Early-Stage Melanoma: Staging Criteria and Prognostic Modeling
Merrick I. Ross

Abstract
Accurate risk assessment is central to the process of making rational surgical and systemic treatment recommendations for melanoma patients and in establishing appropriate clinical trial stratification criteria. The current American Joint Commission on Cancer melanoma staging system incorporated relevant prognostic variables to provide a framework for the estimation of risk for recurrence; however, significant prognostic heterogeneity exists within the stage groupings. In the stage I/II group, survival rates range from 40% to 95% as defined by the combination of tumor thickness and ulceration. The use of novel prognostic factors, such as mitotic rate, sentinel node biopsy, and prognostic modeling using a variety of factors, can minimize this prognostic heterogeneity and provide a more accurate and individualized prognostic profile. Recent modifications in the stage III criteria include the number of positive nodes, whether the nodal disease is microscopic or clinically apparent, and the presence of an ulcerated primary. Through these factors, survival estimates can be provided, but like the stage I/II group, wide ranges in prognosis exist. The complexion of the stage III population is in evolution as a result of increasing numbers of patients being diagnosed as having microscopic sentinel node disease. Contemporary efforts are focused on defining the prognosis and natural history of this group. Through prognostic modeling using the number of nodes involved, ulceration status, and a measure of disease burden—disease in the sentinel node—relatively homogeneous subgroups can be identified. Long-term follow-up of patients staged with PCR molecular techniques on sentinel nodes shows conflicting value in assessing prognosis and therefore cannot be routinely used outside a clinical trial. The combination of genomic profiling using microarray analyses and the development of targeted therapy holds the future promise of individualizing prognosis and therapy.

Author's Affiliation: Department of Surgical Oncology, University of Texas M.D. Anderson Cancer Center, Houston, Texas

individual patient. Newer prognostic factors and novel methods of prognostic analyses augment the predictions for the presence of micrometastatic disease and further define the risk for disease relapse. The focus of this article is to highlight the relevant evidence supporting the use of these novel approaches as adjuncts to the current staging system in the risk assessment process.

Stage I and II Risk Assessment

The vast majority of newly diagnosed melanoma patients will present with disease clinically localized to the primary cutaneous site. This group, from a prognostic perspective, is very heterogeneous, composed of subgroups with survival estimates ranging from 40% to 95% (2). Some of this prognostic heterogeneity is resolved by the predominant prognostic factors of thickness and ulceration status, the combination of which identifies five prognostic groups (substages Ia, Ib, IIa, IIb, and IIc; ref. 2). Recognizing that establishing staging criteria is always a process in evolution and that the current criteria, although improved, have limitations, the AJCC recommended a “prognostic tree” (7). They focused on the thin melanoma (≤1 mm) population and evaluated the importance of mitotic rate as well as some of the other novel histologic features relative to tumor thickness and ulceration in the stage I/II population (4–6). Although these studies differ in design, factors included, and number of patients, a consistent theme has emerged: thickness remains the single most powerful predictor of survival and mitotic rate replaces ulceration. It seems that not only is the presence or absence of mitoses in the dermal vertical growth component important but also the number of mitoses (5, 6). One can speculate why mitotic rate trumps ulceration in multivariate analyses. Although both are probably critical morphologic surrogates for an underlying molecular mechanism controlling cell proliferation, not all lesions with a high proliferative index are ulcerated, as a result ulceration is probably a less sensitive marker. Furthermore, the number of mitoses can be easily counted, facilitating the establishment of ranges of increasing mitoses having prognostic relevance. Over time, with enough data, mitotic rate could, like thickness, become a continuous variable. In contrast, ulceration has only been well studied as a dichotomous variable (present or absent) rather than describing the extent of ulceration when present, measured in width or depth. Although the data promoting the importance of mitotic rate are compelling, the studies have significant limitations in size as well as in the fact that microscopic nodal involvement was not included in the analyses. However, the AJCC melanoma committee, which will reconvene in 2006, will have to formally address the future role of mitotic rate in the microstaging of primary melanomas.

