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CLINICAL REPORT

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

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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:

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size and anatomical location of the primary tumour, and presence or absence of immunosuppression. Date, lymph node basin location, number of positive nodes, and number of total sentinel nodes identified by the SLNB were obtained. Details of the surgical and histological procedures for SLNB were not retrieved. The lymph node analysis procedure was centre-dependent and was not controlled for in the present retrospective setting. Similarly, primary tumour samples were not controlled for other histological criteria. The treatment modalities of the nodal area and their results were also retrieved: additional CLND or not, number of positive nodes, and total number of lymph nodes identified by CLND, adjuvant radiation therapy of the primary tumour and/or of the nodal areas when realized. The date and location of the first progression event, if any, were documented. The date and status of the patient at the final follow-up visit were obtained for each patient, i.e. death attributable to the disease, death due to other causes, disease-free living individual, or alive with disease.

Statistical analysis

Descriptive analyses were first carried out and basic summary statistics, such as proportions, means, and medians, were used to characterize population attributes.

The duration of follow-up for each participant was calculated using the date of the SLNB as the primary date. Progression-free survival (PFS) was calculated between this primary date and the date of the first progression event or the date of the last follow-up if no recurrence occurred. Overall survival (OS) was calculated between the date of the SLNB and the date of death or the date of the final follow-up for surviving patients.

A first set of analyses was conducted on the whole population ($n=108$). The Kaplan–Meier method was used to estimate OS and PFS. The associations of demographic and clinical factors with the 3-year PFS were estimated using a logistic regression procedure including time of follow-up as a co-variate in the model. Odds ratio (OR) significance was determined by Wald test χ^2, and predictors with $p \leq 0.20$ were subsequently assessed using multivariate analysis with a forward stepwise selection procedure. A step-by-step descendant procedure with an α risk of 5% was used to determine variates significantly associated with survival.

As the regional treatment performed after the SLNB, i.e. surgery (CLND) and/or radiotherapy, may influence the prognostic value of the SLN status, and ultimately the 3-year PFS, additional statistical analyses were conducted. We tested the association of demographic and clinical data with the 3-year PFS using Cox proportional hazards models in 2 sub-populations of the study, i.e. patients without lymph node basin radiation therapy ($n=80$) or without CLND ($n=75$) (Fig. S1[1]). Covariates tested in these additional analyses were: gender, age at diagnosis, size of the primary tumour, immunosuppression, SLN status, radiotherapy of the bed of the primary tumour, and/or nodal radiation therapy, and/or CLND.

Hazard ratios (HR) and their corresponding 95% confidence intervals (95% CI) were calculated in univariate analysis, and factors with a $p \leq 0.20$ were included in the multivariate model. A step-by-step descendant procedure with an α risk of 5% was used to determine covariates significantly associated with 3-year disease-free survival. Fig. S1[1] summarizes the population included in each analysis.

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

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

Characteristics	
Gender, *n* (%)	
Female	60 (55.6)
Male	48 (44.4)
Age at diagnosis, years, median [range]	70 [21–87]
Immunosuppression (*n*=95), *n* (%)	
Yes	9 (9.5)
No	86 (90.5)
Location of primary, *n* (%)	
Head and neck	30 (27.8)
Trunk	9 (8.3)
Upper limb	31 (28.7)
Lower limb	38 (35.2)
Tumour size, cm, median [range]	2 [0.3–10]
Status of the sentinel lymph node (*n*=103), *n* (%)	
Positive	33 (32)
Negative	70 (68)
Positive node/total nodes by SLN procedure, mean (*n*=33)	1.4/2
SLNB failure, *n* (%)	5 (4.6)
Complete lymph node dissection (CLND), *n* (%)	
Yes	33 (30.6)
No	75 (69.4)
Additional positive nodes identified by CLND (*n*=33)	10 (30.3)
Positive nodes/Total nodes by CLND, mean (*n*=10)	4.4/13.3
Radiotherapy	
Primary tumour bed, *n* (%)	
Yes	77 (71.3)
No	31 (28.7)
Lymph node basin, *n* (%)	
Yes	28 (26)
No	80 (74)
First site of progression, *n* (%)	
Yes	29 (26.9)
No	79 (73.1)
Time to first progression event, month, median (*n*=29; 26.9%)	6.4
Location of first recurrence (*n*=29)[a], *n* (%)	
Primary tumour bed	4 (12.9)
Cutaneous, in-transit	8 (25.8)
Regional lymph node area	16 (51.6)
Distant	3 (9.7)
Death, *n* (%)	
Yes	16 (14.8)
No	92 (75.2)
Time to death, median, month (*n*=16)	14

[a]29 patients experienced 31 recurrences, 3 patients had simultaneously 2 recurrences at 2 sites, and the site of recurrence was unknown for one patient. SLN: sentinel lymph node.

