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ORIGINAL REPORT

Adjuvant Radiation Therapy Is Associated With Improved Survival in Merkel Cell Carcinoma of the Skin

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A B S T R A C T

Purpose
Merkel cell carcinoma (MCC) is a rare cutaneous malignancy. Because of the absence of randomized studies, the real benefit of adjuvant radiation therapy in MCC is unclear. The aim of this study was to better define the role of adjuvant radiation therapy in the management of MCC.

Methods
The Surveillance, Epidemiology, and End Results (SEER) survey from the National Cancer Institute was queried from 1973 through 2002. Retrospective analysis was performed. The end point of the study was overall survival.

Results
There were 1,665 cases of MCC in the SEER registry. Presentation by stage were 55% stage I, 31% stage II, and 6% stage III. Eight percent of the cases could not be staged because of incomplete data. Surgical intervention was a component of therapy in 89% of the cases (n = 1,487). The median survival for the entire cohort was 49 months, and median follow-up was 40 months. Adjuvant radiation was a component of therapy in 40% of the surgical cases. The median survival for those patients receiving adjuvant radiation therapy was 63 months compared with 45 months for those treated without adjuvant radiation. The use of radiation was associated with an improved survival for patients with all sizes of tumors, but the improvement with radiation use was particularly prominent when analyzing those patients with primary lesions larger than 2 cm.

Conclusion
The use of adjuvant radiation therapy is associated with improved survival in patients with MCC. Prospective evaluation of adjuvant radiation therapy in this setting is warranted.

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INTRODUCTION

Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous malignancy of neuroendocrine origin. First termed "trabecular carcinoma" by Toker in 1972, the nomenclature changed to MCC because of its ultrastructural immunohistochemical similarities to Merkel cells.[1,2] Merkel[3] described the cell of origin as a nondendritic, nonkeratinocyte epidermal cell that functions as a tactile skin receptor.

Data on the natural history of MCC come primarily from single-institution retrospective analyses of relatively small series. The largest series reported only 251 patients.[4] Despite the lack of controlled MCC trials, treatment algorithms based on the limited available data have been generated.[5] Most authors agree that surgical excision of the primary tumor with wide margins (1 to 3 cm) is the mainstay of therapy.[6-9] In addition, MCC has a high propensity for local recurrence, as well as regional and distant metastases.[10] At presentation, 25% to 30% of patients will have regional nodal disease, and elective lymphadenectomy[11,12] or sentinel lymph node biopsy [13-18] have been advocated. In a retrospective study, the use of adjuvant radiation therapy was associated with an improved local control rate, but no survival advantage was demonstrated.[19]

Because the incidence of MCC is so low, large series evaluating the effect of treatment variables on survival are lacking. The purpose of this study was to analyze the role of adjuvant radiation therapy in patients undergoing surgical resection for MCC identified through the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute.

METHODS

The SEER Program currently collects and publishes cancer incidence and survival data from 14 population-based cancer registries and three supplemental registries, covering approximately 26% of the US population. The SEER

database was queried for the diagnosis of MCC from 1973 to 2002. The anatomic information was coded according to the International Classification of Diseases for Oncology (IDC-0-3).[20] Patient demographics, tumor characteristics, and treatment modalities were reviewed. Patient demographics included sex and age at diagnosis. All races/ethnicities are included in the analysis. Tumor characteristics included size at presentation, site of primary tumor, nodal status of the disease, and presence of distant metastases. Treatment modalities reviewed were surgery of the primary site and lymph nodes, and the use of adjuvant radiation therapy. The SEER database does not report on the use of sentinel node biopsy, and no chemotherapy information is available in the database.

Retrospective analysis was performed. Overall survival curves were calculated by the Kaplan-Meier method. Univariate analysis of the various variables was performed with the log-rank test. A Cox proportional hazards ratio model was used to determine independent predictors of overall survival using factors significant on univariate analysis as covariates. A probability value of less than .05 was considered significant.

RESULTS

There were 1,665 cases of MCC identified in the registry from 1973 and 2002. Cancer-directed surgery was a component of therapy in 89% of the cases (n = 1,487). The surgical group was considered for further analysis. Of the 1,487 surgical cases reported, there were 879 males and 608 females with a male-to-female ratio of 1.45:1. MCC presented predominantly in the elderly population, with a median age at presentation of 74 years (range, 22 to 101 years). The median survival for the entire cohort was 49 months, with a median follow-up of 40 months.

