Predictors of sentinel lymph node metastasis in melanoma

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Background: Several studies have examined the correlation between patient and tumour characteristics and sentinel lymph node (SLN) metastasis in patients with melanoma. Although most studies have identified Breslow thickness as an important factor, results for other variables have been conflicting. Much of this variability is probably because of differences in measurement techniques and reporting practices at different institutions. We sought to identify the predictors of SLN melanoma metastasis in our institution and patient population.

Methods: We performed a retrospective chart review of 348 patients with malignant melanoma who underwent SLN biopsy at a single institution from January 1999 to April 2007. We compared multiple variables related to patient demographics, primary tumour characteristics and SLN characteristics between patients in the positive and negative SLN groups.

Results: Breslow thickness and nodular tumour type were independent factors significantly correlated with a positive SLN biopsy result in our study. Head and neck tumour location correlated with a lower likelihood of positive SLN status in univariate but not multivariate analyses.

Conclusion: This study confirms the status of Breslow thickness as a reproducible predictor of positive SLN status. We also found that nodular type was predictive of positive SLN status, an outcome that has not been reported by others.

Contexte : Plusieurs études ont examiné le lien entre les caractéristiques du patient et celles de la tumeur et la présence de métastases dans le ganglion lymphatique sentinelle (GLS) chez des patients atteints d'un mélanome. Même si la plupart des études ont déterminé que l'épaisseur de Breslow constituait un facteur important, les résultats à l'égard d'autres variables sont contradictoires. Cette variabilité est probablement attribuable en grande partie à des techniques de mesure et des méthodes de déclaration différentes à des établissements différents. Nous avons cherché à déterminer les prédicteurs de métastases du mélanome dans le GLS dans notre établissement et dans notre population de patients.

Méthodes : Nous avons effectué une étude rétrospective des dossiers de 348 patients atteints d'un mélanome malin qui ont subi une biopsie du GLS à un seul établissement, de janvier 1999 à avril 2007. Nous avons comparé des variables multiples portant sur les caractéristiques démographiques des patients et sur les caractéristiques de la tumeur primitive et du GLS entre les patients des groupes dont le GLS présentait des résultats positifs et négatifs.

Résultats : L'épaisseur de Breslow et le type de tumeur nodulaire constituaient des facteurs indépendants qui avaient des liens importants avec un résultat positif de la biopsie du GLS au cours de notre étude. Il y avait un lien entre la tumeur à la tête et au cou et une probabilité plus faible que la biopsie du GLS produise des résultats positifs dans les analyses à variable unique mais non dans les analyses à variables multiples.

Conclusion : Cette étude confirme le rôle de l'épaisseur de Breslow comme prédicteur reproductible de l'état positif du GLS. Nous avons aussi constaté que le type nodulaire était un prédicteur de l'état positif du GLS, résultat dont on n'a pas fait état ailleurs.

Sentinel lymph node (SLN) biopsy, in indicated circumstances, is widely accepted as the standard of care for patients with malignant melanoma. Current indications include melanoma with clinically negative nodes in patients with primary tumours that are either more than 1 mm thick, are of Clark level 4 or 5, or are ulcerated. Several studies have reported many other

factors to be predictive of a positive SLN biopsy result. These factors have included mitotic rate, angiolymphatic invasion and lymphocytic response.[1–3] The findings of these studies have not resulted in modification of the indications for SLN biopsy for a number of reasons. First, many of these studies have reported conflicting findings. Second, some of the variables studied are not uniformly reported by pathologists at all institutions. Third, interinstitution variability (as well as interperson variability) in measurement and reporting techniques for many of these variables is considerable. For these and other reasons, the findings of studies in this area have not been translated into guideline changes uniformly applicable to all patients with melanoma.

Because of this variability, it is valuable for each melanoma surgery institution to study its local population to determine the relevant predictors of SLN metastasis. The Misericordia Hospital is a melanoma referral centre that serves the city of Edmonton with a catchment area of 1.6 million people across central and northern Alberta, Canada. We sought to review the clinical and tumour features predictive of a positive SLN biopsy result in this population.

