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ORIGINAL ARTICLE

Prognostic factors in the primary care of patients with Merkel cell carcinoma: A monocentric cohort study of 108 patients from a tertiary referral centre

Jan-Malte Placke[1,2] | **Maximilian Zahn**[1] | **Hannah Zillikens**[1] | **Frederik Krefting**[1] | **Georg C. Lodde**[1] | **Lisa Zimmer**[1] | **Elisabeth Livingstone**[1] | **Eva Hadaschik**[1] | **Antje Sucker**[1] | **Alexander Roesch**[1] | **Alpaslan Tasdogan**[1] | **Nalini K. Srinivas**[3] | **Dirk Schadendorf**[1] | **Jürgen C. Becker**[1,2,3,4] | **Selma Ugurel**[1,2]

[1]Department of Dermatology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

[2]German Cancer Consortium (DKTK), Partner Site Essen/Düsseldorf, Essen/Düsseldorf, Germany

[3]Translational Skin Cancer Research, West German Cancer Center, University Medicine Essen, Essen, Germany

[4]German Cancer Research Center (DKFZ), Heidelberg, Germany

Correspondence
Selma Ugurel, Department of Dermatology, University Hospital Essen, University of Duisburg-Essen, Hufelandstr. 55, 45122 Essen, Germany.
Email: selma.ugurel@uk-essen.de

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Abstract

Background: Merkel cell carcinoma (MCC) is one of the deadliest skin cancers. Despite existing national guidelines, treatment of MCC patients is not as well standardized as for more common skin cancers.

Objectives: The study objective was to investigate factors predisposing to favourable/unfavourable patient outcomes and to which extent guideline-based care affects patient survival.

Methods: This noninterventional study investigated a monocentre real-world patient cohort with a histologically confirmed diagnosis of MCC who presented at the skin cancer centre, University Hospital Essen. Patient and tumour characteristics (age, sex, primary localization, Merkel cell polyomavirus [MCPyV], tumour stage at initial diagnosis and primary treatment measures [surgery, radiation]) were correlated with the patient outcome in terms of recurrence-free survival (RFS) and overall survival (OS).

Results: A total of 108 patients were identified. The median age of the patients was 69.9 years (range 39–88), with patients aged <70 years showing a trend towards a longer RFS ($p = 0.192$). Regarding sex, 69 (63.9%) of the patients were male, with females showing a trend towards a longer RFS (0.189). MCPyV+ primary tumours are less frequently located in the head/neck region ($p = 0.003$). Patients with primary tumours in the head/neck region had a significantly worse OS than patients with primary tumours at the trunk/extremities ($p = 0.007$). Patients with positive sentinel lymph nodes (SLNs) showed a tendency towards shorter RFS

($p = 0.126$) and OS ($p = 0.089$). Patients with American Joint Committee on Cancer stages I, IIA and IIB had a slightly better RFS ($p = 0.803$) and OS ($p = 0.820$) compared to patients with stages IIIA and IIIB. Moreover, the administration of adjuvant radiotherapy resulted in a slightly better RFS ($p = 0.299$) and OS ($p = 0.276$) in patients with tumour stages I, IIA and IIB.

Conclusions: In the present study, the outcome of MCC patients depended on primary tumour localization, SLN status, sex and age. The tumour stage and the adjuvant radiation had only limited effects on patient outcomes.

KEYWORDS
epidemiology, Merkel cell carcinoma

INTRODUCTION

Merkel cell carcinoma (MCC) is a fast-growing, very aggressive and frequently lethal cancer of the skin, with its cell of origin still not been identified. However, the oncogenic Merkel cell polyomavirus (MCPyV) can be detected in 80% of MCC tumours.[1] The estimated disease-specific mortality rate of this metastasis-prone carcinoma is 33%–46%, twice as high as that of malignant melanoma.[2,3] In up to 37% of patients, lymph node metastases can already be detected at initial diagnosis, and in 12% of patients, distant metastases can also be detected. In addition, about one-third of patients have micrometastases in the lymph nodes, which are not clinically detectable and can only be visualized by sentinel lymph node (SLN) diagnostics.[4] The clinical management of patients with nonmetastatic stage MCC consists of surgical removal of the primary tumour, harvesting of the SLN and adjuvant treatment radiation to the primary tumour region and optional to the lymph node drainage stations.[4–6] Finally, the introduction of anti-programmed death ligand 1 (PD-L1)-based and anti-PD1-based immune checkpoint inhibition (ICI) has dramatically improved the prognosis of metastatic-stage MCC patients.[7,8] Despite national guidelines, treatment of rare MCC is not nearly as well standardized as for more common skin cancers such as cutaneous squamous cell carcinoma or melanoma. Therefore, the aim of the present study was to investigate which factors actually predispose to a favourable or unfavourable patient outcome, and to what extent guideline-compliant care affects patient survival, using a monocentric prospectively collected real-world patient cohort from the ADOREG Registry.

