Published in final edited form as:
JAMA Dermatol. 2014 July ; 150(7): 716–723. doi:10.1001/jamadermatol.2013.8116.

Effect of Host, Tumor, Diagnostic, and Treatment Variables on Outcomes in a Large Cohort With Merkel Cell Carcinoma

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Abstract

IMPORTANCE—Merkel cell carcinoma (MCC) is a rare, aggressive, neuroendocrine-derived skin cancer with high rates of recurrence and associated mortality. Few published studies have used comprehensive patient data and long-term follow-up to examine factors that predict MCC outcomes.

OBJECTIVE—To characterize MCC in a large defined-population cohort and analyze predictors of disease recurrence and survival.

SETTING, DESIGN, AND PARTICIPANTS—Retrospective cohort study of 218 patients with MCC from the cancer registry of Kaiser Permanente Northern California, a large integrated health care delivery system. Patients were diagnosed as having MCC and followed up from January 1, 1995, through December 31, 2009. We examined host (age, sex, race, and immunosuppression), tumor (anatomic site, size, and extent), diagnostic (results of imaging and pathologic nodal evaluation), and treatment (surgery, radiation therapy, and chemotherapy) variables for their association with MCC outcomes.

EXPOSURE—Host, tumor, diagnostic, and treatment factors.

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Conflict of Interest Disclosures: Dr Asgari has received grants from Valeant, Genentech, and Pfizer (none relevant to this study). No other disclosures were reported.

Author Contributions: Dr Asgari had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Iyer, Paulson, Nghiem. *Acquisition, analysis, or interpretation of data*: All authors.
Drafting of the manuscript: Asgari, Sokil. *Critical revision of the manuscript for important intellectual content*: Asgari, Warton, Iyer, Paulson, Nghiem.
Statistical analysis: Warton, Paulson.
Obtained funding: Asgari, Iyer, Nghiem.
Administrative, technical, or material support: Asgari, Sokil, Nghiem.
Study supervision: Iyer, Nghiem.

Role of the Sponsors: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

MAIN OUTCOMES AND MEASURES—Recurrence (locoregional and distant) of MCC and patient survival (overall and MCC specific).

RESULTS—We estimated adjusted hazard ratios (AHRs) and 95% CIs for outcomes using Cox proportional hazards regression models. After adjustment for host, tumor, diagnostic, and treatment variables, tumor extent (categorized as local, regional, and distant) remained significantly associated with all outcomes. Immunosuppression was associated with higher MCC-specific mortality (AHR, 4.9 [95% CI, 1.7–14.4]), and an unknown primary site was associated with a lower risk for distant metastasis (0.1 [0.0–0.7]) and improved survival (0.4 [0.2–0.9]). Pathological nodal evaluation was associated with a lower risk for metastasis (AHR, 0.2 [95% CI, 0.0–1.0]) and improved survival. Radiation treatment was associated with a decreased risk for locoregional recurrence (AHR, 0.3 [95% CI, 0.1–0.6]), whereas chemotherapy was not associated with any alteration in outcomes.

CONCLUSIONS AND RELEVANCE—Tumor site and extent, results of pathologic nodal evaluation, and the presence of radiation treatment were associated with MCC recurrence. Immunosuppression, tumor extent, and results of pathologic nodal evaluation were associated with MCC-specific survival, whereas chemotherapy was not associated with any outcomes. Our findings may help to inform diagnostic and therapeutic management of MCCs.

Merkel cell carcinoma (MCC) is a rare, aggressive, neuroendocrine-derived skin cancer that arises predominantly on the sun-exposed skin of elderly white individuals.[1,2] The pathogenesis of MCC is associated with Merkel cell polyomavirus infection.[3] Approximately 1500 cases are diagnosed annually in the United States.[4] Given the rarity of MCC, most published reports on the epidemiology of MCC are derived from tertiary cancer centers.[1,5–7] Although a few studies since 2000[8–10] have used population-based data sources to examine the epidemiology of MCC, many studies have lacked diagnostic and treatment data and therefore could not investigate the effect of these data on MCC recurrence and survival to help improve management of the disease. Data sources with rich clinical information and outcomes are needed to fill knowledge gaps and controversy in MCC management such as optimal diagnostic tests and treatment of MCCs, especially for later-stage disease. These types of data are available in the large, community-based, comprehensive health care system of Kaiser Permanente Northern California (KPNC).