Methods

This study was reviewed and approved by the University of Alberta's health research ethics committee. We performed a retrospective chart review of all patients with melanoma who underwent SLN biopsy at the Misericordia Hospital from January 1999 to April 2007. We included all patients who had a diagnosis of melanoma and no evidence of distant metastasis or clinical lymphadenopathy. Patients with melanoma were selected for SLN biopsy if they had a primary tumour that was more than 1 mm thick, had a Clark level 4 or 5, or was ulcerated. We collected clinical data including patient age, sex and date of SLN biopsy. We collected data about the location of the melanoma, histologic type, Breslow thickness, Clark level, ulceration, angioinvasion, lymphocytic response, site of SLN basin, number of SLNs harvested and the number of positive SLNs.

Sentinel lymph node biopsy technique

Lymphoscintigraphic scanning was performed preoperatively in all patients. The SLN was identified intraoperatively by use of both a gamma probe and lymphazurin blue dye in all cases. All blue nodes and nodes with radioactive counts exceeding 10% of the node with the highest radioactive count were removed.

Pathological analysis of SLN specimens

All SLNs were serially sectioned at 2-mm intervals. Sections were evaluated after hematoxylin–eosin staining and immunohistochemical staining with S-100 and HMB-45. Polymerase chain reaction was not performed for any of the SLN biopsy samples at our institution.

Statistical analysis

The primary outcome in this study was a positive SLN biopsy result, which was defined as one or more SLNs positive for metastatic disease. We calculated descriptive and summary statistics for all recorded variables. We performed univariate analyses using *t* tests for continuous variables and χ^2 tests for categorical variables. Multivariate logistic regression analysis was performed to control for potential confounding factors, and odds ratios and 95% confidence intervals were generated. We generated descriptive statistics (means, medians, frequencies, standard deviations) for all variables. We used logistic regression models to delineate the relation of each variable with positive SLN status. The χ^2 test was used to calculate the statistical significance of the differences between the groups with regard to the variables. The odds ratios and 95% Wald-based confidence intervals were also calculated. Because of the limited data available, we performed multivariate regression analysis using only the factors that were significant in the univariate analysis. We used a significance level of $p < 0.05$ throughout the study.

Results

We identified 348 patients with melanoma who received an SLN biopsy. Of these, 256 (73%) had negative results and 92 (27%) had positive results. We found no significant differences in age or sex between those with positive or negative SLN results. Table 1 shows a comparison of the 2 groups for the studied variables.

We examined all variables by univariate logistic regression to assess for correlation with positive SLN status (Table 2). Two factors were significantly correlated with positive SLN status: Breslow thickness ($p < 0.001$) and nodular type ($p < 0.001$). Head and neck tumour location was identified as a factor significantly correlated with a negative SLN biopsy result ($p = 0.007$). For each unit increase in Breslow value, the odds of a positive SLN biopsy result increased by about 13%. The odds of a positive SLN biopsy result were 40-fold higher among patients with nodular histology than among those with nonnodular histology. Of the 60 patients whose histology was nodular, 1 had a thin melanoma, 5 were of Clark level 3 or lower, and 23 were nonulcerated. Of those with a Clark level 3 or lower and no ulceration, the majority (67%) did not have SLN metastasis. The odds of a positive SLN biopsy result were 20-fold higher among patients with a head or neck tumour than among those with a non–head or neck tumour. This may have been because of high false-negative rates owing to limited experience with head and neck SLN biopsy at our institution.

The other variables (Clark level, ulceration, angioinvasion, lymphocytic response, SLN site, number of SLNs harvested and number of positive SLNs) were not significantly correlated with positive SLN status. For ulceration, the odds of having a negative SLN biopsy result decreased by a factor of 16. This relation is insignificant because the confidence interval included 1. We also examined the effect of multiple SLN drainage basins on SLN status. Our results revealed no significant correlation between multiple basins and positive SLN status ($p = 0.66$).

