seen in cutaneous melanoma, could only been shown for 13% of the HNMM cases in one study (Thierauf et al., 2015). Anti-PD-L1/PD-1 therapy could nonetheless be considered because studies on cutaneous melanoma have shown a benefit, even for PD-L1-negative patients (Weber et al., 2017).

The treatment of node-negative neck is a field of ongoing controversy. Some authors advocate not treating the clinically negative neck, because the benefit of a lower rate of neck recurrence would be undermined by the accompanying distant disease (Shuman et al., 2011; Nandapalan et al., 1998). This is supported by our finding that neck recurrence had no effect on DSS of HNMM. Regarding OMM, there is evidence that elective neck treatment (END) is beneficial for a subset of patients. Unlike macular-type lesions, nodular-type lesions showed a significant increase in overall survival for OMM when treated with END opposed to observation (Wu et al., 2014).

Our policy regarding neck treatment has changed over the years. It went from mainly treating only the node-positive neck in the 1980s to favouring END for around 30% of the patients treated in the 1990s. As no survival benefit for END was found (Borst and Schwipper, 2011), sentinel lymph node biopsy (SLNB) was introduced to our institution in 2012 to replace END. From then on five of 11 patients with node-negative HNMM (45%) were treated with this procedure. To our knowledge, this is the largest case series of SLNB in HNMM. Our findings suggest that SLNB is an accurate staging tool, because all of our SLN-negative patients remained free of distant and regional disease. The two SLN-positive patients developed distant metastases within the first year. Starek et al. and Clark et al. also found that of the two patients each of them examined, only the patient with positive SLN developed distant disease.

Age, surgical margins, tumor thickness, vascular/lymphatic invasion, clinical stage, and distant failure have all been found to be prognostic markers for survival (Patel et al., 2002; Nandapalan et al., 1998). Our analysis showed that surgical margins and distant failure were the only significant and independent prognostic factors for disease-specific survival, and disease-free survival was only predicted by tumor depth. Distant-failure-free survival was strongly predicted by surgical margins and lymph vessel invasion. The predictive value of LVI and BVI for HNMM has been described by Wermker et al. for this cohort. In this particular study, positive double immunostaining with S100/podoplanin for LVI and S100/CD31for BVI identified patients with poor survival (Wermker et al., 2015). These findings support the hypothesis that clinically unapparent, radial lymphatic spread of mucosal melanoma cells is the main factor influencing the appearance of distant metastasis and a subsequently poor survival. This points to the promotion of a wide surgical resection, but also supports the importance of improving systemic treatments. Patients who show an accumulation of certain risk factors (e.g. positive surgical margins, lymph and/or blood vessel invasion, tumor depth greater than 5 mm) should be treated within studies of systemic therapies.

There are important limitations to this study. Retrospective research is always prone to selection bias, and the long-term observation could have been influenced by changes to treatment concepts within our institution. We tried to minimize these biases and discussed only the effect of variables that were not influenced by clinical decision.

5. Conclusion

HNMM is a rare malignancy with a poor prognosis due to delayed diagnosis, a challenging surgical anatomy, and frequent distant spread. Surgical margins and distant failure are prognostic factors for DSS. Other factors like lymph- and blood vessel invasion, together with tumor depth, may play a role in identifying high-risk patients who could benefit from early systemic treatment. SLNB may be a valuable tool for the management of the node-negative neck because all node-negative patients remained free of distant failure. However, further research is necessary.

Ethical statement

This study was approved by the local ethics committee (Ethical Committee of the Westfalian Wilhelms-University Muenster, Approval No. 2006-088-f-S). It was conducted in accordance with the Guidelines for Good Clinical Practice and in compliance with the Declaration of Helsinki. Data were anonymized before analysis, and data acquisition and analysis were performed with respect to data protection regulations.

Disclosure of interest

The authors declare that they have no competing interests.

Acknowledgements

The authors are thankful to Dr M. F. Glaas for critical reading of the manuscript. Preliminary results of this study were presented at the 2018 Germany Society of Otorhinolaryngology and Head & Neck Surgery (DGHNO) Annual Meeting (Luebeck, Germany).

References

Bentzen SM, Overgaard J, Thames HD, Overgaard M, Hansen PV, von der Maase H, et al: Clinical radiobiology of malignant melanoma. Radiother Oncol 16(3): 169–182, 1989

Borst A, Schwipper V: Primary mucosal malignant melanoma of the head and neck. Facial Plast Surg 27(3): 237–242, 2011

Bradburn MJ, Clark TG, Love SB, Altman DG: Survival analysis part III: multivariate data analysis — choosing a model and assessing its adequacy and fit. Br J Cancer 89(4): 605–611, 2003

Chan RC-L, Chan JYW, Wei WI: Mucosal melanoma of the head and neck: 32-year experience in a tertiary referral hospital. Laryngoscope 122(12): 2749–2753, 2012

DeMatos P, Tyler DS, Seigler HF: Malignant melanoma of the mucous membranes: a review of 119 cases. Ann Surg Oncol 5(8): 733–742, 1998

Demizu Y, Fujii O, Terashima K, Mima M, Hashimoto N, Niwa Y, et al: Particle therapy for mucosal melanoma of the head and neck. A single-institution retrospective comparison of proton and carbon ion therapy. Strahlentherapie und Onkologie 190(2): 186–191, 2014

