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Factors Predictive of the Status of Sentinel Lymph Nodes in Melanoma Patients from a Large Multicenter Database

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Abstract

Background—Numerous predictive factors for cutaneous melanoma metastases to sentinel lymph nodes have been identified; however, few have been found to be reproducibly significant. This study investigated the significance of factors for predicting regional nodal disease in cutaneous melanoma using a large multicenter database.

Methods—Seventeen institutions submitted retrospective and prospective data on 3463 patients undergoing sentinel lymph node (SLN) biopsy for primary melanoma. Multiple demographic and tumor factors were analyzed for correlation with a positive SLN. Univariate and multivariate statistical analyses were performed.

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This study is conducted for the Sentinel Lymph Node Working Group

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DISCLOSURE Merck/Schering Oncology Speakers Bureau: Drs. White, Gershenwald, Charney, Hauschild, Vetto, Whitman and Kashani-Sabet. Dr. Leong is a Neoprobe contract recipient.

CONFLICT OF INTEREST Mr. Ayers, Ms. Stell, Drs. Soong, Ding, Salo, Pockaj, Essner, Faries, Averbook, Avisar, Egberts, Garberoglio, Ross, Chu, Trisal, Hoekstra, Wanebo, DeBonis, Vezeridis, Chevinsky, Shyr, Berry, and Zhao indicate no potential conflicts of interest.

Results—Of 3445 analyzable patients, 561 (16.3%) had a positive SLN biopsy. In multivariate analysis of 1526 patients with complete records for 10 variables, increasing Breslow thickness, lymphovascular invasion, ulceration, younger age, the absence of regression, and tumor location on the trunk were statistically significant predictors of a positive SLN.

Conclusions—These results confirm the predictive significance of the well-established variables of Breslow thickness, ulceration, age, and location, as well as consistently reported but less well-established variables such as lymphovascular invasion. In addition, the presence of regression was associated with a lower likelihood of a positive SLN. Consideration of multiple tumor parameters should influence the decision for SLN biopsy and the estimation of nodal metastatic disease risk.

Many researchers have attempted to identify factors that are associated with a positive sentinel lymph node (SLN) in primary melanoma. Factors that have been investigated include patient age,^{1–24} sex,^{1–21,23,24} site of primary tumor,^{1–3,6,8–11,13–21,23–27} Breslow thickness,^{1–27} Clark level,^{1–4,6,8,9,12,13,15–18,20,23,24,27} ulceration,^{1–8,10–20,22–24,26,27} vertical growth phase,^{1,8,14,17} tumor-infiltrating lymphocytes (TIL),^{1,6,10,15,17} tumor mitotic rate (TMR),^{1,6,7,10,11,14–17,20,25} histologic type,^{1,4,7,8,11,17,19,20,22} lymphovascular invasion (LVI),^{1,7,8,10,11,14,22,23} regression,^{1,6–8,10,11,14,22,24,28–30} number of draining basins,^{1,4,7,8,11,12,16,17,22} number of SLNs collected,^{7,11,17} T classification,^{13,17} primary margin status,¹⁴ microsatellitosis,^{7,10,11,14} neurotropism,^{7,11,14} and periadnexal extension.^{11,14} Of these factors, all except number of SLNs collected, margin status, neurotropism, and periadnexal extension have been found to be important predictors of SLN status on at least univariate analysis. However, only a few of these variables have been found to be reproducibly significant—that is, significant by multivariable analysis in more than one study. These factors are Breslow thickness,^{1,6–8,11–20,22–25,27,31} ulceration,^{1,8,12,13,15,17,20,22,23,27,31} TMR,^{6,7,11,14,16,17,25} patient age,^{1,7,8,11,13,14,16,20,22,23,31} primary site,^{11,13,22,25} Clark level,^{8,22} LVI,^{11,22,23} the absence of TIL,^{6,15} and male sex.³¹

The objective of this study was to use a multicenter database to identify factors predictive of positive SLNs.

METHODS

The Sentinel Lymph Node Working Group (SLNWG) consists of 30 member institutions and is based in San Francisco, California. Seventeen institutions contributed a total of 3463 patients for this study. All members obtained approval from their respective institutional review boards before submitting patients for this study. Informed consent was obtained from all patients except where waiver of informed consent was granted by the institutional review board for retrospective data collection.

The SLNWG database is maintained at Vanderbilt University in Nashville, Tennessee. Patient data are submitted by each member institution through a password-protected Web site into this standardized database.

SLN biopsy was performed as previously described using blue dye, radioactive colloid, or both.³² Indications for SLN biopsy and specific operative techniques were determined by individual investigators. In general, the investigators in this multicenter study used a combination of radioactive colloid and blue dye with preoperative lymphoscintigraphy. One pioneer group in the 1980s initially used blue dye only from November 6, 1985, to October 7, 1992, in 45 patients (1.3% of analyzable patients). Pathologic assessment was performed by institutional pathologists and was not standardized.

