Original Article

Recurrence After Complete Resection and Selective Use of Adjuvant Therapy for Stage I Through III Merkel Cell Carcinoma

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BACKGROUND: Merkel cell carcinoma (MCC) is a rare cutaneous neuroendocrine neoplasm whose natural history is poorly understood. Here, the authors describe their experience with a large cohort of patients who were treated at a single institution to describe patterns of recurrence after curative therapy. **METHODS:** Review of a prospective database was performed. Patient-related, tumor-related, and treatment-related variables were recorded, and the site and timing of initial recurrence were recorded. Factors associated with receipt of adjuvant therapy and recurrence were determined. **RESULTS:** In total, 364 patients with stage I through III MCC who underwent complete resection were identified. Adjuvant local radiation therapy (RT), lymph node RT, and chemotherapy were received selectively by 23%, 23%, and 15% of patients, respectively. Factors associated with the receipt of adjuvant therapy included younger age, primary tumor features (larger size, lymphovascular invasion [LVI], positive margin excision), and increasing pathologic stage. With median follow-up of 3.6 years, 108 patients (30%) developed a recurrence, including 11 local recurrences (3%), 12 in-transit recurrences (3%), 43 lymph node recurrences (12%), and 42 distant recurrences (12%). Clinically involved lymph nodes, primary tumor LVI, and a history of leukemia/lymphoma were predictive of recurrence. The majority of recurrences (80%) occurred in patients who had clinically involved lymph nodes or patients who did not undergo pathologic lymph node evaluation. **CONCLUSIONS:** A low recurrence rate in patients with clinically lymph node-negative MCC was achieved with adequate surgery (including sentinel lymph node biopsy) and the selective use of adjuvant RT for high-risk tumors. In contrast, patients with clinically lymph node-positive MCC had significantly higher rates of recurrence, especially distant recurrence. The authors concluded that contemporary natural history studies are critical in designing treatment pathways and clinical trials for MCC. ***Cancer*** **2012;118:3311-20.**

KEYWORDS: Merkel cell carcinoma, surgery, radiation therapy, chemotherapy, treatment, recurrence, outcomes.

INTRODUCTION

Merkel cell carcinoma (MCC) is a cutaneous neuroendocrine neoplasm that has a propensity for metastasis.[1-6] Described in 1972 by Toker[7] and with an age-adjusted incidence of <0.5 per 100,000 person-years,[1] MCC remains incompletely characterized. The staging, treatment, and follow-up of patients with MCC is based on single-institution reports[5,8-13] (usually with <100 patients) and database[2,4] and registry[14] series. However, there is no level 1 evidence to guide the care of patients with MCC.

Treatment of MCC includes surgery, radiation therapy (RT), and chemotherapy.[15-17] In patients who present with clinically localized MCC with no evidence of regional lymph node disease (stage I-II[18]), wide resection of the primary tumor is standard treatment. Pathologic examination of clinically negative regional lymph nodes (LNs) (using sentinel LN biopsy [SLNB]) is recommended for staging and to guide treatment.[4,19,20] In patients with clinically involved regional LNs (stage III), excision of the primary tumor and therapeutic LN dissection (TLND) is recommended.[21]

We demonstrated previously that disease stage at presentation and primary tumor lymphovascular invasion (LVI) are associated with disease-specific death in patients with MCC.[6,20] Here, we further examine the patterns of recurrence in

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patients who underwent treatment for stage I through III MCC. We describe their surgical and adjuvant therapy and analyze the variables associated with recurrence.

MATERIALS AND METHODS

Patients

Patients were identified from a database of patients with MCC who received treatment at Memorial Sloan-Kettering Cancer Center (MSKCC) from 1969 to 2010. The MSKCC Institutional Review Board approved the study design. All patients who were included in the analysis had histologically confirmed MCC reviewed by a dedicated dermatopathologist (K.J.B., M.P.P.).

Surgical Treatment

Surgical treatment of the primary tumor generally consisted of wide excision to negative margins. Before 1996, selected patients with clinically negative LNs underwent elective LN dissection (ELND). Since 1996, we have used SLNB (as described previously[3,20,22]) in place of routine ELND. Treatment after a positive SLNB was based on patient and treating physician preferences. Patients with clinically involved LNs either underwent therapeutic LN dissection (TLND) with or without *adjuvant* RT or received *therapeutic* RT alone (no surgery).

