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# Merkel cell carcinoma – A population-based epidemiological study in Finland with a clinical series of 181 cases

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ABSTRACT

*Background:* Merkel cell carcinoma (MCC) is a rare malignancy of the skin, and its incidence is reported to be rising. The purpose of this study was to calculate its incidence and survival ratios, and to describe the clinical characteristics of Merkel cell carcinoma patients in Finland.

*Methods:* We calculated the incidence of MCC based on data from the Finnish Cancer Registry. In addition, patient files from hospitals and primary health care centres were reviewed for detailed data on the treatment and disease recurrence of 181 patients diagnosed with MCC in Finland during 1983–2004, and relative survival ratios were calculated for them.

*Results:* The incidence (per 100,000) of MCC in Finland in 1989–2008 was 0.11 for men and 0.12 for women, adjusted for age to the world standard population. The mean age at diagnosis was 76 years (range 27–100), and 69% of the patients were women. The most common site of the primary tumour was the head and neck (53%). No extra benefit was gained from a wide surgical margin (⩾2 cm) compared to a margin of 0.1–0.19 cm, but an intralesional excision was more often associated with local recurrence. None of the patients with Stage I–II disease who had received postoperative radiotherapy to the tumour bed had a local recurrence. The 5-year relative survival ratio amongst men was 36% (95% confidence interval 20–54%), and amongst women 69% (56 to –82%).

*Conclusions:* MCC is a rare disease in Finland, with incidence rates similar to those in the other Nordic countries. Our results support the view that complete excision with clear margins and post operative radiotherapy decrease local recurrences.



## 1. Introduction

Merkel cell carcinoma (MCC) is a rare malignant neuroendocrine tumour of the skin. The incidence rates of MCC reported from different countries vary, but are not comparable because of differences in observation periods and in age-adjustment methods. In all studies, the incidence has been less than one per 100,000.[1–6]

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MCC affects mainly the white population with median age at presentation of approximately 70 years, and according to previous studies it is more common in men than in women.[1,2,7,8] The aetiology of MCC may be multifactorial. Exposure to ultraviolet radiation is associated with MCC.[9–11] MCC also occurs more often in immuno-compromised individuals, such as those diagnosed with chronic lymphocytic leukaemia, lymphoma, or a human immunodeficiency virus infection, as well as amongst organ transplant recipients.[12–16] Recently, a novel polyomavirus, named Merkel cell polyomavirus (MCPyV), was identified in MCC tumour tissue suggesting that a viral infection might also be an aetiological factor.[17]

Tumour size has been shown to be a strong prognostic factor,[8,18–21] but the most consistent predictor of survival in MCC to date is the presence or absence of lymph node metastases at time of presentation.[22] Sentinel node biopsy (SNB) is recommended for all patients with localised disease for the purpose of staging. The impact of SNB on survival is still unclear.[7,23] MCC has a high incidence of local recurrences and a propensity for regional and distant metastases. It is usually treated surgically, either with or without postoperative radiation therapy.

The aim of this study was to calculate the incidence and survival of MCC patients in Finland, and to present clinical characteristics of this large national patient series.

## 2. Material and methods

Individuals diagnosed in Finland with MCC or small cell carcinoma of the skin up until 2008 were identified from the Finnish Cancer Registry. The Registry was set up in 1953, and it maintains a nation-wide population-based database on all cancer cases in Finland (population 5.4 million in 2010). All physicians, hospitals and pathology and haematology laboratories are obligated to submit data to the Finnish Cancer Registry on all cancer cases that come to their attention. The Registry has a coverage of more than 99% of all malignancies diagnosed in Finland.[24] The first case of MCC was diagnosed in Finland in 1983, and during 1983–2008, a total of 295 individuals were diagnosed with Merkel cell carcinoma. The dates of death are registered by the Population Register Centre of Finland, and are regularly linked to the Finnish Cancer Registry.

For the clinical patient series, we reviewed the data on all patients diagnosed with MCC during 1983–2004 ($n = 207$). Detailed data on treatment (type of operation, excision margins, radiotherapy) and time and site of recurrence were obtained from the files of hospitals and primary health care centres.

