Treatment and survival of Merkel cell carcinoma since 1993: A population-based cohort study in The Netherlands

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Background: Merkel cell carcinoma (MCC) is a rare and potentially lethal skin cancer. MCC is known for its potential rapid growth and its propensity to metastasize.

Objective: To describe the incidence, treatment, and survival of MCC in a population-based setting.

Methods: All MCCs diagnosed in The Netherlands between 1993 and 2016 were selected from the Netherlands Cancer Registry. Patient and tumor characteristics, therapy, and vital status were obtained. Cox proportional hazards were computed, and relative survival analyses were performed.

Results: Our cohort included 1977 patients with MCC. Incidence increased from 0.17 per 100,000 person-years in 1993 to 0.59 per 100,000 in 2016. The mean age at diagnosis was 75.5. Most MCCs (59.8%) were treated with surgery alone. Relative 5-year survival was low (63.0%) and did not improve. Mortality was higher among males (hazard ratio [HR], 1.24; 95% confidence interval [CI], 1.11-1.39), higher age (HR, 1.07; 95% CI, 1.06-1.07), and nodal (HR, 1.26; 95% CI, 1.08-1.48) and distant spread of disease (HR, 2.44; 95% CI, 1.99-2.99).

Limitations: We lacked data on cause of death, comorbidity, and pathologic margins, which may have led to misinterpretation of the data.

Conclusion: This study shows continuously increasing incidence rates of MCC in The Netherlands. Survival after a diagnosis of MCC remained low. Our results emphasize the need for implementation of new therapies. (J Am Acad Dermatol 2019;81:977-83.)

Key words: Merkel cell carcinoma; survival; The Netherlands; treatment.

Merkel cell carcinoma (MCC) is a rare and potentially lethal nonmelanoma skin cancer with a neuroendocrine origin; it was first described by Toker in 1972.[1] The worldwide annual incidence rates are reported to be between 0.19 and 0.82 per 100.000 person-years and are increasing.[2-6]

Compared with the better-known nonmelanoma skin cancers such as basal cell carcinoma and squamous cell carcinoma, MCC is known for its potentially rapid growth and its propensity to metastasize.[2] The 5-year survival rate is low, and worldwide reported values are around 60%.[2,4,5] Factors that have been described to negatively influence the survival are tumor size, staging, male sex, location in the head and neck area, and immunosuppression.[2,4,7-10] MCC is predominantly localized on the head and neck area and the extremities, most likely

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because of the relationship with ultraviolet radiance, which is a risk factor for development of MCC.[11]

Treatment modalities for MCC may vary and comprise surgery, radiotherapy, immunotherapy, and (less commonly) chemotherapy. Multiple studies have shown that locoregional radiotherapy could be beneficial as an adjuvant therapy after primary excision.[12-15] Depending on the staging and the outcome of a sentinel node procedure, lymph node dissection can be performed.[16] Furthermore, multiple trials assessing different immunotherapies and targeted molecular therapies as possible treatments for MCC are currently ongoing.[17]

The Netherlands Cancer Registry (NCR) registers all pathologically diagnosed MCCs. Previously, these data were evaluated up until 2007,[4] but trends in the most recent years are important to provide additional insights about the characteristics of MCC in The Netherlands, especially in light of new treatment modalities that are becoming available. Therefore, the aim of this study was to give an update including the MCCs newly registered after 2007. Our objective was to describe the incidence, characteristics, treatment, and survival of MCC in The Netherlands between 1993 and 2016.

CAPSULE SUMMARY

- Merkel cell carcinoma is a potentially lethal skin cancer with a rapidly increasing incidence in The Netherlands. The 5-year survival of 63% did not improve over time and is worse for males, elderly individuals, and those with advanced disease.
- Our results emphasize need for implementation of new therapies and research in this field.

METHODS

Patients

All patients with pathologically confirmed MCC in the NCR between 1993 and 2015 were included in this prospective cohort study. The NCR registers in all hospitals in The Netherlands and includes items such as age at diagnosis, sex, localization of the tumor, tumor staging, therapy, vital status (death), and time from diagnosis until death or censoring. Information on sentinel node (yes vs no and positive vs negative results) was collected for the more recent years.

