

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

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# 1 Narrow resection margins are not associated with mortality or recurrence in patients with

#### 2 Merkel cell carcinoma: a retrospective study

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#### 2

#### 3 ABSTRACT

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

6 **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 (0.5-1cm) versus 156 (72.9%) with wide margins (>1cm). 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% CI 61.7-91.9) and 76.2% (95% CI 68.8-83.6)]. 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, AJCC stage III, positive margins.

17 Limitations. Retrospective design, heterogenous baseline characteristics between groups.

18 Conclusion. Excision with narrow margins was not associated with outcome in this cohort, in
19 which most patients had clear margins and post-operative radiation therapy. Residual tumor,
20 mostly found on deep surgical margins, was independently associated with prognosis.

21

Keywords: Skin neoplasms; Merkel Cell Carcinoma; General surgery; Surgical margins;
Wide Local Excision; Prognosis; Mortality

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- 25

#### **1 CAPSULE SUMMARY**

- Wide local excision constitutes the standard of care for Merkel cell carcinoma. In
   this retrospective study, 0.5 to 1 cm margins were not associated with recurrence
   or death.
- Excision of Merkel cell carcinoma with narrow margins does not impact outcome
  when clear margins are obtained.

7

#### 1 **INTRODUCTION**

2 Merkel cell carcinoma (MCC) is a rare primary neuroendocrine skin cancer whose risk factors 3 include older age, fair skin, ultraviolet exposure and immunosuppression [1–4]. Disease stage is the major determinant of prognosis and was recently updated (8th Edition American Joint 4 5 Committee on Cancer [AJCC] Staging System) [5]. MCC carries high metastatic potential, and patients typically have poor prognosis, with 5-year survival rates of 51%, 35% and 14% for 6 local, regional and distant metastatic disease, respectively [5]. Although wide local excision 7 8 (WLE) 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 9 limited morbidity, remain debated. Given the aggressiveness of MCC, surgical clearance of the 10 tumor is a high priority while procedures should also take into account the frequent location of 11 MCC on the head and neck, as well as the frailty of these elderly patients. Margins of 2 to 3 cm 12 were historically excised [6,8–11], but margins of 1 to 2 cm are currently recommended [3,4,7]. 13 Such change in practice is supported by the widespread administration of adjuvant radiotherapy 14 (aRT) on the tumor bed [12-17]. According to a large study from the Surveillance, 15 16 Epidemiology and End Results database, margins > 2 cm were associated with improved 17 survival as compared with narrow margins ( $\leq 1$  cm), including procedures such as shave, punch or incisional biopsies, which are likely incomplete[18]. However, several studies suggest that 18 19 lateral margins of 1 cm do not affect either local recurrences [2,19], any recurrences [20,21] or survival [19,21,22], but were limited by small cohorts [21,23], the unavailability of 20 confounding factors such as disease stage [2,19,24] and histological margin status [21,23], or 21 lack of data on survival [2] or recurrence rates [21,27]. This study assessed whether narrow 22 margins (0.5 to 1 cm) were associated with outcome in a retrospective cohort of MCC patients, 23 24 excluding procedures such as biopsies, and taking into account determinant confounding factors

such as disease stage, margin status and aRT. The primary objective was to evaluate whether
margins were associated with disease-specific survival (DSS). Secondary objectives were to

assess whether margins were associated with overall survival (OS), recurrence-free survival
 (RFS) and pattern of recurrences, and whether narrow margins would decrease reconstruction
 procedures and delay to aRT.

#### 4 PATIENTS AND METHODS

#### 5 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 ten French hospitals [25,26] and approved by the Ethics
Committee of Tours, France (N° ID RCB 2009-A01056-51). As previously described [25,26],
patients were included in the cohort if review of the histological data confirmed the diagnosis of
MCC. Follow-up had been performed as recommended in the National French Guidelines[6].