Formalin-fixed paraffin-embedded archival tumour tissue blocks of these patients were tracked and collected from pathology laboratories, using tissue sample numbers obtained from the Finnish Cancer Registry. A tissue sample of the tumour (biopsy, first excision, re-excision or metastasis) was available for re-evaluation from 193 patients. The diagnoses were confirmed in blinded fashion by two of the authors (TB and HK).

In order to confirm the diagnosis histopathologically, we required that the tumour morphology was consistent with MCC on haematoxylin-eosin – stained tissue sections, and that the specimens were immunohistochemically positive for cytokeratin 20 (CK-20). If CK-20 was negative, but morphology consistent with MCC, the diagnosis was confirmed by immunostaining for synaptophysin and chromogranin A. Negative immunostaining for thyroid transcriptase factor 1 (TTF-1) was required to rule out metastatic small cell lung carcinoma. In 12 patients the diagnosis of MCC could not be confirmed at re-evaluation (10 cases were inconsistent with MCC morphology and 2 cases were TTF-1 positive). The remaining 181 patients were included in the final clinical series of this study.

Tumour size (the greatest surface dimension) was measured from HE-stained slides whenever feasible. Otherwise we used the diameter that was reported in the case records. The minimum excision margin (minimum distance of healthy tissue from disease to resection margin, either lateral or deep) was also measured from the histological samples, and the minimum cumulative excision margin was calculated in the case of re-excisions.

Intralesional excision denotes cases in which tumour cells were observed at the resection margin on histological examination, or the free margin was less than 1 mm, or only biopsy was performed. Marginal excision was defined as the distance from the tumour to the resection margin measuring 0.1–1.9 cm. Wide excision meant a resection margin of at least 2 cm.

For staging, we used the most recent classification of the Memorial Sloan-Kettering Cancer Center (MSKCC). The American Joint Committee on Cancer (AJCC) consensus staging system was published in 2009. Before that, the staging system of MSKCC was used most commonly because it was based on the largest number of patients and was best validated.[7,8,22,25–27] The MSKCC staging system divides cancer patients into four stages: local disease with primary tumour $<2$ cm or $\geqslant 2$ cm (Stages I and II); lymph-node positive disease (Stage III); and distant metastatic disease (Stage IV), with tumours $<2$ cm having a better prognosis. Data on radiotherapy, time and site of recurrence were obtained from hospital records.

Relative survival ratios (RSR) were calculated to describe excess mortality due to MCC.[28] The relative survival ratio closely resembles disease-specific survival. It was calculated from the date of histological diagnosis to the date of death, or to the closing date of this study (December 31, 2007).

The study was approved by the Ethics Committee of the Helsinki University Central Hospital. The Ministry of Health and Social Affairs granted permission to collect patient data, and the National Authority for Medicolegal Affairs granted permission to collect tissue samples for the study.

## 3. Results

### 3.1. *Incidence*

Since the early years of the recognition of MCC, the incidence estimates have become more reliable, and since 1989 they have been fairly stable. The age-adjusted (world standard) incidence of MCC (per 100,000) in 1989–2008 in Finland was 0.11 for men and 0.12 for women (Fig. 1). The corresponding

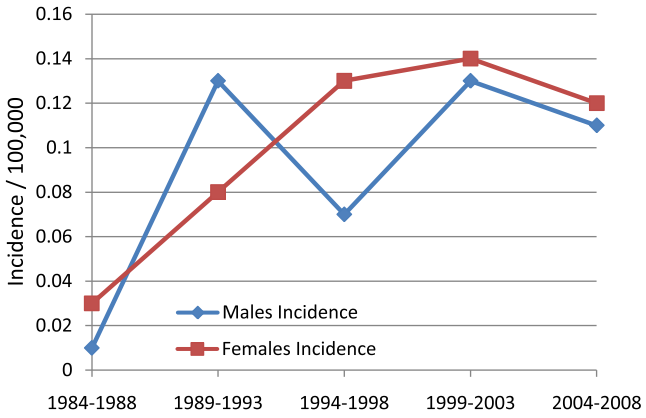


**Fig. 1 – Incidence, age-adjusted to the world standard population, of Merkel cell carcinoma in Finland, by calendar period.**

rates adjusted to the European standard population are 0.19 and 0.20, and to the US 2000 population 0.24 and 0.25.

