our overall median response duration and survival are relatively short. This, at least in part, reflects a selection policy in which fit patients suitable for trials of intensive treatment were generally excluded from this trial. However, our overall median survival is still comparable with the 8–9 months reported by Mead *et al.* [12]. An additional factor which might affect response and survival with ACE was probably our policy of dose reduction to avoid haematological toxicity in this group of patients for whom palliation was a major aim of treatment. In this context, the haematological toxicity with CVM was unexpectedly low even for a regimen designed for palliation. It may well be possible therefore to increase the carboplatin dose to 400 mg/m^2 in this regimen and thereby possibly increase efficacy without losing the benefit of low toxicity. Although the cost of carboplatin as a single agent is high, the total costs of a course of each regimen are comparable making CVM an attractive outpatient-based regimen for the many patients with SCLC for whom intensive therapy is considered inappropriate.

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Stage II Melanoma in the West of Scotland, 1976–1985: Prognostic Factors for Survival

David M. Tillman, Tom Aitchison, Douglas C. Watt and Rona M. MacKie

The outcome of 142 patients undergoing therapeutic lymphadenectomy for clinical stage II malignant melanoma was retrospectively assessed. 5 year survival was 26%, and survival was not altered in the 25 patients who received two courses of adjuvant combination chemotherapy after lymphadenectomy. On univariate analysis, the most significant determinants of survival were the number of malignant nodes removed at lymphadenectomy ($P = 0.00004$), the age of the patient ($P = 0.009$) and the disease-free interval between primary and stage II disease ($P = 0.01$). The following features were not significantly related to survival: sex, site, histogenetic type of primary tumour, tumour thickness and level of invasion. The number of malignant lymph-nodes was confirmed on multivariate analysis as the single most useful and significant predictor of survival, with the patient's age providing an additional significant contribution. In future adjuvant trials in stage II melanoma after therapeutic lymphadenectomy, patients should be stratified for both age and number of malignant nodes.
Eur J Cancer, Vol. 27, No. 7, pp. 870–876, 1991

INTRODUCTION

PATIENTS WITH stage IIb melanoma (clinically detectable metastatic disease in regional lymph-nodes) have a poor prognosis. Reported 5 year survival figures range between 13–38% and 10 year survivors are uncommon. In most previous series, the study populations included both patients undergoing elective (clinical stage I, pathological stage II) and therapeutic (clinical stage II, pathological stage II) lymphadenectomy [1–8]. In such series, although survival figures were often presented for clinical stage II disease separately (Table 1), the prognostic indicators for survival were usually determined for the whole stage II study population [1–8]. Few studies have dealt exclusively with clinical

Table 1. Clinical stage II melanoma: survival figures

Ref.	Year	Period of study	Total stage II	Clinical stage II survival (%)		
				n	5 yr	10 yr
23	1970	1950–1965	456	406	38	–
6	1977	1954–1964	85	45	–	20
5	1977	1955–1974	65	52	–	50
7	1977	1968–1974	74	23	13	–
3	1980	1966–1976	123	111	18	–
1	1982	1954–1976	150	119	36	–
2	1981	1960–1980	185	NS	24	0
10	1982	1967–1974	118	64	23	–
12*	1984	1967–1981	566	566	33	32
4	1985	NS	213	56	21	12
26	1986	1977–1983	56	41	37	–
9*	1987	1960–1983	133	133	28	–

NS = not stated.
* Exclusively clinical stage II.

stage II disease [9, 11, 12]. Moreover, in only a limited number of studies has multivariate statistical analysis been used [1, 2, 5, 9, 12].

The value of elective node dissection at the time of primary diagnosis remains uncertain [13], and it is not current practice in most European centres. Trials of new adjuvant therapy will therefore be undertaken in stage II patients following therapeutic rather than prophylactic lymphadenectomy. It is thus necessary to determine prognostic indicators in this more homogeneous group of patients in each population, in order to correctly stratify future adjuvant studies.

To date, prospective randomised adjuvant trials of chemotherapy, immunotherapy, or both, have shown no significant effect on survival [13, 14]. Biological response modifiers such as interferons [15, 16] and interleukin-2 [17], which have been shown to have activity in stage III melanoma, are now being used or considered in an adjuvant setting.

