Narrow resection margins are not associated with mortality or recurrence in patients with Merkel cell carcinoma: A retrospective study



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Background: Wide local excision constitutes the standard of care for Merkel cell carcinoma, but the optimal margin width remains controversial.

Objectives: To assess whether narrow margins (0.5-1 cm) were associated with outcome.

Methods: Patients were recruited from a retrospective French multicentric cohort and included if they had had excision of primary tumor with minimum lateral margins of 0.5 cm. Factors associated with mortality and recurrence were assessed by multivariate regression.

Results: Among the 214 patients included, 58 (27.1%) had undergone excision with narrow margins (0.5-1 cm) versus 156 (72.9%) with wide margins (>1 cm). During a median follow-up of 50.7 months, cancer-specific survival did not differ between groups (5-year specific survival rate 76.8% [95% confidence interval 61.7%-91.9%] and 76.2% [95% confidence interval 68.8%-83.6%], respectively). Overall survival, any recurrence-free survival, and local recurrence-free survival did not significantly differ between groups. Cancer-specific mortality was associated with age, male sex, American Joint Committee on Cancer stage III, and presence of positive margins.

Limitations: Retrospective design, heterogenous baseline characteristics between groups.

Conclusion: Excision with narrow margins was not associated with outcome in this cohort, in which most patients had clear margins and postoperative radiation therapy. Residual tumor, mostly found on deep surgical margins, was independently associated with prognosis. (J Am Acad Dermatol 2021;84:921-9.)

Key words: general surgery; Merkel cell carcinoma; mortality; neoplasms; prognosis; skin surgical margins; wide local excision.

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INTRODUCTION

Merkel cell carcinoma (MCC) is a rare primary neuroendocrine skin cancer whose risk factors include older age, fair skin, ultraviolet exposure, and immunosuppression. Disease stage is the major determinant of prognosis and was recently updated (8th Edition American Joint Committee on Cancer [AJCC] Staging System). MCC carries high metastatic potential, and patients typically have poor

CAPSULE SUMMARY

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prognosis, with 5-year survival rates of 51%, 35%, and 14% for local, regional, and distant metastatic disease, respectively.⁵ Although wide local excision of the primary tumor is the standard of care for patients with local and nodal disease, ^{3,4,6,7} the optimal surgical margins, achieving minimal risk of recurrence together with limited morbidity, remain debated. Given the aggres-

siveness of MCC, surgical clearance of the tumor is a high priority, whereas procedures should also take into account the frequent location of MCC on the head and neck, as well as the frailty of elderly patients. Margins of 2 to 3 cm were historically excised, 6,8-11 but margins of 1 to 2 cm are currently recommended. 3,4,7 Such change in practice is supported by the widespread administration of adjuvant radiotherapy on the tumor bed. 12-17 According to a large study from the Surveillance, Epidemiology and End Results database, margins greater than 2 cm were associated with improved survival compared with narrow margins (≤1 cm), including procedures such as shave, punch, or incisional biopsies, which are likely incomplete. 18 However, several studies suggest that lateral margins of 1 cm do not affect local recurrences, ^{2,19} any recurrences, ^{20,21} or survival, 19,21,22 but were limited by small cohorts, 21,23 the unavailability of confounding factors such as disease stage^{2,19,24} and histologic margin status,^{21,23} or lack of data on survival² or recurrence rates.²¹ This study assessed whether narrow margins (0.5 to 1 cm) were associated with outcome in a retrospective cohort of MCC patients, excluding procedures such as biopsies and taking into account determinant confounding factors such as disease stage, margin status, and adjuvant radiotherapy. The primary objective was to evaluate whether margins were associated with disease-specific survival. Secondary objectives were to assess whether margins were associated with overall survival, recurrence-free

survival, and pattern of recurrences, and whether narrow margins would decrease reconstruction procedures and delay to adjuvant radiotherapy.

