



Bernard Jean Corneille Pothast, 1882-1966. *Playing with Baby*. Oil on canvas, 20" × 24¼".
Courtesy of the Callan Fine Art gallery, New Orleans, Louisiana.

The clinical and histologic factors related to outcomes in localized and metastatic cutaneous melanoma are reviewed.

Cutaneous Melanoma: Prognostic Factors

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Background: Recent data have changed our views of prognostic factors in cutaneous melanoma. While some newer methods have yielded better prognostic information, some insights have evolved as a result of large-scale population-based analyses.

Methods: We review current data on several different prognostic factors and divide these factors according to their application in localized primary melanoma or metastatic melanoma. For each prognostic factor, the level of evidence supporting its use and its applicability to clinical practice are considered.

Results: For localized primary melanoma, the dominant predictors of survival include lesion thickness, ulceration, and lymph node involvement. Factors such as age, sex, anatomic location, and satellite/in-transit lesions are important in localized melanoma. Factors currently being investigated are tumor vascularity, vascular invasion, mitotic rate, tumor regression, and tumor-infiltrating lymphocytes. For metastatic melanoma, the most important prognostic factors are site of metastases and the presence of elevated serum lactic dehydrogenase. The value of these prognostic factors to clinicians caring for melanoma patients is discussed.

Conclusions: A better understanding of prognostic factors in cutaneous melanoma has evolved over the last decade, allowing oncologists to provide appropriate treatment for their patients. Many of the prognostic factors are interrelated. In the near future, it is expected that several molecular genetic factors will provide more insight into the prognosis of patients with melanoma.

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Submitted February 6, 2005; accepted July 22, 2005.

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Introduction

In 2005, an estimated 59,580 Americans will be diagnosed with cutaneous melanoma and 7,700 will die of the disease.¹ The Surveillance, Epidemiology, and End Results (SEER) Program reported an increase of more than 600% in the diagnosis of cutaneous melanoma from 1950 to 2000.²

In 2002, the American Joint Committee on Cancer (AJCC) approved a new version of the melanoma staging system.^{3,4} The changes were validated with an analysis of prognostic factors that involved 17,600 patients with melanoma.⁴ The revised system includes the following

features: (1) lesion thickness, presence or absence of ulceration but not level of invasion are the dominant predictors of survival in patients with localized melanoma, (2) the number of metastatic lymph nodes rather than their dimensions and the differentiation of microscopic vs macroscopically involved nodes, (3) satellite metastases around a primary melanoma and in-transit metastases were merged into a single staging entity that is grouped into stage III disease, (4) staging information gained from lymphatic mapping and sentinel node biopsy, and (5) for patients with metastatic disease, the site of distant metastases and the serum lactic dehydrogenase level. However, other factors not included in the revised staging system may alter prognosis, survival, and treatment (Table 1).⁵ This review addresses both clinical and histologic factors related to outcomes in cutaneous melanoma.

Patient Age

Older patients present more frequently with thicker and ulcerated melanomas,⁵ and many studies have reported age to be an independent prognostic factor.^{6,8} In a large study of more than 17,000 patients, each 10-year increase in age was associated with a decline in both 5- and 10-year survival rates.⁴ Patients younger than 30 years of age had a 5-year survival rate of 87% compared to 78%, 71%, and 60% for those in their 60s, 70s, and 80s or more, respectively. A smaller study that included 488 patients with no evidence of metastatic disease showed an 84% 10-year survival rate for patients less than 60 years of age compared with 57% for patients 65 years of age or greater (odds ratio, 3.0).⁹ Another study of 442 stage I and II patients demonstrated a 55% relapse-free survival rate at 5 years in patients greater than 65 years of age compared to 65% in patients 65 years or younger.¹⁰ A survival benefit was also reported in patients younger than age 60 years when they underwent elective lymph node dissection vs observation for early-stage disease in 740 patients.¹¹

Table 1. — Prognostic Factors in Cutaneous Melanoma

Factor	Better Prognosis
Clinical:	
Age	<65 years
Sex	Women
Location	Extremities
Number of lymph nodes involved	None
Distant metastasis	Absent
Lactate dehydrogenase level	Normal
Histologic:	
Thickness	<1.0 mm
Ulceration	None
Clark level	Level I
Tumor vascularity	Absent
Vascular invasion	Absent
Microsatellites	None
Mitotic rate	Low
Regression	Absent
Tumor-infiltrating lymphocytes	Present