We retrospectively reviewed all cases in the database for this study. SLN surgery dates ranged from 1985 (data from the John Wayne Cancer Institute) to 2007. Variables analyzed for association with a positive SLN included patient age, sex, site of primary tumor, Breslow thickness, Clark level, ulceration, TMR, LVI, vertical growth phase, histologic type, regression, TIL, the number of draining basins, and the number of SLNs collected.

Tumor parameters were entered directly into the database as described on the original pathology reports. Regression was reported as present or absent. LVI was recorded as present if either lymphatic, vascular, or lymphovascular (angiolymphatic) invasion was noted on the pathology report. TMR was entered into the database as a whole number per square millimeter, as reported on local pathology reports. For the purposes of data analysis, TMR was grouped as <1, 1–5, or >5 as reported by Sondak et al.¹⁴ and subsequent reports from the University of Michigan.^{7,11} Because mitoses recorded per high-power field cannot be directly converted to per square millimeter, TMR reported in this manner was not entered into the database. TIL classification was defined in the database as brisk, nonbrisk, and absent as described by Taylor et al.¹⁵

All variables were summarized in frequency tables by SLN status. Cutpoints of naturally continuous variables were chosen for consistency with presentations in the literature. Nonparametric loess smoothers were used to visualize the underlying association of continuous variables with SLN positivity. Recursive cubic splines were applied to continuous predictors in single and multivariable modeling, as appropriate. SLN positivity was compared by selected covariates, stratified by Breslow thickness, by Cochran-Mantel-Haenszel analysis. Single and multivariable associations between potential predictors and SLN positivity were estimated by logistic regression with odds ratios representing effect size. For multivariable analysis of SLN positivity, four candidate variables were excluded because >50% of their values were missing (TMR, TIL, vertical growth phase, and histological subtype). Of the 3445 evaluable patients, 1526 (44%) had complete records for the remaining 10 candidate variables and formed the basis of the multivariable selection procedure.

Cluster analysis with the nonparametric Spearman correlation used as the similarity metric was used on the 10 remaining candidate variables to assess the multivariable associations among them. The Spearman correlation was less than 0.2 among all variables, so all 10 variables were included in subsequent variable selection. Bootstrapping (300 replicates) was used to identify the most parsimonious model among 10 candidate variables by backward elimination ($P = 0.05$ to stay in the model), and to provide shrinkage estimates of model fit criteria (e.g., c-index). P -values are from the Wald chi-square test. Unless otherwise indicated, “significance” implies P -values of <0.05. Statistical analysis was conducted by SAS, version 9.2 (SAS Institute, Cary, NC), and R, version 2.9.1.

RESULTS

A total of 3463 patients were included in the database. Patients without a clear diagnosis of melanoma (e.g., atypical Spitz nevi) were excluded. Patients were also excluded when the results of the SLN biopsy were not in the database. After these exclusions, 3445 patients were included in the overall analysis. The clinical and pathologic characteristics of the patients and tumors are listed in Table 1. Reporting of all variables was well distributed across all institutions. Of the 3445 analyzable patients, 561 (16.3%; 95% confidence interval 15.1–17.5) had a positive SLN biopsy. The likelihood of a positive SLN based on T classification³³ is provided in Table 2 (only patients where all variables are known are included). Given the selection bias inherent in the use of T1a and T1b patients as the reference, we elected to use the T2a group, whose patients routinely underwent SLN biopsy.

The results of the univariate analysis to predict a positive SLN are presented in Table 3. Increasing Breslow thickness, the presence of ulceration, deeper Clark level, the presence of LVI, younger age, >5 mitoses, and male sex were all significant predictors of positive SLN status on univariate analysis. Additionally, tumor location on the trunk and the absence of regression, nodular or acral lentiginous histologic type, and >1 mapped nodal basin were also significant predictors of positive SLNs. Microsatellitosis was excluded from further consideration because it affected less than 4% of the study population (Table 1). From all factors that were significant in the univariate analysis, multivariable analysis with 1526 cases in the model revealed Breslow thickness ($P < 0.0001$), LVI ($P < 0.0001$), ulceration ($P = 0.002$), age ($P = 0.005$), trunk location ($P = 0.0009$), and regression ($P = 0.005$) to be significant independent predictors of SLN status (Table 4; 257, 16.8%, of these patients had a positive SLN). Among 14 variables, 4 variables (TMR, $n = 1192$; TIL, $n = 823$; histological subtype, $n = 1683$; vertical growth phase, $n = 512$) were excluded from analysis because of a preponderance of missing values for these variables. In this multivariable analysis, tumor location was found to be significant only when comparing trunk location to head and neck location ($P = 0.0009$). Patients with trunk tumors were more than twice as likely to have a positive SLN as patients with tumors on the head and neck, whereas there was no difference in SLN positivity when comparing extremity tumors with head/neck tumors.

