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Prognostic significance of symptoms of hospitalised advanced cancer patients ☆

Saskia C. Teunissen[a,*], *Alexander de Graeff*[a], *Hanneke C. de Haes*[b], *Emile E. Voest*[a]

[a]*Department of Medical Oncology, University Medical Centre, F02.126, P.O. Box 85500, 3508 GA Utrecht, The Netherlands*
[b]*Department of Medical Psychology, Academic Medical Centre, Amsterdam, The Netherlands*

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ABSTRACT

Purpose: To assess the prognostic value of symptoms in hospitalised advanced cancer patients.

Patients and methods: A prospective analysis was performed of 181 hospitalised patients referred to a Palliative Care Team. Comprehensive symptom questionnaire, functional status, estimated life expectancy and survival were assessed. Using a Cox regression model, a predictive survival model was built.

Results: Median survival: 53 d. Median number of symptoms: 4; 20 symptoms occurred in $\geqslant$10%. Multivariate analysis showed nausea, dysphagia, dyspnoea, confusion and absence of depressed mood as independent prognostic factors for survival ($p < 0.05$) with relative risks of dying of 1.96, 1.81, 1.79, 2.35 and 1.79, respectively. Patients with 2, 3 or 4 of these factors at the same time had a relative risk of dying of 2.7, 2.1 and 9.0, respectively.

Conclusion: A cluster of factors comprising nausea, dysphagia, dyspnoea, confusion and absence of depressed mood may be used to accurately predict survival in hospitalised advanced cancer patients.

1. Introduction

'How long do I still have?' is one of the most challenging questions that oncologists have to address when dealing with a patient with advanced cancer. In daily practice this question is answered by estimating the prognosis. Clinical predictions are traditionally based on performance status and symptom prevalence.[1–3] The physician-estimated prognosis also depends on the experience of the clinician who is confronted with the question.[4]

The accuracy of the estimated survival and actual survival has been studied by several groups.[5–8] Between 1995 and 2005 four systematic reviews of physicians' survival predictions were published.[9–12] The complexity of the process of estimating survival is reflected in the frequently reported overestimation of expected survival by medical doctors[1–6,13–15] and sometimes in the underestimation[3,11] thereof. Although performance status together with symptoms of the 'the terminal cancer syndrome'[16] is recommended to guide physicians in predicting survival of patients with advanced disease, the complexity of the disease in the final stages of life is illustrated by the variance of symptoms found to be indicative of survival.

A large number of studies have shown a high prevalence of debilitating symptoms in patients with advanced disease.[13,16–24] To develop a symptom-based assessment of survival, functional status and frequently occurring symptoms were correlated with survival in several studies.[1,3,6–8,13–16,25–29]

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* *Corresponding author*: Tel.: +31 613393609; fax: +31 302506230.
E-mail addresses: saskia.teunissen@12move.nl, S.Teunissen@umcutrecht.nl (S.C. Teunissen).

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Poor performance status (Karnofsky Performance Scale) was found to be the most significant clinical indicator in these studies.[1,6–8,13,14,16,25–27] Furthermore, a small number of specific symptoms such as shortness of breath in rest,[7,14,16,27,28,30] dysphagia,[13,16] dry mouth, [16] appetite loss,[14,16,27] anorexia and weight loss,[7,14,16,24,25,28,29] fatigue/asthenia[3,14] and cognitive impairment[25] were recognised as independent predictors of survival. Reuben *et al.*[16] identified the 'terminal cancer syndrome', including functional status (KPS < 50), dry mouth, shortness of breath, problems with eating, recent weight loss and troubles with swallowing. Vigano *et al.*[10] confirmed the terminal cancer syndrome theory in their systematic review of survival prediction.

The studies that have addressed the relationship between symptoms and survival are mainly based on samples of patients in different care settings[6,16,20,22,26] or in either a hospice or a home care setting.[3,7,8] The population of patients admitted to the hospital for symptom management cannot be compared with patients admitted to a hospice. Hospitalised patients are a heterogeneous group, ranging from ambulatory and independent to moribund and bedbound, with a variety of distressing symptoms.[13,17,18,20,21] The prognostic significance of symptoms with regard to survival in the hospital population has not been systematically studied nor is there a predictive model for survival that has been validated in the setting of an inpatient oncology ward. There is a clear need to gain additional insight into the survival of patients with advanced cancer admitted for symptom management. Such insight may lead to: (i) better clinical estimation of survival during admission for symptom control; (ii) prevention of unnecessary treatment; (iii) timely initiation of specific logistic supportive care measures at home; (iv) better use of specific resources such as hospice care. In the Netherlands, for example, only patients with an estimated survival of less than 3 months may be admitted to a hospice.

