



Hans Dahl, 1849-1937. *Sharing a Joke*. Oil on canvas, 37¾" × 61½".
Courtesy of the Callan Fine Art gallery, New Orleans, Louisiana.

The search continues for pathologic predictors that would indicate the potential for progression of disease in thin melanomas as well as which patients would benefit from sentinel node evaluation.

Sentinel Node Biopsy for Thin Melanomas: Which Patients Should Be Considered?

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Background: As the incidence of melanoma increases, thin melanomas are being diagnosed at an increasingly frequent rate. Currently available prognostic factors are limited in their ability to reliably discriminate which patients will manifest regional nodal metastasis and would be identified early through sentinel node biopsy.

Methods: We summarized our experience with sentinel node biopsy for patients with cutaneous melanomas less than 1.00 mm in Breslow thickness, with evaluation of Clark level as a predictor of positive sentinel node metastasis.

Results: Among the 409 patients identified, micrometastases were found in the sentinel node in 20 patients, for an overall incidence of nodal progression of 4.9%. A total of 252 (62%) were Clark level II or III (11 of whom had a positive sentinel node) and 157 (38%) were Clark level IV (9 of whom had a positive sentinel node). We reviewed the literature to identify reliable indicators that might be helpful in determining which patients with "thin melanomas" would be likely to manifest regional progression to warrant routinely undergoing a preoperative lymphoscintigraphy followed by a sentinel node biopsy.

Conclusions: Based on available data, patients with melanomas between 0.75 and 1.00 mm are appropriate candidates to be considered for sentinel node biopsy after discussing the likelihood of finding evidence of nodal progression, the risks of sentinel node biopsy (including the risk of a false-negative result), and the lack of proven survival benefit from any form of surgical nodal staging.

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Abbreviations used in this paper: AJCC = American Joint Committee on Cancer, TMR = tumor mitotic rate, TIL = tumor-infiltrating lymphocyte.

Introduction

As the incidence of melanoma increases, thin melanomas are being diagnosed at an increasingly frequent rate. In melanoma, progression to the regional nodes is indicative of but not synonymous with decreased disease-free intervals as well as decreased survival. Overall, only approximately half of clinically localized melanomas that have progressed to the regional nodes at the time of diagnosis will ultimately manifest distant metastases, which almost always translates into eventual disease progression. Currently available prognostic factors, which are based on clinical parameters and histologic findings in the primary and metastatic tumor sites, are limited in their ability to reliably discriminate which patients will manifest regional nodal metastasis, making them at high risk for development of disseminated disease.

The widespread use of intraoperative lymphatic mapping and sentinel node biopsy has proven its ability to identify micrometastases in the regional nodes. This then poses the question of the need for all, some, or none of the increasing number of patients with thin melanomas to undergo sentinel node biopsy. Currently, indications for sentinel node biopsy in early-stage melanoma are based primarily on Breslow thickness and the presence of ulceration. The American Joint Committee on Cancer (AJCC) staging system for cutaneous melanoma incorporates Clark level IV or V as a prognostic factor in lesions ≤ 1.00 mm in Breslow thickness. While Clark level IV or V penetration has been shown to be a significant prognostic factor for overall survival in a large database study, its ability to predict the likelihood of regional nodal progression is less clear. Nonetheless, based primarily on the AJCC staging system, melanomas ≤ 1.00 mm in Breslow thickness that penetrate into the reticular dermis or subcutaneous fat have been selected for sentinel node biopsy in many centers, while identical thickness lesions with lesser degrees of dermal penetration have not.

In this review article, we summarize our experience with sentinel node biopsy for patients with cutaneous melanomas ≤ 1.00 mm in Breslow thickness, with particular reference to Clark level as a predictor of progression.

