Original Article

Prediction of Survival in Terminal Cancer Patients in Taiwan: Constructing a Prognostic Scale

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Abstract

We prospectively identified prognostic factors and developed a prognostic scale in 356 Taiwanese terminal cancer patients (training set). Demographic data, severity of symptoms/signs, and survival were statistically analyzed to create the scale, which was tested in another 184 patients (testing set). In the training set, liver and lung metastases, functional performance status, weight loss, edema, cognitive impairment, tiredness, and ascites were independently associated with shorter survival (multivariate analysis). The scale ranged from 0.0 (no altered variables) to 8.5 (maximal alteration for all variables). When scores were <3.5, 2-week survival was predicted with 0.72 and 0.61 accuracy for the training and testing sets, respectively. With scores <6.0, 1-week survival was predicted with 0.72 and 0.66 accuracy, respectively. This scale, which includes lung and liver metastases and severity of symptoms/signs, may help in identifying the stage of dying and its corresponding symptoms/signs and also in improving survival prediction in terminal cancer patients. J Pain Symptom Manage 2004;28:115–122.

Key Words

Prediction, survival, terminal cancer patients, palliative care

Introduction

Previous studies have shown that the ability to predict survival in terminal cancer patients could help in providing timely palliative care and in planning appropriate therapy without overtreatment or undertreatment.[1–3] In addition, the prediction of survival in the late terminal phase could improve patients' preparation for death and quality-of-life closure.[4]

Clinical symptoms and signs not only represent the natural course of terminal illness but also provide information about survival.[5,6] In the ancient Tibetan Buddhist tradition, the terminal dying process in humans was classified into five consecutive stages of disintegration with corresponding symptoms and signs.[7] Several studies have reported that clinical symptoms, signs, and assessments of performance status could improve survival prediction in terminal cancer patients.[5,6,8–17] Furthermore, Maltoni

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et al. and Morita et al., respectively, have developed scoring systems to assign different probabilities of survival for 30 days and to predict 3- and 6-week survival with a sensitivity and specificity of more than 70%.[18–21]

The prevalence of liver cancer and head/neck cancer is higher in Taiwan than in Japan, Europe, or America and similar to the rate in southern areas of Mainland China.[3] In addition, because referral to the palliative care unit usually happens late in the course of terminal disease, the median survival of patients is only about 14 days.[3] To our knowledge, no formal studies of survival prediction have been performed in terminal cancer patients in Taiwan, although it is an important issue in patient care. Thus, we conducted a prospective study involving two data sets in terminal cancer patients to determine the relationships between demographic and clinical data, performance status, severity of symptoms/signs, and subsequent survival. Afterward, we identified the significant prognostic factors and integrated them into a scale for validation, with the aim of constructing a useful prognostic scale for use in patients with terminal cancer.

Methods

Patients

A total of 356 consecutive patients admitted to the palliative care unit at National Taiwan University Hospital between September 1997 and April 1999 were enrolled in this study. Data from these patients served as the training set for developing the prognostic scale. Afterward, 184 consecutive patients admitted to the same unit from December 2001 through July 2002 were enrolled. Their data served as the testing set for the scale. The palliative care unit at National Taiwan University Hospital takes care of patients with incurable cancer who are referred from other wards of the same hospital, as well as from other hospitals or from home. The decision to admit a patient is made after an initial assessment, according to the governmental regulations for hospice and palliative care. About 30% of admitted patients are discharged home in stable condition after receiving active, total inpatient care. Members of the multidisciplinary team invest considerable time in restoring the patient's best possible functional status and in planning the discharge of patients who can possibly return home. The selection of patients and design of this study were approved by the ethical committee in the hospital.

