

# Clinical Perspectives™

## Highlights from the Perspectives in Melanoma XII Conference

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### *ADVANCES IN STAGING AND SURGERY*

#### **AJCC staging: Preview of the factors that may change in 2009**

The 6th Edition of the American Joint Committee on Cancer (AJCC) staging system for cutaneous melanoma first appeared in 2001 and represented a major advance from prior editions.<sup>1</sup> It has since been useful for clinicians involved in managing melanoma patients, in terms of staging disease, evaluating prognosis, and guiding treatment. However, much new information has been gathered since 2001, and clinical practices have evolved to some degree. The latest version (7th Edition) of the AJCC staging system for cutaneous melanoma is expected to be published in 2009 and will contain some changes reflecting new information and evolving practices. **Jeffrey E. Gershenwald**, of the University of Texas M. D. Anderson Cancer Center in Houston, Texas, provided a preview of some of the likely changes.

Before proceeding to outline those changes, Dr. Gershenwald described some key features of any clinically useful staging system. The system should be universally accepted, practical, and reproducible. It needs to incorporate the most relevant prognostic factors that not only reflect current clinical practice, but that also reflect the most current understanding of the biology of the disease. Terms and definitions need to be used consistently to define homogenous prognostic groups of definable risk. Staging tools are important for clinical practice, for clinical trials and national or cooperative datasets, and for communication among clinicians and between clinicians and their patients.

Dr. Gershenwald first reviewed changes that appeared in the 6th Edition of the AJCC staging guidelines, compared with earlier versions, before moving on to discuss likely modifications in the 7th Edition. In terms of the process, the AJCC Melanoma Task Force reconvened in 2007 for an evidence-based approach to making revisions for the proposed 7th Edition. Multiple meetings ensued, and predictive models were developed from a new prospective database involving approximately 60,000 patients from 14 cancer centers and organizations, including nearly 50,000 patients in stage I-III alone. The 7th Edition of the staging guidelines will be published in 2009 by the AJCC in collaboration with the UICC (International Union Against Cancer), and will presumably take effect in early 2010.

Although some fairly significant changes will appear in the 7th as compared with the 6th Edition, no overall major changes will be recommended for TNM and stage grouping criteria for stages I-III. Tumor thickness and ulceration continue to be the dominant independent prognostic factors for primary tumors and will continue to be used in defining strata in the T category. However, one of the recommended changes reflects the growing understanding over the last several years of the importance of mitotic rate (MR), both as a predictor of SLN metastases and survival, particularly in patients with thin melanomas. The 7th Edition of the AJCC guidelines defines MR histologically as number of mitoses/mm<sup>2</sup>, and indicates that a MR  $\geq 1$  (ie,  $\geq 1$  mitoses/mm<sup>2</sup>) reflects heightened risk of metastasis. Consistent with this, the upcoming guidelines will recommend replacing Clark level of invasion with MR  $\geq 1$  as a primary criterion (along with ulceration) for defining the subcategory of T1b. In the 14,000 patients in which MR could be included, tumor thickness, ulceration, and MR were all independent predictors of survival. Clark level of invasion will now only be considered relevant for staging when information on MR is lacking.

Most melanoma practitioners now use immunohistochemical (IHC) means to detect metastases in regional lymph nodes and guide clinical practice. Reflective of this change in clinical practice, the 7<sup>th</sup> Edition of the guidelines will indicate that IHC, in addition to hematoxylin and eosin (H&E) staining may be used to detect nodal micrometastases. The guidelines will not designate a lower threshold of tumor burden for defining the presence of regional nodal metastases (N+ disease), as there are no criteria that unequivocally define such a threshold at this time (ie, that can define a threshold for *clinically insignificant* nodal metastases). Molecular techniques such as RT-PCR to detect micrometastases will not be recommended in the upcoming guidelines. The relevance of such findings is unclear, and the use of RT-PCR and related techniques for this purpose has not been well standardized at this time.

It appears that heterogeneity in the survival curves of subgroups of patients with stage III disease can be demonstrated by using the 3 factors—number of positive nodes, primary tumor ulceration, and tumor burden of the metastasis—that comprise the stage III staging system. With respect to stage IV disease, no significant changes will be proposed in the upcoming guidelines. Analyses using the latest dataset validate the prognostic utility of serum LDH level and site of metastasis for survival, and hence the value in defining subcategories of stage IV disease.