Pathologic Analysis

Staging is reported in accordance with the American Joint Committee on Cancer (AJCC) seventh edition (2010) staging system for MCC (Table 1).[18] Primary and SLNB MCC specimens were analyzed as previously described.[6,20,22,23] LVI was defined as the presence of tumor cells within lymphatic or vascular channels outside the main tumor mass.

Radiation Therapy

RT usually consisted of ≥50 grays (Gy) of external-beam RT for 5 days per week over a 5-week to 6-week course to the primary tumor, the primary tumor excision site, and/or the draining LN basin. *Therapeutic* RT was defined as RT to the primary tumor and/or regional LN basin *without* excision/resection, and *adjuvant* RT was defined as RT to the primary tumor site after wide excision and/or regional LN basin after LN dissection.

Chemotherapy

Chemotherapy consisted of a platinum agent, either alone or in combination with etoposide. Treatment was administered for a total of 4 to 6 cycles over 8 to 12 weeks.

Table 1. Summary of the 2010 American Joint Committee on Cancer Merkel Cell Carcinoma Staging System[a]

Stage	Description
IA	Primary tumor ≤2 cm; regional LN negative by pathologic examination[b]
IB	Primary tumor ≤2 cm; regional LN negative by clinical examination only[c]
IIA	Primary tumor >2 cm; regional LN negative by pathologic examination[b]
IIB	Primary tumor >2 cm; regional LN negative by clinical examination only[c]
IIIA	Primary tumor any size; positive micrometastasis in regional LN[d]
IIIB	Primary tumor any size; clinically detectable regional LN metastasis and/or in-transit metastasis[e]
IV	Primary tumor any size; any distant metastasis

Abbreviations: LN, lymph nodes.
[a] Adapted from 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.
[b] Negative sentinel lymph node biopsy (SLNB) or elective lymph node dissection (ELND).
[c] No pathologic LN evaluation (SLNB or ELND).
[d] Positive micrometastasis by SLNB or ELND.
[e] Confirmed pathologically by biopsy or therapeutic lymph node dissection.

Patients received chemotherapy surgical treatment (neoadjuvant for selected patients with stage III disease), or chemotherapy was initiated within 8 weeks of surgery or after RT, when given.

Follow-Up

Patients were followed every 3 to 4 months for 2 years and every 6 to 12 months thereafter. Recurrence was defined as any patient-discovered, physician-discovered, or radiographically discovered evidence of tumor. Recurrences were categorized as local (LR), in transit, regional LN, or distant recurrences. The date of recurrence was defined as the first notation in the medical record indicating the recurrence. The time to recurrence was defined as the interval from the date of surgery to the date of recurrence.

Statistical Analysis

Statistical analysis was performed using the statistical software packages SAS (version 9.2; SAS Institute, Inc., Cary, NC) and R (version 2.10.1; R Project for Statistical Computing, Vienna, Austria; available at: http://www.r-project.org [accessed October 18, 2011]). Chi-square and Wilcoxon rank-sum tests were used to examine differences in covariates between patients who did and did not receive adjuvant therapies. The cumulative incidence function was used to estimate probabilities of the interval from treatment to recurrence. Patients who died without a

recurrence were treated as competing events. Competing-risks regression was used to examine the factors correlated with recurrence and to build the multivariate model.[24,25] Characteristics with a P value $\leq .05$ were entered into a competing-risks regression model. LR, LN recurrence, and distant recurrence at 2 years were estimated using the cumulative incidence function. The Gray test was used to determine differences in cumulative incidence functions between types of adjuvant therapies.[26]

RESULTS

Patient Characteristics

Three hundred sixty-four patients with clinical stage I through III MCC were identified. All patients received treatment at MSKCC and were either diagnosed at or presented to MSKCC within 6 months of diagnosis. All patients underwent complete gross resection of their disease (R2 resections excluded). One-hundred seventy-two patients (47%) were diagnosed after 2002.

Table 2 lists patient, tumor/pathologic, and follow-up information for the study population. The median age at diagnosis was 70 years (interquartile range [IQR], 61-76 years). Two hundred seventy patients (74%) presented with clinically localized MCC, including 204 patients (56%) with clinical stage I disease and 66 patients (18%) with clinical stage II disease. Ninety-four patients (26%) presented with clinical stage III disease. Final pathologic stage included 95 patients with stage IA disease (36%), 78 patients with stage IB disease (21%), 21 patients with stage IIA disease (6%), 27 patients with stage IIB disease (7%), 49 patients with stage IIIA disease (13%), and 94 patients with stage IIIB disease (26%).

