Sentinel Node Status and Immunosuppression: Recurrence Factors in Localized Merkel Cell Carcinoma


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CLINICAL REPORT

Sentinel Node Status and Immunosuppression: Recurrence Factors in Localized Merkel Cell Carcinoma

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#These authors contributed equally to this work.

The prognostic value of the sentinel lymph node in Merkel cell carcinoma (MCC) has been examined previously in heterogeneous retrospective studies. The current retrospective study included a homogeneous population of patients with a localized MCC, all staged with sentinel lymph node biopsy. Factors associated with 3-year progression-free survival were analysed using logistic regression. The sentinel lymph node was positive in 32% of patients. The recurrence rate was 26.9%. In first analyses (n=108), gender (p=0.0115) and the presence of immunosuppression (p=0.0494) were the only significant independent factors. In further analyses (n=80), excluding patients treated with regional radiotherapy, sentinel lymph node status was the only significant prognostic factor (p=0.0281). Immunosuppression and positive sentinel lymph node are associated with a worse prognosis in patients with MCC. Nodal irradiation impacts on the prognostic value of the sentinel lymph node status. Key words: Merkel cell carcinoma; sentinel node; radiotherapy; prognostic.

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Merkel cell carcinoma (MCC) is a relatively rare neuroendocrine skin tumour, first described by Toker in 1972 (1). Its incidence is low compared with other cutaneous malignancies, e.g. basal cell and squamous cell carcinomas or melanoma, although a rapid increase in incidence of MCC has been estimated (2). According to large epidemiological studies, MCC is particularly aggressive, with local, in-transit and regional metastases (3, 4). Five-year overall survival decreases from 64% in the local stages (I and II) to 18% in stage IV, based on the recent American Joint Committee on Cancer (AJCC) classification (4).

As regional progression in drainage lymph nodes is frequent, estimated at between 18% and 44% in various studies (5), sentinel lymph node biopsy (SLNB) has been recommended for localized MCC by expert guidelines (6, 7). Therefore, sentinel lymph node (SLN) involvement status is of prime importance for accurate staging and prognosis, and may guide and optimize treatment strategy. The treatment strategy for MCC has changed in recent years. Indeed, most national and international guidelines (6, 7) have proposed multimodal management of localized MCC, including wide-margin surgery followed by adjuvant local radiotherapy. The addition of radiotherapy has demonstrated an overall survival benefit. Chemotherapy is not recommended in the localized stages of MCC and is used with a palliative intention in the metastatic stages.

In this setting, a large French multi-centric retrospective study was conducted in a cohort of patients with confirmed localized MCC, all staged using SLNB. The primary objective of the study was to evaluate the factors associated with disease-free survival in this cohort, and in particular, the prognostic significance of SLN status. The secondary objectives included evaluation of SLNB feasibility in this large MCC French cohort.

MATERIALS AND METHODS

Patients

The cohort originated from centres of the “Dermatology Oncology Group”, affiliated to the French Society of Dermatology. Consecutive patients seen in all-inclusive centres between October 1998 and February 2010, presenting with localized MCC staged by SLNB and with 2 years’ follow-up or more, were included in the study. Patients who underwent any alternative lymph node basin investigation (elective node dissection or complete lymph node dissection (CLND) without previous SLNB) were excluded from the study. A specific questionnaire including demographic and clinical data was recorded for each patient. Demographic data included gender and age at diagnosis of MCC. Clinical data were:
A total of 108 patients with localized MCC, treated with excision and SLNB, were included in the study between October 1998 and February 2010. Demographic, clinical and treatment data are presented in Table I. Immunosuppression status data were not available for 13 patients, whereas the size of the tumour was unknown for 5 patients. Median age at diagnosis was 70 years (age range 21–87 years) with a small predominance of females (55.6%). The lower limb was the most frequently involved anatomical location (35.2%), followed by the upper limb (28.7%), the head and neck (27.8%) and the trunk (8.3%). Median tumour size was 2 cm (range 0.3–10 cm). Nine patients (9.5%) were immunosuppressed at the time of SLNB. The SLN was positive in 33 patients (32%) and negative in 70 patients (68%). SLNB failed to identify any sentinel lymph node in 8 (7.4%) patients.

