treatment of metastatic colorectal adenocarcinoma by continuous intravenous infusion of 5-fluorouracil. *J Surg Oncol* 1985, **30**, 60–65.
31. Reiter B, Schreibman S, Adler S, Starrett S. Treatment of colorectal cancer with 5-FU by infusion in a community oncology practice. *ASCO* 1987, **6**, 74.
32. Leichman L, Leichman CG, Kinzie J, Weaver D, Evans L. Long-term low dose 5-fluorouracil (5-FU) in advanced measurable colon cancer: no correlation between toxicity and efficacy. *ASCO* 1985, **4**, 86.
33. Wade JL, Herbst S, Greenburg A. Prolonged venous infusion (PVI) of 5-fluorouracil (5-FU) for metastatic colon cancer. A follow-up report. *ASCO* 1988, **7**, 94.
34. Benedetto P, Bogos M, Morillo G, Sfakianakis G. Chronic continuous infusion of 5-fluorouracil (CCI-FU) in previously untreated patients with measurable metastatic colorectal cancer. *ASCO* 1986, **5**, 92.
35. Moran RG, Scanion KL. Schedule-dependent enhancement of the cytotoxicity of fluoropyrimidines to human carcinoma cells in the presence of folinic acid. *Cancer Res* 1991, **51**, 4618–4623.
36. Aschele C, Sobrero A, Faderan MA, Bertino JR. Novel mechanism(s) of resistance to 5-fluorouracil in human colon cancer (HCT-8) sublines following exposure to two different clinically relevant dose schedules. *Cancer Res* 1992, **52**, 1855–1864.
37. Sobrero AF, Aschele C, Guglielmi AP, *et al.* Synergism and lack of cross-resistance between short-term and continuous exposure to fluorouracil in human colon adenocarcinoma cells. *J Natl Cancer Inst* 1993, **85**, 1937–1944.
38. Schalhorn A, Kühl M. Clinical pharmacokinetics of fluorouracil and folinic acid. *Semin Oncol* 1992, **19** (suppl. 3), 82–92.
39. Wadler S, Schwartz EL. Antineoplastic activity of the combination of interferon and cytotoxic agents against experimental and human malignancies: a review. *Cancer Res* 1990, **50**, 3473–3486.
40. Tsavaris N, Caragiuauris P, Kosmidis P. Reduction of oral toxicity of 5-fluorouracil by allopurinol mouthwashes. *Eur J Surg Oncol* 1988, **14**, 405–406.

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Prognostic Parameters in Localised Melanoma: Gender Versus Anatomical Location

C.P. Karakousis and D.L. Driscoll

Extremity location and female gender are both considered favourable prognostic parameters in primary melanoma, but since they cluster in the same group of patients, the question remains as to whether they are both independent variables. Multivariate analysis of 695 patients with primary, localised melanoma was used. The effects of gender and anatomical location were compared directly by sequentially controlling one factor while the other remained free. Following multivariate analysis, significant prognostic factors related to survival were the thickness of the primary lesion ($P < 0.0001$), the age of the patient at diagnosis ($P < 0.0001$), the gender of the patient ($P = 0.0008$) and the anatomical location of the primary lesion ($P = 0.005$). Thicker lesions, patients older than 50 years, males, and trunk, head and neck locations had poorer prognoses. There was a significant difference in survival according to gender within each location, extremity ($P = 0.002$) or trunk, head and neck ($P = 0.0004$); however, there was no significant difference in survival according to anatomical location within each gender, male ($P = 0.11$) or female ($P = 0.29$). The thickness of the primary lesion, the age of the patient at diagnosis, the gender and the anatomical location of the melanoma are all significant prognostic parameters in localised melanoma. Gender appears to have a more pronounced effect on survival than anatomical location.

Key words: localised melanoma, prognostic parameters
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INTRODUCTION

THE MICROSTAGING METHODS already developed have provided significant prognostic information, put surgical treatment on a rational basis and made possible the assessment of a treatment effect for a truly comparable group of controls in adjuvant studies [1, 2]. Of the two methods, the measurement of thickness has been found to provide more accurate prognosis, although both methods are still being used in pathology reports describing the primary lesion.

