Clinical Survival Predictors in Patients With Advanced Cancer

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Background: The clinical and epidemiological relevance of different prognostic factors for survival in patients with advanced or terminal cancer remains controversial.

Purposes: To establish the survival of patients with cancer after diagnosis of terminal disease and to determine the predictors of survival.

Methods: An inception cohort of 227 consecutive patients aged 18 years or older with terminal cancer of the lung, breast, and gastrointestinal tract were observed from July 1, 1996, through December 31, 1998. Tumor- and treatment-specific, clinical, laboratory, demographic, and socioeconomic variables were recorded at baseline. The relationships between these characteristics and survival time were examined using univariate Kaplan-Meier and multivariate Cox regression analyses.

Results: At the time of data analysis, 208 patients (91.6%) had died; the overall median survival for the sample was 15.3 weeks. Shorter survival was independently associated (P≤.05) with a primary tumor of the lung (vs breast and gastrointestinal tract combined), liver metastases, moderate-to-severe comorbidity levels (vs absent-to-mild levels), weight loss of greater than 8.1 kg in the previous 6 months, serum albumin levels of less than 35 g/L, lymphocyte counts of less than 1 × 10^9/L, serum lactate dehydrogenase levels of greater than 618 U/L, and clinical estimation of survival by the treating physician of less than 2 months (vs 2-6 and >6 months). Performance status, symptoms other than nausea and vomiting, tumor burden, and socioeconomic characteristics such as social support and education and income levels did not appear to be independently associated with survival after adjusting for the effect of prognostic factors.

Conclusions: Simple clinical and laboratory assessments are useful aids in the prediction of survival in patients with solid malignant neoplasms at the onset of terminal stages. Methodological improvements in the design and implementation of survival studies may reduce prognostic uncertainty and ultimately provide better care for the terminally ill patients and their families.

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PATIENTS AND METHODS

Patients were recruited at the Cross Cancer Institute (CCI), Edmonton, Alberta, from July 1, 1996, through December 31, 1998. The CCI represents the only referral center for oncological treatment in northern Alberta and has a catchment population of approximately 1.5 million people. Patients were eligible if aged 18 years or older with a diagnosis of terminal cancer of the lung, breast, or gastrointestinal tract. These tumors were chosen because they rank among the top 4 types for incidence and death rates in developed countries.7

According to information derived from the Physician Data Query statements for health professionals86 and a consensus of oncologists at the CCI, specific criteria were elaborated to define when patients with solid malignant neoplasms were considered to be in a terminal phase. These criteria, which relied on histological findings, disease stage, and treatments received, were used to identify patients to whom no further life-prolonging treatments could be offered. Breast cancer was considered terminal if disease was progressive after the failure of second-line chemotherapy and/or hormonotherapy for metastatic or recurrent disease. An alternative criterion was a recent diagnosis of brain metastases. Patients with gastrointestinal tract cancers were considered to have entered the terminal phase if they presented with inoperable primary tumors, recurrences, and/or unresectable metastatic lesions. Patients with inoperable non-small cell lung cancer or recurrent small cell lung cancer were considered to be in a terminal stage regardless of oncological treatment. These criteria could be overridden if, according to the clinical judgment of the treating oncologists, patients had particularly aggressive diseases, patients were considered unsuitable for any specific treatment at first diagnosis of cancer, or there were coexisting medical conditions that precluded any therapeutic attempts to prolong life.

It was not possible to identify all potential subjects for the study at precisely the time that they entered the terminal phase. Enrollment in the study was considered for patients who, according to our criteria, entered the terminal phase no more than 30 days before the time that baseline assessments could be conducted. Eligible patients were identified and underwent screening by the principal investigator (A.V.) through calculation to determine a distress score.

$$\text{distress score} = \sum \text{symptom scores}$$

Methodological limitations in earlier research diminished the predictive value of putative prognostic factors, ie, difficulties in sampling of populations with terminal cancer, failure to use inception cohorts,79 use of nonstandardized measures,76 variation in the predictors across studies,77 failure to use time-adjusted analyses,75 and estimation of survival at particular times instead of considering the entire survival curve.77 Added to these problems is the inherent difficulty in predicting survival in patients with terminal cancer because of the many causes of death in those patients.78,79

Our study was designed to overcome these limitations and to identify survival predictors in terminally ill patients with common solid malignant neoplasms. To our knowledge, no previous attempts have been made to evaluate the independent value of prognostic factors for survival in a population-based, prospectively accrued inception cohort of patients with terminal cancer.

