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Research Paper

Predictors of occult lymph node metastasis in cutaneous head and neck melanoma

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Abstract *Objective:* To use the Surveillance, Epidemiology, and End Results (SEER) database to verify the findings of a recent National Cancer Database (NCDB) study that identified factors predicting occult nodal involvement in cutaneous head and neck melanoma (CHNM) while identifying additional predictors of occult nodal metastasis and comparing two distinct cancer databases.
Methods: Cases of CHNM in the SEER database diagnosed between 2004 and 2014 were identified. Demographic information and oncologic data were obtained. Univariate and multivariate analysis were performed to identify factors associated with pathologic nodal positivity.
Results: There were 34002 patients with CHNM identified. Within this population, 16232 were clinically node-negative, 1090 of which were found to be pathologically node-positive. On multivariate analysis, factors associated with an increased risk of occult nodal metastasis included increasing depth of invasion (stepwise increase in adjusted odds ratio [*OR*]), nodular histology (a*OR*: 1.47 [95% CI: 1.21—1.80]), ulceration (a*OR*: 1.74 [95% CI: 1.48—2.05]), and mitoses (a*OR*: 1.86 [95% CI: 1.36—2.54]). Factors associated with a decreased risk of occult nodal metastasis included female sex (a*OR*: 0.80 [0.67—0.94]) and desmoplastic histology (a*OR*: 0.37 [95% CI: 0.24—0.59]). Between the SEER database and the NCDB, factors associated with occult nodal involvement were similar except for nodular histology and female sex, which did not demonstrate significance in the NCDB.
Conclusion: Regarding clinically node-negative CHNM, the SEER database and the NCDB have similarities in demographic information but differences in baseline population sizes and tumor

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characteristics that should be considered when comparing findings between the two databases.

Level of evidence: 4.

Introduction

The incidence of melanoma in the United States continues to rise, with 91270 new cases of melanoma and 9320 resulting deaths estimated in 2018.[1] Among malignant melanomas, almost 20% occur in the head and neck region.[2] The complex lymphatic drainage of the head and neck, especially to the sentinel lymph nodes, is of critical importance in determining a patient's prognosis, as nodal metastasis is an important predictor of poor survival in melanoma.

A recent study by Yalamanchi et al[3] using the National Cancer Database (NCDB) identified factors associated with occult nodal involvement in cutaneous head and neck melanoma (CHNM). They found that younger age, primary site of cutaneous scalp, neck or face, increasing thickness, vertical growth phase presence, mitoses, and ulceration were independently associated with positive nodal status by surgical evaluation. They identified lentigo maligna and desmoplastic histologies to be associated with a decreased risk of occult nodal involvement.

Using the Surveillance, Epidemiology, and End Results (SEER) database,[4] we aimed to verify the data found by Yalamanchi et al[3] and potentially identify additional predictors of occult nodal metastasis. We also aimed to use our results to identify similarities and differences between the SEER database and the NCDB.

Materials and methods

Study cohort

Case-based data was obtained using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. Cases from 2004 to 2014 in the SEER database were included. The SEER 18 Registry Research Data (released April 2017, based on the November 2016 submission) was utilized.[4] Institutional Review Board approval was not necessary since a public database was used. Cases were included based on a diagnosis of head and neck melanoma using the International Classification of Diseases for Oncology (ICD-O-3) codes of 8720/3: Malignant Melanoma, NOS, 8721/3: Nodular Melanoma, 8722/3: Balloon Cell Melanoma, 8723/3: Malignant Melanoma, Regressing, 8730/3: Amelanotic Melanoma, 8740/3: Malignant Melanoma in Junctional Nevus, 8741/3: Malignant Melanoma in Precancerous Melanosis, 8742/3: Lentigo Maligna Melanoma, 8743/3: Superficial Spreading Melanoma, 8744/3: Acral Lentiginous Melanoma, Malignant, 8745/3: Desmoplastic Melanoma, Malignant, 8746/3: Mucosal Lentiginous Melanoma, 8761/3: Malignant Melanoma in Giant Pigmented Nevus, 8770/3: Mixed Epithelioid and Spindle Cell Melanoma, 8771/3: Epithelioid Cell Melanoma, 8772/3: Spindle Cell Melanoma, NOS, 8773/3: Spindle Cell Melanoma, Type A. Patients were included based on the following primary sites of melanoma: C44.0: Skin of Lip: NOS, C44.1: Eyelid, C44.2: External Ear, C44.3: Skin of other and unspecified parts of face, and C44.4: Skin: Scalp/Neck. Patients were included if they had a documented clinically negative lymph node status upon lymph node examination. Only patients $\geq$18 years of age were included. Patients were excluded if they had a clinically positive lymph node status or had metastatic disease. Patients were divided into cohorts based on their pathologic lymph node status. Histologies with $<$2.5% occurrence were grouped into a cohort titled "Other". Additionally, unknown racial status was not assessed in the logistic regression analysis.