Other prognostic parameters reported in the literature have been the presence of ulceration in the primary lesion [3], anatomical location [3], and the gender of the patient [4]. Extremity melanomas were generally reported to have a better outlook than trunk melanomas [3]. Some reports indicated that for the so-called BANS area of skin (upper back, upper posterior arm, neck and scalp) the prognosis was poorer [5] than that for melanomas from the skin of other anatomical areas. The prognostic importance of BANS, with the exception of scalp

melanomas [6], has been disproved [7]. In some reports, women have better survival than men [8], although in others this does not appear to be the case [9]. In a review of 4816 cases diagnosed and treated in the U.S.A. during 1980, women had a higher incidence of melanoma in the legs (28%) compared with men (8%) [10]. Since both anatomical location and gender of the patient have been reported to be significant with regard to prognosis, the question is whether they are both independent prognostic indicators of survival, or whether only one is independent, the other having prognostic implications by mere association with the first. The difficulty arises because both favourable prognostic parameters (female gender and extremity location) are present in the same group. Some studies using multivariate analysis have indicated that the gender of the patient is an independent prognostic indicator [4, 8, 11].

In this study the experience at Roswell Park Cancer Institute (RPCI) for patients referred with localised melanoma is recounted. The data were obtained from the Tumour Registry at RPCI.

MATERIALS AND METHODS

In the period 1976–1988, 695 patients were referred with localised melanoma. None of the patients had evidence of regional or distant metastasis at the time of referral. There were 325 men and 370 women. The mean age was 50 years, median 51 (range 12–90). The mean follow-up time from diagnosis was 89 months, median 78 months.

All patients were treated with wide excision of the primary site. Elective regional node dissection was practised selectively depending on the philosophy of the attending staff during this 12-year period. Previous reviews from our Institute regarding the effect of surgical treatment have shown no significant effect on survival by elective dissection [8, 11].

Prognostic parameters which were evaluated were the thickness of the primary lesion, anatomical location, age at diagnosis, the gender of the patient and the year of diagnosis.

The estimated survival distributions were calculated by the method of Kaplan and Meier [12]. Tests of significance with respect to survival distributions were based on the log rank test [13]. Time for survival was computed as months from biopsy to death or date last seen.

RESULTS

Data were missing from 1 patient, who was therefore excluded from analysis. Data on Breslow thickness of lesions was only available in 567 patients. Using the Kruskal–Wallis one way analysis of variance method [14], a significant correlation was found between the location of primary lesion and age. Patients with head and neck lesions were older than patients with trunk, upper or lower extremity lesions ($P = 0.005$). The mean age for patients with head and neck lesions was 56 years, for trunk lesions 49, for lower extremity lesions 49, and for upper extremity lesions 48 years.

Age and thickness using Spearman's correlation [15] were found to be significantly related ($P = 0.001$), with older patients generally having thicker lesions.

A Mann–Whitney test [16] was used to determine that age and gender were significantly related ($P < 0.0001$). Men were older than women. The mean age of men was 53 years and that of women 48 years.

Table 1. Anatomical location and survival in localised melanoma

Location	Number of patients	Estimated 5-year survival (%)
Head and neck	112	70
Trunk	235	80
Lower extremities	181	87
Upper extremities	166	90

Log rank $P < 0.0001$.

Extremity locations were more common in women (68%) than in men (29%) ($P < 0.0001$). Of 253 women with extremity location for the primary melanoma, 43% had the lesion in the upper extremity and 57% in the lower extremity. In men ($n = 94$), the respective figures were 62 and 38% ($P = 0.002$). The higher distribution of melanomas in the legs compared with arms in women is consistent with the evidence that exposure to sunlight is one of the causative factors of malignant melanoma.

The estimated 5-year survival for all patients was 83%. For patients diagnosed and referred between 1976 and 1979 ($n = 179$) the 5-year survival was 83%, for those referred between 1980 and 1983 ($n = 192$) it was 84%, and for those referred between 1984 and 1988 ($n = 324$) it was 82%. There was no statistically significant difference in survival for these groups.

There was a significant difference in survival according to anatomical location ($P < 0.0001$, Table 1, Figure 1). The 5-year survival for the combined group of head, neck and trunk melanomas was 77%, and for all extremity melanomas 88% ($P = 0.0001$, Figure 2).