This study characterizes and follows up a retrospective cohort of all KPNC members diagnosed with MCC from January 1, 1995, through December 31, 2009. We examined the effects of host, tumor, diagnostic, and treatment variables on disease recurrence and survival.

Methods

Study Setting

Kaiser Permanente Northern California is a closed, prepaid health care delivery system that provides comprehensive health care and pharmaceutical benefits to a large and diverse community-based population of 3.2 million persons residing in northern California. The membership represents 33% of the insured population and 28% of the total service area population. The KPNC population has similar sociodemographic and health characteristics

to those of the insured population of Northern California, suggesting that KPNC data are generalizable to the wider insured population.[11]

The computerized record system of KPNC contains administrative and clinical electronic databases linked by a unique patient medical record number, providing a detailed and comprehensive record of members' demographic characteristics, clinical status, results of laboratory, pathologic, and radiological evaluations, pharmacy use, and benefits status. The pathology database contains information on all pathologic specimens received for examination, including the date and type of tissue, tumor location, tumor subtype, and gross and microscopic diagnoses in text format. This system has been fully operational across KPNC since 1995. Data from the electronic pathology database inform the KPNC Cancer Registry, which collects, codes, and reports all cancer data (except nonmelanoma skin cancer) to the Surveillance, Epidemiology and End Results program (http://seer.cancer.gov/). Numerous quality control processes and audits help to verify data accuracy and reporting completeness under standards set forth by the Surveillance, Epidemiology and End Results program.

In addition to clinical mortality information housed in its electronic databases, KPNC links membership data with death certificate files for the State of California, which include cause of death and the United States Social Security Administration Death Master Database. These linkage files are updated annually approximately 1 year after the close of the calendar year in which deaths occur.

This study was approved by the Kaiser Foundation Research Institute institutional review board. It was conducted according to the Declaration of Helsinki principles.

Study Population

The study cohort consisted of all KPNC members with an initial MCC diagnosis from January 1, 1995, through December 31, 2009. Patients were excluded if their initial diagnosis was not made within the KPNC system or if they were not KPNC members at the time of diagnosis. We identified MCCs through the KPNC Cancer Registry based on codes 8247/2 (MCC in situ) and 8247/3 (MCC) from the *International Classification of Diseases for Oncology, Third Revision*. All pathologic reports from the date of diagnosis onward were reviewed by a dermatologist (M.M.A.), and tumor data were abstracted into a tracking database. Additional data on demographics, imaging, and treatment (including surgery, chemotherapy, and radiation therapy) were also abstracted from the KPNC electronic databases, supplemented by outside provider billing data (for radiation therapy and chemotherapy).

Covariates

The covariates were categorized into the following 4 groups:

1. Host variables, including age at diagnosis, sex, race (white vs other), and immunosuppression (including history of human immunodeficiency virus infection, chronic lymphocytic leukemia, and solid organ transplant).

2. Tumor variables, including primary anatomic site (head and neck, limbs, trunk, other, and unknown), tumor size, and extent of disease at diagnosis (local, regional, or distant).
3. Diagnostic variables (testing to determine the extent of disease performed within the first 3 months of initial diagnosis), including results of diagnostic imaging and sentinel lymph node biopsy (SLNB), and lymphadenectomy (LAD) abstracted from the anatomic pathology database.
4. Treatment variables (treatments rendered within the first 3 months of initial diagnosis), including surgical excision (eg, whether tumor had surgically clear margins), radiation therapy, and chemotherapy.

Outcomes

The main outcomes of interest were disease recurrence (locoregional and metastatic) and survival (overall and MCC specific). For MCC-specific survival, death certificates listing "primary malignant neoplasm: other malignant neoplasms of skin" as the cause of death were considered MCC-related deaths. Follow-up data on vital status and cause of death were extracted from the most recently updated mortality files (through February 28, 2011, for KPNC clinical records; through December 31, 2010, for Social Security mortality files; and through December 31, 2009, for State of California death certificate files).