Statistical analysis

Age-standardized incidence was calculated by using the European Standard Population[18] and is presented per 100,000 person-years. Both univariate (including log-log curves to check for proportionality) and multivariate Cox regression analyses were performed using the the following covariates: sex, age, tumor location, staging, and treatment. Relative survival was calculated to estimate disease-specific survival and correct for age- and sex-specific background mortality.[19] Statistical analyses were performed with IBM SPSS software (version 24, IBM, Armonk, NY) and SAS software (version 9.4, SAS Institute Inc, Cary, NC).

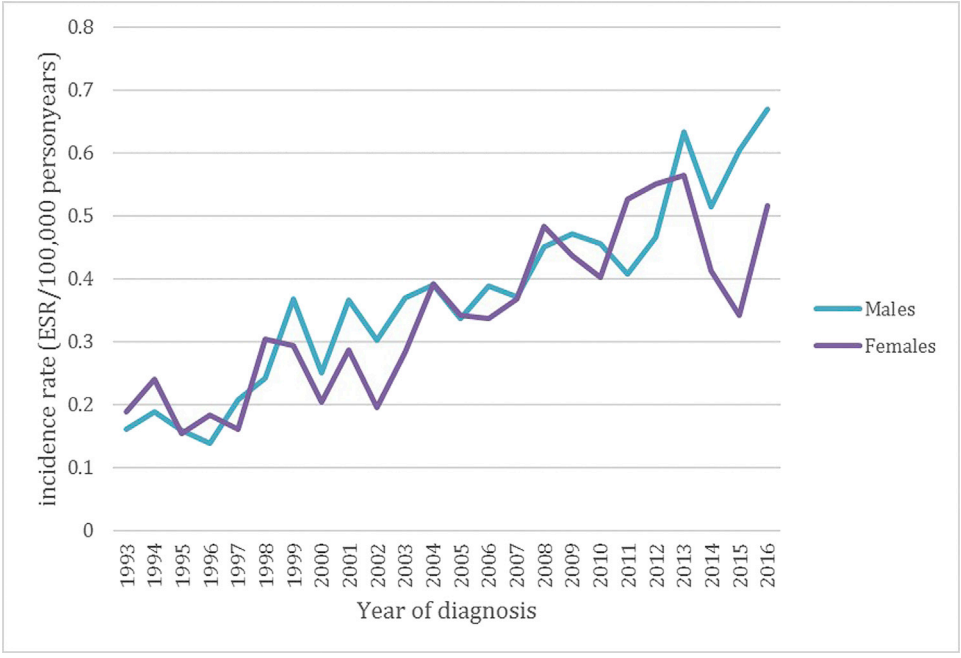

Fig 1. Merkel cell carcinoma. Incidence in The Netherlands per 100,000 inhabitants.

Abbreviations used:

CI: confidence interval
HR: hazard ratio
MCC: Merkel cell carcinoma
NCR: Netherlands Cancer Registry

Results

In total, 1977 MCCs were registered in the NCR database between 1993 and 2016, resulting in about 145 new cases annually in the recent years. The incidence of MCC in The Netherlands has been growing. Age-standardized rates have more than tripled since 1993, from 0.17 per 100,000 person years (European standardized rate) to 0.59 per 100,000 in 2016 (Fig 1). The estimated annual percentage change in incidence over this time period was 5.5% ($P < .0001$). The incidences for males and females were comparable.

General characteristics are described in Table I. The mean age at diagnosis was 75.5 years. MCC most often occurred in the head and neck region (42.7%) and on the extremities (20.8% and 19.3% on the upper and lower extremities, respectively).

Most MCCs (59.8%), were treated with surgery alone. For MCCs with nodal metastasis, surgery was most frequently combined with radiotherapy (45.8%) (Table II). A sentinel node procedure was performed on 249 patients, with a positive sentinel node found in 62 patients (24.9%) (Table III).

The relative 5-year survival after diagnosis of MCC was 63.0%. This rate has not changed much between 1993 and 2016, with relative 5-years survival rates of 62.1% for patients in whom MCC was diagnosed between 1993 and 2000 and 64.9% for those in whom MCC was diagnosed between 2011 and 2016. The relative 5-year survival values for different age groups were 0.74 (<70 years), 0.58 (70-74 years), 0.67 (75-79 years), 0.53 (80-84 years), 0.54 (85-89 years), and 0.65 (≥90 years).

The crude 5-year survival rate of patients with MCC in The Netherlands was 46.0%. Localized tumors 2 cm or smaller had an absolute 5-year survival rate of 53.8%. For localized tumors larger than 2 cm, nodal metastasized tumors, and distant metastasized tumors, the absolute 5-year survival rates were 40.4%, 41.6%, and 19.2%, respectively. Figure 2 shows the survival of MCC for different stages of disease.

