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Surgical resection improves median overall survival with marginal improvement in long-term survival when compared with definitive radiotherapy in Merkel cell carcinoma: A propensity score matched analysis of the National Cancer Database

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ABSTRACT

Background: Definitive radiotherapy has been suggested as a treatment alternative to surgical resection in Merkel cell carcinoma (MCC).
Methods: Patients with MCC were identified from the National Cancer Database. Propensity score matching accounting for age, Charlson-Deyo score, grade, and AJCC stage was used to match patients in 1:1 fashion by primary treatment (surgery vs. radiotherapy).
Results: There were 1227 patients in each group. Median overall survival was improved with surgical resection in stage I/II (76 vs. 25 months, $p < 0.001$) and stage III disease (30 vs. 15 months, $p < 0.001$). For stage I/II, 5- and 8-year overall survival were 61% and 42%, in the surgical resection and 32% and 25% in the definitive radiotherapy groups, respectively. For stage III, 5- and 8-year overall survival were 34% and 21% for surgical resection and 19% and 16% in the radiotherapy group, respectively.
Conclusions: Surgical resection for MCC improves median survival compared to definitive radiotherapy while marginally improving long-term survival.

1. Introduction

Merkel cell carcinoma (MCC) is a rare cutaneous malignancy with incidence of approximately 0.5 per 100,000 person-years in the United States.[1] The primary treatment for MCC has traditionally been radical surgical resection. However, tumors may be quite large at diagnosis making surgical resection difficult to tolerate. This is particularly concerning given this disease is characteristically found in older patients with co-morbidities.

Definitive radiotherapy has been suggested as an alternative to radical surgical resection as MCC has been noted to be highly radiosensitive.[2] Fang et al.,[3] treated patients with lymph node metastases with radiation monotherapy to the affected lymph node basin and found survival results comparable to completion lymphadenectomy + radiotherapy. Harrington and Kwan[4] investigated 57 patients with both localized and regional disease treated with definitive radiotherapy for both the primary tumor and regional metastases and observed excellent local control with 5-year overall survival of 39%.

While radiation has a clear role in MCC, the efficacy of radiation therapy without surgical resection is limited to these, and other small series. We sought to compare outcomes with definitive radiotherapy to a matched surgical resection group using a hospital-based database.

2. Methods

The study was conducted using the National Cancer Database (NCDB). The NCDB is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons.[5] It was established in 1989 and is a nationwide, hospital-based registry that captures 70% of all newly diagnosed malignancies in the US annually. The American College of Surgeons has

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executed a Business Associate Agreement that includes a data use agreement with each of its Commission on Cancer accredited hospitals.

Patients with MCC diagnosed between 2004 and 2014 were identified for study. Those with distant metastases at diagnosis were excluded. Patients who were treated with definitive radiotherapy were selected from the overall cohort. Key variables associated with overall survival were selected to include: age, Charlson-Deyo score, grade, and American Joint Committee on Cancer (AJCC) stage. Patients who were missing values from any of these four categories were excluded. A propensity score was then calculated using logistic regression accounting for these variables assuring that the balancing property was satisfied. Propensity score matching was then performed in 1:1 fashion without replacements using a caliper-matched algorithm with caliper width set to 0.01. The matching algorithm was performed using Stata 14.2 (College Station, TX).

Staging was recorded per the AJCC 7th edition.[6] Based on this classification, stage I is defined as tumors less than or equal to 2 cm in maximal dimension without nodal metastases. Stage II includes patients with tumors greater than 2 cm in dimension without nodal metastases. Stage III includes patients with any primary tumor size but with regional nodal metastases.

