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 $1 \times 10^{9}$/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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At present, cancer will be diagnosed in about one third of the population in developed countries during their lifetime.¹ In approximately 50% of patients with a diagnosis of cancer, a stage is reached when active treatment will not prolong life.² Most authors have defined the period extending from this time to the patient’s death as the terminal cancer phase.³⁻⁴ The terminal cancer phase may last from days to months, but there are no validated criteria to enable adequate predictions of its length.⁵⁻¹⁰ This prognostic uncertainty makes clinical decisions difficult for caregivers, patients, and families¹¹⁻¹⁶ and may lead to inappropriate resource expenditure or denial of potentially beneficial therapy for the terminally ill.¹⁷⁻¹⁸ In the United States¹⁹ and Canada,²⁰ admission criteria for government-funded hospices or certain regional palliative care programs²⁰ require physicians to identify those patients with life expectancies of 6 months or less. In the United States, a 1993 report from the National Hospice Organization showed that more than 50% of patients with terminal cancer were not given access to hospice services²¹ or were referred too late in the course of their illness to take full advantage of the support provided by hospice programs.²² Overly optimistic survival predictions made by different health care providers have affected patient referrals to US hospice programs adversely.²³ On the other hand, premature referral to hospices or palliative care programs may create organizational, financial, clinical, and emotional problems for administrators, health care providers, and patients.²⁴ Several studies have been conducted to elucidate the role of prognostic factors on survival of patients with advanced or terminal cancer, including simple, noninvasive, and clinically based assessments. In studies focusing on prognostic factors of survival, length of survival has been associated with the following factors: clinical estimate of survival by the treating physicians,²⁵⁻²⁹ performance status,³⁰⁻⁴¹ some physical symp-
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.1

According to information derived from the Physician Data Query statements for health professionals50 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 given 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 a daily review of medical records of patients who were scheduled for certain outpatient clinics or were admitted at the CCI. Patients underwent an initial, in-person assessment and monthly follow-ups throughout the course of their disease until death occurred. The following data were recorded at baseline:

1. Demographic data, including age, sex, race, individual and family income, and education level. The level of social support was measured using the Older Americans’ Resources and Services Multidimensional Functional Assessment Questionnaire.81,82 Social support was measured in extent of contact with others, family satisfaction with contact, and availability of help.
2. Primary and secondary tumor sites.
3. Last and concurrent treatments (none, surgery, chemotherapy, radiotherapy, or hormonotherapy).
4. Tumor burden expressed as the total number of cancerous lesions.83
5. Performance status according to the Karnofsky Performance Status (KPS),84 the Eastern Co-operative Oncology Group (ECOG),85 and the Edmonton Functional Assessment Tool.86 The Edmonton Functional Assessment Tool assesses communication, pain, mental status, dyspnea, sitting or standing balance, mobility, walking or wheelchair locomotion, activities of daily living, fatigue, motivation, and judgment of functional performance.
6. Physical indicators of nutritional status, including weight loss in the previous 6 months and triceps skinfold thickness as measured using a caliper (Baseline Skinfold Caliper; Fabrication Enterprise Incorporated, New York, NY).
7. Type and intensity of symptoms experienced at the time of patient enrollment as measured by the Edmonton Symptom Assessment Scale (ESAS).87 The ESAS consists of 9 visual analog scales for measuring pain, shortness of breath, nausea, depression, activity, anxiety, well-being, drowsiness, and appetite. For each patient, the overall mean intensity of all the symptoms recorded using the ESAS was calculated to determine a distress score.
8. Concurrent diseases, as measured using the Charlson comorbidity score.88 This score ranges from 0 to

vival 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.

References 4, 17, 18, 35, 37, 38, 40, 41, 45-50.
a maximum of 33 and is based on the presence of certain
diseases with assigned values or weights. We developed an
adjusted Charlson score, which excluded the diagnosis
of cancer, since our intention was to measure conditions other
than the patient’s principal diagnosis.
9. Cognitive status, as measured using the Mini-
Mental State Examination.” The Mini-Mental State Exami-
nation measures orientation to time and place, immediate
recall, short-term memory, calculation, language, and con-
struct 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 lev-
els of albumin, sodium, calcium, alkaline phosphatase, LDH,
and hemoglobin, and blood cell and differential counts.
11. Clinical estimation of survival (CES) by the treat-
ing oncologist (number of months, weeks, or days).