PATIENTS AND METHODS Study design, participants, and settings

This study was based on an ongoing cohort of MCC cases diagnosed between 1998 and 2019 in the dermatology departments of 10 French hospitals²⁵⁻²⁶

and approved by the Ethics Committee of Tours, France. As previously described, ²⁵⁻²⁶ patients were included in the cohort if review of the histologic data confirmed the diagnosis of MCC. Follow-up had been performed as recommended in the National French Guidelines.⁶

Inclusion and exclusion criteria

Patients were included if they had wide local excision of the primary tumor, with minimum lateral margins of 0.5 cm, according to the surgical report. Patients with excision of margins less than 0.5 cm were considered to have had excision biopsy or palliative surgery and were excluded. Patients with nodal disease were included if they had also undergone potentially curative treatment by lymph node dissection, radiation therapy, or both. ^{3,7} Exclusion criteria were AJCC stage IV, absence of primary tumor (occult or regressive primary), no surgical treatment of the primary tumor (refusal, contraindications, or exclusive radiation therapy), excision biopsy or palliative surgery (excision of margins <0.5 cm), 2 concomitant MCC primary tumors, no treatment of nodal disease at baseline, rapid disease progression before completion of initial treatment, missing surgical margins, or no follow-up visit after surgery.

Clinical data

Data were collected on age, sex, AJCC tumor stage,⁵ primary location, World Health Organization performance status (PS), immunosuppression (solid organ transplant, current hematologic or solid malignancies, HIV infection, or immunosuppressive drugs²⁷), surgical lateral margins of wide local excision (in case of re-excisions, cumulative excision margin was calculated), reconstruction procedures (flap, graft, or both), histologic margin status (negative or positive), sentinel lymph node biopsy,

Abbreviations used:

AJCC: American Joint Committee on Cancer

CI: confidence interval
HR: hazard ratio
MCC: Merkel cell carcinoma

adjuvant radiotherapy (tumor bed, node area, or both), and time from surgery to initiation of adjuvant radiotherapy. Death was categorized as being related to MCC (MCC-specific death) or not (other cause), based on patients' medical files in each hospital. Disease-specific survival was defined as the time from the initial confirmed diagnosis of MCC to the date of death related to MCC, overall survival as the time from diagnosis to the date of death regardless of cause, and recurrence-free survival as the time from diagnosis to the date of a clinical or paraclinical event related to MCC recurrence. Pattern of first recurrence was categorized as local (within 2 cm of the primary site), in transit (>2 cm from the primary site), regional (draining lymph node basin), or distant (beyond the draining lymph node basin). The database was locked on November 20, 2019.

Outcomes

The primary outcome was disease-specific survival with excision of narrow margins (0.5-1 cm) and wide margins (>1 cm). Secondary outcomes were overall survival, recurrence-free survival, pattern of first recurrence, proportion of reconstruction procedures, and delay between surgery and adjuvant radiotherapy.

Statistics

Continuous data are described with mean and standard deviation or median with first and third quartiles (Q1-Q3; range) and categoric data with number (percentage). Patients were classified as having excision of narrow margins (0.5-1 cm) and excision of margins greater than 1 cm. Qualitative data were compared by 2-tailed Fisher's exact test and quantitative data by Mann-Whitney U test. Median follow-up, local and any recurrence-free survival, overall survival, and disease-specific survival with 95% confidence intervals (CIs) were analyzed by Kaplan-Meier survival analysis with log-rank tests. Univariate and multivariate Cox proportional hazards analyses were used to identify factors associated with recurrence and death, estimating hazard ratios (HRs) and 95% CIs. For diseasespecific survival, deaths from MCC were considered to be events, deaths from other causes were censored at the day of death, and living patients were censored

on the date of last follow-up. Covariates were identified as potential prognostic factors on Cox univariate regression at $P \leq .10$ and were included in the multivariate analysis. The proportional hazards assumption was assessed by a nonsignificant relationship between scaled Schoenfeld residuals and time for each of the covariates and for the global test. Statistical analysis involved using XL-Stat-Life (Addinsoft). P < .05 was considered statistically significant.

RESULTS

Patient characteristics by size of margins at baseline

Among the 357 MCC patients included in the cohort, 214 met inclusion criteria (Fig 1). Patient characteristics are presented in Table I. Median lateral margin was 2 cm (Q1-Q3 1-2.8 cm; range 0.5-6 cm). Overall, 58 patients (27.1%) had undergone excision with narrow margins versus 156 (72.9%) with wide margins. Most patients had clear histologic margins (n = 198; 92.5%) and adjuvant radiotherapy (n = 169; 79.0%). Overall, 34 patients (15.9%) had nodal macrometastases at baseline (AJCC stage IIIB) and 180 (84.1%) had no evidence of macrometastases; 69 of 180 (38.3%) had undergone sentinel lymph node biopsy, 14 (20.3%) showing nodal micrometastases (AJCC stage IIIA). The 48 patients with evidence of nodal disease had undergone lymph node dissection (n = 10; 20.8%), radiation therapy of lymph nodes (n = 11; 22.9%), or both (n = 27; 56.3%). Patients with excision of less than or equal to 1-cm margins were significantly older (P = .02), more frequently were women (P = .01) and immunosuppressed (P = .02), and had head and neck tumors (P = .001) compared with those with 1-cm margins. AJCC stages, PS, margin status, reconstruction procedures, frequency of adjuvant radiotherapy, and time to initiation of adjuvant radiotherapy did not differ between groups (Table I).