PATIENTS AND METHODS

Study design

This is a noninterventional study of a monocentric real-world cohort of patients with histologically confirmed diagnoses of MCC who presented to the Department of Dermatology at the University Hospital Essen between 2014 and 2020. Data were prospectively collected within the skin cancer registry ADOREG of the Dermatologic Cooperative Oncology Group. The patient information to be entered into the ADOREG registry was obtained from electronic patient files at the University Hospital Essen, which include all internal documents as well as disease-relevant documents from external clinics or practices, such as physicians' letters or surgery reports. Patients were staged according to the current American Joint Committee on Cancer (AJCC) staging system for MCC.[9] The study investigated the following patient characteristics: Age at initial diagnosis, sex, location of the primary tumour, size of the primary tumour (tumour diameter), molecular tumour markers (e.g., MCPyV), tumour stage according to AJCC at initial diagnosis, treatment measures during initial treatment (surgery, radiation) and treatment measures in case of recurrence or metastasis (surgery, radiation).

Statistics

Statistical analysis was performed using SPSS Statistics (IBM). For statistical tests, the χ^2 test was used to test two variables for independence, and the log-rank test was used to compare survival rates in two or more unrelated samples. A p value of <0.05 was considered significant in

this context. In addition, data on the time of death of patients and data on the time of occurrence of the first relapse/progression were used to define endpoints, based on which Kaplan–Meier estimators were calculated and plotted.

RESULTS

Patient and tumour characteristics

Between 2014 and 2020, a total of 108 patients who met the above inclusion criteria were identified and included in the analysis. A primary tumour was identified in 90/108 (83.3%) patients. The remaining 18/108 (16.3%) were patients with MCC of unknown primary (MUP). After diagnosis on tumour biopsy, the primary tumours were completely excised using microscopic control of the tumour margins, and wide safety margins of 1–2 cm. Moh's surgery was not performed. Primary tumours on the face were excised with anatomically adjusted safety margins. The total patient cohort was divided into 69 males (63.9%) and 39 females (36.1%). The mean age of patients at initial diagnosis was 69.9 years (range, 39–88 years). Regarding the localization of the primary tumour, the majority was found in the extremities in 58 patients (53.7%). In 23 patients (21.3%), the primary tumour was localized in the head and neck region, followed by localization on the trunk, which was detected in nine patients (8.3%). In 18 of 108 patients (16.7%), no primary tumour was detected and thus classified as MUP - (Figure 1a and Table 1). Information on tumour thickness was available for 34 patients (31.5%). The mean value was 8.16 mm (range 0.1–31.0). Overall, the tumour diameter was retrieved from pathologic reports in 33 patients (30.6%), with a mean of 2.3 cm (range, 0.5–6.1 cm). Of the included patients, 59 (54.6%) were tested for the presence of MCPyV DNA in tumour tissue. Of these, the localization of the primary tumour was known in 51/59 (86.4%). Interestingly, there were strong

