EUROPEAN JOURNAL OF CANCER 47 (2011) 579–585

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Epidemiology and survival of Merkel cell carcinoma in the Netherlands. A population-based study of 808 cases in 1993–2007

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ARTICLE INFO

Article history:
Received 28 April 2010
Received in revised form 1 November 2010
Accepted 3 November 2010
Available online 6 December 2010

Keywords:
Merkel cell carcinoma
Epidemiology
Radiotherapy

ABSTRACT

Background: Merkel cell carcinoma (MCC) is a rare and highly malignant neuroendocrine tumour, predominantly located on sun-exposed areas of the skin. The aim of this study was to evaluate data in the Netherlands concerning incidence, stage, age, sex, location, treatment and survival.

Methods: Using nationwide data from the Netherlands Cancer Registry from 1993 to 2007, we compared 808 MCCs with European data and the US Surveillance, Epidemiology and End Results (SEER) Program.

Results: The annual age standardised incidence rate per million of MCC increased from 1.7 in 1993–1997 to 3.5 in 2003–2007. Median age at diagnosis was 76 years. The most common location was the head and neck. Three quarters of patients had localised disease, 16% regional and 6% distant metastasis. Surgery was performed in 89% of patients, with adjuvant radiotherapy in 26% of them. One-, five- and ten-year relative survival was 85%, 62% and 47%, respectively. Negative predictive factors for the risk of death were male sex, increasing T-stage, regional and distant metastasis and no treatment. Survival after combined surgery and radiotherapy was borderline significantly better than surgery alone (HR 0.82, $p = 0.09$). Our results are comparable to SEER data except for the ratio localised/regional disease. We observed less regional cases (16% versus 31%); while ten-year survival of localised cases was lower (51% versus 71%).

Conclusions: MCC incidence rates have doubled in the Netherlands over the period 1993–2007. The relatively high number of localised cases and their relatively low survival as compared to SEER data suggest that a substantial proportion is undertreated.

1. Introduction

Merkel cell carcinoma (MCC) is a rare and highly malignant tumour of the skin. The Merkel cell was first described in 1875 by Merkel[1] and the Merkel cell carcinoma in 1972 by Toker.[2] This tumour has been termed as such because of the ultra structural immunologic similarities to the Merkel cell. Nowadays, MCC is considered to originate from either the Merkel cell, a mechanoreceptor cell from neural crest origin, forming synapse-like contacts with enlarged

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.11.002

nerve terminals, or from a pluripotent stem cell of the basal layer.[3]

MCC occurs predominantly in the older white population, mostly located on sun-exposed areas with approximately 50% of cases occurring in the head and neck, 40% in the extremities and 10% in the trunk and genitalia.[4] It classically presents as a non-tender subcutaneous mass, most often nodular, but also a plaque-like appearance, sometimes surrounded by satellite lesions, is possible. It varies from flesh-coloured to red, lilaceous or blue and can exhibit overlying teleangiectasia or a shiny surface that makes it easily confused with basal cell carcinoma (BCC).[5] Some but not all publications report a male predominance, varying from 1.4:1 to 2.3:1.[6,7]

MCC is seen in association with squamous cell carcinoma of the skin, Bowen disease, BCC, systemic diseases and leukaemia.[8] Besides, there is evidence for an association with immunosuppression and a polyoma virus.[9–11]

During 1989–2005, MCC constituted 0.7% of all non-BCC skin cancer in the Netherlands and the European standardised rate was 0.3 per 100,000 person-years in 2001–2005.[12] Based on data from the US Surveillance, Epidemiology and End Program (SEER) of the National Cancer Institute, the age-adjusted incidence rate in the USA (using the US2000 population as a standard) has tripled from 1.5 per million in 1986 to 4.4 per million in 2001.[13]

