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Scientific Article

Postoperative Radiation Therapy Is Indicated for "Low-Risk" Pathologic Stage I Merkel Cell Carcinoma of the Head and Neck Region but Not for Other Locations

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Purpose: The role of postoperative radiation therapy (PORT) in early stage Merkel cell carcinoma (MCC) is controversial. We analyzed the role of PORT in preventing local recurrences (LR) among patients with low-risk, pathologic stage I MCC based on the location of the primary tumors: head/neck (HN) versus non-HN sites.

Methods and Materials: One hundred forty-seven patients with MCC were identified that had "low risk" disease (pathologic T1 primary tumor, negative microscopic margins, negative pathologic node status, no immunosuppression or prior systemic therapy). LR was defined as tumor recurrence within 2 cm of the primary surgical bed, and its frequency was estimated with the cumulative incidence method.

Results: Seventy-nine patients received PORT (30 HN, 49 non-HN) with a median dose of 50 Gy (range, 8-64 Gy) and 68 patients were treated with surgery alone (30 HN, 38 non-HN). Overall, PORT was associated with a decreased risk of LR (5-year rate: 0% vs 9.5%; $P = .004$) with 6 LRs observed in the surgery alone group. Although the addition of PORT significantly reduced LR rates among patients with HN MCC (0% vs. 21%; $P = .034$), no LRs were observed in patients with non-HN MCC managed with surgery alone. There was no significant difference in MCC-specific survival comparing HN versus non-HN groups, with or without PORT.

Conclusions: For low-risk, pathologic stage I MCC of the extremities and trunk, excellent local control rates were achieved with surgery, and PORT is not indicated. However, PORT was associated with a significant reduction in LRs among low-risk MCC of the HN.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author. Data generated and analyzed during this study are included in this published article (and its supplementary files).

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Introduction

Merkel cell carcinoma (MCC) is a rare, aggressive skin cancer with a recurrence risk of ~40%.[1] MCC primarily affects elderly Caucasian individuals,[2,3] with 60% to 80% of MCC in the United States causally linked to the Merkel cell polyomavirus, whereas the remainder is attributed to ultraviolet exposure.[1] Reported risk factors for MCC recurrence include stage and tumor size, close or positive resection margins, pathologically positive lymph nodes or lack of pathologic staging,[4] head and neck (HN) location,[5-7] and immunosuppression.[8] Patients without clinically apparent disease in the lymph nodes are typically treated with primary resection and a sentinal lymph node biopsy (SLNB).[9] In pathologically node-negative patients, adjuvant postoperative radiation therapy (PORT) to the primary site is recommended to prevent local recurrence (LR) in the presence of ≥1 baseline risk factors: large primary tumor (≥1 cm), chronic T cell immunosuppresion (human immunodeficiency virus, chronic lymphocytic leukemia, solid organ transplant), HN primary site, close or positive margins, or lymphovascular space invasion (LVSI).[9] However, there is a paucity of data that is specific for stage I MCC. In patients with favorable stage I MCC without adverse features, observation without PORT is often recommended, and the need for PORT is controversial.[4,10,11]

Previous work has demonstrated that MCC is radiosensitive,[12] and PORT has been associated with improved local control in several studies.[13-18] PORT is generally recommended for high-risk MCC cases, but studies are mixed on its role in early stage, low-risk disease.[4,10,11,13,19-21] Because MCC is a rare disease, the literature is largely based upon retrospective studies, often with heterogenous patient populations. Although HN location is a recognized risk factor for LR, most studies that included early-stage MCC and suggested a low risk of LR without PORT did not specifically account for the location of the primary tumor.[4,10,11,13,19-21] An earlier study using part of the same cohort as our investigation found that PORT effectively reduces LR rates in a homogenous series of patients with low-risk HN primary disease after demonstrating a 26% LR rate in patients with HN who had surgery alone versus no LRs in the surgery + PORT group.[22] However, there are no such specific data evaluating the role of PORT in the non-HN setting for stage I, low-risk MCC.

To develop a more granular understanding of the role of PORT in low-risk MCC resected with pathologically negative margins, we retrospectively examined the impact of PORT on LR rates in patients with low-risk, pathologic stage I MCC stratified by their primary tumor site: HN versus non-HN.