#### 11 Inclusion and exclusion criteria

Patients were included if they had WLE of the primary tumor, with minimum lateral margins of 12 0.5 cm, according to the surgical report. Patients with excision of margins <0.5 cm were 13 considered to have had excision biopsy or palliative surgery and were excluded. Patients with 14 nodal disease were included if they had also undergone potentially curative treatment by lymph 15 node dissection, radiation therapy or both [3,7]. Exclusion criteria were AJCC stage IV, absence of 16 17 primary tumor (occult or regressive primary), no surgical treatment of the primary tumor (refusal, contraindications, exclusive radiation therapy), excision biopsy or palliative surgery (excision of 18 margins < 0.5 cm), two concomitant MCC primary tumors, no treatment of nodal disease at 19 20 baseline, rapid disease progression before completion of initial treatment, missing surgical margins 21 and/or no follow up visit after surgery.

#### 22 Clinical data

Data were collected on age, sex, AJCC tumor stage [5], primary location, WHO performance status,
immunosuppression (solid organ transplant, current hematological or solid malignancies, HIV
infection, immunosuppressive drugs [27]), surgical lateral margins of WLE (in case of re-excisions,
cumulative excision margin was calculated), reconstruction procedures (flap and/or graft),

histological margin status (negative or positive), sentinel lymph node biopsy (SLNB), aRT (tumor 1 bed, node area or both) and time from surgery to initiation of aRT. Death was categorized as being 2 related to MCC (MCC-specific death) or not (other cause) based on patients' medical files in each 3 hospital. DSS was defined as the time from the initial confirmed diagnosis of MCC to the date of 4 death related to MCC; OS as the time from diagnosis to the date of death regardless of cause; RFS 5 6 as the time from diagnosis to the date of a clinical or paraclinical event related to MCC recurrence. 7 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 8 lymph node basin). The database was locked on November 20, 2019. 9

10 Outcomes

The primary outcome was DSS with excision of narrow margins (0.5-1 cm) and wide margins
(>1 cm). Secondary outcomes were OS, RFS, pattern of first recurrence, proportion of
reconstruction procedures and delay between surgery and aRT.

#### 14 Statistics

Continuous data are described with mean and standard deviation or median (Q1-Q3; range) and 15 categorical data with number (percentage). Patients were classified as excision of narrow margins 16 (0.5-1 cm) and excision of margins > 1 cm. Qualitative data were compared by two-tailed Fisher 17 18 exact test and quantitative data by Mann-Whitney U test. Median follow-up, local and any RFS, OS and DSS with 95% confidence intervals (CI) were analyzed by Kaplan-Meier survival analysis 19 with log-rank tests. Univariate and multivariate Cox proportional hazards analyses were used to 20 21 identify factors associated with recurrence and death, estimating hazard ratios (HRs) and 95% 22 confidence intervals (CIs). For DSS, 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 23 24 last follow-up. Covariates were identified as potential prognostic factors on Cox univariate regression at  $p \le 0.10$  and were included in the multivariate analysis. The proportional hazards 25 assumption was assessed by a non-significant relationship between scaled Schoenfeld residuals 26

2 Stat-Life (Addinsoft, Paris, France). P< 0.05 was considered statistically significant.

#### 3 **<u>RESULTS</u>**

#### 4 Patient characteristics by size of margins at baseline

Among the 357 MCC patients included in the cohort, 214 met inclusion criteria (Figure 1). 5 Patient characteristics are presented in Table I. Median lateral margin was 2 cm (Q1-Q3 1-2.8, 6 7 range 0.5-6). Overall, 58 (27.1%) patients had undergone excision with narrow margins versus 156 (72.9%) with wide margins. Most patients had clear histological margins (n=198, 92.5%) and 8 aRT (n=169, 79.0%). Overall, 34 (15.9%) patients had nodal macrometastases at baseline (AJCC 9 stage IIIB) and 180 (84.1%) had no evidence of macrometastases; 69/180 (38.3%) had undergone 10 SLNB, 14 (20.3%) showing nodal micrometastases (AJCC stage IIIA). The 48 patients with 11 evidence of nodal disease had undergone lymph node dissection (n=10, 20.8%), radiation therapy 12 of lymph nodes (n=11, 22.9%) or both (n=27, 56.3%). Patients with excision of  $\leq$  1-cm margins 13 14 were significantly older (p=0.0005) and more frequently were female (p=0.010) and immunosuppressed (p=0.018) and had head and neck tumors (p=0.001) than those with 1-cm 15 margins. AJCC stages, PS, margin status, reconstruction procedures, frequency of aRT and time 16 to initiation of aRT did not differ between groups (Table I). 17