The most frequently used staging systems divide the MCC in $\leqslant$2 cm, >2 cm, any T N+ and any T, any N, M+, stage Ia, Ib, II and III, respectively.[14] At presentation most patients have stage I disease (55%), followed by stage II (31%) and stage III (6%).[15] Because of the rarity of the disease, widely disparate recurrence (45–75%)[4,6,16–21] and survival (30–75%)[6,16–21] data have been published and no prospective study has assessed the management of this tumour. Depending on the stage of disease and patient's health status, the primary treatment of MCC involves surgical excision, with or without sentinel lymph node biopsy (SNLB), elective lymph node dissection (ELND), radical lymph node dissection (RLND) and postoperative local or locoregional (chemo)radiation.[14–21] Also primary radiotherapy has been described.[22]

The aim of this study was to evaluate epidemiological data of Merkel cell carcinomas in the Netherlands concerning incidence, stage, age and sex, location, initial treatment and survival.

2. Patients and methods

The Netherlands Cancer registry (NCR), which has been operating since 1989, is a population-based cancer registry, with systematic collection of data on all malignant neoplasms in the Netherlands. The NCR is organised by the eight Comprehensive Cancer Centres. In all Dutch hospitals, pathologists enter their coded histological diagnoses in a computer system, which notifies the co-workers of one of the comprehensive cancer centres.[23]

Patients without pathological confirmation who did not visit a hospital are not notified to the NCR. This systematic under-registration is estimated to be less than two percent for all cancers combined.[24,25] Due to occasional errors and shortcomings in notification procedures, some additional incompleteness is possible.

The NCR codes all tumours (topography and morphology) according to the International Classification of Diseases for Oncology (ICD-O). A specific code (M8247) for MCC was introduced in the second version of ICD-O and this version was used by the NCR for cancers diagnosed in 1993 and later. Therefore we were able to select all patients diagnosed with MCC from 1993 until 2007. To compare incidence rates between different populations, age-adjusted incidence rates per million person-years were calculated. For the calculation of the age-standardised rates, the European Standard Population was used.[26] Survival was calculated as relative survival, using the strs-software from Paul Dickman for STATA.[27]

3. Results

The total number of registered MCCs in the Netherlands from 1993 until 2007 was 808. Seven patients had two MCCs, while one patient was diagnosed with three MCCs. There were 467 tumours diagnosed in females and 341 in males with MCC, but the annual age standardised incidence rate (ASR) in 1993–2007 in males was slightly higher than in females: 2.77 per million and 2.53, respectively. This opposite result is caused by the surplus of women in older age groups and the low weights of these age groups in the standard population. During the study period, the ASR roughly doubled from 1.7 per million in 1993–1997 to 3.5 per million in 2003–2007 (Fig. 1). The median age at diagnosis was 76 years (males: 75, females: 77). Fig. 2 shows that the incidence increases with age and reaches its highest level in the oldest age group (90 years or older).

About one third of the cases in males and half of the cases in females are found in the head and neck region (Table 1). About 40% of the cases are found at the extremities. Trunk and genitals account for 15% of the cases in males and 7% in females. No primary tumour is found in five percent of all cases, somewhat more often in males (8%) than in females (3%).

In three quarters of all patients no metastases are clinically apparent at diagnosis. Of these localised cases information about the size was available for 507 cases. Two thirds (336 cases) were 2 cm or smaller, while one third (171) was larger than 2 cm. In 16% of the cases there are regional lymph node metastases and in 6% there are distant metastases. The proportion of patients with regional disease gradually increased over time from 14% in 1993–1997 to 18% in 2003–2007.

3.1. *Multiple tumours*

In 297 out of 799 patients (37%) other invasive cancers were diagnosed, 202 prior to the MCC and 95 after the diagnosis of MCC. Other skin cancers (16 melanomas and 80 squamous cell carcinomas) were the most common second cancers, followed by colorectal cancer ($n = 45$), haematological malignancies ($n = 43$, including 20 cases of CLL) and breast cancer ($n = 25$).