Sex

Many studies report that women have a better prognosis compared to men, even in patients with nodal metastasis.^{9,12-14} A study of 488 patients with no evidence of metastatic disease showed an 86% 10-year survival rate for women compared with 68% for men.⁹ The influence of gender can be confounded by differences in thickness, ulceration, and anatomic site of the melanoma; women have been shown to have thinner lesions with less frequent ulceration compared with men.^{5,14} Melanoma risk is not associated with age at menarche, menopausal status, use of hormone replacement therapy, parity, age at first birth, or oral contraceptive use.¹⁵

Tumor Location

Many studies have reported a correlation between prognosis and anatomic location, showing that lesions of the extremities have a better prognosis than head, neck, and truncal melanomas.^{9,12,16} In a series of 5,093 patients with invasive primary cutaneous melanoma, locations that were associated with a significantly higher risk of death caused by primary cutaneous melanoma included the back, thorax, upper arm, neck, and scalp.¹⁷ In the absence of metastatic disease and for all tumor thickness ranges, a 10-year survival rate of 90% was observed when the primary melanoma was in the extremities compared to 70% when in the trunk, head, or neck.⁹

Lymph Node Involvement

In the 2001 AJCC analysis, 49% of all patients with nodal metastases survived 5 years and 37% survived 10 years.⁴ In the revised melanoma staging system, N1 refers to metastasis to one node, N2 to two to three nodes, and N3 to four or more nodes.^{4,18} This grouping according to the number of metastatic nodes involved correlated best with

Table 2. — Effects of Ulceration, Number of Lymph Nodes, and Tumor Thickness on Five-Year Survival

	Five-Year Survival Rate (%)	
	Ulceration	No Ulceration
Depth (mm)*		
≤1.0	91	95
1.01–2.0	77	89
2.01–4.0	63	79
>4.0	45	67
No. of Nodes Involved (microscopic involvement)		
1	52	69
2–3	50	63
4 or more**	37	27
* Node-negative disease		
** With or without ulceration		
Data from Balch. ^{4,18}		

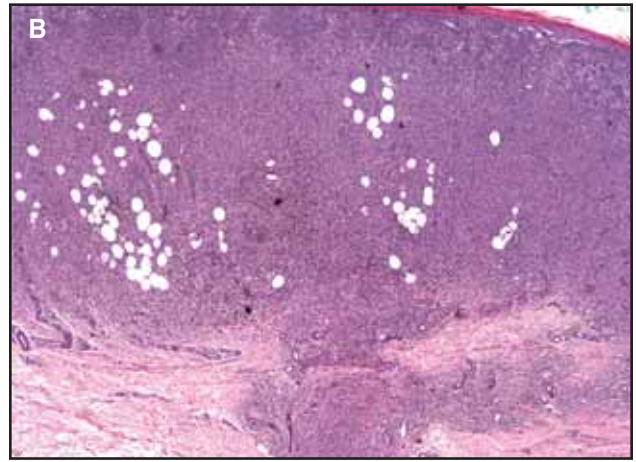
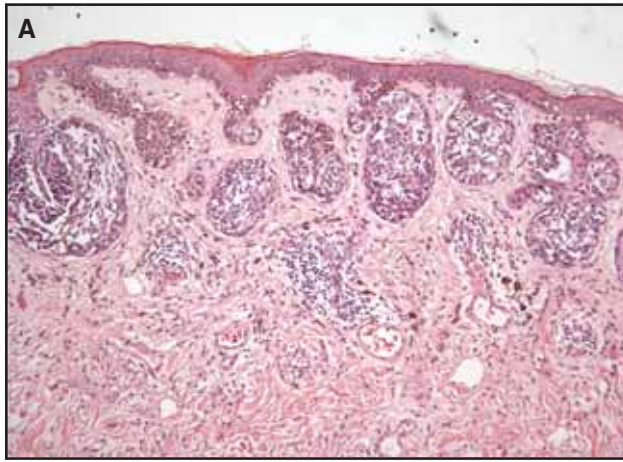


Fig 1A-B. — Tumor thickness in melanoma. (A) shows thin melanoma (original magnification $\times 100$) and (B) shows thick melanoma (original magnification $\times 50$). Increased tumor thickness is associated with poorer survival.