RESULTS

At the closing date of the study (December 31, 1998), 227 patients were accrued, of whom 208 patients (91.6%) had died, and no patient was unavailable for follow-up.
ous variables were substantially the same as when the variable's principal diagnosis.

9. Cognitive status, as measured using the Mini-Mental State Examination. The Mini-Mental State Examination measures orientation to time and place, immediate recall, short-term memory, calculation, language, and construction ability. The maximum score is 30, with a score of 23 or less generally accepted as indicating the presence of cognitive impairment.

10. Serum and hematologic variables, including levels of albumin, sodium, calcium, alkaline phosphatase, LDH, and hemoglobin, and blood cell and differential counts.

Clinical estimation of survival (CES) by the treating oncologist (number of months, weeks, or days).

These variables were selected because they have been found to be of prognostic significance in patients with terminal cancer and were believed to be measurable and reproducible even in seriously ill patients.

To account for the heterogeneity of cancer treatments in the 3 primary sites, the following 3-category classification proposed by McCusker was adopted: patients who entered the terminal phase without ever receiving any tumor-directed therapy (eg, owing to poor medical conditions or too advanced stages of diseases), patients for whom cancer treatments were discontinued (eg, owing to disease progression or recurrence), and patients for whom cancer therapies were started or continued for symptom palliation (Table 1).

The literature does not offer specific indications for categorization of the intensity of symptoms, and patients similar to our population may present with comorbidities and mild symptoms unrelated to their cancer. Therefore, for comorbidity and symptom levels, cutoff points of absent to mild and moderate to severe were used.

The CES was divided into the following 3 categories: less than 2 months, from 2 to 6 months, and longer than 6 months. These prognostic intervals are generally used to determine the eligibility of patients for government-funded hospices or some regional palliative care programs in Canada and the United States. Functioning levels as measured by the ECOG and KPS scales were recoded in 3 comparable categories, according to the simple conversion table recently proposed by Buccheri and colleagues.

Variables were examined in the continuous and categorical form. The cutoff points for the latter were chosen according to reference intervals for all laboratory variables, description in other studies, distribution of cases, clinical meaningfulness, and biological plausibility. Other cut-off points were based on mean values (eg, personal and family incomes), median values (eg, distress score, symptom number, and weight loss), and median for the healthy population (eg, triceps skinfold measurements).

**STATISTICAL ANALYSIS**

Kaplan-Meier survival curves were constructed for each categorical variable. The statistical significance of differences among survival curves was determined using 2-tailed log-rank test. The Cox regression method was also used to examine variables as single main-effect associations with survival for all variables. A stepwise forward regression procedure based on the partial likelihood ratio was applied to select factors of prognostic importance in a multivariate Cox regression model. Power estimates were performed a priori, using the method of Schoenfeld and the EGRET Size software program. In both methods, albumin serum levels were considered as the main exposure. This variable was dichotomized as high-normal (ie, $\geq 35$ g/L) and low (<35 g/L). According to previous reports, a sampling fraction of 46% of patients and conservative hazards ratios for the risk for dying ranging from 2 to 3 were assigned to the low serum albumin level group. Both methods indicated a sample of approximately 80 patients would have a power of at least 80% to detect a hazards ratio of 2.0 at the 5% significance level. The SPSS 6.0 statistical software package was used for all other statistical analyses.
than 6 months had significantly better survivals than patients with poorer prognostications.

Characteristics that had shown some degree of correlation with survival in our data set and/or were previously found to be important prognostic factors were screened using multivariate analysis. These included age; sex; marital status; education level; personal yearly income; tumor type; brain and liver metastases; tumor burden; comorbidity level; antineoplastic treatments (never received or discontinued before study accrual vs continued or initiated after study accrual); asthenia; depression; anorexia; nausea; anxiety; dyspnea; pain; well-being; weight loss; cognitive status; CES; serum levels of sodium, albumin, and LDH; and granulocyte and lymphocyte absolute counts.

