Mitotic Rate a Game Changer in Melanoma Tx

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EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE CALIFORNIA SOCIETY OF DERMATOLOGY AND DERMATOLOGIC SURGERY

SANTA BARBARA, CALIF. – Current American Joint Committee on Cancer melanoma staging criteria incorporate a mitotic rate of 1/mm^2 or greater into the T1b classification, recognizing mitotic rate as an independent prognostic factor in patients with primary melanoma.

This change, which went into effect in January, "is going to have a profound impact in whom we consider eligible for staging with sentinel lymph node biopsy," Dr. Susan Swetter predicted at the meeting. "The reason is that only about 6%-8% of these T1 tumors (1.0 mm) are ulcerated, but it is estimated that up to 30%-40% will have an elevated mitotic rate of 1.0 or more per square millimeter. This leaves us with a conundrum: Are all of these patients going to be eligible for sentinel lymph node biopsy?"

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DR. SWETTER

AJCC melanoma staging criteria are based on data analysis from the 2008 AJCC collaborative melanoma staging database from 14 cancer centers and cooperative oncology organizations worldwide, said Dr. Swetter, professor of dermatology and director of the pigmented lesion and melanoma program at Stanford University Medical Center/VA Palo Alto Health Care System in California.

The criteria are based on prognostic factor analysis of nearly 60,000 patients to validate staging criteria and groupings for the 7th edition of the AJCC Cancer Staging Manual (Springer, New York), which was published in the fall of 2009 and became active in January 2010.

"The concept is that each stage grouping has a uniform risk for survival, and there are a wealth of patients per tumor node metastasis (TNM) categories, with more than 27,000 with stage I and II disease, more than 3,400 with stage III disease, and more than 7,600 with stage IV disease," Dr. Swetter said.

The newest revision of the AJCC staging for melanoma involves no major changes for TNM and stage grouping criteria, with the exception of mitotic rate.

Other changes involve more advanced disease. For example, "immunohistochemical detection of nodal metastases is now acceptable, whereas only routine histology was used previously," Dr. Swetter said. "Also, there is no longer a lower limit to designate node-positive disease. The size of the isolated tumor cells is no longer used, although that is quite controversial."

Thickness of tumors is potentially a marker of duration of growth, with increasing tumor thickness correlating adversely with survival. According to the 2008 AJCC Melanoma Database, patients with tumor thickness of 0.01-0.55 mm have a 10-year survival rate of 95%, while those with a tumor thickness of 4.01-6.0 mm have a 10-year survival rate of 54%.

The most relevant correlate of a mitotic rate increase and its effect on prognosis appears to be in thin tumors, Dr. Swetter said. "This is why the new AJCC guidelines incorporate mitotic rate in tumors that are less than or equal to 1.0 mm thick."

Survival data from the 2008 AJCC Melanoma Database suggest there is little to no value in promoting sentinel lymph node biopsy in patients who have tumors up to 0.50 mm in depth, regardless of mitotic rate, because the survival rate in these patients is excellent. Currently, the T1b designation is used for staging in terms of survival. "It is not a criterion in itself to perform sentinel lymph node biopsy," Dr. Swetter emphasized. "There is some evolving data suggesting that mitotic rate as a continuous variable may be predictive of occult regional nodal disease."

One published study suggests that sentinel lymph node biopsy is appropriate

for patients with T1b melanomas, including those defined by mitotic rate (J. Natl. Compr. Canc. Netw. 2009;7:308-17).

"We are now awaiting publication of a larger analysis of patients with thin melanoma," Dr. Swetter said. "Both the National Comprehensive Cancer Network and the AAD [American Academy of Dermatology] melanoma panels are weighing in to establish an appropriate threshold in these T1b patients."

Dr. Swetter, who serves on both of the panels, noted that there is currently "very little enthusiasm from a surgical perspective to be pursuing sentinel lymph node biopsy on every patient who is T1b by virtue of mitotic rate."

The National Comprehensive Cancer Network recommends that clinicians "discuss and offer" sentinel lymph node biopsy for patients with stage IB and stage II cutaneous melanoma, "recognizing that the sentinel node biopsy is an important staging tool, but its impact on overall survival is unclear," Dr. Swetter said.

The procedure should also be considered for stage IA melanomas with adverse features including positive deep margins, lymphovascular invasion, thickness of 0.75 mm or greater, or younger age.

The decision not to perform sentinel lymph node biopsy can be based on significant patient comorbidities, patient preference, or other factors.

An unresolved question is whether or not sentinel lymph node biopsy is a valid staging technique in older patients. "Older age is associated with worse prognosis, but lower rates of sentinel lymph node positivity," Dr. Swetter said. "The question is, why? One issue is whether there is different biology of melanoma in the elderly, or whether host immune factors come into play. Another [factor] could be delayed lymphatic spread, or it might be that tumors are more likely to disseminate hematogenously in older patients, compared with younger patients."

In the future, Dr. Swetter predicted the emergence of individualized prognoses based on novel weighted mathematical equations using AJCC staging and other factors. A Web-based predictive tool for prognosis developed by the AJCC Melanoma Database is currently available at www.melanomaprognosis.org.

Dr. Swetter stated having no relevant financial conflicts to disclose. ■