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# Development and validation of a prognostic scale for use in patients with advanced cancer

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The aim of this study was to develop a new prognostic indicator to help predict survival in advanced cancer patients more accurately. Data on 329 patients obtained from a multi-centre study in London were analysed. A multifactorial Cox regression model was applied and validated using bootstrapping techniques. Predictive scores were calculated and used to produce a new prognostic index. The value of the index in predicting 14-day survival was then assessed. Four variables were found to be associated with worse survival: primary lung cancer, secondary liver cancer, raised C-Reactive protein and poor performance status (ECOG 4). Survival curves showed that patients designated as 'high' risk by the resulting index had significantly shorter survival than those designated as 'low' risk. A high score on the newly derived prognostic index is associated with poorer survival, but its clinical utility is limited by the relatively low predictive probability of the score. *Palliative Medicine* (2008); **22**: 711–717

**Key words:** neoplasms; palliative care; prognosis; survival; terminal care; theoretical models

## Introduction

Patients want to have access to accurate prognostic information.[1,2] Improved prognostication may also facilitate better patient care, giving patients the ability to make better informed choices about treatment.[3] Prognostic information may help patients to make better use of the time remaining to them, and may give them the opportunity to make appropriate preparations for their own impending death.[4] Conversely, inaccurate prognostic information may cause problems for patients and their families as well as difficulties in providing appropriate care. In particular, over-optimism by health professionals about survival may contribute to late referral to palliative care services,[5] and evidence suggests that both patients and their families may later regret being over-optimistic about the patient's chances of survival.[6,7]

Unfortunately, health care professionals tend to be unreliable in their estimation of survival in this group of patients,[7,8] and rather than being randomly inaccurate, clinical predictions have been found to be systematically over-optimistic.[9] In a recent study, this over-optimism was found not only to be due to physicians' desire to communicate an optimistic message to their patients but also to a genuine belief that survival would be longer.[8] Patients' own estimates of their survival have been shown to be even more over-optimistic than those of physicians.[9]

Systematic reviews[10–12] have identified many putative prognostic factors in patients with advanced cancer, including clinician estimates of survival, performance status, clinical and demographic variables and haematological and biochemical parameters. Some groups have attempted to construct prognostic scales using different combinations of these variables.[13–19] However, these scores tend to suffer from problems such as relying heavily on clinician estimates of prognosis[14] or a lack of independent validation.[13,18] One such prognostic scale is the serum vitamin $B_{12}$/C-Reactive Protein (CRP) Index (BCI). The BCI was originally developed in a cohort of elderly Swiss patients with advanced cancer,[17] and its validity has subsequently been assessed by members of our own group in an independent cohort of UK palliative care patients.[20] As part of this validation study, we collected additional data that we hypothesised would be of further prognostic significance. In particular, we wished to investigate whether the inclusion of data on ECOG performance status in a revised prognostic scale would result in more accurate survival estimates.

## Patients and methods

This study represents a secondary analysis of data collected for the primary purpose of validating the serum

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vitamin $B_{12}$/CRP index (BCI). Data relating to the validation of the BCI have been presented in a separate article.[20]

The study was approved by the Trent Multi Centre Research Ethics Committee. Patients were recruited prospectively between 21st January 2002 and 8th March 2005 and were followed up until death or for a minimum of 90 days after the last patient was recruited. Patients were recruited from seven centres in London, UK (St George's Hospital NHS Trust, Royal Marsden NHS Foundation Trust, Trinity Hospice, St Christopher's Hospice, St Helier Hospital, Princess Alice Hospice and the Sam Beare Unit). The inclusion criteria were that patients should be at least 18 years old, be able to provide written consent, have locally advanced or metastatic cancer, no longer be undergoing disease-modifying treatments and be under the care of a specialist palliative care team. Exclusion criteria were the receipt of vitamin $B_{12}$ injections in the previous 2 years, and previous or current disease of the terminal ileum or pernicious anaemia (both of which may affect serum vitamin $B_{12}$ levels). Because of financial and practical constraints, it was not possible to recruit a consecutive series of patients to this study.