Data Collection

An experienced staff comprising physicians and senior nurses who took care of the patients during the study period recorded each patient's medical condition on a daily basis. All data were analyzed in a weekly team meeting, which helped to ensure that the data were as complete and correct as possible. The information collected in the study included the following: 1) personal data and data related to the patients' state of illness; 2) data related to previous treatment; and 3) clinical data, including performance status and severity of symptoms and signs (Table 1). All of the variables on the recording form were designed after careful scrutiny of the literature.[22–25] The selection of symptoms and signs was on the basis of previous studies in the same unit.[3,26] The recording form was also tested for content validity with a panel and used in a pilot test involving 10 patients to confirm its ease of application. Patients' performance status was assessed by using the Eastern Cooperative Oncology Group (ECOG) performance status. Higher scores on the ECOG (range, 0–4) indicated a poorer performance status. The severity of symptoms and signs on admission were assessed. Symptoms noted included pain, dyspnea, tiredness, anorexia, dysphagia, xerostomia, nausea, vomiting, constipation, restless, depression, and insomnia. These were graded according to the patient's or caregiver's descriptions, as follows: 0 = never happened; 1 = mild or seldom happened; 2 = moderate or sometimes happened; and 3 = severe or continuously happened. For cognitive impairment, the degree of severity was graded as follows: 0 = never happened; 1 = lethargy; 2 = confusion; and 3 = comatose. For edema, jaundice, and ascites, the degree of severity was graded according to the clinical examination results: 1 = pitting edema less than one-half finger breadth, slight yellowish sclera, and ascites noted only by means of ultrasonographic examination; 2 = pitting edema between one-half and one finger breadth, remarkable yellow sclera, and ascites with shifting dullness on physical examination; and 3 = pitting edema greater than one finger

Table 1
Characteristics of Patients in the Training Set (Univariate Survival Analysis) and Testing Set

	Training Set	*P*-value of Log-Rank Test for Training Set	Testing Set
No. of patients	356		184
Median/Mean survival (days)	13/21		15/24
Sex, %		0.7	
Female	46		47
Male	54		53
Age (in years), %		0.9	
<40	9		7
40–64	45		40
≥65	46		53
Referral places, %		0.01	
Emergency room	27		21
Oncology ward	11		15
Other wards	33		33
Other hospitals	7		7
Home	22		25
Primary cancer sites, %		0.3	
Lung	20		19
Liver	16		15
Colorectal	10		10
Stomach	6		4
Head and Neck	6		7
Pancreas	5		10
Male urogenital	4		2
Female urogenital	3		3
Unknown primary site	3		4
Breast	3		7
Esophagus	3		2
Others	21		17
Metastasis		0.3	
Bone	34	0.3	34
Lung	22	0.04	20
Liver	29	0.03	30
Brain	11	1.0	15
Ever surgical treatment, %	51	0.04	50
Ever chemotherapy, %	44	0.6	46
Ever radiotherapy, %	33	0.07	35
Ever herb medication, %	11	0.2	13

breadth, yellow to greenish sclera, and ascites with umbilical protrusion. For weight loss in the recent 3 months, 1 = less than 5%; 2 = between 5% and 10%; and 3 = more than 10%. The staff entered the data of higher value, if different assessments were made of severity and frequency by the patients.

Statistical Analysis

Survival time was calculated from the date of admission to the date of death or to the end of study period for those still alive. Results from patients who were alive at the end of the study period were treated as censoring data and also included in the following analyses. First, using the data of the training set, we traced the survival curves of every variable using the Kaplan-Meier method and compared the survival curves based on the log-rank test. Then, variables with $P < 0.1$ were considered putative prognostic factors and included in the multivariate analysis. We examined the plot of $\ln - \ln(S(t))$, where the $S(t)$ is the Kaplan-Meier estimate of the survival curves, against the logarithm of the time for each level of the variables in the study. The result suggested that the Cox regression model might serve for parametric modeling of the data.[27,28] Hence, the final model was built using the Cox regression model fitted with a backward selection procedure.

To construct a convenient scoring system with the prognostic factors in the final model, the value of the corresponding regression coefficient was divided by 0.5, and the result was rounded to decimal. The total score for a given patient was obtained by adding his or her appropriate partial scores.

Cutoff points for the prediction of survival shorter than 1 or 2 weeks were determined from

the training set to obtain the best accuracy for prediction. Then the accuracy of the prediction was evaluated by using the testing set. All the analyses were performed using SPSS version 10.0 statistical software (SPSS Inc, Chicago, IL).

