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

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Background: Merkel cell carcinoma (MCC) management typically includes surgery with or without adjuvant radiation therapy (aRT). Major challenges include determining surgical margin size and whether aRT is indicated.

Objective: To assess the association of aRT, surgical margin size, and MCC local recurrence.

Methods: Analysis of 188 MCC cases presenting without clinical nodal involvement.

Results: aRT-treated patients tended to have higher-risk tumors (larger diameter, positive microscopic margins, immunosuppression) yet had fewer local recurrences (LRs) than patients treated with surgery only (1% vs 15%; P = .001). For patients who underwent surgery alone, 7 of 35 (20%) treated with narrow margins (defined as ≤1.0 cm) developed LR, whereas 0 of 13 patients treated with surgical margins greater than 1.0 cm developed LR (P = .049). For aRT-treated patients, local control was excellent regardless of surgical margin size; only 1% experienced recurrence in each group (1 of 70 with narrow margins ≤1 cm and 1 of 70 with margins >1 cm; P = .56).

Limitations: This was a retrospective study.

Conclusions: Among patients treated with aRT, local control was superb even if significant risk factors were present and margins were narrow. We propose an algorithm for managing primary MCC that integrates risk factors and optimizes local control while minimizing morbidity. (J Am Acad Dermatol 2021;84:340-7.)

Key words: adjuvant radiation; controversy, margin size; excision; local disease; local recurrence; Merkel cell carcinoma; nonmelanoma skin cancer; surgical margins; radiation; radiation therapy.

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Merkel cell carcinoma (MCC) is a rare, aggressive cutaneous neuroendocrine malignancy. In 2015, there were approximately 2500 cases/year; this is expected to increase to 3300 by 2025.[1] Approximately 65% of patients with MCC present with localized disease based on national cancer registry data.[2] Published local recurrence (LR) rates are highly variable because historical cohorts are retrospective, heterogenous, and often combine LRs with in transit and regional recurrences. Nevertheless, LRs arise in approximately 4% to 30% of patients.[3-7]

Current guidelines for the treatment of primary cutaneous MCC include wide local excision, sentinel lymph node biopsy (SLNB) for pathologic staging, and consideration of adjuvant radiation therapy (aRT). The National Comprehensive Cancer Network (NCCN) currently recommends wide local excision, "1- 2-cm margins to investing fascia of muscle or pericranium should be performed when clinically feasible and with consideration of possible morbidity" (p MS-17).[8] However, there is no consensus on the appropriate surgical margin size.

Prior studies on the relationship between surgical margin size and LR have yielded seemingly conflicting results. An early study found a trend toward fewer recurrences in patients treated with surgical margins greater than 3.0 cm.[9] However, more recent studies found no difference in LR rates when comparing margins of 1.0 cm or less versus greater than 1.0 cm[3,5] or margins of greater than 2.0 cm versus 2.0 cm or less.[4,5] A relevant limitation of some prior studies is that they do not separately consider surgical margins in the absence and presence of aRT. This is important because numerous studies indicate that aRT markedly decreases the rate of LR.[10-13]

An exception is a study of 179 Canadian patients with MCC by Harrington et al[14] in which patients were separated based on aRT status. They found that patients treated with aRT had a low LR rate regardless of margin size.[14] A separate study of low-risk patients with MCC (primary tumor of <2 cm) who did not receive aRT also found a low (<1%) recurrence rate regardless of margin size.[15]

We sought to determine the relationship between surgical margin size, aRT, and local disease control in a large, single-center cohort of patients who presented with a primary cutaneous MCC tumor.

CAPSULE SUMMARY

- Surgical margin size in Merkel cell carcinoma is controversial; however, we found that if adjuvant radiotherapy is given, patients with narrow or even microscopically positive margins have excellent local disease control.
- If adjuvant radiotherapy therapy is planned, narrower surgical margins are adequate, reduce morbidity, and minimize delay in initiating radiotherapy.