The aim of this study is to investigate whether the prognosis of hospitalised advanced cancer patients can be estimated correctly on the basis of their symptoms.

2. Patients and methods

2.1. Patients

A prospective analysis was performed on patients with advanced cancer admitted to several departments of the University Medical Centre Utrecht, who were referred to the Palliative Care Team (PCT) of the Department of Medical Oncology for symptom control. The PCT consists of a medical oncologist, an anaesthesiologist, a psychiatrist and two clinical nurse specialists. After a thorough clinical assessment, the PCT gave advice to the treating clinician about symptom management.

Between October 1998 and March 2004, 203 patients were referred to the PCT. The patients were interviewed by the clinical nurse specialist in order to get a comprehensive problem assessment. For 22 patients the assessment was incomplete because of cognitive impairment, mental or physical exhaustion, or inability to understand the Dutch language, leaving 181 patients with a full assessment.

2.2. Measures

Functional status was measured by the Karnofsky performance status (KPS).[32] Socio-demographic and medical data were obtained from the medical and nursing files.

Symptoms were primarily assessed as a dichotomous variable (absent or present) during a semi-structured interview by the clinical nurse specialist, using a checklist[31] derived from a nationally developed symptom registration instrument by the Dutch Centres for Development of Palliative Care.[18] The list included 49 of the most frequently occurring standardised symptoms of previous prevalence studies,[13,16,19,20,22] with the possibility to add volunteered symptoms.

2.3. Analysis

Analysis of prediction of survival focused on two main questions: (1) the role of symptoms as an independent prognostic factor for death; and (2) clustering of proven prognostic symptoms in order to improve prognostication. Length of survival is defined as the duration between the date of the first consultation of the PCT and the date of the patient's death (event) or the last follow-up (censored) for those who were still alive at the time of data analysis (August 2004). The survival status and the date of death were obtained from the hospital registry or if unavailable by telephone calls to general practitioners.

2.3.1. Variables examined

We analysed the relation between socio-demographic variables, diagnosis and performance status (KPS) on survival. Of the symptoms assessed, we analysed only those occurring in 10% or more of the cases (a minimum of 18 events).

2.3.2. Statistical considerations

Survival and probabilities were determined using the Cox proportional hazard model; survival curves were drawn at the average of other co-variates instead of the one-to-one comparison of the Kaplan–Meier technique. Differences between survival curves were assessed using the log-rank test. Statistical significance was considered if $p < 0.05$. After univariate analysis, all significant prognostic factors were entered into a multivariate Cox regression model to determine independent predictors of survival. The required validation of the prognostic factors was performed by a stepwise ('bootstrap') procedure: the same analysis was performed many times on a series of subsets from the same data set in order to evaluate the stability of the coefficients and the predictability of the model (based on the increment in the χ^2 statistic).[33] Additional analysis with the log-rank test was done.

To study the effect of simultaneous symptoms on survival time, a multivariate regression model was fitted to the logarithms of the observed survival times. This was possible since nearly all of the patients had died at the time of the analysis and there were only three censored cases.

Statistical analysis was performed using Statistical Package for the Social Sciences version 12.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Patient characteristics

Patient characteristics and distribution of cancers by primary sites and metastases are summarised in Table 1. Relatively few patients were treated with chemotherapy (19%) or radiotherapy (28%) during the last three months before their referral to the PCT. Only 12% of the patients had KPS scores of 70–80; almost half of the patients were severely disabled and bed bound (KPS < 50).

At the moment of analysis, all except three patients were dead with a median survival of 53 d (range 1–1915). Most of the patients (43%) died within 1 month, 42% lived for 1–6 months and 15% of the patients lived longer than 6 months after the initial consultation.

3.2. Prognosis based on symptom prevalence

3.2.1. Symptom prevalence

The median number of symptoms per patient was four (range 1–8). We recorded 20 symptoms occurring in ⩾10% of the patients (Table 2). Pain, asthenia, anorexia and anxiety were the most frequent symptoms, occurring in more than half of the patients. Almost all patients (88%) were in pain. Pain was differentiated into 11 sites of pain, with the highest incidence for backache (26%) and abdominal pain (22%). Forty-four percent of the patients had two or more different sites of pain at the moment of the initial visit with a maximum of six sites.