Results

The median survival of our study patients was 13 days for the training set and 15 days for the testing set; survival was not significantly different, as determined by means of the log-rank test. The comparison of demographic characteristics, referral place, primary cancer site, and metastasis site between the training set and the testing set are shown in Table 1. No statistically significant differences were noted. In addition, we examined the survival impact of the aforementioned variables in the training set by conducting a log-rank test. Patients from different referral places had different prognoses, with those referred from an emergency department having the shortest survival. Patients with lung and liver metastasis had a shorter survival time than those without these metastases (Table 1). Performance status, clinical symptoms and signs on admission, and corresponding survival data are shown in Table 2. A total of 17 putative prognostic factors were determined by means of the univariate log-rank test. These were referral place ($P = 0.01$), lung metastasis ($P = 0.04$), liver metastasis ($P = 0.03$), surgical treatment ($P = 0.04$), radiotherapy ($P = 0.07$), dyspnea ($P = 0.002$), tiredness ($P < 0.001$), anorexia ($P < 0.001$), cognitive impairment ($P < 0.001$), dysphagia ($P < 0.001$), restlessness ($P = 0.047$), vomiting ($P = 0.06$), edema ($P < 0.001$), ascites ($P < 0.001$), jaundice ($P < 0.001$), weight loss ($P = 0.002$), and ECOG performance status ($P < 0.001$).

For the 356 patients who underwent complete assessment in the training set, an exponential regression model was used to investigate the independent effect of each putative prognostic factor. Table 3 shows the maximal likelihood estimates of the regression coefficient, Wald statistics, and severity for each prognostic factor retained in the final model. Lung metastasis, liver metastasis, tiredness, ascites, edema, cognitive impairment, body weight loss, and performance status maintained an independent prognostic effect. In addition, Table 3 shows the partial score value for each category, which was obtained by dividing each regression coefficient by 0.5. However, this rule seems to have an exception in the calculation of partial score for the severity of cognitive impairment. In the study, when the severity of cognitive impairment is 1 (lethargy), the coefficient is 0.25 and the partial score is converted into 0.5. When the severity is 2, the coefficient is 0.44, but when the severity is 3, the coefficient is only 0.12. In order to meet our original assumption, we made the average coefficient, which is 0.28

Table 2
Prevalence of Symptoms/Signs by the Severity and Univariate Survival Analysis for the Training Set

Problems	Prevalence (%) by Severity (0/1/2/3) of Training Set	*P*-value of Log-Rank Test for Training Set	Prevalence (%) by Severity (0/1/2/3) of Testing Set
Pain	19/48/23/10	0.3	13/33/33/21
Dyspnea	41/36/14/9	0.002	44/23/21/12
Tiredness	10/29/30/31	<0.001	9/27/41/23
Anorexia	13/28/30/29	<0.001	30/33/25/12
Cognitive impairment	54/18/16/12	<0.001	62/15/11/12
Dysphagia	43/22/17/18	<0.001	64/15/11/10
Restless	39/33/20/8	0.047	39/31/20/10
Depression	38/34/19/9	0.28	40/34/19/7
Vomiting	52/25/15/8	0.06	57/26/13/4
Insomnia	48/26/21/5	0.97	50/24/20/6
Xerostomia	58/25/12/5	0.7	66/27/7/0
Edema	44/24/18/14	<0.001	52/33/11/4
Ascites	61/13/12/14	<0.001	72/15/6/7
Constipation	47/22/21/10	0.7	40/33/25/2
Jaundice	68/11/5/16	<0.001	73/15/8/4
Weight loss	28/39/23/10	0.02	51/25/17/6
ECOG(1/2/3/4)	7/14/30/49	<0.001	0/4/12/33/50

ECOG: Eastern Cooperative Oncology Group performance status.

Table 3
Significant Predictors for the Length of Survival Time in the Final Model by Using Exponential Multiple Regression Analysis

	Severity	Coefficient	*P*-value	Partial Score
Lung metastasis	no	0		0
	yes	0.25	0.06	0.5
Liver metastasis	no	0		0
	yes	0.23	0.07	0.5
Tiredness	0	0		0
	1	−0.22	0.27	0
	2	−0.28	0.18	0
	3	0.47	0.03	1
Ascites	0	0		0
	1	−0.01	0.94	0
	2	0.53	0.01	1
	3	0.49	0.01	1
Edema	0	0		0
	1	0.45	0.006	1
	2	0.59	<0.001	1
	3	0.50	0.006	1
Cognitive impairment	0	0		0
	1	0.25	0.11	0.5
	2	0.44	0.01	0.5
	3	0.12	0.59	0.5
Weight loss	0	0		0
	1	0.11	0.41	0.2
	2	0.37	0.03	0.7
	3	0.55	0.01	1
ECOG	1	0		0
	2	0.83	0.30	1.5
	3	1.00	0.17	2
	4	1.40	0.06	3