The effects of ulceration alone, LVI and ulceration together, and ulceration with regression stratified by Breslow thickness on the percentage of patients with positive SLNs are presented in Figs. 1, 2, and 3. Tumors with LVI and ulceration present a higher risk of SLN metastases across all T categories ($P < 0.0001$).

DISCUSSION

In our study of 3445 patients, 16.3% had one or more positive SLNs. Reported rates of sentinel node positivity have ranged from 12.6% to 31%.³⁴ The rate noted in this report is consistent with several other large series including those from the Italian Multicenter Study (16.9%),²⁴ the Sydney Melanoma Unit (16.8%),²⁰ and the M. D. Anderson Cancer Center (16.9%).¹³ In this large multicenter SLNWG dataset increasing Breslow thickness, younger age, trunk tumor location, the presence of LVI or ulceration, and the absence of regression were found to be independent predictors of a positive SLN in multivariate analysis. The findings of Breslow thickness, ulceration, age, and LVI are consistent with previous published reports.^{1,6-8,11-20,22,23,27}

The prognostic significance of regression, particularly in patients with thin melanomas, has been debated for decades. Some studies have found the presence of regression to be a poor prognostic indicator,^{30,35-37} while other studies have found regression to have no effect on the risk of recurrence or survival.³⁸⁻⁴⁰ On the supposition that the primary tumor was at one time more deeply invasive, the presence of regression in a thin melanoma has been used as justification for SLN biopsy.⁴¹ Although Cook et al. and others have suggested that regression may be required for thin melanomas to metastasize,³⁰ other host immune responses, including vitiligo, have been previously shown either to be beneficial on their own or to correlate with a response to systemic therapy.⁴²⁻⁴⁵ Thus, regression or vitiligo may indicate an autoimmune response to the primary tumor and therefore may be a beneficial prognostic indicator. In accordance with this theory, the presence of regression has been previously found to be statistically significantly associated with a decreased risk of SLN metastases in univariate analysis in several studies.^{7,11,28,29} One recent large study by Testori et al. confirmed the protective effect of regression on the risk of SLN metastases in a multivariate analysis.²⁴ In the Testori study, the presence of regression was a significant predictor of negative lymph nodes when stratified by Breslow thickness, which contrasts a

report from Morris et al. that found regression lost its prediction significance when stratified by Breslow thickness.²⁹ Our current report demonstrating an odds ratio of 2.4 (95% confidence interval 1.3–4.4) further supports the findings of Testori et al.²⁴ on the significance of regression. Together, these large studies lend further credence to the theory that a significant immunologic response in melanoma is suggestive of an improved outcome. Regression in the thin melanoma population was not specifically examined in this report; further study is warranted to elucidate the role of this potential criterion in determining indications for SLN biopsy in patients with thin melanomas.

In our data set, absence of regression and presence of LVI are statistically significant independent predictors of SLN status. In contrast to our results, multiple reports from the Sunbelt Melanoma Trial have found regression carries no significance for predicting SLN metastases.^{1,8,22} With regard to LVI, an early report from the Sunbelt Melanoma Trial found this factor to be statistically significant in univariate analysis but nonsignificant in multivariate analysis.⁸ However, in a subsequent report, LVI was found to be significant in multivariate analysis.²² Figure 2 graphically demonstrates the importance of LVI across Breslow depth and in both ulcerated and nonulcerated tumors. LVI was not investigated as a predictive factor in the recent multi-institutional report from Testori et al.²⁴

Two additional variables that have shown promise in predicting SLN status are the TMR^{6,7,11,14,16,17} and absence of TIL.^{6,15} Although neither of these factors reached statistical significance in this report, high TMR and the absence of TIL both trended toward predicting a positive SLN. It is possible that the lack of clear significance was related to the relative paucity of data for these factors in this data set; 65% of patients had no data for TMR, and 76% had no data reported for TIL. The reporting of TIL is not required by the College of American Pathologists guidelines,⁴⁶ and the routine use of mitotic rate began in January 2010 with the adoption of the 7th edition of the American Joint Committee on Cancer *Cancer Staging Manual*.³³ We have updated the current SLN WG database to include these parameters, which will be analyzed in future reports. Given the potential prognostic significance as evidenced by the trends in our report and the significance reported by others,^{6,7,11,14–17} we encourage pathologists to include TIL status on primary melanoma pathology reports.