Methods

Patients with cutaneous melanomas ≤ 1.00 mm in Breslow thickness who had undergone sentinel node biopsy as part of clinically indicated standard care were identified from a prospectively collected database of all melanoma patients treated from 1992 through 2002 in the Cutaneous Oncology Division at the H. Lee Moffitt Cancer Center & Research Institute in Florida. All patients underwent preoperative lymphoscintigraphy to identify all regional nodal basins at risk for metastatic disease. This was followed by a sentinel node biopsy of the identified regional nodal

basins and an appropriate wide local excision of the primary site. All sentinel node pathology was reviewed at Moffitt Cancer Center, with the sentinel nodes being serially sectioned and evaluated microscopically by routine hematoxylin and eosin evaluation and immunohistochemical staining with a commercially available antibody to S100. When possible, the primary tumors were evaluated by a Moffitt dermatopathologist prior to surgery. Reverse-transcriptase polymerase chain reaction or other extensive sampling methods to evaluate for regional progression were not employed in this series.

Results

A total of 409 patients were identified as having melanomas that had undergone sentinel node biopsy for primary cutaneous melanomas ranging from 0.75 to 1.0 mm in Breslow thickness. Micrometastases were identified in the sentinel node in 20 patients, for an overall incidence of nodal progression of 5.2%. Patients were separated into two groups, based on their penetration into the dermis as classified by Clark level: invasive cutaneous melanoma with no penetration into the reticular dermis (Clark level II or III) and invasive cutaneous melanoma penetrating into the reticular dermis (Clark level IV). None of the 409 patients had melanomas that penetrated into the subcutaneous fat (Clark level V).

Among the 409 patients, 252 were identified as Clark level II or III group, accounting for 62% of the entire group. Eleven of those 252 patients (4.4%) were found to have a positive sentinel node. In comparison, 157 melanomas (38%) were found to be Clark level IV, with 9 of these patients (5.7%) having a positive sentinel node. The difference in the rate of nodal involvement between the two groups was not statistically significant. No patient in either group who had an ulcerated melanoma had a positive sentinel node.

If a strategy of performing sentinel node biopsy only on patients with Clark level IV or V lesions or ulcerated primary tumors had been employed, slightly less than half of our patients would have undergone sentinel node biopsy, but less than half of all potentially identifiable cases of nodal progression would have been detected.

Review of the Literature

Our results pose two important questions concerning the treatment of thin cutaneous primary lesions. First, does an incidence of nodal progression of approximately 5% warrant the added morbidity and cost of sentinel node biopsy? Second, are there specific predictive factors that could be used to determine the need for sentinel node biopsy among thin melanoma patients? A review of all the pertinent current literature was conducted in an attempt to

identify reliable indicators that might be helpful in determining which patients with “thin melanomas” would be sufficiently likely to manifest regional progression to warrant routinely undergoing a preoperative lymphoscintigraphy followed by a sentinel node biopsy.

Many patients and physicians consider a 5% likelihood of nodal positivity adequate to justify the relatively low morbidity of sentinel lymph node biopsy. No specific studies exist of the percentage of patients or physicians holding this view nor the factors influencing this decision-making process. Rates of nodal involvement substantively below 5% make sentinel node biopsy difficult to justify because of the cost involved and because the false-negative rate of the test begins to exceed the true-positive rate. Moreover, given the heterogeneity known to exist even in patients with thin melanomas, it is highly likely that the population of patients with thin melanomas is actually composed of one or more subgroups with a nodal progression risk in excess of 5% and one or more other subgroups with rates well below that mark.

In 2000, Balch et al^{1,2} developed the current AJCC criteria for the staging of cutaneous melanoma, which included comments on the factors to be considered when deciding on the need for sentinel node biopsy. These factors included a Breslow depth of greater than 1 mm, the presence of ulceration, or lesions with a Clark level of IV or V for melanomas 1 mm or thinner. This recommendation was derived from a multivariate analysis of over 17,000 patients with melanoma evaluated from a multicenter data compilation. A recent review suggests that in the United States, over 60% of patients with thin melanomas are managed in accordance with these recommendations.³ However, experience suggests that one modification of the recommendation is commonly employed: melanomas that are exactly 1 mm in thickness are routinely managed with sentinel node biopsy even though the staging system includes them with the category that calls for selective use.

Some institutions, including the Moffitt Cancer Center, have used criteria different from the AJCC recommendations to determine whether or not to perform sentinel node biopsy for lesions 1.0 mm or less in depth. For example, the University of Michigan Multidisciplinary Melanoma Clinic does not recommend sentinel node biopsy for patients with melanomas less than 1 mm, while at Moffitt Cancer Center a cutoff of 0.75 mm was adopted.