### Results

A total of 108 patients with localized MCC, treated with excision and SLNB, were included in the study between October 1998 and February 2010. Demographic, clinical and treatment data are presented in Table I. Immunosuppression status data were not available for 13 patients, whereas the size of the tumour was unknown for 5 patients. Median age at diagnosis was 70 years (age range 21–87 years) with a small predominance of females (55.6%). The lower limb was the most frequently involved anatomical location (35.2%), followed by the upper limb (28.7%), the head and neck (27.8%) and the trunk (8.3%). Median tumour size was 2 cm (range 0.3–10 cm). Nine patients (9.5%) were immunosuppressed at the time of SLNB. The SLN was positive in 33 patients (32%) and negative in 70 patients (68%). SLNB failed to identify any sentinel lymph node in 8 (7.4%) patients.

### Table I. Demographic, clinical and treatment data for the Merkel cell carcinoma population (n = 108)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>60 (55.6)</td>
</tr>
<tr>
<td>Male</td>
<td>48 (44.4)</td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
<td>70 (21–87)</td>
</tr>
<tr>
<td>Immunosuppression(n = 95),</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9 (9.5)</td>
</tr>
<tr>
<td>No</td>
<td>86 (90.5)</td>
</tr>
<tr>
<td>Location of primary,</td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>30 (27.8)</td>
</tr>
<tr>
<td>Trunk</td>
<td>9 (8.3)</td>
</tr>
<tr>
<td>Upper limb</td>
<td>31 (28.7)</td>
</tr>
<tr>
<td>Lower limb</td>
<td>38 (35.2)</td>
</tr>
<tr>
<td>Tumour size, cm</td>
<td>2 (0.3–10)</td>
</tr>
<tr>
<td>Status of the sentinel lymph node(n = 103),</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>33 (32)</td>
</tr>
<tr>
<td>Negative</td>
<td>70 (68)</td>
</tr>
<tr>
<td>Complete lymph node dissection (CLND),</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (30.6)</td>
</tr>
<tr>
<td>No</td>
<td>75 (69.4)</td>
</tr>
<tr>
<td>Positive nodes/Total nodes by CLND, mean (n = 33)</td>
<td>1.4/2</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
</tr>
<tr>
<td>Primary tumour bed,</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>77 (71.3)</td>
</tr>
<tr>
<td>No</td>
<td>31 (28.7)</td>
</tr>
<tr>
<td>Lymph node basin,</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28 (26)</td>
</tr>
<tr>
<td>No</td>
<td>80 (74)</td>
</tr>
<tr>
<td>First site of progression,</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29 (26.9)</td>
</tr>
<tr>
<td>No</td>
<td>79 (73.1)</td>
</tr>
<tr>
<td>Time to first progression event, month</td>
<td>6.4</td>
</tr>
<tr>
<td>Location of first recurrence(n = 29),</td>
<td></td>
</tr>
<tr>
<td>Primary tumour bed,</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (14.8)</td>
</tr>
<tr>
<td>No</td>
<td>92 (75.2)</td>
</tr>
<tr>
<td>Time to death, median, month</td>
<td>14</td>
</tr>
</tbody>
</table>

1 http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2099

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node in 5 patients (4.6%). Thirty-three patients (30.6%), all except one with positive SLN, were treated with additional CLND after the SLNB. The additional CLND identified 10 patients (30.3%) with additional lymph nodes involved in the MCC out of the sentinel node. Seventy-seven patients (71.3%) underwent adjuvant radiation therapy to the bed of the primary tumour. Adjuvant nodal radiation therapy was realized in 28 patients (26%), including 19 with positive SLN and 9 with negative SLN. Among the 33 patients with positive SLN, 19 (57.6%) underwent adjuvant nodal irradiation and 14 (42.4%) did not.

Among the 108 patients, 29 (26.9%) experienced a recurrence of the disease (Fig. 1). There were 11 recurrences in the positive SLN group (n = 33) and 16 in the negative SLN group (n = 70). The median time from SLNB to first recurrence was 6.4 months. The anatomical location of the first recurrence was cutaneous within the primary tumour area in 4 patients (12.9%), cutaneous in-transit in 8 patients (25.8%), drainage lymph node in 16 patients (51.6%) and distant in 3 patients (9.7%). At the date of analyses, 16 patients were deceased. Of these, death was related to the MCC progression in 12 patients and unrelated in 4 patients. The mortality rate was 14.8% and the median time to death was 14 months. Eight patients (24.2% in the SLN positive group (n = 33)) died.

