Prospective Evaluation of Prognostic Variables From Patient-Completed Questionnaires

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Purpose: This study was developed to determine whether descriptive information from a patient-completed questionnaire could provide prognostic information that was independent from that already obtained by the patient's physician.

Patients and Methods: An initial detailed questionnaire was administered to approximately 150 patients with advanced cancer. This questionnaire was subsequently revised and given to a total of 1,115 patients with advanced colorectal or lung cancer. Univariate and multivariate analyses were performed to evaluate the data from these questionnaires.

Results: A total of 36 variables showed statistically significant prognostic information for survival in univariate analyses, even though many of these variables were associated with only a minimal increase in risk. A multivariate analysis demonstrated that there was a high correlation between many variables. Three major groups of variables became apparent as providing strong prognostic information. These included the following: (1) a physician's assessment of performance status (PS); (2) a patient's assessment of their own PS; and (3) a nutritional factor such as appetite, caloric intake, or overall food intake.

Conclusion: Data generated by a patient-completed questionnaire can provide important prognostic information independent from that obtained by other physician-determined prognostic factors.

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PROGNOSTIC FACTORS can provide important information for patients with cancer. A better understanding of an individual patient's prognosis can help both the physician and the affected patient make appropriate therapeutic decisions. In addition, prognostic factors can be valuable for stratifying patients in clinical trials and for interpreting data generated from such trials.

Although various factors such as age, location of dominant disease, or grade of anaplasia may sometimes provide significant prognostic information in advanced disease, one of the strongest, and most consistently significant, prognostic determinants is performance status (PS). PS is usually recorded by the physician using a traditional scoring system such as the Karnofsky performance status (K PS) or the Eastern Cooperative Oncology Group (ECOG) scale.[1] These systems have rather broad definitions of the patient's ability to be physically active. They are vulnerable to the subjective nature of physician judgment. What is declared ECOG performance score 2 or K PS score 50 may vary considerably in the eyes of a physician who deals largely with hospitalized patients versus a physician who deals largely with outpatients. Even when approached with greatest objectivity, the definitions of various strata of performance levels are frequently so vague and overlapping that a clear assignment cannot be made. For example, the definition of K PS score 70 is "care of self . . . unable to carry on normal activity or to do active work." Definition of K PS score 40 is "disabled, requires special care and assistance." Both of these definitions could be applied to the same patient.

Formal evaluations of the validity of the K PS have been performed by several groups.[2-6] These investigators found varying degrees of concordance when different physicians or different health professionals recorded performance scores on the same patient. All of these investigators agreed that additional efforts were required to apply the PS with greater precision. Formal large-scale comparisons of different performance scoring tools (ie, K PS *v* ECOG) have not previously been reported. A relatively recent review of PS assessment among oncology patients called for a better understanding of clinically used performance scoring tools.[7]

There is a widespread belief that nutritional status and caloric intake can have a major influence on patient sur-

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vival and responsiveness to chemotherapy endeavors. However, actual prospective data that support this belief in human cancer are limited. The largest study to address this issue was that reported by DeWys et al,[8] who retrospectively reviewed a large number of solid-tumor patients entered onto ECOG trials. For these trials, data were recorded on the on-study sheet as to weight loss in the preceding months and graded from no weight loss to greater than 10% weight loss. There was a highly significant correlation between weight loss and survival for most types of solid tumors, and weight loss gave prognostic information that was independent of PS. The actual influence of caloric intake at the time a patient is entered onto a chemotherapy trial has had little attention. Any attempt at widespread application of nutritional factors as prognostic determinants has been complicated by the cumbersome nature of many of the tools used for such evaluation and by the expense involved in obtaining reasonable assessments. Measurement of lean-body mass is a difficult laboratory procedure that is not easily adaptable to large-scale clinical trials. Detailed nutritional histories by dietitians or the counting of calories in daily dietary diaries are similarly impractical in most clinical settings. Nevertheless, we felt that reasonably reproducible nutritional information could be obtained from the patient in a form that could lend itself to ease of analysis.