#### 18 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 19 significantly longer for those treated with wide (median 67.6 months, 95% CI 50.8-79.1) versus 20 narrow margins (median 28.9 months,95% CI 19.7-44.4) (log rank test, < 0.0001). Overall, 76 21 patients (35.5%) had died, including 40 (18.7%) due to MCC (Figure 1). The median OS was 22 107.7 months (95% CI 77.4-158.3) and the median DSS was not reached. DSS did not 23 significantly differ between margin groups (log-rank test, p=0.78). As such, 1- and 5-year specific 24 survival rates were 91.2% (95% CI 83.0-99.5) and 76.8% (95% CI 61.7-91.9) in the narrow-25 margin group, versus 92.3 (95% CI 88.0-96.7) and 76.2% (95% CI 68.8-83.6) in the wide-margin 26

group (Figure 2). OS did not significantly differ between margin groups (log-rank test, p=0.93) 1 (Supplemental Figure 1). When stratifying patients on AJCC stage, DSS did not differ between 2 margin groups (Supplemental Figure 2, A-C). On multivariate analysis, risk of death due to 3 MCC was associated with age (HR 1.04, 95% CI 1.00-1.08), male sex (HR 2.06, 95% CI 1.05-4 4.05), AJCC stage III (HR 2.97, 95%CI 1.23-7.20) and positive margins (HR 6.04 (2.21-16.54) 5 (Table II). On multivariate analysis, age (HR 1.06, 95% CI 1.02-1.09), male sex (2.06, 95% CI 6 7 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 of any cause (Supplemental Table I). 8

#### 9 Size of margins and MCC recurrence

Disease recurred in 72 (33.6%) patients (median time to recurrence: 8.0 [Q1-Q3 6.0-13.3] months) 10 (Figure 1). RFS did not significantly differ between margin groups (log-rank test, p=0.86). As 11 such, 1- and 5-year RFS rates were 76.0% (95%CI 64.1-87.9) and 64.3% (95%CI 49.6-79.0) in the 12 13 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 (Figure 3). RFS did not differ significantly between margin groups when stratifying 14 15 by AJCC stage (Supplemental Figure 2, D-F). On multivariate analysis, risk of recurrence was increased with age (HR 1.03, 95% CI 1.00-1.06), male sex (HR 2.00, 95% CI 1.22-3.29) and 16 positive margins (HR 3.49 95% CI 1.61-7.58) (Table II). 17

#### 18 Size of margins and pattern of recurrence.

Among the 72 patients who had recurred, first recurrence was local (n=5), in-transit (16), regional (n=23) or distant (n=26) (unknown, n=2) (**Supplemental Table II**). Local recurrence occurred in 1 (1.7%) and 4 (2.6%) patients from the narrow and wide margin groups, respectively (p=0.78). Intransit recurrence occurred in 4 (6.8%) and 11 (7.0%) patients from the narrow and wide margin groups, respectively ((p=1.0). Local and in-transit RFS did not differ between groups (log-rank test, p=0.56 and p=0.53, respectively). Overall, recurrences patterns did not differ significantly between the four treatment groups (narrow or wide margins, with or without aRT) (**Supplemental Table II**).

26 Characteristics of patients with positive margins

Among the 15 (7.5%) patients with positive margins, margin excised were narrow (0.5-1cm) (n=4) (26.6%) or wide (>1cm) (n=11) (73.3%) (**Supplemental Table III**). Residual tumor was located more frequently on deep rather than lateral sections (n=12 vs n=4). Recurrences occurred in 7/11 patients (63%) who had received aRT versus 3/4 patients (75%) who had not (p=0.63). Among patients with recurrences, location was either local or in-transit in 4/7 patients who had received aRT and 1/3 in those who had not (**Supplemental Table III**).