Limitations of these data include those inherent to a partially retrospective, multi-institutional, multinational report. As is the nature of these types of reports, indications for performing SLN biopsy were not strictly standardized (particularly for the patients with thin lesions), nor was there a single standard procedural approach for SLN biopsy including the methods used by nuclear medicine physicians, surgeons and pathologists. In general, the investigators in this multicenter study used a combination of radioactive colloid and blue dye with preoperative lymphoscintigraphy. One pioneer group in the 1980s initially used blue dye only from November 6, 1985, to October 7, 1992, in 45 patients; thereafter, they used a combination of blue dye and radioactive colloid. For the remaining groups, the usual method was the use of radioactive colloid and blue dye. On some occasions, radioactive colloid was used alone and blue dye omitted. It has been shown that radioactive colloid is far superior in the identification of SLNs to the blue dye.⁴⁷ Because most of the patients in this multicenter database had radiocolloid used as a tracer for preoperative lymphoscintigraphy and intraoperative gamma probe detection, we believe the results reported are reliable. Furthermore, to date, the absolute standard of the technique for SLN identification has not been established and agreed on by the experts in the field. Similarly, the pathology reports were not standardized. All the pathology assessment was performed by institutional pathologists; however, the conventional method to process the SLN and identify micrometastasis was similar in that multiple level sections were made and stained with hematoxylin and eosin. If negative, immunohistochemistry was performed. Given the varied

interests of the investigators and/or their institutions, for some aspects of this report, only small cohorts were studied. Standard definitions of some variables (e.g., TMR, TIL) did not exist. No strict criteria were used in patients with T1a lesions who underwent SLN biopsy (Table 2), limiting extrapolation of this information. Despite these limitations, we believe the data we present here are representative of the broad spectrum of current practice. In the future, a central pathologist may be recruited to review the slides for these specific factors to achieve uniformity among different centers.

This large data set from the SLNWG represents 17 institutions from around the world. Our findings suggest reemphasizing the importance of pathologic factors such as LVI and regression, in addition to the well-established factors of ulceration and Breslow thickness, when selecting candidates for SLN biopsy and estimating the risk of involved lymph nodes.

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References

1. Chao C, Martin RC 2nd, Ross MI, et al. Correlation between prognostic factors and increasing age in melanoma. *Ann Surg Oncol*. 2004; 11:259–64. [PubMed: 14993020]
2. Clary BM, Brady MS, Lewis JJ, Coit DG. Sentinel lymph node biopsy in the management of patients with primary cutaneous melanoma: review of a large single-institutional experience with an emphasis on recurrence. *Ann Surg*. 2001; 233:250–8. [PubMed: 11176132]
3. Gershenwald JE, Thompson W, Mansfield PF, et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J Clin Oncol*. 1999; 17:976–83. [PubMed: 10071292]
4. Jacobs IA, Chang CK, Salti GI. Significance of dual-basin drainage in patients with truncal melanoma undergoing sentinel lymph node biopsy. *J Am Acad Dermatol*. 2003; 49:615–9. [PubMed: 14512905]
5. Joseph E, Brobeil A, Glass F, et al. Results of complete lymph node dissection in 83 melanoma patients with positive sentinel nodes. *Ann Surg Oncol*. 1998; 5:119–25. [PubMed: 9527264]
6. Kruper LL, Spitz FR, Czerniecki BJ, et al. Predicting sentinel node status in AJCC stage I/II primary cutaneous melanoma. *Cancer*. 2006; 107:2436–45. [PubMed: 17058288]
7. McHugh JB, Su L, Griffith KA, et al. Significance of multiple lymphatic basin drainage in truncal melanoma patients undergoing sentinel lymph node biopsy. *Ann Surg Oncol*. 2006; 13:1216–23. [PubMed: 16952026]
8. McMasters KM, Wong SL, Edwards MJ, et al. Factors that predict the presence of sentinel lymph node metastasis in patients with melanoma. *Surgery*. 2001; 130:151–6. [PubMed: 11490343]
9. Morton DL, Thompson JF, Essner R, et al. Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: a multicenter trial. Multicenter Selective Lymphadenectomy Trial Group. *Ann Surg*. 1999; 230:453–63. [PubMed: 10522715]
10. Mraz-Gernhard S, Sagebiel RW, Kashani-Sabet M, Miller JR 3rd, Leong SP. Prediction of sentinel lymph node micrometastasis by histological features in primary cutaneous malignant melanoma. *Arch Dermatol*. 1998; 134:983–7. [PubMed: 9722728]
11. Paek SC, Griffith KA, Johnson TM, et al. The impact of factors beyond Breslow depth on predicting sentinel lymph node positivity in melanoma. *Cancer*. 2007; 109:100–8. [PubMed: 17146784]
12. Porter GA, Ross MI, Berman RS, Lee JE, Mansfield PF, Gershenwald JE. Significance of multiple nodal basin drainage in truncal melanoma patients undergoing sentinel lymph node biopsy. *Ann Surg Oncol*. 2000; 7:256–61. [PubMed: 10819364]