3.2. *Treatment*

Table 2 shows that most patients (89%) received some form of surgery (excision of the tumour and/or regional lymph node

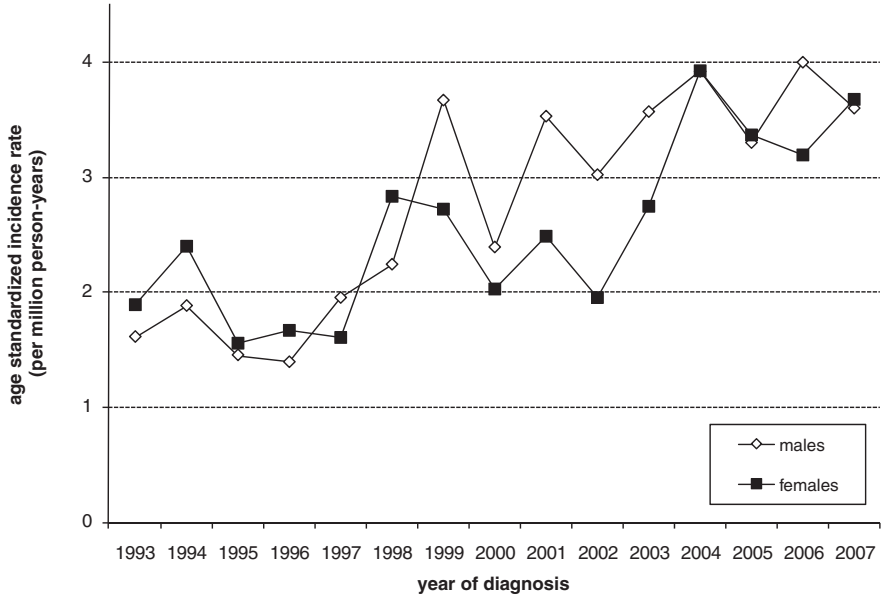

Fig. 1 – Age-standardised incidence rate (standardisation using the European standard population) of Merkel cell carcinoma in the Netherlands, 1993–2007.

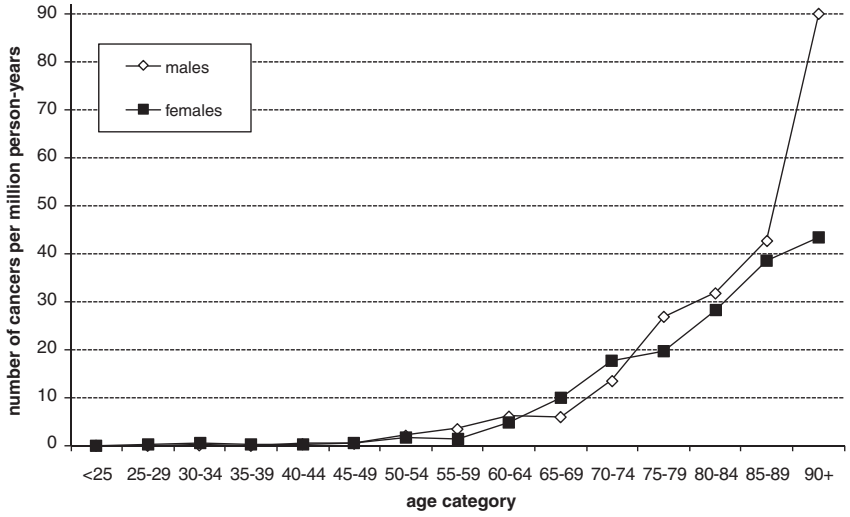

Fig. 2 – Age-specific incidence rate of Merkel cell carcinoma in the Netherlands, 1993–2007.

excision). In 26% of the patients surgery was combined with local and/or regional radiotherapy, while 6% was treated with radiotherapy without surgery. In total, 32% of the patients were treated with radiotherapy. In Stage I 72% of cases were treated with only surgery.

Of all surgical patients with locoregional disease 30% received adjuvant radiotherapy. Chemotherapy (alone or in combination with other treatments) was administered to 4% of the whole group of patients, but to 9% of patients with regional disease and 35% of patients with distant metastasis.