The incidence increases sharply with age and is similar in both sexes (Fig. 2). Because the number of old women in the Finnish population is much larger than that of old men, the absolute number of women with MCC has been considerably greater than of men (Table 1).

### 3.2. *Patients and tumour characteristics*

In the clinical cohort of 181 patients whose MCC diagnosis was reconfirmed, the age at diagnosis ranged from 27–100 years, and the majority of the patients were women (Table 1). The head and neck region was the most common location for the primary tumour. In eight patients (4%) the diagnosis of MCC was confirmed from their lymph node metastasis, but the primary site was unknown.

The mean tumour size was 1.8 cm (range 0.3–8.5 cm). The majority of the patients (86%) presented with a clinically node-negative (Stage I or II) disease. One patient with a clinically node-negative disease was SNB-positive, and was, therefore, classified as Stage III. Eighteen patients had regional

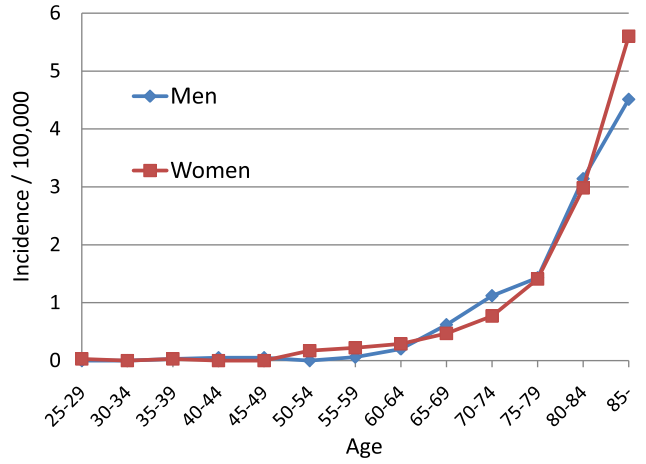


**Fig. 2 – Incidence of Merkel cell carcinoma in Finland, 1989–2008, by age and sex.**

**Table 1 – Patient and tumour characteristics of 181 Merkel cell carcinoma patients in Finland in 1983–2004.**

| Characteristic | Value | No. of patients | % |
|---|---|---|---|
| *Sex* | | | |
| Female | | 125 | 69 |
| Male | | 56 | 31 |
| *Age (years)* | | | |
| Mean | 75.9 | | |
| Median | 78.0 | | |
| Range | 27–100 | | |
| 0–50 | | 6 | 3 |
| 51–74 | | 58 | 32 |
| 75–100 | | 117 | 65 |
| *Tumour location* | | | |
| Head and neck | | 102 | 53 |
| Trunk | | 22 | 12 |
| Upper extremity | | 27 | 15 |
| Lower extremity | | 22 | 12 |
| Primary unknown | | 8 | 4 |
| *Tumour size (cm)* | | | |
| Mean | 1.8 | | |
| Median | 1.4 | | |
| Range | 0.3–8.5 | | |
| *Stage at presentation* | | | |
| I | | 108 | 60 |
| II | | 47 | 26 |
| III | | 18 | 10 |
| IV | | 8 | 4 |
| *Number of patients by period of diagnosis (men/women)* | | | |
| 1984–1988 | | 2 / 10 | |
| 1989–1993 | | 21 / 25 | |
| 1994–1998 | | 15 / 47 | |
| 1999–2003 | | 28 / 59 | |
| 2004–2008 | | 31 / 55 | |

lymph node involvement at presentation, and eight patients had distant metastases.

### 3.3. *Treatment of disease at presentation*

Re-excision after diagnostic excision or biopsy was performed in 55% of the 173 cases with a known primary tumour, and the surgical margins varied from 0.5 to 3 cm. In six cases, only biopsy was performed due to the patient's poor general condition, or death before the planned operation. The primary excision was considered sufficient for the rest.