There were virtually no missing data for domains that considered patient, disease, and symptom characteristics. In 165 patients, blood work was requested and results were obtained for study purposes only. In the remaining patients who refused or were too unwell physically or psychologically to undergo blood work at the time of assessment, we used data from any blood work performed within 2 weeks from the study accrual. Nevertheless, 24.7% of the patients could not be included in the multivariate analyses because of missing data in the laboratory assessments. To reflect both clinical scenarios, we fitted models that considered patient, disease, and symptom characteristics but not laboratory data, and models with laboratory data were included for patients with complete data (n = 171). The final Cox regression models for these analyses will be referred to as models 1 and 2, respectively. In model 1, the most significant hazard ratios were associated with CES, disease-related characteristics, and performance status (Table 2). Patients who were predicted to live from 2 to 6 months or longer than 6 months were 2.0 and 3.3 times, respectively, less likely to die within 24 months than patients who were predicted to die within 2 months. Collinearity was found for variables that corresponded to the KPS and ECOG scales. We chose the ECOG scale because it showed a stronger association with survival than the KPS scale and appeared to differentiate ambulatory (ECOG status, 0-1) from bed-ridden patients (ECOG status, 3-4) better in terms of survival.

Performance status along with tumor burden appear to lose prognostic significance after adjustment for laboratory values in model 2. Besides the time-by-performance status and time-by-serum albumin interactions, other interactions were lung cancer by weight loss (models 1 and 2), serum albumin level by weight loss (model 2), and serum albumin level by lymphocyte counts (model 2). As can be seen from Table 3 and Table 4, when there is interaction between a predictor and another variable, an estimate of the hazard ratio for the predictor depends on the value of the variable that is interacting with it.

The associations of performance status and serum albumin level with survival significantly decreased over time. The hazard ratio for low performance status decreased at an average rate of 2% per week, whereas the same estimates for low albumin level had an average drop of 4% per week (Table 2). The negative effect on survival of having a lung primary tumor is clinically and statistically different according to the amount of weight loss reported for these patients and clearly increases in patients who experienced

### Table 1. Characteristics of the Sample and Summary of Univariate Survival Analyses*

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. (%) of Sample</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schooling &lt;12 y</td>
<td>155 (68.3)</td>
<td>1.4 (1.0-1.9)</td>
</tr>
<tr>
<td>Primary tumors</td>
<td>70 (30.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Breast</td>
<td>80 (35.2)</td>
<td>0.9 (0.6-1.2)</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>77 (33.9)</td>
<td>1.6 (1.2-2.2)</td>
</tr>
<tr>
<td>Lung</td>
<td>57 (25.1)</td>
<td>1.4 (1.0-1.9)</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>74 (32.6)</td>
<td>1.7 (1.2-2.3)</td>
</tr>
<tr>
<td>Tumor burden &gt;5 lesions</td>
<td>152 (67.0)</td>
<td>1.8 (1.3-2.4)</td>
</tr>
<tr>
<td>Comorbidity moderate or greater</td>
<td>63 (27.8)</td>
<td>1.7 (1.2-2.3)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>13 (5.7)</td>
<td>2.0 (1.2-3.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KPS</th>
<th>0-1</th>
<th>2</th>
<th>3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>90 (39.6)</td>
<td>71 (31.3)</td>
<td>66 (29.1)</td>
</tr>
<tr>
<td>2-6</td>
<td>123 (57.7)</td>
<td>60 (28.2)</td>
<td>85 (43.4)</td>
</tr>
<tr>
<td>&gt;6</td>
<td>64 (28.2)</td>
<td>106 (46.7)</td>
<td>85 (43.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECOG</th>
<th>0-1</th>
<th>2</th>
<th>3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>114 (50.2)</td>
<td>109 (49.3)</td>
<td>115 (50.7)</td>
</tr>
<tr>
<td>2-6</td>
<td>98 (43.2)</td>
<td>87 (39.1)</td>
<td>91 (40.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. (% )</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea moderate or worse</td>
<td>50 (22.0)</td>
<td>1.5 (1.1-2.1)</td>
</tr>
<tr>
<td>Impairment of well-being</td>
<td>103 (45.4)</td>
<td>1.4 (1.1-1.9)</td>
</tr>
<tr>
<td>Nausea moderate or worse</td>
<td>50 (22.0)</td>
<td>1.5 (1.1-2.1)</td>
</tr>
<tr>
<td>Distress score &lt;50th percentile</td>
<td>74 (32.6)</td>
<td>1.4 (1.0-1.8)</td>
</tr>
<tr>
<td>Symptom number &gt;50th percentile</td>
<td>115 (50.7)</td>
<td>1.4 (1.1-1.9)</td>
</tr>
<tr>
<td>Serum sodium level</td>
<td>115 (50.7)</td>
<td>1.4 (1.1-1.9)</td>
</tr>
<tr>
<td>Serum albumin level</td>
<td>109 (49.3)</td>
<td>1.4 (1.0-1.8)</td>
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</table>