Table IV shows hazard ratios (HRs) for different variables along with their 95% confidence intervals (CIs). Log-log curves for test proportionality showed no reason to reject the proportionality assumption.

Table I. Characteristics of MCC diagnosed in The Netherlands in 1993-2016

Characteristic	Value
N	1977 (100%)
Mean age at diagnosis ± SD, y	75.5 ± 11.4
Age ≤70 y, n (%)	591 (29.9%)
Age >70 y, n (%)	1386 (70.1%)
Sex, n (%)	
Female	1114 (56.3%)
Male	863 (43.7%)
Site of onset, n (%)	
Head and/or neck	844 (42.7%)
Trunk	197 (10.0%)
Upper extremity	412 (20.8%)
Lower extremity	382 (19.3%)
Skin location unspecified	22 (1.1%)
Non skin	18 (0.9%)
Primary tumor location unknown	102 (5.2%)
Staging, n (%)	
Localized, ≤2 cm	909 (46.0%)
Localized, >2 cm	412 (20.8%)
nodal	295 (14.9%)
Distant	135 (6.8%)
Stage unknown	226 (11.4%)

MCC, Merkel cell carcinoma; *SD*, standard deviation.

Survival was worse for males than for females, with the HRs varying between 1.24 (95% CI, 1.11-1.39) without adjustment and 1.42 (95% CI, 1.26-1.59) with adjustment for age, location, stage, and treatment.

MCCs located on the upper extremity had a significantly lower mortality than did MCCs located on the head and neck, but this difference disappeared when adjusted for other variables. With adjustment for sex, age, staging, and treatment, only the mortality of MCCs located on the trunk differed significantly compared with that of MCCs in the head and neck area. MCCs on the trunk had a higher mortality, with an HR of 1.40.

Nodal and distant spread of disease was associated with a significantly higher mortality than local disease was. The HRs for mortality of nodal and distant disease were 1.36 and 2.23, respectively, with adjustment for other factors (sex, age, location, and treatment).

Patients treated with surgery combined with radiotherapy had a significantly lower mortality than did patients treated with surgery alone, but with adjustment for other variables, this difference was no longer significant. With adjustment for sex, age, location, and staging, patients treated with radiotherapy alone, chemotherapy alone, and no

Table II. Treatment and stage of MCC in The Netherlands in 1993-2016

			Stage					
	Total,		Localized,		Nodal,		Distant,	
Treatment	n	(%)	n	(%)	n	(%)	n	(%)
Surgery alone*	1182	(59.8)	927	(70.2)	95	(32.2)	34	(25.2)
Surgery* + RT	539	(27.3)	323	(24.5)	135	(45.8)	24	(17.8)
Surgery* + CT	18	(0.9)	3	(0.2)	4	(1.4)	11	(8.1)
Surgery + RT + CT	26	(1.3)	6	(0.5)	15	(5.1)	2	(1.5)
RT alone	84	(4.3)	37	(2.8)	21	(7.1)	17	(12.6)
RT + CT	18	(0.9)	0	(0.0)	4	(1.4)	9	(6.7)
CT alone	26	(1.3)	1	(0.1)	6	(2.0)	17	(12.6)
No treatment	75	(3.8)	23	(1.7)	13	(4.4)	18	(13.3)
Unknown	9	(0.5)	1	(0.1)	2	(0.7)	3	(2.2)
Total	1977		1321		295		135	

CT, Chemotherapy; *RT*, radiotherapy.
*Surgery sometimes includes lymph node dissection (n = 183).

Table III. Outcomes of the sentinel node procedures (n = 249) for MCC in The Netherlands in 1993-2016

Outcome	n	%
Negative	181	72.2%
Positive	62	24.9%
Unknown	6	2.4%

treatment had a significantly higher mortality than did patients treated with surgery alone.

DISCUSSION

Findings

This study shows a continuously increasing incidence rate of MCC in The Netherlands, with the numbers more than tripling since 1993. The total number of registered MCCs in The Netherlands between 1993 and 2015 is 1977, which is more than double the amount of the previous study, in which 808 MCCs were analyzed.[4] The mean age at diagnosis was 75.5 years, and MCC was predominantly located on the head and neck area (42.7%) and the extremities (40.1%). Most often, MCCs were treated with surgery alone (59.8%). Relative 5-year survival was low: 63.0%, and this number has not improved in the past 25 years.