13. Rousseau DL Jr, Ross MI, Johnson MM, et al. Revised American Joint Committee on Cancer staging criteria accurately predict sentinel lymph node positivity in clinically node-negative melanoma patients. *Ann Surg Oncol*. 2003; 10:569–74. [PubMed: 12794025]
14. Sondak VK, Taylor JM, Sabel MS, et al. Mitotic rate and younger age are predictors of sentinel lymph node positivity: lessons learned from the generation of a probabilistic model. *Ann Surg Oncol*. 2004; 11:247–58. [PubMed: 14993019]
15. Taylor RC, Patel A, Panageas KS, Busam KJ, Brady MS. Tumor-infiltrating lymphocytes predict sentinel lymph node positivity in patients with cutaneous melanoma. *J Clin Oncol*. 2007; 25:869–75. [PubMed: 17327608]
16. Thompson JF, Shaw HM. Should tumor mitotic rate and patient age, as well as tumor thickness, be used to select melanoma patients for sentinel node biopsy? *Ann Surg Oncol*. 2004; 11:233–5. [PubMed: 14993013]
17. Wagner JD, Gordon MS, Chuang TY, et al. Predicting sentinel and residual lymph node basin disease after sentinel lymph node biopsy for melanoma. *Cancer*. 2000; 89:453–62. [PubMed: 10918179]
18. Cascinelli N, Bombardieri E, Bufalino R, et al. Sentinel and nonsentinel node status in stage IB and II melanoma patients: two-step prognostic indicators of survival. *J Clin Oncol*. 2006; 24:4464–71. [PubMed: 16983115]
19. Roulin D, Matter M, Bady P, et al. Prognostic value of sentinel node biopsy in 327 prospective melanoma patients from a single institution. *Eur J Surg Oncol*. 2008; 34:673–9. [PubMed: 17825518]
20. Sassen S, Shaw HM, Colman MH, Scolyer RA, Thompson JF. The complex relationships between sentinel node positivity, patient age, and primary tumor desmoplasia: analysis of 2303 melanoma patients treated at a single center. *Ann Surg Oncol*. 2008; 15:630–7. [PubMed: 18080717]
21. Guggenheim M, Dummer R, Jung FJ, et al. The influence of sentinel lymph node tumour burden on additional lymph node involvement and disease-free survival in cutaneous melanoma—a retrospective analysis of 392 cases. *Br J Cancer*. 2008; 98:1922–8. [PubMed: 18506141]
22. Federico AC, Chagpar AB, Ross MI, et al. Effect of multiple-nodal basin drainage on cutaneous melanoma. *Arch Surg*. 2008; 143:632–7. [PubMed: 18645103]
23. Niakosari F, Kahn HJ, McCready D, et al. Lymphatic invasion identified by monoclonal antibody D2–40, younger age, and ulceration: predictors of sentinel lymph node involvement in primary cutaneous melanoma. *Arch Dermatol*. 2008; 144:462–7. [PubMed: 18427039]
24. Testori A, De Salvo GL, Montesco MC, et al. Clinical considerations on sentinel node biopsy in melanoma from an Italian multicentric study on 1,313 patients (SOLISM-IMI). *Ann Surg Oncol*. 2009; 16:2018–27. [PubMed: 19132446]
25. Mitra A, Conway C, Walker C, et al. Melanoma sentinel node biopsy and prediction models for relapse and overall survival. *Br J Cancer*. 2010; 103:1229–36. [PubMed: 20859289]
26. Ellis MC, Weerasinghe R, Corless CL, Vetto JT. Sentinel lymph node staging of cutaneous melanoma: predictors and outcomes. *Am J Surg*. 2010; 199:663–8. [PubMed: 20466113]
27. Gershenwald JE, Tseng CH, Thompson W, et al. Improved sentinel lymph node localization in patients with primary melanoma with the use of radiolabeled colloid. *Surgery*. 1998; 124:203–10. [PubMed: 9706139]
28. Kaur C, Thomas RJ, Desai N, et al. The correlation of regression in primary melanoma with sentinel lymph node status. *J Clin Pathol*. 2008; 61:297–300. [PubMed: 17675538]
29. Morris KT, Busam KJ, Bero S, Patel A, Brady MS. Primary cutaneous melanoma with regression does not require a lower threshold for sentinel lymph node biopsy. *Ann Surg Oncol*. 2008; 15:316–22. [PubMed: 18004626]
30. Cook MG, Spatz A, Brocker EB, Ruiter DJ. Identification of histological features associated with metastatic potential in thin (<1.0 mm) cutaneous melanoma with metastases. A study on behalf of the EORTC Melanoma Group. *J Pathol*. 2002; 197:188–93. [PubMed: 12015742]
31. Kretschmer L, Starz H, Thoms KM, et al. Age as a key factor influencing metastasizing patterns and disease-specific survival after sentinel lymph node biopsy for cutaneous melanoma. *Int J Cancer*. 10.1002/ijc.25747