In single factor analysis, both thickness of the primary lesion ($P < 0.0001$, Figure 3) and age at diagnosis ($P < 0.0001$, Figure 4) were significant prognostic indicators of survival. Patients with thicker lesions and those older than 50 years of age had a poorer prognosis. Specifically the estimated 5-year survival

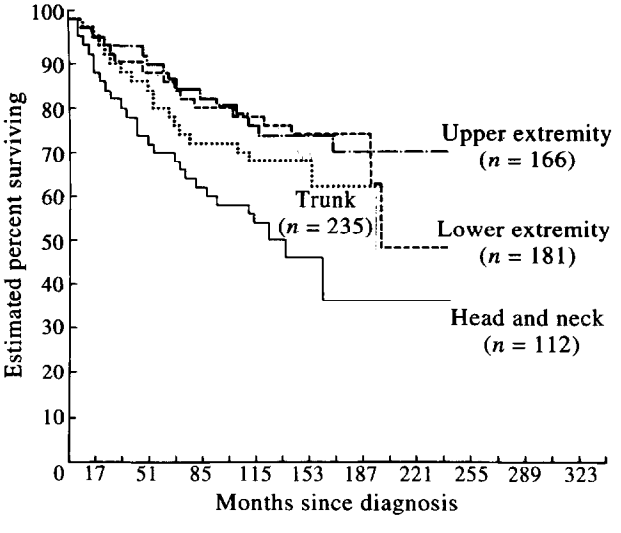

Figure 1. Survival curves according to anatomical location of the primary malignant melanoma.

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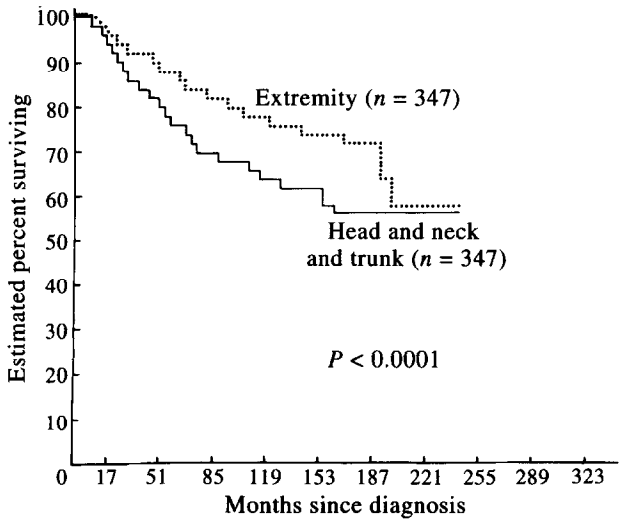

Figure 2. Survival curves in malignant melanomas of the extremities, and in melanomas of the head and neck or trunk areas.

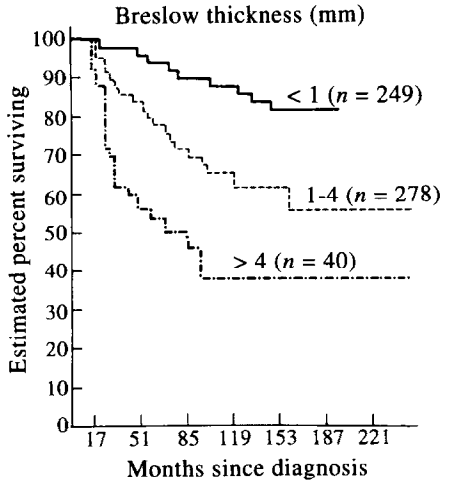

Figure 3. Survival curves of patients with malignant melanoma according to the thickness of the primary lesion.

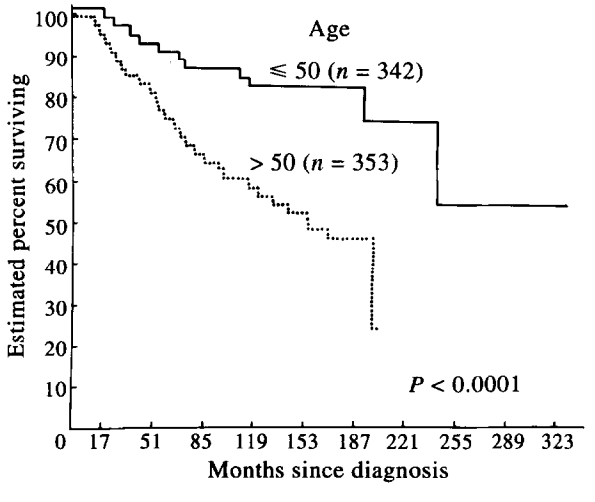

Figure 4. Survival curves of patients with malignant melanoma according to age.

