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ABSTRACT

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 (0.5-1cm) 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.

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 post-operative radiation therapy. Residual tumor, mostly found on deep surgical margins, was independently associated with prognosis.

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

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.**

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare primary neuroendocrine skin cancer whose risk factors 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 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 local, regional and distant metastatic disease, respectively [5]. Although wide local excision (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 limited morbidity, remain debated. Given the aggressiveness of MCC, surgical clearance of the tumor is a high priority while procedures should also take into account the frequent location of MCC on the head and neck, as well as the frailty of these 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 (aRT) on the tumor bed [12–17]. According to a large study from the Surveillance, Epidemiology and End Results database, margins > 2 cm were associated with improved survival as 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 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 confounding factors such as disease stage [2,19,24] and histological margin status [21,23], or lack of data on survival [2] or recurrence rates [21,27]. 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 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.

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 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].

Inclusion and exclusion criteria

Patients were included if they had WLE of the primary tumor, with minimum lateral margins of 0.5 cm, according to the surgical report. Patients with excision of margins <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, exclusive radiation therapy), excision biopsy or palliative surgery (excision of margins < 0.5 cm), two concomitant MCC primary tumors, no treatment of nodal disease at baseline, rapid disease progression before completion of initial treatment, missing surgical margins and/or no follow up visit after surgery.

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 bed, node area or both) and time from surgery to initiation of aRT. Death was categorized as being related to MCC (MCC-specific death) or not (other cause) based on patients' medical files in each hospital. DSS was defined as the time from the initial confirmed diagnosis of MCC to the date of death related to MCC; OS as the time from diagnosis to the date of death regardless of cause; RFS 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 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.

Statistics

Continuous data are described with mean and standard deviation or median (Q1–Q3; range) and categorical data with number (percentage). Patients were classified as excision of narrow margins (0.5-1 cm) and excision of margins > 1 cm. Qualitative data were compared by two-tailed Fisher 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 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% 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 last follow-up. Covariates were identified as potential prognostic factors on Cox univariate regression at $p \leq 0.10$ and were included in the multivariate analysis. The proportional hazards assumption was assessed by a non-significant 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, Paris, France). P< 0.05 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 **(Figure 1)**. Patient characteristics are presented in **Table I**. Median lateral margin was 2 cm (Q1-Q3 1-2.8, 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 aRT (n=169, 79.0%). Overall, 34 (15.9%) patients had nodal macrometastases at baseline (AJCC stage IIIB) and 180 (84.1%) had no evidence of macrometastases; 69/180 (38.3%) had undergone SLNB, 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 ≤ 1-cm margins 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 margins. AJCC stages, PS, margin status, reconstruction procedures, frequency of aRT and time to initiation of aRT 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 those treated with wide (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, < 0.0001). Overall, 76 patients (35.5%) had died, including 40 (18.7%) due to MCC (**Figure 1**). The median OS was 107.7 months (95% CI 77.4-158.3) and the median DSS was not reached. DSS did not significantly differ between margin groups (log-rank test, p=0.78). As such, 1- and 5-year specific survival rates were 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 (**Figure 2**). OS did not significantly differ between margin groups (log-rank test, p=0.93) (**Supplemental Figure 1**). When stratifying patients on AJCC stage, DSS did not differ between margin groups (**Supplemental Figure 2, A-C**)**.** On multivariate analysis, risk of death due 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 (2.21-16.54) (**Table II**). On multivariate analysis, age (HR 1.06, 95% CI 1.02-1.09), male sex (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 of any cause (**Supplemental Table I**)**.**

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) (**Figure 1**). RFS did not significantly differ between margin groups (log-rank test, p=0.86). As 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 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 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 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 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). In-transit 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**).

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**).

