

# 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.<sup>1,2</sup> Despite the large number of established and putative prognostic factors in melanoma, accurate prediction of prognosis in an individual patient remains difficult.<sup>3</sup>

Key determinants of prognosis in localised melanoma (**stages I and II**) are Breslow thickness and ulceration.<sup>4</sup> Clark's level of invasion may have some value in thin melanomas, but this is controversial.<sup>5</sup> 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.<sup>6–12</sup> 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.<sup>5,6,8,13–17</sup> Pregnancy does not appear to significantly affect prognosis.<sup>18</sup>

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

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.<sup>20</sup> In the future, gene expression profiling using cDNA-microarray analysis may be of value.<sup>21</sup> Serum markers such as S100 $\beta$  and melanoma-inhibiting activity protein can provide some prognostic information, but this is mostly relevant in monitoring treatment effects in advanced-stage melanoma.<sup>22</sup>

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.<sup>4</sup>

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.<sup>23</sup> High serum lactate dehydrogenase (a marker of liver involvement) and poor performance status are associated with reduced survival.<sup>24</sup>

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.<sup>4</sup>

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.<sup>5,25-43</sup> However, there is only limited evidence that the probability of death due to melanoma is greater in people of lower socioeconomic status.<sup>30,34,46</sup>

**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.<sup>2</sup>

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.

**Table 8** Survival rates for melanoma TNM and staging categories

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
	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
IIIC	N1b	Any	Yes	1	Macro	–	98	77.9 ± 4.3	54.2 ± 5.2	29.0 ± 5.1	24.4 ± 5.3
	N2b	Any	Yes	2–3	Macro	–	109	74.3 ± 4.3	44.1 ± 4.9	24.0 ± 4.4	15.0 ± 3.9
	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.