Over the last 5 years, as the use of sentinel node biopsy has expanded, there have been a number of attempts to identify those prognostic factors that may be used to justify the use of sentinel node biopsy in the thin melanoma patient. These factors have included such indices as patient age, tumor mitotic rate (TMR), regression, vertical growth phase, gender, and tumor-infiltrating lymphocytes (TILs). These were added to the already reported significance of tumor thickness, ulceration, and increased Clark level in thin melanomas. A review of the most recent literature was conducted to study all of these findings. A limitation of any

effort to synthesize the available data is the relative rarity with which all the findings were examined in the same patient population, making a head-to-head comparison of individual features difficult if not impossible. The available evidence strongly suggests, however, that prognostic factors for regional nodal progression are not identical to the prognostic factors associated with overall disease survival.^{4,7}

Breslow Thickness Subcategories

The original AJCC staging system for melanoma used 0.75 mm as its lowest cutoff, and some institutions (including Moffitt Cancer Center) continue to use this parameter for selecting patients for sentinel node biopsy. Few centers routinely perform sentinel node biopsy for melanomas thinner than 0.75 mm in the absence of some other factor indicating an increased risk for progression. While nodal metastasis has been described in melanomas thinner than 0.75 mm as noted by Stitzenberg et al,⁸ it appears to be exceedingly rare. Kesmodel et al⁹ found only 1 patient with a positive sentinel node among 91 vertical growth phase melanomas less than 0.76 mm in thickness. In a series of 118 patients with melanomas ≤ 0.75 mm, Bleicher et al¹⁰ found only 2 positive sentinel nodes (1.7%). Moreover, according to Agnese and colleagues¹¹ in 2003, the estimated cost of sentinel node biopsy, if applied to all melanomas less than 1.00 mm, would be more than \$900,000 per positive node. Routine use of sentinel node biopsy for melanomas below 0.75 mm did not appear to be justified based on that available data.

Several points bear mentioning when considering Breslow thickness in “thin” melanomas. First and foremost, an incomplete biopsy provides an incomplete and inadequate assessment of Breslow thickness. Tumors that extend to the deep biopsy margin may well be thicker than anticipated, and any decisions about surgical staging should be made with this fact in mind. The second is that sampling error can apply to measurements of Breslow thickness just as in any other pathologic assessment. A study by Dyson et al¹² indicated that adding a minimum of five more serial sections taken while evaluating a primary melanoma pathology specimen increased the reported maximum tumor thickness in over 43%. This inconsistency in the reported depth was found to change the surgical management in many cases. These findings were mirrored in two in-house evaluations completed at Moffitt Cancer Center over the last 4 years by three of us (C.N., L.F.G., J.L.M.). Hence, all recommendations regarding sentinel node biopsy should be made with care (and with a contingency plan in mind) if the initial biopsy transects the base of the lesion or has not been reviewed by an experienced dermatopathologist.

Patient Age

Sondak and colleagues^{13,14} reviewed the University of Michigan experience with over 400 patients with melanomas, with almost all melanomas being at least 1.0 mm in

thickness. Their findings revealed that age was a significant predictor of the likelihood of nodal involvement in patients. In this study, the rate of nodal progression increased steadily as patient age decreased. This relationship, however, was the inverse of the generally observed phenomenon that the risk of decreased survival is greater as patient age increases. The Michigan experience has been mirrored by others as well: an analysis by Chao et al¹⁵ of the prospective Sunbelt Melanoma Trial, which also involves patients with melanomas of at least 1.00 mm in thickness, found that the incidence of sentinel node positivity declined with age. Less is known about the influence of age on the likelihood of nodal progression in thin melanoma patients. In 2003, a retrospective review by Bleicher and colleagues¹⁰ showed that younger age (defined in their study) was associated with nodal progression in patients with melanomas less than or equal to 1.50 mm in depth. Several other single institution series^{8,9} of sentinel node biopsy for melanomas 1.00 mm or thinner have found that patients with nodal progression were confined to those 60 years of age or younger, without finding a direct correlation for age as a continuous variable. However, data presented by Leiter et al¹⁶ showed age was significant only in older men with melanomas less than 0.75 mm in depth.