METHODS

We performed a retrospective analysis using a Seattle-based repository of more than 1400 patients with MCC that has been enrolling individuals since 2003. We included patients with MCC with local and SLNB-detected microscopic nodal disease and excluded patients who had advanced disease including muscle/bone invasion, clinically/radiologically evident nodal disease, and metastatic disease. Patients were excluded if surgical margin, radiation therapy, and follow-up data were unavailable. Patients enrolled more than 180 days from diagnosis were excluded to eliminate ascertainment bias associated with late referral to a tertiary center that could diminish how accurately the cohort represents the natural history of the disease.

Clinical characteristics collected included age, sex, stage, site of primary tumor (head/neck vs trunk/extremities), size of primary tumor (≤1 cm, 1-2 cm, or >2 cm), and presence of immunosuppression (HIV, organ transplant, hematologic malignancy, or chronic use of T-cell immunosuppressive medication[16]). Treatment characteristics were obtained through chart review. Patients were separated based on whether they received aRT to the primary tumor bed after undergoing surgery. These groups were further separated by surgical margin size of the primary tumor as noted in operative reports (≤1 cm vs >1 cm) (Fig 1). Patients who underwent Mohs micrographic surgery were excluded.

Recurrences were categorized into 4 groups: local, in transit, regional, and metastatic. *Local* was a recurrence arising within or adjacent to the primary excision scar and within 2 cm of the primary tumor site; *in transit* was a cutaneous/subcutaneous lesion not involving regional lymph nodes and arising more than 2 cm from the primary scar; *regional* was a lesion arising in the draining lymph node basin; and *metastatic* lesions occurred beyond the draining lymph node basin.

Statistical analyses were performed using Stata software, version 14.0 (StataCorp, College Station, TX). Fisher's exact or Wilcoxon rank sum tests were used to compare clinical and tumor characteristics. LR outcomes were measured by the permutation test, with nonlocal MCC recurrences and death as competing risks.

Abbreviations used:

aRT:	adjuvant radiation therapy
LR:	local recurrence
MCC:	Merkel cell carcinoma
NCCN:	National Comprehensive Cancer Network
SLNB:	sentinel lymph node biopsy

A *P* value of less than .05 was considered to be statistically significant. Competing risk regression curves were used to represent local recurrence-free survival. Patients were grouped based on their aRT status and margin size. Local recurrence-free survival was defined as the length of time from the surgery date to the date of MCC LR, last follow-up, or death. All studies were performed in accordance with Declaration of Helsinki principles and were approved by the Fred Hutchinson Cancer Research Center Institutional Review Board (no. 6585).

RESULTS

Patient and tumor characteristics

A total of 188 patients were identified from the repository, of whom 140 were treated with surgery and aRT and 48 were treated with surgery alone (Fig 1). The majority of patients were male, 65 years or older, and immunocompetent. Of the patients who underwent successful SLNB, 24% had pathologic evidence of tumor invasion into the lymph nodes (Table I). The median follow-up for the entire cohort was 4 years (range, 42 days to 12 years).

The majority of patients had surgical margins of either 1 cm (81 patients) or 2 cm (59 patients), with the remaining 48 patients having other margin sizes. For several known risk factors, patients who received aRT had higher-risk tumors compared to patients who received surgery alone. Specifically, tumor size was larger for aRT-treated patients (29% of tumors ≥2 cm vs 8% for patients treated with surgery alone; $P < .001$). In addition, aRT-treated patients had higher-stage (IIIA) tumors (30% compared to 6.2% in the surgery-only group; $P = .001$). However, they were less likely to have the primary tumor on the head/neck (26% vs 63% in the surgery-only cohort; $P < .001$). Patients who received aRT with surgical margins of 1 cm or less were more likely to have a primary tumor on the head and neck ($P < .003$) and smaller primary tumor size ($P < .020$). For patients who received surgery only to the primary tumor, the only significant difference in patient characteristics between margin groups was that patients with tumors on the head and neck were more likely to receive smaller surgical margins ($P = .049$) (Table I).