3.3. *Survival*

One-, five- and ten-year relative survival of MCC was 85%, 62% and 47%, respectively (Table 3). Survival in males was generally lower than in females (55% five-year survival versus 67%). Age at diagnosis was of limited influence on relative survival.

Stage of disease influenced prognosis significantly. Five-year survival data for localised tumours $\leqslant$2 cm in diameter were 75% compared to 61% for localised tumours >2 cm. In regional and distant disease five-year survival was 52% and 17%, respectively.

In a multivariate Cox-regression analysis male sex, increasing T-stage, regional and distant metastasis, as well as 'no treatment' appeared to be independent prognostic factors for the risk of death (Table 4). Patients who received radiotherapy combined to surgery had a lower risk of death compared to patients who were treated surgically only (HR 0.82, 95% confidence interval 0.65–1.04). However, this difference was not statistically significant ($p = 0.09$).

Table 1 – Characteristics of Merkel cell carcinoma in the Netherlands, 1993–2007.

	Sex					
	Males		Females		Both sexes	
	Number	%	Number	%	Number	%
Age at diagnosis						
<55	24	7.0	26	5.6	50	6.2
55–64	60	17.6	38	8.1	98	12.1
65–74	82	24.0	136	29.1	218	27.0
75–84	125	36.7	163	34.9	288	35.6
85+	50	14.7	104	22.3	154	19.1
Primary site						
Head and neck	121	35.5	236	50.5	357	44.2
Trunk	49	14.4	29	6.2	78	9.7
Arm	73	21.4	83	17.8	156	19.3
Leg	70	20.5	94	20.1	164	20.3
Skin unspecified	–	–	7	1.5	7	0.9
Genitals	2	0.6	4	0.9	6	0.7
Unknown	26	7.6	14	3.0	40	5.0
Stage						
Localised, ⩽2 cm	123	36.1	213	45.6	336	41.6
Localised, >2 cm	74	21.7	97	20.8	171	21.2
Localised, size unknown	44	12.9	74	15.8	118	14.6
Regional	71	20.8	60	12.6	131	16.2
Distant metastasis	29	8.5	23	4.9	52	6.4
All cases	341		467		808	

Table 2 – Merkel cell carcinoma according to treatment and extent of disease, the Netherlands, 1993–2007.

Treatment	Stage							
	Local		Regional		Distant		Total	
	Number	%	Number	%	Number	%	Number	%
Surgery alone	444	71.2	45	34.4	8	15.4	497	61.6
Surgery + RT	143	22.9	51	38.9	5	9.6	199	24.7
Surgery + CT	1	0.2	4	3.1	7	13.5	12	1.5
Surgery + RT + CT	3	0.5	10	7.6	1	1.9	14	1.7
Radiotherapy alone	19	3.0	6	4.6	9	17.3	34	4.2
Radiotherapy + CT	2	0.3	5	3.8	5	9.6	12	1.5
Chemotherapy alone	1	0.2	3	2.3	6	11.5	10	1.2
None/other	11	1.8	7	5.3	11	21.2	29	3.6
Total	624		131		52		807	

RT = radiotherapy; CT = chemotherapy.

4. Discussion

In the Netherlands, the age standardised incidence rate (ASR) for Merkel cell carcinoma roughly doubled between 1993 and 2007 from 1.7 per million to 3.5 per million. The estimated annual percentage change (EAPC) amounted 8% in males and 5% in females. This increase is consistent with data from the US Surveillance, Epidemiology and End Program (SEER) of the National Cancer Institute, which reported that in the USA the ASR (using the US2000 population as a standard) of Merkel cell carcinoma tripled from 1.5 per million in 1986 to 4.4 per million in 2001 (EAPC 8%).[13]

In the Netherlands, the ASR of skin carcinoma and melanoma had been increasing during the past decades, with an EAPC of 4% and 2.3% for skin melanoma and squamous cell carcinoma of the skin, respectively.[12] As a large proportion of Merkel cell carcinoma is located at sites which are generally exposed to sunlight, increasing exposure to ultraviolet light might also have contributed to the increasing incidence.