Although there have been some reports that emphasize major prognostic importance of psychosocial factors in the course of malignant disease,[9,10] it has not been clearly established that these factors provide independent prognostic information. One study concluded that the potential influence of psychosocial factors is overridden by the biology of malignant disease.[11] As with nutritional factors, the assessment of psychosocial factors has generally been accomplished by complex instruments or professional interviewing, both of which are expensive and impractical for adaptation to large-scale clinical trials. Again, we felt there was a reasonable possibility to obtain useful information through simple and direct questioning. We planned to consider the factors of depression, bereavement, and positive attitude, each of which have been presumed to have some possible influence on the course of malignant disease.

Thus, we designed a cooperative group clinical protocol to examine the aforementioned factors and to determine whether we could produce prognostic information that was more highly predictive than, and independently significant from, the usual patient descriptive information obtained by the physician for clinical trials. In addition, this study was devised in a manner that allowed us to compare directly the prognostic value of two widely used performance scales in clinical trials, the K PS and the ECOG PS.

PATIENTS AND METHODS

This prospective clinical trial was designed to be performed in much the same pattern of development as that reported by Schipper et al[12] when they developed a questionnaire addressing an allied subject, quality of life during treatment. The protocol was organized in three phases. The goal of the first phase was to devise a questionnaire that would be readily understandable to adults who were not mentally impaired or educationally deprived. We began with a test questionnaire that contained approximately 30 questions which could be answered by check marks or numbers. These questions related to such concepts as patient activity, disabilities, requirements for daytime rest, appetite, food intake, nausea, vomiting, discomfort, bereavement status, optimistic versus pessimistic outlook, and religious activities. Additionally, it included three pages of questions regarding recent dietary practices. We had previously tested this dietary portion of the questionnaire in 36 cancer patients. It appeared to be easily comprehensible and was shown to correlate reasonably well with 4-day diet diaries completed by the same patients.

This first-phase questionnaire was administered to approximately 150 patients just before they received their first chemotherapy regimen for advanced, incurable, malignant disease. In addition, the attending physician simultaneously completed a short questionnaire regarding his or her judgement of the patient's nutritional status, ECOG PS, K PS, and expected survival compared with other patients in the same treatment protocol. Nurse investigators closely evaluated the patient-completed questionnaires in the first-draft phase and documented the questions that patients had difficulty understanding or answering.

These questions were subsequently collected, tabulated, and reviewed in depth by a committee consisting of medical oncologists, statisticians, nurse oncologists, and a dietitian. A revised questionnaire was then developed in which some questions were reworded and others excluded. In addition, two questions, separated in space, were added. These two questions independently asked the patient to rate his/her own ECOG PS and K PS. The ECOG PS definitions were identical for the patients and the physicians, while the K PS definitions were slightly modified for better lay clarification (Table 1).

In the second phase of the study, this revised questionnaire was given to patients who were each simultaneously entered onto another North Central Cancer Treatment Group treatment protocol. The questionnaire was completed before the patient's first dose of chemotherapy for metastatic disease. As in phase I, the attending physician simultaneously completed a short questionnaire. Data generated by the second phase of this study in patients with metastatic lung or colorectal cancer will be presented in detail below.

The third phase of this study was designed to retest any information that appeared to have independent prognostic significance over and above the routinely obtained physician-recorded PS. The results of study phase III will be reported in the future.

Statistical Methods

Since we planned to use the Cox proportional hazards model to identify the most prognostic variables to be carried into phase III of the study, and since there were initially more than 60 variables, it was impossible to let each category of each variable be included in the model using a zero-one code. For this reason, we first examined

Table 1. Patient Questions Regarding the Determination of their EGOC PS (A) and K PS (B)

A. Which of the following phrases best characterizes you at this time?
_____ Fully active, capable of full-time work activities
_____ Slightly impaired, capable of part-time work activities
_____ Up and about more than 50% of waking hours but not capable of work activities
_____ Ambulatory and capable of self-care but confined to bed or chair more than 50% of waking hours
_____ Totally disabled, not capable of self-care

B. Which of the following phrases best characterizes you at this time?
_____ Normal, no complaints, no symptoms of disease
_____ Able to carry on normal activity, minor symptoms of disease
_____ Normal activity with effort, some symptoms of disease
_____ Care for self, unable to carry on normal activity or to do active work
_____ Require occasional assistance but able to care for most of personal needs
_____ Require considerable assistance for personal care
_____ Disabled, require special care and assistance
_____ Severely disabled, require continuous nursing care

NOTE. In the questionnaire, these 2 questions were separated from each other by 4 other questions.

the categories of each variable individually to determine if the change in prognosis for the variable was clearly monotonically related to category. If so, the variable was entered into the model as a continuous variable with no recoding. For certain other variables, recoding was required. For example, patients with total calorie intakes greater than 1,500 calories a day appeared to have equivalent prognoses, so when the variable calories was entered in the Cox model, all values greater than 1,500 were recoded to 1,500. Recoding was based on an examination of the survival curves for categoric data and by studying a residual plot for the continuous variables.