Local recurrences

Among the 188 patients, there were 9 LRs (Table II). aRT-treated patients had fewer LRs than patients with surgery only (1 vs 15%, $P = .001$). After adjustment for margin size and aRT status, more LRs occurred on the head/neck versus trunk/extremities ($P = .013$) (Table II). Seven of the 9 patients with LR had salvage therapy with surgery and/or radiation, and in 1 case also immunotherapy.

In the 140 patients treated with surgery and aRT, 2 LRs occurred; for the smaller margin group, there was 1 LR on the head/neck, and for the larger surgical margin group, there was 1 LR on the lower limb. There was no statistically significant difference in local recurrence-free survival between the surgical margin groups ($P = .56$) (Fig 2).

In the 48 patients treated with surgery only, 7 LRs occurred, all of which were on the head/neck. There were 7 recurrences in the smaller margin group and none in the larger margin group. There was a significant difference in local recurrence-free survival between the surgical margin size groups ($P = .049$) (Fig 2).

MCC-specific survival

In addition to the 9 LRs, there were 8 in transit, 15 nodal, and 22 distant recurrences. Thirty-seven patients died during follow-up; 21 of these deaths were caused by MCC. Although LR was the focus of this study, we also looked at MCC-specific survival. We saw no difference in MCC-specific survival between the aRT-treated and the surgery-only groups ($P = .22$). Furthermore, within each of these groups, wide versus narrow margin size was not associated with MCC-specific survival, and results were similar when adjusted for immunosuppression, tumor size, and head/neck primary tumor.

DISCUSSION

Previous studies have shown that wider surgical margins are associated with improved local control of MCC. However, the vast majority of these studies did not report whether or not patients also received aRT, a treatment known to be highly effective in MCC local control. This is relevant because aRT is frequently included in MCC management. Specifically, 54% of MCC patients in the National Cancer Database received aRT.[17] In our Seattle-based repository, among patients who had no evidence of distant metastatic disease, 92% of 826 patients received aRT to the primary site (database accessed February 2019). Whether or not aRT is included in initial management could significantly affect the appropriate surgical margin size in MCC. Indeed, the findings presented here support the

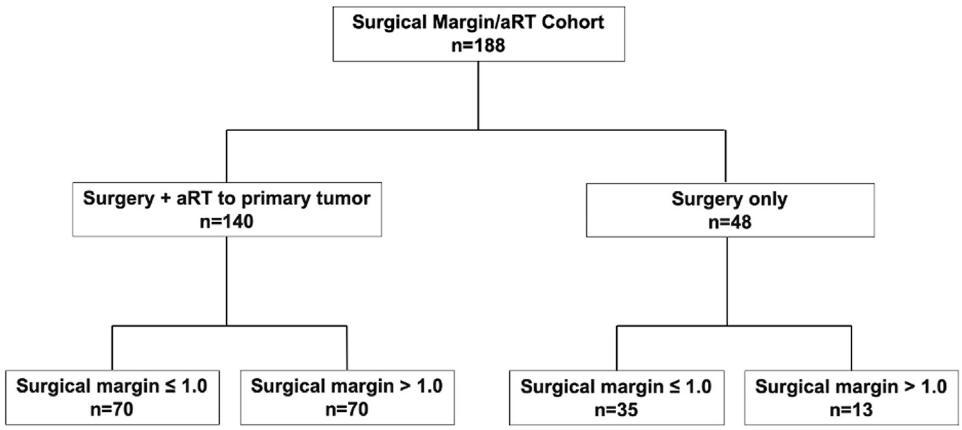

Fig 1. Flowchart of patients with MCC included in this surgical margin/aRT cohort. All 188 patients met the following 5 entry criteria: local-only MCC by clinical examination at diagnosis (stages: pathologic, I; clinical, I; pathologic, IIA; clinical, IIA; pathologic, IIIA), underwent primary lesion excision, aRT status available, surgical margin status available, and enrolled within 180 days from diagnosis. *aRT*, Adjuvant radiation therapy; *MCC*, Merkel cell carcinoma.