Statistical Analysis

We used univariate and multivariate Cox regression models to estimate unadjusted and adjusted hazard ratios (AHRs) and 95% CIs for outcomes. All statistical analysis was performed using commercially available software (SAS, version 9.3; SAS Institute Inc).

Results

From January 1, 1995, through December 31, 2009, we identified 220 cases of MCC in the KPNC population. Two patients were excluded because the initial diagnosis was not made within the KPNC system or because they were not KPNC members at diagnosis, leaving 218 in the cohort. The characteristics of the cohort are presented in Table 1. Cohort members were collectively followed up for outcomes for a total of 803.8 person-years with a median follow-up of 6.3 years among living patients (2.4 years among all patients). Median overall survival was 3.6 years for local disease, 2.0 years for regional disease, and 1.2 years for distant disease.

Host Variables

The mean age at diagnosis was 74.4 (SD, 12.0) years, with a median age of 77 (range, 31–96) years. The age distribution by age categories is shown in Table 1. Age was dichotomized at the approximate mean (<75 and ≥75 years) for the Cox models. Most cases arose in men (62.8%) and among white patients (95.4%). A small fraction of the cohort (6.0%) had chronic immunosuppression before MCC diagnosis due to human immunodeficiency virus infection (n = 2), solid organ transplant (n = 4), or chronic lymphocytic leukemia (n = 7).

In fully adjusted models (Table 2), being older was associated with increased all-cause mortality (AHR, 1.9 [95% CI, 1.3–2.8]) but not MCC-specific mortality. Although men tended to have higher hazard ratios for all outcomes, we found no statistically significantly association between sex and MCC outcomes. We observed no instances of locoregional disease or distant metastasis among the small group of nonwhite individuals (n = 10, including 7 Asian, 2 black, and 1 other); therefore, estimates could not be modeled. Because no significant mortality differences were noted between white and nonwhite patients in unadjusted models, race was not included in the multivariate models. Immunosuppression was significantly associated with disease-specific mortality (AHR, 4.9 [95% CI, 1.7–14.4]).

Tumor Variables

Most MCCs arose on the skin (n = 192), although 26 tumors had no known primary cutaneous site and were only detected in other tissue (such as the parotid gland and lymph nodes). Among tumors with a known primary site, the most common anatomic tumor location was the head and neck region (51.0%), followed by the upper and lower extremities. Anatomic site was further categorized into head and neck, upper and lower limbs, trunk, buttocks, genitalia, and unknown primary sites. In adjusted models, tumors with unknown primary sites had a lower risk for distant metastasis (AHR, 0.1 [95% CI, 0.0–0.7]) and lower all-cause (but not disease-specific) mortality (0.4 [0.2–0.9]).

Most of the tumors had no size documented in the pathology reports (53.7%), but in cases where size was recorded, most were no larger than 2 (mean [SD], 1.65 [1.1]; median, 1.3 [range, 0.1–5.0]) cm. Tumor size did not have a statistically significant association with MCC outcomes.

With regard to stage, 57 tumors (26.1%) were stage I (primary tumor size, ≤2 cm); 6 (2.8%), stage II (primary tumor size, >2 cm); 56 (25.7%), stage III (nodal disease); 33 (15.1%), stage IV (metastases beyond the regional lymph basin); 63 (28.9%), stage I/II (local disease, which could not be classified further because the tumor size was unknown); and 2 (0.9%), stage III/IV (regional).[2] One tumor (0.5%) could not be staged. We collapsed the staging variable into 3 categories termed *extent of disease*, which was defined as local (stages IA, IB, IIA, and IIB), regional (stages IIIA, IIIB, and any nodal disease), and distant (stage IV and regional/distant metastasis not otherwise specified) (Table 1). In unadjusted (data not shown) and adjusted models (Table 2), extent of disease was strongly associated with all MCC outcomes.