Of the surgical group (n = 1,487), 55% presented with local disease, 31% with regional disease, and 6% with distant disease (SEER Historic Staging System). In 8% of the cases, disease extent was unknown. Table 1 summarizes the group demographics. The surgical procedures reported in the surgical cohort included wide local excision/re-excision or minor amputation without lymph node dissection in 82% of cases (n = 1,214), and extended surgery with lymph node dissection or major amputations in 10% of the cases (n = 135). Cancer-directed surgery not otherwise specified was reported in 8% of cases (n = 383). We excluded all patients with distant disease at presentation and those with an unknown type of cancer-directed surgery from further analyses. This yielded 1,187 cases for further analysis. All of the tumors were pathologically confirmed MCC.

Univariate analysis was performed to determine the factors associated with overall survival. Sex, age, stage, size, location of the tumor, and radiation therapy use were associated with improved survival on univariate analysis. On multivariate analysis, the use of adjuvant radiation therapy remained statistically significant in its association with survival. Additional factors associated with survival included sex, age, and tumor size and stage at presentation (Table 2). We chose to evaluate radiation therapy use further because, of the factors evaluated, it was the only significant factor on multivariate analysis that was treatment related.

Of the cancer-directed surgery group, 40% (n = 477) received adjuvant radiation therapy as a component of their treatment. Several forms of radiation therapy were used. These included external-beam radiation (98%), combination of beam with implants or isotopes (< 1%), radioisotopes (< 1%), and method not otherwise specified (1%).

Patients who received adjuvant radiation therapy demonstrated an overall median survival of 63 months, which was significantly better than the median overall survival of 45 months for the patients who did not receive adjuvant radiation therapy ($P = .0002$; Fig 1). The patients receiving adjuvant radiotherapy were compared with the patients who did not receive adjuvant radiation therapy. There were no differences in sex, race/ethnicity, surgical procedure, or size or stage of the tumor between patients who received adjuvant radiation therapy and those who did not (Table 3). The group of patients who received adjuvant radiation therapy presented with higher stage than did those patients who had surgery alone, and this

Table 1. Patient Demographics and Characteristics (N = 1,665)

Variable	No.	%
Age, years		
Median	76	
Range	22-101	
Race		
White	1,408	95
Nonwhite	79	5
Sex		
Male	879	59
Female	608	41
Size, cm		
Median	2.0	
Range	1-30	
Stage*		
Local	814	55
Regional	458	31
Distant	92	6
Unknown	123	8
Adjuvant radiation	591	40
Survival, months		
Median	49	
Range	0-200	

*Surveillance, Epidemiology, and End Results historic staging.

Table 2. Multivariate Analysis of Overall Survival (n = 603)

Variables	RR	95% CI	*P*
Age at diagnosis	1.05	1.043 to 1.069	< .0001
Size, cm			.0005
≤ 2	0.81	0.72 to 0.91	
> 2		Reference	
Sex			.0040
Female	0.84	0.74 to 0.94	
Male		Reference	
SEER historic stage			.0071
Local	0.85	0.76 to 0.95	
Regional		Reference	
Adjuvant radiation therapy	0.85	0.75 to 0.96	.0122
Cancer-directed therapy			.4589
Local resection	0.93	0.79 to 1.11	
Radical/extended resection		Reference	
Location			.8535
Head and neck	1.04	0.88 to 1.25	
Extremity	1.01	0.85 to 1.19	
Trunk		Reference	

Abbreviations: RR, risk ratio; SEER, Surveillance, Epidemiology, and End Results.

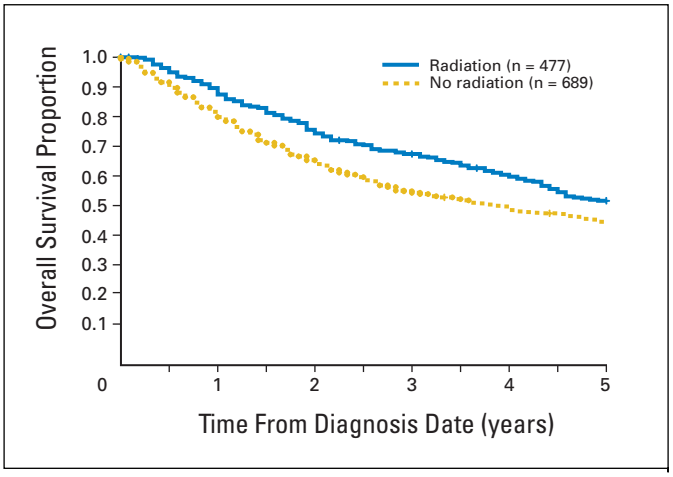

Fig 1. Overall survival for patients with Merkel cell carcinoma. Kaplan-Meier curves for patients who received radiation therapy (n = 477) and for those who did not (n = 689) were compared by log-rank test ($P < .0001$).

difference was statistically significant ($P = .0377$). The median age at presentation for the patients who received adjuvant radiation therapy was 72 years, compared with 76 years for those who did not. This difference was statistically significant ($P < .0001$). Despite this difference, the use of adjuvant radiation therapy was associated with improved overall median survival across all age groups, as shown in the multivariate analysis.