After providing written and informed consent, the following data were obtained from each patient:

- serum vitamin $B_{12}$ and CRP levels obtained from a 10 mL venous specimen of blood
- Eastern Co-operative Oncology Group (ECOG) performance status scores
- age
- gender
- primary diagnosis
- sites of metastases

### Statistical methods

The continuous variables (age, Vitamin $B_{12}$ and CRP) were recoded as categorical variables. The categories were generated using the quartiles of the distributions to produce three categories per variable, the cut-offs being equal to the lower and upper quartiles. Each variable was tested unifactorially using Log Rank $\chi^2$ analysis to determine its relationship with survival. All variables significant at the 10% level in these analyses were then retained to develop a multifactorial model in the form of a stepwise Cox regression. To validate the variable selection for this prognostic model, a bootstrap analysis was undertaken.[21,22] Bootstrapping is a resampling procedure involving taking repeated samples with replacement from the dataset. In this analysis, 1000 replications were used, each representing a new resampling from the dataset. The robustness of the variable selection was assessed according to the percentage of replications in which each variable was selected for inclusion in the multifactorial model. The bootstrap model was also used to estimate robust hazard ratios and bias-corrected 95% confidence intervals (CI) for the variables found to be predictive, and again 1000 replications were used. These hazard ratios and 95% CI's were then compared with those obtained from the original multifactorial Cox regression to assess their robustness.

Finally, a prognostic index was developed by deriving a score for each prognostic variable using the unbootstrapped hazard ratio estimates. Each hazard ratio was divided by the smallest hazard ratio and rounded up to the nearest 0.5 to produce a weighted 'partial score'. The value of these scores in predicting 14-day survival was then assessed in the same group of patients. This time period was judged to be clinically useful as it is commonly used as a clinical guide for determining which patients would be most suitable for a 'terminal care' admission to a hospice unit in the United Kingdom. The unifactorial analysis was carried out in SPSS v14 for Windows (SPSS Inc., Chicago, Illinois, USA), the remaining analyses in Stata v9.2 for Unix (StataCorp LP, College Road, Texas, USA).

## Results

A total of 379 patients were recruited into the original BCI validation study,[20] but 50 of these had incomplete datasets and were therefore excluded. Consequently, 329 patients were included in the final analyses. Disease-related and basic demographic variables are shown in Table 1. No survival data were available for nine patients, and data for these subjects were censored at the last date that they were known to be alive.

The unifactorial analyses showed that CRP, ECOG performance status, gender, primary lung cancer, primary breast cancer and secondary liver cancer were all associated with survival at the 10% significance level (see Table 2). These variables were, therefore, entered into a multifactorial stepwise Cox regression analysis, with performance status and the categorised CRP entered as a series of dummy variables. Since only few patients had a performance status of 0, the lowest two categories (ECOG 0 and 1) were combined. The significance level for entry to and removal from the model was set at 10%.

The results of the multifactorial analyses showed that gender, primary breast cancer and performance status 2 and 3 were not significant at the 10% level and were therefore dropped from the model. The remaining variables significant at the 10% level were performance status 4 (indicating the poorest performance status), a diagnosis of primary lung cancer, the presence of liver metastases and raised CRP (both dummy variables). These variables were subsequently included in a bootstrap analysis undertaken to validate the multifactorial model.

**Table 1** Summary of patient characteristics

| | Number of patients |
|---|---|
| Gender | |
| Male | 172 |
| Female | 157 |
| Age in years | |
| 18–29 | 1 |
| 30–39 | 3 |
| 40–49 | 19 |
| 50–59 | 61 |
| 60–69 | 83 |
| 70–79 | 102 |
| 80–89 | 55 |
| 90–99 | 5 |
| ECOG performance status | |
| 0 | 6 |
| 1 | 38 |
| 2 | 74 |
| 3 | 155 |
| 4 | 54 |
| Missing | 2 |
| Primary tumour site[a] | |
| Neurological | 6 |
| Head and neck | 8 |
| Lung | 83 |
| Urological | 58 |
| Haematological | 17 |
| Upper GI | 34 |
| Lower GI | 51 |
| Gynaecological | 27 |
| Breast | 32 |
| Rare tumour groups | 24 |
| Unknown | 9 |
| Number of sites of metastases | |
| None | 20 |
| One | 143 |
| More than one | 136 |
| Unknown | 30 |
| Clinical evidence of infection? | |
| Yes | 80 |
| No | 237 |
| Not recorded | 12 |

[a]Figures do not sum to 329 because some subjects had more than one primary tumour.