Methods and Materials

We conducted an institutional review board–approved (Fred Hutchinson Cancer Center #6585) retrospective analysis of 147 patients with low-risk MCC from a Seattle-based repository of over 1500 patients with MCC treated between 2006 and 2020. This repository is a longitudinal database containing information on participant demographic characteristics, tumor features, treatment factors, and disease course. The database is updated annually with information from physician notes (electronic medical records), radiologic imaging reports, pathology reports, and communication with patients and their outside providers.

Inclusion criteria

Patients included in this study were enrolled in our repository ≤180 days from the date of surgical excision of the primary tumor to minimize ascertainment bias, had American Joint Committee on Cancer eight edition pathologic stage I disease (primary tumors ≤2 cm with a negative SLNB, and negative pathologic margins), no profound immunosuppression (including organ transplants, concurrent lymphoproliferative malignancies such as chronic lymphocytic leukemia, or human immunodeficiency virus infection), and no other prior systemic therapies. Before 2016, patients who fulfilled all these criteria were offered a choice of surveillance versus PORT. After 2016, based on findings reported by Takagishi et al, all patients with HN MCC were offered PORT to reduce risk of LR.[22]

Radiation therapy

Specific radiation techniques were at the discretion of the treating clinician. All patients received PORT to the primary resection bed. PORT was delivered using photon (IMRT or 3-dimensional conformal) or electron therapy (typically 6-10 MeV prescribed to the 90% isodose line) with a bolus to the entire surgical bed plus anatomically constrained 3 to 5 cm margins. Regional nodes were irradiated in a minority of cases as described further in the results section. Most patients were treated to a standard PORT dose of ~50 Gy with conventional fractionation, and a minority were treated with a single fraction to 8 Gy as described further in the results section.

Endpoints

The primary endpoint was MCC LR, and the secondary endpoints were other MCC recurrences and MCC-specific mortality. For all endpoints, the date of initial

surgery was considered time 0, and times were calculated until the date of recurrence, date of last follow-up (in the absence of an event), or date of death. Recurrences were categorized as local, in-transit, nodal, and distant. An LR was defined as a tumor recurrence within 2 cm of the primary surgical bed, in-transit as a cutaneous/subcutaneous lesion not involving region lymph nodes and arising >2 cm from the primary surgical bed, regional recurrence as occurring in the draining lymph node bed, and distant recurrence as arising beyond the draining lymph node bed. For all recurrence outcomes, only first recurrence events were considered in our statistical analyses.

Statistical analysis

Statistical analyses were performed using the Stata software version 14.0 (StataCorp, College Station, TX) and R (version 4.0.0; R Foundation for Statistical Computer, Vienna, Austria).

Patient and tumor characteristics were compared between groups using Fisher's exact test or the Wilcoxon rank-sum test. Event rates were estimated using cumulative incidence curves, accounting for competing risks. The competing risks were dependent on the endpoint. The competing risks for LRs and each other MCC recurrence type were any other MCC recurrence and death from any cause. Non-MCC death was a competing risk for MCC-specific survival. Five-year event rate estimates were extracted from these cumulative incidence curves. Differences in event rates between surgery alone and surgery + PORT groups were assessed using Cox regression models, censored by any competing risks and with PORT coded as a time-varying covariate. The time-varying covariate was used to minimize potential bias due to early recurrences or death not preventable by PORT due to later initiation of treatment. In these models, all patients start in the surgery alone group at time 0 (time of initial surgery) and enter the surgery + PORT group at the time PORT is initiated. Due to the small number of events in some groups, permutation tests were used to test for differences between surgery alone and surgery + PORT, using the Cox model partial likelihood ratio as the test statistic.

Results

Patient and pathologic tumor characteristics

The 147 individuals included in this cohort were patients with low-risk, pathologic stage I MCC (Fig. 1). Seventy-nine patients in this cohort received PORT (30 HN, 49 non-HN), while 68 patients were treated with surgery alone (30 HN, 38 non-HN). The median follow-up time was 5.1 years for the entire cohort (range, 7 days to 6 years). The surgery-alone group had a median follow-up time of 4.1 years (range, 7 days to 15 years), whereas the surgery + PORT group had a median follow-up of 5.2 years (range, 73 days to 16 years).