PATIENTS AND METHODS

The clinical records of 182 patients undergoing therapeutic lymphadenectomy for stage II melanoma at the West of Scotland Regional Plastic Surgery Unit, Canniesburn Hospital, Glasgow, between January 1976 and December 1985 were reviewed. Excluded from the study were 5 patients in whom the site of the primary melanoma was unknown, 15 patients with no histological evidence of melanoma in lymph-nodes and 20 patients found to have more widespread disease (stage III). This resulted in a homogeneous study group of 142 patients with clinical stage IIb disease in whom we assessed survival in relation to clinical and histological features.

The following patient details were recorded: age and sex; site, histogenetic type, Breslow thickness and Clark level of invasion of the primary tumour; the disease-free interval between primary diagnosis and the development of regional nodal metastases; the number of lymph-nodes removed, the number involved pathologically with melanoma and whether or not the capsule of the node had been breached; adjuvant therapy, if any, and type. Survival was calculated from the time of lymphadenectomy.

In 133 cases lymphadenectomy involved a radical procedure. In 9 patients a functional clearance of clinically involved tissue was performed. In only 1 of these patients did the first recurrence of melanoma occur at the site of previous lymphadenectomy. Neither the survival figures nor the analysis of prognostic indicators were significantly altered by inclusion of this group. 90% of the node dissections were carried out by 4 consultant plastic surgeons, all working in the West of Scotland Plastic Surgery Unit at Canniesburn Hospital. These surgeons have a similar approach to node dissections. 90 patients (63.4%) received no adjuvant therapy after node dissection. 25 (17.6%) received two courses of adjuvant BELD (bleomycin, vindesine, lomustine and dacarbazine) chemotherapy 1 month apart. We have previously reported a 45% response rate with this combination in stage III melanoma [18] and therefore wished to assess its possible role as an adjuvant chemotherapeutic regimen. 27 patients (19%) received other adjuvant monotherapy, mainly as participants in multicentre trials (vindesine, 11; dacarbazine, 7; BCG, 4; other, 5).

The median (interquartile range) follow-up period from lymphadenectomy was 20 (10–53) months (range 1–163) and for survivors was 83 (64–121) months (range 60–163). 5 year survival figures are thus available for all 142 patients. To date, 112 (79%) patients have died—103 (73%) from melanoma—and 30 patients (21%) remain alive and disease-free.

STATISTICAL METHODS

Survival functions were estimated using the method of Kaplan and Meier [19]. The log-rank test was used to assess the prognostic significance of the various parameters categorised as in Table 2. In addition, the Cox proportional hazards model was used to assess individually each of the following, treating these variables as continuous: age, Breslow thickness of primary lesion, disease-free interval and number of malignant nodes. This avoids arbitrary and possibly inappropriate categorisation. The Cox model with forward variable selection [20] was then used to ascertain the order of importance and interdependent significance of all the possible prognostic factors.

As a further guide to the importance and structural form of the variables chosen by this method, the technique of non-parametric logistic regression [21] was used for several variables including age and number of involved nodes both separately and jointly and for different survival time points including 1, 2 and 5 years. The advantage of non-parametric logistic regression as an exploratory tool is that it allows us to investigate whether or not the 'linear logistic' assumptions in the Cox proportional hazards model (as well as in linear logistic regression) are reasonable.

In all cases, patients who died without evidence of melanoma were considered alive and disease-free for the time interval from lymphadenectomy to death. It is important to note that survival figures in relation to time, e.g. 5 year survival, in this paper relate to time from lymphadenectomy, not from primary therapy.

RESULTS

There were 68 males (48%) and 74 females (52%). The median age at primary diagnosis was 50 years (range 17–87).

The median age of patients at the time of lymphadenectomy was 51 years (range 18–87). 22 patients (15.5%) presented with synchronous nodal metastases at the time of primary diagnosis.