Table 1 – Patient characteristics (*n* = 181)

	n (%)
Gender	
Male	80 (44)
Age (years)	
Median (range)	58 years (18–91)
Primary cancer site	
Breast	25 (14)
Gynaecological	21 (12)
Gastrointestinal	35 (19)
Head- and neck	21 (12)
Lung	20 (11)
Prostate	13 (7)
Others	46 (25)
Metastases	
Bone	81 (45)
Lymph node	56 (31)
Lung	35 (19)
Liver	36 (20)
Brain	20 (11)
Viscera	29 (16)
Other	27 (15)
Unknown	5 (3)
Karnofsky performance score	
10–20	8 (4)
30–40	80 (44)
50–60	72 (40)
70–80	21 (12)
90–100	–

Table 2 – Prevalence of symptoms occurring in ⩾10% of patients

Symptom	Patients (%)
Pain[a]	160 (88)
Asthenia	108 (60)
Anorexia	101 (56)
Anxiety	96 (53)
Constipation	70 (39)
Nausea	68 (38)
Sleeplessness	65 (36)
Dyspnoea[b]	54 (30)
Depressed mood[c]	49 (27)
Drowsiness	49 (27)
Vomiting	44 (24)
Dry mouth	42 (23)
Weight loss > 10	31 (17)
Sore mouth	30 (17)
Confusion[d]	30 (17)
Diarrhoea	28 (16)
Paralysis	26 (14)
Cognitive impairment	26 (14)
Dysphagia	21 (12)
Pressure ulcers	21 (12)

* 20 symptoms out of a standardised list of 49.
* Median number of symptoms per patient 4 (range 1–8).
a Differentiation in 11 sites.
b In rest.
c Answer to the question 'are you depressed?'
d Single symptom, without other prodromes of the delirium syndrome at the time of assessment.

3.2.2. Cluster of five prognostic symptoms

By univariate analysis 11 out of 49 symptoms were correlated with survival: headache, abdominal pain, anorexia, weight loss >10%, nausea, vomiting, dysphagia, dyspnoea, drowsiness, confusion and depressed mood ($p < 0.05$). In this analysis, gastro-intestinal cancer was highly significant for poor survival ($p < 0.001$); gender ($p = 0.114$), age ($p = 0.076$) and KPS ($p = 0.269$) were not.

Multivariate analysis was performed after correcting for diagnosis, including all 20 symptoms occurring in more than 10% of the sample. After stepwise selection nausea, dysphagia, dyspnoea, confusion and depressed mood were found to be independent prognostic factors for survival ($p < 0.05$) in the final proportional hazard regression model. The presence of nausea, dysphagia, dyspnoea and confusion significantly increased the likelihood of dying with a relative risk of dying

Table 3 – Multivariate model: prognostic significance of symptoms, relative risk of dying

Symptom	Relative risk of dying	95% Confidence interval	*p*-Value
Nausea 1.960	1.328–2.892	0.001	
Dysphagia	1.812	1.111–2.955	0.017
Dyspnoea	1.795	1.274–2.531	0.001
Confusion	2.352	1.524–3.630	<0.001
Depressed mood	0.561	0.385–0.817	0.003

Cox regression coefficients with associated *p*-values and hazard rates.

of 1.96, 1.81, 1.79 and 2.35, respectively (Table 3). In contrast, the presence of depressed mood significantly decreased the likelihood of dying with a relative risk of 0.56; in other words, the absence of a depressed mood was associated with a relative risk of dying of 1/0.56 = 1.79. Fig. 1 shows survival curves for patients with and without these symptoms. None of the