We next used a multivariate regression model that included the 3 significant factors from the univariate analysis (Breslow, nodular type, head and neck location; Table 3). Both Breslow thickness and nodular type remained significant predictors of positive SLN status ($p < 0.001$, $p = 0.01$, respectively). For each unit increase in Breslow thickness, the odds of a positive SLN result increased by about 10%. Head and neck location, however, was no longer significantly associated with negative SLN status ($p = 0.65$).

Overall, 22% of patients had thin melanomas (< 1 mm thickness). All of these patients had either Clark level 4 or 5 tumours or had ulceration.

Table 1. Demographic and tumour characteristics of patients who underwent sentinel lymph node biopsy between January 1999 and April 2007, by SLN status

Characteristic	No. of patients	SLN status, no. (%)* Negative, *n* = 256	Positive, *n* = 92	*p* value
Age, yr, median	349	55	54	0.81
Sex				
Male	180	120 (67)	60 (33)	0.29
Female	169	127 (75)	42 (25)	
Tumour location	342			0.56
Head and neck	44	38 (86)	6 (14)	
Upper extremity	60	39 (65)	21 (35)	
Lower extremity	71	53 (75)	18 (25)	
Trunk	138	102 (74)	36 (26)	
Limb	27	18 (67)	9 (33)	
Perianal	2	2 (100)	0 (0)	
Histologic type	213	145	68	
Superficial spreading	114	87 (60)	27 (40)	
Nodular	60	29 (48)	31 (52)	< 0.001
Lentigo maligna	7	7 (100)	0 (0)	
Acral lentiginous	19	13 (68)	6 (32)	
Amelanotic	2	1 (50)	1 (50)	
Spitzoid	8	5 (62)	3 (38)	
Desmoplastic	2	2 (100)	0 (0)	
Nevoid	1	1 (100)	0 (0)	
Breslow thickness, mm, median	295	1.2	1.8	< 0.001
Clark level, median	250			
Ulceration	82	52	30	0.09
Angioinvasion	173	136 (79)	37 (21)	
Lymphocytic response	136	92	44	0.54
SLN site	337			0.15
Axilla	151	108 (72)	43 (28)	
> 1 axilla site	18	12 (67)	6 (33)	
Inguinal	104	75 (72)	29 (28)	
> 1 inguinal site	27	2 (100)	0 (0)	
Inguinal and axilla	7	5 (71)	2 (29)	
Cervical	43	37 (86)	6 (14)	
> 1 cervical site	4	4 (100)	0 (0)	
Cervical and axilla	3	2 (67)	1 (33)	
Miscellaneous	5	1 (20)	4 (80)	
Mean no. of SLNs	348	1.7	2.4	
Mean no. of positive SLNs	348	0	1.4	

SLN = sentinel lymph node.
*Unless otherwise indicated.

Discussion

Biopsy of SLNs has emerged as an integral element in the evaluation and management of melanoma. It is critical for the staging of melanoma and, hence, is a major determinant of therapy and prognosis. In addition, SLN biopsy has recently been found to be of therapeutic value compared with observation followed by therapeutic lymph node dissection.[4] Most centres, including our own, offer SLN biopsy to patients with localized melanomas that are either 1 mm thick or greater or that have adverse features (ulceration or Clark level 4 or 5). The rate of positive SLN biopsy results in this group of patients ranges from 13% to 30%.[3–6]

Several studies have sought to predict SLN status on the basis of various demographic and histologic tumour characteristics. Such knowledge may improve the prediction of prognosis and the treatment of certain types of melanoma; for example, a melanoma patient with a tumour less than 1-mm thick with no adverse features who turns out to have occult nodal metastasis. The ability to predict a higher likelihood of SLN metastasis in certain patients will no doubt enhance the effectiveness of the care for melanoma

Table 2. Results of the univariate regression analysis of factors hypothesized to be predictive of negative sentinel lymph node status

Variable	Negative SLN status, no. (%)	Unadjusted relative risk	95% CI	*p* value
Breslow thickness		1.20	0.90–1.95	< 0.001
Head and neck location	38 (86.36)	1.20	1.05–1.38	0.007
Nodular type	29 (48.33)	0.60	0.47–0.80	< 0.001
Multiple SLN sites	35 (76.09)	0.96	0.80–1.15	0.66

CI = confidence interval; SLN = sentinel lymph node.