Tumor Mitotic Rate

Investigators at the Sydney Melanoma Unit in Australia^{17,18} evaluated TMR as a prognostic indicator for disease progression (Fig 1). Their finding in a series of 3,661 patients showed that those with a TMR of 0 mitoses per mm² had a significantly better survival rate than patients with 1 or more mitoses per mm². In their data, mitotic rate was a more significant prognostic factor than ulceration when both were taken into account. Sondak and colleagues¹⁴ also found mitotic rate to be a significant predictor of nodal progression, and in this series ulceration did not retain statistical significance as a prognostic factor in multivariate analyses if mitotic rate was taken into account. In the University of Pennsylvania experience with patients with vertical growth phase melanomas 1.00 mm or thin-

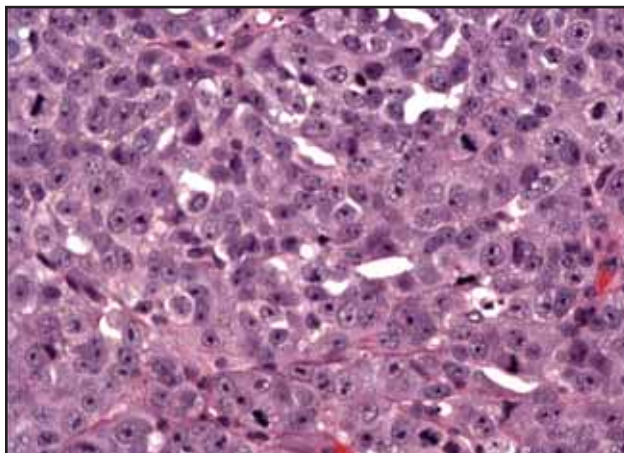


Fig 1. — Mitoses (400×).

ner, Kesmodel et al⁹ and Gimotty et al¹⁹ found that mitotic rate correlated with both nodal progression and decreased overall survival. Other single institution series of sentinel node biopsy for thin melanomas generally did not review mitotic rate for all included patients,^{20,21} but rather looked at the mitotic rate only in patients with nodal metastases. Reviews of small numbers of sentinel node-positive thin melanoma patients by Stitzenberg et al⁸ and others from the University of North Carolina and Roswell Park Cancer Institute did not suggest that nodal progression was most commonly from higher mitotic rate tumors.

Ulceration

Ulceration is an uncommon pathologic finding in thin melanomas (Fig 2), and when present may be secondary to trauma. While ulceration correlated with increased rates of disease progression in patients with thin melanomas in the large AJCC data set (in which mitotic rate was not evaluated), it has not correlated with nodal progression in most series of sentinel node biopsy for the same patients. In a number of series, including the previously described analysis of the Moffitt Cancer Center data and reports from the University of Pennsylvania⁹ and the University of North Carolina at Chapel Hill,⁸ no patients with ulcerated thin primary melanomas were found to have evidence of nodal metastases.

Regression

Regression is a pathologic finding suggesting that a melanoma had at one time penetrated to a greater degree than was evident at the time of biopsy (Fig 3) and could theoretically identify thin lesions with a particularly high risk of nodal progression. To date, however, no study has found regression to be a statistically significant independent predictor of nodal metastasis either for all patients with melanoma or only for patients with thin melanoma.

Gender

Many studies suggest that men are more likely to die of melanomas than women are. This is in accordance with

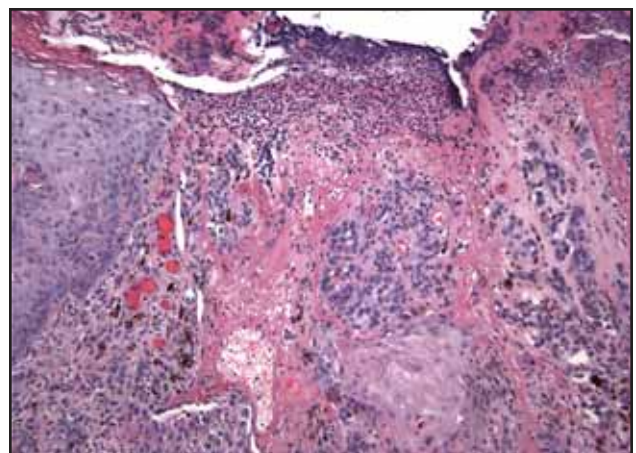


Fig 2. — Ulceration (100×).