32. Leong SP. Selective sentinel lymphadenectomy for malignant melanoma. *Surg Clin North Am.* 2003; 83:157–85. [PubMed: 12691454]
33. Balch, CM.; Gershenwald, JE.; Soong, S., et al. Melanoma of the skin. In: Edge, S.; Byrd, D.; Compton, C.; Fritz, A.; Greene, F.; Trotti, A., editors. *AJCC cancer staging manual*. 7. New York: Springer; 2009. p. 325–43.
34. Lock-Andersen J, Horn J, Sjøstrand H, Nürnberg BM, Stokholm KH. Sentinel node biopsy in cutaneous melanoma. *Scand J Plast Reconstr Surg Hand Surg.* 2006; 40:24–31. [PubMed: 16428210]
35. Gromet MA, Epstein WL, Blois MS. The regressing thin malignant melanoma: a distinctive lesion with metastatic potential. *Cancer.* 1978; 42:2282–92. [PubMed: 719608]
36. Slingluff CL Jr, Vollmer RT, Reintgen DS, Seigler HF. Lethal “thin” malignant melanoma. Identifying patients at risk. *Ann Surg.* 1988; 208:150–61. [PubMed: 3401060]
37. Guitart J, Lowe L, Piepkorn M, et al. Histological characteristics of metastasizing thin melanomas: a case-control study of 43 cases. *Arch Dermatol.* 2002; 138:603–8. [PubMed: 12020220]
38. Leiter U, Buettner PG, Eigentler TK, Garbe C. Prognostic factors of thin cutaneous melanoma: an analysis of the central malignant melanoma registry of the German Dermatological Society. *J Clin Oncol.* 2004; 22:3660–7. [PubMed: 15302905]
39. Gimotty PA, Guerry D, Ming ME, et al. Thin primary cutaneous malignant melanoma: a prognostic tree for 10-year metastasis is more accurate than American Joint Committee on Cancer staging. *J Clin Oncol.* 2004; 22:3668–76. [PubMed: 15302909]
40. Kelly JW, Sagebiel RW, Blois MS. Regression in malignant melanoma. A histologic feature without independent prognostic significance. *Cancer.* 1985; 56:2287–91. [PubMed: 4052972]
41. Homsí J, Kashani-Sabet M, Messina JL, Daud A. Cutaneous melanoma: prognostic factors. *Cancer Control.* 2005; 12:223–9. [PubMed: 16258493]
42. Gogas H, Ioannovich J, Dafni U, et al. Prognostic significance of autoimmunity during treatment of melanoma with interferon. *N Engl J Med.* 2006; 354:709–18. [PubMed: 16481638]
43. Phan GQ, Attia P, Steinberg SM, White DE, Rosenberg SA. Factors associated with response to high-dose interleukin-2 in patients with metastatic melanoma. *J Clin Oncol.* 2001; 19:3477–82. [PubMed: 11481353]
44. Boasberg PD, Hoon DS, Piro LD, et al. Enhanced survival associated with vitiligo expression during maintenance biotherapy for metastatic melanoma. *J Invest Dermatol.* 2006; 126:2658–63. [PubMed: 16946711]
45. Nordlund JJ, Kirkwood JM, Forget BM, Milton G, Albert DM, Lerner AB. Vitiligo in patients with metastatic melanoma: a good prognostic sign. *J Am Acad Dermatol.* 1983; 9:689–96. [PubMed: 6643767]
46. College of American Pathologists. [April 6, 2011] Melanoma of the skin cancer protocol. http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2011/SkinMelanoma_11protocol.pdf
47. Liu L-C, Parrett BM, Jenkins T, et al. Selective sentinel lymph node dissection for melanoma: importance of harvesting nodes with lower radioactive counts without the need for blue dye. *Ann Surg Oncol.* 10.1245/s10434-011-1689-0

Percent of patients with positive SLNs

$P < 0.0001$

FIG. 1.

Association between ulceration ($P < 0.0001$) and positive SLNs stratified by Breslow thickness; total $n = 2781$. *Numbers above the bars* represent the percentage of patients with positive SLNs in each category; *numbers below the x-axis labels* represent the number of patients in each category. P -value for independent effect of ulceration in a multivariable logistic regression model containing both predictor variables

FIG. 2.

Associations among lymphovascular invasion (LVI; $P < 0.0001$), ulceration ($P < 0.003$), and positive SLNs by Breslow thickness; total $n = 1836$. *Numbers above the bars* represent the percentage of patients with positive SLNs in each category; *numbers below the x-axis labels* represent the number of patients in each category. P -values for independent effect of ulceration and lymphovascular invasion in a multivariable logistic regression model containing all 3 predictor variables

FIG. 3.

