Adjuvant prophylactic regional radiotherapy versus observation in stage I Merkel cell carcinoma: a multicentric prospective randomized study


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Background: The treatment of stage I Merkel cell carcinoma (MCC) usually includes wide local excision (WLE) combined with irradiation of the tumor bed (ITB). No randomized study has ever been conducted in MCC. The purpose of this study was to assess the efficacy and safety of prophylactic adjuvant radiotherapy on the regional nodes.

Patients and methods: In this randomized open controlled study, patients for a stage I MCC treated by WLE and ITB were randomly assigned to regional adjuvant radiotherapy versus observation. Overall survival (OS) and probability of regional recurrence (PRR) were primary end points. Progression-free survival (PFS) and tolerance of irradiation were secondary end points.

Results: Eighty-three patients were included before premature interruption of the trial, due to a drop in the recruitment mainly due to the introduction of the sentinel node dissection in the management of MCC. No significant improvement in OS (P = 0.989) or PFS (P = 0.4) could be demonstrated after regional irradiation, which, however, significantly reduced the PRR (P = 0.007) with 16.7% regional recurrence rate in the observation arm versus 0% in the treatment arm. The treatment was well tolerated.

Conclusion: The adjuvant regional irradiation significantly decreased the PRR in MCC, but benefit in survival could not be demonstrated.

Key words: adjuvant radiotherapy, Merkel cell carcinoma, overall survival, probability of regional recurrence, randomized trial

introduction

Merkel cell carcinoma (MCC) is a rare primary cutaneous neoplasm first described by Toker [1] in 1972. This carcinoma is known for its particular aggressive behavior with regional recurrence in 55%–64% of patients [2]. The prognosis of this neoplasm remains poor according to the tumor’s stage with a 5-year overall survival (OS) of 80%, 60% and <25% in stages I, II and III, respectively [3]. The estimated incidence rate of MCC is low with 470 incident MCC patients compared with 31 000 incident melanoma patients per year in the United States [4]. Though, an 8.08% increasing annual incidence rate has been estimated from 1986 to 2001 in two retrospective studies in the United States [3, 5].

The staging system used for MCC is not consensual. The TNM (tumor–node–metastasis) classification from the American Joint Committee on Cancer [6] could be used. Alternatively, the modified and simplified version from Yiengpruksawan et al. [7]
is used by a large part of the medical community. Most authors recommend a surgical excision of localized tumors with margins from 1 to 3 cm [2, 8], even though a margin of ≥1 cm is still debated [9, 10]. In this setting, Mohs micrographic surgery has been proposed in locations where wide margins cannot be easily applied [11]. These surgical recommendations have been proposed recently in guidelines algorithms [12].

The local recurrence rate of MCC is high, from 27% to 32% in patients treated with wide local excision (WLE) alone [7, 13] and 70% to 89% in patients treated with limited margins only [14–16]. This local aggressiveness and high tendency to locally recur justify WLE associated with local large-field radiotherapy, as supported by retrospective analyses [2, 17–19]. A first meta-analysis of retrospective studies conducted by Lewis et al. [17] on 1254 patients found a significant benefit in favor of combined treatment (surgery associated with local irradiation) for local and regional disease control but failed to demonstrate an advantage in OS. Another large analysis of Surveillance Epidemiology and End Results data found an association between adjuvant local radiotherapy in stage I and II MCC and OS improvement [18]. However, patients in the latter study, who received local radiotherapy, tended to be younger and to have higher disease stages than those who had surgery alone. Furthermore, MCC is known for its radiosensitivity and some authors have even demonstrated high local control rate with large-field radiotherapy alone [20] and adjuvant local radiotherapy has been proposed as a standard treatment option in recent guidelines [12, 21]. This management is based on the propensity of MCC to spread to intradermal lymphatic vessels, explaining the high rate of in-transit cutaneous metastases. Consequently, a large 3- to 4-cm margin is advised for local definitive or adjuvant radiotherapy to the primary tumor location [20]. Despite the weakness of retrospective uncontrolled studies [2, 17–19, 20], the benefit of irradiation in local control is nowadays accepted worldwide in stage I MCC patients.

MCC has a high propensity to spread to the drainage lymph node basin. Approximately 15%–30% of patients have a regional disease at first presentation [22, 23] and a high regional recurrence rate from 50% to 66% [4, 17, 24] in various retrospective studies. These high regional recurrence rates are, however, difficult to interpret since patients received heterogeneous treatments of the primary tumor, including surgery carried out with various margins, associated or not with local adjuvant radiotherapy. This regional aggressiveness has raised the question of adjuvant prophylactic radiotherapy of the drainage lymph node basin in MCC patients without palpable nodes, i.e. stage I patients.