These variables were selected because they have been
found to be of prognostic significance in patients with ter-
minal cancer90,91 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 en-
tered 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 progres-
sion 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 ab-
sent 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.9,10 Functioning levels as
measured by the ECOG and Karnofsky performance status scales
were recoded in 3 comparable categories, according to the simple conver-
sion table recently proposed by Buccheri and colleagues.94

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

STATISTICAL ANALYSIS

Kaplan-Meier survival curves were constructed for each cat-
egorical variable.92 The statistical significance of differ-
ences among survival curves was determined using 2-tailed
log-rank test.93 The Cox regression method94 was also used
to examine variables as single main-effect associations with
survival for all variables. A stepwise forward regression pro-
cedure based on the partial likelihood ratio was applied to
select factors of prognostic importance in a multivariate Cox
regression model. P<.06 and P>.10 were set, respec-
tively, as limits for variable inclusion and exclusion.

The proportionality of hazards associated with all in-
dependent predictors of survival was checked by visual in-
spection of the log-minus-log survival plots. For levels of
performance status and serum albumin, the difference be-
tween the hazards was found to steadily decrease over time.
For these variables, Cox regression with time-dependent
covariates was used.95 Interaction terms that were biologi-
cally meaningful were also investigated. Regression diag-
nostics included detection of outliers from Martingale re-
siduals96 and identification of influential observations from
plots of DBeta.97

SAMPLE SIZE

Power estimates were performed a priori, using the method
of Schoenfeld98 and the EGRET Size software program.99
In both methods, albumin serum levels were considered as
the main exposure. This variable was dichotomized as high-
normal (ie, ≥35 g/L) and low (<35 g/L). According
to previous reports, a sampling fraction of 46% of pa-
tients51 and conservative hazards ratios for the risk for dy-
ning 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 package100 was used for
all other statistical analyses.

Mean age for the sample was 62 years (range, 29–92 years).
The median and mean survival times of the overall group
were 15.3 and 25.0 weeks, respectively. The Kaplan-
Meier estimates of the 2-, 4-, and 6-month survival rates
were 69.0%, 48.8%, and 34.3%, respectively.

As can be seen from Table 1, most of the patients
were white (91.6%), presented with high tumor burden
(67.0%) with a prevalence of visceral metastasis
(85.9%), and received cancer treatments in the terminal
phase (64.8%). They also presented with triceps skin-
folds in the lower range (67.0%) and experienced moderate-to-severe fatigue (68.7%), anorexia (62.1%)
and impairment of well-being (68.3%).