To eliminate the less prognostic variables from the Cox proportional hazards model, we used a backward (stepdown) regression. A variable was kept in the model if the P value associated with the standardized maximum likelihood estimator for the variable was less than .05.

In Table 3, which appears in the Results section, we used Atkinson's R statistic to compare models that had varying degrees of freedom, since it includes a penalty for the number of parameters estimated.[13]

When analyzing the data, it became apparent that the variables clustered in the following sense. Nutritional variables were highly correlated and more nearly interchangeable in a Cox model than a nutritional variable and a performance variable. The same property held for variables related to a physician's assessment of the patient's condition, and for variables related to a patient's assessment of his/her own condition. To illustrate this, we used a multidimensional scaling technique as described in Torgerson.[14] The program was cmdscale, which is available in the S language and described by Becker et al.[15] To define the distance between two variables, we let fit1 (fit2) be the log-likelihood for the model using just the first (second) variable, let fit12 be the log-likelihood for the model using both variables, and defined the distance to be $(2 \cdot \text{fit12} - [\text{fit1} + \text{fit2}])/\text{fit12}$. If the variables are completely correlated, this distance is zero, while if they are completely uncorrelated, the distance is one. Although this method is still exploratory in nature, it does give a nice graphical summary of the approximate relationship between variables.

In the Cox proportional hazards model, the (natural) logarithm of the hazard function associated with each patient is assumed to be equal to a linear combination of patient characteristics. We defined the Cox score for each patient to be the combination obtained by multiplying the observed patient characteristics for the patients by the corresponding regression coefficients and adding the resulting products. The regression coefficients for this linear combination are estimated based on observed data.

RESULTS

A total of 1,115 patients were entered onto this study. The patients were concurrently participating in one of six clinical trials, all for advanced lung cancer patients or advanced colorectal cancer patients. The patients were entered onto therapy trials during the period July 17, 1987 to June 15, 1990. Thirty-eight of these patients (3.4%) were found to be ineligible for their treatment protocols and were excluded from analyses. Of the remaining 1,077 patients, 1,008 (93.6%) have died. The minimum follow-up for any living patients is more than 18 months, and all but four patients were monitored for at least 2 years. The primary analyses presented herein are those performed using the entire cohort. For certain analyses, the sample sizes were smaller due to missing values, and these will be noted. Included are further analyses performed on 515 advanced colorectal cancer patients (491 deaths), 357 small-cell lung cancer patients (314 deaths), and 205 non–small-cell lung cancer patients (203 deaths). Survival curves for the entire patient group and the three disease subsets are shown in Fig 1.

Due to the large number of patients and events, we had the ability to detect prognostic effects of even minimal clinical importance. In fact, when all patients were considered, 36 variables were statistically significant

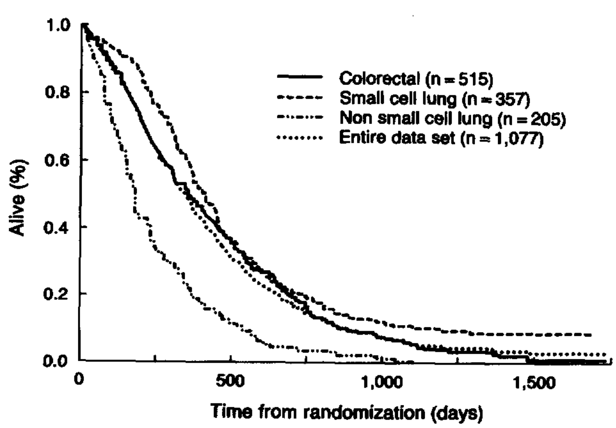

Fig 1. Survival curves for the entire patient group and for the 3 major subgroups.

prognostic factors ($P < .05$) for survival in univariate analyses, even though many of these variables were associated with only a minimal increase in risk. In the remainder of our analyses, we restricted our attention to the 25 variables that were significant at level $P < .0001$ in the univariate analyses for all patients. The results of univariate analyses for the most significant 25 factors are listed in Table 2. Every variable for which the univariate P value was .001 in an analysis of lung cancer patients only or colon cancer patients only also satisfied P .0001 in the all-patients analysis.