Study variables

The primary study variable was the presence of lymph node metastasis on pathological examination. Demographic data included age at diagnosis, sex, race, and primary site. Oncologic variables included tumor histological type, depth of invasion, mitosis, and ulcerative status.

Statistical analysis

All data analyses were performed with SPSS 24.0 (IBM Corporation, Armonk, NY), SigmaPlot 12.5 (Systat Software, San Jose, CA), and MedCalc software 16.8 (MedCalc Software bvba, Ostend, Belgium). All continuous variables were tested for normal distribution as determined by the Kolmogorov–Smirnov test. Continuous variables were described as mean (SD) or median (range). Comparisons between continuous variables were performed with a *t*-test or Mann–Whitney test as appropriate. Categorical variables were described as frequency, percentage, and/or range. Comparisons between categorical variables were performed with a Chi–Square test. To assess for variables potentially associated with a pathologic positive lymph node status, univariate and multivariate logistic regression analyses were performed. Variables significant at the 0.10 α level were included into the multivariate logistic regression model. A backward stepwise regression approach was used to determine the final multivariate model. A *P*-value of $<$0.05 was considered statistically significant.

Results

Patient demographics

A total of 34002 patients were diagnosed with CHNM. Of these patients, 16232 clinically node-negative patients

were included in our analysis based on our search criteria. Of this group, 1090 (6.7%) patients had positive nodal status confirmed via pathological examination. Overall, 4221 (56.6%) patients were female and 15459 (95.2%) were Caucasian (Table 1).

Tumor characteristics

We studied primary tumor sites and found that of the pathologic node-positive cohort, 590 (54.1%) patients had melanoma of the "Skin of Scalp and Neck" as compared to 5967 (39.4%) in the pathologic node-negative cohort ($P < .001$). Study of histological type in the pathologic node-positive cohort identified266 (24.4%) patients with nodular CHNM as compared to 1028 (6.8%)in the pathologic node-negative cohort ($P < .001$). For depth of invasion, we found that 124 (11.4%) patients in the pathologic node-positive cohort had a depth of invasion <1 mm as compared to 9498 (62.7%) patients in the pathologic node-negative cohort ($P < .001$). Regarding rates of ulceration, we found that 417 (38.3%) patients in the pathologic-node positive cohort had ulceration as compared to 1867 (12.3%) patients in the pathologic-node negative cohort ($P < .001$). We also studied mitoses and found that 436 (40.0%) of patients in the pathologic node-positive cohort had mitoses as compared to 5475 (36.2%) of patients in the pathologic node-negative cohort ($P < .001$, Table 1).

Factors associated with pathologic nodal positivity

On univariate analysis, black race (odds ratio [*OR*]: 4.47 [95% CI: 2.18–9.18]), nodular histology (*OR*: 3.86 [95% CI: 3.28–4.55]), ulceration (*OR*: 4.55 [95% CI: 3.98–5.19]), mitoses (*OR*: 8.94 [95% CI 6.73–11.90]), and increasing depth of invasion ≥1 mm (stepwise increase in *OR*) were associated with an increased risk of nodal metastasis. Eyelid primary site (*OR*: 0.24 [95% CI: 0.07–0.81]), age at diagnosis (*OR*: 0.971 [95% CI: 0.970–0.974), female sex (*OR*: 0.81 [95% CI: 0.70–0.94]), and lentigo maligna histology (*OR*: 0.28 [95% CI: 0.21–0.37]) were associated with a decreased risk of nodal metastasis (Table 2).