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Table 2. Univariate analysis of prognostic variables

	n	Survival Median (mo)	Survival 5-year (%)
Age			
< 40	35	28	46
⩾ 40	107	18	19
$P = 0.009$ ($P = 0.009$)*			
Sex (M/F)	68/74	22/20	29/24
$P = 0.67$			
Primary melanoma			
Site			
Head/neck	22	17	17
Trunk	29	18	24
Lower limb	67	23	31
Upper limb	24	20	25
$P = 0.45$			
Type			
Nodular	45	17	22
SSM	58	26	36
A/L	10	27	25
LMM	6	25	0
Unclassifiable	4	10	0
$P = 0.68$			
Thickness (mm)			
Median 3.4			
< 1.5	12	25	25
1.5–3.49	50	26	40
⩾ 3.5	60	18	15
$P = 0.29$ ($P = 0.54$)*			
Level of invasion			
II	3	25	33
III	19	24	28
IV	82	21	31
V	18	22	13
$P = 0.95$			
Disease-free interval			
< 2 years	113	18	22
⩾ 2 years	29	57	46
$P = 0.0008$ ($P = 0.01$)*			
Adjuvant chemotherapy			
Nil	90	19	27
BELD	25	21	28
Other	27	26	26
$P = 0.17$			
Number of involved nodes			
1	42	25	33
2	25	23	29
3	21	23	19
⩾ 4	31	11	20
$P = 0.017$ ($P = 0.00004$)*			

SSM = superficial spreading melanoma, A/L = acral-lentiginous melanoma, LMM = lentigo maligna melanoma.
P values relate to the logrank test, with variables categorised as shown. *Where appropriate, single variables were considered individually and as continuous in the proportional hazards model (*P* values in parenthesis). All *P* values relate to overall survival, not survival at one time point only.

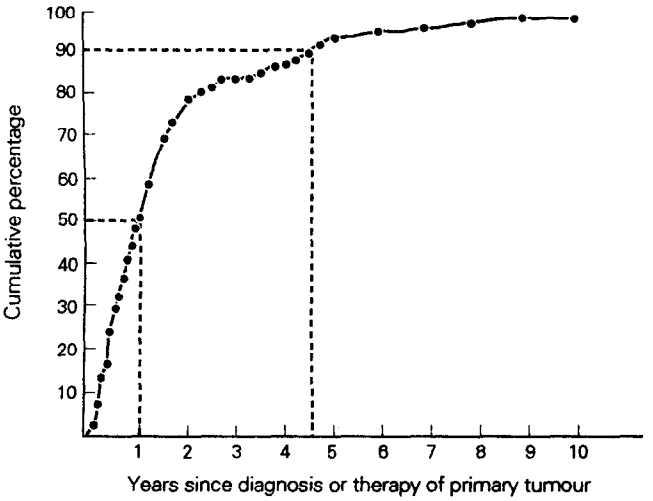

Fig. 1. Cumulative incidence of nodal metastases in patients with clinical stage II melanoma ($n = 120$) (excludes patients with synchronous metastatic nodes).

The remaining 120 patients (84.5%) developed stage II disease after a delay (Fig. 1). 50% of these patients required lymphadenectomy for clinical stage II disease within 1 year of primary diagnosis and 90% by 4.7 years. Only 8 patients (6.7%) had a disease-free interval of over 5 years. In 2 cases, however, the delay was greater than 10 years (156 and 197 months).

Information on the number of involved lymph-nodes was available in 119 cases (83.8%). In 42 (35.3%) of these patients one node was involved with melanoma, 25 (21%) two nodes, 21 (17.6%) three nodes and 31 (26.1%) had evidence of metastatic disease in four or more nodes.

Survival

The survival curve for all 142 patients is shown in Fig. 2. Median survival was 22 months with an overall 5 year survival of 26%. To date, 7 patients have survived for more than 10 years since lymphadenectomy. Table 2 shows the results of univariate analysis of the various clinical and histological prognostic indi-

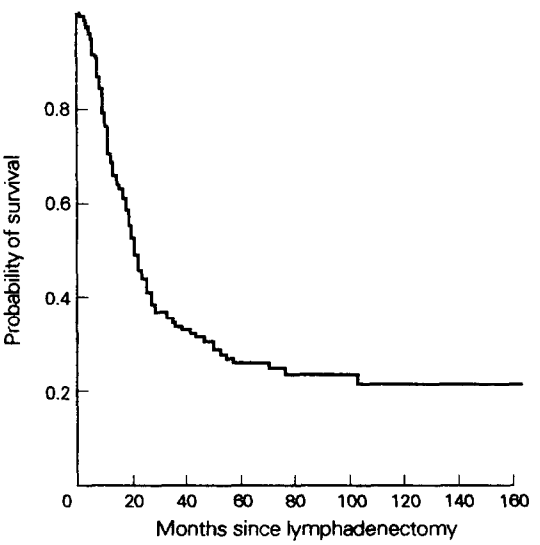

Fig. 2. Actuarial survival curve for all patients with clinical stage II melanoma ($n = 142$).