Males had a significantly higher mortality than females did (HR, 1.24), and the chance of dying increased with age, with an increase of around 7% per additional year of age at the time of diagnosis; these findings held up when adjusted for other characteristics. The increasing mortality with age is likely due to aging, for relative 5-year survival does not evidently decrease for higher age groups.

Nodal (HR, 1.26) and distant (HR, 2.44) spread of disease were associated with a significantly higher mortality when compared with local disease, and also when adjusted for other factors. Patients treated with surgery combined with radiotherapy had a significantly lower mortality than did patients treated with surgery alone (HR, 0.87), but this finding did not hold up upon adjustment for other characteristics.

We found an increasing incidence of MCC, which is in line with the findings of studies in other countries.[3,5,6] A recent study by Paulson et al in the United States even showed an increase in incidence of 95% between 2000 and 2013.[3] In our study, the increase between 2000 and 2013 was 84%. Explanations for this increasing incidence could include increasing exposure to known risk factors such as ultraviolet radiance, more use of immunosuppressants, and—probably most importantly—the aging of society,[3,11] but it might also be due to better detection or more specific diagnosis by physicians. However, the most substantial improvement in the diagnosis of MCC came with the introduction of the cytokeratin 20 immunohistochemical staining in the 1990s,[20,21] which does not explain the continuous increase of incidence in recent years. Furthermore, we calculated age-standardized incidence, excluding the aging of society as a possible factor. Patient characteristics are mostly comparable with those in other countries; MCC is known for developing at an older age, and it predominantly develops in the head and neck area and extremities.[2,3,5] We did find that MCC is diagnosed in more females than males, but this is due to the higher proportion of females in general in older age: the difference disappears when looking at standardized incidence rates.

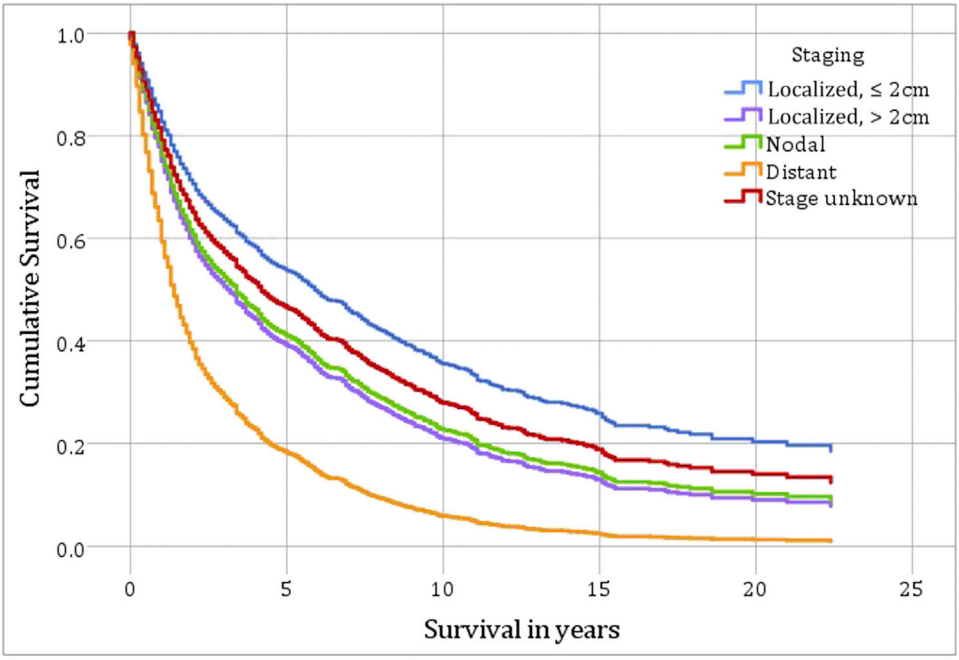

Fig 2. Merkel cell carcinoma (MCC). Survival per stage of MCC in The Netherlands 1993-2016.

