

27 Prognostic factors and survival outcomes in cutaneous melanoma

27.1 Prognostic factors

Clinical stage is the most important determinant of prognosis in melanoma. Patients with thin early-stage melanomas have an excellent prognosis in general, but even in these patients there is no certainty of cure. Prognosis is poorer with increasing stage, but some patients may survive for extended periods with known metastatic disease. The American Joint Committee on Cancer (AJCC) Staging system, validated in a series of 17,600 patients with melanoma, uses T (Primary Tumour), N (Regional Lymph Nodes) and M (Distant Metastasis) categories to predict survival outcome.^{1,2} Despite the large number of established and putative prognostic factors in melanoma, accurate prediction of prognosis in an individual patient remains difficult.³

Key determinants of prognosis in localised melanoma (**stages I and II**) are Breslow thickness and ulceration.⁴ Clark's level of invasion may have some value in thin melanomas, but this is controversial.⁵ The importance of mitotic rate has been emphasised in a number of recent studies, and is one of the key prognostic determinants in thin melanomas in some series.⁶⁻¹² Most other suggested prognostic factors, including lymphocytic infiltration, regression, vascular invasion and cell type, are of lesser importance in the majority of studies, or findings are controversial and conflicting.^{5,6,8,13-17} Pregnancy does not appear to significantly affect prognosis.¹⁸

Tumour growth phase has been shown to be poorly reproducible and of limited value, although it may assist in stratifying thin melanomas.⁶ Histological subtype provides little prognostic information when Breslow thickness is considered, while pure desmoplastic melanomas may have a slightly better prognosis.¹⁹

Although many molecular and immunohistochemical studies have identified possible prognostic markers, multivariate analyses show that in general, these are no better than standard morphologic criteria.²⁰ In the future, gene expression profiling using cDNA-microarray analysis may be of value.²¹ Serum markers such as S100 β and melanoma-inhibiting activity protein can provide some prognostic information, but this is mostly relevant in monitoring treatment effects in advanced-stage melanoma.²²

A number of prognostic models have been developed using a combination of clinical and pathological features. Some are complex and although they may show promise in whole populations, all suffer from the problem of limited predictive value for an individual patient.⁴

The site of a primary melanoma has been shown to have prognostic relevance in some studies, but not others, even when tumour thickness is controlled for in the analysis. In some series, tumours sited on the palms, soles and subungual regions have a worse prognosis. When controlled for thickness, ethnicity has been shown to be relevant in some populations, with African Americans having a somewhat worse outcome.

In **stage III** disease (regional metastases), the most important determinant of prognosis is the number of lymph nodes affected. The size of the metastases is also important, with clinically detected disease faring worse than that only identified microscopically. Ulceration of the primary tumour confers an adverse prognosis, and tumours in older patients, and those sited on the trunk, head and neck, may have a worse prognosis.

In **stage IV** (distant metastases), prognosis is worse, with increasing number of metastatic sites and with metastasis to viscera.²³ High serum lactate dehydrogenase (a marker of liver involvement) and poor performance status are associated with reduced survival.²⁴

Approximately 5% of patients present with metastatic melanoma for which a primary cannot be identified. In these patients, the prognosis is much the same as that of patients with similar disease distribution associated with a known primary.⁴

Independent of the stage of disease, there are additional host-related factors that affect the prognosis of a melanoma patient. These include age, gender, and socioeconomic status. The risk of death due to melanoma is greater in older people (60+ years of age) than it is in younger people, and greater in men than in women.^{5,25-43} However, there is only limited evidence that the probability of death due to melanoma is greater in people of lower socioeconomic status.^{30,34,46}

Table 7 Prognostic factors in melanoma

		Prognostic factor
Tumour-related	Key factors	TNM Stage Breslow thickness
	Generally considered to be of importance	Ulceration Mitotic rate Regression Clark's level (mainly of importance in thin melanomas) Lymphovascular invasion
	Of uncertain or disputed importance	Tumour infiltrating lymphocytes Growth phase Desmoplastic type
Host-related		Age Gender Site Raised serum LDH* Poor performance status*

* In stage IV disease

27.2 Survival outcomes

The most recent comprehensive analysis of survival outcomes, based on the results of over 17,000 melanoma patients from several countries around the world, is reproduced below. This analysis was used to develop the 2002 AJCC melanoma staging system.²

The AJCC Melanoma Staging Committee reconvened in 2006 to begin preparation of the next version of the AJCC staging system, scheduled to become official with publication of the seventh edition of the AJCC Cancer Staging Manual which is expected to be published in late 2009.