Table I. Comparison of clinical and tumor characteristics between all patients and specified subgroups

		Surgery + aRT			Surgery only		
Variables	**All patients**	**Margins ≤ 1 cm**	**Margins > 1 cm**	***P* value***	**Margins ≤ 1 cm**	**Margins > 1 cm**	***P* value***
n	188	70	70		35	13	
Female sex, n (%)	72 (38.3)	26 (37.1)	22 (31.4)	.59	16 (45.7)	8 (61.5)	.52
Age ≥ 65 y, n (%)	121 (64.4)	44 (62.9)	46 (65.7)	.86	24 (68.6)	7 (53.8)	.50
Immunosuppressed, n (%)	18 (9.6)	10 (14.3)	5 (7.1)	.27	3 (8.6)	0 (0.0)	.55
Nodal stage (path stage IIIA), n (%)†	45 (23.9)	17 (24.3)	25 (35.7)	.20	2 (5.7)	1 (7.7)	>.99
Head and neck primary tumor, n (%)‡	66 (35.1)	26 (37.1)	10 (14.3)	.003	25 (71.4)	5 (38.5)	.049
Size of primary tumor, cm, n (%)§				.020			.92
≤1	82 (44.1)	30 (42.9)	18 (26.5)		25 (71.4)	9 (69.2)	>.99
1-2	60 (32.3)	25 (35.7)	25 (36.8)		7 (20.0)	3 (23.1)	
≥2	44 (23.7)	15 (21.4)	25 (36.8)		3 (8.6)	1 (7.7)	
SLNB performed, n (%)	164 (87.2)	63 (90.0)	65 (92.9)	.76	25 (71.4)	11 (84.6)	.47
Unknown	36 (19.1)	13 (18.6)	17 (24.3)		3 (8.6)	3 (23.1)	

aRT, Adjuvant radiation therapy; *SLNB*, sentinel lymph node biopsy.
*Fisher's exact test or the Wilcoxon rank sum test (size of primary tumor).
†Compared to local stage of diagnosis.
‡Compared to primaries on extremities and trunk.
§Two patients did not have a tumor size available.

concept that wider surgical margins are not indicated for patients who will receive aRT.

A recent summary of the current literature on this topic suggested that the appropriate surgical margin size for primary MCC is 1- to 3 cm.[18] However, wide margins often cause significant morbidity[5,19] and can delay the start of aRT if a graft or flap is required for closure.[5] The 2020 NCCN guidelines recommend "wide excision with 1- to 2-cm margins to investing fascia of muscle or pericranium when clinically feasible" (p MS-17) but also note that if aRT is planned, then primary closure should be prioritized over wider margins.[8]

Consistent with the existing literature, in the present cohort, among patients treated with only surgery, margin size did affect the risk of LR: 20% of patients who were treated with a smaller (≤1 cm) surgical margin developed LR compared to 0% of patients with a larger (>1 cm) surgical margin. These findings are concordant with a study of 179 patients with MCC in British Columbia[14] in which surgical margin size mattered only among patients who did not receive aRT. Specifically, in the Canadian study, among patients who had narrow margin excision (<1 cm), only 5% (1/19) had LR if they received aRT, whereas 25% (3/12) who did not receive aRT

Table II. Characteristics of 9 patients who experienced local recurrence of MCC

Patient ID*	aRT	Age and sex	Stage†	Site of primary tumor	Size of primary tumor, cm	Surgical margin, cm	LVI	Narrowest radial margin via pathology, cm
1	No	73 M	C-I	Head and neck	0.7	0.5	Unknown	No residual tumor
2		59 F	P-I	Head and neck	0.5	1.0	Unknown	0.2
3		76 M	P-I	Head and neck	0.5	1.0	Absent	No residual tumor
4		58 M	P-I	Head and neck	0.5	1.0	Absent	No residual tumor
5		84 M	P-I	Head and neck	0.4	1.0	Absent	No residual tumor
6		80 M	P-I	Head and neck	0.8	1.0	Present	0.4
7		70 F	P-I	Head and neck	0.6	1.0	Absent	0.4
8	Yes	71 F	P-IIA	Lower limb	2.4	2.0	Unknown	Unknown
9		67 M	P-I	Head and neck	0.8	1.0	Absent	Unknown