On multivariate analysis, nodular histology (adjusted odds ratio [a*OR*]: 1.47 [95% CI: 1.21–1.80]), ulceration (a*OR*: 1.74 [95% CI: 1.48–2.05]), mitoses (a*OR*: 1.86 [95% CI: 1.36–2.54]), and increasing depth of invasion (stepwise increase in a*OR*) continued to maintain significance. Age at diagnosis (a*OR*: 0.961 [95% CI: 0.960–0.970]) and female sex (a*OR*: 0.80 [0.67–0.94]) continued to maintain significance as factors that decreased risk of nodal metastasis. In addition, desmoplastic histology, which did not demonstrate significance on univariate analysis (*OR*: 0.82 [95% CI: 0.54–1.25]), was found to be significantly associated with a decreased risk of nodal metastasis on multivariate analysis (a*OR*: 0.37 [95% CI: 0.24–0.59]) (Table 2).

Discussion

The utility of sentinel lymph node biopsy (SLNB) was demonstrated in the Multicenter Selective Lymph adenectomy Trial (MSLT-I), which showed that early sentinel-node biopsy provided a survival benefit for intermediate-thickness primary melanomas with nodal metastases.[5,6] However, the indications to perform SLNB in thin (<1 mm) melanomas are unclear. Thus, it is reasonable to consider other tumor characteristics beyond Breslow's depth when determining whether the benefits of SLNB outweigh the risks.

One objective of our study was to verify the data found by Yalamanchi et al,[3] who found that younger age, primary site of cutaneous scalp, neck, or face, increasing thickness, mitoses, ulceration, and vertical growth phase were independent predictors of nodal positivity. In our study, multivariate analysis confirmed that mitoses (a*OR*: 1.86 [95% CI: 1.36–2.54]), ulceration (a*OR*: 1.74, 95% CI [1.48–2.05]), and increasing depth of invasion ≥ 1 mm (stepwise increase in a*OR*) were predictors of nodal positivity. However, we did not find any primary head and neck sites to be significant predictors of positive nodal status. Yalamanchi et al[3] also demonstrated that lentigo maligna melanoma, malignant desmoplastic, and other histologies were associated with a decreased risk of occult nodal status. Our study confirmed that desmoplastic melanoma was associated with a decreased risk of nodal status (a*OR*: 0.37 [95% CI:[0.24–0.59]) and also uniquely identified female sex to decrease risk of occult nodal status (a*OR*: 0.80 [95% CI: 0.67–0.940), but did not find any significant association between lentigo maligna histology (a*OR*: 0.83 [95% CI: 0.61–1.14]) and positive nodal status. Unlike in the NCDB study, nodular (a*OR*: 1.47 [95% CI: 1.21–1.80]) and superficial spreading (a*OR*: 1.25 [95% CI: 1.03–1.51]) histologies were found to be predictors in our study.[3]

The finding of nodular histology as a predictor of nodal metastasis is perhaps the most distinctive one of our study. As nodular melanoma uniquely has a more prominent vertical as opposed to radial growth phase,[7] it has unsurprisingly been shown to be significantly associated with tumor thickness.[8] The increased thickness demonstrated by this histology logically increases the risk of metastatic disease. The literature on nodular melanoma, however, is limited and conflicting. Cadili and Dabbs, in a retrospective review of 348 patients, found that nodular type was a predictor of positive SLN status, even after tumor thickness was adjusted for.[9] Kunte et al,[10] in an analysis of 1049 patients, also found nodular histology to be an independent risk factor for SLN positivity in melanoma, with 36.8% of patients with this particular histology demonstrating SLN positivity. However, Bonett et al[11] found that after adjustment for tumor thickness and level, nodular histology did not result insignificantly different mortality as compared to lentigo maligna or superficial spreading melanomas. In our study, prior to adjusting for relevant covariates, nodular melanoma had an *OR* of 3.86 (95% CI: 3.28–4.55) on univariate analysis. After other variables, including depth of invasion, were adjusted for on multivariate analysis, nodular histology continued to maintain significance (a*OR*: 1.47 [95% CI: 1.21–1.80]). The clinical relevance of our finding is that providers may want to give special consideration to nodular melanoma when determining whether or not to perform a SLNB.