Surgical Treatment

Among the patients who underwent surgery of their primary tumor (excluding 37 patients with unknown primary tumors), 93% underwent a margin-negative excision. The median excision margin width was 10 mm (IQR, 9-20 mm). Of the 270 patients (74%) who presented with clinically negative LNs, 105 (39%) had no further LN treatment or evaluation. The remaining 165 patients underwent either ELND (23 patients; 9%), SLNB alone (122 patients; 45%), or SLNB followed by completion LN dissection (CLND) (20 of 49 patients who had a positive SLNB). Of the 94 patients (26%) who presented with clinically positive LNs and no evidence of metastatic disease, all underwent TLND.

Adjuvant Local Radiation Therapy

Adjuvant local RT was received by 75 patients (23% of the 326 patients with known primary tumors) (Table 3). Twenty of 153 patients (13%) with stage I MCC received adjuvant local RT compared with 15 of 48 patients (31%) with stage II MCC, 20 of 49 patients (41%) with stage IIIA MCC, and 20 of 56 patients (36%) with stage IIIB disease who had known primary tumors. Forty-nine of 162 patients (30%) who had primary tumor LVI received adjuvant local RT compared with 19 of 132 patients (14%) without LVI. Ten of 22 patients (45%) who underwent margin-positive (R1) excision received adjuvant local RT compared with 64 of 304 patients (21%) who underwent margin-negative excision.

Lymph Node Radiation Therapy

LN RT was received by 85 patients (23%) (Table 3). The receipt of LN RT increased with increasing pathologic stage. LN RT was received by 7 of 153 patients (5%) with stage I MCC, 7 of 48 patients (15%) with stage II MCC, 28 of 49 patients with stage IIIA MCC (17 patients [35%] received *therapeutic* LN RT after a positive SLNB with no further surgery and 11 patients [22%] received *adjuvant* LN RT after LND [either ELND or SLNB plus CLND]), and 43 of 94 patients (46%) with stage IIIB MCC received adjuvant LN RT after TLND.

Adjuvant Chemotherapy

Chemotherapy was received by 53 of 364 patients (15%) (Table 3). The median age of patients who received chemotherapy was 61 years (IQR, 54-70 years). All patients received cisplatin or carboplatin. Forty-eight patients (91%) received concurrent etoposide. Among the 221 patients with stage I/II disease, chemotherapy was received as adjuvant treatment by 3 patients (1%). In patients with pathologically involved LNs, chemotherapy was received as adjuvant treatment by 50 of 143 patients (35%), including 11 patients with stage IIIA disease (22%) and 39 patients with stage IIIB disease (41%).

Recurrence

At a median follow-up of 3.6 years (IQR, 1.3-7.2 years) for surviving patients, 108 patients (30%) developed a recurrence (Table 2). One hundred eight of 163 surviving patients (66%) had $\geq$2 years of follow-up. The cumulative incidence of recurrence at 2 years, 3 years, and 5 year was 29% (95% confidence interval [CI], 23%-33%), 30% (95% CI, 25%-35%), and 32% (95% CI, 26%-36%), respectively (Fig. 1A).

Table 2. Patient, Tumor, and Follow-Up Characteristics of 364 Patients With Clinical Stage I Through III Merkel Cell Carcinoma who Underwent Complete Resection at Memorial Sloan-Kettering Cancer Center

Variable	No. of Patients (%)
Median age at diagnosis [IQR], y	70 [61-76]
Sex	
Women	146 (40)
Men	218 (60)
Previous or synchronous other malignancy	175 (48)
Type of other malignancy, n = 175 patients[a]	
Leukemia/lymphoma	34 (20)
Skin malignancy (including melanoma)	109 (62)
Solid malignancy	54 (31)
Location of primary tumor	
Extremity	137 (38)
Head/neck	129 (36)
Trunk, torso, or buttock	61 (17)
Unknown	37 (9)
Primary tumor size, cm[b]	
≤2	246 (75)
>2	80 (25)
Median primary greatest tumor dimension [IQR], cm[c]	1.2 [8-20]
Primary tumor with lymphovascular invasion[c]	
Yes	162 (45)
No	132 (36)
Unknown	70 (19)
Clinical stage[d]	
I	204 (56)
II	66 (18)
III	94 (26)
Pathologic stage[d]	
IA	95 (36)
IB	78 (21)
IIA	21 (6)
IIB	27 (7)
IIIA	49 (13)
IIIB	94 (26)
Disease recurrence	
Yes	108 (30)
No	
Alive without recurrence	163 (44)
Died without recurrence	93 (26)
Site of first recurrence, n = 108 patients[f]	
Local	11 (3)[e]
In transit	12 (3)
Lymph node	43 (12)
Distant	42 (12)

Abbreviations: IQR, interquartile range.