aRT, Adjuvant radiation therapy; *C*, clinical; *ID*, identification; *LVI*, lymphovascular invasion; *MCC*, Merkel cell carcinoma; *P*, pathologic.
*Stage is according to American Joint Committee on Cancer staging system, 8th edition.
†No patients were immunosuppressed.

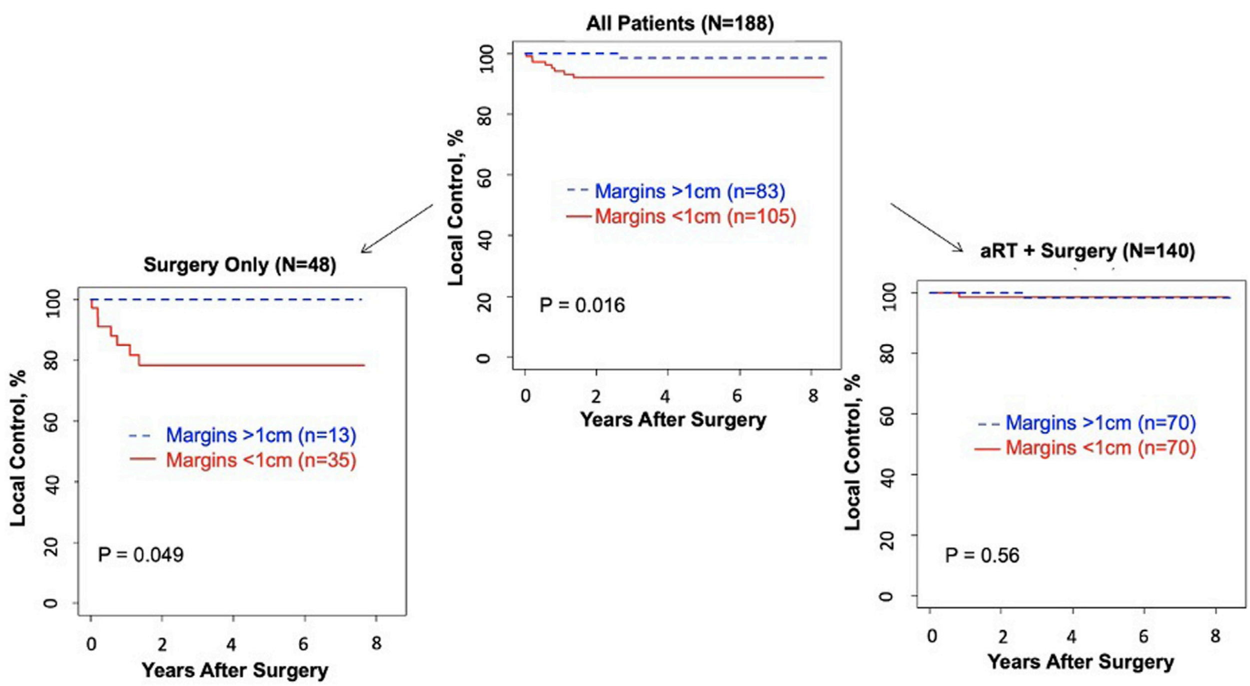

Fig 2. Control of Merkel cell carcinoma at the primary site as a function of surgical margin size and whether or not adjuvant radiation was given. Cumulative incidence curves are shown, with death and any nonlocal Merkel cell carcinoma recurrence being competing risks.

had LR.[14] Also similar to the present study, among patients who had surgical margins of 1.0 cm or greater, there was no improved local control with the addition of aRT.[14] In contrast, most of the existing literature does not separately consider whether or not patients received aRT. Interpretation of appropriate margin size from studies that do not describe aRT status is not feasible because of the high efficacy of aRT in controlling local disease. For example, in one of the larger studies, Allen et al[3] found no difference in LR rate when comparing margins of less than 1 cm versus 1 cm or greater, but the margin analysis was not stratified based on whether or not patients received aRT,[7] making it difficult to interpret the relationship between margin size and local control.