cators with significance of each factor tested first by the log-rank test and where appropriate by means of its individual inclusion as the only variable in the proportional hazards model.

Age. Survival was significantly and inversely related to age. This was most marked when survival figures for patients aged less than 40 years at the time of diagnosis (median 28 months: 5 years, 46%) were compared to those aged 40 years or over (median 18 months: 5 years, 19%). Younger females had the best overall prognosis: of 17 females aged less than 40, 10 (59%) have survived 5 years and all of these patients remain alive at a median follow-up time of 102 months (range 60–128).

Sex. In contrast to patients with primary melanoma, where females have a better prognosis, there was no significant difference in survival figures for males and females in this stage II population (Table 2).

Site of primary melanoma. There was a tendency for patients with primary tumours on the head and neck to have poorer 5 year survival (17%) than those with lesions at other sites but this was not statistically significant (Table 2).

Histogenetic type. Patients with superficial spreading melanomas tended towards a better overall prognosis with median and 5 year survival of 26 months and 36%, respectively. Corresponding figures for nodular lesions were 17 months and 22%. Of 16 patients with acral lentiginous or lentigo maligna melanoma, only 1 survived for 5 years. Overall, however, histogenetic type was not a significant prognostic variable.

Breslow thickness. (Table 2, Fig. 3) Patients with thick primary melanomas (≥ 3.5 mm) had a reduced survival (15% at 5 years) after node dissection when compared to those with thin (< 1.5 mm) and intermediate (1.5–3.49 mm) lesions combined (37% at 5 years). Paradoxically, however, 5 year survival for those with thin primary lesions (25%) was less than those with intermediate lesions (40%). There were 5 cases of stage II melanoma where the Breslow thickness was less than 0.76 mm and only one of these patients survived for 5 years.

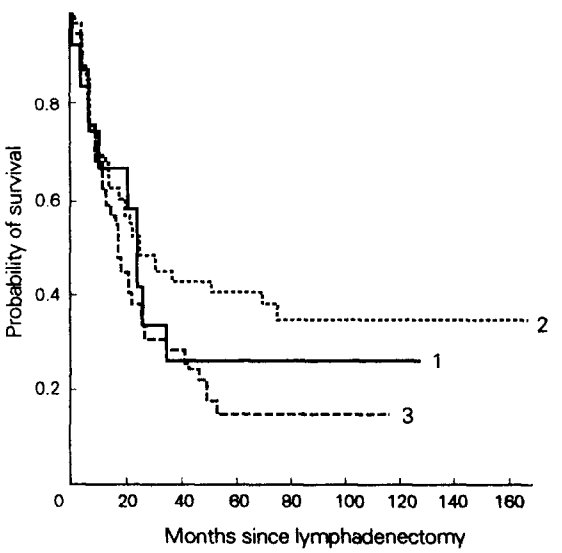

Fig. 3. Actuarial survival curve for patients with clinical stage II melanoma in relation to tumour thickness (*n* = 122). 1 = thin (< 1.5 mm), 2 = intermediate (1.5–3.49 mm) and 3 = thick (≥ 3.5 mm).