[a] Twenty-eight patients had >1 prior or synchronous other malignancy and are recorded in multiple categories.

[b] Primary tumor size was measured in 327 patients who had primary tumor information available (excludes 38 patients who had unknown primary tumors).

[c] Staging was determined according to the *American Joint Committee Cancer Staging Manual*, 7th edition, 2010.

[d] Seven patients had synchronous recurrences at >1 site (3 in transit and lymph node recurrences and 4 local and lymph node recurrences) and are categorized in the lymph node group.

[e] There were 11 local recurrences among 327 patients (3%) who had known primary tumors (excluding 37 patients who had stage III disease with Merkel cell carcinoma of unknown primary origin).

Table 3. Receipt of Radiation Therapy and Chemotherapy in 364 Patients With Clinical Stage I Through III Merkel Cell Carcinoma who Underwent Complete Resection at Memorial Sloan-Kettering Cancer Center

	No. of Patients (%)					
			LN RT[a]		Chemotherapy[b]	
Pathologic Stage[c]	No RT	Local RT[a]	Therapeutic[d]	Adjuvant[d]	No	Yes
IA, n = 95	82 (86)	13 (14)	0 (0)	5 (5)	95 (100)	0 (0)
IB, n = 78	71 (91)	7 (9)	0 (0)	2 (3)	77 (99)	1 (1)
IIA, n = 21	16 (76)	5 (24)	0 (0)	3 (3)	21 (100)	0 (0)
II, n = 27	17 (63)	10 (37)	0 (0)	4 (15)	25 (93)	2 (7)
IIIA, n = 49	20 (41)	20 (41)	17 (35)	11 (22)	38 (78)	11 (22)
IIIB, n = 94	49 (52)	20 (36)[e]	0 (0)	43 (46)	55 (59)	39 (41)[f]
Total	255 (70)	75 (23)	17 (5)	68 (19)	311 (85)	53 (15)

Abbreviations: LN, lymph node; RT, radiation therapy.
[a] Fifty-one patients received a combination of adjuvant local RT and LN RT and are counted in both categories.
[b] Twenty-seven patients (7%) received combined chemoradiotherapy (1 with local RT, 14 with LN RT, and 12 with local and LN RT).
[c] Staging was determined according to the American Joint Committee (AJCC) *AJCC Cancer Staging Manual*, 7th edition, 2010.
[d] For the distinction between *therapeutic* RT and *adjuvant* LN RT, see Materials and Methods in the text..
[e] Adjuvant local RT was received by 20 of 57 patients with stage IIIB disease (35%) who had known primary tumors.
[f] Thirty patients (77%) received adjuvant chemotherapy, and 9 patients (23%) received neoadjuvant chemotherapy.

The distribution of first recurrence was as follows: There were 11 LRs (3% of all patients with known primary tumors, 10% of all recurrences), 12 in-transit recurrences (3% of all patients, 11% of all recurrences), 43 LN recurrences (12% of all patients, 40% of all recurrences), and 42 distant recurrences (12% of all patients, 39% of all recurrences). Seven patients (2% of all patients, 6% of all recurrences) had synchronous first recurrences (3 in-transit recurrences and LN recurrences, 4 LRs and LN recurrences) and were included in the LN recurrence group. The distribution of distant recurrence was as follows: There were 26 intra-abdominal recurrences (7% of all patients, 62% of all recurrences), 10 bone recurrences (3% of all patients, 24% of all recurrences), 6 lung recurrences (2% of all patients, 14% of all recurrences), 5 distant LN recurrences (1% of all patients, 12% of all recurrences), 1 brain recurrence (<1% of all patients, 2% of all recurrences), and 1 distant skin recurrence (<1% of all patients, 1% of all recurrences). Intra-abdominal recurrence locations included pancreas (12 recurrences; 46%), liver (10 recurrences; 38%), and other/multiple (4 recurrences; 15%).