Patient and tumor characteristics are summarized in Table 1. Patients with non-HN had larger tumors than patients with HN in both the surgery-alone group (median, 1.00 cm vs 0.55 cm; $P < .001$) and surgery + PORT group (median, 1.10 vs 0.60 cm; $P < .001$; Table E1). Patients with HN had smaller intended surgical margins (margin width as reported by operative report) than patients with non-HN, although no

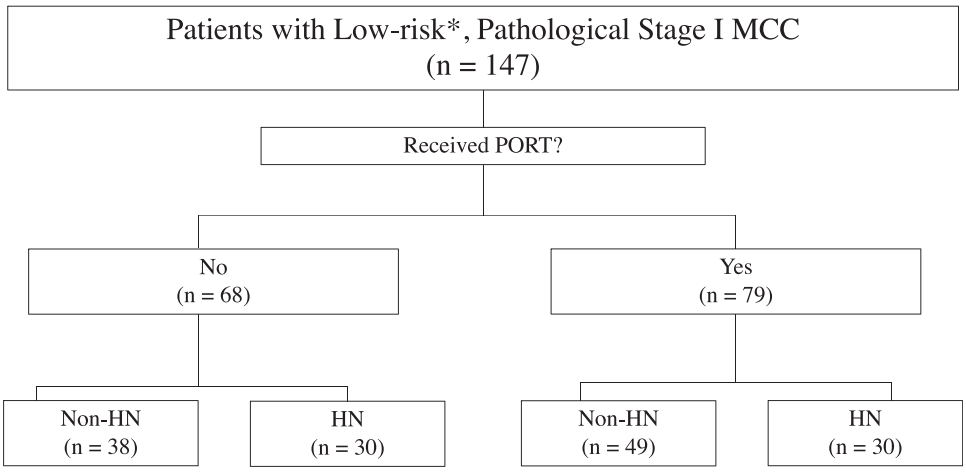

Figure 1 Study cohort. Identification of 147 patients with resected, pathologic stage I, Merkel cell carcinoma included in this cohort. *All patients met the following criteria: primary tumor ≤2 cm, no profound immunosuppression, microscopically clear surgical margins, negative sentinel lymph node biopsy, no chemotherapy, and enrollment within 180 days from surgical excision of primary tumor. *Abbreviations*: HN = primary tumor of the head and neck; non-HN = primary tumor of the trunk, extremities, or buttocks; PORT = postoperative radiation therapy following primary surgical excision.

Table 1 Clinical and tumor characteristics by treatment type (n = 147)