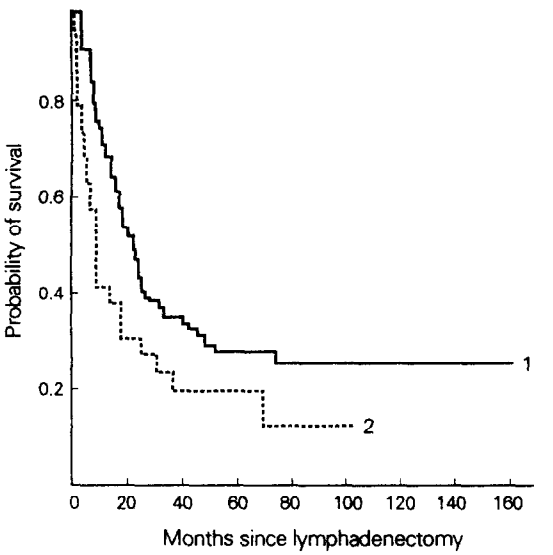

Fig. 4. Actuarial survival curve for patients with clinical stage II melanoma in relation to number of involved lymph-nodes (*n* = 119). 1 = 1–3 nodes and 2 = ≥ 4 nodes.

Clark level of invasion. Patients with level II, III and IV primary tumours had a similar 5 year survival (Table 2). Level V lesions, however, were associated with a very poor 5 year survival of only 13%.

Disease-free interval There was no significant difference in 5 year survival between patients who presented with synchronous (22%) or metachronous (27%) nodes. Patients with a disease-free interval between primary surgery and lymphadenectomy of 2 years or over, however, had a more than 2-fold greater 5 year survival (46%) compared with those who developed stage II disease less than 2 years after primary diagnosis (22%) (Table 2).

Number of malignant nodes. Survival was significantly related to the number of malignant nodes removed at lymphadenectomy (Table 2, Fig. 4). Median and 5 year survival were similar when

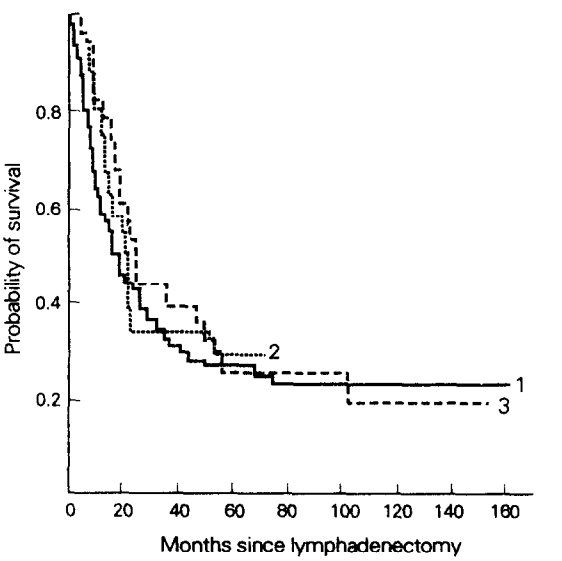

Fig. 5. Actuarial survival curve for patients with clinical stage II melanoma in relation to adjuvant therapy (*n* = 142). 1 = nil, 2 = BELD and 3 = other.