Univariate comparisons between groups were made using the chi-squared test for categorical variables and Mann Whitney *U* test for continuous variables as the data were non-parametric. The primary outcome measure was overall survival. Kaplan-Meier analyses were performed and survival was compared between groups using the log-rank testing. These analyses were stratified by localized (stage I/II) and regional (stage III) disease per the study design submitted in the NCDB Participant Use File application. Additionally, sensitivity analyses based on comparison of individual stage groups demonstrated similar trends for stage I and II so these were included together. Significance was considered for $p < 0.05$.

3. Results

There were 1227 patients who were treated with definitive radiotherapy and a matched pair surgical resection patient was achieved for each. The median age of the cohort was 70 (IQR = 27) and patients were predominantly white (Table 1). Patients who underwent surgical resection were more likely to have private insurance, higher incomes, upper extremity primary tumors, and smaller tumors. They also had a shorter time to diagnosis and were more likely to be treated at an academic hospital. Surgical resection resulted in negative margins in 911 (78%) and amputation was required in 16 patients (1%). Among resected patients, 480 (39%) received adjuvant radiotherapy.

For patients who underwent definitive radiotherapy, surgery was recommended but not performed in 99 (8%) and contra-indicated due to patient risk factors in 125 (10%). Radiation modalities included conventional external beam in 800 (65%), intensity modulated in 269 (22%), conformal or 3-D in 127 (10%), proton beam in 8 (1%), and the modality was not specified in 23 (2%). The median dose administered was 5000 cGy (IQR = 640) and 180 patients (15%) received a boost dose with median boost dose of 1980 cGy (IQR = 1600). The median duration of radiotherapy was 37 days (IQR = 15). There was no difference in survival for patients who received greater than or equal to 5000 cGy compared to those who received less than 5000 cGy.

Table 1
Descriptive statistics.

Variable		Surgery (n = 1227)	Radiation (n = 1227)	P value
Age (years; median:IQR)		70 (27)	70 (27)	0.92
Gender (% male)		686 (56%)	703 (57%)	0.49
Race	White	1065 (87%)	1023 (83%)	0.04
	Black	105 (9%)	147 (12%)	
	Asian-PI	35 (3%)	34 (3%)	
	Other	16 (1%)	12 (1%)	
Primary Payer	Medicare	669 (55%)	649 (54%)	0.02
	Medicaid	57 (5%)	93 (8%)	
	Private	435 (36%)	391 (33%)	
	Other Government	17 (1%)	21 (2%)	
	No insurance	36 (3%)	41 (3%)	
Median Income	<$38,000	183 (15%)	227 (19%)	0.01
	$38,000 – $47,999	274 (22%)	290 (24%)	
	$48,000 – $62,999	326 (27%)	321 (27%)	
	$63,000	440 (36%)	367 (31%)	
Academic Hospital		574 (47%)	480 (39%)	<0.01
Great Circle Distance (mi.; med:IQR)		14 (39)	11 (22)	<0.01
Charlson-Deyo Score	0	1006 (82%)	1002 (82%)	0.96
	1	165 (13%)	166 (14%)	
	2	56 (5%)	59 (5%)	
Primary Site	Head & Neck	115 (10%)	107 (9%)	<0.01
	Trunk	396 (33%)	509 (42%)	
	Upper Extremity	191 (16%)	111 (9%)	
	Lower Extremity	499 (42%)	479 (40%)	
Grade	Well differentiated	83 (7%)	87 (7%)	0.98
	Moderately differentiated	175 (14%)	179 (15%)	
	Poorly differentiated	567 (46%)	565 (46%)	
	Undifferentiated	402 (33%)	396 (32%)	
Tumor Size (mm; median:IQR)		70 (72)	100 (84)	<0.01
AJCC[a] Stage	I	213 (17%)	211 (17%)	0.99
	II	277 (23%)	280 (23%)	
	III	737 (60%)	736 (60%)	
Time from Diagnosis to Treatment (days; med:IQR)		15 (33)	34 (34)	<0.01
Systemic chemotherapy		207 (17%)	393 (32%)	<0.01

[a] AJCC = American Joint Committee on Cancer.