Univariate logistic regression revealed that factors associated with 3-year PFS were gender and presence of immunosuppression on the whole population (n = 108). Gender (Fig. 2) and IS were the only independent factors significantly associated with prognostic factors for 3-year PFS in the multivariate model (Table II). The primary tumour’s size, SLN status (Fig. 3) and local or regional radiation therapy were not statistically associated with 3-year PFS.

The second set of analyses was performed in order to investigate the effect of treatments toward the lymph node drainage area on potential prognostic factors. The first sub-population comprised patients without nodal radiation therapy (n = 80, see Fig. S1). The univariate logistic regression identified gender (HR 5.008; 95% CI 1.61–15.64; p = 0.0053), presence of immunosuppression (HR 6.67; 95% CI 1.41–31.56; p = 0.0168) and SLN status (HR 5.44; 95% CI 1.59–16.67; p = 0.007) as prognostic factors for 3-year PFS. The multivariate model demonstrated that the SLN status (HR 4.83; 95% CI 1.18–19.70; p = 0.0281) was the only significant prognostic factor associated with 3-year PFS (Table III). In this analysis, the size of the primary tumour and local radiation therapy were not associated with 3-year PFS.

The second sub-population comprised patients with out CLND (n = 75, see Fig. S1). In this group, all patients except one presented with a negative SLNB (69/70). The 5 patients with indeterminate SLN status did not undergo CLND (5/5). Only one patient with positive SLN did not have CLND (1/33). As there was only one patient with positive SLN without further CLND, statistical analyses for factors associated with recurrence-free progression could not be conducted in this sub-population.

**DISCUSSION**

A procedure for the management of patients with localized MCC has been proposed in international guidelines (6, 7). These guidelines have been elaborated mostly on the basis of retrospective studies, case-series and large databases as MCC remains a rare disorder challenging any prospective trial. The same authors recognized, however, that the level of evidence required to recommend SLNB in MCC is low. Despite considerations of possible bias linked to retrospective analyses, the benefit of SLNB is currently recognized by the medical community, even though the definitive criteria indicating SLNB remain a matter of debate (8, 9). Similarly, local radiation therapy has been validated in the initial management of localized MCC (10–12). A major bias in all retrospective series published in MCC is the length of the recruitment period, which leads to heterogeneity in patient’s characteristics, staging procedures and treatments. In that sense, patients included in long-term retrospective analyses may have undergone various staging procedures, such as SLNB,
Table II. Univariate and multivariate logistic regression analyses for factors associated with 3-year progression-free survival in the whole population (n = 108)

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>n</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate regression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td>3.774</td>
<td>1.657–8.598</td>
<td>108</td>
<td>0.0016</td>
</tr>
<tr>
<td>Age (≤60 vs. &gt;60 years)</td>
<td>1.389</td>
<td>0.524–3.684</td>
<td>108</td>
<td>0.5086</td>
</tr>
<tr>
<td>Primary tumour size (&gt;2 vs. ≤2 cm)</td>
<td>1.368</td>
<td>0.639–2.924</td>
<td>103</td>
<td>0.4196</td>
</tr>
<tr>
<td>Immunosuppression (yes vs. no)</td>
<td>3.039</td>
<td>1.117–8.269</td>
<td>95</td>
<td>0.0295</td>
</tr>
<tr>
<td>Sentinel lymph node status (positive vs. negative)</td>
<td>1.566</td>
<td>0.727–3.376</td>
<td>103</td>
<td>0.2521</td>
</tr>
<tr>
<td>Radiotherapy of the primary tumour bed (yes vs. no)</td>
<td>1.231</td>
<td>0.523–2.897</td>
<td>108</td>
<td>0.6333</td>
</tr>
<tr>
<td>Lymph node basin radiotherapy (yes vs. no)</td>
<td>1.114</td>
<td>0.490–2.530</td>
<td>108</td>
<td>0.7972</td>
</tr>
<tr>
<td>Radiotherapy (any vs. no)</td>
<td>1.431</td>
<td>0.580–3.530</td>
<td>108</td>
<td>0.4361</td>
</tr>
<tr>
<td>Complete lymph node dissection (yes vs. no)</td>
<td>2.397</td>
<td>0.984–5.839</td>
<td>108</td>
<td>0.0543</td>
</tr>
<tr>
<td><strong>Multivariate regression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td>3.372</td>
<td>1.313–8.659</td>
<td>108</td>
<td>0.0115</td>
</tr>
<tr>
<td>Immunosuppression (yes vs. no)</td>
<td>2.739</td>
<td>1.003–7.483</td>
<td>95</td>
<td>0.0494</td>
</tr>
</tbody>
</table>

