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Tumor Location Predicts Survival in Cutaneous Head and Neck Melanoma

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Abstract

Background—Prior studies documented poorer outcomes in patients with cutaneous head and neck melanoma (CHNM) relative to those with melanoma at other sites. We evaluated survival differences attributable to tumor location in patients with CHNM.

Methods—We queried the Surveillance, Epidemiology, and End Results (SEER) database for patients undergoing surgery for CHNM from 1988 to 2006, excluding patients without biopsy-proven diagnoses, those diagnosed at autopsy, and patients with distant metastases. Using the Kaplan-Meier method, we assessed patient, tumor, and treatment-specific factors on overall survival (OS) and melanoma specific survival (MSS). Cox proportional hazards models assessed the role of tumor location (ear, eyelid, face, lip, scalp/neck) on OS and MSS while controlling for patient age, sex, race, tumor thickness, tumor ulceration, lymph node status, histologic subtype, type of surgery, and use of radiation. Risks of overall and melanoma-specific mortality were reported as hazard ratios (HR) with 95% confidence intervals (CI).

Results—Among 27,097 patients, 10-year rates of OS and MSS were 56.1% and 84.7%, respectively. On multivariate analysis, scalp/neck primary site was associated with an increased risk of overall (HR 1.20, CI 1.14-1.26; $p < 0.001$) and melanoma-specific mortality (HR 1.64, CI 1.49-1.80, $p < 0.001$) relative to melanomas of the face. Tumors of the lip had poorer MSS (HR 1.55; CI 1.05-2.28, $P = 0.03$) but not OS (HR 1.03, CI 0.80-1.34; $p = 0.80$).

Conclusions—Patients with melanomas of the scalp/ neck have poorer OS and MSS and those with lip melanomas have poorer MSS. These anatomic areas should not be overlooked when performing skin examinations.

Keywords

head and neck neoplasms; melanoma; tumor location; population analysis; survival

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Introduction

Cutaneous head and neck melanomas (CHNM) constitute 12-21% of melanomas diagnosed annually(1-5). CHNM have poorer outcomes relative to melanomas of other sites (MOS) (2-3,6). CHNM may be thicker at the time of diagnosis relative to MOS and present at a more advanced stage(2,5). Anatomic constraints of the head and neck region may make optimal resection margins difficult or impossible to achieve(5,7-11). Furthermore, the lymphatic drainage of the head and neck is variable and complex(12-16). Each of these factors are hypothesized to account for the relatively poor prognosis attributed to CHNM. It is unclear if CHNM represents an entity separate from MOS(9,17).

While prior studies have evaluated the survival differences between CHNM and MOS(2-3,9,18), few have assessed survival differences attributable to tumor location among patients with CHNM. Our objective was to use a large, population-based database to evaluate tumor location as a prognostic factor in patients with CHNM.

Materials and Methods

We used the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute to identify all patients with CHNM diagnosed from 1988 to 2006. Characteristics of the SEER database, including the registries represented and the data fields included, have been reported by our group previously(19-22). All cases of primary, histologically confirmed, CHNM were eligible. Those with metastatic disease or mucosal melanoma were excluded. Patients identified by death certificate or autopsy, and those with missing cause of death were also excluded.

Using rules developed by SEER, we calculated survival time as the number of completed months between the date of diagnosis and whichever occurred first: date of death, date last known to be alive, or December 31, 2006. The endpoints for the present study were OS and MSS. For calculations of OS and MSS, patients who were lost to follow-up or survived beyond December 31, 2006 were coded as censored observations. Similarly, for calculations of MSS, patients who died from non-melanoma related causes were coded as censored observations.

We performed univariate analyses of patient, tumor, and treatment-specific factors on OS and MSS using the Kaplan-Meier method. The log rank test assessed differences among survival curves. Variables assessed included tumor location (ear, eyelid, face, lip, scalp/neck), patient age, sex, race/ethnicity (white, Asian, black, and Hispanic), histologic subtype (melanoma not otherwise specified [NOS], superficial spreading, lentigo maligna, nodular, desmoplastic, and other [includes acral, amelanotic, balloon cell, epithelioid, and spindle cell]), tumor depth (Clark level and Breslow depth), presence of tumor ulceration (present, absent, unknown), lymph node status (positive, negative, unknown/not assessed), type of surgery (wide local excision, local excision, and Mohs excision), and use of radiation (yes, no, unknown). Clinicopathological characteristics of those patients with tumors of the scalp/neck were compared to patients with tumors of other head and neck locations using Chi square.