Clear histological margins (at least 1 mm) were achieved in 72% of the 173 patients. In 22 patients (13%), a cumulative minimum margin $\geqslant$20 mm was achieved. In 37 (21%) patients the margin status remained positive. Further operations were withheld because of the patient's poor general health, advanced age or unawareness of the malignant nature of the disease. In 11 patients, the final excision margin could not be determined. Of the 173 patients, 24 received post-operative radiotherapy to the primary tumour bed.

Most of the 155 patients with localised Stage I–II disease were operated on with a marginal excision, and 22 (14%) received postoperative radiotherapy to the tumour bed (Table 2). In Finland, the first SBN to a MCC patient was performed in

**Table 2 – Treatment of the primary lesion and subsequent recurrences in Merkel cell carcinoma patients in Finland, 1983–2004, presenting with clinically local disease (Stage I–II) with known primary tumour ($n$ = 155).**

| Excision margin status | No. of patients (100%) | Recurrence No. of patients (%) | | | |
|---|---|---|---|---|---|
| | | Only local | Nodal (±local) | Distant (±local or nodal) | Overall |
| Intralesional exc. | 27 | 7 (26%) | 6 (22%) | 1 (4%) | 14 (52%) |
| Intralesional exc.+RT | 6 | 0 | 2 (33%) | 0 | 2 (33%) |
| Marginal exc. | 81 | 10 (12%) | 10 (12%) | 8 (10%) | 28 (35%) |
| Marginal exc.+RT | 13 | 0 | 2 (15%) | 2 (15%) | 4 (31%) |
| Wide exc. | 18 | 2 (11%) | 4 (22%) | 1 (6%) | 7 (39%) |
| Wide Exc + RT | 2 | 0 | 0 | 1 (50%) | 1 (50%) |
| Unknown | 7 | 2 (29%) | 1 (14%) | 0 | 3 (43%) |
| Unknown + RT | 1 | 0 | 0 | 0 | 0 |
| Total | 155 | 21 (14%) | 25 (16%) | 13 (8%) | 59 (38%) |

exc. = excision.
RT = radiotherapy.

**Table 3 – Site of first recurrence of Merkel cell carcinoma in Finnish patients in 1983–2004 amongst the 59 patients with Stage I–II disease with a recurrence.**

| Recurrence | No. of patients | % | Median time, months (range) |
|---|---|---|---|
| Local | 35 | 59 | 3 (1–61) |
| In-transit | 3 | 5 | 7 (4–34) |
| Regional lymph node | 19 | 32 | 8 (2–56) |
| Distant metastasis | 2 | 3 | 9 and 27 |

**Table 4 – Five-year relative survival ratio (%) amongst 180[a] Merkel cell carcinoma patients in Finland in 1983–2004, with 95% confidence interval, by sex and stage (closing date Dec. 31, 2007).**

| Stage | Men | Women | Both sexes |
|---|---|---|---|
| I | 58 (31–86) | 72 (55–87) | 69 (54–82) |
| II | 29 (7–60) | 88 (57–114) | 67 (44–89) |
| III | 0 | 29 (4–66) | 17 (3–44) |
| IV | 0 | 0 | 0 |
| All stages | 36 (20–54) | 69 (56–82) | 59 (49–70) |

a One 100-year-old patient was dropped because the population life table did not go beyond the age of 99 years.

2001. In this study, SNB was performed to 11 patients with a clinically localised disease. One patient had positive nodes and underwent complete lymph node dissection. Two other patients with Stage I–II disease at presentation underwent evacuation: one because of failed sentinel node lymphoscintigraphy and the other because of the assumed aggressive nature of the disease. In the majority of patients with Stage I–II disease (92%) no evaluation of draining lymph node basin was performed.

Complete lymph node clearance was performed in four (22%) of the 18 patients with Stage III disease. In seven patients, only the affected lymph node was removed, and seven patients had no surgery at all. Eight patients received radiotherapy to the lymph node area, and one patient received chemotherapy. Five of the eight patients with Stage IV disease received chemotherapy.