Prognostic Modeling

The most notable published work is from the group at the University of Pennsylvania describing a novel approach to prognostic modeling, a “prognostic tree” (7). They focused on the thin melanoma (≤1 mm) population and evaluated the relative importance of 11 prognostic variables. At first glance, it would seem that studying such a low risk group would be of little value. In actuality, because the thin group represents >60% of the newly diagnosed patients, the absolute number of patients who develop stage III and IV disease, who initially presented with a thin melanoma, is significant and the contribution on a percentage basis to the stage IV group from this early-stage population is high. On completion of a multivariate analysis, four factors emerged as independent predictors: mitotic rate (0 versus ≥1), tumor-infiltrating lymphocytes, gender, and growth phase (radial or vertical). Using these four variables, a hierarchical prognostic tree was developed (Fig. 1A), which defined four risk categories with their associated metastases-free survival rates (Fig. 1B). Overall, two thirds of the patients separate out into the minimal-risk and low-risk groups with predicted risk of metastases ≤4%. The remaining patients are categorized as moderate or high risk with risks of metastases of 12% and 30%, respectively. Such analyses can be helpful in determining which of the thin melanoma

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Table 1. Summary of changes to tumor-node-metastasis criteria incorporated in 2002 AJCC staging system

<table>
<thead>
<tr>
<th>Stage I and II</th>
<th>Tumor thickness ranges of ≤1, 1.2, 2-4, and &gt;4 mm (T1, T2, T3, and T4, respectively)</th>
<th>Clark level only for ≤1 mm group</th>
<th>Level IV is T4a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III</td>
<td>No. positive nodes replaces size of nodes</td>
<td>Microscopic vs macroscopic (grossly evident) burden of disease</td>
<td></td>
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<tr>
<td></td>
<td>Ulceration included in all thickness ranges</td>
<td>N(T1-3)a vs N(T1-3)b</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ulcerated primary is classified as T(1-4)b</td>
<td>Ulceration of primary advances to next higher stage (i.e., stage IIIa becomes IIb and stage IIb becomes IIIc)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Local recurrence, satellites, classified with in-transits as N2a, with positive nodes, N2c</td>
<td></td>
<td></td>
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<tr>
<td>Stage IV</td>
<td>M1a, M1b, M1c (distant soft tissue vs lung vs all other visceral)</td>
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patients should undergo sentinel node biopsy and/or receive adjuvant therapy or participate in adjuvant therapy trials.

**Sentinel Node Staging**

The technique of lymphatic mapping and SLN biopsy is a well-established, minimally invasive surgical procedure used to accurately determine the presence or absence of microscopic regional nodal metastases (8, 9). Several large single- and multiinstitutional stage I/II studies consistently show that the presence of microscopic nodal involvement is prognostically relevant, that node-negative status established by careful scrutiny of the SLN identifies a favorable risk group, and that multivariate analyses, including the established important prognostic factors, reveal that SLN status is the most powerful independent predictor of survival in stage I/II patients (10–13). Therefore, the prognostic heterogeneity that is prevalent in the clinically localized patient population can be significantly reduced by incorporating this approach in the initial surgical management of a significant percentage of patients. In addition to providing valuable staging information (10, 13), the approach of selective lymphadenectomy (regional node dissection for patients with positive SLN) may optimize the chance for long-term regional disease control and improve survival (11, 14–16). Despite these reported benefits and the low associated morbidity (17), it is still a surgical procedure that is responsible for some toxicity and for generating significant health care costs. Therefore, the routine use of SLN biopsy has been challenged, appropriately so, for those patient groups at low risk of harboring occult nodal metastases. Establishing rational guidelines on which patients should be offered this approach has been the center of some controversy.

Several melanoma centers around the world have published their findings about the incidence and predictors of SLN metastases. Consistently, the incidence ranges from 15% to 22%, depending on the patient population studied and the extent of pathologic assessment of the SLN employed (8, 9, 18–21). Multivariate analyses most frequently identify increasing tumor thickness and primary tumor ulceration as the strongest predictors of SLN involvement, and some report young age (<50 years) as an additional important variable (19, 20). One of the clearest data presentations illustrating the combined effect of increasing tumor thickness and ulceration status on the presence of SLN disease is from the M.D. Anderson Cancer Center group derived from an analysis of more than 1,300 stage I/II patients (ref. 22; Table 2). More recent publications have included mitotic rate in such analyses, and findings from both the University of Michigan and the Sydney Melanoma Unit similarly show three independent predictors: thickness, number of mitoses, and young age (20, 21). The finding of mitotic rate replacing ulceration is consistent with the data described above about the relative

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**Fig. 1.** Results of hierarchical prognostic tree analysis in 884 thin melanomas using a combination of mitotic rate (MR), gender, and growth phase. A, definition of the four established prognostic groups. B, graphic display of metastases-free survival according to prognostic group.
Table 2. Incidence of SLN metastases according to AJCC thickness stage and ulceration