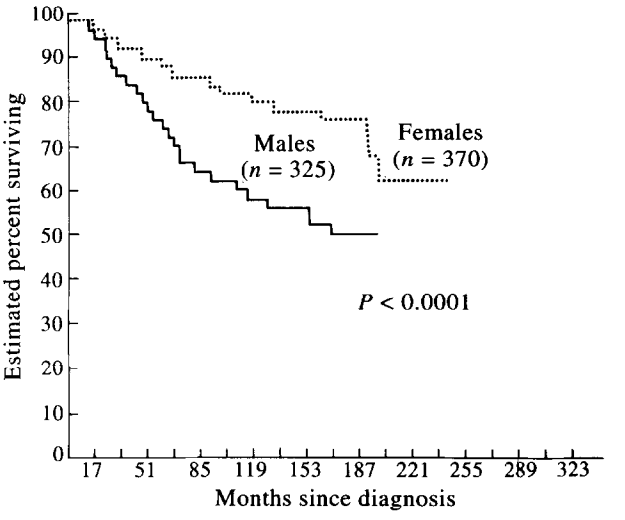

Figure 5. Survival curves of patients with malignant melanoma according to gender.

rate was 94% for patients with lesions < 1 mm, 78% for those with lesions 1–4 mm thick, and 54% for those with lesions > 4 mm thick. Gender was significantly related to survival ($P < 0.0001$, Figure 5). The estimated 5-year survival for men was 75% and for women 89%. In order to further test the validity of gender as a prognostic indicator and to separate it from the effect of anatomical location, the effect of gender within each location (Table 2, Figures 6, 7) and the effect of location within each gender (Table 3, Figures 8, 9) was examined. It is clear from this analysis that the gender of the patient is a significant prognostic indicator of survival within each anatomical location (extremity, or head and neck–trunk) and therefore gender is a prognostic parameter independent of location of the primary lesion (Table 2). However, there was no significant difference in survival according to location within each sex. Although there was a trend toward improved survival for men with extremity location of the primary lesion over those with other locations ($P = 0.11$), in women the estimated 5-year survival was almost identical for the extremity and other locations of the primary lesions ($P = 0.29$, Table 3).

In multivariate analysis, factors related significantly to sur-

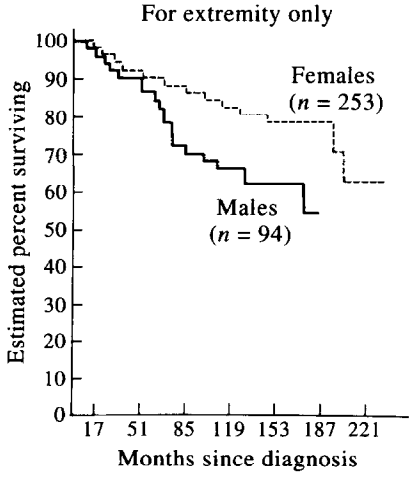

Figure 6. Among extremity melanomas there was a significant difference in survival distributions according to gender ($P = 0.002$).

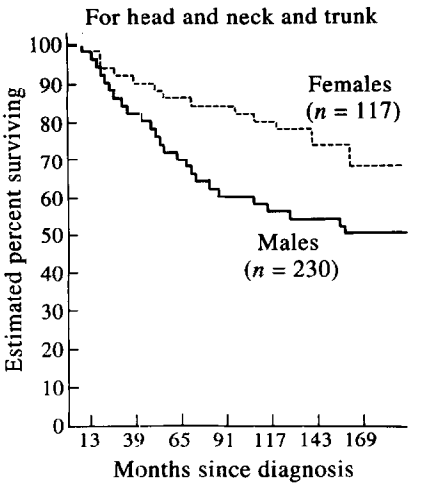

Figure 7. Among head and neck, and trunk melanomas there was a significant difference in survival distributions according to gender ($P = 0.004$).

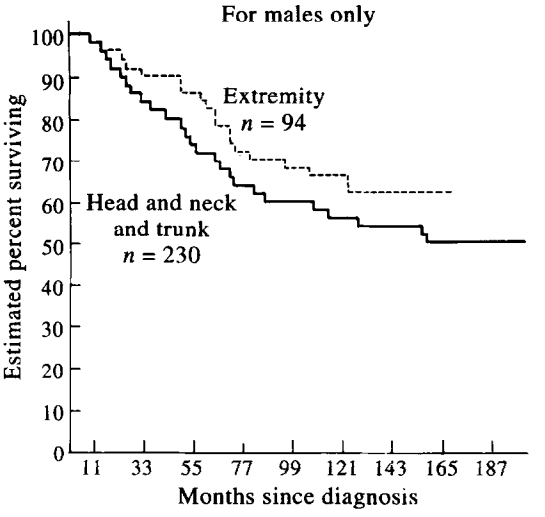

Figure 8. Among men there was no significant difference in the survival distributions according to anatomical location of the primary melanoma ($P = 0.11$).