Size of margins and death from MCC

The median follow-up after diagnosis was 50.7 months (95% CI 44.3-62.1). Follow-up was significantly longer for patients treated with wide margins (median 67.6 months; 95% CI 50.8-79.1) versus narrow margins (median 28.9 months; 95% CI 19.7-44.4) (log-rank test, P < .0001). Overall, 76 patients (35.5%) died, including 40 (18.7%) owing to MCC (Fig 1). The median overall survival was 107.7 months (95% CI 77.4-158.3) and the median disease-specific survival was not reached. Disease-specific survival did not significantly differ between margin groups (log-rank test, P = .78). As such, 1- and

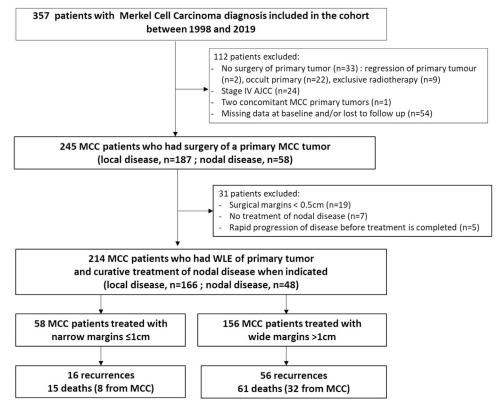


Fig 1. Of the 357 patients included in the cohort, 214 had wide local excision of primary tumor with minimal margins of 0.5 cm and curative treatment of nodal disease when indicated. *AJCC*, American Joint Committee on Cancer; *MCC*, Merkel cell carcinoma; *WIE*, wide local excision.

5-year specific survival rates were, respectively, 91.2% (95% CI 83.0%-99.5%) and 76.8% (95% CI 61.7%-91.9%) in the narrow-margin group versus 92.3% (95% CI 88.0%-96.7%) and 76.2% (95% CI 68.8%-83.6%) in the wide-margin group (Fig 2). Overall survival did not significantly differ between margin groups (log-rank test, P = .93) (Supplemental Fig 1 available via Mendeley at https://data.mende ley.com/datasets/5df3rpd4hb/1). When patients were stratified by AJCC stage, disease-specific survival did not differ between margin groups (Supplemental Fig 2, A-C, available via Mendeley at https:// data.mendeley.com/datasets/5df3rpd4hb/1). On multivariate analysis, risk of death owing to MCC was associated with age (HR 1.04; 95% CI 1.00-1.08), male sex (HR 2.06; 95% CI 1.05-4.05), AJCC stage III (HR 2.97; 95% CI 1.23-7.20), and positive margins (HR 6.04; 95% CI 2.21-16.54) (Table II). On multivariate analysis, age (HR 1.06; 95% CI 1.02-1.09), male sex (HR 2.06; 95% CI 1.25-3.39), AJCC stage II (HR 2.26; 95% CI 1.25-4.08), and positive margins (HR 3.02; 95% CI 1.42-6.43) were associated with death from any cause (Supplemental Table I, available via Mendeley at https://data.mendeley.com/ datasets/5df3rpd4hb/1).

Size of margins and MCC recurrence

Disease recurred in 72 patients (33.6%) (median time to recurrence 8.0 months [Q1-Q3 6.0-13.3]) (Fig 1). Recurrence-free survival did not significantly differ between margin groups (log-rank test, P = .86). As such, 1- and 5-year recurrence-free survival rates were, respectively, 76.0% (95% CI 64.1%-87.9%) and 64.3% (95% CI 49.6%-79.0%) in the narrow-margin group versus 75.0% (95% CI 68.0%-82.0%) and 61.1% (95% CI 53.0%-69.3%) in the wide-margin group (Fig 3). Recurrence-free survival did not differ significantly between margin groups when stratifying by AJCC stage (Supplemental Fig 2, D-F, available via Mendeley at https://data.mendeley.com/datasets/5df3rpd4hb/1). On multivariate analysis, risk of recurrence increased with age (HR 1.03; 95% CI 1.00-1.06), male sex (HR 2.00; 95% CI 1.22-3.29), and positive margins (HR 3.49; 95% CI 1.61-7.58) (Table II).