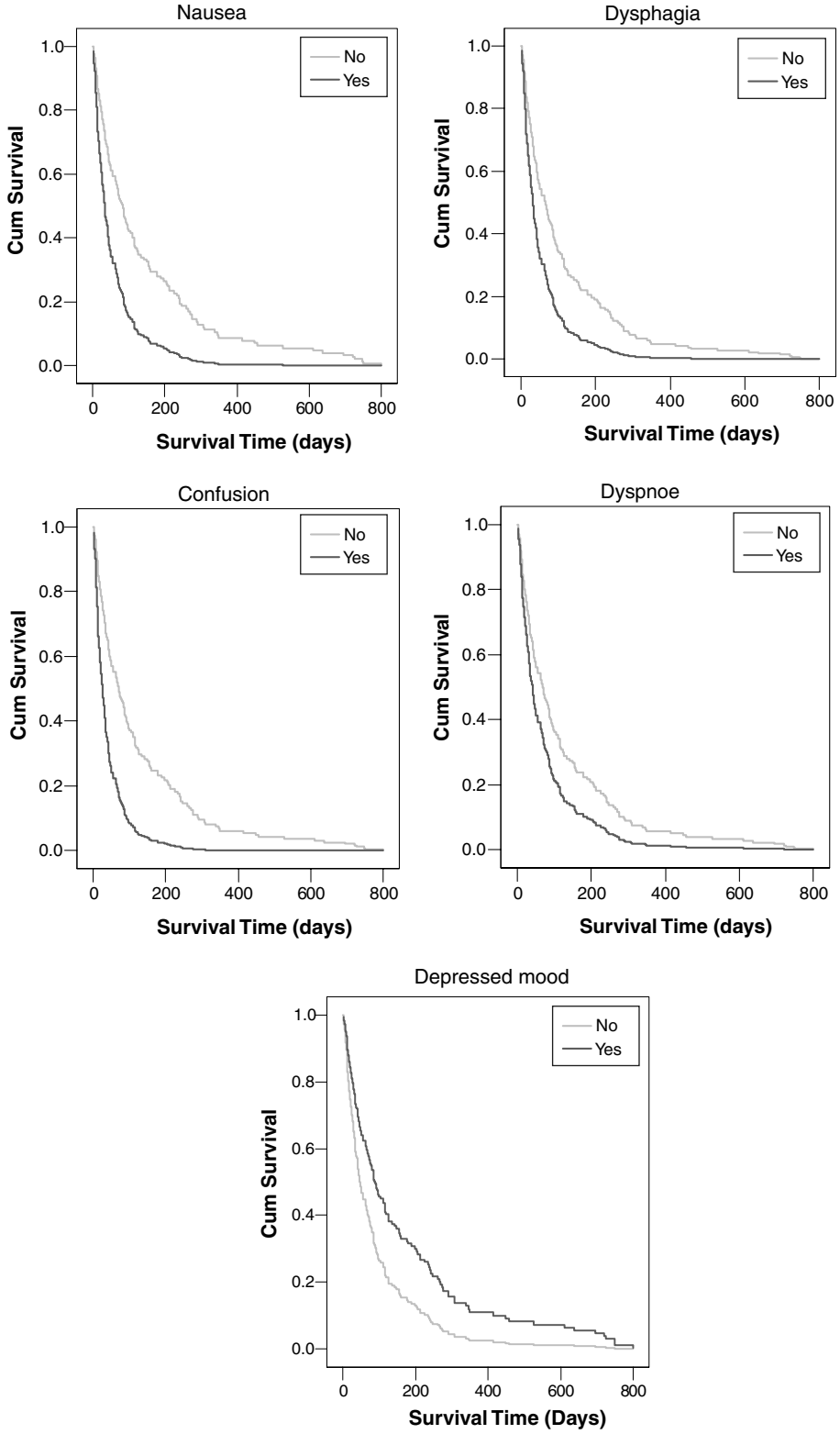

Fig. 1 – Survival curves for each of the five significant symptoms. *Note 1*. The survival curves for each of the symptoms are drawn at the mean values of the other symptoms. *Note 2*. Since all symptoms are simultaneously used as covariates in the Cox regression model, the effects of these symptoms will differ from those tested for a symptom ignoring the influence of the other symptoms.

Table 4 – Relative risk of dying based on the Cox proportional hazard model

Number of simultaneous factors[a]	Patients (%)	Regression coefficients	Relative risk of dying	*p*-Value
0	29 (15)	–	1	–
1	62 (34)	−0.388	1.47	0.111
2	54 (30)	−1.002	2.73	<0.001
3	32 (18)	−0.752	2.12	0.006
4	6 (3)	−2.202	9.01	<0.001

a Nausea, dysphagia, dyspnoea, confusion and absence of depressed mood.

patients in our study had more than four of these five prognostic factors (nausea, dysphagia, dyspnoea, confusion and absence of depressed mood) at the same time; 34% reported only one of these factors.

From the multivariate regression model that was fitted to the logarithms of the observed survival, it appears that the survival time drastically decreases with increasing numbers of the above mentioned factors. All but one of the coefficients of this regression model are highly significant ($p < 0.01$). Patients with 2, 3 or 4 of these five factors simultaneously had an estimated risk of dying of, respectively, 2.7, 2.1 and 9.0 times higher than patients without any of these symptoms. Median survival was 122, 71, 36, 35 and 14 d for patients with 0, 1, 2, 3, and 4 of these factors, respectively. The presence of four of the significant factors resulted in an 83% mortality rate at 1 month and a 100% mortality rate at 6 months, compared to a 1-month mortality of 20% and a 6-month mortality of 48% in patients without these factors. The Cox proportional hazard regression model fitted to the same data supports the above-mentioned results (Table 4).