5-year survival rates (Table 2).^{4,18} Staging for node-negative patients with intermediate to thick melanomas (>1 mm) has improved with the use of lymphatic mapping and sentinel lymph node biopsy.¹⁹ This procedure has evolved over the last few years and involves the injection of a blue dye and radiolabeled sulfur colloid into the skin around the tumor site, followed by dissection of the radiolabeled and dye-labeled lymph node. The node is then carefully examined for metastatic deposits. Pathologically documented nodal metastases (by either sentinel or elective node dissection) are defined as microscopic, and clinically or radiologically documented nodal metastases are defined as macroscopic. Survival rates for these two patient groups are significantly different. Ten-year survival rates in the presence of a single microscopic vs macroscopic node are 63% vs 47%, respectively.⁴ Studies of the detection of submicroscopic levels of disease in lymph nodes are currently under way.^{20,21}

Tumor Thickness

Tumor thickness and ulceration are consistently the most powerful independent prognostic factors in localized cutaneous melanoma.^{4,9,22,23} Tumor depth is measured in millimeters from the granular layer of the epidermis to the deepest tumor cell. Fig 1A-B shows images of thin and thick melanomas. Increased tumor thickness is associated with poorer survival. In the 1997 version of the melanoma staging system, the cutoff point between a T1 and T2 melanoma was defined as 0.75 mm.²⁴ In the 2002 AJCC system, melanoma thickness is stratified into four categories: ≤ 1.0 mm, 1.01–2.0 mm, 2.01–4.0 mm, and >4.0 mm.¹⁸ Five-year survival rates in all four categories in the presence or absence of ulceration are shown in Table 2. The 5-year overall survival rate in patients with thin tumors without other adverse prognostic factors is 95% or greater.^{18,25} Less than 5% of patients with these characteristics have micrometastasis in the regional nodal basin.²⁶

Ulceration

Ulceration (Fig 2) is defined histologically as the absence of an intact epidermis overlying a significant portion of the primary tumor.²⁷ As noted above, the two most powerful independent characteristics of the primary melanoma are ulceration (which was not included in the older staging system) and tumor thickness. These factors are highly correlated with each other; studies have shown that the incidence of melanoma ulceration rose with increasing tumor thickness, ranging from 6%–12.5% for thin melanomas to 63%–72.5% for thick (>4.0 mm) lesions.^{4,27} The presence of ulceration decreases survival in all tumor thickness categories (Table 2). Thin (<1.0 mm) ulcerated tumors have approximately a 4% decreased 5-year survival rate compared to non-ulcerated tumors. This survival decrement is as high as 22% in thick (>4.0 mm) tumors.⁴ This observation led to the inclusion of ulceration as the second determinant for the T classification in the new staging system and the only primary tumor factor to modify the prognosis of node-positive disease.³

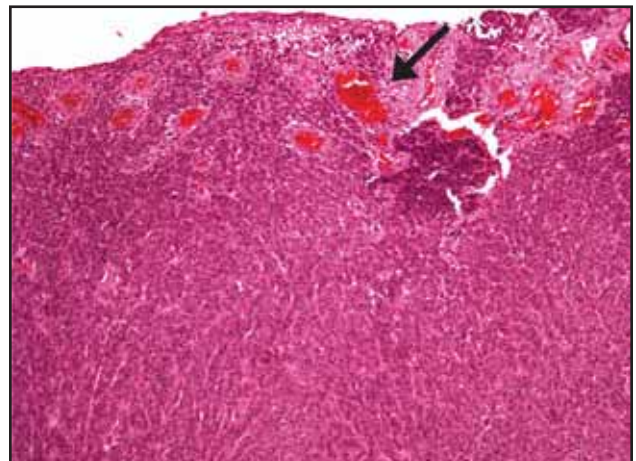


Fig 2. — Melanoma ulceration (arrow). The presence of ulceration decreases survival in all tumor thickness categories (original magnification $\times 200$).

Clark Level

The Clark level has been used to describe the anatomic involvement of the tumor within the cutaneous and subcutaneous structures. Level I is intraepidermal growth with intact basement membrane, level II is invasion of the papillary dermis, level III is tumor involvement filling the papillary dermis and involvement of the junction between the papillary and reticular dermis, level IV is invasion of tumor into the reticular dermis, and level V is invasion of tumor cells into the subcutaneous fat.²⁸ The 5-year survival rate is 95% for Clark level II melanomas, between 80% and 85% for Clark level III and IV melanomas, and 55% for Clark level V melanomas.²² The Clark level was found to be most predictive of survival in thin (<1 mm) melanoma, and it is part of the staging system only in patients with such lesions.²⁹ Eighty-four percent of thin melanomas are level II or III, and less than 1% are level V. The 10-year survival rate decreased from 86% in level II to 80% in thin, non-ulcerated, level IV lesions.⁴ However, other studies have shown that Clark's level is not an independent predictor of outcome, even in thin melanomas.³⁰ For tumors thicker than 1 mm, Clark level is less predictive than ulceration, patient age, or anatomic location and also has limited utility.