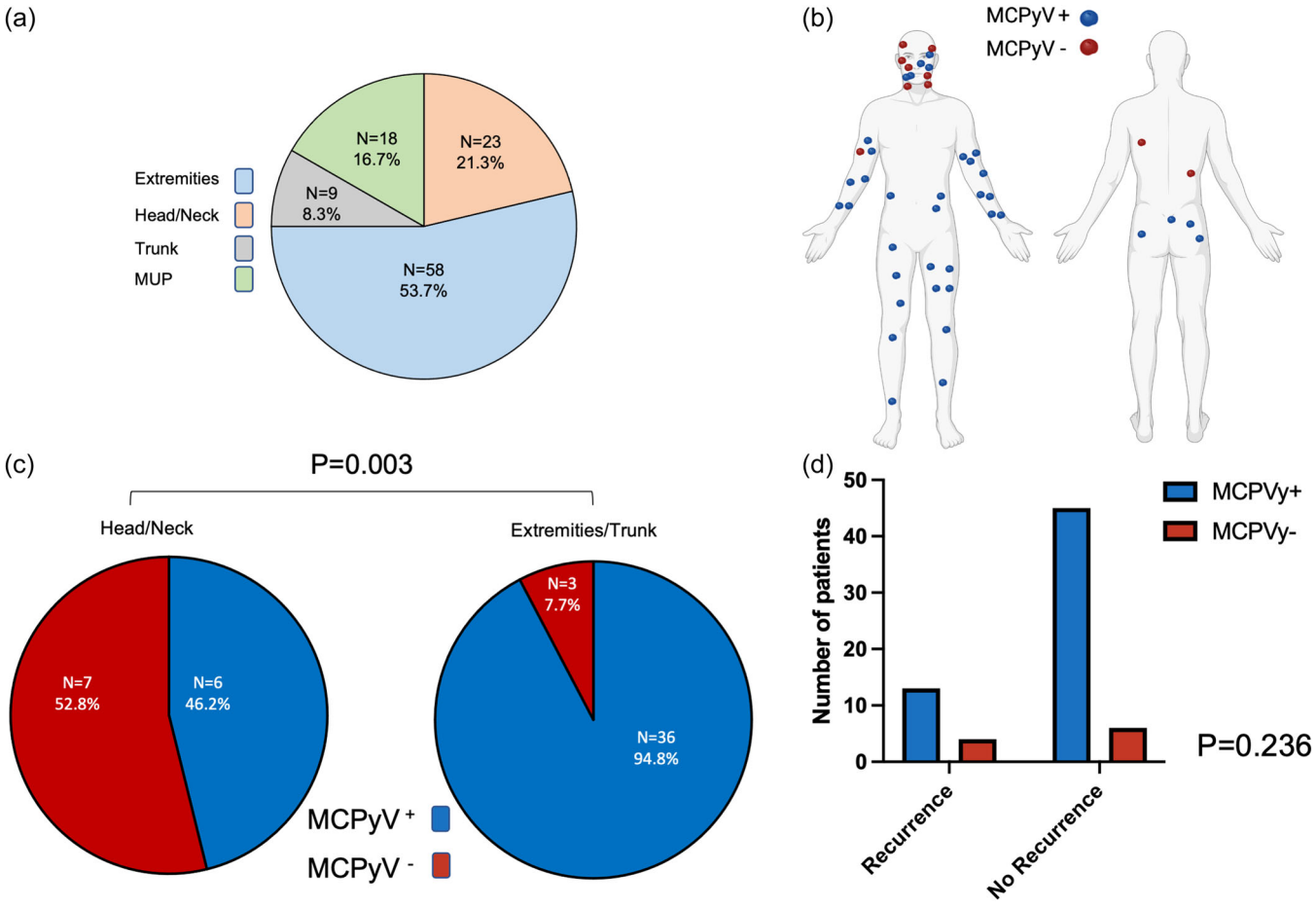

FIGURE 1 Distribution of MCC primary tumour localization in relation to Merkel cell polyomavirus (MCPyV) positivity. (a) Absolute and percentage distribution of patients' MCC primary tumour localization. (b) Distribution of MCC primary tumours according to MCPyV status, created with BioRender.com. (c) Absolute and percentage distribution of MCPyV+ versus MCPyV− MCC primary tumours in head/neck versus extremities/trunk. (d) Number of patients with MCC recurrence depending on MCPyV status. MCC, Merkel cell carcinoma.

TABLE 1 Patient and tumour characteristics.

	N (%)
Total	108 (100)
Mean age (range), years	69.9 (39–88)
Sex	
Male	69 (63.9)
Female	39 (36.1)
Localization of primary tumour	
Head/neck	23 (21.3)
Extremities	58 (53.7)
Trunk	9 (8.3)
Unknown	18 (16.7)
Primary tumour diameter	
<2 cm	16 (14.8)
≥2 cm	17 (15.7)
Unknown	75 (69.4)
SLN biopsy performed	
Yes	55 (50.9)
No	53 (49.1)
SLN metastasis in SLNB performed	
Yes	19 (34.5)
No	36 (65.5)
Adjuvant radiotherapy	
Yes	75 (69.4)
No	33 (30.6)
MCPyV	
Negative	11 (10.2)
Positive	48 (44.4)
Unknown	49 (45.4)
Recurrence	
Yes	31 (28.7)
No	77 (71.3)
Death	
No	98 (90.7)
Yes	10 (9.3)