Size of margins and pattern of recurrence

Among the 72 patients who had recurrence, first recurrence was local (n = 5), in transit (n = 16), regional (n = 23), or distant (n = 26) (unknown n = 2) (Supplemental Table II, available via Mendeley at

Table I. Clinical characteristics and surgical and radiotherapy outcome of the 214 patients, according to surgical margins of the primary tumor

| Patient characteristics | All (no., %) | Margins ≤1 cm (no., %) (n = 58) | Margins >1 cm (no., %) (n = 156) | P value (Fisher's exact test) |
|---|--------------|------------------------------------|-------------------------------------|-------------------------------|
| Age, y | | | | .02 |
| <77.6 | 105 (49.1) | 21 (36.2) | 84 (53.8) | |
| ≥77.6 | 109 (50.9) | 37 (63.8) | 72 (46.2) | |
| Sex | | ` ' | , , | .01 |
| Female | 121 (56.5) | 41 (70.7) | 80 (51.3) | |
| Male | 93 (43.5) | 17 (29.3) | 76 (48.7) | |
| Primary location | | | | .001 |
| Head and neck | 77 (36) | 32 (55.2) | 45 (28.8) | |
| Limb | 109 (50.9) | 23 (39.6) | 86 (55.1) | |
| Trunk | 28 (13.1) | 3 (5.2) | 25 (16.1) | |
| AJCC stage | , | , | , , | NS |
| I | 97 (45.3) | 34 (58.6) | 63 (40.4) | |
| II | 69 (32.3) | 12 (20.7) | 57 (36.5) | |
| III | 48 (22.4) | 12 (20.7) | 36 (23.1) | |
| Immunosuppression | (==::, | (, | (==:::) | .02 |
| Present | 28 (13.1) | 13 (22.4) | 15 (9.6) | |
| Absent | 186 (86.9) | 45 (77.6) | 141 (90.4) | |
| Performance status | .00 (00.0) | .5 (//.5) | (201.) | NS |
| 0-1 | 191 (89.2) | 54 (93.1) | 137 (87.8) | |
| 2–3 | 16 (7.5) | 4 (6.9) | 12 (7.7) | |
| Unknown | 7 (3.3) | 0 | 7 (4.5) | |
| Type of surgery | , (3.3) | ŭ | , (1.5) | NS |
| WLE only | 101 (47.2) | 30 (51.7) | 71 (45.5) | 113 |
| Graft | 67 (31.3) | 13 (22.4) | 54 (34.6) | |
| Flap | 38 (17.8) | 12 (20.7) | 26 (16.7) | |
| Flap and graft | 8 (3.7) | 3 (5.2) | 5 (3.2) | |
| Margins status | 0 (3.7) | 3 (3.2) | 3 (3.2) | NS |
| Negative | 198 (92.5) | 54 (93.1) | 144 (92.3) | 113 |
| Positive | 15 (7) | 4 (6.9) | 11 (7.1) | |
| Unknown | 1 (0.5) | 0 | 1 (0.6) | |
| Sentinel lymph node biopsy* | 1 (0.5) | · · | 1 (0.0) | NS |
| Conducted | 69 (38.3) | 20 (40.8) | 49 (37.4) | 145 |
| Not conducted | 111 (61.7) | 29 (59.2) | 82 (62.6) | |
| Adjuvant radiotherapy | 111 (01.7) | 25 (35.2) | 02 (02.0) | NS |
| Conducted, primary bed only | 86 (40.2) | 29 (50) | 57 (36.5) | NO |
| Conducted, primary bed only Conducted, node area only | 3 (1.4) | 29 (30) | 3 (1.9) | |
| Conducted, flode area only Conducted, primary bed and node area | 76 (35.5) | 19 (32.8) | 57 (36.5) | |
| Conducted, primary bed and node area Conducted, location unknown | 4 (1.9) | 0 | 4 (2.7) | |
| Not conducted | 45 (21) | 10 (17.2) | 35 (22.4) | |
| Delay before radiation therapy, median (Q1—Q3), wk | 8 (6–12) | 8 (6–12) | 8 (6–12) | NS |
| —————————————————————————————————————— | 0 (0 12) | 0 (0 12) | 0 (0 12) | CNI |

WLE, Wide local excision.