### 3.4. *Recurrence*

The disease recurred in 38% of the 155 patients with Stage I–II disease. The association between excision margin and radiotherapy with recurrence is presented in Table 2. The median time to recurrence was 6 months. More than half (59%) of the recurrences occurred at the primary tumour site, and 32% in regional lymph nodes (Table 3).

Twelve (86%) out of 18 patients with nodal disease at presentation had a recurrence in a median time of 8.5 months (range 1–97 months) after the primary operation; six had distant metastases and three had a nodal recurrence.

### 3.5. *Survival*

The 5-year relative survival ratio for Stage I disease was 68%, for Stage II 67%, for Stage III 16% and for Stage IV 0% (Table 4). The 5-year relative survival ratio amongst men was 36% and amongst women 69%. The relative excess risk of death was significantly lower amongst women than amongst men in all stages combined ($p$ = 0.002) and in Stage II ($p$ = 0.49). There was no significant difference in relative survival ratios between different tumour sites or age groups. Neither was there any difference in survival according to calendar period of diagnosis (data not shown).

## 4. Discussion

The age-adjusted (world standard) incidence rates of MCC based on a nationwide Finnish cancer registry are 0.11 and 0.12 per 100,000 person-years for men and women, respectively. The incidence increased during the early years (1979–1993), but thereafter the incidence has stabilised. The data before year 1989 are most likely incomplete due to diagnostic difficulties before immunohistochemical techniques, and, therefore, probably do not reflect the real incidence. Increased awareness of MCC amongst clinicians and pathologists may also explain the increased incidence during early years.

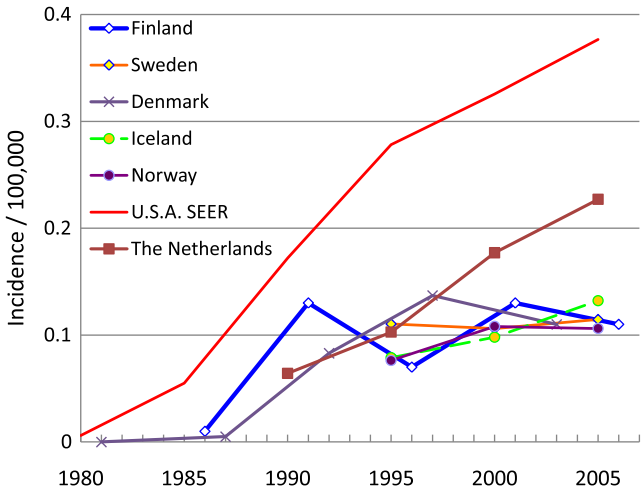


**Fig. 3 – Incidence of Merkel cell carcinoma in men, 1/100,000, age-adjusted to the world standard population, by 5-year averages (according to the Finnish Cancer Registry for Finland, the Swedish Cancer Registry for Sweden, Statens Serum Institut for Denmark, the Nordic Cancer Database for Norway and Iceland, the Netherlands Cancer Registry for the Netherlands and SEER – Surveillance, Epidemiology, and End Result – database for USA).**

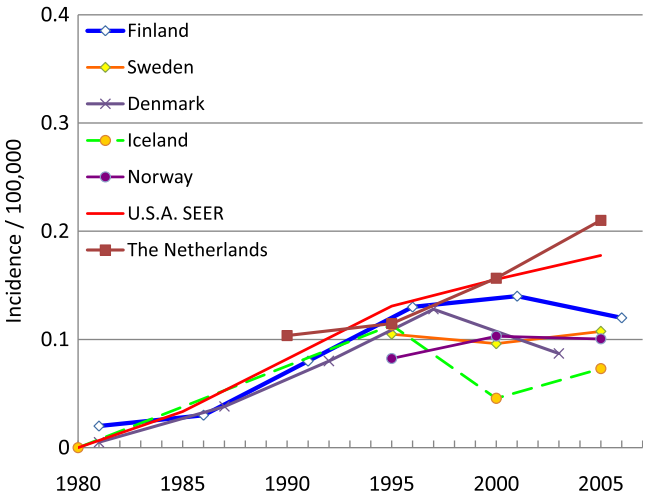


**Fig. 4 – Incidence of Merkel cell carcinoma in women, 1/100,000, age-adjusted to the world standard population, by 5-year averages (according to the Finnish Cancer Registry for Finland, the Swedish Cancer Registry for Sweden, Statens Serum Institut for Denmark, the Nordic Cancer Database for Norway and Iceland, the Netherlands Cancer Registry for the Netherlands, and SEER – Surveillance, Epidemiology, and End Result – database for USA).**