Variable	All patients			HN			Non-HN		
	Surgery (n = 68), n (%)	Surgery + PORT (n = 79), n (%)	*P* value*	Surgery (n = 30), n (%)	Surgery + PORT (n = 30), n (%)	*P*- value*	Surgery (n = 38), n (%)	Surgery + PORT (n = 49), n (%)	*P*- value*
Sex			.181			.796			.273
Male	36 (52.9)	50 (63.3)		15 (50.0)	17 (56.7)		21 (55.3)	33 (67.4)	
Female	32 (47.1)	29 (36.7)		15 (50.0)	13 (43.3)		17 (44.7)	16 (32.6)	
Age at diagnosis (y)			.863			.412			.502
<65	24 (35.3)	28 (35.4)		12 (40.0)	8 (26.7)		12 (31.6)	20 (40.8)	
≥ 65	44 (64.7)	51 (64.6)		18 (60.0)	22 (73.3)		26 (68.4)	29 (59.2)	
Size of primary tumor (cm)			.035			.254			.129
0-1	52 (76.5)	46 (58.2)		28 (93.3)	24 (80.0)		24 (63.2)	22 (44.9)	
>1	16 (23.5)	33 (41.8)		2 (6.7)	6 (20.0)		14 (36.8)	27 (55.1)	
Median (cm)	0.80	1.00	.020	0.55	0.60	.31	1.00	1.10	.073
Intended surgical margins (cm)†			.319			.064			.144
≤0.5	4 (6.3)	3 (4.2)		0 (0)	2 (7.7)		4 (11.4)	1 (2.2)	
>0.5-1.0	36 (57.1)	33 (46.5)		19 (67.8)	18 (69.2)		17 (48.6)	15 (33.3)	
>1.0-1.5	3 (4.8)	5 (7.0)		0 (0)	1 (3.9)		3 (8.6)	4 (8.9)	
≥2.0	10 (15.9)	22 (31.0)		4 (14.3)	5 (19.2)		6 (17.1)	17 (37.8)	
Wide excision, not further specified	10 (15.9)	8 (11.3)		5 (17.9)	0 (0)		5 (14.3)	8 (17.8)	
Microscopic margins (cm)†			.638			.318			.518
<0.1	1 (1.5)	5 (6.5)		0 (0)	0 (0)		1 (2.6)	5 (10.6)	
0.1-0.49	9 (13.4)	12 (15.6)		6 (20.6)	5 (16.7)		3 (7.9)	7 (14.9)	
0.5-0.99	8 (11.9)	7 (9.1)		1 (3.5)	2 (6.7)		7 (18.4)	5 (10.6)	
≥1	3 (4.5)	4 (5.2)		1 (3.5)	1 (3.3)		2 (5.3)	3 (6.4)	
No residual tumor detected	44 (65.7)	44 (57.1)		21 (72.4)	18 (60.0)		23 (60.5)	26 (55.4)	
Margins negative	2 (3.0)	5 (6.5)		0 (0)	4 (13.3)		2 (5.3)	1 (2.1)	
LVSI†									
Positive	13 (21.3)	20 (29.0)	.42	2 (7.4)	5 (18.5)	.42	11 (32.4)	15 (35.7)	.81
Negative	48 (78.7)	49 (71.0)		25 (92.6)	22 (81.5)		23 (67.6)	27 (64.3)	

Abbreviations: HN = Merkel cell carcinoma of the head and neck; intended surgical margins = margin width as reported by operative report; LVSI = lymphovascular space invasion; non-HN = Merkel cell carcinoma of the trunk, extremities, or buttocks; PORT = postoperative radiation therapy.

* Fisher's exact text or Wilcoxon rank-sum test.

† Patients with missing values were excluded from the corresponding summary: intended surgical margins (n = 13), microscopic margins (n = 3), and LVSI (n = 17).

significant differences in final pathologic margin status was observed in patients with HN versus non-HN (Table E1).

LVSI was more common in patients with non-HN compared with patients with HN (26/76 [34%] vs 7/54 [13%]; $P = .008$; Table E1). There was no significant difference in LVSI status between the surgery only and surgery + PORT groups overall (13/61 [21%] vs 20/69 [29%]; $P = .42$; Table 1). Similarly, after stratifying by primary tumor site, there were no significant differences in LVSI status by treatment modality for patients with HN (2/27 [7%] vs 5/27 [19%]; $P = .42$) or patients with non-HN (11/34 [32%] vs 15/42 [36%]; $P = .81$). In this low-risk cohort, there was not a significant difference in LR rates between LVSI-negative and LVSI-positive patients (5-year rate: 5.6% vs 0%; $P = .18$).

Among the 79 patients who received PORT, dose information was available for 72. The median dose was

50 Gy (range, 8-64 Gy), and the median dose per fraction was 2 Gy (range, 1.8-8.0 Gy/fraction). Sixty patients (83%) received 50 Gy in 25 fractions, 10 patients (14%) received a single fraction of 8 Gy, 1 patient (1%) received 50.4 Gy in 28 fractions (1.8 Gy/fraction), and 1 patient received 50 Gy in 24 fractions (2.1 Gy/fraction). PORT began a median of 41 days after surgery (range, 8-183 days). Given that this cohort had patients who were all SLNB negative, the majority of patients received PORT to the primary site alone. Eleven patients received PORT to the draining lymph node basin in addition to the primary tumor site (11/75, 15%), including 7/30 patients with HN (23%) and 4/45 patients with non-HN (9%); in 4 cases this information was missing.