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 outcome in MCC patients are reported in **Supplemental Table IV**. In most of the recent studies [2,19–21,22, 23,24], decreasing margins below 2 cm did not affect outcome. Accordingly, recent guidelines [3,4,7] recommend margins between 1 to 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 al did not find increased risk of local recurrence between margin groups (<1-cm versus ≥1cm margins) [2]. Similarly, Perez et al did not evidence increased risk of local recurrence, in-transit recurrence or death between MCC patients treated with margins of 1cm, 1.1 to 1.9cm or ≥ 2cm [19]. One limitation was the absence of comparisons of confounding factors between groups, such as AJCC stage at baseline[2,19], margin status [2] or aRT on tumor bed [2]. The necessity of aRT for 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 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 four treatment

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 from MCC, in line with previous studies [2,17,20,29]. In our cohort, i) the proportion of patients 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 received aRT on tumor bed and those who did not. To note, residual tumoral cells were mostly located on the deep histological section, which highlights the crucial 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 be re-excised when possible, as stated by others[14] 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 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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Tables.

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

	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 (70.7)	80 (51.3)	
Male	93 (43.5)	17 (29.3)	76 (48.7)	
Primary location (N, %)				0.001
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 (N, %)				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 (N,%)				0.018
Present	28 (13.1)	13 (22.4)	15 (9.6)	
Absent	1860 (86.9)	45 (77.6)	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, %)				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 biopsy(*) (N,%)				NS
Done	69 (38.3)	20 (40.8)	49 (37.4)	
Not done	111 (61.7)	29 (59.2)	82 (62.6)	
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)	
Not done	45 (21)	10 (17.2)	35 (22.4)	
Delay before radiation therapy (median Q1-Q3) (weeks)	8 (6-12)	8 (6-12)	8 (6-12)	NS

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

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

	Death from 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								
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								
≤ 1cm versus > 1cm	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

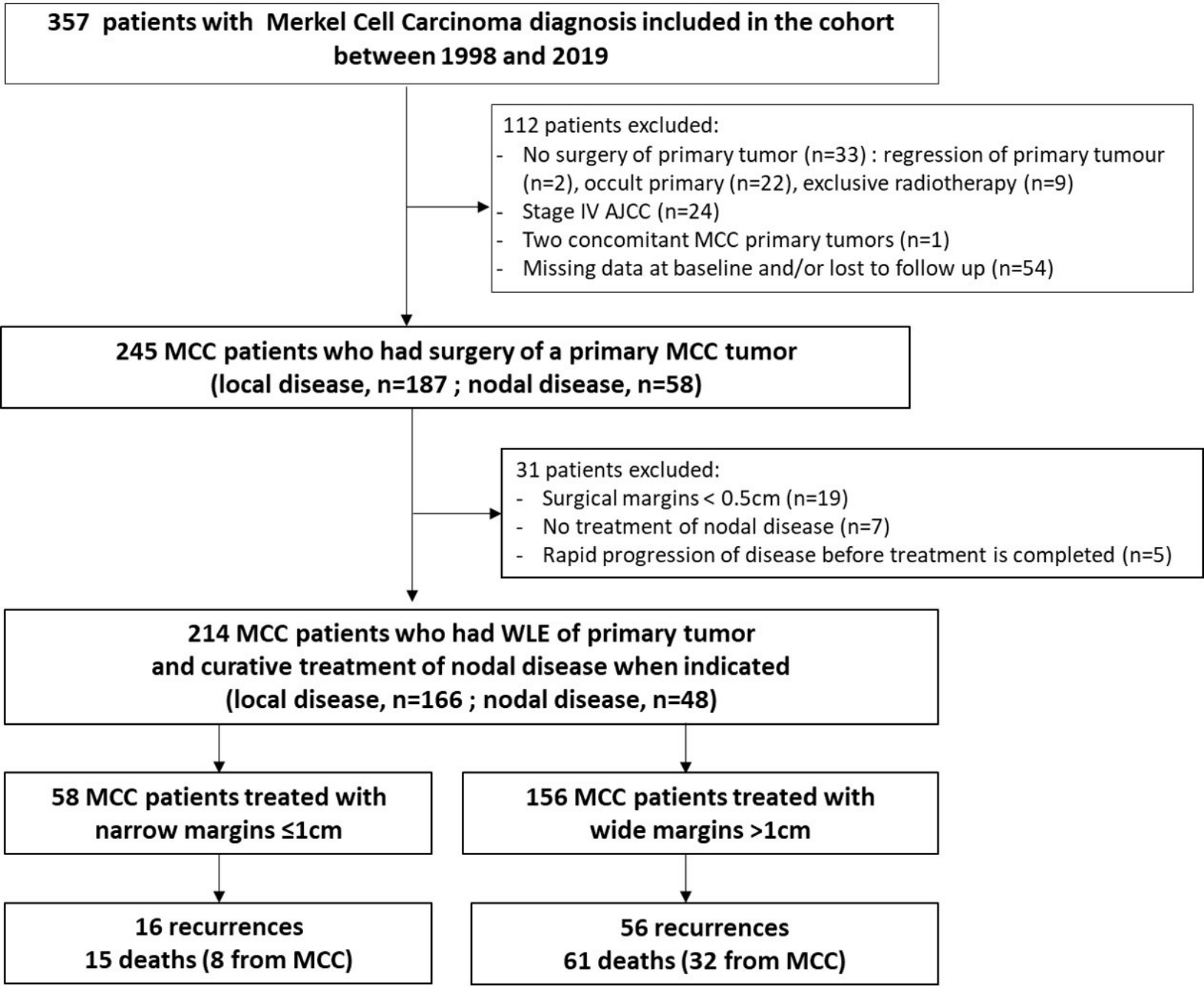
HR, Hazard Ratio; aHR, adjusted HR ; CI, confidence interval; MCC, Merkel cell carcinoma