Diagnostic Variables

Pathologic nodal evaluation included SLNB in 49 individuals (22.5% of cohort) and partial and complete LAD in 63 individuals (28.9% of cohort). Of those undergoing SLNB, 18 (36.7%) had tumor identified in a node and of those undergoing LAD, 24 (38.1%) had microscopic evidence of tumor in at least 1 node in fully adjusted models. Patients who underwent SLNB alone had a reduction in all-cause mortality (AHR, 0.4 [95% CI, 0.2–0.7]). Sentinel lymph node biopsy combined with LAD was also associated with reductions in all-cause (AHR, 0.2 [95% CI, 0.1–0.5]) and MCC-specific (0.1 [0.0–0.4]) mortality and with reduction in the risk for metastasis of borderline significance (0.2 [0.0–1.0]).

We determined which imaging studies were completed in MCC cohort members within 3 months of the initial diagnosis. These studies included computed tomography, magnetic resonance imaging, positron emission tomography, radiography, and ultrasonography. More than half of the cohort underwent computed tomography (58.7%); 12.4%, magnetic resonance imaging; and 22.9%, positron emission tomography. Most of the cohort members (70.6%) underwent some form of other imaging within 3 months of their initial diagnosis, the most common of which was chest radiography. Computed tomography and positron emission tomography had no association with MCC outcomes in fully adjusted models.

Treatment Variables

Review of electronic surgical pathology records revealed that most of the tumors underwent surgical excision (158 [72.5%]) and of the surgical procedures, most achieved clear surgical margins (137 [86.7%]). However, in 15 cases (9.5%), the final surgical margin was not clear, and 6 (3.8%) cases were missing information on final margins. Surgery as the sole modality of treatment (surgery alone) was performed on 79 tumors (36.2%). Radiation therapy as the sole treatment modality was administered to 18 cohort members (8.3%); chemotherapy as the sole treatment modality, to 7 members (3.2%). Table 1 describes the administration of combination treatments.

Surgery (with or without clear margins) had no statistically significant effect on outcomes compared with no surgery, although cohort members who underwent surgery with residual positive or unknown findings in the margins had an increased risk for all-cause mortality of borderline significance (AHR, 1.9 [95% CI, 1.0–3.9]; $P = .07$). Radiation treatment showed a significant protective effect on locoregional recurrence (AHR, 0.3 [95% CI, 0.1–0.6]). Chemotherapy was not associated with disease recurrence or mortality outcomes (Table 3).

Discussion

This study is, to our knowledge, one of the most detailed descriptions of MCC cases arising within a community-based population of a large integrated health care delivery system. Adjusted models demonstrate that tumors of unknown primary site, extent of disease at diagnosis, pathologic nodal evaluation, and radiation treatment are associated with MCC recurrence, whereas immunosuppression, extent of disease, and pathologic nodal evaluation are associated with MCC-specific survival.

More specifically, the data indicate that immunosuppression is associated with a higher likelihood of disease-specific mortality, a finding reported in other published studies on immunosuppressed populations.[12–14] Merkel cell carcinomas are known to arise more frequently and behave more aggressively in diverse immunocompromised populations,[15] including those with human immunodeficiency virus infection,[16] solid organ transplant,[14] or chronic lymphocytic leukemia,[17] suggesting that immune function plays a critical role in MCC outcomes.

With regard to tumor-related factors, we found that tumors of unknown primary sites were associated with a decreased risk for distant metastasis and all-cause mortality. Recent publications of MCCs with an unknown primary site found that patients with occult tumors

have significantly improved MCC outcomes (recurrence and survival).[18,19] One possible explanation for the improved outcome of occult MCCs is that MCCs are highly immunogenic tumors and may undergo spontaneous T-cell–mediated regression. Alternatively, neuroendocrine tumors may arise in other noncutaneous organs and those MCCs may have improved outcomes compared with those of cutaneously derived MCCs. The finding of decreased risk for metastasis in MCCs when the primary site is unknown is especially important for clinicians, who may need to modify the aggressiveness of therapeutic management of occult primary MCCs (eg, not treating such patients with chemotherapy, which in this study is not associated with improved MCC outcomes). The data also validate previously published reports of extent of disease at diagnosis[8,20] as an important predictor of MCC outcomes. We saw no statistically significant association between tumor size and MCC outcomes, but this study may have been under-powered to detect the association owing to a small number of tumors with a known size of greater than 2 cm.[21]