Cox proportional hazards models were constructed utilizing all covariates from the univariate analysis, regardless of significance. For each variable, we included missing or unknown data as a separate category in the analysis.

Risks of overall and melanoma-specific mortality were reported as hazard ratios (HR) with 95% confidence intervals (CI); significance was set at $p \leq 0.05$. All statistical analyses were

two-tailed and performed using STATA version 11 (StataCorp, College Station, Texas) and SPSS version 18.0.0 (SPSS, Chicago, Illinois).

Results

Patient, tumor, and treatment characteristics are presented in Table 1. Briefly, the majority of patients were older (mean age = 65 years) white (94.3%) men (69.8%). Tumors were most commonly noted on the face (48.1%) and scalp/neck (34.3%), with less than 20% arising from the ear, eyelid, or lip. The majority of melanomas (57.4%) were < 1 mm thick, with 6% > 4 mm thick. Lymph nodes were not evaluated or their status was unknown in 70.2% of patients. Of patients with known lymph node status (n=8075), 94.6% were node-negative. The three most prevalent histologic subtypes were Melanoma NOS (42.6%), superficial spreading (23.4%), and lentigo maligna (19.9%); nodular melanomas constituted 8.2% of cases.

Univariate analysis revealed increasing age, gender, histologic subtype, Breslow depth, Clark's level, tumor ulceration, lymph node status, and radiation therapy as predictors of OS and MSS (all $p < 0.001$). Additionally, tumor location and surgery type predicted MSS (both $p < 0.001$).

Kaplan-Meier survival curves depicting OS and MSS dependent on location of tumor are shown in Figure 1 and Figure 2, respectively. Ten-year OS was 55.1% and ten-year MSS was 84.7% for all patients with CHNM. For tumors of the scalp/neck, 10-year rates of OS and MSS were 57.2% and 78.3%, respectively. 10-year OS and MSS for CHNM at sites other than the scalp/neck were 55.6% and 88.0%, respectively. Patient and tumor characteristics of those with melanomas of the scalp/neck relative to CHNM at other sites locations are presented in Table 2.

Multivariate analysis (Table 3) revealed tumors of the scalp and neck to be associated with poorer OS (HR 1.20, 95% CI 1.14-1.26; $p < 0.001$). Other factors associated with poorer OS included increasing age (HR 1.06, 95% CI 1.06-1.06; $p < 0.001$), nodular histology (HR 1.14, 95% CI 1.06-1.23; $p = 0.001$), increasing Breslow thickness (HR 1.29-1.95, 95% CI 1.20-2.15; $p < 0.001$), increasing Clark's level (HR 1.20-1.76, 95% CI 1.11-1.97; $p < 0.001$), nodal involvement (HR 1.92-3.98, 95% CI 1.36-5.95; $p < 0.001$), tumor ulceration (HR 1.50, 95% CI 1.28-1.77; $p < 0.001$), and administration of radiation therapy (HR 1.54, 95% CI 1.35-1.76; $p < 0.001$). Factors associated with improved OS included female gender (HR 0.76, 95% CI 0.72-0.80; $p < 0.001$), wide excision surgery (HR 0.83, 95% CI 0.78-0.87; $p < 0.001$), and lentigo maligna (HR 0.90, 95% CI 0.85-0.96; $p < 0.01$) and desmoplastic (HR 0.78, 95% CI 0.68-0.89; $p < 0.001$) histologies.

Multivariate analysis of MSS is presented in Table 4. Tumors of the scalp/ neck were associated with decreased MSS (HR 1.64, 95% CI 1.49-1.80; $p < 0.001$), as were tumors of the lip (HR 1.55, 95% CI 1.05-2.28; $p = 0.03$). Other factors associated with poorer MSS included increasing age (HR 1.02, 95% CI 1.01-1.02; $p < 0.001$), nodular histology (HR 1.26, 95% CI 1.12-1.41; $p < 0.001$), increasing Breslow thickness (HR 1.75-2.90, 95% CI 1.53-3.41; $p < 0.001$), increasing Clark's level (HR 2.63-6.04, 95% CI 2.17-7.46; $p < 0.001$), nodal involvement (HR 2.05-3.09, 95% CI 1.34-4.82; $p < 0.001$), tumor ulceration (HR 1.92, 95% CI 1.48-2.50; $p < 0.001$), and administration of radiation therapy (HR 2.41, 95% CI 2.05-2.83; $p < 0.001$). Factors associated with improved MSS included female gender (HR 0.70, 95% CI 0.63-0.77; $p < 0.001$), wide excision surgery (HR 0.97, 95% CI 0.80-0.95; $p < 0.01$), and lentigo maligna (HR 0.55, 95% CI 0.46-0.64; $p < 0.001$), and desmoplastic (HR 0.65, 95% CI 0.53-0.80; $p < 0.001$) histologies.