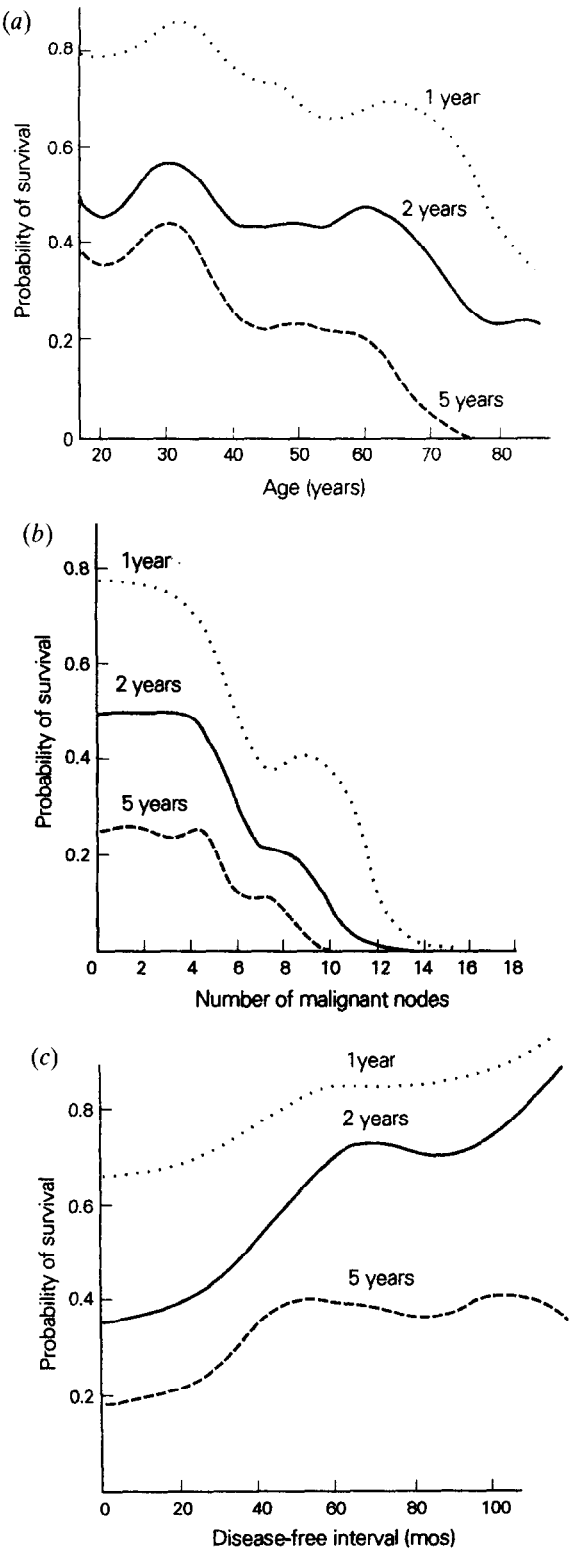

Fig. 6. Non-parametric logistic regression estimates of the probability of survival for 1, 2 and 5 years in relation to age (a), number of malignant nodes (b) and disease-free interval from primary to stage II disease (c).

1 or 2 nodes proved histologically positive. Patients with 4 or more positive nodes had a 2-fold decrease in median survival (11 vs. 23 months) and a significant decrease in 5 year survival (20% vs. 28.5%) when compared to the group with 1–3 nodes. In 25 patients there was evidence that the node capsule had been breached by melanoma. In no case, however, were large extranodal tumour deposits identified. Survival time in this group (median 15 months, 5 years 19.4%) tended to be poorer than in patients in whom the node capsule was intact (median 22 months, 5 years 28%). This, however, only reached borderline significance ($P = 0.08$, logrank test).

Adjuvant therapy. There was no evidence of a trend towards increased survival in patients who received adjuvant therapy after lymphadenectomy (Table 2, Fig. 5).

Multivariate analysis

Using the proportional hazards model with forward stepwise variable selection, only two factors, the number of malignant nodes and age proved significant and complementary determinants of survival. When the number of malignant nodes was excluded from the analysis, disease-free interval proved a marginally less significant replacement as a complement to age in predicting survival.

Additional confirmation of the importance of these three factors, even when unfettered by the restrictions of the proportional hazards model is shown in Fig. 6. This presents indications of the structural form (as estimated by non-parametric logistic regression) of the relation between the probability of survival for 1, 2 and 5 years and age (Fig. 6a), number of malignant nodes (Fig. 6b) and disease-free interval (Fig. 6c). It is clear that the probability of survival falls off between the age of 30–40 years and again at around 60 years. The prospect of survival in relation to number of malignant lymph-nodes shows a plateau until 4–5 nodes are involved, with a sharp decline thereafter (Fig. 6b). A virtual doubling of 5 year survival prospects occurs over a disease-free interval range of 24–48 months (Fig. 6c).

Contours of the probability of 5 year survival equal to 15%, 25% and 35% are shown in Fig. 7. These are based on a non-parametric logistic regression of the number of malignant nodes and age, and further emphasise the importance of these two prognostic factors. Again it is clear that to have a better chance of survival (i.e. > 35%) a patient has to be young and have few involved nodes.

DISCUSSION

This study demonstrates that over two thirds of melanoma patients who develop metachronous palpable regional nodal metastases do so within 2 years of treatment of their primary tumour. In addition, the first occurrence of regional nodal disease more than 5 years from primary diagnosis is uncommon (6.7%). This is in agreement with previous studies [2, 12].