Tumor Vascularity

Tumor vascularity is the formation of new microvessels in the dermis at the base of an invasive melanoma. It is associated with the development of vertical growth phase in thin melanoma.^{28,31} Four patterns of tumor vascularity are described: absent, sparse, moderate, and prominent. Increased tumor vascularity is more likely with thick, ulcerated tumors.^{32,33} The mean tumor thickness of melanomas with prominent vascularity is 4.01 mm, compared with 1.55 mm in melanomas with absent vascularity, and almost half tumors with prominent vascularity are ulcerated. Prominent vascularity was found to have a 69% risk of relapse and 42% death rate over a 2-year follow-up compared to 33% and 12%, respectively, for absent vascularity ($P<.00005$).³² The broad utilization of this factor is limited by subjectivity of the pathologist when measuring tumor vascularity and thus the reproducibility of the measurement among observers. Although one study showed that the degree of vascularity was the most important histopathologic factor determining overall survival, more studies are needed to further clarify the impact of tumor vascularity in predicting survival.³²

Lymphovascular Invasion

Vascular involvement denotes invasion of tumor cells into the microvasculature in the dermis by either abutting the

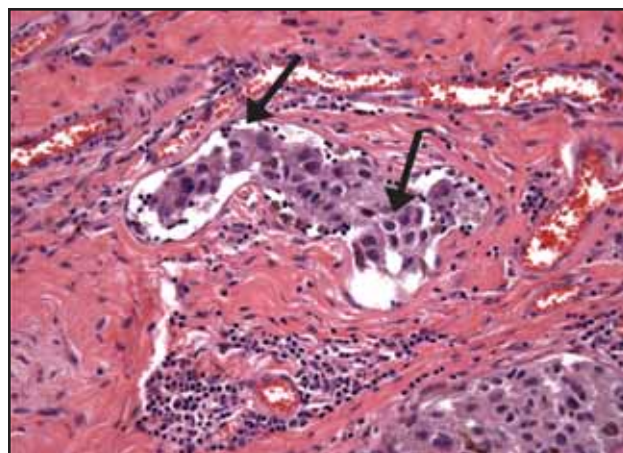


Fig 3. — Vascular invasion (arrows) (original magnification $\times 200$).

endothelium (incipient invasion) or penetrating the endothelium and lodging within the vessel lumen (vascular invasion) (Fig 3). Several reports noted that vascular invasion significantly increased the risk of relapse, lymph node involvement, distant metastases, and death, and its impact on melanoma outcomes was similar to that of ulceration.³⁴⁻³⁶ Vascular invasion was present in 57% of nodular melanomas with lymph node metastasis at the time of diagnosis compared with only 12% of those confined to the skin ($P=.001$).³⁷ Distant metastases were observed in up to 74% of patients with vascular involvement and in 22% of patients without vascular involvement.³⁴ In thick melanomas (>4 mm) the presence of vascular involvement by tumor cells is associated with a 5-year overall survival rate of 25% compared to 50% without vascular involvement.³⁸ A recent study³⁹ has shown that vascular invasion is more common with increased vascularity and has implicated the signaling pathway involving nuclear factor kappa B (NF- κ B) in the development of these vascular factors. Finally, recent molecular analyses of the vasculature in primary cutaneous melanoma have suggested that lymphangiogenesis (as opposed to angiogenesis) has a powerful role in further characterizing the nature of the specific vessels concerned with melanoma progression.^{36,39}

Microsatellites

Microsatellites are discrete tumor nests greater than 0.05 mm in diameter that are separated from the main body of the tumor by normal reticular dermal collagen or subcutaneous fat.⁴⁰ Only a few studies have evaluated the role of microsatellites as a prognostic factor in cutaneous melanoma. Satellite metastasis is shown in Fig 4. The presence of macrosatellites increases from 4.6% in tumors less than 1.5 mm to 65% in those greater than 4 mm.^{40,41} Although microsatellites rarely occur in tumors less than 1.5 mm, the 5-year survival rate for patients with microsatellites was 36% compared to 89% for those with-