Subgroup analysis was performed to further identify which patients derived the greatest benefit from adjuvant radiation therapy. Analysis of adjuvant radiation therapy use for patients with a tumor size of less than 1 cm demonstrated an improved overall median survival, from 48 to 93 months, associated with radiation use ($P = .0447$; Fig 2A). For patients with tumors 1 to 2 cm, the overall median survival improved from 52 to 86 months ($P = .0126$; Fig 2B), and for patients with tumors larger than 2 cm, the overall median survival improved from 21 to 50 months with the use of adjuvant radiation therapy ($P = .0003$; Fig 2C).

Table 3. Comparisons of Surgery and Surgery + Radiation Groups (n = 1,166)

Variables	Surgery		Surgery + Radiation		*P*
	No.	%	No.	%	
Age, years	76		72		< .0001
Sex					.2773
Female	297	43	190	40	
Male	392	57	287	60	
Race					.1925
White	646	94	456	96	
Nonwhite	43	6	21	4	
Median follow-up, months	51		49		.5667
Surgery					.1272
Local therapy	622	90	417	87	
Radical Resection	67	10	60	13	
Size, cm	1.8		2.0		.8565
Stage					.0377
Local	473	69	299	63	
Regional	216	31	178	37	

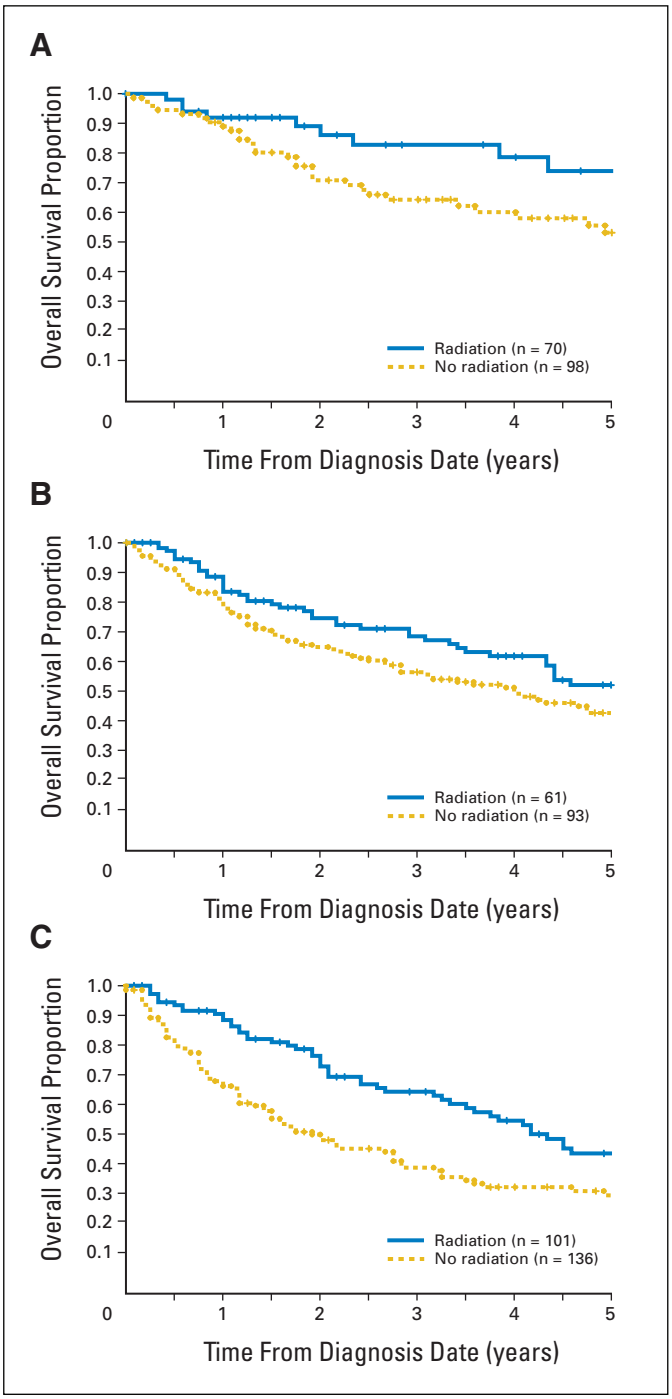

Fig 2. Overall survival for patients with large- and small-size primary Merkel cell carcinoma. Kaplan-Meier curves for patients who received radiation therapy and for those who did not were compared by log-rank test (A) for tumors smaller than 1 cm ($P = .0447$), (B) for tumors 1 cm to 2 cm ($P = .0126$), and (C) for tumors larger than 2 cm ($P = .0003$).