Associations among regression ($P < 0.008$), ulceration ($P < 0.003$) and positive SLNs by Breslow thickness; total $n = 2003$. *Numbers above the bars* represent the percentage of patients with positive SLNs in each category; *numbers below the x-axis labels* represent the number of patients in each category. P -values for independent effect of ulceration and regression in a multivariable logistic regression model containing all 3 predictor variables

TABLE 1

Patient characteristics by SLN status

Variable	All, n (%)	SLN status, n (%)	
		Positive	Negative
Total	3445	561 (16.3)	2884 (83.7)
Age (years)	3175	515 (16.2)	2660 (83.8)
<30	205 (6.5)	46 (22.4)	159 (77.6)
30–49	968 (30.5)	192 (19.8)	776 (80.2)
50–69	1305 (41.1)	183 (14)	1122 (86)
70	697 (22)	94 (13.5)	603 (86.5)
Sex	3286	537 (16.3)	2749 (83.7)
Male	1976 (60.1)	352 (17.8)	1624 (82.2)
Female	1310 (39.9)	185 (14.1)	1125 (85.9)
Tumor location	3441	560 (16.3)	2881 (83.7)
Head/neck	941 (27.3)	111 (11.8)	830 (88.2)
Extremity	1380 (40.1)	322 (15.3)	1169 (84.7)
Trunk	1120 (32.5)	238 (21.3)	882 (78.8)
Breslow thickness (mm)	3377	548 (16.2)	2829 (83.8)
1.00	735 (21.8)	45 (6.1)	690 (93.9)
1.01–2.00	1421 (42.1)	166 (11.7)	1255 (88.3)
2.01–4.00	845 (25.0)	214 (25.3)	631 (74.7)
4.00	376 (11.1)	123 (32.7)	253 (67.3)
Clark level	3044	512 (16.8)	2532 (83.2)
II	129 (4.2)	7 (5.4)	122 (94.6)
III	942 (30.9)	111 (18.8)	831 (88.2)
IV	1776 (58.3)	335 (18.9)	1441 (81.1)
V	197 (6.5)	59 (29.9)	138 (70.1)
Ulceration	2809	464 (16.5)	2345 (83.5)
Present	747 (26.6)	197 (26.4)	550 (73.6)
Absent	2062 (73.4)	267 (12.9)	1795 (87.1)
Regression	2145	349 (16.3)	1796 (83.7)
Present	280 (13.1)	25 (8.9)	255 (91.1)
Absent	1865 (86.9)	324 (17.4)	1541 (82.6)
Microsatellitosis	2086	366 (17.5)	1720 (82.5)
Yes	79 (3.8)	38 (48.1)	41 (51.9)
No	2007 (96.2)	328 (16.3)	1679 (80.2)
Lymphovascular invasion	1902	336 (17.8)	1563 (82.2)
Present	163 (8.6)	63 (38.7)	100 (61.3)
Absent	1739 (91.4)	276 (15.9)	1463 (84.1)
Histologic subtype	1683	262 (15.6)	1421 (84.4)
Superficial spreading	843 (50.1)	120 (14.2)	723 (85.8)
Nodular	272 (16.2)	65 (23.9)	207 (76.1)

Variable	All, <i>n</i> (%)	SLN status, <i>n</i> (%)	
		Positive	Negative
Lentigo maligna	85 (5.1)	11 (12.9)	74 (87.1)
Acral lentiginous	36 (2.1)	9 (25)	27 (75)
Desmoplastic	51 (3.0)	3 (5.9)	48 (94.1)
Unclassified	297 (17.6)	44 (14.8)	253 (85.2)
Other	99 (5.9)	10 (10.1)	89 (89.9)
Tumor mitotic rate (/mm ²)	1192	211 (17.7)	981 (82.3)
<1	206 (17.3)	26 (12.6)	180 (87.4)
1–5	748 (62.8)	126 (16.8)	622 (83.2)
>5	238 (20.0)	59 (24.8)	179 (75.2)
Tumor-infiltrating lymphocytes	823	137 (16.6)	686 (83.4)
Absent	342 (41.6)	71 (20.8)	271 (79.2)
Nonbrisk	322 (39.1)	51 (15.8)	271 (84.2)
Brisk	159 (19.3)	15 (9.4)	144 (90.6)
Vertical growth phase	512	93 (18.2)	419 (81.8)
Present	392 (76.6)	71 (18.1)	321 (81.9)
Absent	120 (23.4)	22 (18.3)	98 (81.7)
No. of SLNs collected	3040	498 (16.4)	2542 (83.6)
1	944 (31.1)	128 (13.6)	816 (86.4)
2–4	1473 (48.5)	248 (16.8)	1225 (83.2)
4	623 (20.5)	122 (19.6)	501 (80.4)
No. of basins	3105	520 (16.7)	2585 (83.3)
1	2399 (77.3)	368 (15.3)	2031 (84.7)
>1	706 (22.7)	152 (21.5)	554 (78.5)

.SLN sentinel lymph node

TABLE 2SLN incidence by AJCC T classification (7th edition; $N = 2426$)

