ORIGINAL ARTICLE

Identifying prognostic factors for survival in advanced cancer patients: a prospective study

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Objective To identify potential prognostic factors affecting the survival in patients with advanced cancer in a local palliative care unit.

Design Prospective cohort study.

Setting Palliative Care Unit of a regional hospital in Hong Kong.

Patients All advanced cancer in-patients and out-patients who were enrolled into the palliative care service of the United Christian Hospital between January and December 2002 were recruited.

Main outcome measures Potential prognostic factors including demographic data, tumour characteristics, blood parameters, functional status, co-morbidities, total symptom score, and psychosocial parameters were recorded upon enrolment.

Results A total of 170 patients were eligible for analysis; their mean age was 69 (standard deviation, 12) years, of which 106 (62%) were male. Overall median survival was 77 (interquartile range, 31-160) days. The most frequent primary malignancy was lung (n=58, 34%), followed by liver (n= 24, 14%) and lower gastro-intestinal tract (n=24, 14%). By univariate analysis, 11 factors affected survival, including: age (P=0.040), number of metastatic sites involved (P=0.001), peritoneal metastases (P=0.009), skin metastases (P=0.011), tachycardia (P=0.009), serum albumin concentration (P<0.001), white cell count (P=0.002), Karnofsky Performance Status score (P<0.001), Hamilton Depression Scale score (P=0.004), Edmonton Symptom Assessment System score (P=0.003), and McGill Quality of Life (Hong Kong)–single item score (P=0.002). Multivariable Cox regression analysis revealed that only age (hazard ratio=0.84; 95% confidence interval, 0.73-0.96), number of metastatic sites involved (1.33; 1.13-1.56), serum albumin concentration (0.95; 0.92-0.98), Karnofsky Performance Status score (0.86; 0.78-0.96), and Edmonton Symptom Assessment System score (1.22; 1.05-1.41) were independent prognosticators.

Conclusion Age, number of involved metastatic sites, serum albumin, Karnofsky Performance Scale score, and Edmonton Symptom Assessment System score were independent prognosticators. Further studies are needed to provide a prognostic instrument applicable in local clinical settings.

Introduction

While life prolongation is often not the goal of care for advanced cancer patients, predicting survival can facilitate the provision of appropriate palliative care. However predicting the life expectancy of advanced cancer patients is one of the most difficult tasks for clinicians, who are often asked, "How long have I got, doctor?" Traditionally, clinicians often rely on intuition or clinical experience in estimating survival, though it is recognised that such estimation has a tendency to overestimate by a factor of two,[1-8] whereas survival prediction becomes more accurate closer to the date of death.[5,6,8]

Hence identification of objective measurable factors that can improve the prognostic accuracy can assist clinicians to decide upon the most appropriate management plan, to help patients and families develop better insight into their terminal phase, so that they can set their goals, priorities, and expectations with more confidence.