We designed the first prospective randomized trial ever conducted in MCC, to assess the benefit of systematic adjuvant radiotherapy of the regional lymph nodes after resection of stage I MCC and radiotherapy of the tumor bed.

patients and methods
design
In this randomized open controlled trial, patients for a stage I MCC treated by wide excision and local radiotherapy were randomly assigned to prophylactic radiotherapy of the drainage lymph node basin versus observation.

objectives
The primary objectives of our study were to compare adjuvant radiotherapy to lymph node basin versus observation, in terms of OS rate and probability of regional recurrence (PRR). Secondary objectives included the following: (i) the progression-free survival (PFS), (ii) an evaluation of the tolerance and the toxicity of this combined treatment and (iii) a descriptive analysis of a large stage I population receiving an homogeneous treatment toward the primary tumor’s bed, combining surgery and local radiotherapy.

inclusion and exclusion criteria
Adult patients (18–80 years old) with histological and immunohistochemical confirmed MCC who met the following eligibility criteria were included in the study: signed informed consent; life expectancy >3 months; global WHO health status ≤2; surgical excision of the primary tumor with a 1.5-cm margin on the skin and deep margin down to the perimuscular aponeurosis; confirmed stage I MCC based on a complete physical examination, a chest radiography and an abdominal ultrasonography (other radiological investigations were allowed guided by clinical examination). Exclusion criteria were as follows: primary tumor’s location with possible multiple drainage lymph node basins (median head and trunk areas), coexistence of another neoplasm at presentation with the exception of basal cell carcinoma surgically removed in a different area from the MCC, any cytostatic or immunosuppressive drugs, constitutional or acquired immune suppression, a delay >6 weeks between definitive excision and radiotherapy onset or any history of radiotherapy in the same location of the primary tumor or drainage lymph node areas.

Local ethic committee and institutional review board approved the study. All patients gave written informed consent before random assignment. All histological samples were centrally reviewed by two pathologists (BV and C Leyral) for confirmation of the histological type of the lesion.

treatment
The primary tumor was treated homogeneously in all patients of both groups with a ≥1.5-cm margin local excision on the skin and deep margin to the perimuscular aponeurosis. The radiation field includes a 3-cm margin around the excision area when possible, and, in the intervention arm, the regional draining nodal area. A 50-Gy dose was advised for both tumor’s bed and the regional area, but the radiation technique was left at the choice of the radiotherapist in order to adapt to different situations. Most commonly, a megavoltage photon beam of 6 MV at a dosage of 50 Gy associated with a 10-Gy boost on the tumor’s bed with classical fraction of 2 Gy, 5 days a week during 6 weeks, was applied on the primary site area (with or without the addition of tissue equivalent bolus depending on the location of the primary tumor and the anatomical body site), whereas a mixed of 9-MV electron beam and 6-MV photon beam at a dosage of 50 Gy with classical fractioning as described above was applied to regional area in the intervention arm. In circumstances where the 3-cm margin around the excision site cannot be applied safely, the choice of the best and safest radiation field was let under the decision of the radiotherapist. The radiation field in the intervention arm could be ‘en bloc’ when the primary tumor was near the regional area (see supplemental Figures S1A and B and S2A and B, available at Annals of Oncology online), whereas two radiation fields were used when the primary site was distant from the regional area (see supplemental Figures S3A and B and S4A and B, available at Annals of Oncology online). The prescription point was 90% for all radiation fields.

Each patient was randomly assigned to a treatment group: group A received a prophylactic electron beam irradiation to the drainage lymph node basin with a total dose of 50 Gy; group B did not receive any treatment on the lymph node basin. The lymph node drainage area and the tumor’s bed were treated simultaneously.
tumor assessment and follow-up

Patient surveillance was planned every 6 weeks after the end of irradiation during the first year, every 3 months for the second and third years and every 6 months for the fourth and fifth years, with a complete physical examination at each visit and a chest radiography every 3 months for the first 3 years. Additional radiological investigations were allowed guided by physical examination. At each visit, the side-effects of irradiation were assessed. A three-level grading scale was used, in which grades 0, 1 and 2 meant absence of any side-effect from radiation therapy, mild-to-moderate skin alterations (atrophy, sclerosis, telangiectasia and dyschromia) and severe skin alterations (ulcerations for >6 months duration and squamous cell carcinoma), respectively.