Our study and the NCDB study both found that desmoplastic melanoma was associated with a lower risk of nodal metastasis.[3] Other results in the literature have brought attention to the utility, or lack thereof, of SLNB in

Table 1 Patient demographics and tumor characteristics.

Characteristic	Number of Patients: n (%)	Pathologic Node-Negative, n (%)	Pathologic Node-Positive, n (%)	*P*-value
Total cases	16232 (100)	15142 (92.3)	1090 (6.7)	
Age: mean (SD, range)	68.0 (15.7, 18.0–106.0)	68.6 (15.5, 18.0–106.0)	60.4 (16.5, 18.0–98.0)	<0.001
Sex				0.01
Female	4221 (26.0)	3977 (26.3)	244 (22.4)	
Male	12011 (74.0)	11165 (73.7)	846 (77.6)	
Race				<0.001
White	15459 (95.2)	14387 (95.0)	1072 (98.3)	
Other	76 (0.5)	68 (0.4)	-[a]	
Black	40 (0.2)	30 (0.2)	-[a]	
Unknown	657 (4.0)	657 (4.3)	-[a]	
Primary Site				<0.001
Skin of lip, NOS	117 (0.7)	109 (0.7)	-[a]	
Eyelid	232 (1.4)	228 (1.5)	-[a]	
External ear	2279 (14.0)	2121 (14.0)	158 (14.5)	
Skin of other and unspecified parts of face	7047 (43.4)	6717 (44.4)	330 (30.3)	
Skin of scalp and neck	6557 (40.4)	5967 (39.4)	590 (54.1)	
Histology				<0.001
Superficial spreading melanoma	3440 (21.2)	3222 (21.3)	218 (20.0)	
Nodular melanoma	1294 (8.0)	1028 (6.8)	266 (24.4)	
Lentigo maligna melanoma	2926 (18.0)	2873 (19.0)	53 (4.9)	
Desmoplastic melanoma, malignant	460 (2.8)	436 (2.9)	24 (2.2)	
Spindle cell melanoma, NOS	360 (2.2)	332 (2.2)	28 (2.6)	
Malignant melanoma, NOS	7503 (46.2)	7032 (46.4)	471 (43.2)	
Mixed epithelioid and spindle cell melanoma	47 (0.3)	41 (0.3)	-[a]	
Epithelioid cell melanoma	36 (0.2)	30 (0.2)	-[a]	
Acral lentiginous melanoma, malignant	-[a]	-[a]	-[a]	
Other	157 (1.0)	139 (0.9)	18 (1.7)	
Depth of Invasion				<0.001
<1 mm	9622 (59.3)	9498 (62.7)	124 (11.4)	
1–2 mm	2662 (16.4)	2376 (15.7)	286 (26.2)	
2.01–3 mm	948 (5.8)	775 (5.1)	173 (15.9)	
3.01–4 mm	865 (5.3)	694 (4.6)	171 (15.7)	
4.01–5 mm	440 (2.7)	353 (2.3)	87 (8.0)	
5.01–6 mm	282 (1.7)	221 (1.5)	61 (5.6)	
>6 mm	567 (3.5)	433 (2.9)	134 (12.3)	
Unknown	846 (5.2)	792 (5.2)	54 (5.0)	
Ulceration				<0.001
Absent	13470 (83.0)	12839 (84.8)	631 (57.9)	
Present	2284 (14.1)	1867 (12.3)	417 (38.3)	
Unknown	478 (2.9)	436 (2.9)	42 (3.9)	
Mitoses				<0.001
Absent	6119 (37.7)	6065 (40.1)	54 (5.0)	
Present	5911 (36.4)	5475 (36.2)	436 (40.0)	
Unknown	4202 (25.9)	3602 (23.8)	600 (55.0)	