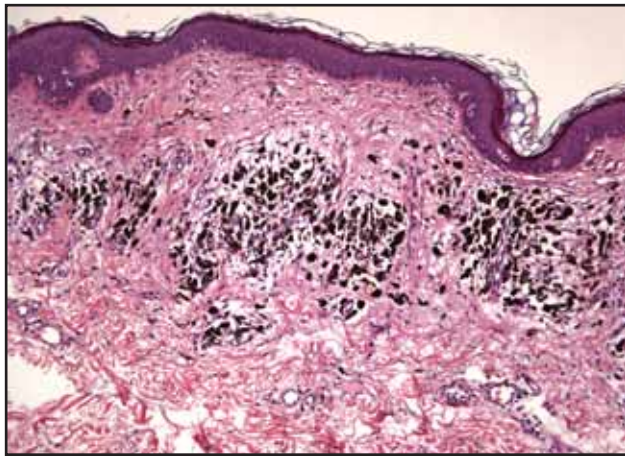


Fig 3. — Regression (100×).

the findings of Gimotty et al,¹⁹ who found gender to be prognostically significant for progression in thin melanomas. In another analysis from the same institution, male gender also correlated with nodal disease in thin melanoma patients.

Tumor Infiltrating Lymphocytes

Clark and colleagues²² are credited with first evaluating and categorizing TILs as a prognostic biomarker in primary melanoma (Fig 4). He described “brisk” tumor infiltration by lymphocytes as a favorable factor, while “nonbrisk” infiltration was intermediate, and “absent or slight” infiltration was unfavorable. A subsequent study by Clemente et al²³ in a different cohort of patients also established the presence of brisk TILs to be an independent positive predictive factor. A prospective randomized clinical trial of vitamin A in patients with clinically localized melanoma conducted by the Southwest Oncology Group found the presence of brisk TILs (defined as lymphocytes completely surrounding the nodule in a band-like manner, with no defect in the band of greater than 0.30 mm) to be strongly correlated with outcome.²⁴ Whether the patient had “nonbrisk” or “absent or slight” TILs was not associated with any difference in outcome. The 10-year survival rate for 30 patients out of 259 with brisk TILs was 93% compared with 58% for nonbrisk and 55% for absent or slight TILs. The relative risk of recurrence in this study superseded both ulceration and mitotic rate in multivariate analysis. The study stresses the importance of including all known potential prognostic factors in any multivariate model of outcome in melanoma.

Much less is known about the implications of TILs for melanoma progression as assessed by regional nodal metastasis. However, most recent studies have not included this factor. Kruper et al²⁵ from the University of Pennsylvania recently described TILs as an independent prognostic factor for sentinel node metastasis in patients with stage I and II melanoma, with patients with absent TILs having a 3-fold increased relative risk of nodal metastasis. They found that the presence or absence of TILs was sec-

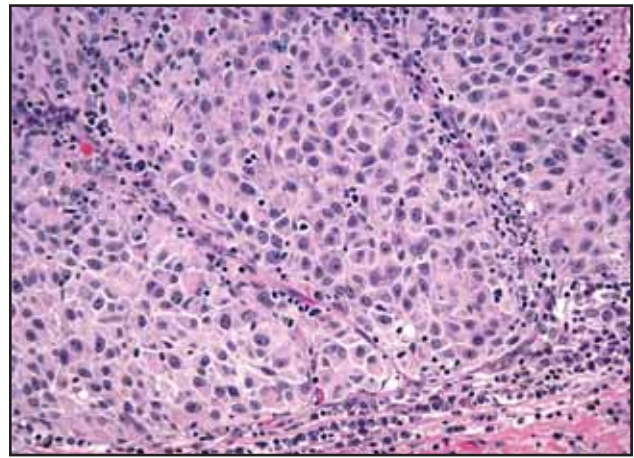


Fig 4. — Tumor-infiltrating lymphocytes (200×).

ond only to tumor thickness in a regression tree analysis for predicting risk of sentinel node metastasis in melanomas greater than 1 mm. These findings, which have yet to be validated in an independent data set, support the potential role of TILs as a biomarker for melanoma regional progression, particularly along with TMR.