Abbreviation: MCPyV, Merkel cell polyomavirus; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy.

region-specific differences with respect to MCPyV status. In the head/neck region, 6/13 (46.2%) of primary tumours were MCPyV+. On the trunk and extremities, 36/39 (92.3%) were MCPyV+ and only 3/39 (7.7%) were MCPyV−, so primary tumours in the head and neck region were significantly more likely to be MCPyV− ($p = 0.003$) (Figure 1b,c). Patients with MCPyV− primary tumours showed recurrences in 40.0% and patients with MCPyV+ primary tumours showed recurrences in 22.4% ($p = 0.236$) (Figure 1d). Furthermore, patients with MCPyV+ primary tumours showed a tendency towards slightly better recurrence-free survival (RFS) ($p = 0.695$) and overall survival (OS) ($p = 0.259$) compared to patients with MCPyV− primary tumours (Figure 2a,b). In addition to MCPyV status, the primary tumour localization was also considered in relation to patient outcomes. Patients whose primary tumour was localized in the head/neck region had a worse median RFS than patients with primary tumours in the trunk/extremity region ($p = 0.150$). The median OS was significantly longer in patients whose primary tumour was located in the trunk/extremity region compared to patients with primary tumours in the head/neck region ($p = 0.007$) (Figure 2c,d).

Sentinel status and AJCC stage correlate with RFS and OS

Regarding prognostic factors, the occurrence of recurrences of MCC within the investigated patient cohort could be identified as a major factor influencing OS ($p = 0.004$). Thus, the 5-year survival rate was 98.1% for patients without recurrence, and 67.6% for those with recurrence. Surgical interventions with excision and SLN biopsy continue to be the backbone of therapy for patients with primary MCC and no evidence for macrometastasis. Therefore, the influence of the involvement of the SLN and AJCC tumour stage on the disease course in relation to recurrence was investigated. Regarding SLN status, it was found that 7/36 patients (19.4%) with a negative SLN and 7/19 patients (36.8%) with a positive SLN had a recurrence ($p = 0.19$). Median RFS and OS were not achieved for both groups; nevertheless, there was a trend for longer survival in terms of RFS ($p = 0.126$) and OS ($p = 0.089$) in patients without SLN metastases (Figure 3a,b). In terms of tumour stage, it was found that patients with higher stages IIIA and IIIB did not have significantly shorter RFS ($p = 0.275$) or OS ($p = 0.159$) compared with patients with lower tumour stages I, IIA and IIB (Figure 3c,d).

Younger age and female sex correlate positively with RFS in MCC patients

Furthermore, the patient characteristics age and sex were examined with respect to RFS and OS. Patients with an