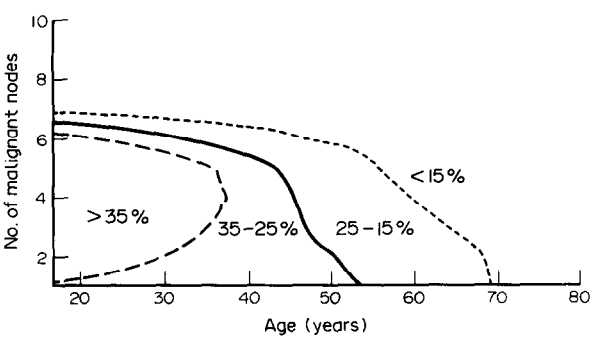

Fig. 7. Specific contours of the probability of 5-year survival based on non-parametric logistic regression on the number of malignant nodes and age.

The poor prognosis in patients with clinical stage IIb melanoma is confirmed, with an overall 5 year survival from the time of node dissection of 26%. This is within the range 13–38% reported by other authors for patients with clinical stage IIb disease [1–10, 12, 23, 26] (Table 1). 10 year survival figures, where available, vary considerably. In Balch *et al.*'s study [2] there were no 10 year survivors in the group with palpable metastatic nodes, while Roses *et al.* [4] and Fortner *et al.* [6] reported figures of 12% and 20%, respectively. Cohen *et al.* [5], on the other hand, reported a 50% 10 year survival in 52 patients with clinical stage II disease, and in Cascinelli *et al.*'s large series of 566 patients there was little difference between 5 year (33.4%) and 10 year (31.9%) survival [12].

There is consensus among most authors that the major determinant of survival in patients with stage II melanoma is the extent of nodal metastatic disease. On univariate analysis, reduced survival was associated with increasing numbers of involved nodes but the threshold varied from greater than 1 node [2, 6, 11], 2 nodes [3, 12], 3 nodes [1, 5, 9] or when more than 20% of excised nodes are involved [22]. Multivariate analysis has confirmed that the extent of nodal metastasis is the single most important prognostic indicator [2, 5, 9, 12] or at least a major contributor [1] to overall survival prospects. In the present study, using univariate analysis, the number of involved nodes was the most important determinant of survival. When 4 or more nodes were involved, median and 5 year survival (11 months and 20%) were significantly lower than in patients with 1–3 involved nodes (23 months and 28.5%). The number of malignant nodes was confirmed on multivariate analysis as the single most useful and significant predictor of survival. In addition, we have generated probability of survival curves for 1, 2 and 5 years after lymphadenectomy in relation to the number of involved nodes (Fig. 6b). It can clearly be seen that there is a plateau in the early phase when low numbers (< 4) of nodes are involved, survival falling off rapidly thereafter. Our results are consistent with other series which deal exclusively [9, 12] or predominantly [1] with clinical stage II patients in which multivariate analysis was used. There are, however, large differences between survival figures within each nodal subgroup. For example, 5 year survival in patients with 4 or more involved nodes was 2% [9] and 21% [1], while Cascinelli *et al.* reported a 26% 10 year survival in patients with 3 or more positive nodes [12]. In the latter series, the extent of nodal disease was more significant than the absolute number of involved nodes. In addition, when the node capsule was breached by melanoma, survival was significantly reduced [12]. In the present study the 25 patients in whom there was evidence that the node capsule had been breached had poorer survival, but this only reached borderline statistical significance ($P = 0.08$).

Several authors have stressed the importance of clinically detectable nodal metastases as a poor prognostic sign in stage II disease. In Roses *et al.*'s series [4], 5 and 10 year survival figures were more than halved when nodes were palpable prior to lymphadenectomy (5 year survival reduced from 44% to 21%; 10 year survival reduced from 28% to 12%). This agrees with earlier studies [5–7]. In contrast, in Balch *et al.*'s study, node palpability was of borderline significance and Callery *et al.* [1], Karakousis *et al.* [3] and Goldsmith *et al.* [23] showed no reduction in survival in patients with clinical in comparison to those with pathological stage II disease. There are subtle differences between these studies. In some [4, 6, 7], lymphadenectomy was performed at the time of primary diagnosis and survival calculated from this time. In others, patients who had undergone lymphadenectomy either synchronously or metachronously were included and survival calculated from the time of primary diagnosis [2] or from node dissection [1, 3]. Moreover, in studies showing no significant effect of node palpability on survival, the proportion of patients with clinical stage I, pathological stage II disease, was small: 9.6% [3], 11% [23] and 19.6% [1]. Veronesi *et al.* [10], in a large prospective randomised trial including 54 patients undergoing elective and 64 patients having delayed therapeutic lymphadenectomy, showed that node palpability is associated with reduced survival when calculated from the time of node dissection but not from the time of primary diagnosis. It seems clear that patients with clinical stage II disease have a poorer prognosis than their pathological counterparts, and that node palpability correlates with the extent of nodal disease [5, 6]. Indeed, on this basis Day and colleagues [24] have emphasised that patients with stage II melanoma should be analysed separately, according to clinical stage.