With regard to pathologic nodal evaluation, adjusted models revealed that SLNB alone was associated with a reduction in risk for all-cause but not disease-specific mortality. We did not see a statistically significant association between SLNB and risk for locoregional recurrence, a similar finding to a previously published study of 17 MCCs[22] that found SLNB to be an inaccurate predictor of locoregional recurrence. When SLNB and LAD were performed, they were associated with a reduction of all-cause and MCC-specific mortality. Pathologic nodal evaluation is well known to improve prognostic accuracy,[2] and our findings of improved outcomes may simply reflect more accurate staging.[23] Several other explanations are possible. Aggressive lymph node exploration may be associated with decreased risk for recurrence by virtue of a physiological mechanism, such as disruption of lymphatic spread of the tumor. On the other hand, the association may be confounded by unmeasured variables, such as comorbidities. For example, healthier individuals may be more likely to undergo more aggressive surgical resections that combine SLNB with additional lymph-node sampling, and future studies examining the effect of patient comorbidities on diagnostic testing would be useful. Pathologic nodal evaluation may benefit MCC patients in many cases because it improves staging accuracy and could have important implications for treatment selection.

Finally, with regard to treatment, the data showed that radiation treatment was associated with a reduced risk for locoregional recurrence but had no effect on the risk for metastasis or mortality outcomes. The effect of radiation therapy on local, but not distant, disease is supported by a recently published study that examined patterns of relapse and noted that disease relapse after radiation therapy tended to occur at distant sites.[24] Our findings are nearly identical to those from a meta-analysis on 1254 MCC patients,[25] which reported a significantly lower rate of locoregional recurrence with adjuvant radiation therapy and improved (although not statistically significant) overall and disease-specific survival. A more recently published retrospective multicenter study[26] of 180 patients with MCC treated from 1988 through 2009 compared patients undergoing surgery alone with those who received surgery and postoperative radiation therapy and reported improved locoregional relapse-free survival and distant metastasis-free survival with radiation treatment but no difference in overall survival rates. In aggregate, our data support previously published

studies that strongly suggest improved locoregional recurrence rates with adjuvant radiation treatment.

A key finding in this study is the lack of association of chemotherapy with MCC relapse or survival in adjusted models, a finding that has also been reported in numerous previous published studies.[6,27,28] Lack of benefit from chemotherapy was shown after adjusting for variables known to affect MCC outcomes, such as disease extent at diagnosis. The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology recommend consideration of adjuvant chemotherapy for patients with lymph node–positive MCC.[29] However, substantial morbidity (16% of those 65 years or older who undergo chemotherapy for MCC die of complications related to chemotherapy)[30] and mortality (3%)[31] are associated with chemotherapy. Given the lack of benefit of adjuvant chemotherapy on MCC outcomes and the potential for harm, the role of currently available chemotherapy may best be limited to palliation.

The major strength of this study is the KPNC setting, which is a large integrated health care delivery system that closely approximates a community-based population. This cohort appears to avoid ascertainment bias by age when compared with cohorts from tertiary-referral centers (K.G.P. and P.N.; written communication; July 23, 2011). Thus, our study's findings may be more generalizable than those from tertiary referral centers, which may tend to draw on younger, healthier patients. This generalizability is also supported by the similarity of the KPNC cohort's age, sex, and race distribution to those of previously published population-based studies.[8,9,32]

Limitations of this study include lack of inclusion of possible confounding factors such as comorbidities, including prior cancers. In addition, a small number of MCCs may have been diagnosed and treated outside of health plan facilities and therefore was not captured by the KPNC registry. However, this number is likely to be very small because MCCs are reportable tumors and cancer reporting is mandated by the State of California. Also, tumors diagnosed outside KPNC but treated within KPNC are still captured by the KPNC Cancer Registry (n = 2). Given that MCCs are rare cancers, some analyses may have been underpowered, as evidenced by the wide 95% CIs around many of the calculated hazard ratios. Nevertheless, the KPNC MCC cohort is among the largest published data sets on MCC and serves as a baseline to explore future trends for reproducibility. Because no specific mortality code for MCC exists, some of the deaths attributed to MCC-specific causes may have been misclassified. However, given that a specific disease code for the most common malignant neoplasms of the skin that leads to mortality (ie, melanoma) exists, and given that very few other malignant neoplasms of the skin are lethal, attributing MCC-related deaths to the mortality code "primary malignant neoplasm: other malignant neoplasms of skin" in a cohort of MCC patients appeared to have face validity. Finally, because this study was conducted among insured adults in Northern California, these results may not be completely generalizable to uninsured persons and other health care or geographic settings.