[a] Indicates n ≤ 10.

desmoplastic melanomas. Pawlik et al[12] confirmed lower rates of SLN-positivity in desmoplastic melanoma as compared to non-desmoplastic melanomas. Even with Breslow's depth accounted for in a case-matched control study by Livestro et al,[13] the risk of SLN-positivity was still lower in desmoplastic melanoma than other forms of melanoma. However, they also found that survival rates are similar between DM and other types of melanoma when of similar thickness. A SEER database study by Smith and Lentsch found that among patients with desmoplastic melanoma diagnosed between 1998 and 2007, positive SLN status did not have a significant effect on disease-specific survival, adding further skepticism to performing SLNB for this histology.[14] Although data is inconclusive, when determining whether SLNB should be performed in thin melanomas with desmoplastic histology, added caution in regards to risks and benefits of the procedure may be warranted.

Table 2 Variables associated with occult nodal positivity.

Variable	Univariate Analysis: Odds Ratio (95% CI)	Multivariate Analysis: Odds Ratio (95% CI)
Primary Site		
Skin of lip, NOS	Reference	Reference
Eyelid	0.24 (0.07–0.81)	0.37 (0.10–1.30)
External ear	1.02 (0.49–2.12)	1.25 (0.56–2.81)
Skin of other and unspecified parts of face	0.67 (0.32–1.38)	1.10 (0.48–2.36)
Skin of scalp and neck	1.35 (0.65–2.78)	1.48 (0.67–3.26)
Age at Diagnosis	0.971 (0.970–0.974)	0.961 (0.960–0.970)
Sex		
Male	Reference	Reference
Female	0.81 (0.70–0.94)	0.80 (0.67–0.94)
Race		
White	Reference	Reference
Black	4.47 (2.18–9.18)	2.25 (0.92–5.47)
Other[a]	1.58 (0.76–3.29)	1.10 (0.48–2.52)
Histology		
Malignant melanoma, NOS	Reference	Reference
Superficial spreading melanoma	1.01 (0.86–1.19)	1.25 (1.03–1.51)
Desmoplastic melanoma, malignant	0.82 (0.54–1.25)	0.37 (0.24–0.59)
Lentigo maligna melanoma	0.28 (0.21–0.37)	0.83 (0.61–1.14)
Nodular melanoma	3.86 (3.28–4.55)	1.47 (1.21–1.80)
Other	1.57 (1.18–2.09)	0.79 (0.57–1.10)
Ulceration		
Absent	Reference	Reference
Present	4.55 (3.98–5.19)	1.74 (1.48–2.05)
Unknown	1.96 (1.41–2.72)	1.10 (0.75–1.61)
Mitoses		
Absent	Reference	Reference
Present	8.94 (6.73–11.90)	1.86 (1.36–2.54)
Unknown	18.71 (14.12–24.79)	8.75 (6.47–11.84)
Depth of Invasion		
<1 mm	Reference	Reference
1–2 mm	9.22 (7.43–11.44)	7.74 (6.13–9.78)
2.01–3 mm	17.10 (13.42–21.78)	13.31 (10.10–17.54)
3.01–4 mm	18.87 (14.79–24.08)	15.28 (11.50–20.28)
4.01–5 mm	18.88 (14.10–25.33)	15.37 (10.90–21.70)
5.01–6 mm	21.14 (15.14–29.53)	17.31 (11.71–25.60)
>6 mm	23.70 (18.23–30.82)	18.66 (13.61–25.59)
Unknown	5.22 (3.76–7.25)	2.45 (1.70–3.53)

[a] American Indian/Alaskan Natives, Asian and Pacific Islanders, Unknown.