Due to the fast increase of Merkel cell carcinoma this tumour constituted 0.6% of all skin cancers in 1993–1997 and 0.9% in 2003–2007 (BCC excluded). Part of the increase of Merkel cell carcinoma may be explained by improved detection or to increased case ascertainment and reporting, but as Merkel cell carcinoma as a proportion of all skin cancers also increased and Merkel cell carcinoma has since long been recognised as a distinct entity by pathologists, this effect was probably of limited relevance.

Furthermore, as Merkel cell carcinoma is associated with immunosuppression[8–10] and a polyoma virus[11] a larger

Table 3 – Relative survival of patients with Merkel cell carcinoma in the Netherlands, 1993–2007.

	Number of cases	Number of years after diagnosis			
		1	3	5	10
All cases	798	85%	70%	62%	47%
Sex					
Males	337	81%	64%	55%	37%
Females	461	87%	73%	67%	54%
Age group					
15–54	50	94%	71%	64%	65%
55–64	96	92%	71%	64%	53%
65–74	214	87%	71%	62%	49%
75–84	285	81%	71%	64%	39%
85+	153	79%	61%	53%	
Stage					
Localised, ⩽2 cm	331	96%	84%	75%	54%
Localised, >2 cm	171	80%	63%	61%	46%
Localised, size unknown	113	89%	72%	60%	50%
Regional	131	76%	58%	52%	44%
Distant	52	41%	22%	17%	16%
Period of diagnosis					
1993–1997	162	82%	70%	63%	46%
1998–2002	254	84%	70%	62%	51%
2003–2007	382	86%	69%	61%	

Table 4 – Risk of death of patients with Merkel cell carcinoma in the Netherlands, 1993–2007.

	Number of cases	Model 1 (excl. treatment)		Model 2 (incl. treatment)	
		HR	95% CI	HR	95% CI
Sex					
Male	337	1	(ref)	1	(ref)
Female	461	0.72	0.59–0.87	0.71	0.58–0.86
Primary site					
Head and neck	353	1	(ref)	1	(ref)
Trunk and genitals	84	0.97	0.70–1.35	0.97	0.70–1.34
Arm	152	0.98	0.76–1.27	0.97	0.75–1.26
Leg	162	0.92	0.72–1.18	0.88	0.69–1.14
Unspecified skin or unknown	47	0.97	0.61–1.54	0.73	0.44–1.21
T-stage					
T1 (⩽2 cm)	361	1	(ref)	1	(ref)
T2 (2–5 cm)	183	1.35	1.07–1.71	1.35	1.06–1.71
T3 (>5 cm)	45	1.76	1.21–2.63	1.76	1.18–2.61
T4 (invasion of deep extradermal tissues)	19	2.13	1.25–3.64	2.10	1.20–3.68
TX (size unknown)	190	1.18	0.91–1.52	1.16	0.89–1.50
N-stage					
N0	643	1	(ref)	1	(ref)
N1	155	1.36	1.05–1.76	1.43	1.09–1.86
M-stage					
M0	746	1	(ref)	1	(ref)
M1	52	3.22	2.28–4.54	2.58	1.77–3.76
Treatment					
Surgery	501			1	(ref)
Surgery + radiotherapy	209			0.82	0.65–1.04
Radiotherapy	48			1.32	0.89–1.95
Chemotherapy	10			1.50	0.66–3.38
Other/none	30			1.90	1.18–3.07
Total	798				