Conclusions

Certain host (age at diagnosis and immunosuppression), tumor (extent of disease at diagnosis), diagnostic (pathologic nodal evaluation), and treatment (radiation therapy) variables are associated with MCC outcomes in multivariate analysis. These findings have clinical implications. Clinicians may need to be more mindful of MCC patients with immunosuppressive conditions who are more likely to die as a result of MCC. Pathologic nodal evaluation is associated with improved outcomes, supporting its continued use in prognostication. Radiation treatment may reduce MCC locoregional recurrence and may be the preferred adjuvant treatment modality. Although chemotherapy is important for palliation, the present study further supports the notion that adjuvant chemotherapy is not associated with recurrence or survival benefit in MCC. Future studies that include factors that may be associated with selection of diagnostic and treatment variables, such as host comorbidities, could help further elucidate the relationship of imaging, pathologic nodal evaluation, and treatment on MCC outcomes.

Acknowledgments

Funding/Support: This study was supported in part by grants RC2-CA147820-01, K24-CA139052, and R01-CA162522 from the National Cancer Institute; by the Michael Piepkorn Endowment; and by the University of Washington MCC Patient Gift Fund.

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Table 1

Host, Tumor, Diagnostic, and Treatment Characteristics of the KPNC MCC Cohort (1995–2009)

Characteristic	No. (%) of Patients[a]
Host Variables	
Age at diagnosis, y	
<60	23 (10.6)
60–74	72 (33.0)
75–85	88 (40.4)
>85	35 (16.1)
Sex	
Male	137 (62.8)
Female	81 (37.2)
Race	
White	208 (95.4)
Other[b]	10 (4.6)
Immunosuppression	
None	205 (94.0)
Yes[c]	13 (6.0)
Tumor Variables	
Site of primary lesion	
Head and neck	98 (45.0)
Upper limb	52 (23.9)
Lower limb	23 (10.6)
Trunk	8 (3.7)
Buttocks	9 (4.1)
Genitalia	2 (0.9)
Unknown primary site	26 (11.9)
Size, cm	
≤2	77 (35.3)
>2	24 (11.0)
Unknown[d]	117 (53.7)
Extent at diagnosis[e]	
Local	126 (57.8)
Regional	56 (25.7)
Distant	35 (16.1)
Unknown	1 (0.5)
Diagnostic Variables[f]	
Imaging	
Computed tomography	128 (58.7)

Characteristic	No. (%) of Patients[a]
Magnetic resonance imaging	27 (12.4)
Positron emission tomography	50 (22.9)
Other, including chest radiography	154 (70.6)
None	27 (12.4)
Pathologic nodal evaluation	
None	129 (59.2)
SLNB only	26 (11.9)
LAD only, other than SLNB	40 (18.3)
Both SLNB and LAD	23 (10.6)
Pathologic nodal evaluation results	
Positive SLNB finding (of 49 SLNB)	18 (36.7)
Positive LAD finding (of 63 LAD)	24 (38.1)
Treatment Variables[f]	
Initial treatment modality	
None	28 (12.8)
Surgery alone	79 (36.2)
Radiation therapy alone	18 (8.3)
Chemotherapy alone	7 (3.2)
Surgery and radiation therapy	64 (29.4)
Surgery and chemotherapy	11 (5.0)
Radiation therapy and chemotherapy	7 (3.2)
Surgery, radiation therapy, and chemotherapy	4 (1.8)
Initial tumor treatment	
Any surgery	158 (72.5)
Clear margins	137 (62.8)
Positive margins	15 (6.9)
Missing information on margins	6 (2.8)
Any radiation therapy	93 (42.7)
Any chemotherapy	29 (13.3)

Abbreviations: KPNC, Kaiser Permanente Northern California; LAD, lymphadenectomy; MCC, Merkel cell carcinoma; SLNB, sentinel lymph node biopsy.