T classification	n (%)	Positive SLN, n (%)	Odds ratio ^a (95% CI)	P-value
T1a	58 (2)	5 (9)	0.87 (0.34–2.23)	0.773
T1b	145 (6)	10 (7)	0.68 (0.35–1.35)	0.272
T2a	941 (39)	92 (10)	Ref	
T2b	231 (10)	35 (15)	1.65 (1.08–2.51)	0.020
T3a	431 (18)	95 (22)	2.61 (1.91–3.57)	<0.0001
T3b	295 (12)	93 (32)	4.25 (3.06–5.89)	<0.0001
T4a	147 (6)	42 (29)	3.69 (2.43–5.60)	<0.0001
T4b	178 (7)	68 (38)	5.70 (3.94–8.27)	<0.0001

T1 category only includes patients with TMR recorded. T1a = 1 mm, no ulceration, TMR <1 per mm²; T1b = 1 mm, ulceration and/or TMR 1 per mm²

SLN sentinel lymph node, AJCC American Joint Committee on Cancer; CI confidence interval, TMR tumor mitotic rate

^aVersus T2a

TABLE 3

Univariable logistic regression analysis of factors predicting a positive SLN

Variable	n (%)	Odds ratio	95% CI	P-value
Age (years)	3175			
<30	205 (6.5)	Ref		
30–49	968 (30.5)	0.85	0.51–1.23	0.400
50–69	1305 (41.1)	0.56	0.39–0.81	0.002
70	697 (22)	0.54	0.36–0.80	0.002
Sex	3286			
Female	1310 (39.9)	Ref		
Male	1976 (60.1)	1.32	1.09–1.60	0.005
Tumor location	3441			
Head/neck	941 (27.3)	Ref		
Extremity	1380 (40.1)	1.35	1.05–1.73	0.017
Trunk	1120 (32.5)	2.02	1.58–2.58	<.0001
Breslow thickness (mm)	3377			
1.00	735 (21.8)	Ref		
1.01–2.00	1421 (42.1)	2.03	1.44–2.86	<.0001
2.01–4.00	845 (25.0)	5.20	3.70–7.30	<.0001
4.00	376 (11.1)	7.45	5.15–10.80	<.0001
Clark level	3044			
II	129 (4.2)	Ref		
III	942 (30.9)	2.33	1.06–5.11	<.0001
IV	1776 (58.3)	4.05	1.87–8.76	0.0004
V	197 (6.5)	7.45	3.28–16.93	0.035
Ulceration	2809			
Absent	2062 (73.4)	Ref		
Present	747 (26.6)	2.41	1.96–2.96	<.0001
Regression	2145			
Present	280 (13.1)	Ref		
Absent	1865 (86.9)	2.14	1.40–3.29	0.0005
Lymphovascular invasion	1902			
Absent	1739 (91.4)	Ref		
Present	163 (8.6)	3.34	2.38–4.69	<.0001
Histologic subtype	1683			
All others	1375 (81.7)	Ref		
Nodular or acral lentiginous	308 (18.3)	2.00	1.47–2.70	<.0001
Tumor mitotic rate (/mm ²)	1192			
<1	206 (17.3)	Ref		
1–5	748 (62.8)	1.40	0.89–2.21	0.144
>5	238 (20.0)	2.28	1.38–3.78	0.001
Tumor-infiltrating lymphocytes	823			

Variable	n (%)	Odds ratio	95% CI	P-value
Brisk	159 (19.30)	Ref		
Nonbrisk	322 (39.1)	1.81	0.98–3.32	0.057
Absent	342 (41.6)	2.51	1.39–4.55	0.002
Vertical growth phase	512			
Absent	120 (23.4)	Ref		
Present	392 (76.6)	1.01	0.60–1.72	0.956
No. of SLN collected	3040			
1	944 (31.1)	Ref		
2–4	1473 (45.5)	1.29	1.02–1.63	0.030
4	623 (20.5)	1.55	1.18–2.04	0.002
No. of basins	3105			
1	2399 (77.3)	Ref		
>1	706 (22.7)	1.51	1.23–1.87	0.0001

SLN sentinel lymph node, *CI* confidence interval

TABLE 4Multivariable logistic regression model of factors predicting a positive SLN ($n = 1526$)

Variable	Odds ratio	95% CI	P-value
Age (years)			
<30	Ref	–	–
30–49	0.83	0.48–1.43	0.498
50–70	0.54	0.31–0.94	0.029
70	0.41	0.22–0.77	0.005
Tumor location			
Head/neck	Ref	–	–
Extremity	1.27	0.80–2.00	0.307
Trunk	2.17	1.37–3.43	0.0009
Breslow thickness (mm)			
1.00	Ref	–	–
1.01–2.00	1.82	1.05–3.14	0.032
2.01–4.00	4.96	2.87–8.58	<.0001
4.00	7.65	4.20–13.95	<.0001
Ulceration			
Absent	Ref	–	–
Present	1.67	1.21–2.30	0.002
Regression			
Present	Ref	–	–
Absent	2.39	1.30–4.37	0.005
Lymphovascular invasion			
Absent	Ref	–	–
Present	3.18	2.00–5.06	<.0001

SLN sentinel lymph node, CI confidence interval