Discussion

CHNM has a poorer prognosis relative to MOS(2-3,9,18). Data regarding the prognostic importance of tumor location in CHNM are limited. Utilizing population-based data, we have reported on the largest series of CHNM patients to date.

We identified scalp/neck melanomas as having a greater risk of melanoma-specific mortality as well as death due to any cause. Although upon univariate Kaplan-Meier survival analysis in which tumor location did not appear to offer prognostic significance, after adjusting for important tumor and patient related characteristics, patients with scalp/neck melanoma demonstrated a 20% increased risk of death due to any cause and a 64% increased risk of melanoma-related death relative to patients with facial melanomas. These findings confirm the findings reported by Leong and the Sentinel Lymph Node Working Group(23). They reported a series of 614 patients with CHNM who underwent sentinel node biopsy and found that those with scalp melanomas had more than a 3-fold increased risk of death relative to melanomas of the face. In our study, lymph node status was unknown for approximately 70% of patients. It is possible that those in the scalp/neck melanoma group had higher rates of lymph node metastasis than those with CHNM at other sites, but information regarding these metastases was missing or not obtained. The high rate of patients with unknown lymph node status is likely due to our data incorporating a decade (1988-1998) where rates of lymphatic mapping and sentinel node biopsy for CHNM nodal staging was quite low. In the absence of sentinel node biopsy to facilitate nodal staging, use of elective lymph node dissection for CHNM can be fraught with difficulty due to the variable and complex lymphatic drainage of the head and neck. We surmise that many patients with CHNM did not have lymph node staging performed prior to the era of sentinel node biopsy. Even among those patients that did undergo lymphatic mapping and sentinel node biopsy, higher false negative rates for sentinel lymph node biopsies of the neck are well-documented(14-15,24-31). Up to 30% of patients with lymph node metastases from neck melanomas bypass the nearest node and involve nodes at more distant sites(32). Additionally, we found that patients with CHNM involving the lip had a 55% increase in the risk of melanoma-related death relative to melanomas of the face, which is previously unreported.

Along with suggesting that tumor location influences survival in CHNM, our data validate known prognostic factors for melanoma such as increasing age, male gender, histologic subtype, Breslow depth, Clark's level, tumor ulceration, and nodal status(9,33-35).

Lachiewicz et al. have previously used SEER data to evaluate CHNM patients, but restricted their study to survival differences between patients with scalp/neck melanomas and those with melanomas of all sites(3). Their study also used the smaller SEER-13 registry, which excludes Arizona Indian, greater California, Kentucky, and New Jersey cancer registries. Furthermore, Lachiewicz et al. excluded all non-white (including Hispanic) patients, and only included cases from 1992-2003. They found that patients with melanoma of the scalp/neck had an 84% greater chance of melanoma-related death as compared to those with melanomas of the extremity (HR 1.84, 95% CI 1.62-2.10). Unlike the current study, their endpoints did not include OS. Our study utilized the SEER-17 database, which captures an estimated 26% of cancers diagnosed annually in the United States. Unlike data from single and multi-institution studies that can be saddled with referral and reporting biases, our population-based data reflect the care of CHNM across a spectrum of community hospitals, health maintenance organizations, county hospitals, and academic medical centers, and may therefore be more generalizable.

Moreover, to our knowledge, ours is the first study to examine the importance of tumor location within the head and neck melanoma population. We have confirmed that tumors of the scalp/ neck are associated with poorer MSS as previously reported but have also shown a significant effect on OS as well. Likewise we have demonstrated that melanomas of the lip are associated with poorer MSS as compared to melanomas of the face.

Limitations of SEER data have been reported previously(36). Briefly, SEER does not provide information regarding patient co-morbidities, adequacy of surgery (including margin status), use of systemic adjuvant or neoadjuvant therapy, socioeconomic status, or insurance status. Even among data fields included within SEER, data may be missing or incomplete. In our study, missing or incomplete data were analyzed as a separate category so that we could estimate the effects of this missing data on survival outcomes. In our study, increased risk of death due to any cause was predicted by unknown Breslow depth (11% increased risk), unknown Clark level (40% increased risk), and unknown nodal status (20% increased risk). Similarly, melanoma-specific mortality was predicted by unknown Breslow depth (43% increased risk), unknown Clark level (nearly 4-fold increase risk), and unknown nodal status (30% increased risk).