Data are presented as No. (%) unless otherwise indicated.

https://data.mendeley.com/datasets/5df3rpd4hb/1). Local recurrence occurred in 1 (1.7%) and 4 (2.6%) patients from the narrow and wide margin groups, respectively (P = .78). In-transit recurrence occurred in 4 (6.8%) and 11 (7.0%) patients from the narrow and wide margin groups, respectively (P > .99). Local and in-transit recurrence-free survival did not differ between groups (log-rank test, P = .56 and .53, respectively). Overall, recurrence patterns did not differ significantly between the 4 treatment groups (narrow or wide margins, with or without adjuvant radiotherapy) (Supplemental Table II, available via Mendeley at https://data.mendeley.com/datasets/ 5df3rpd4hb/1).

^{*}Data provided for the 180 patients who had no evidence of macrometastases at baseline.

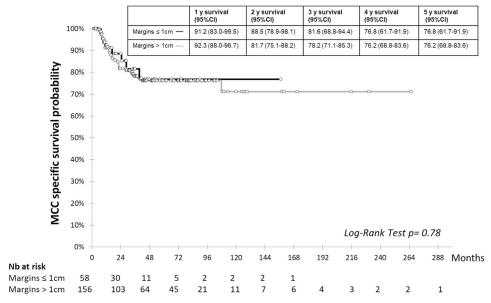


Fig 2. Merkel cell carcinoma—specific survival, according to surgical margins (≤1 cm versus >1 cm) of the primary tumor. *CI*, Confidence interval; *MCC*, Merkel cell carcinoma.

Table II. Univariate and multivariate Cox proportional hazard analysis for death and recurrence from Merkel cell carcinoma

| | Death from MCC | | | MCC recurrence | | | | |
|-----------------------|---------------------|-------|-----------------------|----------------|---------------------|------|-----------------------|------|
| | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | |
| Covariate | HR (95% CI) | P | aHR (95% CI) | P | HR (95% CI) | P | aHR (95% CI) | P |
| Sex | | | | | | | | |
| Men vs women | 1.75 (0.93-3.28) | .08 | 2.01 (1.03-3.95) | .04 | 1.83 (1.15-2.92) | .01 | 1.93 (1.18-3.18) | .09 |
| Age, y | | | | | | | | |
| <77.6 vs ≥77.6 | 1.55 (0.82-2.91) | .17 | 1.50 (0.72-3.15) | .28 | 1.57 (0.98-2.51) | .06 | 1.67 (0.99-2.80) | .052 |
| AJCC | | | | | | | | |
| II vs I | 3.68 (1.66-8.16) | .001 | 2.29 (0.94-5.55) | .07 | 1.90 (1.11-3.24) | .01 | 1.32 (0.72-2.42) | .38 |
| III vs I | 3.03 (1.28-7.19) | .012 | 2.87 (1.18-6.97) | .02 | 1.65 (0.90-3.02) | .10 | 1.66 (0.87-3.05) | .12 |
| Immunosuppression | | | | | | | | |
| Yes vs no | 1.32 (0.55-3.13) | .054 | 0.86 (0.29-2.49) | .78 | 1.09 (0.56-2.12) | .80 | 0.87 (0.41-1.85) | .72 |
| Performance status | | | | | | | | |
| 0-1 vs 2-3 | 2.06 (0.80-5.30) | .13 | 1.95 (0.69-5.49) | .20 | 1.19 (0.51-1.52) | .65 | 1.03 (0.43-2.47) | .95 |
| Margins size, cm | | | | | | | | |
| ≤1 vs >1 | 0.90 (0.41-1.95) | .78 | 1.06 (0.45-2.47) | .90 | 0.95 (0.54-1.66) | .85 | 1.10 (0.60-2.02) | .74 |
| Adjuvant radiotherapy | | | | | | | | |
| Yes vs no | 1.31 (0.58-2.95) | .52 | 1.47 (0.63-3.42) | .37 | 0.88 (0.51-1.52) | .65 | 0.89 (0.51-1.56) | .70 |
| Margins status | | | | | | | | |
| Positive vs negative | 5.83 (2.56-13.34) | <.001 | 6.51 (2.37-17.91) | <.001 | 3.28 (1.67-6.46) | .001 | 3.54 (1.63-7.70) | .01 |

aHR, Adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; MCC, Merkel cell carcinoma.