<table>
<thead>
<tr>
<th>Tumor thickness (mm)</th>
<th>Total no. patients (n)</th>
<th>Positive SLN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All (%)</td>
</tr>
<tr>
<td>≤1.00</td>
<td>326</td>
<td>4.2</td>
</tr>
<tr>
<td>1.01-2.00</td>
<td>490</td>
<td>11.4</td>
</tr>
<tr>
<td>2.01-4.00</td>
<td>310</td>
<td>28.5</td>
</tr>
<tr>
<td>4.01+</td>
<td>190</td>
<td>45.5</td>
</tr>
<tr>
<td>Total</td>
<td>1,316</td>
<td>17.4</td>
</tr>
</tbody>
</table>

Several studies have assessed the incidence of SLN involvement in patients with thin melanomas and report a range of 0% to 13%, varying according to the constellation of prognostic factors (31–39). One study did a cost analysis and reported that the routine use of SLN biopsy in this subgroup costs $600,000 to identify one patient with a positive SLN; however, the incidence of SLN involvement in that study was only 1.2% (34). Clearly, a very selective approach is warranted in this group, which should be directed by an accurate risk assessment for the incidence of SLN metastases. Higher-risk subsets have been identified by the presence of regression in the primary tumor (38) or the presence of vertical growth phase (39). Prognostic modeling as described above has been used to help better define a high-risk cohort. Again, the group from the University of Pennsylvania is singled out as taking the lead in this endeavor. They report the findings of a prognostic analysis including 181 patients with thin melanomas, all with lesions exhibiting a vertical growth phase component (32). More than 50% of the patients had lesions in the thickness range of 0.76 to 1 mm; 50% of the primary lesions had a mitotic rate of at least 1; only 6% of the melanomas were ulcerated; and the overall incidence of SLN involvement was 5%, all of whom had melanomas with a mitotic rate of at least 1. Univariate analysis identified tumor thickness and mitotic rate as predictors of SLN metastases and a prognostic tree constructed by using these two factors defined a high-risk group with a 12.3% incidence of SLN metastases. A large database of >5,000 patients with thin melanoma who have undergone SLN biopsy is being established by the M.D. Anderson Cancer Center group through contributions of data from more than 15 melanoma centers around the world. A definitive prognostic analysis is planned to better determine predictors of SLN involvement in this low risk group.

The SLN-negative population, identified by the accurate removal and careful pathologic scrutiny of the SLN, is a relatively homogeneous prognostic group whose natural history should approximate what we would expect from a “true” stage I and II population. Long-term follow-up reveals that 15% of these patients will experience disease relapse and that such events are best predicted by tumor thickness and ulceration. Although nodal disease is the most powerful predictor of distant relapse, the fact that distant failure occurs in a pathologically defined node-negative population suggests the following: hematogenous micrometastatic disease occurs in some patients in the absence of lymphatic spread, and/or lymphatic disease is present in the SLN in patients who develop distant relapse but is undetected by standard histologic and immunohistochemical techniques. The latter possibility is being
investigated using the molecular technique of reverse transcription-PCR to identify the presence of submicroscopic melanoma metastases in SLNs through the amplification of melanocyte or melanoma specific RNA codes. Promising data reported by the Moffitt Cancer Center showed that within the SLN-negative population, clinically relevant subgroups could be defined by PCR status (40). As a result, single- and multi-institutional prospective trials were conducted to validate these findings. One report from Memorial Sloan Kettering showed that early in the follow-up period, a PCR-positive finding was associated with a worse disease-free survival compared with patients with PCR-negative SLNs. However, on longer follow-up, these differences were lost (41). Such findings may be partially explained by false-positive PCR results caused by the presence of nodal nevi, false-negative histologic events occurring in the PCR-positive SLN patients as a result of the only focus of histologically detectable microscopic nodal disease being present in the portion of the SLN used for the PCR analysis, and false-negative PCR results. In contrast, a report from the John Wayne Cancer Institute corroborated the Moffitt group’s experience and showed persistence of survival differences in the PCR-positive and PCR-negative patients even after long-term follow-up (42). Differences in PCR techniques (resulting in fewer false-negative PCR results) and PCR targets used (resulting in fewer false-positive PCR events) could explain the contrasting findings in these two studies. Given the current state of the science, however, routine use of PCR in SLNs to better define a more pure SLN-negative population cannot be justified and should be conducted only as part of a clinical trial (Fig. 2).