When the bootstrap analysis was undertaken, the percentage of replications in which each variable was included varied considerably, although all the variables previously significantly associated with survival were included in more than 60% of the replications (see Table 3). The percentage of times that each variable was included in the model varied from 63.3% for performance status 4 to 99.7% for the highest quartile of CRP (a CRP score of >136 mg/L) and indicated that all the previously included variables were still associated with survival. The bootstrap estimates of the hazard ratios for the prognostic model were little different from the original estimates calculated using the Cox regression technique (see Table 3). However, all the bootstrap hazard ratios were slightly larger and had slightly wider CI's.

When the potential prognostic variables were allocated a 'partial score' using their un-bootstrapped hazard ratio estimates, all predictive variables were calculated to have a 'partial score' of 1 apart from the highest quartile of CRP, which was allotted a score of 2 (Table 4). To calculate the total prognostic score, a clinician should sum all the partial scores. This would mean that, for example, if a patient had a performance status of 4, a CRP of 180 mg/L and liver metastases, they would have a total prognostic score of 4. Alternatively, if a patient had a performance status of 3, a CRP of 11 mg/L and a diagnosis of primary lung cancer, they would have a prognostic score of 1. Therefore, prognostic scores could range from 0 (none of the prognostic features) to 5 (performance status of 4, CRP of >136 mg/L, primary lung cancer and liver metastases).

Two different cut-offs were assessed for their ability to identify 'high' and 'low' risk groups in terms of being able to predict death within 14 days. When a cut-off point of ≥2 on the scale was used to separate patients into 'high' and 'low' risk groups, the sensitivity of the test was found to be 70.0%, but the specificity was only 48.8%. Increasing the cut-off point to ≥3 resulted in a greater specificity (83.9%) but a lower sensitivity (35.7%); therefore, the cut-off of 2 was retained. Survival curves (Figure 1) of the high- and low-risk groups showed that the two groups were significantly (Log rank statistic = 37.8, $P < 0.001$) different from one another. Median survival for the low-risk group was 72 days (95% CI 48.0–96.0), and for the high-risk group was 28 days (95% CI 22.8–49.2).

## Discussion

The purpose of this study was to develop and validate a new prognostic tool for use in palliative care patients. We have reported that a readily obtainable blood test (the CRP) when combined with some basic details about disease sites and performance status can be used to divide palliative care patients into 'high' risk and 'low' risk groups with respect to survival. Those patients with the best prognostic scores have a median survival of 72 days and those patients with the worst scores only have a median survival of 28 days. This prognostic scale has been validated using bootstrap methods that have confirmed the robustness of the variable selection and the magnitude of the associated hazard ratios and CI's. Previous palliative care prognostic indices have been validated using a two-step approach.[13,18] In this approach, a model is first developed in one population (the training set) and is subsequently validated in a second population (the testing set). On the contrary, bootstrap validation uses the entire dataset in the model development and has been found to be more reliable than the training-and-test method for the purposes of model building.[23] It is a computer resource-intensive approach, but has the advantage