In the present study, head and neck primary tumors were associated with a higher risk of LR compared to those on the trunk and extremities, with 89% (8/9) of LRs occurring on the head or neck. The head/neck is a unique site where tissue-sparing surgery is important to optimize cosmetic and functional outcome but also where radiation adverse effects could be morbid, especially in elderly

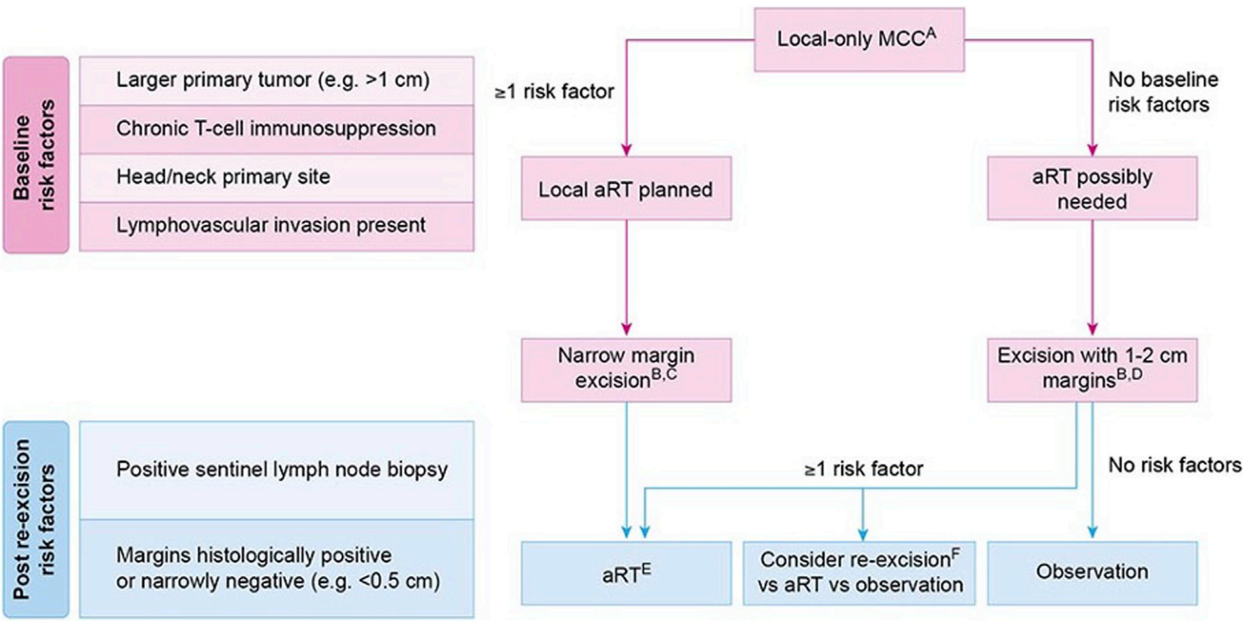

Fig 3. Suggested local MCC treatment management. This flowchart integrates treatment options with risk factors that are associated with local recurrence. Certain risk factors are available at the time of diagnosis (baseline), whereas others are available only after surgical excision (post re-excision). [A]Criteria for local-only MCC were as follows: clinically node negative, no in transit disease, and imaging negative for distant disease. [B]Sentinel lymph node biopsy was typically performed at this time. [C]Narrow excision margins minimize morbidity, and if aRT is performed microscopically positive margins are acceptable. [D]The goal should be primary tissue closure (ie, without a flap or graft) allowing aRT initiation within 3 to 4 weeks.[5,19,20] [E]If the sentinel lymph node biopsy result is positive, nodal aRT would typically be given in addition to primary site aRT. [F]The decision on re-excision is based on clinical setting (narrow path margins, eg, <0.5 cm) and patient preference: re-excision versus aRT versus observation. *aRT,* Adjuvant radiation therapy; *MCC,* Merkel cell carcinoma.

