

## Staging for Melanoma - Toward a New Paradigm?

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In this issue of the Journal, Bajaj and colleagues present an assessment of the accuracy of the *American Joint Committee on Cancer Staging Manual Eighth Edition* melanoma staging system (AJCC8) (1). Their study was prompted by concerns that the implementation of AJCC8 might disrupt analysis of active clinical trials for stage III patients, largely because of perceived difficulty of comparing patients staged according to AJCC8 vs previous systems. The authors reanalyzed 1357 stages I–III patients from AJCC7 into AJCC8, concluding that AJCC8 enabled a more accurate prognosis and that restaging a large cohort of patients not only was possible but also could enhance the analysis of active clinical trials.

In this and in other contexts, concerns regarding the validity of AJCC staging have been raised especially in regard to stages I and III melanoma. Regarding stage I, it is often (and at least in part correctly) stated that there is a paradoxically substantial mortality from these melanomas for whom the prognosis overall is excellent, because a high fraction of melanomas present in stage I. Prognosis in melanoma is related especially to Breslow thickness and ulceration. In AJCC8, the thickness cutoff for stage I was changed from the previous 1.0 mm to 0.8 mm, a prognostic attribute that dates back to Breslow's seminal study in 1970 (2). Modern data sets have also indicated that this cutoff has biological relevance (3,4). With the use of a few additional attributes, including absence of mitoses and ulceration, and perhaps a few other criteria, a subset of stage I patients can be identified in whom metastasis and death are effectively zero. This subset of melanoma patients is closely but not perfectly represented in AJCC8 stage IA, in whom the 5-year survival is 99% and the 10-year survival is 96% (5). In a study of "ultra-low stage" melanomas, the observed 10-year survival of a prospectively registered population of 2389 patients was literally 100% (3). There is evidence from population-based datasets that many lesions diagnosed as melanoma do not cause death, because incidence rates have risen steadily over several decades, whereas mortality has remained stable. This phenomenon is termed *overdiagnosis* and is not the same as *erroneous diagnosis* (6). Such nonlethal lesions could perhaps better be classified using a term that does not include the word *melanoma*, which has frightening connotations. Similar changes were made in a subset of thyroid tumors that

were called *carcinomas* but are now called *noninvasive neoplasms* (7), a term better reflective of their benign biology and more reassuring to patients. Nevertheless, with long-term follow-up, some patients with thin melanomas have been reported to suffer disease-related mortality decades after their initial diagnosis, emphasizing the importance of a cautious approach (4).

With regard to stage III, as Bajaj and colleagues (1) noted, there is another paradox; the overall survival of stage IIC patients (26.5% 5-year relapse-free survival) is worse than that of stage IIIA patients (56%). A similar effect was observed in the AJCC8 database (5). The underlying explanation for this paradigm is the TNM system that is used for AJCC staging in which stages I and II are localized disease, III requires lymph node metastasis (but also incorporates aspects of the primary tumor), and IV indicates distant metastasis. The paradox can be explained by understanding that stage IIC is represented by ulcerated melanomas greater than 4 mm in thickness (ie, T4b), and that even in the absence of sentinel node metastasis, thickness and ulceration are dominant prognostic variables in patients with clinically localized melanoma. In contrast, stage IIIA melanomas range up to only 2 mm in thickness, and most of them are not ulcerated. This paradox indicates that although lymph node status is a strong predictor in melanoma, primary tumor characteristics in aggregate can carry substantial prognostic weight irrespective of nodal status.

As highlighted by Bajaj et al. (1), concerns that implementation of AJCC8 might disrupt analysis of active clinical trials for stage III patients have been overstated. Clinical trials commenced prior to AJCC8 implementation will continue to enroll and stratify patients according to the trial protocol. Conversion of patient staging from historical AJCC7 data to AJCC8 will be easily possible because the data elements required for initial stage assignment did not change appreciably from AJCC7 (8).

Although various iterations of the AJCC staging system have for decades represented the benchmark for separating patients into prognostic groups for clinical trials, data collection in tumor registries, and patient management, it may be time finally to consider revamping the TNM staging system to provide more robust individualized prognostic estimates. Prognosis can otherwise be estimated, for example, in terms of tree diagrams that

have branches and leaves in which prognosis is relatively homogeneous (3). Prognosis can also be estimated in continuous algorithms or nomograms that utilize attributes including not only the already-used Breslow thickness and ulceration but also mitotic rate and sentinel node positivity, which would in this context be one of the strongest but not an overriding variable. Powerful prognostic cutoffs could then be used for entry into trials. Such efforts are already underway in the AJCC group (8,9). Given the remarkable improvement in survival for advanced stage melanoma patients who are responsive to targeted and immune therapies, response to these therapies must also be included as a prognostic attribute in future models. Criteria for entry into trials of these therapies will need to rely on historical data sets, because future data sets will be skewed in the salutary direction of higher survival rates for those patients who are fortunate enough to be responders, while remaining “historical” in nonresponders. A host of additional prognostic variables, including molecular and genomic attributes of the tumors and measures of the antitumoral immune response, has been proposed in individual and in retrospective studies. None of these as yet has been subjected to the stringent criteria of the REMARK group (10). This approach should attract research funding comparable to that already invested in basic science and clinical therapeutics. Only with accurate diagnostic and staging information can patients be appropriately treated and care improved.

### Notes

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