**Table 2** Unifactorial survival analysis of potential prognostic variables

| | % | Median survival (days) | 95% CI | $\chi^2$ | *P* value |
|---|---|---|---|---|---|
| Potential prognostic variables | | | | | |
| Age | | | | | |
| ≤60 | 25.5 | 34 | 17.8–50.2 | 0.52 | 0.771 |
| 61–77 | 48.8 | 43 | 31.4–54.6 | | |
| ≥78 | 25.8 | 41 | 30.4–51.6 | | |
| C-Reactive Protein (CRP) | | | | | |
| (≤23 mg/L) | 24.9 | 72 | 36.2–107.8 | 31.3 | 0.000 |
| (23.1–136 mg/L) | 50.5 | 41 | 30.6–51.4 | | |
| (≥136.1 mg/L) | 24.6 | 26 | 21.1–30.9 | | |
| Serum Vitamin B12 | | | | | |
| (<323 pg/mL) | 25.2 | 54 | 30.3–77.7 | 2.1 | 0.350 |
| (323–540 pg/mL) | 49.8 | 42 | 31.9–52.1 | | |
| (>540 pg/mL) | 24.9 | 31 | 18.7–43.3 | | |
| ECOG performance status | | | | | |
| PS0&1 | 13.5 | 62 | 36.3–87.7 | 8.84 | 0.032 |
| PS2 | 22.6 | 46 | 31.1–60.9 | | |
| PS3 | 47.4 | 41 | 31.8–50.2 | | |
| PS4 | 16.5 | 26 | 15.2–36.8 | | |
| Gender | | | | | |
| Female | 47.7 | 48 | 37.4–58.6 | 9.50 | 0.002 |
| Male | 52.3 | 35 | 25.7–44.3 | | |
| Primary site (brain) | | | | | |
| Yes | 1.8 | 41 | 33.9–48.1 | 0.43 | 0.511 |
| No | 98.2 | 72 | 0.0–157.2 | | |
| Primary site (head and neck) | | | | | |
| Yes | 2.4 | 20 | 0.0–40.8 | 2.53 | 0.112 |
| No | 97.6 | 42 | 33.9–50.1 | | |
| Primary site (lung) | | | | | |
| Yes | 24.9 | 29 | 20.2–37.8 | 7.55 | 0.006 |
| No | 75.1 | 47 | 39.5–54.5 | | |
| Primary site (urological) | | | | | |
| Yes | 17.6 | 46 | 40.1–52.0 | 0.07 | 0.793 |
| No | 82.4 | 40 | 31.6–48.5 | | |
| Primary site (haematological) | | | | | |
| Yes | 5.5 | 62 | 28.7–95.3 | 1.54 | 0.214 |
| No | 94.5 | 40 | 33.3–46.7 | | |
| Primary site (upper gastro-intestinal) | | | | | |
| Yes | 10.3 | 35 | 23.0–47.0 | 1.22 | 0.269 |
| No | 89.7 | 43 | 35.0–51.0 | | |
| Primary site (lower gastro-intestinal) | | | | | |
| Yes | 15.2 | 40 | 29.6–50.4 | 0.10 | 0.752 |
| No | 84.8 | 43 | 34.5–51.5 | | |
| Primary site (gynaecological) | | | | | |
| Yes | 8.2 | 93 | 38.4–147.6 | 0.81 | 0.368 |
| No | 91.8 | 40 | 33.3–46.7 | | |
| Primary site (breast) | | | | | |
| Yes | 9.7 | 51 | 39.1–63.0 | 3.93 | 0.047 |
| No | 90.3 | 40 | 32.8–47.2 | | |
| Primary site (rare tumour) | | | | | |
| Yes | 7.3 | 28 | 2.8–53.2 | 0.01 | 0.935 |
| No | 92.7 | 42 | 33.9–50.1 | | |
| Secondary site (liver) | | | | | |
| Yes | 24.6 | 31 | 17.5–44.5 | 6.43 | 0.011 |
| No | 75.4 | 47 | 37.3–56.7 | | |
| Secondary site (lung) | | | | | |
| Yes | 22.8 | 37 | 23.1–51.0 | 0.03 | 0.856 |
| No | 77.2 | 43 | 33.8–52.2 | | |
| Secondary site (brain) | | | | | |
| Yes | 7.6 | 37 | 23.5–50.5 | 0.13 | 0.723 |
| No | 92.4 | 42 | 33.9–50.1 | | |
| Secondary site (bone) | | | | | |
| Yes | 36.8 | 44 | 32.1–55.9 | 1.32 | 0.252 |
| No | 63.2 | 40 | 32.2–47.8 | | |
| Secondary site (lymph node) | | | | | |
| Yes | 20.1 | 33 | 7.0–59.0 | 0.04 | 0.838 |
| No | 79.9 | 42 | 35.3–48.7 | | |

*(continued)*

**Table 2** *(continued)*

| | % | Median survival (days) | 95% CI | $\chi^2$ | *P* value |
|---|---|---|---|---|---|
| Single metastases | | | | | |
| Yes | 43.5 | 47 | 37.1–56.9 | 0.02 | 0.897 |
| No | 56.5 | 37 | 26.1–47.9 | | |
| Multiple metastases | | | | | |
| Yes | 41.6 | 35 | 23.8–46.2 | 0.78 | 0.379 |
| No | 58.4 | 48 | 38.0–58.1 | | |
| Number of metastases | | | | | |
| None | 14.9 | 54 | 9.7–98.3 | 1.30 | 0.523 |
| Single | 43.5 | 47 | 37.1–57.0 | | |
| Multiple | 41.6 | 35 | 23.8–46.2 | | |