FIGURE LEGENDS

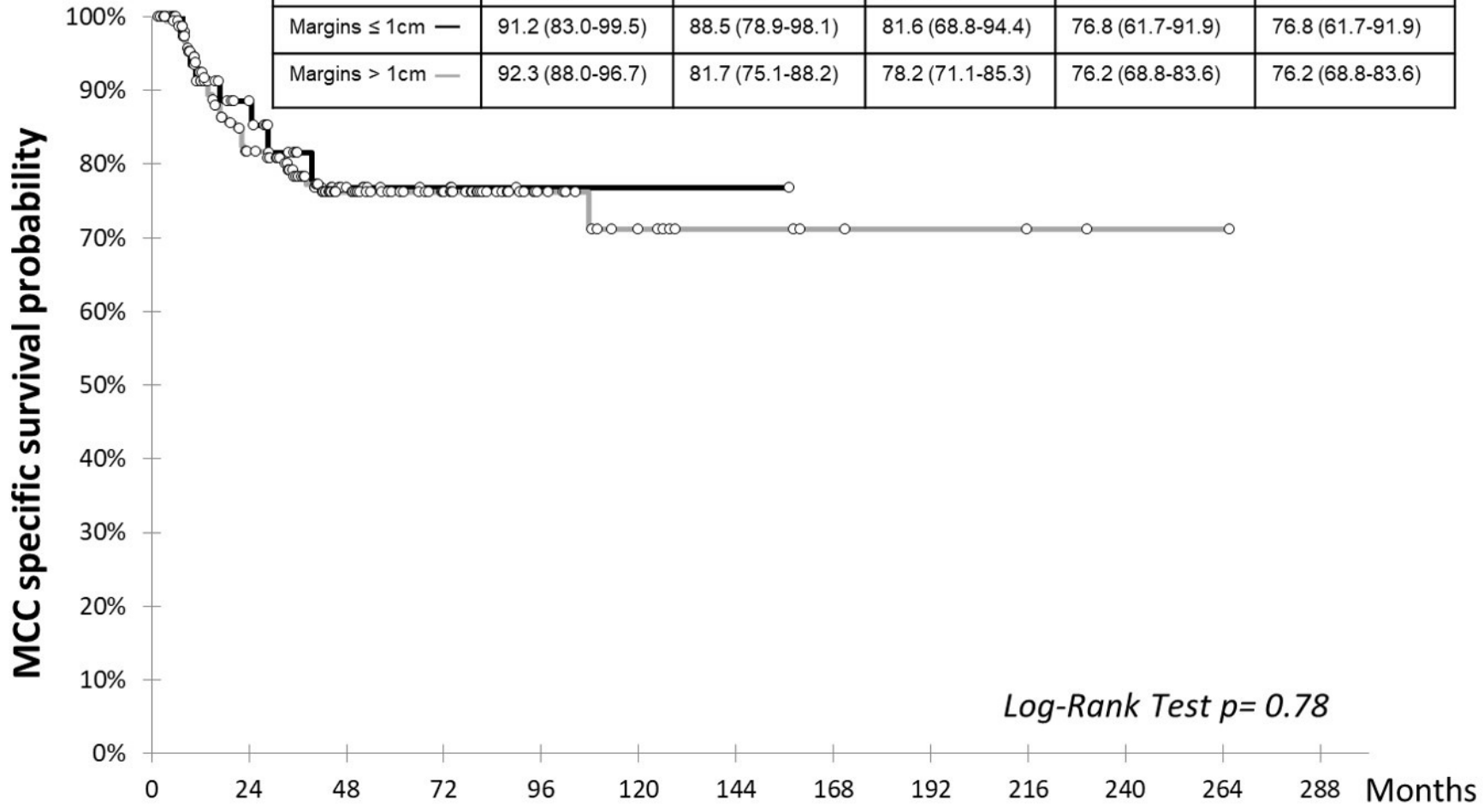
Figure 1. Flow chart diagram. Of the 357 patients included in the cohort, 214 patients had wide local excision of primary tumor with minimal margins of 0.5cm, and curative treatment of nodal disease when indicated.