Characteristics of patients with positive margins

Among the 15 patients (7.5%) with positive margins, margins excised were narrow (0.5-1 cm) (n = 4; 26.6%) or wide (>1 cm) (n = 11; 73.3%) (Supplemental Table III, available via Mendeley at https://data.mendeley.com/datasets/5df3rpd4hb/1). Residual tumor was located more frequently on deep rather than lateral sections (n = 12 vs n = 4).

Recurrences occurred in 7 of 11 patients (63%) who had received adjuvant radiotherapy versus 3 of 4 patients (75%) who had not (P = .63). Among patients with recurrences, location was either local or in transit in 4 of 7 patients who had received adjuvant radiotherapy and 1 of 3 in those who had not (Supplemental Table III, available via Mendeley at https://data.mendeley.com/datasets/5df3rpd4hb/1).

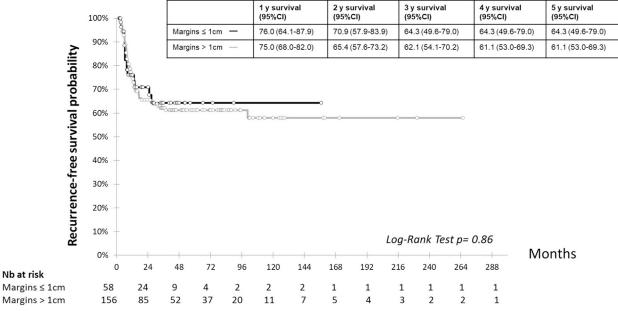


Fig 3. Recurrence-free survival, according to surgical margins (≤ 1 versus > 1 cm) of the primary tumor. CI, Confidence interval.

DISCUSSION

In this retrospective study of 214 MCC patients, wide local excision of the primary tumor with narrow margins (0.5-1 cm) was not associated with increased risk of local recurrence, any recurrence, death from MCC, or death from any cause compared with excision with wide margins (>1 cm). Overall, 15 patients (7.5%) had positive margin results after wide local excision, which was independently associated with increased risk of MCC recurrence and death owing to MCC.

Studies that had previously assessed whether size of surgical margins was associated with outcome in MCC patients are reported in Supplemental Table IV, available via Mendeley at https://data.mendeley. com/datasets/5df3rpd4hb/1. In most of the recent studies, 2,19-24 decreasing margins narrower than 2 cm did not affect outcome. Accordingly, guidelines^{3,4,7} recommend margins between 1 and 2 cm. A few retrospective series suggest that MCC can be removed with 1-cm margins. In one study reporting 224 MCC patients, Allen et al² did not find increased risk of local recurrence between margin groups (<1 cm versus \geq 1 cm). Similarly, Perez et al¹⁹ did not find evidence of increased risk of local recurrence, in-transit recurrence, or death between MCC patients treated with margins of 1 cm, 1.1 to 1.9 cm, or greater than or equal to 2 cm. One limitation was the absence of comparisons of confounding factors between groups, such as AJCC stage at baseline, 2,19 margin status,² or adjuvant radiotherapy on tumor bed.² The necessity of adjuvant radiotherapy for

decreasing local recurrences in the case of narrow margins was suggested by Tarabadkar et al,²² based on 188 MCC patients from Seattle. Accordingly, adjuvant radiotherapy on the tumor bed was previously found to improve local control in MCC. 12,13,17,28 Bearing in mind that only 5 local recurrences (2.3%) occurred in our cohort, we did not observe differences in local control between the 4 treatment groups (wide or narrow margins, with or without adjuvant radiotherapy). Given that adjuvant radiotherapy was widely administered in our cohort—indeed, 76% of our patients had had adjuvant radiotherapy on the primary tumor bed, which is similar to the Moffitt Cancer Center (69%)¹⁹ and Seattle (74%)²² cohorts—we can extrapolate our findings only in settings in which most patients receive adjuvant radiotherapy of the tumor bed.