**Table 3** Bootstrap validation of model including percentage of replications in which each variable was included in the model, and comparison of original and bootstrapped hazard ratios (with 95% CI's)

| Variable | % of replications included | Cox regression hazard ratios (95% CI) | Bootstrapped hazard ratios (95% CI) |
|---|---|---|---|
| Secondary liver cancer | 83.4 | 1.45 (1.12, 1.92) | 1.47 (1.11, 1.93) |
| ECOG PS = 4 | 63.3 | 1.33 (0.98, 1.80) | 1.36 (0.90, 1.91) |
| CRP 23.1–136 (middle 50%) | 87.3 | 1.52 (1.14, 2.03) | 1.53 (1.11, 2.01) |
| CRP >136 (highest quartile) | 99.7 | 2.39 (1.70, 3.35) | 2.45 (1.63, 3.37) |
| Primary lung cancer | 67.5 | 1.37 (1.06, 1.78) | 1.38 (1.02, 1.79) |

of providing protection against over-fitting of the data associated with variable selection in model building.

Although the survival curves and median survival figures for the high- and low-risk patients in our study were significantly different, the clinical usefulness of the prognostic score is less certain. A common clinical scenario in palliative care practice is the decision whether or not to admit a patient to an inpatient hospice unit for terminal care. Although this decision will be based on a number of factors (including symptom burden, patient dependency and the need for family and carer support), one of the considerations that needs to be taken into account is the expected survival. Patients expected to survive less than 2 weeks are more likely to be offered an inpatient bed than patients with a prognosis of 'months'. Of the 182 patients in our study who scored 2 or greater on the prognostic scale, only 51 actually died within 2 weeks. The positive predictive value (PPV) of the test in this population is therefore only 28%. However, of the 147 patients scoring less than 2 on our prognostic scale, 125 actually survived for more than 2 weeks. Thus, the negative predictive value (NPV) of the score is 85%. This means that our prognostic scale would have more value for identifying those patients *not* suitable for hospice admission (at least on the grounds of estimated survival) than it would have for positively identifying those patients with a poor prognosis. Even using a cut-off of ≥3 only results in a PPV of 39%.

**Table 4** Scores for component variables of prognostic index and relationship between total score and survival

| | Present | Absent |
|---|---|---|
| Primary lung cancer | 1 | 0 |
| Secondary liver cancer | 1 | 0 |
| CRP 23–136 mg/L | 1 | 0 |
| CRP > 136 mg/L | 2 | 0 |
| ECOG PS = 4 | 1 | 0 |
| Total score is calculated as sum of partial scores | | |
| Interpretation of scores | | |
| | | Median survival |
| Score <2 | | 72 days |
| Score ≥2 | | 28 days |