Prognostic scale score = Lung mets score + Liver mets score + Tiredness score + Ascites score + Edema score + Cognitive impairment score + Weight loss score + ECOG score.

([0.44+0.12]/2), and the partial score both in the severity of 2, and 3 was converted into 0.5. Further discussion in the future studies toward this assumption and rule is a worthwhile effort.

The results in Table 3 also revealed three types of relationships between the magnitude of the effect on survival and the severity of symptoms. First, the impact of some prognostic factors, such as tiredness and ascites, on survival were observed up to a certain degree of severity. Second, the impact of some prognostic factors, such as edema and cognitive impairment, had equal magnitude throughout each degree of severity. Third, the impact of still other prognostic factors, such as weight loss and performance status, increased with each degree of severity.

For a given patient, the score on the prognostic scale was calculated by adding his or her partial scores (Table 3). Scores ranged from 0.0 (no altered variables) to 8.5 (maximal alteration for all variables). Table 4 shows the result of survival prediction. When the cutoff score was more than 3.5, the positive predictive value and negative predictive values for patients with survival time shorter than 2 weeks were 0.76 and 0.71 (accuracy, 0.72) in the training set. For the testing set, values were 0.63 and 0.60, respectively (accuracy, 0.61). When the cutoff score was more than 6.0, the positive predictive value and negative predictive value for patients with survival time shorter than 1 week were 0.75 and 0.70 in the training set (accuracy, 0.72). For the testing set, values were 0.43 and 0.76, respectively (accuracy, 0.66).

Discussion

Results of previous studies seem to suggest a consensus concerning survival prediction in patients with advanced or terminal cancer. That is, performance status and clinical symptoms and signs such as anorexia, dysphagia, weight loss, cognitive impairment, and dyspnea seem to be reliable prognostic factors.[6–17] In their studies, Pirovano and Maltoni and colleagues[18–19] started to integrate the prognostic factors into

Table 4
Accuracy of Prognostic Scale in Survival Prediction for Training and Testing Sets

	Training Set			Testing Set		
	Positive Predictive Value	Negative Predictive Value	Accuracy	Positive Predictive Value	Negative Predictive Value	Accuracy
Prediction of shorter than 2 weeks (cutoff score ≥ 3.5)	0.76	0.71	0.72	0.63	0.60	0.61
Prediction of shorter than 1 week (cutoff score ≥ 6.0)	0.75	0.70	0.72	0.43	0.76	0.66

a scoring system called the Palliative Prognostic Score (PaP Score) by using the clinical prediction of survival (by physicians), the Karnofsky Performance Status, the presence of anorexia and/or dyspnea, and the white blood cell count and lymphocyte percentage. The PaP Score successfully classifies terminal cancer patients into three stages based on a 30-day survival probability of more than 70%, between 30% and 70%, and less than 30%. Morita et al.[20–21] also reported a scoring system called the Palliative Prognostic Index (PPI), which includes a palliative performance scale and an assessment of oral intake (moderately reduced, severely reduced), edema, dyspnea at rest, and delirium. They could predict 3- and 6-week survival with acceptable accuracy. However, the median survival of patients referred for inpatient palliative care was usually about 2 weeks, which is also noted in Taiwan.[3,13,14] Developing a scoring system for patients with survival less than 2 weeks is important in planning for death and for optimizing hospice palliative care.