#### 7 Discussion

In this retrospective study of 214 MCC patients, WLE 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, as compared with excision with wide margins (>1cm). Overall, 15
(7.5%) patients had positive margins after WLE, which was independently associated with
increased risk of MCC recurrence and death due to MCC.

Studies which had previously assessed whether size of surgical margins was associated with 13 outcome in MCC patients are reported in Supplemental Table IV. In most of the recent studies 14 [2,19–21,22, 23,24], decreasing margins below 2 cm did not affect outcome. Accordingly, recent 15 guidelines [3,4,7] recommend margins between 1 to 2 cm. A few retrospective series suggest that 16 MCC can be removed with 1-cm margins. In one study reporting 224 MCC patients, Allen et al did 17 not find increased risk of local recurrence between margin groups (<1-cm versus  $\geq$ 1cm margins) 18 [2]. Similarly, Perez et al did not evidence increased risk of local recurrence, in-transit recurrence or 19 20 death between MCC patients treated with margins of 1cm, 1.1 to 1.9cm or  $\geq$  2cm [19]. One limitation was the absence of comparisons of confounding factors between groups, such as AJCC 21 stage at baseline[2,19], margin status [2] or aRT on tumor bed [2]. The necessity of aRT for 22 23 decreasing local recurrences in case of narrow margins was suggested by Tarabadkar et al, based on 188 MCC patients from Seattle [22]. Accordingly, aRT on the tumor bed was previously found to 24 improve local control in MCC [12,13,17,28]. Bearing in mind that only 5 local recurrences (2.3%) 25 occurred in our cohort, we did not observe differences in local control between the four treatment 26

groups (wide or narrow margins, with or without aRT). Given that aRT was widely administered in
our cohort - 76% of patients had had aRT on the primary tumor bed, similar to the Moffitt
(69%)[19] and Seattle (74%) [22] cohorts - we can extrapolate our findings only in settings where
most patients receive aRT of the tumor bed.

Importantly, positive margins were clearly associated with increased risk of recurrence and death 5 6 from MCC, in line with previous studies [2,17,20,29]. In our cohort, i) the proportion of patients 7 with positive margins was similar between margin groups, and ii) among these high-risk patients, recurrence rates - including local/in-transit recurrences - were similar between those who had 8 received aRT on tumor bed and those who did not. To note, residual tumoral cells were mostly 9 located on the deep histological section, which highlights the crucial importance of removing the 10 underlying fascia layer [3,4,6,7]. Depth of excision is rarely retrievable from surgical reports, which 11 limits the retrospective assessment of surgical procedures. Overall, our data suggest that patients 12 with positive resection margins should be re-excised when possible, as stated by others[14] and 13 14 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 with the frequent practice of secondary closure in our cohort. To note, narrow margins did not either allow shorter delays before aRT, which suggests that such delays are related to logistical issues rather than the surgical procedure itself.

Some authors suggest that 1cm 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 stratifying patients 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; 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 cohortwhere most patients had achieved clear margins and had had aRT 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.