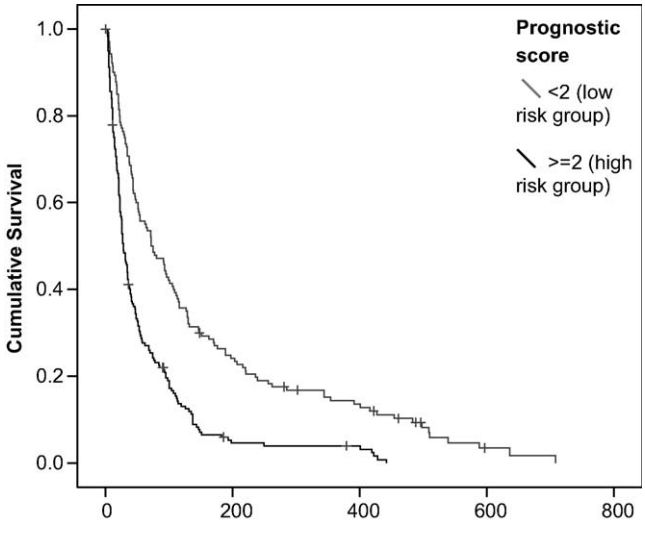


**Figure 1** Kaplan–Meier survival curve comparing high- and low-risk groups.

There were a number of limitations to our study. Only relatively few variables were included in our model development stage. This was because the primary aim of the project had not been to create a new prognostic index as such, but to validate the previously proposed $B_{12}$/CRP index in an independent cohort of patients.[20] We wished to test the hypothesis that inclusion of information about performance status and diagnosis would lead to a better prognostic scale. Performance status has previously been reported to be a significant predictor of poor survival in patients with advanced cancer.[10,11] Information on diagnosis and performance status is nearly always routinely recorded in oncology clinical practice and we reasoned that it would be relatively quick and easy to use a palliative prognostic index that only relied upon such readily available clinical information. Indeed, it is likely that our prognostic scale could be applied to most patients currently referred to UK hospice units without the need to request any additional tests or assessments from the referring clinicians. However, by focussing on such a small number of variables, our prognostic model is likely to be much less accurate than it could have been if it had been developed using a dataset including more potential prognostic indicators. Previous reviews have identified at least 30 such indicators[10–12] that should be investigated in future prognostic studies. We are currently undertaking a national UK study to develop a prognostic scale using these variables as the starting point for model development.

Another limitation of our study was the failure to recruit a consecutive series of patients. Undertaking multi-centre studies in palliative care patients is notoriously difficult.[24] This study was unfunded and thus data collection relied upon research nurses and clinical staff in recruiting centres identifying eligible patients. Inevitably, in the absence of key clinical staff or outside of normal working hours, eligible patients were missed. The study population, therefore, represents a convenience sample. Although it would have been methodologically much more robust to have recruited a consecutive series of patients, this is not an easy methodological problem to overcome. Research infrastructure in palliative care is quite limited and most recruiting centres did not have dedicated research staff. Even those that did have such staff did not have dedicated 'cover' arrangements to deal with periods of sickness absence or annual leave. To recruit a consecutive series of patients, it would have been necessary to have staff available to recruit patients every day of the year, and this would have entailed an unreasonable financial cost and/or administrative burden on clinical staff.

The convenience nature of our sample makes it likely that the patients included in our study had a better prognosis than the 'average' palliative care patient. A further reason to suppose that the patients in our study were not typical of palliative care patients more generally was the requirement for written informed consent before patients were entered into the research. There is a high prevalence of cognitive impairment among palliative care inpatients and evidence suggests that confusion is a poor prognostic sign.[10–12] There are many practical and ethical issues surrounding the recruitment of patients into clinical trials without obtaining informed consent, and it was not possible to satisfactorily overcome these problems in the original study. Future studies should endeavour to recruit patient populations that more closely resemble the type of patients seen in day-to-day palliative care practice.

In this study, we have reported that a simple blood test, when combined with some readily available clinical information, can provide valuable prognostic information for patients with advanced cancer. However, further research is urgently needed to improve upon existing prognostic scales. Our own group is currently undertaking a multicentre prospective study involving 1200 patients over 2 years. This study will be adequately resourced to overcome some of the methodological limitations described above, and will investigate the prognostic significance of key variables identified in previous systematic reviews.

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**Conflict of interest statement**

None declared.

## References

1 Blanchard, CG, Labrecque, MS, Ruckdeschel, JC, Blanchard, EB. Information and decision-making preferences of hospitalized adult cancer patients. *Soc Sci Med* 1988; **27**: 1139–1145.

2 Degner, LF, Kristjanson, LJ, Bowman, D, Sloan, JA, Carriere, KC, O'Neil, J, *et al*. Information needs and decisional preferences in women with breast cancer. *JAMA* 1997; **277**: 1485–1492.

3 Den Daas, N. Estimating length of survival in end-stage cancer: a review of the literature. *J Pain Symptom Manage* 1995; **10**: 548–555.