## Reference

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## Alternative staging approaches: The role of ultrasound in prospective follow-up.

**Christine Voit**, of Charité-University Medicine Berlin in Berlin, Germany, discussed the potential to use ultrasound (US) with fine needle aspiration cytology (FNAC) as an alternative approach to SLN biopsy (SLNB) for staging earlier-stage melanoma. While SLNB is a minimally invasive staging procedure, US-FNAC staging is even less invasive and would be preferred if it could be demonstrated to provide similar sensitivity and specificity in detecting nodal metastases. In addition, unlike SLNB, US-FNAC could theoretically be repeated a number of times during patient follow-up and be used to examine multiple lymph node basins.

Dr. Voit said that initial studies from her group showed that US more accurately detected lymph node recurrences than regular lymph node palpation,<sup>1</sup> and US-FNAC detected SLNs prior to SLNB with a high degree of sensitivity (82%) and specificity (72%).<sup>2</sup> Two key US features for the presence of nodal metastases described so far had been (1) node thickness greater than two-thirds of the node length and (2) the presence of low-level echoes in the node. One study showed that nodal metastases were present in all cases in which these 2 features were present, although the authors cautioned that a normal US finding does not necessarily exclude micrometastases.<sup>3</sup>

Dr. Voit then described key initial findings from an ongoing study aimed at analyzing 6 US morphologic criteria, and different combinations of these criteria, for sensitivity and specificity in detecting nodal metastases. For this purpose, they used a prospective database consisting of more than 850 consecutive patients with stage I/II melanoma treated at the institution. Additional study aims were to demonstrate the value of US-FNAC prior to SLNB, evaluate the survival of US-FNAC staged patients, and correlate US-FNAC findings with SLN tumor burden. Four hundred patients with follow-up >6 months were available for the first analysis. The 6 morphologic US criteria evaluated were central echoes, hump structure, echo-poor islands, balloon-shaped lymph node, cap structure, and central and/or peripheral perfusion. US-FNAC was considered positive if *either* US or FNAC was positive.

**Table 1** presents the results with respect to sensitivity, specificity, and positive and negative predictive values (PPV and NPV) for the 6 morphologic US criteria evaluated. Balloon-shape plus peripheral perfusion

was the best combination in terms of sensitivity (82%), specificity (80%), PPV (52%), and NPV (93%). The sensitivity of US-FNAC increased with T stage (50% and 80% reduction in T2-T3 and T4 node-positive patients, respectively). Overall survival (OS) worsened when peripheral perfusion was present and turned out to be significantly shorter in patients with US demonstrating both a balloon-shaped lymph node and peripheral perfusion versus those with a US in which neither of these criteria was met ( $P<.001$ ). Similarly, OS was significantly lower in patients with positive versus negative US-FNAC status ( $P<.001$ ). US-FNAC status correlated with SLN tumor burden (per Rotterdam criteria).<sup>4</sup> US-guided FNAC became more sensitive with increasing tumor load. SLN deposits  $>1.0$  mm were detected in 86% of cases, whereas 0.1- to 1.0-mm deposits were detected in 46% of cases.

**Table 1. Six US Morphologic Criteria and Their Sensitivity, Specificity, and PPV and NPV in Detecting SLN Metastases**

|                              | Sensitivity | Specificity | PPV | NPV | P-value |
|------------------------------|-------------|-------------|-----|-----|---------|
| Absence of central echoes    | 60%         | 92%         | 65% | 90% | <.001   |
| Hump structure present       | 55%         | 72%         | 34% | 86% | <.001   |
| Echo-poor islands present    | 21%         | 96%         | 59% | 82% | <.001   |
| Cap-like structure present   | 8%          | 87%         | 14% | 78% | .221    |
| Balloon-shaped LN present    | 30%         | 100%        | 96% | 85% | <.001   |
| Central perfusion absent     | 25%         | 77%         | 22% | 80% | .701    |
| Peripheral perfusion present | 77%         | 82%         | 52% | 93% | <.001   |

The size of the lymph node was not a useful characteristic to predict involvement.