SEER groups tumors of the scalp and neck together—thus it is not possible to analyze melanomas of the scalp independently. Table 2 presents the differences between melanomas of the scalp/ neck and melanomas of other head and neck sites. There are significant differences in respect to Breslow thickness, tumor ulceration, and N stage. Importantly, however, tumor location remained an important predictor of survival upon multivariate analysis with inclusion of these other tumor and patient variables (Table 3). Data from other studies have suggested that tumors in these areas may have clinically different behavior(9,33,37). It is possible that melanomas of the scalp present at an advanced stage as compared to melanomas of other locations within the head and neck. Future studies are needed to evaluate differences between melanomas of the scalp and melanomas of the neck.

Routine skin screening is an integral component of early melanoma detection. Early detection of disease, when followed closely thereafter by adequate surgical resection, increases the likelihood of cure(38). In this regard, our data have several public health implications. Distinct from melanomas of other sites, wound closure is often challenging in patients with CHNM undergoing wide local excision. If these melanomas could be diagnosed earlier, thinner depth of invasion could allow for narrower margins and the need for sentinel node biopsy may be obviated. Patients and primary health care providers should be educated that routine evaluation of the head and neck, and especially of the lips, scalp and neck, should be performed as part of the standard skin examination.

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Figure 1.
Univariate Kaplan-Meier survival curves of overall survival according to primary melanoma site.

Figure 2.
Univariate Kaplan-Meier survival curves of melanoma-specific survival according to primary melanoma site.

Table 1

Clinicopathological characteristics of 27,097 patients with cutaneous head and neck melanoma.

Variable	Mean or Percent
Age	65
Male	69.8
Race/Ethnicity	
White	94.3
Hispanic	2.5
Black	0.2
Asian	0.4
Other	2.6
Tumor Location	
Face	48.1
Scalp/Neck	34.3
Ear	15.1
Eyelid	1.7
Lip	0.8
Histologic Subtype	
Melanoma NOS	42.6
Superficial Spreading	23.4
Lentigo Maligna	19.9
Nodular	8.2
Desmoplastic	2.8
Other	3.2
Breslow Thickness	
<1 mm	57.4
1-2 mm	15.6
2-4 mm	10.0
>4 mm	6.0
Unknown	11.0
Clark Level	
I/II	35.7
III	18.1
IV	24.1
V	6.1
Unknown	16.0
N Stage	
N0	28.2

Variable	Mean or Percent
N1	0.8
N2	0.6
N3	0.2
Unknown/ Not examined	70.2
Tumor Ulceration	
Yes	7.9
No	24.9
Unknown	67.1
Radiation	
Yes	2.1
No	97.9

Table 2

Clinicopathological characteristics of patients with scalp/ neck melanomas vs. melanomas at other head and neck sites.

Variable	Scalp/ Neck	Other Head and Neck Sites	P value
	% or mean		
Age	61	66	P<0.001
Female	25.8	32.5	P<0.001
Ethnicity			P<0.001
White	94.9	93.9	
Asian	0.4	0.4	
Black	0.3	0.2	
Hispanic	1.9	2.8	
Histologic Subtype			P<0.001
Melanoma NOS	44.2	41.7	
Superficial Spreading	28.3	20.8	
Lentigo Maligna	11.7	24.2	
Nodular	9.6	7.5	
Desmoplastic	3.1	2.7	
Breslow Thickness			P<0.001
<1 mm	54.4	59.0	
1-2 mm	15.9	15.4	
2-4 mm	11.1	9.4	
>4 mm	8.8	4.6	
Unknown	9.8	11.6	
Clark's Level			P<0.001
I/II	31.8	37.8	
III	18.9	17.7	
IV	25.7	23.3	
V	8.3	4.9	
Unknown	15.3	16.3	
Tumor Ulceration	9.8	7.0	P<0.001
N stage			P<0.001
N0	28.6	28.0	
N1	1.3	0.5	
N2	1.0	0.4	
N3	0.5	0.1	
Unknown/ Not examined	68.7	71.0	

Variable	Scalp/ Neck	Other Head and Neck Sites	P value
	% or mean		
Surgery Type			P<0.001
Local	52.3	57.9	
Wide	45.7	39.1	
Mohs	1.2	2.3	
Radiation Therapy	2.7	1.8	P<0.001

Table 3

Multivariate analysis model incorporating multiple patient and tumor-related characteristics for overall survival.