Since the results of survival analyses using continu-
ous variables were substantially the same as when the vari-
ables were categorized, and since the latter are more easily
described and clinically interpreted, findings are pre-
sented in terms of categorical variables (Table 2). Vari-
bles more discriminant for worse survival in the univari-
ate analysis (P<.01) were lung cancer; liver metastasis; more
than 5 cancerous lesions; moderate-to-severe comorbid-
ity; cognitive impairment; weight loss above the 50th per-
centile of the sample; triceps skinfold measurements less
than the 50th percentile for a standard population of North
American men and women of the same mean age as our
sample101; lower performance status; above-average num-
ber of symptoms; serum levels of sodium, albumin, LDH,
and alkaline phosphatase beyond reference ranges; and
granulocyte and lymphocyte absolute counts beyond ref-
ence ranges. Patients with CES of 2 to 6 months and longer
### 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><strong>Significant†</strong></td>
<td></td>
<td></td>
</tr>
<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></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>70 (30.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>80 (35.2)</td>
<td>0.9 (0.6-1.2)</td>
</tr>
<tr>
<td>Lung</td>
<td>77 (33.9)</td>
<td>1.6 (1.2-2.2)†</td>
</tr>
<tr>
<td>Brain metastases</td>
<td>57 (25.1)</td>
<td>1.4 (1.0-1.9)</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>74 (32.8)</td>
<td>1.2 (1.2-2.3)</td>
</tr>
<tr>
<td>Tumor burden &gt;5 lesions</td>
<td>192 (87.0)</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>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>90 (39.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>2-6</td>
<td>71 (31.3)</td>
<td>1.8 (1.3-2.4)‡</td>
</tr>
<tr>
<td>3-4</td>
<td>66 (29.1)</td>
<td>2.3 (1.6-3.2)‡</td>
</tr>
<tr>
<td>Karnofsky performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥80</td>
<td>64 (28.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>70-60</td>
<td>106 (46.7)</td>
<td>1.6 (1.2-2.2)‡</td>
</tr>
<tr>
<td>≤50</td>
<td>57 (25.1)</td>
<td>2.3 (1.6-3.2)‡</td>
</tr>
<tr>
<td>EFAT performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>114 (50.2)</td>
<td>1.6 (1.2-2.1)‡</td>
</tr>
<tr>
<td>Weight loss &gt;8.1 kg</td>
<td>109 (48.3)</td>
<td>1.6 (1.2-2.2)‡</td>
</tr>
<tr>
<td>Triceps skinfold &lt;50th percentile</td>
<td>152 (67.0)</td>
<td>1.6 (1.2-2.3)‡</td>
</tr>
<tr>
<td>Clinical estimation of survival, mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>30 (14.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>2-6</td>
<td>123 (57.7)</td>
<td>0.4 (0.3-0.7)†</td>
</tr>
<tr>
<td>&gt;6</td>
<td>60 (28.2)</td>
<td>0.2 (0.1-1.0)‡</td>
</tr>
<tr>
<td>Fatigue moderate or worse</td>
<td>156 (68.7)</td>
<td>1.4 (1.0-1.9)</td>
</tr>
<tr>
<td>Nausea moderate or worse</td>
<td>50 (22.0)</td>
<td>1.5 (1.1-1.8)</td>
</tr>
<tr>
<td>Drowsiness moderate or worse</td>
<td>98 (43.2)</td>
<td>1.3 (1.0-1.8)</td>
</tr>
<tr>
<td>Anorexia moderate or worse</td>
<td>141 (62.1)</td>
<td>1.4 (1.1-1.9)</td>
</tr>
<tr>
<td>Impairment of well-being</td>
<td>155 (68.3)</td>
<td>1.4 (1.0-1.9)</td>
</tr>
<tr>
<td>Dyspnea moderate or worse</td>
<td>74 (32.6)</td>
<td>1.4 (1.0-1.8)</td>
</tr>
<tr>
<td>Distress score &lt;50th percentile</td>
<td>115 (50.7)</td>
<td>1.4 (1.1-1.9)</td>
</tr>
<tr>
<td>Symptom number &lt;50th percentile</td>
<td>95 (41.9)</td>
<td>1.4 (1.1-1.9)</td>
</tr>
<tr>
<td>Serum sodium level &lt;135 mmol/L</td>
<td>42 (23.1)</td>
<td>1.8 (1.3-2.5)</td>
</tr>
<tr>
<td>Serum albumin level &gt;35 g/L</td>
<td>109 (49.3)</td>
<td>1.9 (1.4-2.5)‡</td>
</tr>
<tr>
<td>Leukocyte count &gt;11×10^9/L</td>
<td>48 (22.4)</td>
<td>1.5 (1.1-1.2)</td>
</tr>
<tr>
<td>Granulocyte count &gt;7.5×10^9/L</td>
<td>58 (28.8)</td>
<td>1.5 (1.1-1.2)</td>
</tr>
<tr>
<td>Lymphocyte count &lt;1×10^9/L</td>
<td>104 (51.5)</td>
<td>2.1 (1.6-2.6)‡</td>
</tr>
<tr>
<td>LDH level &gt;618 U/L</td>
<td>85 (43.4)</td>
<td>1.9 (1.5-2.6)‡</td>
</tr>
<tr>
<td>Alkaline phosphatase level &gt;130 U/L</td>
<td>53 (40.4)</td>
<td>1.9 (1.3-2.8)‡</td>
</tr>
</tbody>
</table>

### Nonsignificant§

| Variables                        | No. (%) of Sample | Hazard Ratio (95% CI) |
|----------------------------------|-------------------|                      |
| Male                             | 82 (36.1)         |                      |
| Age ≥65 y                        | 94 (41.4)         |                      |
| White                            | 208 (91.6)        |                      |
| Married                          | 159 (70.5)        |                      |
| Personal yearly income less than | 115 (50.7)        |                      |
| mean                              | 63 (28.7)         |                      |
| Family yearly income less than   | 47 (20.7)         |                      |
| mean                              | 34 (15.0)         |                      |
| Impairment in social support     | 76 (33.5)         |                      |
| Staging (inoperable vs metastatic)| 79 (34.8)       |                      |
| Bone metastases                  | 84 (37.0)         |                      |
| Lymphonodal metastases           | 10 (4.4)          |                      |
| Lung metastases                  | 195 (85.9)        |                      |
| Cancer treatments (stopped vs    | 147 (64.8)        |                      |
| continued in terminal phase)     | 103 (45.4)        |                      |
| Pain moderate or worse           | 88 (38.8)         |                      |
| Anxiety moderate or worse        | 59 (26.9)         |                      |
| Depression moderate or worse     | 13 (6.6)          |                      |
| Serum calcium level >2.65 mmol/L | 32 (15.1)         |                      |

*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.

