

## *Metastatic Thin Melanoma: Can We Identify At-risk Patients?*

Survival rates for thin melanoma are high, but some individuals develop potentially fatal metastatic disease.

By Jonathan Wolfe, MD

For most patients diagnosed with thin melanomas (measuring 1mm or less), excision is curative (survival rates exceed 90 percent), though a subset of these individuals have the potential to develop metastatic disease. Several prognostic indicators have been evaluated in hopes of identifying those patients at highest risk for developing metastases so that they can receive appropriate follow-up and monitoring. The most recent American Joint Committee on Cancer (AJCC) staging criteria predict survival based on thickness, anatomic level, and ulceration.<sup>1</sup> Researchers suggest that tumor cell mitotic rate may be an additional important indicator of survival among patients with thin tumors.<sup>2</sup>

### **Perspective**

The current AJCC staging criteria, published in 2001 and adopted in 2002, assess both clinical and pathologic characteristics of the tumor, including thickness, anatomic level, and ulceration, as detailed in Table 1.<sup>1</sup> Among changes incorporated into the 2002 criteria versus the previous (1997) model is emphasis on tumor ulceration as a significant prognostic indicator and expansion of the upper limit for thickness of Stage I melanoma from less than .75mm to 1mm.

Advanced age and male sex have also been associated with worse prognosis for individuals with melanoma; findings document lower disease-free survival and overall survival for men

with melanoma compared to women.<sup>3</sup> Researchers determined that male sex is associated with a greater incidence of unfavorable primary tumor characteris-

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tics, including thicker tumors and ulceration. However, sex was not associated with increased risk for nodal metastasis in this study.

### **Risk and Thin Melanomas**

The “reclassification” of thin or Stage I melanomas to include tumors up to 1mm in thickness has instigated some minor controversy. Some argue that due to the reclassification, thin melanoma is now associated with a “good” rather than “excellent” prognosis.<sup>4</sup> According to AJCC data, the

10-year survival rate for Stage Ia melanoma is 87.9 percent, and the survival rate for Stage Ib is 83.1 percent.<sup>1</sup> It’s worth noting that comparison of data from patients in the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) registry with data from the AJCC registry actually found higher survival rates in the SEER population, especially for thin melanomas, emphasizing the population-specific nature of survival rates.<sup>5</sup>

Though the long-term prognosis for patients diagnosed with thin melanomas is generally favorable, certain patients are at risk for metastasis and possibly death. Early identification of these high-risk patients would presumably improve survival. Unfortunately, there is no agreed-upon set of prognostic indicators that would help to identify at-risk patients with thin melanomas. Now, however, one proposed method has been validated in two large populations.<sup>2</sup>

### **Another Approach**

In 2004, Gimotty et al studied biologic tumor characteristics and long-term outcomes in a prospective cohort study of 884 patients with thin (less than or equal to 1mm in thickness) invasive melanomas from the Pigmented Lesion Group (PLG) at the University of Pennsylvania.<sup>6</sup> They identified prognostic value associated with vertical growth phase, mitotic rate, and sex. Vertical growth phase

**Table 1. AJCC Staging 2002**

Stage	Primary Tumor (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
0	Tis	NO	MO
IA	T1a: $\leq$ 1mm, Level II-III, no ulceration	NO	MO
IB	T1b: $\leq$ 1mm, Level IV-V or w/ulceration	NO	MO
	T2a: 1.01-2mm, no ulceration		
IIA	T2b: 1.01-2mm, ulceration	NO	MO
	T3a: 2.1-4mm, no ulceration		
IIB	T3b: 2.1-4mm, ulceration	NO	MO
	T4a: 4mm no ulceration		
IIC	T4b: 4mm, ulceration	NO	MO
III	Any T	N1, N2, N3	MO
IV	Any T	Any N	M1

**Table 2. University of Pennsylvania PLG Risk Categories**

	Sex	Vertical Growth Phase (VGP)	Mitotic Rates (MRs)	10-year Metastasis Rate, 2004 Study <sup>6</sup>
High-risk	Male	Tumorigenic	>0	31%
Moderate-risk	Female	Tumorigenic	>0	13%
Low-risk	Male or Female	Tumorigenic	0	4%
Minimal-risk	Male or Female	Nontumorigenic	N/a	0.5%

and mitotic rate can be determined through routine pathologic evaluation. Tumor cell mitotic rate was a strong prognostic indicator in this cohort, but it is absent from the current AJCC staging. Based on these biologic indicators, the team identified four risk groups: high, moderate, low, and minimal, as described in Table 2.


This spring, Gimotty et al published new findings regarding biologic indicators of risk among patients diagnosed with thin melanomas.<sup>2</sup> Based on analysis of patients in the SEER registry from 1998-2001 (n=26,291), they developed a “prognostic tree” to allow sequential classification of patients based on a series of if-then assessments. They then validated their proposed diagnostic tree by applying it to patients seen by University of

Pennsylvania’s Pigmented Lesion Group from 1972-2001, (n=2,389). The PLG criteria—with survival rates ranging from 83.4 to 100 percent—offer better discrimination than AJCC criteria (survival rates 89.1 to 99 percent). The four prognostic factors studied by Gimotty’s team included: radical or vertical growth phase (RGP or VGP, respectively), presence of RGP regression, presence of VGP mitogenicity, and presence of tumor-infiltrating lymphocytes (TILs). Level, tumor cell mitotic rate, and sex are the primary indicators in the new PLG-based tree. The team urges that tumor cell mitotic rate be incorporated into the next iteration of AJCC staging.

### Prognosis in Practice

Any patient diagnosed with thin melanoma requires regular follow-up

with their dermatologist and must be properly educated in the process of skin self-examination and acceptable and effective strategies for sun protection. Patients with melanoma *in situ* may be seen in the office twice a year for two to three years after excision, then annually. Those with thicker melanomas require more frequent follow-up, the specific nature of which will depend on assessment of various factors including presence of known risk factors for recurrence. Generally, patients may be seen three to four times per year for two to three years, then twice a year for two to three years, then once a year after five years. These exams largely focus on identifying any recurrence at an early stage.

The current data suggest we in the clinic may now be able to better identify patients at risk for metastasis so that we may make more informed decisions about the type of treatment, referral, and follow-up we recommend for these individuals. Basic pathologic evaluation allows determination of both mitotic rates and presence of TILs, though these may not be automatically reported. Dermatologists may be wise to specifically request these data in pathology orders. 

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