Variable	Overall Survival		
	HR	95% CI	P value
Age	*1.06	1.06-1.06	<0.001
Female	*0.76	0.72-0.80	<0.001
Ethnicity			
White	Ref		
Asian	0.78	0.52-1.19	0.25
Black	1.19	0.73-1.95	0.48
Hispanic	1.14	0.97-2.88	0.09
Histologic Subtype			
Melanoma NOS	Ref		
Superficial Spreading	0.96	0.90-1.02	0.16
Lentigo Maligna	*0.90	0.85-0.96	0.002
Nodular	*1.14	1.06-1.23	0.001
Desmoplastic	*0.78	0.68-0.89	<0.001
Tumor Location			
Face	Ref		
Ear	0.94	0.87-1.00	0.06
Eyelid	0.92	0.77-1.10	0.37
Lip	1.03	0.80-1.34	0.80
Scalp/neck	*1.20	1.14-1.26	<0.001
Breslow depth			
<1mm	Ref		
1-2mm in depth	*1.29	1.20-1.39	<0.001
2-4mm in depth	*1.62	1.50-1.76	<0.001
>4mm in depth	*1.95	1.77-2.15	<0.001
Unknown depth	*1.11	1.03-1.20	<0.001
Clark level			
I/II	Ref		
III	*1.20	1.11-1.29	<0.001
IV	*1.38	1.28-1.49	<0.001
V	*1.78	1.60-1.97	<0.001
Unknown	*1.40	1.30-1.52	<0.001

Variable	Overall Survival		
	HR	95% CI	P value
N stage			
N0	Ref		
N1	*2.64	1.90-3.66	<0.001
N2	*1.92	1.36-2.70	<0.001
N3	*3.98	2.67-5.95	<0.001
Unknown/ Not examined	*1.20	1.03-1.39	0.02
Surgery Type			
Local	Ref		
Wide	*0.83	0.78-0.87	<0.001
Mohs	0.86	0.65-1.16	0.33
Tumor ulceration			
No	Ref		
Yes	*1.50	1.28-1.77	<0.001
Unknown	1.14	0.97-1.35	0.12
Radiation			
No	Ref		
Yes	*1.54	1.35-1.76	<0.001

* Designates statistical significance at $p \leq 0.05$

Table 4

Multivariate analysis model incorporating multiple patient and tumor-related characteristics for melanoma-specific survival.

Variable	Melanoma- Specific Survival		
	HR	95% CI	P value
Age	*1.01	1.01-1.02	<0.001
Female	*0.70	0.63-0.77	<0.001
Ethnicity			
White	Ref		
Asian	1.05	0.55-2.03	0.88
Black	1.36	0.70-2.64	0.37
Hispanic	1.19	0.92-1.54	0.20
Histologic Subtype			
Melanoma NOS	Ref		
Superficial Spreading	1.03	0.92-1.15	0.65
Lentigo Maligna	*0.55	0.46-0.64	<0.001
Nodular	*1.26	1.12-1.41	<0.001
Desmoplastic	*0.65	0.53-0.80	<0.001
Tumor Location			
Face	Ref		
Ear	0.92	0.81-1.06	0.25
Eyelid	1.02	0.71-1.47	0.91
Lip	*1.55	1.05-2.28	0.03
Scalp/neck	*1.64	1.49-1.80	<0.001
Breslow depth			
<1mm	Ref		
1-2mm in depth	*1.75	1.53-2.00	<0.001
2-4mm in depth	*2.69	2.34-3.10	<0.001
>4mm in depth	*2.90	2.46-3.41	<0.001
Unknown depth	*1.43	1.22-1.68	<0.001
Clark level			
I/II	Ref		
III	*2.63	2.17-3.18	<0.001
IV	*3.78	3.14-4.55	<0.001
V	*6.04	4.90-7.46	<0.001
Unknown	*3.96	3.28-4.79	<0.001

Variable	Melanoma- Specific Survival		
	HR	95% CI	P value
N stage			
N0	Ref		
N1	*3.09	2.10-4.56	<0.001
N2	*2.05	1.34-3.13	0.001
N3	*2.97	1.83-4.82	<0.001
Unknown/ Not examined	*1.30	1.02-1.65	0.03
Surgery Type			
Local	Ref		
Wide	*0.87	0.80-0.95	0.02
Mohs	1.21	0.72-2.03	0.47
Tumor ulceration			
No	Ref		
Yes	*1.92	1.48-2.50	<0.001
Unknown	1.24	0.94-1.64	0.12
Radiation			
No	Ref		
Yes	*2.41	2.05-2.83	<0.001

* Designates statistical significance at $p \leq 0.01$