Just as different grades of performance status have different influences on survival, our study demonstrated that different degrees of severity of the prognostic factors also had different effects on survival. With the prognostic scale that we developed, three types of relationships were observed between the magnitude of the effect on survival and the degree of severity of the symptoms. The impact of tiredness and ascites on survival were observed up to a certain degree of severity. The impact of edema and cognitive impairment had equal magnitude throughout each degree of severity. The impact of weight loss and performance status increased with each degree of severity. We might infer that the symptoms and signs affecting a patient's survival until they became moderate or severe appear at an earlier stage in the dying process, whereas symptoms and signs affecting survival when they were just mild appear at a relatively late stage. That is, the process of dying could be classified by stages according to the presentation of symptoms and signs. This inference mimics the dying process described in Tibetan Buddhist teachings.[5]

The process of dying explained in Tibetan Buddhist teachings consists of two phases of dissolution: an outer dissolution, when the senses and elements dissolve, and an inner dissolution of the gross and subtle thought states and emotions. The senses include hearing, sight, smell, taste, and touch, and their dissolution means that they are no longer fully experienced. The dissolution of the elements involves earth, water, fire, and air. Symptoms and signs correspond to each stage of the dissolution of elements as well. For example, dyspnea and cognitive impairment are the symptoms corresponding to the fourth stage, dissolution of air element. When these symptoms appear, the later stage of the dying process has begun; therefore, dyspnea and cognitive impairment would affect survival, even if their degree of severity is mild. Moreover, the performance status relating to the physical weakness is corresponding to the process of earth dissolution. The Tibetan Buddhist teachings described, "During the process of earth dissolution, our body begins to lose all its strength. We are drained of any energy. We cannot get up, stay upright, or hold anything."[5]

Why these prognostic factors appeared in our prognostic scale is interesting. First, the impact of performance status and weight loss on survival increased with each degree of severity, similar to the result of Morita et al.[20] The relationship indicated that these prognostic factors might result from tumoral growth and a decrease in the patient's overall energy level. Second, unlike cognitive impairment, edema was seldom identified as a prognostic factor in

previous studies. The reason may be that edema is often iatrogenic and due to excessive artificial fluid supplementation, especially in terminal cancer patients in Taiwan; this practice might have caused edema in our study population. Third, we included ascites in our initial assessment because hepatocellular carcinoma is a major cause of death in Taiwan. This may also be the reason why liver metastasis appeared in our scoring system. Finally, lung metastasis, and not dyspnea, was noted on our prognostic scale. In our terminal cancer patients, lung metastasis was possibly so extensive that it represented failure of the respiratory system better than dyspnea.

Regarding the predictive accuracy of our prognostic scale, two points should be improved in future studies. First, the significant difference in the prevalence of weight loss between the two data sets might have lowered the predictive accuracy of our prognostic scale in the testing set. It was difficult for patients or caregivers to recall changes in body weight in the past 3 months; thus degrees of severity could easily have been misclassified. To improve accuracy in the assessment of weight loss, we suggest selecting a more reliable baseline body weight, such as the careful measurement and recording of body weight throughout the patient's illness. However, the prevalence of weight loss in the training set was 70%, similar to observations in previous studies.[3,10] Thus, the prognostic scale developed from the training set might still have improved survival prediction in similar populations. In comparison with the PPI,[20] the predictive accuracy for 1- and 2-week survival with our prognostic scale is not as high as the PPI for the accuracy of survival prediction for 3 and 6 weeks. Because the prognostic factors of the two scoring systems are similar (e.g., performance status, edema, delirium), other prognostic factors may need to be considered in patients with a median survival of about 2 weeks. These factors especially include those related to vital organ failure, such as oxygen saturation, peripheral cyanosis, and so on. Research in this area will be a worthwhile effort.

Our study had the same limitation in generalizability as that of previous studies. Vigano et al. proposed that variability in the inclusion of predictors for analysis and the lack of a representative inception cohort decreased the generalizability of many previous results.[29] Because the degree of hospice and palliative care varies around the world,[30] it is difficult to include a representative population at similar and specific points during the course of their terminal illness. The conclusion from one study population might not be applicable to other populations with different malignancies and different lengths of survival. In the future, a multicenter study in Taiwan could help in developing a more reliable prognostic scale for use in terminal cancer patients here.

In conclusion, constructing a prognostic scale that includes metastasis to lung and liver and the severity of symptoms/signs can help in identifying the stage of dying and its corresponding symptoms/signs. Such a scale may improve the prediction of survival in Taiwanese patients with terminal cancer.

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