outcome

Primary outcomes were (i) OS and (ii) PRR. Secondary outcomes were (iii) PFS, (iv) probability of recurrence and (v) regional PFS. Corresponding events were, respectively, (i) death all causes; (ii) regional recurrence; (iii) first local, regional or distant recurrence or death; (iv) first local, regional or distant recurrence and (v) regional recurrence or death. For each outcome, time to event was defined as the time between randomization and first event, or censored at the date of last follow-up if no event occurred.

statistical analyses

Sample size was determined based on the hypothesis of an expected 40% OS rate in group B and in order to prove a 20% survival gain at 3 years in the lymph node irradiation group A, with a 0.05 risk alpha (unilateral test) and 90% power. This resulted in 105 patients in each group. An interim analysis was planned after inclusion of 45 patients per group in order to compare the 1-year recurrence rate between groups (60% recurrence rate expected in control group, as compared with 30% recurrence rate expected in the lymph node irradiation group, alpha risk 0.05, unilateral test, 90% power).

The randomization was carried out by fax, centralized in the center of the coordinator (MMD), by block of four patients and stratified on the center. Statistical analyses were carried out using the SAS software, 9.1 version (SAS Institute Inc., Cary, NC). OS rate, PPR and PFS were calculated using the Kaplan–Meier method and then compared using the log-rank test. The origin date was the date of randomization. The Fisher’s exact test was used for proportions’ comparison. The Wilcoxon’s test was used for comparison of quantitative data. Analysis was carried out with 0.05 bilateral alpha risk, which is more conservative than the unilateral type I error used in sample size calculation in this setting where two primary end points had been selected in the trial design.

results

The study was conducted in 20 tertiary referral French centers from June 1993 to July 2005 (1–17 patients per center). The study had to be stopped prematurely in 2005 due to a rapid decrease in the recruitment (Figure 1) with only seven and two patients included in 2003 and 2004, respectively. Most centers explained their decreasing recruitment by their choice to use sentinel node procedure in MCC according to recent publications. In order to maintain a homogeneous population with a homogeneous management in our study, we could not accept sentinel node positivity as a new artificial inclusion criteria. Follow-up was thus updated on 31 July 2005. Eighty-three patients have been included in the study: 39 patients in group A (prophylactic adjuvant irradiation of the lymph node basin) and 44 patients in group B. The difference in the frequency of the treatment allocation is due to incomplete blocks linked to the stratification of the randomization by center. All patients were treated in accordance with the study’s protocol. All patients but one had confirmed primary MCC. One patient, from group A, was diagnosed to have MCC first but was not confirmed by definitive histological and immunohistochemical analyses. Another patient, from group B, withdrew from the study after randomization and refused further treatment and follow-up. These two patients were excluded from the study and analyses.

patients

Patients’ characteristics, including age, sex, primary tumor’s location and median follow-up, are presented in Table 1. The two groups were similar considering age, sex, location of the primary tumor, interval between surgery and onset of radiotherapy.

survival and probability of recurrence

In 2005, median follow-up was 58 months between the date of randomization and the date of last follow-up, without difference between the two groups (P = 0.20). The 3- and 5-year OS rates in the whole population were 92.3% and 89.2%, respectively. The overall probability to experience a recurrence in the whole population was 8.4% and 17.7% at 1 and 5 years, respectively. The site of first recurrence is detailed in Table 2.

As to the two main objectives, the OS rates did not differ between groups of treatment, P = 0.989 (Figure 2), but the PRR was significantly lower in the group receiving the regional radiation therapy compared with the observation group, P = 0.007 (Figure 3). Indeed, eight patients in group B experienced regional recurrence and none in group A (3-year PRR 16.7%, 95% confidence interval 8.3% to 32.0%, in the control group as compared with 0% in the regional radiation therapy group; Table 3).

The PFS was not significantly different between the two groups, P = 0.4 (Figure 4), although PFS tended to be higher in the regional irradiation group (3-year PFS 89.7% in the regional radiation therapy group versus 81.2% in the control group). The regional PFS did not differ between groups (P = 0.21).

irradiation-related skin toxicity

Skin toxicity from radiation therapy was mainly observed on the primary tumor’s bed area, as 19.3% and 7.2% of the whole
Table 1. Patient and tumor characteristics and median follow-up of the population (n = 83)