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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.

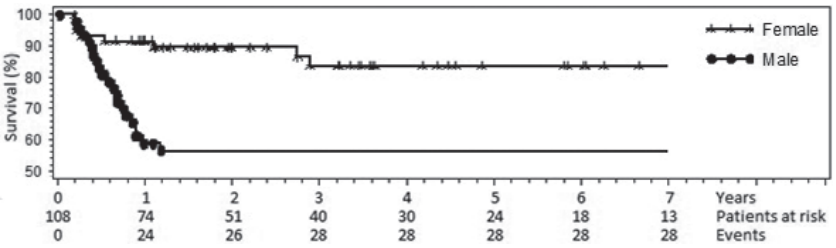

Fig. 2. Recurrence-free survival by gender for 108 patients with Merkel cell carcinoma.

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[1]). 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 without CLND ($n=75$, see Fig. S1[1]). 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.

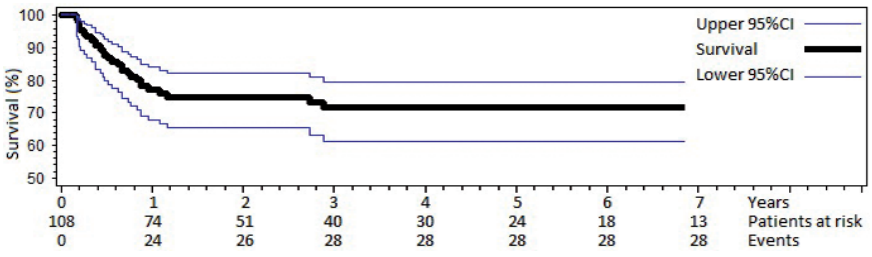

Fig. 1. Recurrence-free survival in 108 patients with Merkel cell carcinoma. Blue lines indicate 95% confidence interval (95% CI).

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)*

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

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

elective 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

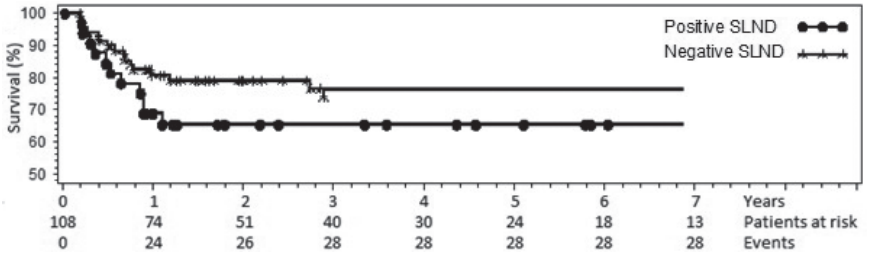

Fig. 3. Recurrence-free survival by sentinel lymph node (SLND) status (positive vs. negative) in 103 patients with Merkel cell carcinoma.

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)*

	HR	95% CI	*n*	*p*
Univariate regression				
Gender (male vs. female)	5.008	1.614–15.539	80	**0.0053**
Age (≤60 vs. >60 years)	1.805	0.627–5.200	80	0.2737
Primary tumour size (>2 cm vs. ≤2 cm)	1.877	0.658–5.359	76	0.2393
Immunosuppression (yes vs. no)	6.666	1.408–31.564	73	**0.0168**
Sentinel lymph node status (positive vs. negative)	5.444	1.587–18.672	75	**0.0070**
Radiotherapy of the primary tumour bed	1.714	0.582–5.046	80	0.3282
Multivariate regression				
Sentinel lymph node status (positive vs. negative)	4.830	1.184–19.703	75	**0.0281**

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

SLNB (100% of patients), associated with irradiation of the tumour bed (71.3% of patients). All patients with a positive SLN except one had additional CLND. Furthermore, 26% of patients underwent adjuvant nodal radiation therapy. The homogeneity of these treatments may explain the low recurrence rate in our population (29 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 precisely, 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 recurrence 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 negative 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 recurrences). 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 location, 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 (21.4%) 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).

Conclusion

This study demonstrates that male gender and immunosuppression 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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