4 Forster, LE, Lynn, N. Predicting life span for applicants to inpatient hospice. *Arch Intern Med* 1988; **148**: 2540–2543.
5 The, AM, Hak, T, Koeter, G, van der Wal, G. Collusion in doctor-patient communication about imminent death: an ethnographic study. *BMJ* 2000; **321**: 1376–1381.
6 Christakis, NA, Lamont, EB. Extent and determinants of error in doctors' prognoses in terminally ill patients: prospective cohort study. *BMJ* 2000; **320**: 469–472.
7 Glare, P, Virik, K, Jones, M, Hudson, M, Eychmuller, S, Simes, J, *et al*. A systematic review of physicians' survival predictions in terminally ill cancer patients. *BMJ* 2003; **327**: 195 10.1136/bmj.327.7408.195.
8 Lamont, EB, Christakis, NA. Prognostic disclosure to patients with cancer near the end of life. *Ann Intern Med* 2001; **134**: 1096–1105.
9 Weeks, JC, Cook, EF, O'Day, SJ, Peterson, LM, Wenger, N, Reding, D, *et al*. [comment][erratum appears in JAMA 2000 12; 283: 203] Relationship between cancer patients' predictions of prognosis and their treatment preferences. *JAMA* 1998; **279**: 1709–1714.
10 Vigano, A, Dorgan, M, Buckingham, J, Bruera, E, Suarez-Almazor, ME. Survival prediction in terminal cancer patients: a systematic review of the medical literature. *Palliative Med* 2000; **14**: 363–374.
11 Maltoni, M, Caraceni, A, Brunelli, C, Broeckaert, B, Christakis, N, Eychmueller, S, *et al*. Prognostic factors in advanced cancer patients: evidence-based clinical recommendations – a study by the Steering Committee of the European Association for Palliative Care. *J Clin Oncol* 2005; **23**: 6240–6248.
12 Stone, P, Lund, S. Predicting prognosis in patients with advanced cancer. *Ann Oncol* 2007; **18**: 971–976.
13 Bruera, E, Miller, MJ, Kuehn, N, MacEachern, T, Hanson, J. Estimate of survival of patients admitted to a palliative care unit: a prospective study. *J Pain Symptom Manage* 1992; **7**: 82–86.
14 Maltoni, M, Nanni, O, Pirovano, M, Scarpi, E, Indelli, M, Martín, C, *et al*. Successful validation of the palliative prognostic score in terminally ill cancer patients. Italian Multicenter Study Group on Palliative Care. *J Pain Symptom Manage* 1999; **17**: 240–247.
15 Morita, T, Tsunoda, J, Inoue, S, Chihara, S. The Palliative Prognostic Index: a scoring system for survival prediction of terminally ill cancer patients. *Support Care Cancer* 1999; **7**: 128–133.
16 Pirovano, M, Maltoni, M, Nanni, O, Marinari, M, Indelli, M, Zaninetta, G, *et al*. A new palliative prognostic score: a first step for the staging of terminally ill cancer patients. Italian Multicenter and Study Group on Palliative Care. *J Pain Symptom Manage* 1999; **17**: 231–239.
17 Geissbuhler, P, Mermillod, B, Rapin, CH. Elevated serum vitamin B12 levels associated with CRP as a predictive factor of mortality in palliative care cancer patients: a prospective study over five years. *J Pain Symptom Manage* 2000; **20**: 93–103.
18 Yun, YH, Heo, DS, Heo, BY, Yoo, TW, Bae, JM, Ahn, SH. Development of terminal cancer prognostic score as an index in terminally ill cancer patients. *Oncol Rep* 2001; **8**: 795–800.
19 Chuang, R-B, Hu, W-Y, Chiu, T-Y, Chen, C-Y. Prediction of survival in terminal patients in Taiwan: constructing a prognostic scale. *J Pain Symptom Manage* 2004; **28**: 115–122.
20 Kelly, L, Stone, P, White, S. The B12 / CRP index (BCI) as a simple prognostic indicator in patients with advanced cancer: a confirmatory study. *Ann Oncol* 2007; **18**: 1395–1399.
21 Chen, CH, George, SL. The bootstrap and identification of prognostic factors via Cox's proportional hazards regression model. *Stat Med* 1985; **4**: 39–46.
22 Schumacher, M, Hollander, N, Sauerbrei, W. Resampling and cross-validation techniques: a tool to reduce bias caused by model building. *Stat Med* 1997; **16**: 2813–2827.
23 Brunelli, A, Rocco, G. Internal validation of risk models in lung resection surgery: Bootstrap versus training-and-test sampling. *J Thorac Cardiovasc Surg* 2006; **131**: 1243–1247.
24 Ling, J, Hardy, J, Penn, K, Davis, C, Kreeger, L. The recruitment difficulties in palliative care clinical trials. *Palliat Med* 1997; **10**: 68–69.