When multivariate analyses were performed, it became immediately apparent that there was high correlation between many variables. In fact, when the 25 analyses variables were all entered into a Cox proportional hazards model, only five remained significant ($P < .05$). These were the patient-judged K PS, the patient-judged ECOG PS, the physician-judged ECOG PS, the physician's estimate of the patient's survival potential, and the assessment of the patient's caloric intake during mealtime (excluding snacks and desserts) calculated from dietary-intake questions. This overall analysis was complicated by the fact that there were 534 patients omitted due to

Table 2. Top 25 Prognostic Factors in Order by Descending χ^2 Values

Prognostic Factor	% Missing (N = 1,077)	χ^2	P
Food intake	0.6	103.78	.0000
Appetite	0.8	101.22	.0000
Patient-judged K PS	1.3	100.37	.0000
Physician-judged K PS	0.7	80.89	.0000
Physician-judged ECOG PS	0.1	80.52	.0000
Physician-judged survival	2.0	69.66	.0000
Physician-judged nutritional status	0.7	60.20	.0000
Pain status	2.4	59.35	.0000
Physical activity level	0.9	57.45	.0000
Patient-judged ECOG PS	1.7	55.15	.0000
Driving ability	11.2	50.50	.0000
Evening meal calories	2.0	49.34	.0000
Weight loss	7.1	44.52	.0000
Meal calories per day	11.4	42.03	.0000
Recent weight change	7.1	34.95	.0000
Activity restriction	0.0	25.56	.0000
Average meal serving size	1.4	25.10	.0000
Evening meal composition	1.8	24.76	.0000
Vomiting frequency	0.9	23.22	.0000
Amount of solid food per day	0.5	21.45	.0000
Daytime hours in bed	4.8	20.03	.0000
Hours of rest per day	0.8	19.97	.0000
Noon meal calories	4.1	19.59	.0000
Leisure time physical activity	9.0	18.97	.0000
Total daily calories	29.4	18.03	.0000

NOTE. The patient questionnaire used is available from the authors on request.

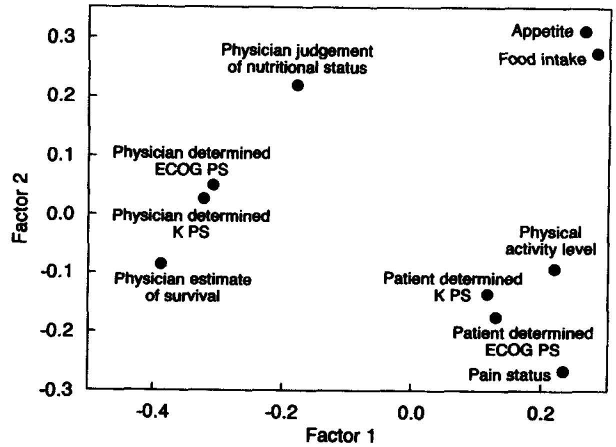

Fig 2. Plot indicates predictive correlation of variables. See Results for details.

missing values for at least one of the original 25 variables. When a model was fit using the patients who had known values for the preceding five variables (starting with only those five variables), the patient's assessment of ECOG PS did not remain in the model. Since 988 patients had known values for the 10 most significant (univariate) variables in Table 2, we did a second analysis starting with these 10 variables in a Cox proportional hazards model. Four variables remained significant, but this time a variable regarding the patient's assessment of his/her appetite replaced the more complex caloric intake. The variables physician-judged ECOG PS, physician estimate of survival, patient-judged appetite, and patient-judged K PS were all significant at P less than .002, while the six other variables were associated with P values more than .21.

The fact that appetite replaced caloric intake with almost no change in significance illustrated another facet of the data analyses, namely, that there appeared to be three separate groups of factors that added complimentary prognostic information. These three groups were defined by (1) physicians' assessment of factors such as the K PS, the ECOG PS, or their estimate of patient survival; (2) patients' assessment of factors such as their K PS, their ECOG PS, or a measure of their physical activity; and (3) nutritional factors such as appetite, caloric intake, or overall food intake. To illustrate this, Fig 2 presents a plot of the relative closeness of the 10 most important prognostic variables. Details of what is meant by close are given in the Statistical methods section, but the essential idea is that the closer two variables are on the figure, the more interchangeable they are in a Cox proportional hazards model, while variables for which the distance is great provide independent (complimentary) information.