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### 2 **References**

- [1] 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. https://doi.org/10.1016/j.ejca.2018.02.003.
- [2] 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;23:2300–9.
   https://doi.org/10.1200/JCO.2005.02.329.
- 9 [3] Bichakjian CK, Olencki T, Aasi SZ, Alam M, Andersen JS, Blitzblau R, et al. Merkel Cell Carcinoma,
  10 Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2018;16:742–
  11 74. https://doi.org/10.6004/jnccn.2018.0055.
- [4] Lebbe C, Becker JC, Grob J-J, Malvehy J, del Marmol V, Pehamberger H, et al. Diagnosis and treatment
   of Merkel Cell Carcinoma. European consensus-based interdisciplinary guideline. Eur J Cancer
   2015;51:2396–403. https://doi.org/10.1016/j.ejca.2015.06.131.
- [5] Harms KL, Healy MA, Nghiem P, Sober AJ, Johnson TM, Bichakjian CK, 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;23:3564–71. https://doi.org/10.1245/s10434-016-5266-4.
- [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 Vénéréologie 2011;138:475–82.
  https://doi.org/10.1016/j.annder.2011.01.029.
- [7] Becker JC, Eigentler T, Frerich B, Gambichler T, Grabbe S, Höller U, et al. S2k guidelines for Merkel cell
   carcinoma (MCC, neuroendocrine carcinoma of the skin) update 2018. JDDG J Dtsch Dermatol Ges
   2019;17:562–76. https://doi.org/10.1111/ddg.13841.
- [8] Yiengpruksawan A. Merkel Cell Carcinoma: Prognosis and Management. Arch Surg 1991;126:1514.
   https://doi.org/10.1001/archsurg.1991.01410360088014.
- [9] Kokoska ER, Kokoska MS, Collins BT, Stapleton DR, Wade TP. Early aggressive treatment for Merkel cell
   carcinoma improves outcome. Am J Surg 1997;174:688–93. https://doi.org/10.1016/S0002 9610(97)00193-1.
- [10] Ott MJ, Tanabe KK, Gadd MA, Stark P, Smith BL, Finkelstein DM, et al. Multimodality Management of
   Merkel Cell Carcinoma. ARCH SURG 1999;134:6.
- [11] 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;59:1294–9.
   https://doi.org/10.1016/j.bjps.2006.03.044.
- [12] Fields RC, Busam KJ, Chou JF, Panageas KS, Pulitzer MP, Allen PJ, et al. Recurrence after complete
   resection and selective use of adjuvant therapy for stage I through III Merkel cell carcinoma:
- 37 Recurrence in Merkel Cell Carcinoma. Cancer 2012;118:3311–20. https://doi.org/10.1002/cncr.26626.
- [13] Strom T, Naghavi AO, Messina JL, Kim S, Torres-Roca JF, Russell J, 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. https://doi.org/10.1002/hed.24527.
- [14] 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;47:885–92. https://doi.org/10.1067/mjd.2002.125083.
- [15] Han AY, Patel PB, Anderson M, Diaz MFP, Chin R, St. John MA. Adjuvant radiation therapy improves
   patient survival in early-stage merkel cell carcinoma: A 15-year single-institution study. The
   Laryngoscope 2018;128:1862–6. https://doi.org/10.1002/lary.27031.
- [16] Decker RH, Wilson LD. Role of Radiotherapy in the Management of Merkel Cell Carcinoma of the Skin. J
   Natl Compr Canc Netw 2006;4:713–8. https://doi.org/10.6004/jnccn.2006.0061.
- 49 [17] 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–
  8. https://doi.org/10.1245/s10434-015-4812-9.
- 52 [18] Yan L, Sun L, Guan Z, Wei S, Wang Y, Li P. Analysis of cutaneous Merkel cell carcinoma outcomes after