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.


357 patients with Merkel Cell Carcinoma diagnosis included in the cohort between 1998 and 2019
112 patients excluded:
- No surgery of primary tumor (n=33) : regression of primary tumour (n=2), occult primary (n=22), exclusive radiotherapy (n=9)
- Stage IV AJCC (n=24)
- Two concomitant MCC primary tumors (n=1)
- Missing data at baseline and/or lost to follow up (n=54)
245 MCC patients who had surgery of a primary MCC tumor (local disease, n=187 ; nodal disease, n=58)
31 patients excluded:
- Surgical margins < 0.5cm (n=19)
- No treatment of nodal disease (n=7)
- Rapid progression of disease before treatment is completed (n=5)
214 MCC patients who had WLE of primary tumor and curative treatment of nodal disease when indicated (local disease, n=166 ; nodal disease, n=48)
58 MCC patients treated with narrow margins ≤1cm
156 MCC patients treated with wide margins >1cm
16 recurrences
15 deaths (8 from MCC)
56 recurrences
61 deaths (32 from MCC)

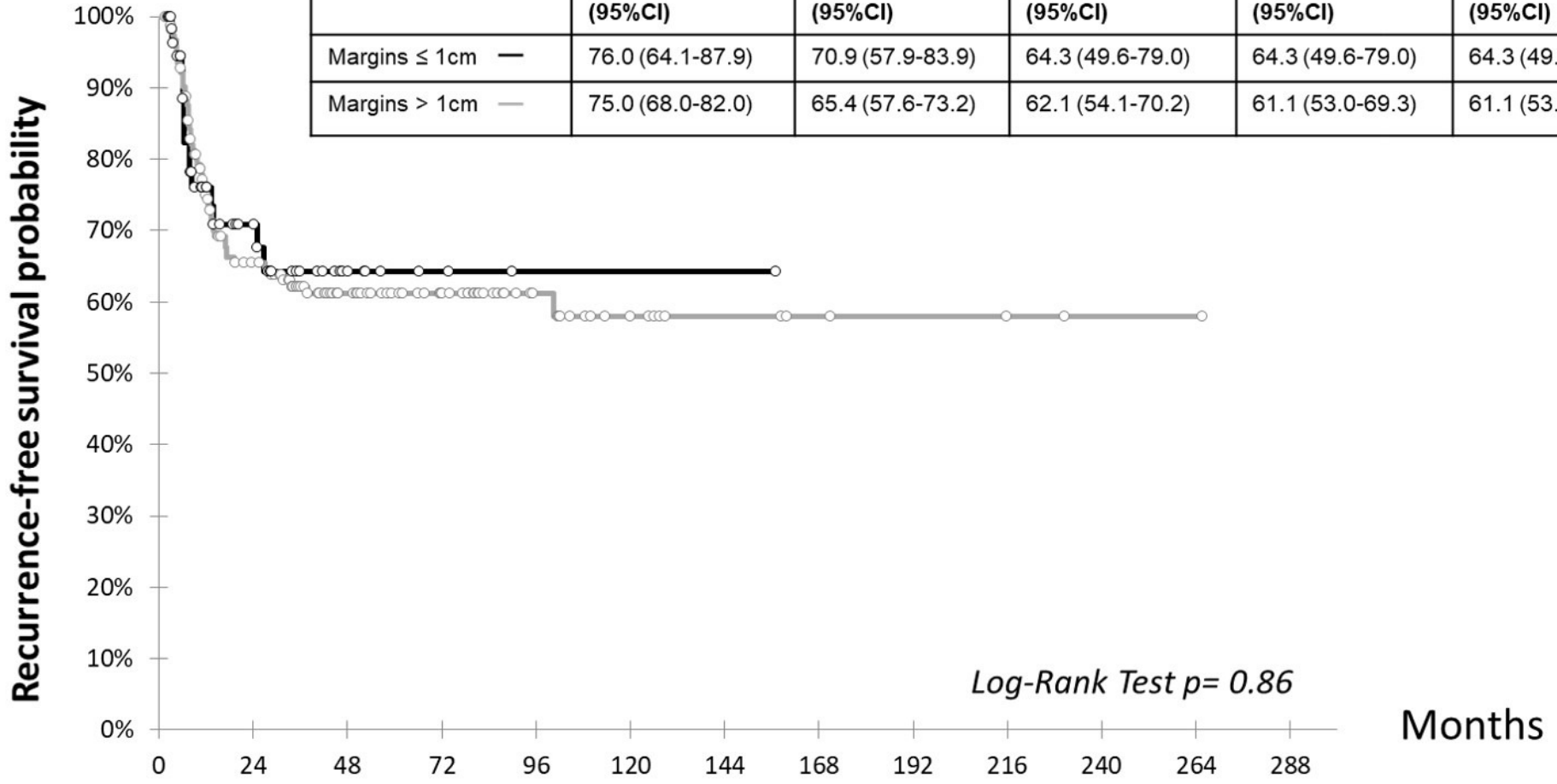
	1 y survival (95%CI)	2 y survival (95%CI)	3 y survival (95%CI)	4 y survival (95%CI)	5 y survival (95%CI)
Margins ≤ 1cm	91.2 (83.0-99.5)	88.5 (78.9-98.1)	81.6 (68.8-94.4)	76.8 (61.7-91.9)	76.8 (61.7-91.9)
Margins > 1cm	92.3 (88.0-96.7)	81.7 (75.1-88.2)	78.2 (71.1-85.3)	76.2 (68.8-83.6)	76.2 (68.8-83.6)



Nb at risk

Margins ≤ 1cm	58	30	11	5	2	2	2	1					
Margins > 1cm	156	103	64	45	21	11	7	6	4	3	2	2	1

	1 y survival (95%CI)	2 y survival (95%CI)	3 y survival (95%CI)	4 y survival (95%CI)	5 y survival (95%CI)
Margins ≤ 1cm	76.0 (64.1-87.9)	70.9 (57.9-83.9)	64.3 (49.6-79.0)	64.3 (49.6-79.0)	64.3 (49.6-79.0)
Margins > 1cm	75.0 (68.0-82.0)	65.4 (57.6-73.2)	62.1 (54.1-70.2)	61.1 (53.0-69.3)	61.1 (53.0-69.3)



Nb at risk

Margins ≤ 1cm	58	24	9	4	2	2	2	1	1	1	1	1	1
Margins > 1cm	156	85	52	37	20	11	7	5	4	3	2	2	1