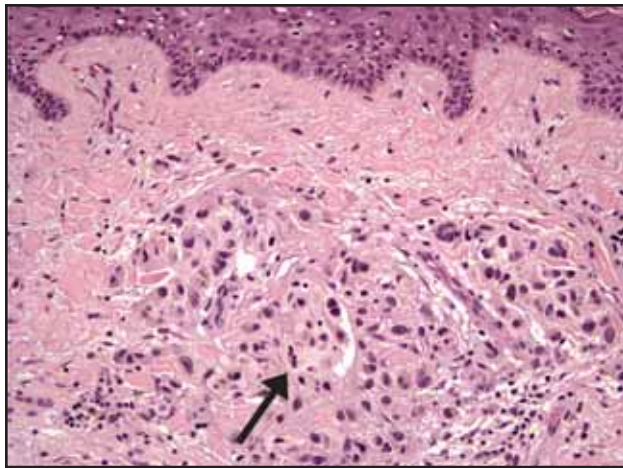


Fig 4. — Satellite metastasis (satellitosis, arrow) in melanoma (original magnification $\times 200$).

out these microsattelites.⁴⁰ Microsattelites are also associated with an increased frequency of regional lymph node metastasis (from 12% to 53%) in tumors greater than 1.5 mm.⁴¹ The presence of clinical or microscopic satellite metastases around a primary melanoma as well as in-transit metastases between the primary melanoma and the regional lymph nodes was included in the revised staging system for stage III as N2c.¹⁸

Mitotic Rate

The mitotic rate is measured as the number of mitoses per square millimeter.⁴² It has been suggested that a higher mitotic index may simply represent cells with higher doubling times that eventually grow and invade into adjacent lymphatic and blood vessels, and thus may be a predictor of poor prognosis.⁴³ The adjusted odds ratio of survival for patients with a mitotic rate of 0 was shown to be 12 times that of patients with a mitotic rate of $>6/\text{mm}^2$ in stage I melanoma.²⁵ In the same stage, only 4% of lesions displaying low mitotic activity recur compared to 24% of those with a high mitotic rate.³⁸ Mitotic rate and younger age are predictors of sentinel lymph node positivity.^{44,45} Thus, the role of mitotic rate as an independent prognostic factor has become more important.⁴⁶

Regression

Regression is the replacement of tumor tissue with fibrosis, degenerated melanoma cells, lymphocytic proliferation, and telangiectasia formation.⁴² The incidence of regression is up to 58% in melanomas of 0.75 mm or less.⁴⁷ Although most studies have not found a significant role for regression in determining survival, one study showed that regression is an adverse prognostic factor in predicting survival in thin melanoma.¹³ Another study reported that no metastasis occurred in the 73 patients who had thin

melanomas without histologic evidence of regression.⁴⁸ However, the definition and measurement of regression were not consistent in these studies. At the University of California at San Francisco Melanoma Center, tumors less than 1 mm with evidence of greater than 50% regression are recommended for a sentinel lymph node biopsy to evaluate for spread to the regional lymphatics.

Tumor-Infiltrating Lymphocytes

Tumor-infiltrating lymphocytes (Fig 5) are believed to represent the immune reaction/response to melanoma cells. This response is usually measured by the level of lymphocytic infiltrate present at the base of the vertical growth phase of the tumor and is sometimes categorized as brisk, nonbrisk, or absent.⁴⁹ The most brisk tumor-infiltrating lymphocytes response is found in thin tumors.⁵⁰ The 5- and 10-year survival rates for melanoma with a vertical growth phase and a brisk infiltrate were 77% and 55%, respectively. For tumors with a nonbrisk infiltrate, the 5- and 10-year survival rates were 53% and 45%, respectively, and for tumors with absent tumor-infiltrating lymphocytes, the 5- and 10-year survival rates were 37% and 27%, respectively.⁵⁰ There is a need for a uniform definition of host response in terms of type and location of infiltrate before the role of tumor-infiltrating lymphocytes can be clarified. Tumor-infiltrating lymphocytes could be an important new therapy for melanoma,^{51,52} although more research is needed on this treatment modality.