[a] Sample size totals 218 unless otherwise specified. Percentages have been rounded and might not total 100.

[b] Includes Asian (n = 7), black (n = 2), and other (n = 1).

[c] Includes human immunodeficiency virus (n = 2), solid organ transplant (n = 4), and chronic lymphocytic leukemia (n = 7).

[d] Includes unknown primary site (n = 26) and no size available (n = 91).

[e] Staging is described by Lemos et al[2] with grouping as follows: local includes stages IA, IB, IIA, IIB, and localized disease with no size available to further stage; regional, stages IIIA and IIIB and nodal; and distant, stage IV and regional/distant metastasis not otherwise specified.

[f] Defined as occurring within 3 months of initial diagnosis. Categories are not exclusive.

Table 2

Cox Proportional Hazard Models of Host and Tumor Variables on Outcomes in 217 Patients[a]

	Outcome							
	Locoregional Recurrence (47 Events)		Distant Metastasis (38 Events)		All-Cause Mortality (147 Events)		Disease-Specific Mortality (56 Events)	
	AHR (95% CI)	Events, No.	AHR (95% CI)	Events, No.	AHR (95% CI)	Events, No.	AHR (95% CI)	Events, No.
Host Variables								
Age, y								
<75	1 [Reference]	21	1 [Reference]	20	1 [Reference]	48	1 [Reference]	27
≥75	0.7 (0.4–1.4)	26	0.8 (0.4–1.6)	18	1.9 (1.3–2.8)	99	1.2 (0.6–2.2)	29
Sex								
Female	1 [Reference]	12	1 [Reference]	12	1 [Reference]	52	1 [Reference]	20
Male	1.4 (0.7–2.8)	35	1.7 (0.8–3.4)	26	1.3 (0.9–1.8)	95	1.2 (0.7–2.2)	36
Immunosuppression								
None	1 [Reference]	45	1 [Reference]	37	1 [Reference]	138	1 [Reference]	51
Yes	1.1 (0.2–5.3)	2	0.6 (0.1–4.6)	1	1.9 (0.9–4.0)	9	4.9 (1.7–14.4)	5
Tumor Variables								
Anatomic site								
Limbs/trunk/other	*b*	24	1 [Reference]	18	1 [Reference]	60	1 [Reference]	22
Head/neck		23	1.1 (0.5–2.3)	18	0.9 (0.6–1.3)	69	0.9 (0.4–1.7)	23
Unknown		0	0.1 (0.0–0.7)	2	0.4 (0.2–0.9)	18	0.6 (0.2–1.9)	11
Size, cm								
≤2	1 [Reference]	19	1 [Reference]	14	1 [Reference]	45	1 [Reference]	15
>2	1.7 (0.7–4.3)	8	1.1 (0.4–3.1)	6	0.8 (0.5–1.6)	17	1.1 (0.4–2.9)	9

	Outcome							
	Locoregional Recurrence (47 Events)		Distant Metastasis (38 Events)		All-Cause Mortality (147 Events)		Disease-Specific Mortality (56 Events)	
	AHR (95% CI)	Events, No.	AHR (95% CI)	Events, No.	AHR (95% CI)	Events, No.	AHR (95% CI)	Events, No.
Unknown	0.7 (0.4–1.5)	20	0.8 (0.4–1.8)	18	1.0 (0.7–1.5)	85	0.8 (0.4–1.7)	32
Extent, at diagnosis								
Local	1 [Reference]	27	1 [Reference]	19	1 [Reference]	79	1 [Reference]	18
Regional	2.9 (1.2–7.3)	13	4.2 (1.6–10.7)	12	2.7 (1.5–4.7)	36	5.3 (2.3–12.3)	21
Distant	3.8 (1.3–11.4)	7	3.2 (1.1–9.2)	7	3.6 (2.1–6.1)	32	7.0 (2.9–16.5)	17

Abbreviation: AHR, adjusted hazard ratio.