Recurrence and survival

There were 6 total LRs, all in the surgery-alone group and none in the surgery + PORT group (5-year rate: 9.5% vs 0%; $P = .004$; Fig. 2A). Of those with an LR, the median time to LR was 10 months from surgical excision of the primary tumor (range, 14 days-27 months). When patients were further stratified by site of disease, the addition of PORT significantly reduced LR rates among patients with HN (5-year rate: 21% [6 LRs] vs 0%, $P = 0.034$; Fig. 2B), whereas no LRs were observed in the non-HN cohort (Fig. 2C).

As shown in Table 2, LRs occurred in patients with primary tumors on the forehead,[2] cheek,[3] and ear.[1] The primary tumor size among patients with an LR was ≤0.5 cm in 5 patients and 0.7 cm in the sixth patient. Salvage treatment (as described in Table 2) was successful in obtaining local control in 4 of the 6 (67%) LR patients. Among the patients with LR, 1 patient died of MCC, and 2 patients died of non-MCC causes (Table 2).

There was no significant difference in MCC-specific survival in the surgery versus surgery + PORT groups in the cohort as a whole (Fig. 3A) nor when stratified by HN (Fig. 3B) or non-HN (Fig. 3C). There were 9 patients with regional nodal recurrences, 5 patients with distant recurrences, and 2 patients with an in-transit recurrence as first events (Table 3). Both in-transit recurrences occurred in patients with non-HN. One patient had PORT and an in-transit recurrence outside of the radiation therapy field on the lower extremity. One patient was managed with surgery alone at the elbow and had an in-transit recurrence in the upper arm.

Discussion

This study aimed to develop a more granular understanding of the role of PORT in low-risk MCC and to identify those patients who may benefit from PORT versus cases where it may be safely excluded. Toward this goal, we retrospectively examined 147 patients with low-risk, pathologic stage I MCC who were treated with surgery versus surgery + PORT, stratified by primary tumor site (HN vs non-HN).

Among this entire cohort of patients with low-risk MCC, the 5-year LR rate of patients who had surgery