Table 3. Cox Model Variables Indicating Interchangeability of Variables

Variable	Run No. 1	2	3	4	5	6	7	8	9	10
Physician assessment										
ECOG PS	*		*	*	*	*		*	*	
Survival estimate	*	*		*	*		*	*	*	
K PS		*	*							
Nutritional assessment										
Appetite	*	*	*		*	*	*	*		*
Food intake				*						
Patient assessment										
K PS	*	*	*	*		*	*		*	*
ECOG PS					*					
R score	.140	.139	.136	.139	.134	.135	.137	.134	.128	.127

NOTE. A detailed explanation of this table is presented in Results.
*Indicates variable is included in the run. Run no. 1 is the model with the highest *R* score.

Note that the patient-defined performance variables group together, the physician-defined performance variables group together, the patient-defined nutritional variables group together, and the physician-judged nutritional status is approximately halfway between the patient nutritional variables and the physician performance variables.

To illustrate the effect of interchanging highly correlated variables, Table 3 lists the best four-variable model, followed by models in which each of these four variables is replaced by the next most significant variable in the same group (physician assessment, patient assessment, nutritional status). We also present four models, each with one of the four primary variables missing. The table shows which variables are included and presents the Atkinson's *R* score. The *R* score is a well-known criterion for assessing the ability of the model to explain the data with as few variables as possible; the larger the value of *R*, the better the model. The *R* scores change little when one variable replaces another from the same group relative to the change when one of the variables is dropped completely.

Since data from a heterogeneous population were used in the preceding analyses, we were interested in whether the model that provided an optimal fit using all the data would be effective in identifying prognostically different subgroups in specific diseases. To address this question, we first defined a scoring variable that categorized the estimated risk of a patient from the optimal model (the Cox score described in the Statistical methods section). We then used the variable to define four subgroups of patients in which the first subgroup consisted of the 25% of patients with the worst estimated risk and so on. Figure 3 shows the survival of the four subgroups identified using the scoring variable in which all patients were included, provided the four variables in the optimal model were defined. The three survival curves on the left of Fig 4 were generated using the four variables identified from all patients, but fitting the model and obtaining scores from only patients within the subset of colorectal, small-cell lung, and non–small-cell lung cancer patients, respectively. On the right of Fig 4, the survival curves shown were generated using a scoring system based on a model using variables that were optimal for the subgroup of patients in question. As can be seen, the model fit using the four best variables from the entire heterogeneous group of patients divided the patients into prognostic groups for specific diseases nearly as well as a model fit using only the subgroup of patients with the specific disease.

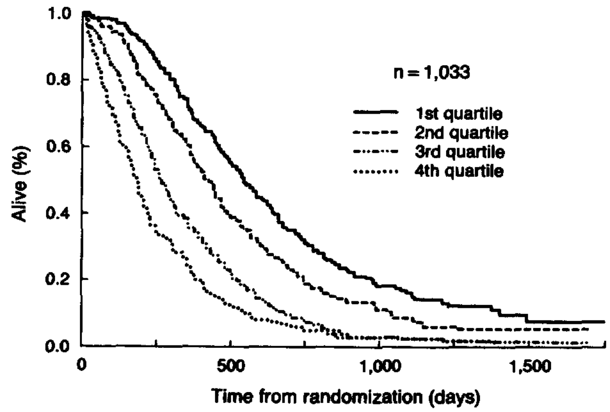

Fig 3. Survival of the 4 subgroups of patients identified using the Cox proportional hazards model to divide the population into quartiles with different prognoses.