[a] Adjusted for all other variables listed in table, except the race variable, which is excluded due to sparse data in nonwhite strata. One individual with no staging data was excluded from all adjusted models.

The 95% CIs were calculated using the Wald method.

[b] No locoregional recurrences in individuals with no known primary by definition of recurrence.

Table 3

Cox Proportional Hazard Models of Diagnostic, and Treatment Variables on Outcomes in 217 Patients[a]

	Outcome							
	Locoregional Recurrence (47 Events)		Distant Metastasis (38 Events)		All-Cause Mortality (147 Events)		Disease-Specific Mortality (56 Events)	
	AHR (95% CI)	Events, No.	AHR (95% CI)	Events, No.	AHR (95% CI)	Events, No.	AHR (95% CI)	Events, No.
Diagnostic Variables[b]								
Computed tomography								
None	1 [Reference]	26	1 [Reference]	17	1 [Reference]	64	1 [Reference]	16
Yes	0.6 (0.3–1.3)	21	0.6 (0.3–1.4)	21	0.9 (0.6–1.4)	83	1.0 (0.5–2.1)	40
Positron emission tomography								
None	1 [Reference]	43	1 [Reference]	28	1 [Reference]	120	1 [Reference]	40
Yes	0.4 (0.1–1.2)	4	1.1 (0.5–2.5)	10	0.7 (0.4–1.2)	27	1.2 (0.6–2.3)	16
Pathologic nodal evaluation								
None	1 [Reference]	33	1 [Reference]	21	1 [Reference]	103	1 [Reference]	35
SLNB only	0.4 (0.2–1.2)	5	1.1 (0.4–3.1)	7	0.4 (0.2–0.7)	13	0.4 (0.1–1.1)	6
LAD only	0.4 (0.4–1.2)	5	1.2 (0.4–3.6)	7	0.8 (0.5–1.4)	24	0.8 (0.3–1.8)	13
Both	0.4 (0.1–1.6)	4	0.2 (0.0–1.0)[c]	3	0.2 (0.1–0.5)	7	0.1 (0.0–0.4)	2
Treatment Variables[b]								
Surgery								
None	1 [Reference]	12	1 [Reference]	10	1 [Reference]	49	1 [Reference]	24
With clear margins	1.1 (0.5–2.4)	29	0.6 (0.2–1.7)	25	0.7 (0.4–1.1)	82	0.8 (0.3–1.8)	26
With margin not clear/missing	1.7 (0.6–5.3)	6	0.7 (0.2–3.4)	3	1.9 (1.0–3.9)[d]	16	1.5 (0.5–4.4)	6

	Outcome							
	Locoregional Recurrence (47 Events)		Distant Metastasis (38 Events)		All-Cause Mortality (147 Events)		Disease-Specific Mortality (56 Events)	
	AHR (95% CI)	Events, No.	AHR (95% CI)	Events, No.	AHR (95% CI)	Events, No.	AHR (95% CI)	Events, No.
Radiation therapy								
None	1 [Reference]	37	1 [Reference]	19	1 [Reference]	90	1 [Reference]	33
Yes	0.3 (0.1–0.6)	10	1.5 (0.8–3.1)	19	0.9 (0.6–1.3)	57	0.8 (0.4–1.5)	23
Chemotherapy								
None	1 [Reference]	43	1 [Reference]	32	1 [Reference]	130	1 [Reference]	46
Yes	0.5 (0.2–1.7)	4	1.9 (0.6. 5.8)	6	1.2 (0.6–2.2)	17	0.9 (0.4–2.3)	1

Abbreviations: AHR, adjusted hazard ratio; LAD, lymphadenectomy; SLNB, sentinel lymph node biopsy.

[a] Adjusted for all other variables listed in table, except the race variable, which is excluded due to sparse data in nonwhite strata. One individual with no staging data was excluded from all adjusted models. The 95% CIs were calculated using the Wald method.

[b] Defined as part of the initial diagnostic process or within 3 months after the initial diagnosis.

[c] $P = .05$.

[d] $P = .07$.

JAMA Dermatol. Author manuscript; available in PMC 2014 August 22.