We had access to the MCC incidence figures in the other Nordic countries from national cancer registries or the NORDCAN cancer database.[29] The incidence rates are comparable, and they are similar in all Nordic countries. The rates have been similar for men and women in all countries (Figs. 3 and 4). Also in other Nordic countries, the incidence rates have been stable since 1995.

The data from the Netherlands Cancer Registry show increased incidence rates even after 1995 (Figs. 3 and 4). A study from the Netherlands reports that the incidence rates of MCC have doubled over the period 1993–2007,[6] which differs from the trend seen in the Nordic countries.

Studies from the American Surveillance, Epidemiology, and End Result (SEER) database have reported higher incidence rates, especially for men.[1,2] The incidence rates from SEER (age-adjusted to the world standard population) are shown in Figs. 3 and 4. The incidence amongst men was much higher in the USA than in Nordic countries (Fig. 3), and amongst women in the USA it was somewhat higher (Fig. 4). The higher prevalence of HIV-positive men in the SEER population[1,3] might explain the higher incidence compared to countries with fewer HIV -infected people, since the risk of MCC is approximately 13-fold in people with HIV infection/AIDS.[12,30]

To the best of our knowledge, this is the first nationwide study on MCC in which the diagnosis has been reconfirmed from histological specimens. An original tissue sample was available from 93% of all MCC cases identified from the Finnish Cancer Registry during 1983–2004. In 6% of the samples, the diagnosis of MCC could not be confirmed at re-evaluation.

As in other studies, the disease stage at presentation was the most significant prognostic factor in our study. The limitation of this study is that nodal staging was based primarily on clinical evaluation. It is very likely that some of the patients who were classified as Stage I or II might have been Stage III if histopathological nodal evaluation had been performed. The survival of the patients with Stage I and II disease was nevertheless clearly better than the survival of patients with nodal or distant metastases. In local disease, there was no difference in survival between patients with a tumour <2 cm compared to those with a tumour ⩾2 cm. The overall survival rate (59%) was similar to that reported previously.[1,6,7]

Women had a significantly better overall relative survival ratio than men, and the most striking difference was noted in Stage II disease. We have no explanation for this, since there was no statistical difference in tumour size or stage at presentation between the men and women. A lower relative survival rate in men than women was observed also the Dutch study.[6]

Surgical treatment protocols usually recommend excision with a lateral surgical margin of 1–2 cm, whereas a deep surgical margin is less emphasised. Some studies also indicate that the width of the excision margin does not influence loco-regional control.[31,32] In our series, 55% of the patients underwent re-operation after diagnostic biopsy. In six cases, the margin remained positive even after the last re-excision (repeated re-excisions were not considered necessary). We did not observe additional benefit from a wide margin (⩾2 cm) compared to a margin of 0.1–1.9 cm, but intralesional excision was more often associated with local recurrence. Remarkably, none of the patients with Stage I–II disease who had received postoperative radiotherapy had local recurrence, although this finding did not reach statistical significance. The relatively high number of nodal recurrences reflects the occult nodal disease already at presentation.

In conclusion, MCC is a rare disease in Finland; its incidence rates are equal amongst men and women, and similar to those seen in other Nordic countries. The survival of women is significantly better than of men. In our patient series consisting of cases from a long time period, the treatment schemes were heterogeneous. Our results support the current concept of treating MCC with margin-negative excision followed by radiotherapy to the tumour bed to reduce local recurrence.[22,33]

## Conflict of interest statement

None declared.

## Acknowledgment

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