BRAF Mutations

The BRAF gene is the most frequent (60%–80%) mutation observed in human melanoma.^{53,54} Eighty percent of these mutations are found at exon 15, at a single amino acid residue, usually a substitution for valine by glutamic acid, V599E (now referred to as V600E). This mutation causes increased kinase activation and signaling through the MAP

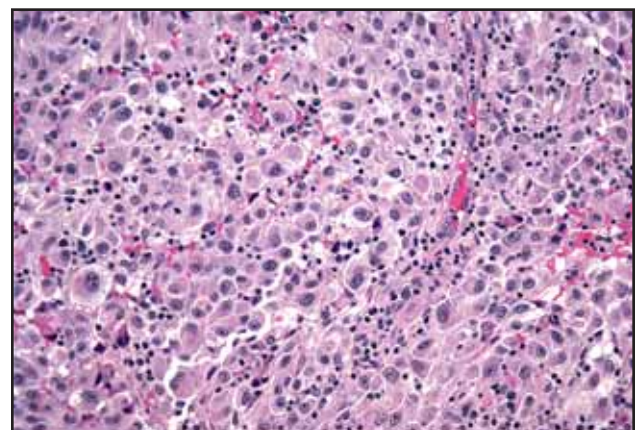


Fig 5. — Tumor infiltrating lymphocytes (original magnification $\times 200$).

kinase pathway and causes activation of the Brn-3 transcription factor.⁵⁵⁻⁵⁸ Surprisingly, this event occurs at a high frequency in benign nevi as well as in melanoma.⁵⁹ In a study of 38 metastatic melanomas, BRAF mutations were associated with slower disease progression, although this was not statistically significant.⁶⁰ A specific signature has been identified with the activating BRAF mutations that could be useful therapeutically.⁶¹ New RAF kinase inhibitors such as BAY 43-9006 are currently in clinical trials. Other mutations have been reported in patients with melanoma, albeit with less frequency. The CDKN2A mutations that encode two different transcripts — p16INK4A and p14ARF — were recently reported to be present in patients with familial history of melanoma (35.5%) compared with patients without (8.2%), with a relative risk of 4.32 (95% confidence interval, 1.76 to 10.64; $P=.001$).⁴⁹ The age of onset was significantly lower and the number of primary melanomas was higher in patients with mutations.⁴⁹

Distant Metastasis

The median survival time of 1,521 treated cutaneous melanoma patients with distant metastases was reported to be 7.5 months.⁶² The revised melanoma staging system divides patients with distant metastases into three groups based on the location of the involved organ: subcutaneous spread or distant lymph nodes, lung involvement, and other visceral organ involvement. A 1-year median survival difference was found among these groups. In 1,158 patients with distant metastases, those with subcutaneous or distant lymph nodes had a better prognosis than those with lung or other visceral organ involvement (1-year survival rates were 59%, 57%, and 41%, respectively).^{4,18} In addition to the site of metastases, disease-free interval before distant metastases and stage of disease preceding distant metastases were reported to have a role in predicting survival in metastatic disease.⁶³ An uncommon but widely recognized presentation of melanoma is the unknown primary site. This presentation is seen most often in the regional nodes, lung, liver, and subcutaneous tissue but can occur in numerous other sites. Histologic stains are often useful in determining the origin of the tumor.

Lactate Dehydrogenase

The lactate dehydrogenase (LDH) serum level is one of the factors most predictive of decreased survival in a multivariate analysis, even after accounting for site and number of metastases.¹⁸ One study reported an elevated LDH to have 79% sensitivity and 92% specificity in detecting disease progression in stage IV melanoma.^{19,20} Other potential prognostic markers (eg, S100, melanoma-inhibitory activity [MIA], and TA90) are being studied.

Conclusions

A better understanding of prognostic factors in cutaneous melanoma has evolved over the last decade. Many of the prognostic factors discussed are interrelated. While the importance of Breslow thickness and lymph node involvement has been supported in multiple studies, Clark level has not proven useful except perhaps in thin (1 mm) melanoma. The importance of ulceration as a prognostic factor has emerged in recent studies. Newer factors such as vascular invasion and mitotic rate may continue to refine the prognostic information gained by knowledge of the tumor thickness alone. Finally, genetic (such as BRAF mutation status) and molecular prognostic factors (such as reverse transcription-polymerase chain reaction [RT-PCR]) await further validation before they enter routine clinical use. Currently, the most useful prognostic factors in clinical practice for localized melanoma are Breslow thickness, presence of lymph node involvement, and ulceration. In metastatic disease, they are location of metastatic site and lactate dehydrogenase elevation in metastatic disease. In the near future, it is expected that several molecular genetic factors will become important as prognostic factors in melanoma.

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