The majority of recurrences (80%) developed in patients who had clinically involved LNs or in patients who did *not* undergo pathologic LN evaluation (Table 4). It is noteworthy that there were no LRs among the patients who underwent pathologic LN staging (stage IA, IIA, or IIIA) compared with 8 LRs (8%) in patients with stage IB and IIB disease. The LN recurrence rate was 6% in patients with clinically and pathologically negative LNs (stage IA and IIA) compared with 21% in patients clinically negative LNs who did not undergo pathologic LN staging (stage IB and IIB). In contrast, the rate of distant recurrence was similar for patients with stage IA and IIA disease and patients with stage IB and IIB disease (4% for both). The rates of LN recurrence (4%) and distant recurrence (6%) were low in patients who had microscopically positive LNs (stage IIIA). In contrast, the rates of LN recurrence and distant recurrence in patients who had clinically involved LNs (stage IIIB) were 13% and 32%, respectively. Of the 43 patients with stage IIIB disease who received adjuvant LN RT (46%), 3 developed an LN recurrence (7%), and 13 developed a distant recurrence (30%). Of the 51 patients with stage IIIB disease who did *not* receive adjuvant LN RT (54%), 9 (17%) developed an LN recurrence, and 17 developed a distant recurrence (33%).

Factors Associated With Any Recurrence

A diagnosis of lymphoma/leukemia, increasing stage, and receipt of any adjuvant therapy were associated with recurrence on univariate analysis (Table 5). In the multivariate model, a synchronous or previous diagnosis of lymphoma/leukemia and increasing pathologic stage remained significantly associated with recurrence. Compared with patients who had pathologic stage I MCC, patients who had stage II or IIIA MCC had similar incidences of recurrence. In contrast, patients who had stage IIIB MCC were 3.1 times more likely to have a recurrence of their MCC compared with those who had stage I disease ($P < .01$). In patients who presented with clinically negative LNs, those who underwent pathologic LN staging (stage IA and IIA) had a lower recurrence rate than

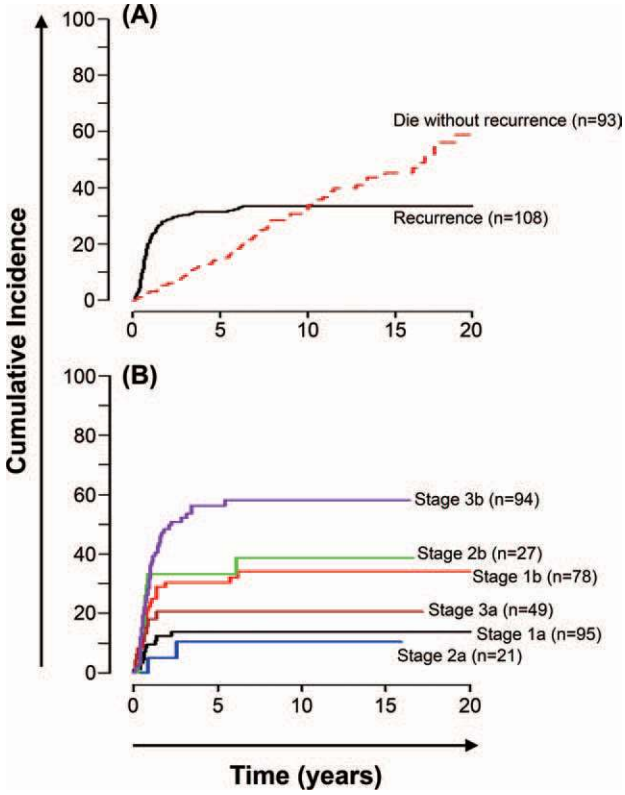

Figure 1. Disease recurrence is illustrated in 364 patients with clinical stage I through III Merkel cell carcinoma who underwent complete resection at Memorial Sloan-Kettering Cancer Center. The median follow-up for surviving patients was 3.6 years (interquartile range [IQR], 1.3-7.2 years). (A) Cumulative incidence of any recurrence or death without recurrence is illustrated. The cumulative incidence of recurrence was 29% (95% confidence interval [CI], 235%-33%) at 2 years, 30% (95% CI, 25%-35%) at 3 years, and 32% (95% CI, 26%-36%) at 5 years. (B) Cumulative incidence of any recurrence is illustrated according to pathologic stage. The cumulative incidence of recurrence at 2 years according to pathologic stage was 2% (95% CI, 5%-20%) for patients with stage IB disease, 30% (95% CI, 20%-40%) for patients with stage IB disease, there were not enough events to evaluate patients with stage IIA disease, 33% (95% CI, 15%-51%) for patients with stage IIB disease, 21% (95% CI, 9%-33%) for patients with stage IIIB disease, and 49% (95% CI, 38%-59%) for patients with stage IIIB disease.

those who only underwent clinical LN evaluation (stage IB and IIB) (Fig. 1B).