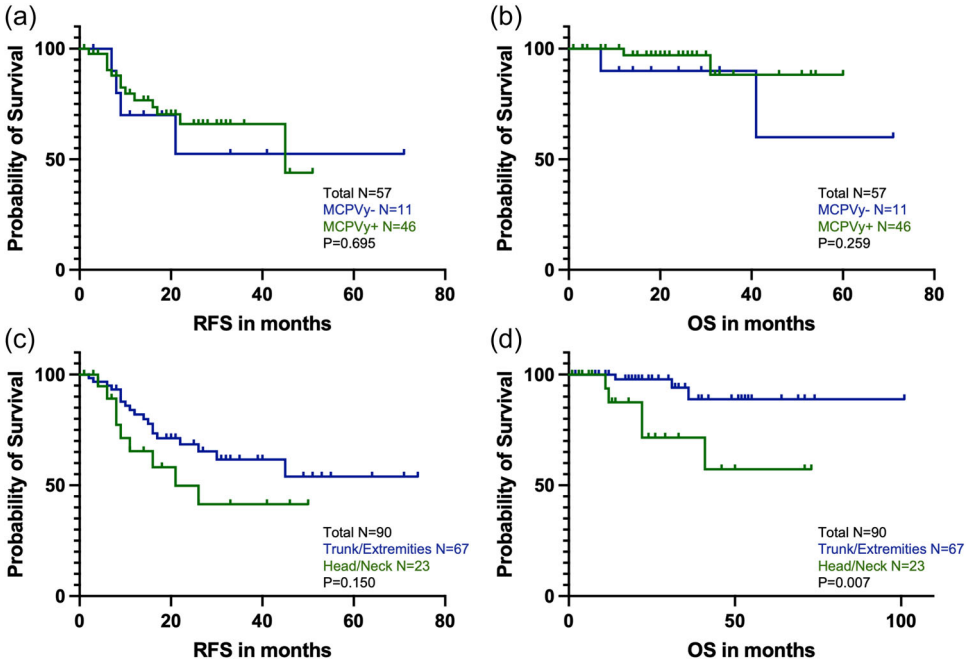

FIGURE 2 Relapse-free survival (RFS) and overall survival (OS) of MCC patients in relation to MCPyV-status and localization of primary tumours. The Kaplan-Meier curves show the RFS (a) and OS (b) of patients with MCPyV− versus MCPyV+ primary tumours and RFS (c) and OS (d) of patients with primary tumours localized in the head/neck region versus trunk/extremities. MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus.

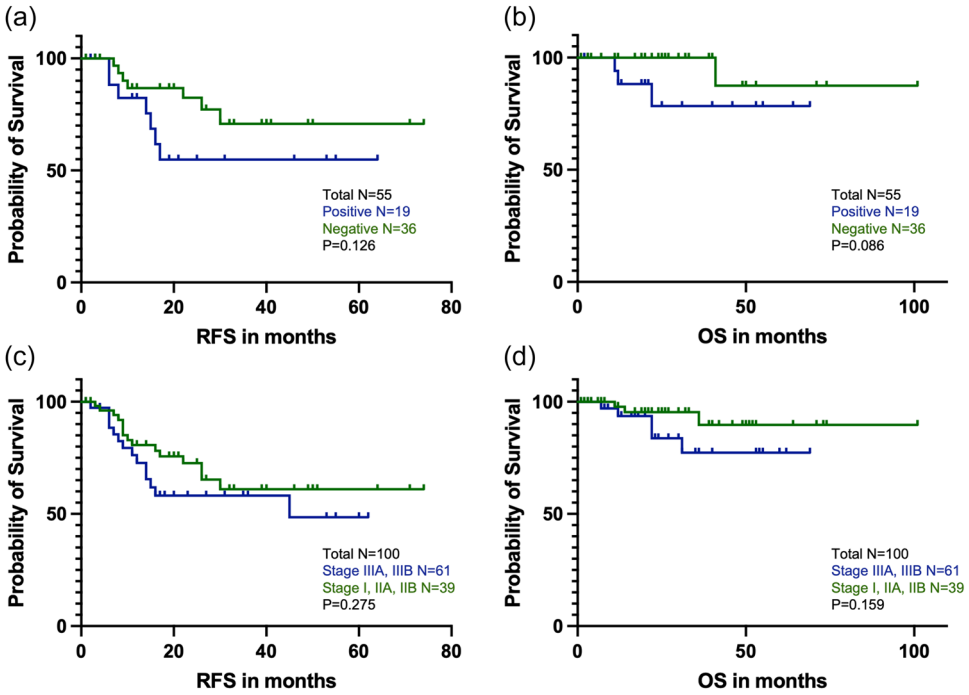

FIGURE 3 Relapse-free survival (RFS) and overall survival (OS) of MCC patients in relation to SLN status and AJCC tumour stage. The Kaplan–Meier curves show the RFS (a) and OS (b) of patients with SLN metastases compared to patients without SLN metastases, and the RFS (c) and OS (d) of MCC patients as a function of tumour stage. AJCC, American Joint Committee on Cancer; MCC, Merkel cell carcinoma; SLN, sentinel lymph node.