<table>
<thead>
<tr>
<th>Laboratory values</th>
<th>No. (% )</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>66 (29.1)</td>
<td>2.3 (1.6-3.2)</td>
</tr>
<tr>
<td>Serum hemoglobin</td>
<td>152 (67.0)</td>
<td>1.8 (1.3-2.4)</td>
</tr>
<tr>
<td>Serum sodium level</td>
<td>115 (50.7)</td>
<td>1.4 (1.1-1.9)</td>
</tr>
<tr>
<td>Serum albumin level</td>
<td>115 (50.7)</td>
<td>1.4 (1.1-1.9)</td>
</tr>
</tbody>
</table>

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*ECOG indicates Eastern Cooperative Oncology Group; EFAT, Edmonton Functional Assessment Scale; LDH, lactate dehydrogenase; and CI, confidence interval. Missing data were recorded for the following variables: clinical estimation of survival, 14; serum sodium, 45; serum albumin, 26; serum hemoglobin, 14; leukocyte count, 13; granulocyte count, 24; lymphocyte count, 25; platelet count, 15; alkaline phosphatase, 96; serum calcium, 28; and LDH, 31.

†<.05
‡<.01
§Nonsignificant

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greater weight loss (Table 3). However, high weight loss and low lymphocyte counts are in themselves important poor survival indicators only in patients with serum albumin levels of at least 35 g/L. In patients with lower serum albumin levels, the hazard ratios for low lymphocyte counts and high weight loss become almost insignificant.

Examination of the outliers did not show particular trends (ie, outlier observation was not typical of patients with specific lengths of survival). Some data points were found to be more influential with respect to some of the estimated coefficients. The removal of these observations from the database did not modify substantially these coefficients, and because they were correctly recorded, they were included in the final models.

**COMMENT**

A major difficulty in this type of study arises from the lack of clinical criteria to define the onset of the terminal phase in these patients. We established simple criteria to define the onset of the terminal stage in patients with breast, lung,
crucial was confirmed by the nonsignificant differences in survival between patients in whom these therapies were discontinued, continued, or initiated in the terminal phase. Our sample seems to comply with most theoretical definitions of patients with terminal cancer.3,7

The median survival in our sample was 15.3 weeks, which is longer than that observed in studies of patients with end-stage disease,90 but shorter than that reported for patients with advanced cancer.91 However, in contrast to most studies dealing with survival in patients with advanced or terminal cancer, our study was population based and not hospice based, and our patients were not accrued in clinical trials. All patients were examined while seeking regular cancer care in the referral center for oncological treatment in northern Alberta.

PERFORMANCE STATUS was no longer a significant predictor of survival in the presence of laboratory variables such as serum albumin level. This is in agreement with the work of Cohen et al.31 Performance status is well recognized as an important prognostic factor for survival in patients with end-stage and advanced cancer.90,91 However, several studies, including ours, have shown that the strength of the association between performance status and survival may vary with length of follow-up.18,53 In addition, performance status is a subjective rating that may be markedly influenced by acute but self-limited events. An ECOG performance status of 0 or 1 in an ambulatory and relatively asymptomatic patient may temporarily drop to an ECOG performance status of 3 or 4 resulting from the occurrence of acute infectious illnesses or a bone pathologic fracture.