HR: hazard ratio; 95% CI: 95% confidence interval. p-values in bold are statistically significant.

effective node dissection (overall before year 2000) or therapeutic CLND (before 1990) according to staging procedures and treatment strategies in these periods. Similarly, patients may have undergone radiotherapy to the primary tumour bed or lymph node basin, or neither of these. These heterogeneous data may have precluded definitive conclusions in previous studies.

One of the strengths of the present study is that it was conducted in a relatively homogeneous population of patients with MCC. Factors associated with recurrence-free survival in patients with MCC who were all staged using SLNB during a relative short-term recruitment period (October 1998 to February 2010) were analysed. In this cohort, a majority of patients were treated in accordance with recent guidelines, i.e. wide local excision of the primary tumour associated with local irradiation (77/108; 71.3%). The demographic and clinical data of patients in our study were comparable to those of previously published studies (4, 5, 8, 13–16).

The results of the current study show that the male gender was associated with decreased 3-year PFS and is thus a strong adverse predictive factor (p = 0.0115, see Table II and Fig. 2). This finding has also been reported by other groups (11, 17–19). Similarly, in the current study, multivariate analysis showed that immunosuppression confers a significantly higher recurrence risk in patients with MCC (p = 0.04, see Table II). The latter was demonstrated in other studies based on a univariate model (16, 20). Unexpectedly, our analyses demonstrated that age at diagnosis, primary tumour diameter, anatomical location, local or nodal radiation therapy, and SLN status were not predictive of 3-year PFS in the total population (n = 108, see Table II). We hypothesized that these negative results could be explained, on the one hand, by a lack of power of our study, as previous larger studies demonstrated that radiation therapy and SLN status were associated with prognosis in MCC (4, 5, 11) and, on the other hand, by the possible impact of adjuvant regional irradiation on the prognostic value of SLN status.

Indeed, as 57.6% (19/33) of patients with positive SLN underwent adjuvant nodal radiation therapy, we tested the hypothesis that nodal radiation therapy might have influenced the prognostic value of SLN status in the total population. We further conducted an additional analysis in which patients with nodal radiation therapy were excluded. This second analysis included 75 patients without adjuvant nodal irradiation, comprising 14 (18.7%) patients with positive SLN and 61 (81.3%) patients with negative SLN. In the latter analysis, gender (p = 0.0053), immunosuppression (p = 0.0168) and SLN status (p = 0.007) were significantly associated with 3-year PFS by univariate assessment (see Table III). Interestingly, SLN status remained the only prognostic factor for the 3-year PFS in the multivariate regression model (p = 0.02, see Table III). Altogether, our results demonstrate that SLN status is a major prognostic factor in patients with localized MCC. However, it appears that regional irradiation impacts negatively on this prognostic value as SLN status was not prognostic of 3-year PFS in the whole population (n = 108), whereas this status becomes prognostic when patients treated with regional irradiation are excluded from analyses. This is a striking finding of the current study. Indeed, in patients with SLN positive MCC in our population regional irradiation seems to decrease the recurrence risk, leading to a comparable 3-year PFS between patients with positive or negative SLN. This is in keeping with a trial from our group, in which nodal irradiation demonstrated a significant reduction in recurrence risk, without knowledge of SLN status (21).

