Research Paper

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

Jonathan S. Ni*, Tyler A. Janz, Shaun A. Nguyen, Eric J. Lentsch

Department of Otolaryngology- Head and Neck Surgery, Medical University of South Carolina, Charleston, SC, USA

Received 4 July 2018; accepted 26 February 2019
Available online 28 September 2019

KEYWORDS
Head and neck melanoma; Lymph node metastasis; Occult nodal metastasis; Sentinel lymph node biopsy

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 (aOR: 1.47 [95% CI: 1.21–1.80]), ulceration (aOR: 1.74 [95% CI: 1.48–2.05]), and mitoses (aOR: 1.86 [95% CI: 1.36–2.54]). Factors associated with a decreased risk of occult nodal metastasis included female sex (aOR: 0.80 [0.67–0.94]) and desmoplastic histology (aOR: 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
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. Among malignant melanomas, almost 20% occur in the head and neck region. 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 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, we aimed to verify the data found by Yalamanchi et al 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. 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 ≥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 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 [aOR]: 1.47 [95% CI: 1.21—1.80]), ulceration (aOR: 1.74 [95% CI: 1.48—2.05]), mitoses (aOR: 1.86 [95% CI: 1.36—2.54]), and increasing depth of invasion (stepwise increase in aOR) continued to maintain significance. Age at diagnosis (aOR: 0.961 [95% CI: 0.960—0.970]) and female sex (aOR: 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 (aOR: 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 Lymphadenectomy Trial (MSLT-I), which showed that early sentinel-node biopsy provided a survival benefit for intermediate-thickness primary melanomas with nodal metastases. 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, 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 (aOR: 1.86 [95% CI: 1.36—2.54]), ulceration (aOR: 1.74, 95% CI [1.48—2.05]), and increasing depth of invasion ≥1 mm (stepwise increase in aOR) 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 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 (aOR: 0.37 [95% CI:0.24—0.59]) and also uniquely identified female sex to decrease risk of occult nodal status (aOR: 0.80 [95% CI: 0.67—0.940], but did not find any significant association between lentigo maligna histology (aOR: 0.83 [95% CI: 0.61—1.14]) and positive nodal status. Unlike in the NCDB study, nodular (aOR: 1.47 [95% CI: 1.21—1.80]) and superficial spreading (aOR: 1.25 [95% CI: 1.03—1.51]) histologies were found to be predictors in our study.

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, it has unsurprisingly been shown to be significantly associated with tumor thickness. 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. Kunte et al, 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 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 (aOR: 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. Other results in the literature have brought attention to the utility, or lack thereof, of SLNB in...
desmoplastic melanomas. Pawlik et al\textsuperscript{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,\textsuperscript{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.\textsuperscript{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 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) | |

\textsuperscript{a} Indicates n \leq 10.
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. 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. 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. 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. 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. The NCDB contains data representative of over 70% of all new cancer diagnoses in the country. 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.

### 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**  |                                        |                                          |
| <10 years              | 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)                         |
| Othera                 | 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  | 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)                        |

* American Indian/Alaskan Natives, Asian and Pacific Islanders, Unknown.
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. However, this study uniquely finds nodular histology to increase 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.

Conflict of interest

There are no conflicts of interest.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7–30.
2. Garbe C, Böttner P, Bertz J, et al. Primary cutaneous melanoma. Prognostic classification of anatomic location. Cancer. 1995;75:2492–2498.
3. Yalamanchi P, Brant JA, Chen J, Newman JG. Clinicopathologic factors predictive of occult lymph node involvement in cutaneous head and neck melanoma. Otolaryngol Head Neck Surg. 2018;158:489–496.
4. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat database: SEER 18 Registry Research data, Surveillance Research Program, released April 2017, based on the November 2016 submission.
5. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med. 2006;355:1307–1317.
6. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med. 2014;370:599–609.
7. McGovern VJ, Mihm MC, Bailly C, et al. The classification of malignant melanoma and its histologic reporting. Cancer. 1973;32:1446–1457.
8. Chamberlain AJ, Fritschi L, Giles GG, Dowling JP, Kelly JW. Nodular type and older age as the most significant associations of thick melanoma in Victoria, Australia. Arch Dermatol. 2002;138:609–614.
9. Cadili A, Dabbs K. Predictors of sentinel lymph node metastasis in melanoma. Can J Surg. 2010;53:32–36.
10. Kunte C, Geimer T, Baumert J, et al. Prognostic factors associated with sentinel lymph node positivity and effect of sentinel status on survival: an analysis of 1049 patients with cutaneous melanoma. Melanoma Res. 2010;20:330–337.
11. Bonett A, Roder D, Esterman A. Melanoma case survival rates in South Australia by histological type, thickness and level of tumour at diagnosis. Med J Aust. 1986;144:680–682.
12. Pawlik TM, Ross MI, Prieto VG, et al. Assessment of the role of sentinel lymph node biopsy for primary cutaneous desmoplastic melanoma. Cancer. 2006;106:900–906.
13. Livestro DP, Muzikansky A, Kaine EM, et al. Biology of desmoplastic melanoma: a case-control comparison with other melanomas. J Clin Oncol. 2005;23:6739–6746.
14. Smith VA, Lentsch EJ. Sentinel node biopsy in head and neck desmoplastic melanoma: an analysis of 244 cases. Laryngoscope. 2012;122:116–120.
15. Arce PM, Camilion PR, Stokes WA, Nguyen SA, Lentsch EJ. Is sex an independent prognostic factor in cutaneous head and neck melanoma. Laryngoscope. 2014;124:1363–1367.
16. Kemeny MM, Busch E, Stewart AK, Menck HR. Superior survival of young women with malignant melanoma. Am J Surg. 1998;175:437–444. discussion 444-445.
17. Joosse A, Collette S, Suciu S, et al. Superior outcome of women with stage I/II cutaneous melanoma: pooled analysis of four European Organisation for research and treatment of cancer phase III trials. J Clin Oncol. 2012;30:2240–2247.
18. Stidham KR, Johnson JL, Seigler HF. Survival superiority of females with melanoma. A multivariate analysis of 6383 patients evaluating the significance of gender in prognostic outcome. Arch Surg. 1994;129:316–324.
19. Mohanty S, Bilimoria KY. Comparing national cancer registries: the National cancer data base (NCDB) and the surveillance,
epidemiology, and end results (SEER) program. *J Surg Oncol.* 2014;109:629–630.

20. Steele GD, Jessup LM, Winchester DP, Murphy GP, Menck HR. Clinical highlights from the National cancer data base: 1995. *CA Cancer J Clin.* 1995;45:102–111.

21. Reyes SA, De La Cruz LM, Ru M, Pisapati KV, Port E. Practice changing potential of TAILORx: a retrospective review of the National cancer data base from 2010 to 2015. *Ann Surg Oncol.* 2019;26:3397–3408.

22. Overview of the SEER Program. Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/about/overview.html. Accessed April 14, 2018.

Edited by Yu-Xin Fang