A secondary goal of the study was to compare the physician-judged ECOG PS to the K PS. The two PS scales are highly correlated (Spearman correlation coefficient, .85; $P < .0001$; Table 4). When the ECOG PS

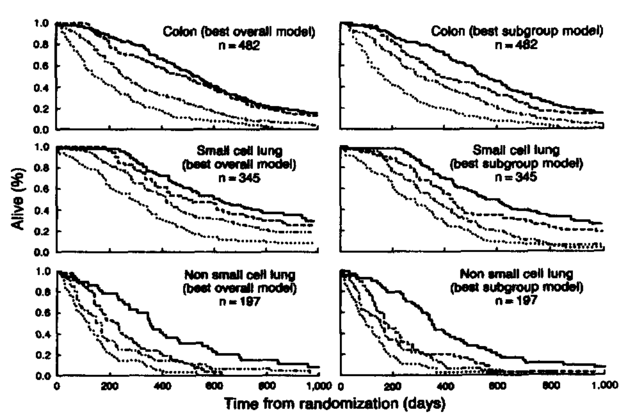

Fig 4. Survival curves for colorectal, small-cell lung, and non–small-cell lung cancer patients, respectively. See Results for details.

was entered as the only variable in a Cox model, the *R* score was .094 and the χ^2 value was 80.25. The corresponding values when the K PS was entered were .094 and 80.65, respectively, indicating the similarity of the two performance scores in prognostic utility.

In a final set of analyses, we started with the routinely collected histologic grade, age, and sex, then added the four most significant variables from our study. The only variable that was not statistically significant was age, leaving a six-variable model which kept ECOG PS, patient-judged appetite, patient-judged K PS, and physician estimate of survival, as well as histologic grade and sex.

We examined the relationship between physician-judged ECOG score and patient-judged ECOG score. Although they were highly correlated, physicians tended to rate patients as healthier than patients themselves. Physicians assessed 83% of patients as ECOG PS 0 or 1 (able to perform work of a light or sedentary nature), while only 59% of the patients rated themselves as being able to carry out such work activities.

A number of individual queries in the questionnaire evaluated patients' feelings regarding faith, religion, and attitude (optimistic *v* pessimistic) and also their amount of perceived stress. None of these questions appeared to provide any significant prognostic information in univariate analyses.

DISCUSSION

The physician-judged K PS and ECOG PS were each developed in a relatively empiric manner. However, both have withstood the test of time, consistently demonstrating important prognostic information among cancer patients. The current study again confirms the powerful prognostic information generated by each of these tools, but does not suggest that either is superior to the other.

Practicing oncologists are well aware of the subjectivity associated with the determination of a patient's PS. Some investigators, on a small-scale basis, have questioned whether it would be more appropriate to have the patient more directly judge their own PS by either defining their own K PS[16] or completing other questionnaires.[6,17] The present study clearly demonstrates that the patient-defined ECOG PS and K PS were strong prognostic indicators. In concert with our data, several other groups of investigators have demonstrated that data generated from patient-completed questionnaires contain powerful prognostic information.[18-21]

Multivariate analyses of our data demonstrated the independent prognostic information afforded by three items: a physician-judged PS, a patient-judged PS, and a question regarding the patient's nutritional status. We are proceeding with the planned third phase of our project to test whether a simplified one-page patient questionnaire will again provide helpful prognostic information in a new series of advanced cancer patients. It is conceivable that the new questionnaire format (only four questions as opposed to several pages of questions) may change patient responses. In addition, it may be that new physician awareness regarding patients' ability to define accurately their own PS might lead the physician to discuss more thoroughly PS issues with the patient and thus lead to a positive evolution of the physician-scored PS.

Table 4. Correlation of Physician-Judged ECOG PS and K PS (n = 1,068)

Physician's ECOG Score	Physician's Karnofsky Score						
	40	50	60	70	80	90	100
0	0	0	0	3	24	157	156
1	0	1	6	43	285	198	17
2	0	10	57	74	25	1	0
3	1	2	7	1	0	0	0

There has been considerable debate regarding the value of, or lack thereof, using psychologic factors as prognostic determinants of patient outcome.[9-11] Admittedly, the present study was not specifically designed to study this issue in depth. Nonetheless, none of our questions regarding patient mood, faith, religion, depression, outlook, or stress factors appeared to have any suggestion of having prognostic importance. It is likely that any potential influence of these psychosocial factors is overpowered by the biology of these patients' malignant diseases.[11]

In conclusion, this study indicates that data generated by a patient-scored PS and a score of a patient's nutritional status can provide important prognostic information independent from that obtained by a physician-scored PS. This information may be helpful for deciding on therapeutic options in clinical practice and for conducting and interpreting controlled clinical trials.

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NOTE

A copy of the questionnaire used in this trial is available from the authors on request.

APPENDIX

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