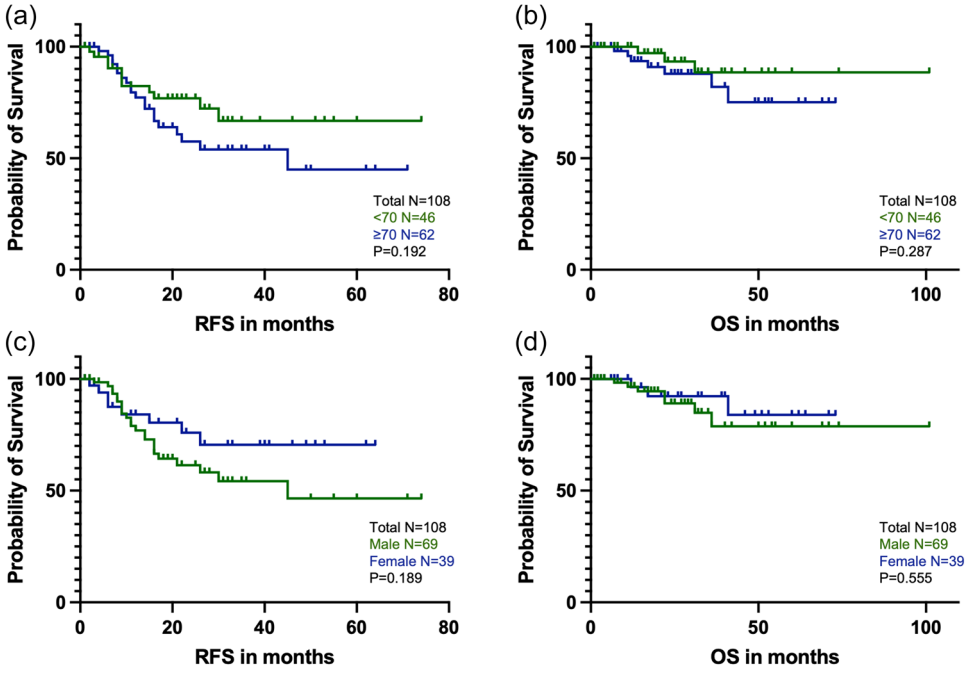

FIGURE 4 Relapse-free survival (RFS) and overall survival (OS) of MCC patients in relation to age and sex. The Kaplan–Meier curves show the RFS (a) and OS (b) of patients by age (≥70 vs. <70 years), and the RFS (c) and OS (d) of MCC patients as a function of sex. MCC, Merkel cell carcinoma.

age ≥70 years had a median RFS of 45 months, whereas median RFS was not achieved in patients aged <70 years, showing a not statistically significant tendency for a longer RFS in younger patients ($p = 0.192$) (Figure 4a). Median OS was not reached for either patient group, but again there was a statistically nonsignificant trend for longer OS in patients aged <70 years ($p = 0.278$) (Figure 4b). With regard to sex, women did not reach the median RFS and men showed a median RFS of 45 months, thus showing a statistically nonsignificant longer RFS in women ($p = 0.189$) (Figure 4c). Interestingly, this trend was not visible for OS, with median OS not reached for either women or men ($p = 0.555$) (Figure 4d).

Adjuvant radiotherapy results in slightly better RFS in stages I, IIA and IIB MCC patients

As part of primary therapy, 75 of 108 patients (69.4%) received adjuvant radiotherapy. Of these, 29/75 patients (38.7%) received radiotherapy to the primary tumour region only, 18/75 patients (24.0%) received radiotherapy to the locoregional lymph nodes alone and 28 patients (37.3%) received combined radiotherapy to both sites. The radiotherapy was performed with a total dose of 50 Gy over 25 cycles (2 Gy per radiation cycle) in the majority of cases. We considered the impact of adjuvant radiation therapy on MCC recurrence and patient survival since its administration is strongly recommended for the primary care of MCC patients according to German guidelines. Patients with lower tumour stages (I, IIA and IIB) and patients with higher tumour stages (IIIA and IIIB) were compared separately in terms of the efficacy of adjuvant radiotherapy. For the tumour stages I, IIA and IIB, a slightly better RFS ($p = 0.299$) and OS ($p = 0.276$) was shown for patients who received adjuvant radiotherapy (Supporting Information: Figure 1A,B). There was no relevant difference in terms of RFS ($p = 0.658$) or OS ($p = 0.590$) for patients in stages IIIA and IIIB who did or did not receive adjuvant radiation (Supporting Information: Figure 1C,D).