Table 2. Effect of gender on survival in each anatomical location

	Location of primary lesion			
	Extremity		Other	
	Number of patients	Estimated 5-year survival (%)	Number of patients	Estimated 5-year survival (%)
Male	94	83	230	72
Female	253*	90	117†	87

* Log rank $P = 0.002$; † log rank $P = 0.004$.

Table 3. Effect of location on survival in each gender

	Men		Women	
Location	Number	Estimated 5-year survival (%)	Number	Estimated 5-year survival (%)
Extremity	94	83	253	90
Other	230*	72	117†	87

* Log rank $P = 0.11$; † log rank $P = 0.29$.

vival were found to be the thickness of the primary lesion ($P < 0.0001$), the age of the patient at diagnosis ($P < 0.0001$), the gender of the patient ($P = 0.0008$) and the anatomical location of the primary lesion ($P = 0.005$). The year of diagnosis and referral to RPCI was not a significant parameter ($P = 0.66$).

DISCUSSION

Clark's method of microstaging of the primary lesion by level of skin layer involvement was the first to be described and correlates well with recurrence and survival rates [1]. The method of Breslow by thickness then described [2] was found to provide more accurate prognostication which could not be further improved with the additional information of Clark's level [16].

Ulceration of the primary lesion described first by Balch and colleagues [17] has been confirmed by other subsequent studies to be a significant prognostic parameter. Unfortunately, the presence or absence of this valuable prognostic indicator did not become part of the standard pathology report at RPCI until the mid 1980s. Therefore, this histological feature was not available for the majority of patients reviewed.

The significance of other prognostic parameters is more tenuous. However, anatomical location of the primary lesion (extremity versus other skin locations) and gender of the patient (female versus male) have often been found, but not invariably, to relate significantly to survival.

Since both favourable indicators, i.e. extremity location and female gender, occur in the same group of patients there has always been the question whether these two parameters are both independent or whether one of them may affect survival by virtue of its association with the other.

Some reports have indicated that anatomical location is a significant prognostic parameter, and others that it is the gender of the patient. In a multifactorial analysis, it was found that thickness of the lesion, melanoma ulceration and anatomical location were the dominant prognostic factors, whereas four

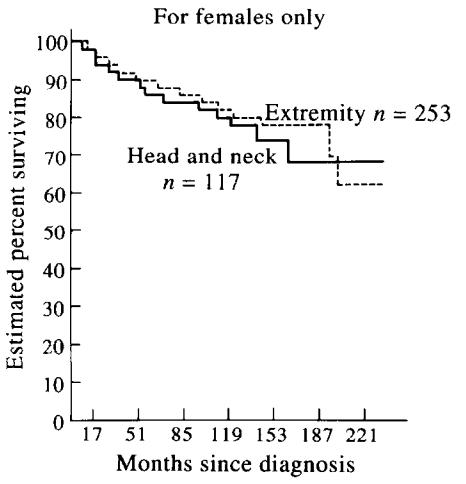

Figure 9. Among women there was no significant difference in the survival distributions according to anatomical location of the primary melanoma ($P = 0.29$).

other factors (one of which was the gender of the patient) correlated with survival in certain subgroups of patients to a lesser extent [7].

In a previous analysis of 371 patients treated at our Institute in an earlier period, it was found that gender was a significant prognostic indicator. In an attempt to provide the practising physician with formulae, calculating survival for each 1 mm increment in thickness, the survival difference between the two sexes was so vast it became necessary to have a separate formula for each gender [11].

Multivariate analysis is presumed to provide not only the significance of each parameter, but also the independence of the various parameters. It is therefore useful for distinguishing an effect by association with another parameter from an independent effect. However, although mathematics is an exact science, hidden assumptions (which may be false) in the application of statistical methods may result in false conclusions. In our analysis, the independence of the two parameters (anatomical location versus gender) was subjected to a more direct and unambiguous test. Each parameter was allowed to vary while the other was kept stable. Any effect on survival would therefore be the effect of the "free" parameter, provided there were no hidden or unknown associations with a third or fourth parameter.