†P < .05
‡P < .01
§Hazard ratios and 95% CIs were not calculated for statistically nonsignificant variables.

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 more than 6 months had significantly better survivals than patients with poorer prognostic features.
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.

Table 2. Final Cox Regression Models Based on Clinical Variables (Model 1) and Clinical and Laboratory Variables (Model 2)*

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Reference Category</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung primary tumor</td>
<td>Breast or gastrointestinal tract tumors</td>
<td>2.0 (1.2-3.6)†</td>
<td>1.9 (1.1-3.3)†</td>
</tr>
<tr>
<td>Presence of liver metastases</td>
<td>Absence</td>
<td>2.2 (1.6-3.3)</td>
<td>2.4 (1.6-3.4)</td>
</tr>
<tr>
<td>Tumor burden &gt;5 lesions</td>
<td>&lt;5 lesions</td>
<td>1.8 (1.2-2.8)</td>
<td>1.5 (0.9-2.2)</td>
</tr>
<tr>
<td>Moderate-to-severe comorbidity</td>
<td>Absent-mild</td>
<td>1.7 (1.2-2.6)</td>
<td>1.7 (1.1-2.6)</td>
</tr>
<tr>
<td>Weight loss &gt;8.1 kg</td>
<td>=8.1 kg</td>
<td>1.4 (0.8-2.1)</td>
<td>2.4 (1.3-4.4)†</td>
</tr>
<tr>
<td>Performance status ECOG 2-4</td>
<td>ECOG 0-1</td>
<td>2.3 (1.3-4.0)†</td>
<td>1.6 (0.9-2.9)†</td>
</tr>
<tr>
<td>Moderate-to-severe nausea</td>
<td>Absent-mild</td>
<td>1.5 (1.0-2.3)</td>
<td>1.7 (1.1-2.7)</td>
</tr>
<tr>
<td>Clinical estimation of survival</td>
<td>=2 mo</td>
<td>0.4 (0.1-0.4)</td>
<td>0.5 (0.3-0.8)</td>
</tr>
<tr>
<td>2-6 mo</td>
<td>&gt;6 mo</td>
<td>0.2 (0.1-0.4)</td>
<td>0.3 (0.2-0.6)</td>
</tr>
<tr>
<td>Serum albumin level &lt;35 g/L</td>
<td>≥35 g/L</td>
<td>Not included</td>
<td>7.3 (2.9-18.1)†</td>
</tr>
<tr>
<td>Lymphocyte count &lt;1×10^9/L</td>
<td>≥1×10^9/L</td>
<td>Not included</td>
<td>2.4 (1.5-4.2)†</td>
</tr>
<tr>
<td>LDH &gt;618 U/L</td>
<td>≤618 U/L</td>
<td>Not included</td>
<td>1.8 (1.2-2.7)</td>
</tr>
<tr>
<td>Performance status by time covariate</td>
<td>NA</td>
<td>0.98 (0.96-1.00)</td>
<td>0.98 (0.96-1.00)</td>
</tr>
<tr>
<td>Serum albumin level &lt;35 g/L by time covariate</td>
<td>NA</td>
<td>Not included</td>
<td>0.96 (0.94-0.99)</td>
</tr>
<tr>
<td>Lung cancer by weight loss &gt;8.1 kg</td>
<td>NA</td>
<td>2.5 (1.2-5.2)</td>
<td>2.4 (1.1-5.1)</td>
</tr>
<tr>
<td>Serum albumin level &lt;35 g/L by weight loss &gt;8.1 kg</td>
<td>NA</td>
<td>Not included</td>
<td>0.4 (0.2-0.9)</td>
</tr>
<tr>
<td>Serum albumin level &lt;35 g/L by lymphocyte count &lt;1×10^9/L</td>
<td>NA</td>
<td>Not included</td>
<td>0.4 (0.2-0.9)</td>
</tr>
</tbody>
</table>

*NA indicates not applicable. Other abbreviations are given in the first footnote to Table 1.
†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.