Of the 294 patients who had known LVI status, 85 (29%) developed a recurrence. It is noteworthy that, of the 132 patients who did *not* have LVI of their primary tumor (45% of total), only 2 patients (<2%) developed a recurrence. Of the 162 patients who were positive for LVI (55% of total), 83 (51%) developed a recurrence. Because of the very low frequency of recurrence *without* LVI (2 patients), LVI could not be entered into a multivariate model of factors associated with recurrence.

Associations Between Adjuvant Therapy and Specific Recurrence

The associations between LR and adjuvant local RT, between LN recurrence and LN RT, and between distant recurrence and chemotherapy were analyzed (Table 6). Because 90% of all recurrences developed within 2 years of follow-up, the cumulative incidence of recurrence (LR, LN recurrence, and distant recurrence) at 2 years was analyzed. Two-hundred ninety patients had ≥2 years of follow-up and were included in the cumulative incidence analysis. The median follow-up for 108 surviving patients with >2 years follow-up was 6.9 years (IQR, 2.0-23.4 years). There was no significant difference in the cumulative incidence of LR at 2 years between patients who were selected to receive adjuvant local RT (1.7%) compared with those who were not selected (3.8%; $P = .77$). There was no significant difference in the LN recurrence rate at 2 years between patients who were selected to receive LN RT (5.2%) compared with those who were not selected (13.8%; $P = .15$). Patients who were selected to receive chemotherapy were more likely to develop distant recurrence at 2 years compared with those who were not selected (30.5% vs 15.4%, respectively; $P = .02$). It is noteworthy that, of the 25 patients with stage IIIA disease who were included in this analysis, only 3 patients (12%) developed a distant recurrence. In contrast, of the 61 patients with stage IIIB disease, 24 patients (39%) developed a distant recurrence.

DISCUSSION

To our knowledge, this is the largest report to date describing recurrence in patients with MCC. In 2005, we reported on recurrence and survival in 251 patients with MCC.[3] Recently, we described the factors associated with disease-specific death[6] and reported on the use of SLNB in MCC.[20] Here, we completely describe patterns of recurrence in 364 patients who underwent surgery with or without adjuvant treatment for stage I through III MCC.

The National Comprehensive Cancer Network (NCCN) *Clinical Practice Guidelines in Oncology* for MCC recommends *consideration* of adjuvant local RT for all patients with MCC and LN RT as either primary or adjuvant therapy after CLND in patients who have evidence of LN metastases.[21] However, there is no level 1 evidence to guide its application.[27-31] In the largest series

Table 4. Recurrence by Pathologic Stage in 364 Patients With Clinical Stage I Through III Merkel Cell Carcinoma who Underwent Complete Resection at Memorial Sloan-Kettering Cancer Center

	Type of Recurrence: No. of Patients (%)				
Pathologic Stage[a]	None, n = 256	Local, n = 11	In Transit, n = 12	LN, n = 43	Distant, n = 42
IA, n = 95	84 (88)	0 (0)	1 (1)	7 (7)	3 (3)
IB, n = 78	53 (68)	6 (8)	1 (1)	16 (21)	2 (3)
IIA, n = 21	19 (90)	0 (0)	0 (0)	0 (0)	2 (10)
IIB, n = 27	17 (63)	2 (7)	0 (0)	6 (22)	2 (7)
IIIA, n = 49	40 (82)	0 (0)	4 (8)	2 (4)	3 (6)
IIIB, n = 94	43 (46)	3 (5)[b]	6 (6)	12 (13)	30 (32)
Total	256 (70)	11 (3)	12 (3)	43 (12)	42 (12)

Abbreviations: LN, lymph node.
[a] Staging was determined according to the *American Joint Committee Cancer Staging Manual*, 7th edition, 2010.
[b] Local recurrences developed in 3 of 57 patients with stage IIIB disease who had known primary tumors (the analysis excluded 37 patients with stage IIIB disease who had unknown primary tumors).