Jethanamest D, Vila PM, Sikora AG, Morris LGT: Predictors of survival in mucosal melanoma of the head and neck. Ann Surg Oncol 18(10): 2748–2756, 2011

Lawaetz M, Birch-Johansen F, Friis S, Eriksen JG, Kiss K, Gade S, et al: Primary mucosal melanoma of the head and neck in Denmark, 1982–2012:

demographic and clinical aspects. A retrospective DAHANCA study. Acta Oncol (Stockholm, Sweden); 2016: 1–8, 2016

Lazarev S, Gupta V, Hu K, Harrison LB, Bakst R: Mucosal melanoma of the head and neck: a systematic review of the literature. Int J Radiat Oncol Biol Phys 90(5): 1108–1118, 2014

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): diagnostik, Therapie und Nachsorge des Melanoms, Langversion 3.1, http://www.leitlinienprogramm-onkologie.de/leit-linien/melanom/; AWMF Register number: 032/024OL, 2018

Li W, Yu Y, Wang H, Yan A, Jiang X: Evaluation of the prognostic impact of postoperative adjuvant radiotherapy on head and neck mucosal melanoma: a meta-analysis. BMC Cancer 15(1): 758, 2015

Lyu J, Wu Y, Li C, Wang R, Song H, Ren G, et al: Mutation scanning of BRAF, NRAS, KIT, and GNAQ/GNA11 in oral mucosal melanoma: a study of 57 cases. J Oral Pathol Med 45(4): 295–301, 2016

Mackintosh JA: The antimicrobial properties of melanocytes, melanosomes and melanin and the evolution of black skin. J Theor Biol 211(2): 101–113, 2001

McLean N, Tighiouart M, Muller S: Primary mucosal melanoma of the head and neck. Comparison of clinical presentation and histopathologic features of oral and sinonasal melanoma. Oral Oncol 44(11): 1039–1046, 2008

Meleti M, Leemans CR, de Bree R, Vescovi P, Sesenna E, van der Waal I: Head and neck mucosal melanoma: experience with 42 patients, with emphasis on the role of postoperative radiotherapy. Head Neck 30(12): 1543–1551, 2008

Nandapalan VV, Roland NJN, Helliwell TRT, Williams EME, Hamilton JWJ, Jones ASA: Mucosal melanoma of the head and neck. Clin Otolaryngol 23(2): 107–116, 1998

National Comprehensive Cancer Network: Head and neck cancers (version 1.2019), https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf; Retrieved from

Öztürk Sari Ş, Yilmaz İ, Taşkin OÇ, Narli G, Şen F, Çomoğlu Ş, et al: BRAF, NRAS, KIT, TERT, GNAQ/GNA11 mutation profile analysis of head and neck mucosal melanomas: a study of 42 cases. Pathology 49(1): 55–61, 2017

Patel SG, Prasad ML, Escrig M, Singh B, Shaha AR, Kraus DH, et al: Primary mucosal malignant melanoma of the head and neck. Head Neck 24(3): 247–257, 2002

Prasad ML, Busam KJ, Patel SG, Hoshaw Woodard S, Shah JP, Huvos AG: Clinicopathologic differences in malignant melanoma arising in oral squamous and sinonasal respiratory mucosa of the upper aerodigestive tract. Arch Pathol Lab Med 127(8): 997–1002, 2003

Shuman AG, Light E, Olsen SH, Pynnonen MA, Taylor JMG, Johnson TM, et al: Mucosal melanoma of the head and neck. Arch Otolaryngol Head Neck Surg 137(4): 331–337, 2011

Smith IE, Courtenay VD, Mills J, Peckham MJ: In vitro radiation response of cells from four human tumors propagated in immune-suppressed mice. Cancer Res 38(2): 390–392, 1978

Sobin LH, Gospodarowicz MK, Wittekind C: TNM classification of malignant tumours. John Wiley & Sons, 2011

Thierauf J, Veit JA, Affolter A, Bergmann C, Grünow J, Laban S, et al: Identification and clinical relevance of PD-L1 expression in primary mucosal malignant melanoma of the head and neck. Melanoma Res 25(6): 503–509, 2015

Tseng WH, Martinez SR: Tumor location predicts survival in cutaneous head and neck melanoma. J Surg Res 167(2): 192–198, 2011

Weber J, Mandala M, Del Vecchio M, et al: Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 377(19): 1824–1835, 2017

Wermker K, Brauckmann T, Klein M, Haßfeld S, Schulze H-J, Hallermann C: Prognostic value of S100/CD31 and S100/podoplanin double immunostaining in mucosal malignant melanoma of the head and neck. Head Neck 37(9): 1368–1374, 2015

Wu Y, Zhong Y, Li C, Song H, Guo W, Ren G: Neck dissection for oral mucosal melanoma: caution of nodular lesion. Oral Oncol 50(4): 319–324, 2014

Yanagi T, Mizoe J-E, Hasegawa A, Takagi R, Bessho H, Onda T, et al: Mucosal malignant melanoma of the head and neck treated by carbon ion radiotherapy. Int J Radiat Oncol Biol Phys 74(1): 15–20, 2009