Stage III Nodal Risk Assessment

The stage III patient population is also very heterogeneous, exhibiting survival rates ranging from 13% to 69% as predicted by the number of positive nodes, the burden of disease in the nodes (microscopic versus macroscopic), and primary tumor ulceration (1, 2). The complexity of the stage III population is in evolution, primarily a result of the routine use of SLN biopsy. As the percentage of stage III patients with microscopic nodal disease (SLN-positive group) increases, contemporary analyses should focus on the natural history of these patients. Intuitively, this group should be relatively homogeneous, but ongoing survival analyses suggest that significant prognostic heterogeneity exists within this favorable group as well. The 5-year survival of this group overall is ~70% but ranges from 40% to 90%. The established stage III factors of number of positive nodes and primary tumor ulceration are also important prognostic risk factors for the SLN-positive (microscopic) cohort (43, 44). Newer discriminates of tumor burden at the microscopic level, such as number of metastatic foci, largest focus measured in millimeters, square area of microscopic involvement, location of disease in the node (subcapsular versus intramammillary), and depth of nodal involvement, have all been reported as powerful independent predictors of survival and represent the third factor relevant in this group (44–47). The M.D. Anderson Cancer Center group has developed a prognostic model using these three risk factors to define substrata, reduce the prognostic heterogeneity, and provide more specific and personalized risk assessment. The three subgroups are defined as follows: low risk (1 positive SLN, nonulcerated tumor, and SLN burden of <2 mm), intermediate risk (>1 positive SLN, or SLN tumor burden >2 mm, or ulcerated primary), and high risk (two or more of the adverse factors described in the intermediate group; ref. 44). Such prognostic classifications may have important implications in the design of future randomized systemic adjuvant trials and help in the risk benefit analysis when making individual decisions to pursue adjuvant systemic therapy.

Stage IV Nodal Risk Involvement

Although prognostic subgroups within the stage IV population can be identified by stratifying patients by site of metastases (soft tissue/nodal versus lung versus other visceral) overall, the prognosis for this group is dismal and little relevant prognostic heterogeneity exists (1, 2). Therefore, investigative efforts for these patients should be focused on identifying predictors of response to therapy. Few data are available predicting a response to systemic therapy; however, information about the selection of patients who would have a favorable outcome after surgical resection of distant disease has been reported. Most of the stage IV population have widely disseminated disease and are therefore not surgical candidates; however, some patients can undergo resection with little morbidity and experience long-term survival. The factors reported to help identify the patients likely to have a favorable outcome are as follows: long disease-free interval after treatment for earlier stage disease, limited number of metastatic nodules and anatomic sites, and the ability to resect all measurable disease (48). In these settings, 5-year survival rates of at least 25% can be achieved.

Conclusions and Future Directions

Accurate risk assessment using established prognostic factors is central to the process of helping patients make rational treatment decisions and critical in establishing relevant stratification criteria in the design of clinical trials. The current staging system provides an excellent framework from which general prognoses can be derived, and through the use of more recently identified prognostic markers or through the process of prognostic modeling by incorporating an array of markers in the risk assessment process, prognosis can be more exact and/or individualized. Some of these novel markers, in time, may be incorporated into a future rendition of the AJCC system as an addition to or to replace one or more of the current criteria. The AJCC is planned to reconvene in late 2005 and early 2006 because the next iteration of the system will be published in 2009. The most likely new factor to change the complexion of the classification scheme is mitotic rate. As described above, this factor may be more discriminating than ulceration in the stage I/II patients. What is missing is a multivariate analysis done with mitotic rate in the context of a pathologically staged stage I/II group using SLN biopsy. Investigating the effect of mitotic rate in the stage III population is also important and most critically so in SLN-positive patients. Examples of prognostic modeling as described above are attempts to minimize the prognostic heterogeneity inherent within the framework of the current AJCC staging system. The process of prognostic modeling using the basic AJCC criteria combined with additional variables will become more commonplace. Such analyses could lead to the establishment of nomograms providing more individualized prognostic profiles (49).
The value of reverse transcription-PCR to detect submicroscopic disease in the SLN or in the blood (ref. 50; not discussed in this article) requires more extensive studies to establish standard techniques, defining the most reliable PCR targets along with long-term follow-up before such staging endeavors can be incorporated in the routine risk assessment process. The evolving technology of microarray analysis offers exciting prospects for the future not only to establish more definitive and individualized prognosis but also to provide predictions of response to particular therapies. In the future advances in clinical staging, the identification of specific targeted therapies and genomic profiling should be combined to allow not only accurate prediction of recurrence but also appropriate selection of therapy.

Open Discussion

Dr. Atkins: I remember data from M.D. Anderson that suggested that ulceration identified a group of tumors that metastasize through the blood rather than through the sentinel node. It seems your new data suggest that this may not be the case. How do tumors get to distant sites in sentinel node-negative patients?