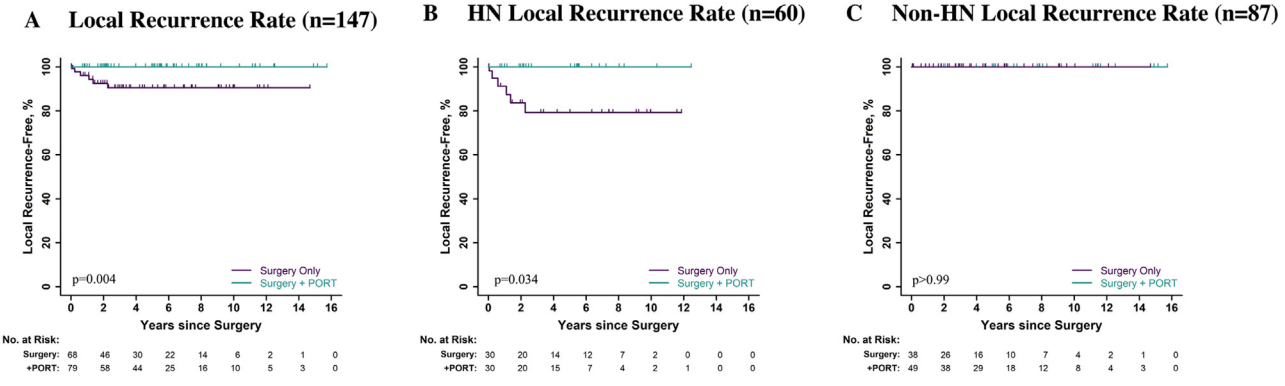

Figure 2 Local recurrence rate by primary tumor site and treatment modality. Cumulative incidence curves depicting probability of local recurrence is illustrated for 147 patients with resected, pathologic stage I, low-risk MCC stratified by (A) treatment type (surgery vs surgery + PORT), (B) MCC of the head and neck (HN), and (C) MCC of the trunk, extremities, or buttocks (non-HN). Across all disease sites, estimated local recurrence rates were significantly higher in patients treated with surgery alone than surgery + PORT (panel A, 5-year local recurrence rate: 9.5% vs 0.0%; $P = .004$). There was a significant difference in local recurrence rates among patients with HN treated with surgery alone versus surgery + PORT (panel B, 5-year rate: 21% vs 0%; $P = .034$), but not for patients with non-HN (panel C; 5-year rate: 0% vs 0%; $P > .99$). Nonlocalized MCC recurrences and death were treated as competing risks when estimating the cumulative incidence functions. *Abbreviations:* HN = primary tumor of the head and neck; non-HN = primary tumor of the trunk, extremities, or buttocks; MCC = Merkel cell carcinoma; PORT = postoperative radiation therapy following primary surgical excision.

Table 2 Patient and tumor characteristics for local MCC recurrences (n = 6)

Primary tumor site	Primary treatment modality	Age at dx (y)	Time to LR (d)*	Sex (M/F)	Primary tumor subsite	Primary tumor size (cm)	Primary tumor depth (cm)	Intended surgical margins (cm)	LVSI (Y/N)	Salvage treatment	Salvaged (Y/N)	Status
HN	Surgery	59	404	F	Forehead	0.5	0.21	1.0	N	RT	Y	Alive
HN	Surgery	70	824	F	Cheek	0.3	N/A	WE	N/A	WLE	N†	Alive
HN	Surgery	76	14	M	Forehead	0.5	0.11	1.0	N	RT	Y	Non-MCC death
HN	Surgery	58	211	M	Cheek	0.5	0.40	1.0	N	RT	Y	Alive
HN	Surgery	84	82	M	Cheek	0.4	0.08	1.0	N	RT	N‡	MCC death
HN	Surgery	80	497	M	Ear	0.7	0.30	1.0	Y	RT	Y	Non-MCC death

Abbreviations: dx = diagnosis; F = female; HN = MCC of the head and neck; intended surgical margins = margin width as reported by operative report; LR = local MCC recurrence as a first event; LVSI = lymphovascular space invasion; M = male; MCC = Merkel cell carcinoma; N = no; N/A = no data; RT = radiation therapy; WE = wide excision not further specified; WLE = wide local excision; Y = yes.

* Days since surgical excision of the primary tumor.

† Second LR 3 years after first LR; treated w/ WLE; now no evidence of disease.

‡ Distant recurrence 1 year after LR; no cancer-directed therapy.

alone was 9.5% compared with 0% for those who were treated with surgery + PORT (P = .004). However, when stratified by site of primary tumor, the addition of PORT significantly decreased the LR risk among patients with MCC of HN (21% for surgery alone vs 0% for surgery + PORT) whereas no LRs were observed in patients with MCC of non-HN locations. These findings confirm prior reports that PORT is associated with lower LR rates in patients with primary HN MCC, even among patients with the lowest-risk disease.[13-18,22] One possible explanation is that MCC in the HN may not always lend to wide surgical margins due to cosmetic and functional limitations. However, in this cohort there was no significant difference in the pathologic margin status between HN and non-HN locations. These data also indicate that patients with low-risk MCC of non-HN locations likely derive little or no benefit from PORT and may be safely observed after surgery. Thus, although PORT could be safely omitted for non-HN sites, it would be prudent to consider MCC of the HN as an indication for PORT, and our data support the current National Comprehensive Cancer Network guidelines that designate HN primary MCC as a baseline risk factor meriting consideration of PORT.[9]