Positive margins were clearly associated with increased risk of recurrence and death from MCC, in line with previous studies. 2,17,20,29 In our cohort, the proportion of patients with positive margins was similar between margin groups, and among these high-risk patients, recurrence rates, including local and in-transit recurrences, were similar between those who had received adjuvant radiotherapy on tumor bed and those who did not. Residual tumoral cells were mostly located on the deep histologic section, which highlights the importance of removing the underlying fascia layer. 3,4,6,7 Depth of excision is rarely retrievable from surgical reports, which limits the retrospective assessment of surgical procedures. Overall, our data suggest that patients

with positive resection margins should receive reexcision when possible, as stated by others¹⁴ and provided as an option in the algorithm proposed by Tarabadkar et al.²²

Although reducing margins aims to minimize surgical morbidity, we did not find wide margins to be associated with increased reconstructive procedures, which is likely related to the frequent practice of secondary closure in our cohort. Narrow margins did not allow shorter delays before adjuvant radiotherapy, which suggests that such delays are related to logistic issues rather than the surgical procedure itself.

Some authors suggest that 1-cm margins should be limited to patients with small tumors. 3,7,30 To our knowledge, there are no data to support which patients are eligible for narrow margins. In our cohort, narrow margins were not associated with increased risk of recurrence or death when patients were stratified according to disease stage at baseline, although our sample size in each group was rather small

Overall, our study is limited by its retrospective design with heterogenous baseline characteristics between groups; the limited number and shorter follow-up of patients treated with narrow margins, which might have underestimated the number of events; and the limited number of patients in the subgroup analysis based on AJCC stages.

To conclude, removing primary MCC tumor with a narrow margin (0.5-1 cm) was not associated with increased risk of local recurrence, any recurrence, or death in this cohort in which most patients had achieved clear margins and had had adjuvant radiotherapy of the tumor bed. Residual microscopic tumor, mostly found on deep margins, remained associated with prognosis. These findings highlight the necessity of extending the surgery down to the underlying fascia and would support re-excisions of positive margins when feasible.

Conflicts of interest

Dr Dreno reports personal fees from Board Merck Pfizer, outside the submitted work. Dr Saiag reports personal fees from Novartis, Pierre Fabre, BMS, MSD, Merk Serono, and Pfizer; and grants from Pierre Fabre and MSD outside the submitted work. Drs Jaouen, Kervarrec, Caille, Le Corre, Esteve, Wierzbiecka-Hainault, Maillard, Dinulescu, Blom, and Samimi have no conflicts of interest to declare.

REFERENCES

 Stang A, Becker JC, Nghiem P, Ferlay J. The association between geographic location and incidence of Merkel cell carcinoma in comparison to melanoma: an international assessment. Eur J Cancer. 2018;94:47-60.

- Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. J Clin Oncol. 2005;23:2300-2309
- Bichakjian CK, Olencki T, Aasi SZ, et al. Merkel cell carcinoma, version 1.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2018;16:742-774.
- Lebbe C, Becker JC, Grob J-J, et al. Diagnosis and treatment of Merkel cell carcinoma. European consensus-based interdisciplinary guideline. Eur J Cancer. 2015;51:2396-2403.
- Harms KL, Healy MA, Nghiem P, et al. Analysis of prognostic factors from 9387 Merkel cell carcinoma cases forms the basis for the new 8th Edition AJCC Staging System. *Ann Surg Oncol*. 2016;23:3564-3571.
- 6. Boccara O, Girard C, Mortier L, Bens G, Saiag P, Guillot B. Recommandations du groupe de cancérologie cutanée de la Société française de dermatologie pour la prise en charge diagnostique et thérapeutique du carcinome à cellules de Merkel. Ann Dermatol Venereol. 2011;138:475-482.
- Becker JC, Eigentler T, Frerich B, et al. S2k guidelines for Merkel cell carcinoma (MCC, neuroendocrine carcinoma of the skin) update 2018. J Dtsch Dermatol Ges. 2019;17:562-576.
- Yiengpruksawan A. Merkel cell carcinoma: prognosis and management. Arch Surg. 1991;126:1514-1519.
- Kokoska ER, Kokoska MS, Collins BT, Stapleton DR, Wade TP. Early aggressive treatment for Merkel cell carcinoma improves outcome. Am J Surg. 1997;174:688-693.
- Ott MJ, Tanabe KK, Gadd MA, et al. Multimodality management of Merkel cell carcinoma. Arch Surg. 1999;134:388-392.
- Dancey AL, Rayatt SS, Soon C, Ilchshyn A, Brown I, Srivastava S. Merkel cell carcinoma: a report of 34 cases and literature review. J Plast Reconstr Aesthet Surg. 2006;59:1294-1299.
- Fields RC, Busam KJ, Chou JF, et al. Recurrence after complete resection and selective use of adjuvant therapy for stage I through III Merkel cell carcinoma: recurrence in Merkel cell carcinoma. Cancer. 2012;118:3311-3320.
- Strom T, Naghavi AO, Messina JL, et al. Improved local and regional control with radiotherapy for Merkel cell carcinoma of the head and neck: improved local and regional control for Merkel cell carcinoma. *Head Neck*. 2017;39:48-55.
- Boyer JD, Zitelli JA, Brodland DG, D'Angelo G. Local control of primary Merkel cell carcinoma: review of 45 cases treated with Mohs micrographic surgery with and without adjuvant radiation. J Am Acad Dermatol. 2002;47:885-892.
- Han AY, Patel PB, Anderson M, Diaz MFP, Chin R, John MA St. Adjuvant radiation therapy improves patient survival in earlystage Merkel cell carcinoma: a 15-year single-institution study. *Laryngoscope*. 2018;128:1862-1866.
- Decker RH, Wilson LD. Role of radiotherapy in the management of Merkel cell carcinoma of the skin. J Natl Compr Canc Netw. 2006;4:713-718.
- Harrington C, Kwan W. Radiotherapy and conservative surgery in the locoregional management of Merkel cell carcinoma: the British Columbia Cancer Agency experience. *Ann Surg Oncol*. 2016;23:573-578.
- Yan L, Sun L, Guan Z, Wei S, Wang Y, Li P. Analysis of cutaneous Merkel cell carcinoma outcomes after different surgical interventions. J Am Acad Dermatol. 2020;82:1422-1434.
- Perez MC, de Pinho FR, Holstein A, et al. Resection margins in Merkel cell carcinoma: is a 1-cm margin wide enough? *Ann Surg Oncol*. 2018;25:3334-3340.
- Kukko H, Böhling T, Koljonen V, et al. Merkel cell carcinoma a population-based epidemiological study in Finland with a clinical series of 181 cases. Eur J Cancer. 2012;48:737-742.