Dr. Ross: Ulceration has been identified as a phenotype or morphologic surrogate for molecular mechanisms that we do not yet understand. Tumor cells probably gain access to either the lymphatic vessels or the hematogenous vessels at the local tumor environment, which is why ulceration is predictive of both lymph node metastases and distant disease in patients without positive nodes.

Dr. Atkins: Do you think that the distant metastases can come from the local primary, or do they come from the nodal disease?

Dr. Ross: They come from both. It would be naive to think that lymph node metastases cannot metastasize hematogenously, because tumor cells got to the nodes through invasion of lymphatic vessels. There may be some clones of cells that
like the lymphatics rather than the systemic vasculature, but I would imagine as the tumor cells grow within the lymph node, clonal heterogeneity probably develops and some of those clones may be more prone to metastasize systemically. If you look at patients who have bulky nodal disease, there are greater volumes of disease in the lymph node than there are in the primary tumor, so we would be naive to think that metastases are only generated from the primary tumor, which is why I think some of the data suggest that early node dissection for microscopic disease may impart a survival advantage in some patients.

Dr. Ross: What are your thoughts about sentinel node-positive patients and the performance of completion node dissections?

Dr. Sosman: One of the reasons that we do node dissections is to avoid the development of clinically evident regional nodal disease. That is what we are trying to avoid by doing the sentinel node dissection in the first place. It is certainly an important clinical trial question that is going to be addressed in MSLT-2.

Dr. Slingluff: Are there certain circumstances, other than patients being bad operative candidates, where you would not recommend a completion of node dissection?

Dr. Ross: Outside of a clinical trial I always recommend a completion node dissection. If patients have a positive sentinel lymph node, I offer them a node dissection. Whether they agree to that is something different. Certainly, you can identify very low-risk groups, which include those with a tumor thickness <2 mm and a tumor burden of <2 mm within the sentinel node. Based on our data set, the incidence of additional positive nodes in that setting is zero, and it represents a little less than a third of the entire patient population. We probably underestimate the amount of clinically relevant disease, because the other nodes are not examined as carefully as the sentinel node is. Therefore, there is probably more clinically relevant disease than is evident in the pathology report. Maybe it is the patients with the earliest disease who really benefit from the surgery.

Dr. Slingluff: Do you like to treat people with solitary intransit metastases like patients with local recurrences? We are doing wide excisions and sentinel nodes in these cases.

Dr. Ross: That is certainly one option. The sentinel node information is so important for prognosis that you can map some of these patients and you will find positive nodes, which upstage them to stage 3C and may motivate you to put them on a systemic therapy trial. In general, I would excise a single intransit lesion and perform a sentinel node biopsy if the patient had not already had a node dissection.

Dr. Slingluff: What are you doing for a patient who comes in with a melanoma of 1 mm or thinner, in terms of performing a sentinel node biopsy?

Dr. Ross: If they have any high-risk factors, then we would offer them a sentinel node biopsy.

Dr. Slingluff: Which factors would these be?

Dr. Ross: That is currently being modified because of the recent data with mitotic rate, but before that information was available, if they had Clark level IV, we would offer a sentinel lymph node biopsy.

Dr. Slingluff: How about gender?

Dr. Ross: Based on the data from UPenn, we probably should consider offering SLN biopsies to men with thin melanomas.

Dr. Sondak: I haven’t been convinced from any of our data that gender is influential. In fact, women are well represented among our patients with high mitotic rate and many of them have positive nodes. To me, age makes sense to consider in the thin melanoma patient for a lot of reasons. For example, all of us see patients from a decade ago who did not get a sentinel node biopsy who show up with a palpable node in their groin or their axilla. The first thing I say to them is, “Your doctor told you that you had a thin melanoma and a really good prognosis.” They say, “How did you know?” I say, “Because you are here today, 10 years later, with your lymph node disease.” Obviously, their immune system has not kept the disease in check; they just had relatively small-volume disease and it took 10 years to manifest as a nodal relapse.

Dr. Slingluff: Something that puzzles me is the patient who comes in with a biopsy specimen that is read as a regressed melanocytic lesion. I saw a patient recently who I had first treated 10 years ago for a melanoma. Originally, I did a wide excision; 10 years later he comes back from his primary care physician with a node in the ipsilateral axilla that is melanoma. I tend to do sentinel lymph node excisions in that setting and for people with thin primaries with regression.

Dr. Ross: When I see a lesion that is significantly regressed, it is defined by fibrosis within the dermis, I ask the pathologist to tell me how thick the fibrosis is. That is a useful piece of information because if it is a relatively thick area of fibrosis then I make the assumption it was a significant lesion in the past and I will probably be more aggressive from a sentinel node perspective.

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