Table 3. Hazard Ratios for Interacting Covariates in Model 1*

<table>
<thead>
<tr>
<th>Interacting Covariate</th>
<th>Among Patients With</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung primary tumor</td>
<td>Weight loss &gt;8.1 kg</td>
<td>5.6 (2.9-1.3)</td>
</tr>
<tr>
<td></td>
<td>No weight loss &gt;8.1 kg</td>
<td>2.4 (1.4-4.3)</td>
</tr>
<tr>
<td>Weight loss &gt;8.1 kg</td>
<td>Lung primary tumor</td>
<td>3.7 (1.7-8.1)</td>
</tr>
<tr>
<td></td>
<td>No primary tumor</td>
<td>1.2 (0.7-2.0)</td>
</tr>
<tr>
<td>Performance status ECOG 2-4</td>
<td>At 8-wk follow-up</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>At 24-wk follow-up</td>
<td>...</td>
</tr>
</tbody>
</table>

*Ellipses indicate not applicable. Other abbreviations are given in the first footnote to Table 1.

Table 4. Hazard Ratios for Interacting Covariates in Model 2*

<table>
<thead>
<tr>
<th>Interacting Covariate</th>
<th>Among Patients With</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung primary tumor</td>
<td>Weight loss &gt;8.1 kg</td>
<td>4.0 (3.1-4.9)</td>
</tr>
<tr>
<td>Weight loss &gt;8.1 kg</td>
<td>No weight loss &gt;8.1 kg</td>
<td>1.8 (1.2-2.4)</td>
</tr>
<tr>
<td></td>
<td>No lung primary tumor</td>
<td>2.5 (2.0-3.0)</td>
</tr>
<tr>
<td></td>
<td>Low albumin level</td>
<td>1.1 (0.2-2.0)</td>
</tr>
<tr>
<td>Lymphocyte count &lt;1×10^9/L</td>
<td>Low albumin level</td>
<td>1.1 (0.2-2.0)</td>
</tr>
<tr>
<td></td>
<td>No low albumin level</td>
<td>2.7 (2.2-3.2)</td>
</tr>
<tr>
<td>Serum albumin level &lt;35 g/L</td>
<td>At 8-wk follow-up</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>No weight loss &gt;8.1 kg</td>
<td>5.9 (3.0-6.8)</td>
</tr>
<tr>
<td></td>
<td>Low lymphocyte count</td>
<td>2.4 (1.3-3.5)</td>
</tr>
<tr>
<td></td>
<td>Weight loss &gt;8.1 kg</td>
<td>1.3 (0.1-2.5)</td>
</tr>
<tr>
<td></td>
<td>No weight loss &gt;8.1 kg</td>
<td>3.1 (2.0-4.1)</td>
</tr>
<tr>
<td></td>
<td>Low lymphocyte count</td>
<td>1.2 (0.1-2.4)</td>
</tr>
<tr>
<td>Performance status ECOG 2-4</td>
<td>At 8-wk follow-up</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>At 24-wk follow-up</td>
<td>...</td>
</tr>
</tbody>
</table>

*Ellipses indicate not applicable. Other abbreviations are given in the first footnote to Table 1.

and gastrointestinal tract cancers. These criteria present certain limitations. They rely on specific therapeutic schemes (eg, those undergoing treatment of advanced breast cancer may not contemplate chemotherapy sequential trials); they may change according to the state of the art in the management of neoplastic diseases; and they are influenced by the time patients seek cancer care (eg, disease progression may be discovered earlier through a 3-month instead of 6-month follow-up). However, these criteria provide benchmarks by which to enroll patients at common points in the course of their terminal disease that would otherwise be difficult to define. Furthermore, the palliative nature of the tumor-directed treatments administered after the study ac-

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,
crual 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.\textsuperscript{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,\textsuperscript{90} but shorter than that reported for patients with advanced cancer.\textsuperscript{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.\textsuperscript{51} Performance status is well recognized as an important prognostic factor for survival in patients with end-stage and advanced cancer.\textsuperscript{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.\textsuperscript{18,43} 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 LDH level. This has been correlated with the disease extent of different malignant neoplasms\textsuperscript{102,103} 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.\textsuperscript{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.\textsuperscript{105}

Several studies have advocated the inclusion of CES in multivariate models for the survival prediction of patients with advanced and terminal cancer.\textsuperscript{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,\textsuperscript{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,\textsuperscript{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,\textsuperscript{107} this symptom frequently reflects dysfunctions in the autonomic nervous system of this population.\textsuperscript{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 advanced\textsuperscript{37} or end-stage cancer.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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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