DISCUSSION

MCC is a relatively rare, but aggressive, cutaneous malignant tumor. The incidence of MCC appears to be increasing from a rate of 0.15 cases per 100,000 in 1986 to 0.44 cases per 100,000 in 2001.[21] It is associated with a high rate of local failure, regional recurrence, and

distant metastases.[22] The overall recurrence rate ranges from 50% to 79%, most often manifesting as local or locoregional recurrence.[3,22] In addition, MCC is a highly radiosensitive tumor,[23-24] and small retrospective studies have suggested an association between the use of adjuvant radiotherapy and reduced recurrence risk.[25,26] Unfortunately, there have been no prospective randomized clinical trials of adjuvant therapy, and the management of MCC remains controversial.[22] The mainstay of therapy is surgical resection, but optimal resection margins are also controversial, with some investigators suggesting that wide resection margins of 3 cm or more are needed to improve local control.[27,28] The high local and regional recurrence rate, along with its radiosensitive nature, provide a rationale for the use of adjuvant radiation therapy as a component of the multimodality therapy for MCC.

Morrison et al[29] investigated the role of adjuvant radiation therapy after surgery in 45 patients. They reported a decrease in locoregional recurrence rate from 89% with surgery alone to 41% with the use of adjuvant radiation therapy (50 to 55 Gy). In addition, Meeuwissen et al[30] analyzed the use of radiation therapy in the adjuvant setting. They reported, in a cohort of 38 patients, an absolute decrease of 70% in locoregional recurrence rate with the use of radiation therapy after surgery. More recently, Eich et al[31] reported their experience in 31 patients with MCC. Locoregional control improved, and recurrence rate dropped from 36% for surgery alone to a 6% recurrence rate with the addition of adjuvant radiation therapy. In addition, Eng et al[32] reported on a cohort of 88 patients demonstrating a reduction in locoregional recurrence from 52.7% in the surgery-alone group to 32.5% in the surgery plus adjuvant radiation group. Most of the patients who received radiation in these studies underwent radiation therapy to both the primary site and regional lymph node basins, and all of these studies support the use of adjuvant radiation therapy to address both the primary site and the regional nodal basin. However, the use of adjuvant radiation therapy for MCC has been challenged by others.[4] Allen et al[4] reported their experience in MCC in a cohort of 251 patients. The use of adjuvant radiation therapy was not associated with an improved local control ($P = .76$). Unfortunately, in that study, only 17% of the patients received adjuvant radiation therapy, and this small number of patients may reflect an underpowered study. It is important to point out that, in an institution with a high number of cases, surgeons may have more experience treating this disease, which may influence the treatment outcome. The effect of adjuvant radiation therapy on survival has not been adequately analyzed in prior reports.

The present study demonstrated a positive association between adjuvant radiation therapy and overall survival. This association remained statistically significant on multivariate analysis. The overall median survival for the entire surgical cohort in the SEER data set was 49 months, with an improvement in the overall median survival from 45 months to 63 months associated with the use of adjuvant radiation therapy. Subgroup analysis demonstrated that the larger the tumor, the greater the improvement in overall survival associated with the use of adjuvant radiation therapy. The association of adjuvant radiation therapy and improved overall median survival for tumor size less than 1 cm is marginally significant, so the use of radiation in this patient population should be individualized, taking into consideration tumor characteristics, staging, and patient factors.

There are several limitations to the present study. The SEER database does not report on completeness of resection, and the margin status of resections is unknown. In addition, the number of cases in which lymph node dissection was performed is small, precluding meaningful conclusions as to the necessity of elective lymph node treatment. The number of patients who completed their adjuvant therapy is unknown, and there are no details as to treatment fields or dosages. The SEER database provides no information as to whether chemotherapy was administered, and we cannot make conclusions regarding the impact of chemotherapy in MCC. One of the greatest limitations of the database is the lack of information regarding recurrence. In addition, the average age of the patients who received adjuvant radiation therapy was younger that that of the patients who did not receive radiation. This raises the possibility of bias toward better postoperative performance status in those patients treated with adjuvant radiation therapy. Despite theses limitations, the data support the continued development of adjuvant radiation therapy for MCC, particularly because of the high local and regional recurrence rate after surgery alone.

In conclusion, MCC is a rare skin cancer with a high rate of local failure, regional recurrence, distant metastases, and death. The use of adjuvant radiation therapy after cancer-directed surgery is associated with improved survival, particularly in larger tumors. Prospective evaluation of adjuvant radiation in MCC is warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Pablo Mojica, Joshua Ellenhorn
Provision of study materials or patients: Pablo Mojica
Collection and assembly of data: Pablo Mojica
Data analysis and interpretation: David Smith, Joshua Ellenhorn
Manuscript writing: Pablo Mojica, Joshua Ellenhorn
Final approval of manuscript: Joshua Ellenhorn

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