- 1 different surgical interventions. J Am Acad Dermatol 2020;82:1422–34.
- 2 https://doi.org/10.1016/j.jaad.2018.10.001.
- [19] Perez MC, de Pinho FR, Holstein A, Oliver DE, Naqvi SMH, Kim Y, et al. Resection Margins in Merkel Cell
   Carcinoma: Is a 1-cm Margin Wide Enough? Ann Surg Oncol 2018;25:3334–40.
   https://doi.org/10.1245/s10434-018-6688-v
- 5 https://doi.org/10.1245/s10434-018-6688-y.
  6 [20] Kukko H, Böhling T, Koljonen V, Tukiainen E, Haglund C, Po
- [20] Kukko H, Böhling T, Koljonen V, Tukiainen E, Haglund C, Pokhrel A, et al. Merkel cell carcinoma A
   population-based epidemiological study in Finland with a clinical series of 181 cases. Eur J Cancer
   2012;48:737–42. https://doi.org/10.1016/j.ejca.2011.06.001.
- 9 [21] Sattler E, Geimer T, Sick I, Flaig MJ, Ruzicka T, Berking C, et al. Sentinel lymph node in Merkel cell
  10 carcinoma: To biopsy or not to biopsy? J Dermatol 2013;40:374–9. https://doi.org/10.1111/134611 8138.12072.
- [22] Tarabadkar ES, Fu T, Lachance K, Hippe DS, Pulliam T, Thomas H, 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 2020.
   https://doi.org/10.1016/j.jaad.2020.07.079.
- [23] Gillenwater. Merkel Cell Carcinoma of the Head and Neck: Effect of Surgical Excision and Radiation on
   Recurrence and Survival. ARCH OTOLARYNGOL HEAD NECK SURG 2001;127:6.
- [24] Frohm ML, Griffith KA, Harms KL, Hayman JA, Fullen DR, Nelson CC, 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. https://doi.org/10.1001/jamadermatol.2016.1428.
- [25] Samimi M, Molet L, Fleury M, Laude H, Carlotti A, Gardair C, 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;174:813–22. https://doi.org/10.1111/bjd.14313.
- [26] Kervarrec T, Zaragoza J, Gaboriaud P, Le Gouge A, Beby-Defaux A, Le Corre Y, 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.
   https://doi.org/10.1016/j.jaad.2017.11.037.
- [27] Paulson KG, Iyer JG, Blom A, Warton EM, Sokil M, Yelistratova L, et al. Systemic Immune Suppression
   Predicts Diminished Merkel Cell Carcinoma–Specific Survival Independent of Stage. J Invest Dermatol
   2013;133:642–6. https://doi.org/10.1038/jid.2012.388.
- [28] Petrelli F, Ghidini A, Torchio M, Prinzi N, Trevisan F, Dallera P, et al. Adjuvant radiotherapy for Merkel
   cell carcinoma: A systematic review and meta-analysis. Radiother Oncol 2019;134:211–9.
   https://doi.org/10.1016/j.radonc.2019.02.015.
- [29] Bhatia S, Storer BE, Iyer JG, Moshiri A, Parvathaneni U, Byrd D, 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. https://doi.org/10.1093/jnci/djw042.
- [30] Ellis DL, Davis RS. Evidence-based management of primary and localized Merkel cell carcinoma: a
   review. Int J Dermatol 2013;52:1248–58. https://doi.org/10.1111/ijd.12091.
- 39 40

- 2 Table I. Clinical characteristics, surgical and radiotherapy outcome of the 214
- 3 patients, according to surgical margins of the primary tumor.
- 4

	All (N,%)	Margins ≤ 1cm (N,%) (n=58)	Margins > 1cm (N,%) (n=156)	P-value (Fisher's exact test)
Age (N, %)				0.020
<77.6 years	105 (49.1)	21 (36.2)	84 (53.8)	
≥77.6 years	109 (50.9)	37 (63.8)	72 (46.2)	
Sex (N, %)				0.010
Female	121 (56 5)	41 (707)	80 (51 3)	
Male	93 (43.5)	17 (29.3)	76 (48.7)	
Primary location (N %)				0.001
Head and neck	77 (26)	22 (55 2)	45 (29.9)	0.001
Limb	//(30)	32 (55.2)	45 (28.8)	
Trunk	109(50.9)	23 (39.6)	86 (55.1)	
A ICC stage (N %)	28 (13.1)	5 (5.2)	25 (10.1)	NS
I	07(452)	24(59.6)	(2, (40, 4))	110
II	97 (45.3)	34 (58.6) 12 (20.7)	63 (40.4) 57 (26.5)	
III	09 (32.3)	12(20.7) 12(20.7)	37(30.3) 36(22.1)	
Immunosuppression (N %)	48 (22.4)	12 (20.7)	50 (25.1)	0.018
Present	29(121)	12 (22 4)	15 (0.6)	0.010
Absent	20 (13.1)	15 (22.4)	13(9.0) 141(90.4)	
Absent	1000 (00.9)	45 (77.0)	141 (90.4)	
Performance Status (N, %)				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 (0)	7 (4.5)	
Type of surgery (N,%)				NS
WLE only	101 (47.2)	30 (51.7)	71 (45.5)	
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 (N, %)		54 (02.4)	1 1 1 (02 2)	NS
Negative	198 (92.5)	54 (93.1)	144 (92.3)	
Positive	15 (7)	4 (6.9)	11(7.1)	
Unknown	1 (0.5)	0(0)	1 (0.6)	
Sentinel lymph node $hionsy(*)$ (N %)				NS
Done	69 (38.3)	20 (40.8)	49 (37.4)	110
Not done	111 (61.7)	29 (59.2)	82 (62.6)	
Not dolle				
Adjuvant radiotherapy (N,%)				NS
Done, primary bed only	86 (40.2)	29 (50)	57 (36.5)	
Done, node area only	3 (1.4)	0 (0)	3 (1.9)	
Done, primary bed and node area	76 (35.5)	19 (32.8)	57 (36.5)	
Done, location unknown	4 (1.9)	0(0)	4 (2.7)	
	45 (21)	10 (17.2)	35 (22.4)	
Delay before				NS
radiation therapy (median Q1-Q3) (weeks)	8 (6-12)	8 (6-12)	8 (6-12)	