For all extremity melanoma lesions, there was a significant difference in survival according to the gender of the patient ($P = 0.002$). For all trunk, head and neck lesions there was also a significant survival difference according to gender ($P = 0.004$). The reverse, however, was not true. For men, there was merely a trend toward improved survival with extremity locations but the difference was not significant ($P = 0.11$). In women, there was no appreciable difference in survival according to location ($P = 0.29$).

The above analyses suggest that the gender of the patient is a significant, independent prognostic indicator of survival. Specifically, it is independent of any effect that anatomical location may exert. Anatomical location, although it did not significantly affect survival within each gender (Table 3), also appeared to be an independent prognostic parameter in multivariate analysis, but to be substantially weaker than the gender. Interestingly, in our analysis the age of the patient at diagnosis was also found to be of major prognostic importance in addition to the already well established prognostic factor of lesion thickness. The effect of age could be explained either by younger patients having a higher immunoreactivity capable of reducing the recurrence rate or prolonging the onset of recurrence, or simply by younger people having a higher tolerance to the effects of disease and treatment after recurrence, and therefore a more prolonged survival. It was also found that the patients with head and neck location were older than those with lesions in other locations, males were older than females and older people had thicker lesions.

1. Clark WH, From L, Bernardino EA, Mihm MC. The histogenesis and biologic behavior of primary human malignant melanomas of the skin. *Cancer Res* 1969, **29**, 705–726.
2. Breslow A. Thickness, cross-sectional area, and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg* 1970, **172**, 902–908.
3. Balch CM, Soong S-J, Milton GW, *et al.* A comparison of prognostic factors and surgical results in 19 786 patients with localized melanoma treated in Alabama, U.S.A., and New South Wales, Australia. *Ann Surg* 1984, **196**, 677–684.
4. Cascinelli N, Morabito A, Bufalino R, va Esch EP, Preda F, Paglini M, *et al.* Prognosis of stage I melanoma of the skin. *Int J Cancer* 1980, **26**, 733.
5. Day CL Jr, Mihm MC Jr, Lew RA, Kopf AW, Sober AJ, Fitzpatrick TB. Cutaneous malignant melanoma: prognostic guidelines for physicians and patients. *CA* 1982, **32**, 113.
6. Urist MM, Balch CM, Soong S, *et al.* Head and neck melanoma in 536 clinical stage I patients: a prognostic factors analysis and results of surgical treatment. *Ann Surg* 1984, **200**, 769.
7. Balch CM, Soong SJ, Shaw HM, Urist MM, McCarthy WH. An analysis of prognostic factors in 8500 patients with cutaneous melanoma. In CM Balch, AN Houghton, GW Milton, AJ Sober and SJ Soong, eds. *Cutaneous Melanoma*. Lippincott, Philadelphia, 1992, 165–187.
8. Johnson OK, Emrich LJ, Karakousis CP, Rao U, Greco WR. Comparison of prognostic factors for survival and recurrence in malignant melanoma of the skin, clinical stage I. *Cancer* 1985, **55**, 1107–1117.
9. Balch CM, Soong S-J, Murad TM, Ingalls AL, Maddox WA. A multifactorial analysis of melanoma: II. Prognostic factors in patients with stage I (localized) melanoma. *Surgery* 1979, **86**, 343–351.
10. Balch CM, Karakousis CP, Mettlin C, *et al.* The assessment of the current management of malignant melanoma of the skin in the U.S. *Surg Gynecol Obstet* 1984, **158**, 311–318.
11. Karakousis CP, Emrich LJ, Rao U. Tumor thickness and prognosis in clinical stage I malignant melanoma. *Cancer* 1989, **64**, 1432–1436.
12. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–486.
13. Cox DR. Regression models and life-tables. *J R Stat Soc B* 1971, **34**, 187–220.
14. Siegel S. *Nonparametric Statistics for the Behavioral Sciences*. New York, McGraw-Hill, 1956.
15. Spearman C. The proof and measurement of association between two things. *Am J Psych* 1904, **15**, 72–101.
16. Mann HB, Whitney DR. On a test of whether one of two random variables is stochastically larger than the other. *Ann Math Stat* 1947, **18**, 50–60.
17. Balch CM, Wilkerson JA, Murad TM, Soong S-J, Ingalls AL, Maddox WA. The prognostic significance of ulceration of cutaneous melanoma. *Cancer* 1980, **45**, 3012–3017.