Table 3. Results of multivariate regression analyses that included the 3 factors that were significant predictors of sentinel lymph node status in univariate analysis

Variable	Unadjusted relative risk	95% confidence interval	*p* value
Breslow thickness	0.90	0.84–0.95	< 0.001
Nodular type	0.70	0.53–0.92	0.01
Head and neck location	1.05	0.85–1.29	0.65

patients.[7,8] In addition, the ability to predict SLN status before performing the biopsy will increase our understanding of the prediction of prognosis and the natural history of the disease. Most studies examining this subject have found increasing Breslow thickness to be predictive of positive SLN status in melanoma patients.[1–3,9–11]

Results for other variables, however, have been conflicting.[1–3,5,8–10,12] After a review of 910 melanoma patients who underwent SLN biopsy, Paek and colleagues[1] found that Breslow depth, younger age, angiolymphatic invasion, mitotic rate and trunk or lower extremity location were predictive of a positive SLN biopsy result. In a review of 682 patients with melanoma who underwent SLN biopsy, Kruper and colleagues[3] found that only Breslow thickness, tumour infiltrating lymphocytes and mitotic rate were predictive of positive SLN status. Nguyen and coworkers[9] found Breslow thickness, ulceration and lymphovascular invasion to be predictive of positive SLN status in a review of 112 patients. Given the agreement about Breslow thickness as a predictor of SLN status, some studies have focused on predicting SLN metastasis in tumours with Breslow thickness of 1 mm or less. Kesmodel and colleagues[8] found that Breslow thickness and mitotic rate were predictive of a positive SLN biopsy result in 181 patients with melanomas of 1 mm or less in thickness.

We hypothesize that much of the variability in the results in the literature is a consequence of institution- or region-specific differences in measurement and reporting of histologic variables. Breslow thickness, which is a much more objective and accurately reproducible variable than the others, has been the only constant finding throughout these reports. In this study, we reviewed the patient characteristics and those of the tumours and SLNs of patients with melanoma in our region. Our aim was to identify predictors of SLN metastasis that are relevant to our particular melanoma population. Our results revealed that our patient population did not deviate from what is reported in the literature with regard to major attributes. The rate of positive SLN status was 27% in this population, which is in keeping with what has been reported in the literature.[4–6,13,14] Overall, 22% of SLN biopsies were performed for patients with primary tumours less than 1 mm thick. These represented patients with either ulceration, Clark level 4 or 5, or both. The positive SLN rate in this subgroup was 6%. Once again, these values are in keeping with rates reported in the literature.[6,8,10] Also in keeping with other studies, we found Breslow thickness to be a significant independent predictor of SLN metastasis in our melanoma patients ($p < 0.001$).

Perhaps the most interesting finding of this study was the identification of nodular histology as a significant and independent predictor of positive SLN status. Controversy still exists as to whether nodular melanoma projects any features of a distinct entity beyond a melanoma with an advanced stage at the time of diagnosis. It is certainly true that nodular melanomas have unique clinical characteristics: they are morphologically distinct, lack a radial growth phase and are much less likely than nonnodular melanomas to develop in pre-existing nevi. They have also been found to be associated with greater tumour thickness and a delayed presentation, characteristics that have been held entirely responsible for the adverse prognosis associated with these types of melanomas. However, Richard and colleagues[11] found that patients with nodular melanomas who had shorter delays before medical attention than those with superficial spreading types still presented with greater tumour thickness. This observation seems to suggest an inherent biological characteristic of nodular melanomas that may preclude the attribution of the poorer prognosis solely on tumour thickness.