Clark Level

One finding that was consistent in nearly all of the reviewed reports was that Clark level did not correlate with nodal progression in thin melanomas. The available evidence strongly suggests that if Clark level and ulceration are used as the primary selection criteria for recommending sentinel node biopsy in patients with melanomas of 1.00 mm or thinner, then a substantial number of node-positive cases would be missed (more than half in the Moffitt series).

Discussion

Currently available data do not support the use of any pathologic or clinical parameters to identify subsets of thin melanoma patients with a substantially higher than baseline risk of nodal progression. Clark level should not be used to select patients with thin melanomas for sentinel node biopsy, and even a pathologic finding of ulceration in such lesions should be interpreted with caution. It is likely that no single parameter will prove sufficient to identify those subsets that most warrant sentinel node biopsy. There is a need for a combination of specifically sought identifiers to be used in selecting thin melanomas for this procedure. Gimotty et al¹⁹ propose the use of a prognostic tree to stratify patients. By establishing more exacting criteria for completing a sentinel node biopsy in thin melanomas, we may begin to identify more easily those patients who are most likely to have recurrence and progression of their disease, thereby allowing them to receive earlier aggressive treatment. Conversely, we may then be able to identify those patients whose recurrence rates are relatively low, giving them a better understanding

and allowing for easier management. However, until a universally agreed on “prognostic tree” can be identified, perhaps we can aid our patients only in making an educated decision on the treatment of their thin melanomas. Prospective multicenter trials are needed, because even at high-volume melanoma centers, relatively few node-positive thin melanomas are encountered per year (and only these cases will truly inform us as to what parameters determine nodal progression).

In the meantime, our primary care, dermatology, and surgery colleagues face increasingly complex decisions when they evaluate which patients with thin melanomas to send to secondary centers for nodal staging. At present, our practice is to explain to each patient with thin melanomas the nature of their condition, the risk of nodal positivity (average of 5%), and the potential risks and benefits of early detection of microscopic nodal metastases. Those with melanomas between 0.75 and 1.00 mm are offered sentinel node biopsy if they are in good health otherwise. Younger patients are particularly likely to undergo nodal staging, both because of the reported increased risk of nodal progression and the greater likelihood they will live long enough to manifest clinical nodal progression if involved nodes are not identified and removed.

Conclusions

As the emphasis on early detection of melanoma increases, dermatologists and surgeons are seeing more patients than ever before with melanomas 1.00 mm in thickness or less. Based on available data, the vast majority of patients (if not all) with melanomas <0.75 mm should be treated with a 1-cm wide excision without sentinel node biopsy. Patients with melanomas between 0.75 and 1.00 mm are appropriate candidates to be considered for sentinel node biopsy after a thorough discussion of the likelihood of finding evidence of nodal progression, the risks of sentinel node biopsy (including the risk of a false-negative result), and the lack of proven survival benefit from any form of surgical nodal staging.

References

1. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol.* 2001;19:3622-3634.
2. Balch CM, Buzaid AC, Atkins MB, et al. A new American Joint Committee on Cancer staging system for cutaneous melanoma. *Cancer.* 2000;88:1484-1491.
3. Cormier JN, Xing, Y, Ding M, et al. Population-based assessment of surgical treatment trends for patients with melanoma in the era of sentinel lymph node biopsy. *J Clin Oncol.* 2005;23:6054-6062.
4. Halpern AC, Marghoob AA. Thin melanoma: still “excellent prognosis” disease? *J Clin Oncol.* 2004;22:3651-3653. Epub 2004 Aug 9.
5. Jacobs IA, Chang CK, DasGupta TK, et al. Role of sentinel lymph node biopsy in patients with thin (<1 mm) primary melanoma. *Ann Surg Oncol.* 2003;10:558-561.
6. Roaten JB, Pearlman N, Gonzalez R, et al. Identifying risk factors for complications following sentinel lymph node biopsy for melanoma. *Arch Surg.* 2005;140:85-89.
7. Zapas JL, Coley HC, Beam SL, et al. The risk of regional lymph node metastases in patients with melanoma less than 1.0 mm thick: recommenda-