Pathologic Stage	TNM	Thickness (mm)	Ulceration	No. + Nodes	Nodal Size	Distant Metastasis	No. of Patients	Survival ± SE			
								1-Year	2-Year	5-Year	10-Year
IA	T1a	1	No	0	–	–	4,510	99.7 ± 0.1	99.0 ± 0.2	95.3 ± 0.4	87.9 ± 1.0
IB	T1b	1	Yes or level IV, V	0	–	–	1,380	99.8 ± 0.1	98.7 ± 0.3	90.9 ± 1.0	83.1 ± 1.5
IB	T2a	1	No	0	–	–	3,285	99.5 ± 0.1	97.3 ± 0.3	89.0 ± 0.7	79.2 ± 1.1
IIA	T2b	1.01–2.0	Yes	0	–	–	958	98.2 ± 0.5	92.9 ± 0.9	77.4 ± 1.7	64.4 ± 2.2
	T3a	1.01–2.0	No	0	–	–	1,717	98.7 ± 0.3	94.3 ± 0.6	78.7 ± 1.2	63.8 ± 1.7
IIB	T3b	2.01–4.0	Yes	0	–	–	1,523	95.1 ± 0.6	84.8 ± 1.0	63.0 ± 1.5	50.8 ± 1.7
	T4a	2.01–4.0	No	0	–	–	563	94.8 ± 1.0	88.6 ± 1.5	67.4 ± 2.4	53.9 ± 3.3
IIC	T4b	> 4.0	Yes	0	–	–	978	89.9 ± 1.0	70.7 ± 1.6	45.1 ± 1.9	32.3 ± 2.1
IIIA	N1a	> 4.0	No	1	Micro	–	252	95.9 ± 1.3	88.0 ± 2.3	69.5 ± 3.7	63.0 ± 4.4
	N2a	Any	No	2–3	Micro	–	130	93.0 ± 2.4	82.7 ± 3.8	63.3 ± 5.6	56.9 ± 6.8
IIIB	N1a	Any	Yes	1	Micro	–	217	93.3 ± 1.8	75.0 ± 3.2	52.8 ± 4.1	37.8 ± 4.8
	N2a	Any	Yes	2–3	Micro	–	111	92.0 ± 2.7	81.0 ± 4.1	49.6 ± 5.7	35.9 ± 7.2
IIIC	N1b	Any	No	1	Macro	–	122	88.5 ± 2.9	78.5 ± 3.7	59.0 ± 4.8	47.7 ± 5.8
	N2b	Any	No	2–3	Macro	–	93	76.8 ± 4.4	65.6 ± 5.0	46.3 ± 5.5	39.2 ± 5.8
	N3	Any	Any	4	Micro/Macro	–	396	71.0 ± 2.4	49.8 ± 2.7	26.7 ± 2.5	18.4 ± 2.5
IV	M1a	Any	Any	Any	Any	Skin, SQ	179	59.3 ± 3.7	36.7 ± 3.6	18.8 ± 3.0	15.7 ± 2.9
	M1b	Any	Any	Any	Any	Lung	186	57.0 ± 3.7	23.1 ± 3.2	6.7 ± 2.0	2.5 ± 1.5
	M1c	Any	Any	Any	Any	Other visceral	793	40.6 ± 1.8	23.6 ± 1.5	9.5 ± 1.1	6.0 ± 0.9
Total							17,600				

Reproduced from Balch CM, Soong SJ, Gershenwald JE, Thompson JF, Reintgen DS, Cascinelli N et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol* 2001; 19(16):3622–3634.

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