At any rate, the implication of nodular histology to sentinel lymph node metastasis is far less clear than it is to survival. Even though nodular histology tends to correlate with higher mortality, no significant relation to mortality persists after correction for tumour thickness.[14] Nodular histologic characteristics have been found, however, to be significant predictors of false-negative SLN biopsy results, even after tumour thickness is controlled for.[1,3] Prior studies that have examined predictors of SLN metastasis have not found a significant correlation between SLN metastasis and nodular histology. In our study, nodular histology correlated with higher rates of SLN metastasis even after adjustment for tumour thickness. Although this finding is definitely a feature of melanoma patients who underwent biopsy in this population, it may not be replicable in other melanoma populations. Our data also indicated that 67% of patients with nodular tumours that were nonulcerated and had a Clark level 3 or lower had no SLN metastases. This finding merits further study and provides an impetus to further clarify the exact biology and implications associated with nodular histology.

Our study had several limitations that may have biased the findings. The first is the retrospective nature of this study with the incomplete availability of data. Also, the lack of standardized pathologic examination within our institution could have biased our findings. Nevertheless, we believe that these results are representative of our patient cohort.

Conclusion

We have identified 2 factors predictive of SLN metastasis in melanoma patients in central and northern Alberta: Breslow thickness and nodular histology. We verified the role of Breslow thickness as a significant predictor of SLN metastasis. Despite the limitations, our study has shed light on the possible relation between nodular histology and SLN metastasis, although this conclusion should be interpreted with caution and needs further clarification.

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Contributors: Drs. Cadili and Dabbs designed the study. Dr. Cadili acquired the data. Drs. Cadili and Dabbs analyzed the data. Dr. Cadili wrote the article and Dr. Dabbs reviewed it.

References

1. 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.
2. Wagner JD, Gordon MS, Chuang TY, et al. Predicting sentinel and residual basin disease after sentinel lymph node biopsy for melanoma. *Cancer* 2000;89:453-62.
3. Kruper LL, Spitz FR, Czerniecki BJ, et al. Predicting sentinel node status in AJCC stage 1/11 primary cutaneous melanoma. *Cancer* 2006; 107:2436-45.
4. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med* 2006;355:1307-17.
5. Landi G, Polverelli M, Moscatelli G, et al. Sentinel lymph node biopsy in patients with primary cutaneous melanoma: study of 455 cases. *J Eur Acad Dermatol Venereol* 2000;14:35-45.
6. Gershenwald J, Thompson W, Mansfield P, et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel node status in 612 stage I or II melanoma patients. *J Clin Oncol* 1999;17:976-83.
7. Bedrosian I, Faries MB, Guerry D IV, et al. Incidence of sentinel node metastasis in patients with thin primary melanoma (1 mm) with vertical growth phase. *Ann Surg Oncol* 2000;7:262-7.
8. Kesmodel SB, Karakousis GC, Botbyl JD, et al. Mitotic rate as a predictor of sentinel lymph node positivity in patients with thin melanomas. *Ann Surg Oncol.* 2005;12:1-10.
9. Nguyen CL, McClay EF, Cole DJ, et al. Melanoma thickness and histology predict sentinel lymph node status. *Am J Surg* 2001;181:8-11.
10. Mraz-Gernhard S, Sagebiel RW, Kashani-Sabet M, et al. Prediction of sentinel lymph node micrometastasis by histological features in primary cutaneous malignant melanoma. *Arch Dermatol* 1998;134:983-7.
11. Richard MA, Grob JJ, Avril MF, et al. Melanoma and tumor thickness. *Arch Dermatol* 1999;135:269-74.
12. 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.
13. Morton DL, Hoon DSB, Cochran AJ, et al. Lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma. *Ann Surg* 2003;238:538-50.
14. 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;144:680-2.