<sup>5</sup> 

6 (\*) Data provided for the 180 patients who had no evidence of macrometastases at baseline

		Death	from	MCC recurrence				
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Covariate	HR (95% CI)	р	aHR (95%CI)	p	HR (95% CI)	р	aHR (95%CI)	р
Sex								
male vs female	1.75 (0.93-3.28)	0.08	2.01 (1.03-3.95)	0.04	1.83 (1.15-2.92)	0.01	1.93 (1.18-3.18)	0.09
Age								
< 77.6 versus ≥ 77.6	1.55 (0.82-2.91)	0.17	1.50 (0.72-3.15)	0.28	1.57 (0.98-2.51)	0.06	1.67 (0.99-2.80)	0.052
AJCC								
II versus I	3.68 (1.66-8.16)	0.001	2.29 (0.94-5.55)	0.07	1.90 (1.11-3.24)	0.01	1.32 (0.72-2.42)	0.38
III versus I	3.03 (1.28-7.19)	0.012	2.87 (1.18-6.97)	0.02	1.65 (0.90-3.02)	0.10	1.66 (0.87-3.05)	0.12
Immunosuppression								
yes versus no	1.32 (0.55-3.13)	0.054	0.86 (0.29-2.49)	0.78	1.09 (0.56-2.12)	0.80	0.87 (0.41-1.85)	0.72
Performance status								
0-1 versus 2-3	2.06 (0.80-5.30)	0.13	1.95 (0.69-5.49)	0.20	1.19 (0.51-1.52)	0.65	1.03 (0.43-2.47)	0.95
Margins size								
$\leq 1$ cm versus > 1 cm	0.90 (0.41-1.95)	0.78	1.06 (0.45-2.47)	0.90	0.95 (0.54-1.66)	0.85	1.10 (0.60-2.02)	0.74
Adjuvant radiotherapy								
yes versus no	1.31 (0.58-2.95)	0.52	1.47 (0.63-3.42)	0.37	0.88 (0.51-1.52)	0.65	0.89 (0.51-1.56)	0.70
Margins status								
positive versus negative	5.83 (2.56-13.34)	< 0.0001	6.51 (2.37-17.91)	0.0003	3.28 (1.67-6.46)	0.001	3.54 (1.63-7.70)	0.01

Table II. Univariate and multivariate Cox proportional hazard analysis for death and recurrence from MCC

HR, Hazard Ratio; aHR, adjusted HR; CI, confidence interval; MCC, Merkel cell carcinoma

### **FIGURE LEGENDS**

Figure 1. Flow chart diagram. Of the 357 patients included in the cohort, 214 patients had wide local excision of primary tumor with minimal margins of 0.5cm, and curative treatment of nodal disease when indicated.

Figure 2. MCC-specific survival, according to surgical margins (≤1 cm versus > 1cm) of the primary tumor.

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