SLN, sentinel lymph node; PPV, positive predictive value; NPV, negative predictive value; LN, lymph node.

Estimated 5-year OS rates were 93% for US-guided FNAC-negative versus 49% for FNAC-positive patients. The 5-year OS rates according to the Rotterdam Criteria for SLN tumor burden were 93% for SLN-negative patients, 92% for metastases  $<0.1$  mm, 40% for 0.1- to 1.0-mm, and 48% for  $>1.0$  mm. The 5-year distant metastasis-free survival rates were 93% for the US-FNAC and histology-negative patients (true-negative patients), 40% for the US-FNAC-positive and histology-positive patients (true-positive patients), and 80% for the US-FNAC-negative, but histology-positive patients (US-FNAC false-negative patients).

Dr. Voit concluded that US of SLNs is very accurate and clinically useful when used in combination with FNAC, and can be used to avoid SLNB in a large percentage of patients. She estimated that up to 65% of all SLN-positive patients could have avoided a SLNB and undergone immediate completion lymph node dissection by using US-FNAC. This translates into a 13% reduction in SLNB procedures for the overall stage I/II melanoma population ( $n=400$ ). Approximately 7% of patients with positive SLNs by SLNB are incorrectly not identified by US-FNAC. This raises the question of whether a 7% false-negative rate is acceptable for replacing SLNB with US-FNAC, or whether SLNB should still be considered the best diagnostic/staging option for patients with negative US-FNAC status.

## References

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## **The sentinel node: Rotterdam criteria of tumor load and prognostic false positivity.**

Sentinel lymph node biopsy (SLNB) is a highly accurate technique in melanoma for staging nodal basins at risk for regional metastases, and a positive sentinel node (SN) status is a powerful independent prognostic factor for recurrence and survival.<sup>1,2</sup> However, more extensive pathologic work-up and technological advances now enable identification of very limited tumor burden in the SN, and the relative significance of relatively limited burden is currently unclear. **Alexander C. J. van Akkooi** of Erasmus University Medical Center–Daniel den Hoed Cancer Center in Rotterdam, the Netherlands, presented the results from a study looking at the impact of SN tumor burden on prognosis.

A total of 388 SN-positive patients from the prospective melanoma databases of 3 major EORTC (European Organization of Research and Treatment of Cancer) centers were entered in the study, and slides of positive SNs were reviewed for tumor burden according to Rotterdam criteria. Based on these criteria, SN tumor burden was divided into 3 groups based on maximum diameter of the largest lesion (<0.1 mm, 0.1-1.0 mm, >1.0 mm). Calculations were made of disease-free survival (DFS) and overall survival (OS). In addition, results for the subgroup of SN-positive patients from Rotterdam were compared with matched melanoma patients who had not undergone a SLNB, but who subsequently developed regional lymph node metastases during follow-up. Patients in the latter cohort only underwent wide local excision (WLE), followed by therapeutic lymph node dissection.

Median Breslow thickness for the entire population was 4.00 mm, and ulceration was present in 56% of cases. Submicrometastases (<0.1 mm) were observed in 40 patients, including 1 with additional non-SN positivity. Degree of SN tumor burden correlated with increase in primary tumor thickness. Estimated 5-year OS after a median follow-up of 35 months was 91% for patients with submicrometastases (<0.1 mm), compared with 61% for patients with 0.1-1.0 mm tumor burden and 51% for those with burden >1.0 mm ( $P<.001$ ). SN-negative patients had identical 5-year OS (91%) to those with submicrometastases (<0.1 mm). There was a trend for longer 5-year OS in SN patients versus WLE patients (68% vs 54%,  $P=.06$ ), but this disappeared when the results were corrected for submicrometastases patients (62% vs 54%,  $P=.33$ ).

Dr. van Akkooi concluded that patients with submicrometastases (<0.1 mm) have excellent survival that is identical to that in SN-negative patients. This suggests patients with submicrometastases (<0.1 mm) could possibly be safely spared a completion lymph node dissection.<sup>3</sup> The results further suggest that both SN status (positive vs negative) and tumor burden are important stratification criteria for adjuvant therapy trials.<sup>3</sup>

## **References**

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