Also, the influence of tumor burden on survival was superseded by the influence of laboratory variables such as serum albumin level. This has been correlated with the disease extent of different malignant neoplasms102,103 and may represent a more accurate measure of the tumor burden than the clinical assessment of the number of tumor lesions.

The independent prognostic values of weight loss, low lymphocyte counts, and low serum albumin levels confirm the detrimental role of malnutrition in survival of patients with terminal cancer.104 The hazard ratios found for low lymphocyte counts and weight loss among patients with low serum albumin levels show that the association between malnutrition and survival is probably better measured by serum albumin level than by lymphocyte counts or the amount of weight loss. However, the correlation between low serum albumin levels and survival seems to decrease in magnitude over time, whereas the association of low lymphocyte counts and weight loss with survival, although smaller in magnitude, appear to be constant over time. These findings suggest that survival in patients with shorter prognoses (<2 months) is associated with the decrease in serum albumin level. For terminally ill patients with cancer who survive longer than 2 months, the prognosis appears to be more correlated with other consequences of malnutrition such as the impairment in the immune system and the decrease in body weight.105

Several studies have advocated the inclusion of CES in multivariate models for the survival prediction of patients with advanced and terminal cancer.14,106 In our study, CES remained independently and strongly associated with survival.

The independent prognostic role of tumor-related characteristics (presence of malignant neoplasms of the lung and liver metastases) contradict the theory of the terminal cancer syndrome. Although patients appear to present with similar symptomatic features in the terminal phase,35,45 their individual survival is highly variable and appears to be correlated with disease-specific features. The association between lung cancer and worse prognosis is explained partly by the positive interaction between primary tumors of the lung and weight loss found in our study.

Nausea was the only symptom that remained independently correlated with survival in our final model. In contrast to previous studies,14,34,37 the prognostic importance of anorexia and dyspnea was not significant. Although the pathogenesis of nausea remains multifactorial in patients with terminal cancer,107 this symptom frequently reflects dysfunctions in the autonomic nervous system of this population.108 Our data may confirm an early and independent prognostic role of autonomic dysfunctions in the terminal cancer phase that has been suggested in patients with advanced37 or end-stage cancer.41

An independent prognostic role for the presence of moderate to severe comorbidity in patients with terminal cancer is suggested by our data. To our knowledge, this is the first study that shows such a finding. Two previous studies did not find any significant association between comorbidity and survival in patients with advanced gastrointestinal tract cancer.109,110 Further studies are needed to better determine the prognostic value of comorbidity in these patients.

Our study had some limitations. The sample sizes used in the multiple regression models were affected by missing data in the laboratory assessments. However, sample sizes were adequate in most cases to guarantee enough power for the estimated hazard ratios according to sample size calculations that we performed a priori. Furthermore, the magnitude of the confidence intervals calculated for our estimates were found to be relatively small. These results would need to be validated in an independent data set gathered on similar patients. It was believed that the relatively small sample sizes obtained for our models would not allow meaningful split-sample or cross-validation techniques.111

Conclusions

Prognostic uncertainty in terminal cancer will always be a reality for health care providers, patients, and families. Our results, however, indicate that primary lung cancer, presence of liver metastases, amount of weight loss, levels of LDH and serum albumin, and lymphocyte count are important factors to reduce this uncertainty.

Other prognostic factors of secondary importance appear to be nausea intensity and the level of comorbidity experienced at the onset of the terminal phase. No other symptoms (eg, dyspnea or anorexia) or socioeconomic characteristics, such as social support or education and income levels, appeared as independent survival predictors when adjusted for the above prognostic factors. The major role of malnutrition in the survival of
these patients is suggested by the prognostic predominance of serum albumin level, lymphocyte counts, and weight loss found in our study.

Our data indicate that simple and objective clinical assessments may be useful aids to determine patient survival at the onset of their terminal stages. Certain routine laboratory measurements appear to be complementary to other clinical information, but a limited availability of the former should be taken into account in palliative care settings.

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