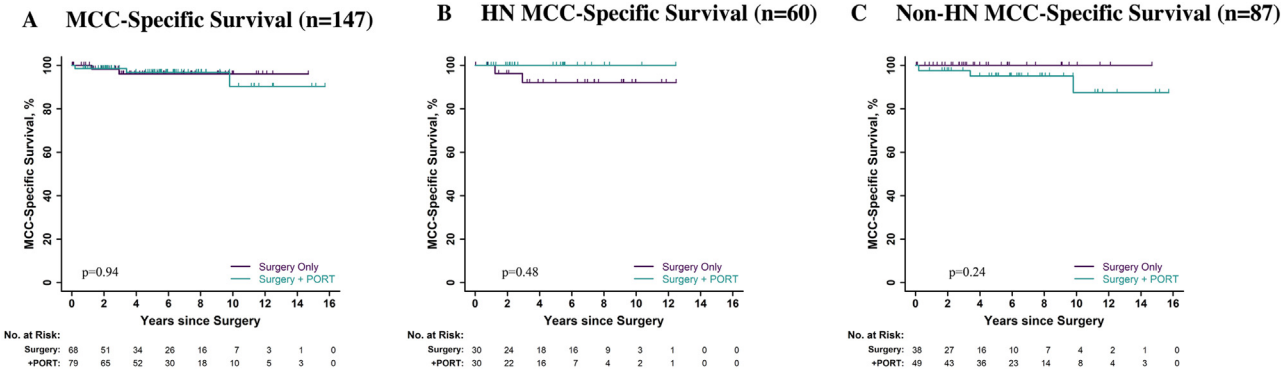

Figure 3 MCC-specific survival based on primary tumor site and treatment type. Cumulative incidence curves illustrating MCC-specific survival for 147 patients with pathologically stage I low-risk disease stratified by (A) treatment type (surgery vs surgery + PORT), (B) disease of the head and neck (HN), and (C) MCC of the trunk, extremities, or buttocks (non-HN). There were no significant differences in disease-specific mortality between patients who received PORT and those with did not for the entire cohort (panel A, 5-year rate: 3.2% vs 3.9%; P = .94), nor for patients with HN (panel B, 5-year rate: 0% vs 7.9%; P = .48) and non-HN (panel C, 5-year rate: 4.9% vs 0%; P = .24) individually. Non-MCC-related death was treated as a competing risk when estimating the cumulative incidence functions. *Abbreviations:* HN = primary tumor of the head and neck; non-HN = primary tumor of the trunk, extremities, or buttocks; MCC = Merkel cell carcinoma; PORT = postoperative radiation therapy following primary surgical excision.

Table 3 Patient and tumor characteristics for nonlocal MCC recurrences (n = 16)

Type of first MCC recurrence	Primary tumor site	Primary treatment modality	Time to recurrence (d)*	Age at dx (y)	Sex (M/F)	Primary tumor subsite	Primary tumor size (cm)	Primary tumor depth (cm)	Surgical margins (cm)	LVSI (Y/N)	Salvage treatment	Salvaged (Y/N)	Status
In-transit	Non-HN	Surgery + PORT	342	70	F	Limb	1.5	1.10	1.5	N	RT	Y	Alive
In-transit	Non-HN	Surgery	267	72	M	Limb	1.2	0.60	1.0	N	SFRT	Y	Alive
Regional	Non-HN	Surgery + PORT	349	72	M	Limb	1.2	0.20	1.0	N	IMTX	Y	Alive
Regional	Non-HN	Surgery + PORT	1240	80	M	Limb	1.1	N/A	2.0	N/A	IMTX	Y	MCC death
Regional	Non-HN	Surgery + PORT	267	76	M	Limb	1.2	0.62	1.0	N	WLE	Y	Alive
Regional	Non-HN	Surgery + PORT	320	71	M	Limb	1.6	0.60	WE	Y	RT	Y	Alive
Regional	HN	Surgery + PORT	304	67	M	Forehead	0.8	0.31	1.0	N	IMTX	Y	Alive
Regional	Non-HN	Surgery + PORT	349	59	F	Limb	1.0	0.40	1.1	Y	RT	Y	Alive
Regional	HN	Surgery	788	63	F	Cheek	0.5	0.08	1.0	N	RT	Y	Alive
Regional	HN	Surgery + PORT	358	55	M	Forehead	1.0	0.11	1.0	Y	WLE	Y	Alive
Regional	HN	Surgery + PORT	100	65	M	Neck	0.8	0.35	1.5	N	WLE	Y	Alive
Distant	Non-HN	Surgery + PORT	1157	62	M	Limb	1.5	0.32	ME	N	IMTX	N	MCC death
Distant	Non-HN	Surgery + PORT	834	68	M	Limb	2.0	1.30	2.0	N	RT	Y	Alive
Distant	Non-HN	Surgery + PORT	598	70	F	Limb	1.5	N/A	WE	N	SFRT	Y	Alive
Distant	HN	Surgery	769	71	M	Neck	1.2	0.14	2.0	N	IMTX	N	MCC death
Distant	Non-HN	Surgery + PORT	73	68	M	Trunk	1.9	0.21	2.0	Y	None	N	MCC death