- Sattler E, Geimer T, Sick I, et al. Sentinel lymph node in Merkel cell carcinoma: to biopsy or not to biopsy? *J Dermatol*. 2013; 40:374-379.
- Tarabadkar ES, Fu T, Lachance K, et al. Narrow excision margins are appropriate for Merkel cell carcinoma when combined with adjuvant radiation: analysis of 188 cases of localized disease and proposed management algorithm. *J Am Acad Dermatol*. 2021;84(2):340-347.
- 23. Gillenwater AM, Hessel AC, Morrison WH, et al. Merkel cell carcinoma of the head and neck: effect of surgical excision and radiation on recurrence and survival. *Arch Otolaryngol Head Neck Surg.* 2001;127:149-154.
- 24. Frohm ML, Griffith KA, Harms KL, et al. Recurrence and survival in patients with Merkel cell carcinoma undergoing surgery without adjuvant radiation therapy to the primary site. *JAMA Dermatol.* 2016;152:1001-1007.
- **25.** Samimi M, Molet L, Fleury M, et al. Prognostic value of antibodies to Merkel cell polyomavirus T antigens and VP1 protein in patients with Merkel cell carcinoma. *Br J Dermatol.* 2016;174:813-822.

- 26. Kervarrec T, Zaragoza J, Gaboriaud P, et al. Differentiating Merkel cell carcinoma of lymph nodes without a detectable primary skin tumor from other metastatic neuroendocrine carcinomas: the ELECTHIP criteria. J Am Acad Dermatol. 2018; 78:964-972.e3.
- Paulson KG, Iyer JG, Blom A, et al. Systemic immune suppression predicts diminished Merkel cell carcinoma—specific survival independent of stage. *J Invest Dermatol*. 2013;133: 642-646.
- 28. Petrelli F, Ghidini A, Torchio M, et al. Adjuvant radiotherapy for Merkel cell carcinoma: a systematic review and meta-analysis. *Radiother Oncol.* 2019;134:211-219.
- **29.** Bhatia S, Storer BE, Iyer JG, et al. Adjuvant radiation therapy and chemotherapy in Merkel cell carcinoma: survival analyses of 6908 cases from the National Cancer Data Base. *J Natl Cancer Inst.* 2016;108:djw042.
- Ellis DL, Davis RS. Evidence-based management of primary and localized Merkel cell carcinoma: a review. *Int J Dermatol*. 2013;52:1248-1258.