4. Discussion

We conducted this prospective study to support physicians in predicting the survival of hospitalised patients with advanced cancer on the basis of comprehensive symptom assessment. We have identified five symptoms which independently predicted survival in advanced cancer patients who were admitted to a university medical centre and referred to a palliative care team for symptom control. The predictive value of nausea, dysphagia, dyspnoea, confusion and absence of depressed mood could be enhanced by clustering these factors. The presence of several of these factors simultaneously indicated a significantly decreased rate of survival.

The majority of studies have reported that some symptoms and performance status may have a predictive value.[1,6–14,16,25–27] The prognostic value of nausea, dysphagia, dyspnoea and confusion in hospitalised patients is consistent with the findings of others.[9–12] Clustering of the five significant factors increased their prognostic value. We fail to support the findings of others who have reported a correlation between gender, age, anorexia, weight loss, asthenia and survival.[9–12] An explanation for this discrepancy may be the differences in: (i) patient population, *e.g.* home care *versus* hospice *versus* hospital; differences in stage of disease and life expectancy; (ii) the way data were collected, for example different measures, prospective *versus* retrospective studies and convenience sampling *versus* selection based on difficulties in symptom management; (iii) single centre *versus* multicentre, data collection by one or two researchers *versus* several research teams; and (iv) statistical analysis. Criticism on previous studies included the validation process of the prognostic significance of factors. To evaluate the stability and predictive ability of our model, we used the 'bootstrap' procedure in which the same analysis was performed many times on a series of subsets from the same data as suggested in the systematic review of Chow *et al.*[11]

Our finding that confusion as a single factor without other clinical symptoms of delirium and depressed mood have prognostic significance was not reported earlier in the hospital setting, although cognitive impairment has been recognised as a prognostic factor.[25] We hypothesise that confusion may be interpreted as a prodrome for delirium, which has been reported as an independent factor for survival in (elderly) patients.[27,34]

Surprisingly, this study suggests that patients in a depressed mood have a lower risk of dying than patients not in a depressed mood (relative risk of dying: 0.56). It is important to realise that this refers to the question 'Are you depressed?'[35,36] and does not reflect a psychiatric assessment of depression. It is intriguing to speculate on an explanation for this finding.

The majority of studies in this area show a relationship between depression or depressed mood and cancer progression.[37] It should be noted that almost all studies used questionnaires to assess depression and that psychiatric (DSM)-criteria were almost never applied. These associations may merely reflect the underlying physiologic processes mimicking symptoms of depression but that are markers for tumour burden or cancer progression. We assessed depressed mood by a simple question and did not take into account any symptoms for this diagnosis that have been caused by the disease. This may explain why we failed to find a decreased rate of survival in patients with a depressed mood, but still does not explain their increased rate of survival. There are some possible explanations. First, it might be possible that patients with depressed mood in an advanced disease stage are sooner referred to palliative care consultants. If so, earlier referral may lead to apparent longer survival (lead time bias). Second, earlier referral could also result in more adequate symptom management in particular of the prognostic symptoms we found in this study. However, it must be noted that there is no evidence that better symptom control results in prolonged survival. Third, it might be argued that better psychosocial support (both professional and non-professional) of patients with depressed mood might result in better survival. However, the literature on the result of psychosocial treatment of depression on survival is highly controversial and intuitively, it does not seem very likely that any form of psychosocial support of intervention would have an effect on survival in this population with a very poor prognosis. Thus, the positive correlation between depressed mood and survival in this study remains largely unexplained.

Two limitations of this study deserve some comments.

First, we assessed symptoms rather crudely as a dichotomous variable (absent or present). This has the practical

advantage that it can readily be used in clinical practice. Whether the prognostic value of our symptom cluster can be improved by using questionnaires completed by the patient and by symptom intensity scores should be a matter of further study.

Second, the present findings are based on a single comprehensive symptom assessment at the first consultation of a PCT. The first consultation was defined by the clinician without subcategorising the patient according to the stage of his advanced disease. In a certain way, our sample of hospitalised advanced cancer patients is heterogeneous as well. However, for each patient in our sample the consultation of the Palliative Care Team could be seen as the start of a new treatment cycle of comprehensive symptom management. Further study is needed to increase our insight into the development of the prognostic factors over time in subcategories, for example along functional status, during interventions and symptom management. Application of the symptom cluster might provide a new strategy for initial assessment, daily monitoring and clinical decision-making during the entire period of admission and specific information and advice to the general practitioner for affiliation afterwards at home.

In conclusion, the cluster of five factors we found in this study may contribute to a more accurate prediction of survival in advanced cancer patients admitted to the hospital. This will aid physicians to develop an individualised programme for symptom control in order to prevent unnecessary treatment and transfers between settings of care. This could result in a realistic planning of professional and logistic support and improve the remaining time together for the patient and his nearest.

Conflict of interest statement

None declared.

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