<table>
<thead>
<tr>
<th></th>
<th>Treatment groups</th>
<th>Radiotherapy of primary tumor’s bed and lymph node basin: group A (n = 39)</th>
<th>Radiotherapy of primary tumor’s bed only: group B (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>No. of patients</td>
<td>%</td>
</tr>
<tr>
<td>Age at diagnosis, mean (intervals), years</td>
<td>70.9 (41.2–86.2)</td>
<td>71.2 (53.9–86.2)</td>
<td>70.7 (41.2–86)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30</td>
<td>16</td>
<td>41</td>
</tr>
<tr>
<td>Female</td>
<td>53</td>
<td>23</td>
<td>59</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>36 (43.4%)</td>
<td>18</td>
<td>46.2</td>
</tr>
<tr>
<td>Upper limb</td>
<td>14 (16.9%)</td>
<td>5</td>
<td>12.8</td>
</tr>
<tr>
<td>Lower limb</td>
<td>28 (33.7%)</td>
<td>14</td>
<td>35.9</td>
</tr>
<tr>
<td>Trunk</td>
<td>5 (6%)</td>
<td>2</td>
<td>5.1</td>
</tr>
<tr>
<td>Median follow-up (intervals), months</td>
<td>57.7 (12.8–130)</td>
<td>54 (14.3–130)</td>
<td>58.4 (12.8–114.8)</td>
</tr>
</tbody>
</table>

Table 2. Sites of first recurrence in the two groups of treatment

<table>
<thead>
<tr>
<th>Sites of first recurrence</th>
<th>All</th>
<th>No. of patients</th>
<th>%</th>
<th>Radiotherapy of primary tumor’s bed and lymph node basin: group A (n = 39)</th>
<th>No. of patients</th>
<th>%</th>
<th>Radiotherapy of primary tumor’s bed only: group B (n = 44)</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>70</td>
<td>84.3</td>
<td>35</td>
<td>89.7</td>
<td>35</td>
<td>79.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irradiated site&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3</td>
<td>3.6</td>
<td>1</td>
<td>2.6</td>
<td>2</td>
<td>4.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not irradiated site&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2</td>
<td>2.4</td>
<td>2</td>
<td>5.1</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional recurrence</td>
<td>6</td>
<td>7.2</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>13.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>2</td>
<td>2.4</td>
<td>1</td>
<td>2.6</td>
<td>1</td>
<td>2.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>This line included the cutaneous recurrences within the irradiated tumor’s bed.

<sup>b</sup>This section included the cutaneous recurrences outside the irradiated tumor’s bed area.

Figure 2. Patients’ overall survival according to the randomization group (group A: n = 39 patients; group B: n = 44 patients), P = 0.989.
population experienced grades 1 and 2 skin toxicity, respectively (group A: grade 1, 15.4% and grade 2, 7.7%; group B: grade 1, 22.7% and grade 2, 6.8%). No significant difference was found between both groups ($P = 0.051$). Six patients presented with grade 2 severe skin toxicity. Among them, four patients had chronic ulcers and two required a surgical management. One squamous cell carcinoma (grade 3) was found in one patient on the irradiated tumor’s bed, 33 months after the end of irradiation, and was surgically removed. One patient experienced an ocular complication related to radiotherapy with sclerosis of the lower eyelid requiring a surgical correction. No irradiation-induced skin side-effect was reported on the regional area in group A patients.

**discussion**

This is the first randomized therapeutic trial ever done in MCC patients. This study assessed the effect of a regional adjuvant irradiation after a standardized treatment of the primary MCC tumor, combining surgical resection and irradiation on the tumor’s bed. This trial had to be interrupted prematurely due to a secondary drop in enrollment. The increasing place of the sentinel node procedure in the clinics, while the trial was ongoing, is likely to be the main reason of this drop, particularly from 2001 and 2002 (see Figure 1). Although this trial failed to demonstrate a gain in OS (Figure 2), a significant decrease in probability of regional relapse was demonstrated (Figure 3). None of the patients receiving the regional radiotherapy experienced a regional relapse, whereas eight patients (18.2%) without regional radiotherapy did ($P = 0.007$; Figure 3). The regional recurrence rate at 3 years observed in the regional radiotherapy arm was 0% versus 16.7% in the other arm (Table 3). However, this benefit did not convert into a significant result on PFS (Figure 4), probably because of a lack of power linked to premature trial interruption and because of an unexpectedly low rate of events as compared with retrospective series.

The course of the whole population was much more favorable than in the retrospective series from the literature [14, 25–28]. The recurrence rate in this series was only 8.4% and 17.7% at 1 and 5 years, respectively, instead of the 50%–79% recurrence rates observed in retrospective studies [4, 24]. The local recurrence rate was only 3.6% in the whole population of the study (Table 2) instead of the 27%–32% local recurrence rates in patients treated with WLE alone [7, 13] and 70%–89% rates in patients treated with limited margins only [14–16] in retrospective studies. The wide margins, with 1.5 cm on the skin, realized in the present study are debatable in head and neck MCC. In these areas in which such margins cannot be feasible, more limited margins might be proposed but with a strongly recommended local irradiation, based on previous presented data. The demographic characteristics of the present population and the characteristics of the tumor did not clearly differ from other previously published studies [3, 4, 14, 25–28] and cannot account for this surprisingly favorable course. According to the protocol, tumors with an unpredictable drainage were excluded since they did not permit an adjuvant irradiation of draining areas. Therefore, MCCs located on median head and trunk areas were excluded de facto, which may explain some difference with unselected historical controls. However, the most likely hypothesis to account for the overall excellent prognosis in this study is the standardization of a strategy combining surgical