Table IV. Survival analysis of MCC in The Netherlands in 1993-2016

	Univariate		Multivariate without treatment (N = 1976)		Multivariate with treatment (N = 1976)	
Covariate	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Sex						
Female	1 (ref)		1 (ref)		1 (ref)	
Male	1.24	1.11-1.39*	1.37	1.22-1.54*	1.42	1.26-1.59*
Age (per year)	1.07	1.06-1.07*	1.08	1.07-1.08*	1.07	1.07-1.08*
Location						
Head and/or neck	1 (ref)		1 (ref)		1 (ref)	
Trunk	0.98	0.81-1.19	1.45	1.19-1.77*	1.40	1.14-1.71*
Upper extremity	0.75	0.64-0.88*	1.06	0.91-1.25	1.06	0.90-1.24
Lower extremity	0.89	0.76-1.03	1.11	0.96-1.29	1.10	0.94-1.28
Skin location unspecified	1.47	0.88-2.46	0.97	0.58-1.64	0.66	0.39-1.12
Nonskin	1.06	0.60-1.87	0.83	0.46-1.49	0.90	0.50-1.61
PLU	1.02	0.79-1.31	1.22	0.92-1.61	1.05	0.79-1.40
Staging						
Localized	1 (ref)		1 (ref)		1 (ref)	
Nodal	1.26	1.08-1.48*	1.43	1.22-1.67*	1.36	1.15-1.61*
Distant	2.44	1.99-2.99*	2.63	2.11-3.26*	2.23	1.75-2.84*
Unknown	1.08	0.92-1.28	1.24	1.04-1.48*	1.17	0.98-1.40
Treatment						
Surgery alone	1 (ref)					
Surgery + RT	0.87	0.76-0.99*			0.89	0.77-1.02
Surgery + CT	2.13	1.27-3.55*			1.20	0.70-2.07
Surgery + RT + CT	0.88	0.54-1.45			1.15	0.69-1.92
RT alone	2.25	1.76-2.87*			1.63	1.26-2.10*
RT + CT	1.01	0.57-1.79			1.23	0.68-2.22
CT alone	2.28	1.49-3.49*			2.98	1.88-4.73*
No treatment	5.04	3.94-6.45*			3.45	2.67-4.47*
Unknown	1.65	0.79-3.49			1.30	0.61-2.79

CI, Confidence interval; *CT*, chemotherapy; *HR*, hazard ratio; *PLU*, primary location unknown; *ref*, reference value; *RT*, radiotherapy.
*Significant.

We found a low survival rate in general and a significantly lower survival rate for male patients, older patients, and MCCs located on the trunk with adjustment for other characteristics. These findings are comparable with the findings of other studies.[2,5,22] The worse prognosis for MCC located on the trunk is difficult to explain. One explanation could be that lesions on the trunk are less notable and therefore might be detected at a later stage, when they are more difficult to treat.

We did not see any improvements in survival despite recent advances in MCC treatment with the successful introduction of immune checkpoint blockade for metastatic MCC.[23,24] These drugs were approved only recently (in November 2017) in The Netherlands, and therefore, it is logical that this effect is not yet visible.

Our study suggests that surgery combined with radiotherapy might be more valuable than surgery alone. This finding is in line with those of other studies that showed higher survival for patients treated with surgery combined with adjuvant radiotherapy.[12-15]

On the basis of introduction of immune checkpoint blockade, the observed heterogeneous treatment pattern, and the lack of a national guideline for MCC in The Netherlands, we believe that the quality of care and survival can be improved by centralization of care for this rare disease, development of guidelines, quick introduction of effective systemic therapy, and participation in clinical trials to further improve the future of patients with MCC. The introduction of immune checkpoint inhibitors could make a difference in survival in the future. This analysis has captured a snapshot of the survival statistics with no improvement of survival for many years. This snapshot could be used as a comparison for survival statistics in the future, when possible effects of the new therapies become visible.

Limitations

We did not register data on cause of death, so we were unable to calculate the disease-specific survival. To obtain an estimation of disease-specific survival, we calculated relative survival rates, stratified by period of diagnosis and sex. Even though we found that patients with MCC have a lower relative survival than the average population of their age, we do not know whether they died because of MCC. Furthermore, data on whether lymphadenectomy was performed were lacking for too many patients to include this in our analysis. Also, we lacked sufficient data on comorbidity, and therefore, we could not adjust for other diseases or risk factors in our analysis.

CONCLUSION

This study shows a continuously increasing incidence rate of MCC in The Netherlands. Survival after diagnosis of MCC is low and has not been improving over time. The results of this study emphasize the need for centralization of expertise for this rare cancer in The Netherlands.

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