The treatment strategy for patients included in the present study was very homogeneous. Indeed, in accordance with recent guidelines, most of the patients were treated by wide local excision and
tumour correlates with SLN positivity and recurrence—
the lymphovascular invasion observed in the primary
cess). As demonstrated in the study of Fields et al. (24),
and in the present population (8/31; 25.8% of recurren-
rate observed in previous studies (24, 25)
rate in historical case-series, but also the high in-transit
lymphatic spread explains the high nodal recurrence
rate is high compared with the 15% rate in the study by
30 patients/108; 26.9%) with a median follow-up of
30 months, while historical case-series have observed
recurrence rates as high as 50–79% (22, 23). More pre-
cisely, the local recurrence rate was only 3.7% (4/108).
As we, and other groups, have demonstrated previously
(10–12, 21), this low local recurrence rate is probably
the result of a combination of wide-margin excision
with local irradiation. In our study the regional recur-
rence rate was 14.8%, which is low compared with the
50–66% recurrence rate found in other case-series (10,
22, 23). Interestingly, 9 patients experienced a regional
recurrence while the SLN was negative (false-negative
population). In these 9 patients, none underwent CLND,
and only one had nodal radiation therapy. The failure
of the SLNB to detect nodal tumoural involvement
has been discussed by Fields et al. (24). The false-negative
rate in our study was 21.4% ([false-negative]/[false
negative+true positive]=9/[9+33]). This false-negative
rate is high compared with the 15% rate in the study by
Fields et al. (24). Our high false-negative rate could be
explained by the multicentre recruitment with different
surgical teams with heterogeneous experience in SLNB.
More probably, this high nodal recurrence rate in nega-
tive SLN patients may issue from a secondary delayed
repopulation of the lymph node basin by malignant
cells. The latter is in line with the hypothesis that MCC
demonstrated a high propensity to metastasize via the
lymphatic subcutaneous vasculature. This particular
lymphatic spread explains the high nodal recurrence
rate in historical case-series, but also the high in-transit
recurrence rate observed in previous studies (24, 25)
and in the present population (8/31; 25.8% of recurren-
ces). As demonstrated in the study of Fields et al. (24),
the lymphovascular invasion observed in the primary
tumour correlates with SLN positivity and recurrence-
free survival. The in-transit recurrences observed in MCC raise the question of
how the in-transit area between the primary tumour and the drainage lymph
node area should be treated. In-bloc
radiation therapy may be a favourable
option if it is possible for the radiation
field to include the area of the primary
tumour and the drainage lymph node.
Conversely, when the drainage lymph
node basin is far from the primary loca-
tion, this option is not adequate.
A total of 36 patients presented with
primary tumours of 1 cm diameter or
less in our study. Of these, 6 patients
were SLN positive, which is in accordance with
earlier findings (9) and confirms that SLNB should not
be omitted in patients with a small primary MCC (8).

### Table III. Univariate and multivariate logistic regression analyses for factors
associated with 3-year progression-free survival in the population excluding patients
who underwent lymph node basin radiotherapy (n = 75)

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>n</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate regression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td>5.008</td>
<td>1.614–15.539</td>
<td>80</td>
<td>0.0053</td>
</tr>
<tr>
<td>Age (≤ 60 vs. &gt; 60 years)</td>
<td>1.805</td>
<td>0.627–5.200</td>
<td>80</td>
<td>0.2377</td>
</tr>
<tr>
<td>Primary tumour size (&gt; 2 cm vs. ≤ 2 cm)</td>
<td>1.877</td>
<td>0.658–5.359</td>
<td>76</td>
<td>0.2393</td>
</tr>
<tr>
<td>Immunosuppression (yes vs. no)</td>
<td>6.666</td>
<td>1.408–31.564</td>
<td>73</td>
<td>0.0168</td>
</tr>
<tr>
<td>Sentinel lymph node status (positive vs. negative)</td>
<td>5.444</td>
<td>1.587–18.672</td>
<td>75</td>
<td>0.0070</td>
</tr>
<tr>
<td>Radiotherapy of the primary tumour bed</td>
<td>1.714</td>
<td>0.582–5.046</td>
<td>80</td>
<td>0.3282</td>
</tr>
<tr>
<td>Multivariate regression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sentinel lymph node status (positive vs. negative)</td>
<td>4.830</td>
<td>1.184–19.703</td>
<td>75</td>
<td>0.0281</td>
</tr>
</tbody>
</table>

HR: hazard ratio; 95% CI: 95% confidence interval; n: number of patients within the analysis.
p-values in bold are statistically significant.

### Conclusion

This study demonstrates that male gender and immu-
osuppression are independent prognostic factors for
3-year PFS in patients with localized MCC, based on
a multivariate model. Similarly, SLN status is a major
risk factor for recurrence in patients with MCC who
have not undergone regional radiotherapy. Treatments
targeting the lymph node basin should be precisely
documented in localized MCC prognostic studies.
Similarly, large prospective studies on localized MCC
are still needed and should be optimally conducted in
accordance with the most recently published standard
of care in MCC (26).

The authors declare no conflicts of interest.

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