## References

1. AJCC (American Joint Committee on Cancer) Cancer Staging Handbook: TNM Classification of Malignant Tumors. 6th ed. 2002. New York: Springer-Verlag.
2. 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.
3. Beer TW, Heenan PJ. Prognostic factors in cutaneous melanoma. In: Gospodarowicz MK, editor. *Prognostic Factors in Cancer UICC*. 2006. New Jersey: Wiley & Sons.
4. Gershenwald JE, Balch CM, Soong S-J, et al. Prognostic factors and natural history. In: Balch CM, Houghton AN, Sober A.J., Soong S-J, editors. *Cutaneous Melanoma*. 2003. St Louis: Quality Medical Publishing.
5. Leiter U, Buettner PG, Eigentler TK, Garbe C. Prognostic factors of thin cutaneous melanoma: an analysis of the central malignant melanoma registry of the German Dermatological Society. *J Clin Oncol* 2004; 22(18):3660–3667.
6. Gimotty PA, Guerry D, Ming ME, Elenitsas R, Xu X, Czerniecki B et al. Thin primary cutaneous malignant melanoma: a prognostic tree for 10-year metastasis is more accurate than American Joint Committee on Cancer staging. *J Clin Oncol* 2004; 22(18):3668–3676.
7. Gimotty PA, Van Belle P, Elder DE, Murry T, Montone KT, Xu X et al. Biologic and prognostic significance of dermal Ki67 expression, mitoses, and tumorigenicity in thin invasive cutaneous melanoma. *J Clin Oncol* 2005; 23(31):8048–8056.
8. Gimotty PA, Elder DE, Fraker DL, Botbyl J, Sellers K, Elenitsas R et al. Identification of high-risk patients among those diagnosed with thin cutaneous melanomas. *J Clin Oncol* 2007; 25(9): 1129–1134.
9. Azzola MF, Shaw HM, Thompson JF, Soong SJ, Scolyer RA, Watson GF et al. Tumor mitotic rate is a more powerful prognostic indicator than ulceration in patients with primary cutaneous melanoma: an analysis of 3661 patients from a single center. *Cancer* 2003; 97(6):1488–1498.
10. Barnhill RL, Katzen J, Spatz A, Fine J, Berwick M. The importance of mitotic rate as a prognostic factor for localized cutaneous melanoma. *J Cutan Pathol* 2005; 32(4):268–273.
11. Attis MG, Vollmer RT. Mitotic rate in melanoma: a reexamination. *Am J Clin Pathol* 2007; 127(3):380–384.
12. Francken AB, Shaw HM, Thompson JF, Soong SJ, Accortt NA, Azzola MF et al. The prognostic importance of tumor mitotic rate confirmed in 1317 patients with primary cutaneous melanoma and long follow-up. *Ann Surg Oncol* 2004; 11(4):426–433.
13. Kashani-Sabet M, Sagebiel RW, Ferreira CM, Nosrati M, Miller JR, III. Vascular involvement in the prognosis of primary cutaneous melanoma. *Arch Dermatol* 2001; 137(9):1169–1173.
14. Taylor RC, Patel A, Panageas KS, Busam KJ, Brady MS. Tumor-infiltrating lymphocytes predict sentinel lymph node positivity in patients with cutaneous melanoma. *J Clin Oncol* 2007; 25(7):869–875.
15. Clark WH, Jr., Elder DE, Guerry D, Braitman LE, Trock BJ, Schultz D et al. Model predicting survival in stage I melanoma based on tumor progression. *J Natl Cancer Inst* 1989; 81(24):1893–1904.
16. Guitart J, Lowe L, Piepkorn M, Prieto VG, Rabkin MS, Ronan SG et al. Histological characteristics of metastasizing thin melanomas: a case-control study of 43 cases. *Arch Dermatol* 2002; 138(5):603–608.
17. Cook MG, Spatz A, Brocker EB, Ruiter DJ. Identification of histological features associated with metastatic potential in thin (<1.0 mm) cutaneous melanoma with metastases. A study on behalf of the EORTC Melanoma Group. *J Pathol* 2002; 197(2):188–193.
18. O'Meara AT, Cress R, Xing G, Danielsen B, Smith LH. Malignant melanoma in pregnancy. A population-based evaluation. *Cancer* 2005; 103(6):1217–1226.