Table 5. Variables Associated With Recurrence in 364 Patients With Clinical Stage I Through III Merkel Cell Carcinoma who Underwent Complete Resection at Memorial Sloan-Kettering Cancer Center

	Univariate Model		Multivariate Model	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Increase in age at diagnosis per 10-y increase	1.1 (0.89-1.9)	.45		
Sex				
Women, N = 146	1.2 (0.8-1.8)	.34		
Men, N = 218	1.0			
Other malignancy				
Leukemia/lymphoma, N = 34	2.0 (1.1-3.4)	<.01[a]	2.0 (1.2-5.1)	.01[a]
Other, N = 141	0.80 (0.50-1.2)		0.80 (0.51-1.2)	
No, N = 189	1.0		1.0	
Location of primary tumor				
Unknown primary, N = 37	1.6 (0.97-2.59)	.07		
Known primary, n = 327	1.0			
Primary tumor greatest dimension per 1-cm increase[b]	1.1 (0.97-1.33)	.24		
Primary tumor lymphovascular invasion[b]	NA[c]			
Yes, n = 162				
No, n = 132				
Unknown, n = 33				
Primary tumor excision margin status[b]				
Positive, n = 22	1.1 (0.48-2.68)	.77		
Negative (n = 304)	1.0			
Primary tumor excision margin width per 1-cm increase in margin width[b]	1.1 (0.78-3.4)	.56		
Pathologic stage[d]				
IIIB, n = 94	2.9 (1.9-4.4)	<.01[a]	3.1 (1.8-6.1)	<.01[a]
IIIA, n = 49	1.0 (0.46-2.1)		1.0 (0.46-2.2)	
IIA or IIB, n = 48	1.1 (0.58-2.2)		1.1 (0.56-2.2)	
IA or IB, n = 173	1.0		1.0	
Adjuvant therapy				
Yes, n = 135	1.5 (1.01-3.5)	.04[a]	0.91 (0.58-1.4)	
No, n = 229	1.0		1.0	.695

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not available.
[a] Significant *P* value.
[b] The analysis included 327 patients who had primary tumor information available and excluded 37 patients who had unknown primary tumors.
[c] Univariate and multivariate analysis using lymphovascular invasion as a modeling variable could not be performed, because only 2 patients *without* lymphovascular invasion had recurrent Merkel cell carcinoma (for further details, see text).
[d] Staging was determined according to the *American Joint Committee Cancer Staging Manual*, 7th edition, 2010.

Table 6. Associations Between Adjuvant Therapy and Recurrence in Patients With Clinical Stage I Through III Merkel Cell Carcinoma who Underwent Complete Resection With a Minimum 2 Years of Follow-Up at Memorial Sloan-Kettering Cancer Center

Treatment	Recurrence: No. of Patients		Cumulative Incidence at 2 Years: (95% CI), %	*P*
	Yes	No		
LR at 2 years[a]				
Total	11	316		
Local RT, n = 75	2	73	1.7 (0-5.2)	.77
No local RT, n = 252	9	243	3.8 (1.3-6.2)	
LN recurrence at 2 y				
Total	43	321		
LN RT, n = 85	6	79	5.2 (1.0-11.5)	.15
No LN RT, n = 279	37	242	13.8 (9.8-18.1)	
Distant recurrence at 2 y[b]				
Total	33	110		
Chemotherapy, n = 94	17	77	30.5 (16.9-44)	.02[c]
No chemotherapy, n = 49	16	33	15.4 (7.6-23)	

Abbreviations: CI, confidence interval; DR, distant recurrence; LN, lymph node; LR, local recurrence RT, radiation therapy.
[a] The evaluation included 327 patients who had primary tumor information available and excluded 37 patients with unknown primary tumors.
[b] The analysis was limited to patients with stage III disease (n = 143).
[c] Significant *P* value.

addressing adjuvant RT in MCC, Lewis et al performed a literature search that identified 669 patients in 116 studies.[32] The addition of adjuvant RT (n = 169; 40%) to surgery alone (n = 418; 60%) reduced the 5-year LR rate from 39% to 12% and reduced the LN recurrence rate from 66% to 23% (both $P < .001$). That analysis formed the basis for the NCCN guidelines; however, several issues bear discussion. First, those data came from 116 individual series over 38 years (<1 patient per center per year). Second, no differentiation was made between *local* RT and *LN* RT. Third, it is unclear why certain patients were *selected* to receive RT. With these limitations, it is impossible to draw conclusions about the effect of RT on recurrence. Furthermore, in the study by Lewis et al, the rates of LR and LN recurrence after surgery alone (27% and 39%, respectively) were exceedingly high and are not consistent with contemporary experience. Other centers also have advocated for the use of adjuvant local RT[32-34] and LN RT.[25,26,29,33,34] They are similarly limited by both methodological flaws and high LR/LN recurrence rates with surgery alone (approaching 40%). The opinion of the NCCN to consider RT for patients with MCC represents actual practice of member institutions rather than evidence-based recommendations.

An analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database by Mojica et al concluded that adjuvant RT is associated with improved survival.[29] On the basis of the current report and our prior analyses of SLNB[20] and survival[6] in patients with MCC, we believe their conclusion is unlikely. Selection bias and the lack of data in the SEER database regarding adjuvant treatment, recurrence, and disease-specific death make it impossible to conclude a cause-effect relation between RT and survival.

In the current series, 3% of patients developed an LR with the *selective* use of adjuvant local RT in patients with high-risk tumors (larger primary tumors, positive surgical margins, presence of LVI, increasing stage). In patients who had with ≥2 years of follow-up, we observed a 3.8% LR rate at 2 years *without* adjuvant local RT, which was significantly less than the 39% rate reported by Lewis et al.[32] With adequate surgery, it is unlikely that the routine use of adjuvant local RT will be of benefit to the vast majority of patients with MCC.

We also observed that 12% of patients developed LN recurrence with the *selective* use of LN RT in patients with high-risk tumors (predominantly stage III disease). In patients who had ≥2 years of follow-up, we observed a 13.8% LN recurrence rate at 2 years *without* LN RT, which was significantly less than the 60% rate reported by Lewis et al.[32] The majority of LN recurrences developed in patients who either had clinically involved LNs (stage IIIB) or who did not undergo pathologic analysis of their regional LNs (stage IB or IIB) (Table 4).

Both in the current analysis and in our prior report of SLNB in MCC,[20] patients with evidence of microscopic LN disease (pathologic stage IIIA) had low rates of LN recurrence and distant recurrence (4% in the current analysis). Primary LN RT or CLND appear to be equally effective in achieving regional control in stage IIIA MCC. Similarly, Fang et al reported on patients with stage III MCC who underwent CLND with or without *adjuvant* RT or *therapeutic* RT alone and observed equivalent rates of regional control.[35] Our observation that pathologic LN staging leads to decreased recurrence (Fig. 1B) is consistent with the report by Lemos et al, which formed the basis for the AJCC staging system.[4] This supports the program of routine LN staging for all patients with MCC to guide the *selective* use of adjuvant therapies.

In contrast to patients who had microscopically positive LNs, patients who had clinically involved LNs had a >3-fold increase in recurrence. However, the risk of distant recurrence was nearly 3 times that of LN recurrence in patients with stage IIIB disease (32% vs 13%). There also was a higher rate of LN recurrence in patients with stage IIIB disease who did *not* receive LN RT compared with those who did receive LN RT (17% vs 7%, respectively). However, both groups had higher rates of distant recurrence compared with LN recurrence (30% and 33%, respectively).

The NCCN recommends consideration of adjuvant chemotherapy for patients with LN-positive MCC.[21] Available data do not suggest an improvement in recurrence or survival with this strategy[3,36,37] With the low incidence of recurrence and death from MCC (12% and 6% at 2 years, respectively) in the absence of clinically involved LNs[20] and the substantial morbidity (63% overall with a 40% hospitalization rate) and mortality (3%) associated with chemotherapy,[38,39] it is unlikely that the addition of unproven systemic chemotherapy will benefit all patients with LN-positive MCC. We previously demonstrated that the incidence of distant recurrence in patients with a positive SLNB who did *not* receive adjuvant chemotherapy was only 6%.[20] In contrast, the incidence of distant recurrence in patients with stage IIIB disease was 32%. Accordingly, any discussion of a clinical trial of adjuvant chemotherapy for MCC should focus on stage IIIB disease.

Our data, along with any study that retrospectively evaluates patients who received treatment for MCC, must be interpreted with caution with respect to drawing any direct cause-effect relation. Selection bias, nonstandardized treatment regimens, and the wide range of time periods included (to name a few confounding points) make efficacy statements impossible. The strength of our analysis is in describing the *natural history* of a large cohort of patients with complete follow-up who received treatment for MCC at our institution. These data should provide a platform for which new hypothesis can be generated and tested.

In summary, a low recurrence rate in patients with clinically LN-negative MCC (stage I-IIIA) can be achieved with adequate surgery (including SLNB) and the *selective* use of adjuvant RT for high-risk tumors. Patients who have clinically LN-positive MCC (stage IIIB) have significantly higher recurrence rates. However, the low response rates and significant toxicity argue against the routine use of adjuvant chemotherapy. Recurrence is rare in the absence of primary tumor LVI. Future research should focus on identifying other novel predictors of recurrence (such as anti-MCC polyomavirus antibodies[40,41] or primary tumor lymphocyte infiltration[42]) to further guide the use of multimodality treatment. Continued efforts to engage in accurate natural history studies are of paramount importance to better design rational treatment pathways for MCC.

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