- tions for sentinel lymph node biopsy. *J Am Coll Surg.* 2003;197:403-407.
8. Stitzenberg K, Groben P, Stern S, et al. Indications for lymphatic mapping and sentinel lymphadenectomy in patients with thin melanoma. Breslow thickness <or = 1.0 mm). *Ann Surg Oncol.* 2004;11:900-906.
9. 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;12:449-458. Epub 2005 Apr 19.
10. Bleicher RJ, Essner R, Foshag LJ, et al. Role of sentinel lymphadenectomy in thin invasive cutaneous melanomas. *J Clin Oncol.* 2003;21:1326-1331.
11. Agnese DM, Abdessalam SF, Burak WE Jr, et al. Cost-effectiveness of sentinel lymph node biopsy in thin melanomas. *Surgery.* 2003;134:542-558.
12. Dyson SW, Bass J, Pomeranz J, et al. Impact of thorough block sampling in the histologic evaluation of melanomas. *Arch Dermatol.* 2005;141:734-736.
13. Sondak V. New approaches to the treatment of advanced melanoma. Presented at the 40th Annual Meeting of the American Society of Clinical Oncology; June 5-8, 2004; New Orleans, La.
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;11:247-258.
15. Chao C, Martin RC 2nd, Ross MI, et al. Correlation between prognostic factor and increasing age in melanoma. *Anal Surg Oncol.* 2004;11:259-264.
16. Leiter U, Buettner PG, Eigentler TK, et al. Prognostic factors of thin cutaneous melanoma: an analysis of the central malignant melanoma registry of the german dermatological society. *J Clin Oncol.* 2004;22:3660-3667. Epub 2004 Aug 9.
17. 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;11:233-235.
18. Azzola MF, Shaw HM, Thompson JF, et al. Tumor mitotic rate is a more powerful prognostic indicator than ulceration in patients with primary cutaneous melanoma: an analysis of 3661 patients from a single center. *Cancer.* 2003;97:1488-1498.
19. 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;22:3668-3676. Epub 2004 Aug 9. Erratum in: *J Clin Oncol.* 2005;23:656.
20. Busam KJ. The prognostic importance of tumor mitotic rate for patients with primary cutaneous melanoma. *Ann Surg Oncol.* 2004;11:360-361. Epub 2004 Mar 15.
21. Francken AB, Shaw HM, Thompson JF, et al. The prognostic importance of tumor mitotic rate confirmed in 1317 patients with primary cutaneous melanoma and long follow-up. *Ann Surg Oncol.* 2004;11:426-433. Epub 2004 Mar 15.
22. Clark WH Jr, Elder DE, Guerry D 4th, et al. Model predicting survival in stage I melanoma based on tumor progression. *J Natl Cancer Inst.* 1989;81:1893-1904.
23. Clemente CG, Mihm MC Jr, Bufalino R, et al. Prognostic value of tumor infiltrating lymphocytes in the vertical growth phase of primary cutaneous melanoma. *Cancer.* 1996;77:1303-1310.
24. Tuthill R, Unger J, Liu P, et al. Risk assessment in localized primary cutaneous melanoma: Southwest Oncology Group study evaluating nine factors and a test of the Clark logistic regression prediction model. *Am J Clin Pathol.* 2002;118 504-511.
25. Kruper L, Botbyl J, Czerniecki B, et al. Predicting sentinel lymph node status in stage I/II melanoma. *Proc Annu Meet Am Soc Clin Oncol.* 2005;23 (16S):7501. Abstract. http://meeting.jco.org/cgi/content/abstract/23/16_suppl/7501.