19. Busam KJ, Mujumdar U, Hummer AJ, Nobrega J, Hawkins WG, Coit DG et al. Cutaneous desmoplastic melanoma: reappraisal of morphologic heterogeneity and prognostic factors. *Am J Surg Pathol* 2004; 28(11):1518–1525.
20. Carlson JA, Ross JS, Slominski A, Linette G, Mysliborski J, Hill J et al. Molecular diagnostics in melanoma. *J Am Acad Dermatol* 2005; 52(5):743–775.
21. Nambiar S, Mirmohammadsadegh A, Bar A, Bardenheuer W, Roeder G, Hengge UR. Applications of array technology: melanoma research and diagnosis. *Expert Rev Mol Diagn* 2004; 4(4):549–557.
22. Li N, Mangini J, Bhawan J. New prognostic factors of cutaneous melanoma: a review of the literature. *J Cutan Pathol* 2002; 29(6):324–340.
23. Unger JM, Flaherty LE, Liu PY, Albain KS, Sondak VK. Gender and other survival predictors in patients with metastatic melanoma on Southwest Oncology Group trials. *Cancer* 2001; 91(6):1148–1155.
24. Manola J, Atkins M, Ibrahim J, Kirkwood J. Prognostic factors in metastatic melanoma: a pooled analysis of Eastern Cooperative Oncology Group trials. *J Clin Oncol* 2000; 18(22):3782–3793.
25. Garbe C, Buttner P, Bertz J, Burg G, d’Hoedt B, Drepper H et al. Primary cutaneous melanoma. Identification of prognostic groups and estimation of individual prognosis for 5093 patients. *Cancer* 1995; 75(10):2484–2491.
26. Corona R, Scio M, Mele A, Ferranti G, Mostaccioli S, Macchini V et al. Survival and prognostic factors in patients with localised cutaneous melanoma observed between 1980 and 1991 at the Istituto Dermopatico dell’Immacolata in Rome, Italy. *Eur J Cancer* 1994; 30A(3):333–338.
27. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer* 1998; 83(8):1664–1678.
28. Scoggins CR, Ross MI, Reintgen DS, Noyes RD, Goydos JS, Beitsch PD et al. Gender-related differences in outcome for melanoma patients. *Ann Surg* 2006; 243(5):693–698.
29. Balzi D, Carli P, Giannotti B, Buiatti E. Skin melanoma in Italy: a population-based study on survival and prognostic factors. *Eur J Cancer* 1998; 34(5):699–704.
30. Berwick M, Dubin N, Luo ST, Flannery J. No improvement in survival from melanoma diagnosed from 1973 to 1984. *Int J Epidemiol* 1994; 23(4):673–681.
31. Heenan PJ, English DR, Holman CD, Armstrong BK. Survival among patients with clinical stage I cutaneous malignant melanoma diagnosed in Western Australia in 1975/1976 and 1980/1981. *Cancer* 1991; 68(9):2079–2087.
32. Brenner B, Borok S, Rakowsky E, Fenig E, Gutman H, Sulkes J et al. Older age and second skin cancer as prognostic factors in localized malignant melanomas. *Oncol Rep* 2003; 10(6):2051–2057.
33. Karakousis CP, Driscoll DL. Prognostic parameters in localised melanoma: gender versus anatomical location. *Eur J Cancer* 1995; 31A(3):320–324.
34. Chang CK, Jacobs IA, Vizgirda VM, Salti GI. Melanoma in the elderly patient. *Arch Surg* 2003; 138(10):1135–1138.
35. Ringborg U, Afzelius LE, Lagerlof B, Adami HO, Augustsson I, Blomqvist E et al. Cutaneous malignant melanoma of the head and neck. Analysis of treatment results and prognostic factors in 581 patients: a report from the Swedish Melanoma Study Group. *Cancer* 1993; 71(3):751–758.
36. Tillman DM, Aitchison T, Watt DC, MacKie RM. Stage II melanoma in the west of Scotland, 1976–1985: prognostic factors for survival. *Eur J Cancer* 1991; 27(7):870–876.
37. Chang JW, Yeh KY, Wang CH, Yang TS, Chiang HF, Wei FC et al. Malignant melanoma in Taiwan: a prognostic study of 181 cases. *Melanoma Res* 2004; 14(6):537–541.
38. Masback A, Westerdahl J, Ingvar C, Olsson H, Jonsson N. Cutaneous malignant melanoma in southern Sweden 1965, 1975, and 1985. Prognostic factors and histologic correlations. *Cancer* 1997; 79(2):275–283.

39. Levi F, Randimbison L, La Vecchia C, Te VC, Franceschi S. Prognostic factors for cutaneous malignant melanoma in Vaud, Switzerland. *Int J Cancer* 1998; 78(3):315–319.
40. Cohen HJ, Cox E, Manton K, Woodbury M. Malignant melanoma in the elderly. *J Clin Oncol* 1987; 5(1):100–106.
41. Vossaert KA, Silverman MK, Kopf AW, Bart RS, Rigel DS, Friedman RJ et al. Influence of gender on survival in patients with stage I malignant melanoma. *J Am Acad Dermatol* 1992; 26(3 Pt 2):429–440.
42. Kuehnl-Petzoldt C, Fischer S. Tumor thickness is not a prognostic factor in thin melanoma. *Arch Dermatol Res* 1987; 279(7):487–488.
43. MacKie RM, Hole DJ. Incidence and thickness of primary tumours and survival of patients with cutaneous malignant melanoma in relation to socioeconomic status. *BMJ* 1996; 312(7039):1125–1128.