DISCUSSION

MCC is a highly aggressive malignant skin cancer. The MCPyV is involved in its etiopathology to approximately 80% of Europeans, whereby it has been described that MCPyV− MCC frequently occur in UV-exposed body regions.[1] Accordingly, in the monocentric study performed here, we found a significantly higher proportion of MCPyV− MCC primary tumours localized in the head/neck region. Also, it should be noted that patients with MCPyV− primary tumours showed more frequent

recurrences than patients with MCPyV+ primary tumours, although this difference was not statistically significant. Furthermore, the influence of patient characteristics such as age and sex, tumour characteristics such as tumour stage and SLN status, and treatment approach, especially radiation, on patient outcome was investigated using real-world data from 108 MCC patients. Regarding the patient age in our study cohort, the predominance of the age group older than 70 years and the mean age at initial diagnosis of 69.9 years are consistent with the experience of other authors and confirm that MCC is a cancer of the elderly.[2] The sex distribution, with significantly more male patients, is also consistent with previously published studies, with these retrospective case collections also showing a 3 to 2 distribution of incidence between men and women.[10] In the present work, demographic data such as age (≥70 vs. <70 years) and sex were examined with respect to RFS and OS. There was a trend that patients with younger ages, as well as females, had longer RFS and OS, although this was not statistically significant. This result is also consistent with previously published studies, which showed that younger or female MCC patients had better outcomes than older or male patients.[11,12] Another important prognostic factor is still considered to be the tumour stage. The tumour stage is also recommended as a prognostic parameter as part of the current AJCC classification. Studies have shown that patients with lower tumour stages have better survival than patients with higher tumour stages.[13] The data collected in the present study showed a slight tendency that patients with lower tumour stages I, IIA and IIB had slightly better RFS and OS than patients with higher tumour stages IIIA and IIIB. However, the SLN status appeared to play a distinct role in patients' RFS and OS. Since in approximately every third MCC patient, at least micrometastases can be detected in the lymph nodes, an SLN biopsy is recommended, unlike in melanoma, regardless of the size of the primary.[14,15] Furthermore, epidemiological studies on large patient collectives have shown that MCC patients with detectable SLN metastases have a significantly worse prognosis than patients without SLN metastases.[13] The association between positive SLN status and poor patient prognosis was confirmed in the present study. In addition to the complete excision of the primary tumour, radiation of the primary tumour region and possibly also of the lymphatic drainage area, plays a role in localized tumour disease, as adjuvant radiotherapy has been shown in various retrospective studies to benefit MCC patients in terms of RFS and OS.[16,17] In patients with tumour stage ≤IIB, there was a slightly better RFS and OS for patients who received adjuvant radiotherapy. This beneficial effect of adjuvant radiation was not observed in patients with tumour stage > IIB; however, it has to be noted that here the number of cases was small. Interestingly, current efforts are aimed at offering adjuvant systemic treatment to patients with MCC who are considered tumour-free, analogous to advanced melanoma.[18,19] First promising results are already available for PD1-based ICI.[20,21] Therefore, it will be interesting to reevaluate the role of adjuvant radiation after a possible introduction of adjuvant ICI in MCC patients.

The present study has some limitations. One limitation is its retrospective character. In addition, only univariate statistical analyses were performed. Multivariate analyses were not reasonable with the included patient number of 108. In this context, however, it must be noted that for such rare cancers as MCC, a patient number of 108 in a monocentric approach is quite high. This high number was only reached since the Skin Cancer Center Essen functions as a German-wide referral centre for MCC.

Summing up, the present study could verify relevant correlations in the context of epidemiology, therapy as well as prognosis of MCC. However, some correlations were found to be less pronounced compared to previously published data, especially regarding adjuvant radiation which showed only a small benefit for stage I/II MCC patients. In this regard, new prospective studies are needed analyzing large real-world MCC patient cohorts, such as the German-wide recruiting translational study MCC-TRIM, to reassess the prognostic factors as well as adjuvant therapy strategies currently recommended for MCC patients by the German guidelines.

AUTHOR CONTRIBUTIONS

Jan-Malte Placke and **Selma Ugurel**: Conceptualization. **Jan-Malte Placke, Maximilian Zahn, Jürgen C. Becker** and **Selma Ugurel**: Methodology. **Jan-Malte Placke, Jürgen C. Becker** and **Selma Ugurel**: Validation. **Jan-Malte Placke** and **Maximilian Zahn**: Investigation. **Dirk Schadendorf, Jürgen C. Becker** and **Selma Ugurel**: Resources. **Jan-Malte Placke** and **Maximilian Zahn**: Formal analysis. **Jan-Malte Placke** and **Selma Ugurel**: Writing—original draft. **Maximilian Zahn, Hannah Zillikens, Frederik Krefting, Georg C. Lodde, Lisa Zimmer, Elisabeth Livingstone, Eva Hadaschik, Antje Sucker, Alexander Roesch, Alpaslan Tasdogan, Nalini K. Srinivas, Dirk Schadendorf** and **Jürgen C. Becker**: Writing—review and editing. **Selma Ugurel**: Supervision and project administration. The remaining authors declare no conflict of interest.