Unlike the NCDB study, which did not find sex to be associated with nodal metastasis, we found that female sex was associated with a decreased risk of nodal metastasis.[3] This finding supports a prior SEER database study that concluded that female sex was associated with an improved 5-year disease-specific survival as compared to male sex.[15] In addition, other studies in the literature have endorsed the notion that female sex is associated with a more favorable prognosis in melanoma, with theories revolving around an underlying biological or hormonal difference being responsible.[16–18] However, the true etiology responsible for this difference in prognosis is still unclear and requires further investigation.

Another objective of our study was to compare data within the SEER database to data within the NCDB, two databases that have important and distinct differences.[19] The National Cancer Database (NCDB) is a joint program between the Commission of Cancer (CoC) of the American College of Surgeons and the American Cancer Society that provides annual data regarding care of patients with cancer treated throughout hospitals nationwide.[20] The NCDB contains data representative of over 70% of all new cancer diagnoses in the country.[21] The SEER Program of the National Cancer Institute contains data collected from population-based cancer registries that represent approximately 28% of the nation's population.[22] An important distinction between the two databases is that the NCDB is hospital-based while the SEER database is population-based. While the NCDB studies a larger population of patients, the hospital-based nature of the database may render it less representative of the actual U.S. population than the smaller sample of patients studied in the SEER

database. The NCDB identified many more cases of CHNM (66495) than the SEER database (34002). However, the SEER database had a much higher proportion of clinical node-negative patients (47.7% [16232]) than the NCDB (28.4% [18882]). Demographic information between the clinical node-negative populations were similar in terms of age (SEER: 68.0; NCDB: 62.9), sex (SEER: 26.0% female; NCDB: 24.6% female), and race (SEER: 95.2% white; NCDB: 98.2% white). Some data regarding tumor characteristics, such as primary site (SEER: skin of other and unspecified parts of face − 43.4%, skin of scalp and neck − 40.4%; NCDB: skin of face − 40.2%; skin of scalp and neck: 42.2%) and mitoses (SEER: 36.4%; NCDB: 23.0%), were also similar. However, the SEER database had higher rates of lentigo maligna melanoma (18.0% vs. 8.9%) and lower rates of nodular melanoma (SEER: 8.0%; NCDB: 13.9%), as well as thinner depth of invasion overall (depth $<$ 1 mm, SEER: 59.3%; NCDB: 33.7%) and lower rates of ulceration (SEER: 14.1%; NCDB: 23.0%) than the NCDB. The important differences in melanoma characteristics between the two databases may have been responsible for differences in the predictive factors identified between this study and the NCDB study.[3]

There were several strengths and limitations of this study. Vertical growth phase presence was not an available variable in the SEER database, unlike in the NCDB. Unfortunately, this prevented us from accounting for a potentially significant predictor of nodal positivity. It is also possible that there was an overlap of patients included in both databases, but it is impossible to know the degree to which this occurred. There is also the potential for coding errors within this database. A strength of this study is the large sample size of patients evaluated in the context of a population-based dataset. In addition, the ability of this study to confirm several findings of the NCDB study adds additional significance to these pre-existing findings.[3]

Conclusions

This study confirms several findings of the NCDB study while also identifying distinct factors impacting nodal status in CHNM. Similar findings between the two studies include mitoses, ulceration, and increasing depth of invasion increasing risk of occult nodal status, and desmoplastic histology decreasing risk of occult nodal status.[3] However, this study uniquely finds nodular histology to increase risk and female sex to decrease risk of occult nodal status. The SEER database and the NCDB, in regards to cutaneous head and neck melanoma, are similar in terms of demographic information but can have substantial differences in terms of tumor characteristics. It is important to interpret any similarities and differences, regarding cutaneous head and neck melanoma, between the two databases with caution. Further studies on predictors of nodal status are necessary to ensure that significant factors are considered when determining whether or not an SLNB should be performed in indeterminate cases.

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Conflict of interest

There are no conflicts of interest.

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