patients. In a retrospective study of 46 low-risk (primary tumor ≤ 2 cm, immunocompetent, negative SLNB results, negative pathologic margin results) head and neck tumors from the Seattle repository, the addition of aRT to the primary site significantly reduced LRs compared to surgery only.[13] Furthermore, in a separate study of 106 patients with head/neck MCC, when aRT was included, local control was more than 96%.[21] In a Tampa-based, single-institution study of 113 patients with head/neck MCC, aRT was associated with improved local control (3-year local control of 89% vs 68% with surgery only; $P = .005$).[22] In summary, multiple studies suggest that head and neck MCC tumors are at higher risk of recurrence after surgical monotherapy (perhaps because of limitations of margin size for this site) and that aRT should be considered for these tumors.

Given the important cosmetic and functional considerations for head and neck MCC management, Mohs micrographic surgery is often considered. Currently, NCCN guidelines do not routinely recommend Mohs surgery for MCC, in part because SLNB is often indicated,[8,23,24] requiring separate hospital-based surgical procedures in addition to Mohs surgery. The findings from the present study suggest that in the absence of aRT, the unique ability of Mohs surgery to attain narrow, pathologically negative surgical margins may not be as beneficial for MCC as for other skin cancers, because MCC often recurs beyond pathologically negative margins (multiple patients had LR after pathologically negative excision) (Table II).

Based on the results presented here and in the existing literature, we have created a treatment algorithm (Fig 3) to aid clinicians in determining the appropriate management for primary MCC tumors. Using clinical factors such as primary tumor size, primary site, and immunosuppression status, this algorithm first separates patients into a higher-risk group for which aRT is indicated. Such patients can then avoid the morbidity of wide surgical margins and potential delays in initiating aRT. For lower-risk patients who may not need aRT, clinicians may consider a wider margin with primary closure at the time of SLNB. Depending on the pathology results of excision and SNLB, aRT may not be indicated.

Although aRT decreased LR among patients with narrower surgical margins (<1 cm), there was no difference in disease-specific survival. The findings presented here and from the literature[14] show that for low-risk MCCs, surgical margins of greater than 1 cm are sufficient and that aRT is not required for excellent local disease control. In contrast, if narrow surgical margins are required to reduce morbidity and obtain primary closure, there is agreement that aRT can provide excellent local control. In terms of whether survival can be affected by aRT, the present study did not observe this association. However, 3 cancer registry studies that were far larger than our study showed that aRT was associated with significantly better overall survival.[12,17,25] It is possible that with a larger sample size, we might have detected survival differences based on whether or not aRT was given. Although links to survival are controversial, current evidence suggests that optimal local control (sometimes involving aRT) can minimize LRs. This is beneficial because LR leads to patient anxiety, increased medical costs, and salvage therapies that can increase morbidity.

Limitations of this study are its retrospective design and unavailable clinical data for some cases (50/188 patients lacked pathologic margin size, and 2/188 lacked primary tumor size). Because the sample size for the surgery-only group was 48, further subgrouping of surgical margin size was not statistically feasible. Also, because our site is a tertiary referral center for MCC, patients in this cohort often received their treatment closer to their homes. This cohort represents a heterogeneous group with regard to surgery and radiation therapy techniques.

This study lends support to earlier literature that suggests if localized cutaneous MCC is also treated with aRT, then narrow surgical margins are sufficient. Although this study indicates that aRT plays an important role in the management of higher-risk MCC tumors, it is possible that emerging approaches in aRT (eg, a single fraction of 8-Gy radiation[26]) may provide good local control with markedly diminished morbidity and enhanced patient convenience. As summarized in the flowchart (Fig 3), we believe that surgical margins for patients with MCC should be determined with careful consideration of risk factors and the potential role of aRT in optimizing a patient's outcome.