number of patients with immunosuppression may also be an explanation for the increasing incidence of Merkel cell carcinoma. Unfortunately, like in the SEER data, there is no information available about immunosuppression in our cancer registry. The rates in males in the Netherlands are only slightly higher than in females, 2.77 per million and 2.53 per million, respectively, while SEER reported almost threefold higher rates for males.[13] However, the age pattern with a median age of 76 years and incidence reaching its highest level in the oldest age group (90 years or older), is consistent with SEER data.[28] The rates in Sweden in males and females are 4.2 per million and 3.3 per million, respectively, but in Denmark 2 per million and 2.5 per million.[29,30] About 45% of our cases were found in the head and neck region, 40% in the extremities, about 10% in trunk and genitals and in 5% of the cases no primary tumour was found. These findings are also in consistence with SEER data[7,28] and European data.[29,30] At presentation three quarters of our patients had localised disease, 16% had lymph node metastasis and 6% distant metastasis. Compared to SEER data (49%, 31% and 8%, respectively, and 11% unknown stage)[28] we and the Danish[30] have less patients with lymph node metastasis in their material. This difference is remarkable and may be related to differences in staging procedures between the US and the Netherlands/Denmark. No precise information on these procedures, including sentinel node biopsy or elective lymphadenectomy, was available from all registries. However, SEER reported extended surgery with lymph node dissection or major amputation in only 10% of the surgical cases,[15] while in our series nodal status was pathologically confirmed in 20% of the surgical cases (pN≠X). Although it is difficult to interpret this information, they do not support the assumption of more extensive staging procedures in the US compared to the Netherlands. On the other hand, we cannot exclude the possibility that the lower proportion of regional disease in the Netherlands is related to a more reserved policy towards lymph node dissections in patients with clinically localised disease in comparison to the USA.

Surgery has been the mainstay of treatment and most patients (89%) received some form of surgery. In almost 30% of the patients with locoregional disease surgery was combined with local or locoregional radiotherapy, while in the SEER data this was 40% of cases.[15] The higher percentage is probably related to a higher proportion of regional disease in the USA.

Stage of disease influenced prognosis significantly. Five and ten-year relative survival rates of localised disease were 68% and 51% respectively, whereas these rates for regional disease were 52% and 44% and for distant stages 17% and 16%, respectively. SEER reported a ten-year relative survival for localised disease of 71% and for regional and distant disease 48% and 20%, respectively.[28] While our results are comparable to the SEER results for regional and distant disease, survival of the localised cases in the Netherlands is much worse. While we cannot exclude a different clinical behaviour in the USA, the poorer results can also be related to less aggressive treatment regimens for localised tumours (72% received surgery only) or less extensive staging procedures. The five-year relative survival rate of 17% for cases with distant disease seems high for an aggressive cancer such as Merkel cell carcinoma. This rate was based on four five-year survivors out of 52 cases with distant disease. We could not review all four cases, but in one case review revealed a spontaneous regression of the tumour, while two other cases were treated with chemotherapy and metastatectomy, respectively. For the fourth case supplementary information was not available. We cannot exclude some misclassification, but survival of distant disease seems possible in rare cases.

Relative survival rates for the different age groups only showed small differences. In the oldest age group (85 or older) five-year relative survival was slightly lower (53%) in comparison to younger patients (63%), but this difference was not statistically significant. The lower survival in the oldest age group may be related to a lower proportion of patients receiving adjuvant radiotherapy (12% in patients 85 years or older compared to 30% in younger patients), while none of the patients 85 years or older received chemotherapy. Like in many other cancers, including skin melanoma, five and ten-year relative survival in males (55% and 37%) was somewhat lower than in females (67% and 54%) but these differences did not reach statistical significance either. The poorer survival in males was probably due to the relatively unfavourable stage distribution in males.

The location of the tumour had no influence on prognosis in our series, nor did we observe an improvement over time.

While the SEER data demonstrated a positive association between adjuvant radiation and overall survival, statistically significant on multivariate analysis (HR 0.85, $p = 0.0122$),[15] this study showed only a trend (HR 0.82, $p = 0.09$). However, our series comprised half of the number of patients.

In summary, Merkel cell carcinoma is a rare but increasing skin cancer representing 0.9% of skin cancers (BCC excluded) in 2003–2007. Since 1993, the ASR roughly doubled. The relatively high proportion and relatively poor survival of localised Merkel cell carcinoma (five-year survival 68% and ten-year survival 51%) in comparison to the SEER data gives the impression that a substantial proportion of the localised cases is undertreated in the Netherlands.

Conflict of interest statement

None declared.

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