![Figure 3](image-url) Regional recurrence probability according to the randomization group (group A: $n = 39$ patients; group B: $n = 44$ patients), $P = 0.007$. The group A curve intermingles with the absciss line as no patient experienced regional recurrence in this group.

**Table 3.** Three-year OS, PRR and PFS

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Radiotherapy of primary tumor’s bed and lymph node basin: group A (n = 39), %</th>
<th>Radiotherapy of primary tumor’s bed only: group B (n = 44), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>91.9</td>
<td>92.6</td>
</tr>
<tr>
<td>PRR</td>
<td>0.0</td>
<td>16.7</td>
</tr>
<tr>
<td>PFS</td>
<td>89.7</td>
<td>81.2</td>
</tr>
</tbody>
</table>

OS, overall survival; PRR, probability of regional recurrence; PFS, progression-free survival.
treatment and local radiotherapy in all stage I MCC patients which by itself is probably a way to improve prognosis, as suggested by retrospective studies [17, 18].

The tolerance of the regional adjuvant irradiation was excellent in the present study. Only 7.2% of patients experienced grade 2 side-effects on the irradiated tumor’s bed. The latter might be explained by the additional 10-Gy boost delivered on the tumor’s bed.

Methodological limits of the trial have to be discussed. First, the interruption of the trial reduced the power of the study but was the only solution in the context of a change of practice in favor of sentinel node. The trial was also designed with two co-primary end points. Then, the conclusions of this trial have to be considered carefully as we could not conclude on an efficacy on both these co-primary end points but only on one of both (PRR). Finally, two patients were not included in the analyses as both did not receive any treatment, and the trial was therefore not analyzed in a strict intent-to-treat manner. Inclusion of these patients in a survival analysis would have needed several statistical imputations as evaluation criteria could not be collected for both. As one patient in each arm was concerned and treatment groups were comparable (Table 1), we believe that randomization balance was not broken. Despite these limitations, these results are the best evidence available in this setting.

Our data deserve discussion in the context of sentinel node dissection (SLND) recently instructed in the management of stage I MCC patients [12]. Some authors have proposed that the status of SLND could guide the regional therapy [29, 30]. The lymph node basin management of stage I MCC patients is still controversial. Recent guidelines proposed the realization of sentinel lymph node biopsy in stage I MCC patients [12]. This attitude is still discussed as results in SLND studies for MCC are contradictory, mostly retrospective and included nonhomogeneous series of patients [29–33]. In a recent meta-analysis, Warner et al. found that 30% of clinically stage I MCC patients had positive SLND at diagnosis. This meta-analysis, a positive sentinel node seems to be associated with a higher further risk of recurrence [29, 32, 33]. In contrast, some studies have reported recurrences despite a negative sentinel node [29]. Consequently, no strong recommendations can be given in this setting. Despite this uncertainty, the increasing place of SLND in the management of skin cancers explains the decreasing inclusion rate in the last years of the trial, which led to its premature interruption. Our study also illustrates how difficult it is to validate therapeutic strategies in rare tumors. Indeed, trials focusing on rare neoplasms require a very long recruitment period; meanwhile attitudes (such as SLND) might change, without validation by clinical trials, and hamper clinical trials.

More recently, a new consensual TNM classification was proposed based on the survival analyses of a retrospective cohort including 5823 MCC patients [21]. The latter study demonstrated that patients with micrometastatic nodal involvement had a worse prognosis than patients with pathological negative node, even though the status of the drainage node was assessed by various surgical techniques, i.e. sentinel biopsy, elective or therapeutic lymphadenectomy, fine-needle aspirate or other techniques.

conclusions

Although a benefit could not be demonstrated in OS, the present trial strongly suggests that regional irradiation provides a benefit in the regional control in patients with stage I MCC. Consequently, regional prophylactic irradiation could be recommended in clinically node-negative stage I MCC patients, regardless of the result of the sentinel node biopsy. Furthermore, the present results sustain a standardized management of stage I MCC with WLE associated with local irradiation achieving a low local recurrence risk and probably decreasing the regional recurrence rate.

acknowledgements

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disclosure
The authors declare no conflict of interest.

references