In the present study, the only other significant additional indicator of survival on multivariate analysis was age, with reduced survival in older patients. This has not been seen in previous studies. In our survival analysis we have been careful to include only patients who died of melanoma. Indeed, the 9 patients who died of other or unknown causes had a mean age of 70 years and if they had been included would have made age a much more significant determinant of survival. Why age should be significant in our series and not in others is unclear. The median age of 51 with a range of 18–87 years is similar to other studies [1–3, 9]. Possibilities include a tendency towards less aggressive surgery in the elderly or that they had a higher prevalence of occult disease.

Combining the two major determinants of survival, the best prognosis was seen in patients under 40 years of age with 1–3 involved nodes (median 28 months; 5 year survival 46%). In patients aged 40 or over with 4 or more involved nodes, median survival was 11 months and 5 year survival 10.5%.

Some previous series [1, 2] reported a trend towards improved survival when the disease-free interval between primary diagnosis and detection of stage II disease exceeded 2 years. In the present study, duration of disease-free interval was highly significant when considered alone. However, using multivariate analysis, it was the third most important prognostic factor after number of involved nodes and age. In this model, it provided little additional prognostic information.

Although most reported series agree that the prime determinant of survival for patients with stage II melanoma relates to features of stage II disease and in particular extent of nodal metastatic disease, in some studies, features of the primary melanoma retained prognostic significance. These include Breslow thickness of the tumour [1, 4, 9, 12], Clark level of invasion [4, 9, 12], ulceration [1, 2], histogenetic type [12] and site [5, 6]. In studies dealing exclusively or predominantly with clinical stage II disease, and using multivariate analysis to examine the results, the only features of stage I disease which retained prognostic value were Breslow thickness [1] and type of primary tumour [12].

Our study shows none of these factors to be significant either as a single variable or on multivariate analysis. It is well established that the most important prognostic feature in stage I melanoma is the Breslow thickness [25]. Day and colleagues [24] have shown that tumour thickness retains its prognostic significance in clinical stage I, pathological stage II melanoma. They argue that once clinical stage II is reached, the extent of

nodal disease predominates and features of the primary lesion no longer have an effect on survival. This is sound reasoning, and would explain why tumour thickness was not a significant factor in the studies by Cohen *et al.* [5] and Balch *et al.* [2], both of which had a high proportion of clinical stage II patients. It does not, however, explain the findings of Callery and colleagues [1], who found Breslow thickness to be the most important factor ($P = 0.001$) in a series of 150 patients of whom 80.4% had palpable nodal disease.

Of the 142 patients in the present study, 52 received adjuvant therapy (25 BELD, 27 monotherapy). There was no significant benefit in survival terms in the adjuvant therapy groups whether analysed separately or together. These results are in agreement with previous studies [13], showing no benefit of adjuvant chemotherapy, immunotherapy or both.

This study represents one of the largest series of patients with clinical stage II melanoma. Its strengths are that it comes from a single centre where a uniform surgical approach is used, good and comprehensive clinical and pathological data are available, and all patients have been followed up for at least 5 years. Moreover, elegant and appropriate statistical analysis has been used. It has shown that, in addition to the number of involved lymph-nodes, age is a significant determinant of survival in clinical stage II disease. In conclusion, we suggest that future adjuvant studies in patients with stage II melanoma after lymphadenectomy should be stratified for age as well as the extent of nodal disease. Although we must continue our strategy aimed at early detection and prevention of malignant melanoma, only by carefully controlled clinical trials may we improve on the current 26% 5 year survival for those unfortunate patients who have already progressed to stage II disease.

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