REFERENCES

1. Paulson KG, Park SY, Vandeven NA, et al. Merkel cell carcinoma: current US incidence and projected increases based on changing demographics. *J Am Acad Dermatol*. 2018;78:457-463.
2. 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.
3. 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.
4. 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.
5. 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.
6. Medina-Franco H, Urist MM, Fiveash J, Heslin MJ, Bland KI, Beenken SW. Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases. *Ann Surg Oncol*. 2001;8:204-208.
7. Fields RC, Busam KJ, Chou JF, et al. Five hundred patients with Merkel cell carcinoma evaluated at a single institution. *Ann Surg*. 2011;254:465-473.
8. Merkel Cell Carcinoma (Version 1.2020). National Comprehensive Cancer Network. Accessed January 1, 2020. https://www.nccn.org/professionals/physician_gls/pdf/mcc.pdf
9. Yiengpruksawan A, Coit DG, Thaler HT, Urmacher C, Knapper WK. Merkel cell carcinoma. Prognosis and management. *Arch Surg*. 1991;126:1514-1519.
10. Lewis KG, Weinstock MA, Weaver AL, Otley CC. Adjuvant local irradiation for Merkel cell carcinoma. *Arch Dermatol*. 2006;142:693-700.
11. Jouary T, Leyral C, Dreno B, et al. Adjuvant prophylactic regional radiotherapy versus observation in stage I Merkel cell carcinoma: a multicentric prospective randomized study. *Ann Oncol*. 2012;23:1074-1080.
12. Mojica P, Smith D, Ellenhorn JD. Adjuvant radiation therapy is associated with improved survival in Merkel cell carcinoma of the skin. *J Clin Oncol*. 2007;25:1043-1047.
13. Takagishi SR, Marx TE, Lewis C, et al. Postoperative radiation therapy is associated with a reduced risk of local recurrence among low risk Merkel cell carcinomas of the head and neck. *Adv Radiat Oncol*. 2016;1:244-251.
14. 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.
15. 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.
16. Cook M, Baker K, Redman M, et al. Differential outcomes among immunosuppressed patients with Merkel cell carcinoma: impact of immunosuppression type on cancer-specific and overall survival. *Am J Clin Oncol*. 2019;42:82-88.
17. 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(9):djw042.

18. Tello TL, Coggshall K, Yom SS, Yu SS. Merkel cell carcinoma: an update and review: current and future therapy. *J Am Acad Dermatol*. 2018;78:445-454.
19. Garbutcheon-Singh KB, Veness MJ. The role of radiotherapy in the management of non-melanoma skin cancer. *Australas J Dermatol*. 2019;60:265-272.
20. Limawararut V, Leibovitch I, Sullivan T, Selva D. Periocular squamous cell carcinoma. *Clin Exp Ophthalmol*. 2007;35:174-185.
21. Bishop AJ, Garden AS, Gunn GB, et al. Merkel cell carcinoma of the head and neck: favorable outcomes with radiotherapy. *Head Neck*. 2016;38(Suppl 1):E452-E458.
22. Strom T, Naghavi AO, Messina JL, et al. Improved local and regional control with radiotherapy for Merkel cell carcinoma of the head and neck. *Head Neck*. 2017;39:48-55.
23. Fields RC, Busam KJ, Chou JF, et al. Recurrence and survival in patients undergoing sentinel lymph node biopsy for merkel cell carcinoma: analysis of 153 patients from a single institution. *Ann Surg Oncol*. 2011;18:2529-2537.
24. Lemos BD, Storer BE, Iyer JG, et al. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. *J Am Acad Dermatol*. 2010;63:751-761.
25. 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.
26. Cook MM, Schaub SK, Goff PH, et al. Postoperative, Single-Fraction Radiation Therapy in Merkel cell Carcinoma of the head and Neck. *Adv Radiat Oncol*. 2020;5(6):1248-1254.