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CONFLICTS OF INTEREST STATEMENT

Jan-Malte Placke served as a consultant and/or has received honoraria from Bristol-Myers Squibb, Novartis, Sanofi and received travel support from Bristol-Myers Squibb, Novartis, Pierre Fabre and Therakos. Georg C. Lodde has received financial support for scientific projects from Novartis and travel support from Sun Pharma and Pierre-Fabre. Frederik Krefting received travel support for participation in congresses and/or (speaker) honoraria from Novartis and Almirall outside the submitted work. Lisa Zimmer declares speakers and advisory board honoraria from Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Sanofi, Sunpharma, research support from Novartis and travel support from Merck Sharp & Dohme, Bristol-Myers Squibb, Pierre Fabre, Sanofi, Sunpharma and Novartis; outside the submitted work. Elisabeth Livingstone served as consultant and/or has received honoraria from Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre-Fabre, Sanofi, Sunpharma, Takeda and travel support from Bristol-Myers Squibb, Pierre Fabre, Sunpharma and Novartis, outside the submitted work. Alexander Roesch reports consulting/advisory role for and honoraria from Novartis and Bristol-Myers Squibb and received research funding from Novartis, Bristol-Myers Squibb. Dirk Schadendorf reports partial financial support from Bristol Myers Squibb for the conduct of this study and drug supply (nivolumab and ipilimumab) support; grants (or contracts) from Amgen, Array/Pfizer, Bristol-Myers Squibb, MSD, Novartis and Roche; consulting fees from 4SC, Amgen, Array Biopharma, AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo, Haystick, Immunocore, InFlarX, Innocent, LabCorp, Merck Serono, MSD, Nektar, NeraCare, Novartis, OncoSec, Pfizer, Philogen, Pierre Fabre, Replimune, Roche, Sandoz, Sanofi/Regeneron, Sun Pharma; honoraria from Bristol-Myers Squibb, MSD/Merck, Merck Serono, Novartis, Roche, Sanofi and Sun Pharma; support for attendings meetings or travel support from Bristol-Myers Squibb, MSD, Merck Serono, Novartis, Pierre Fabre and Sanofi; participation on drug safety monitoring or advisory boards for 4SC, Amgen, Array Biopharma, AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo, Immunocore, InFlarX, Merck Serono, MSD, Nektar, NeraCare, Novartis, OncoSec, Pfizer, Philogen, Pierre Fabre, Replimune, Roche, Sandoz, Sanofi/Regeneron and SunPharma; leadership roles for DeCOG, German Cancer Society, Hiege-Stiftung, Deutsche Hautkrebsstiftung, NVKH e.V. and EuMelaReg. Jürgen C. Becker is receiving speaker's bureau honoraria from Amgen, Pfizer, Recordati and Sanofi, is a paid consultant/advisory board member/DSMB member for Almirall, Boehringer Ingelheim, InProTher, ICON, MerckSerono, Pfizer, 4SC and Sanofi/Regeneron. His group receives research grants from Bristol-Myers Squibb, Merck Serono, HTG, IQVIA and Alcedis. Selma Ugurel declares research support from Bristol Myers Squibb and Merck Serono; speakers and advisory board honoraria from Bristol Myers Squibb, Merck Sharp & Dohme, Merck Serono and Novartis, and travel support from Bristol Myers Squibb, Merck Sharp & Dohme and Pierre Fabre. Maximilian Zahn, Hannah Zillikens, Eva Hadaschik, Antje Sucker, Alpaslan Tasdogan and Nalini K. Srinivas declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the local medical ethics committee of the University of Duisburg-Essen 14-5921-BO; 18-8254-BO). All patients in this manuscript have given written informed consent for participation in the study and the use of their deidentified, anonymized, aggregated data and their case details for publication.

ORCID

Jan-Malte Placke http://orcid.org/0000-0002-7842-4669
Frederik Krefting http://orcid.org/0000-0002-6164-3726
Georg C. Lodde http://orcid.org/0000-0002-6930-2694
Alexander Roesch http://orcid.org/0000-0002-0773-6067
Dirk Schadendorf http://orcid.org/0000-0003-3524-7858

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SUPPORTING INFORMATION

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