Abbreviations: dx = diagnosis; HN = MCC of the head and neck; IMTX = immunotherapy; LR = local MCC recurrence as a first event; LVSI = lymphovascular space invasion; MCC = Merkel cell carcinoma; ME = Mohs excision; N/A = no data; NED = no evidence of disease (MCC); non-HN = MCC of the trunk, extremities, or buttocks; RT = radiation therapy; SFRT = single fraction radiation therapy; WE = wide excision not further specified; WLE = wide local excision.

* Days since surgical excision of the primary tumor.

To our knowledge, this is the largest homogeneous cohort of patients with pathologic stage I MCC and low-risk features (clear surgical margins, negative SLNB, and no immunosuppression). All primary tumors that had an LR among patients with HN were ≤0.7 cm. Five of the 6 patients who had a local failure had surgical margins of 1.0 cm, and 1 patient had a wide excision. LVSI was evenly distributed and was not associated with LR risk. Therefore, we recommend PORT to all patients with HN MCC given a risk of LR of approximately 20% to 25%. In contrast, excellent local control outcomes were achieved with surgery alone in patients with low-risk non-HN MCC. Indeed, no local failures were observed in the 38 patients with non-HN treated with surgery alone, nor in the 49 patients with non-HN treated with surgery + PORT. In nonimmunosuppressed patients with low-risk pathologic stage I MCC of the trunk or extremities, we recommend close observation. In addition, while treating HN sites, the regional lymph nodes and in-transit sites could also be comprehensively incorporated in the PORT volume, especially when there is a failed SLNB. This contrasts with treating limbs and trunk where there may be a dissociation between the primary site and regional nodes (eg, primary in the calf versus treating groin lymph nodes).

The efficacy of PORT in treating primary, stage I MCC tumors has been widely debated in the literature. Previous studies demonstrating the benefit of PORT to reduce LR rates and increase overall survival[13-18] included cohorts of patients with a mix of stages, risk factors, and primary tumor sites. Similarly, studies of node-negative MCC that suggest a low risk of LR without PORT[4,10,11,13,19-21] also included patients with a mix of pathologic stages, risk factors, and primary tumor sites and do not account for the differential risk of LR based on location of the primary. It is not known why there are differences in biologic behavior and recurrence rates for HN versus non-HN MCC. We can hypothesize that sun exposure, even in virus-positive MCC, may play a role.[23,24] It is interesting to speculate that the heterogeneity in skin may provide a different tumor microenvironment in sun-exposed versus non-sun-exposed areas.[23-25]

We recognize several limitations to this study including its retrospective nature and potential for selection bias, eg, larger tumors received PORT. Given that there were no events in the non-HN group, the study was not powered for multivariate analyses or to assess risk factors for LR, such as primary tumor size or surgical margin width. Although this is essentially a single-institution study, surgery and/or radiation may have occurred at other institutions. As such, there is some variability in patterns of practice including the dose and fractionation of radiation therapy while contributing to the generalizability of this data.

To our knowledge, this is the first study to characterize the efficacy of PORT stratified by disease site in low-risk, pathologic stage I MCC. Identifying patients with low-risk MCC of HN that may be spared PORT without increasing their LR risk will be the subject of future investigation.

Conclusion

One hundred forty-seven patients with low-risk, pathologic stage I MCC were stratified by the location of the primary (HN vs non-HN) and by treatment with surgery versus surgery + PORT. PORT did not benefit patients with non-HN MCC in whom no LR were observed. However, in keeping with multiple prior cohorts, our analysis identified the HN location as a significant risk factor for LR, and in our cohort, PORT was associated with a significant reduction in LRs among low-risk MCC in the HN (21% for surgery alone vs 0% for surgery + PORT).

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101364.

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