For the past decade, prognostic studies in advanced cancer patients have been

Key words
Life expectancy; Prognosis; Neoplasms; Survival analysis

Hong Kong Med J 2007;13:453-9

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一項探討末期癌症病人存活期預後因素的前瞻性研究

目的 探討在本地一間紓緩治療科的末期癌症病人存活期的潛在性預後因素。

設計 前瞻性定群研究。

安排 香港一所地區醫院的紓緩治療科。

患者 在2002年1月至12月期間於基督教聯合醫院紓緩治療科的住院及門診病人。

主要結果測量 潛在性預後因素，包括個人資料、癌症種類、血液參數、功能性症狀、全面症狀評估、病徵總分、心理及社交狀況等。

結果 共170位末期癌症病人參與此研究，平均年齡為69歲（標準差：12歲），其中106位病人（62%）為男性。而整體存活率中位數為77日（四分值域：31-160日）。大部份病理確診為肺癌（58例，34%），其次為肝癌（24例，14%）及大腸癌（24例，14%）。在一元方差分析中，發現有11個主要因素影響存活期，包括年齡（P=0.040）、癌症遷移數目（P=0.001）、腹腔遷移（P=0.009）、皮膚遷移（P=0.011）、心動快速（P=0.009）、蛋白量（P<0.001）、白血球數量（P=0.002）、遠期生活質量量表（KPS）得分（P<0.001）、漢密頓抑鬱量表（HDS）得分（P=0.004）、Edmonton Symptom Assessment System（ESAS）得分（P=0.003）及生活質素（P=0.002）。使用多因素回歸分析顯示只有年齡（風險比=0.84；95%置信區間：0.73-0.96）、癌症遷移數目（1.33；1.13-1.56）、蛋白量（0.95；0.92-0.98）、KPS得分（0.86；0.78-0.96）、和ESAS得分（1.22；1.05-1.41）為獨立預後因素。

結論 年齡、遷移位置的數目、蛋白量、KPS及ESAS得分都是獨立的預後因素，須進一步研究可供本地醫生使用的預後工具。

performed extensively in western and Asian societies.[9-11] To our knowledge, no such formal studies have been undertaken in Hong Kong. The aim of this study was to identify potential objective measurable prognostic factors affecting survival among advanced cancer patients in a local palliative care unit.

Methods

This was a prospective cohort study of all patients with advanced cancer older than 18 years with an estimated life expectancy of less than 6 months according to the referring clinicians, and who were newly enrolled into our palliative care service between January 2002 and December 2002 inclusive, either as in-patients or out-patients. The cancer was defined as advanced, when further attempts to arrest or control progression were deemed inapplicable. At the time of study, the in-patient Palliative Care Unit of the United Christian Hospital is a 20-bed ward, serving a population of over 600 000.

Upon study entry, the following information was recorded: demographic data (age, sex); tumour characteristics (primary site, site of metastases, and number of metastatic sites); co-morbidities (Charlson's co-morbid score).[12] Clinical data collected soon after admission included tachycardia (pulse rate >100 beats/min), blood parameters (haemoglobin, calcium, serum albumin,[13] total white cell count, lymphocyte percentage); total symptom score (Edmonton Symptom Assessment System, ESAS[14]); functional status (Karnofsky Performance Status, KPS[15]); cognitive status (Mini-mental State Examination—Cantonese version[16]), and psychospiritual factors (presence or absence of religious support, Hamilton Depression Scale score [HDS[17]], and the McGill Quality of Life [Hong Kong] (QOL [HK])–single item[18] score). The maximum dose of morphine taken and use of herbal medicine during the period of service utilisation were also recorded.

These variables were chosen because they were objective, measurable, and quantifiable and some had been found to be of prognostic significance in patients with advanced cancer in previous overseas studies. Apart from HDS and McGill QOL (HK)–single item, which were additional assessments, all others were part of our routine assessment upon initial enrolment.

This study was an observational study. Other than the additional initial assessments, the patients did not receive any extraordinary intervention or burden. Verbal consent from the patients was obtained prior to entry. Exclusion criteria were: (1) unwillingness to participate in the initial assessments, (2) inability to communicate, and (3) death within 24 hours of enrolment into the service (prior to assessment).

Statistical analysis

Survival time was defined as the period from the day of enrolment into the service to the day of death. Patients who were lost to follow-up in public hospitals, their date of death could not be determined from computer records. For those who were still surviving at the end of study, they would be censored at last contact, either at their last out-patient follow-up date or the date of last discharge for in-patients.

For the univariate analysis of categorical variables, median survival times were estimated by the Kaplan-Meier method and survival distributions compared using the two-tailed log-rank test. For univariate analysis of continuous variables, the Cox regression model was used to examine single main-effect associations with survival. Variables that were significant (P<0.05) were subjected to multiple regression analysis also by the Cox proportional

TABLE 1. Patient characteristics (n=170)

Characteristic	Value*
Gender	
Male	106 (62)
Female	64 (38)
Mean age (SD) [years]	69 (12)
Median duration of advanced malignancy before enrolment into palliative care service (IQR) [days]	74 (37-210)
Primary cancer site	
Lung	58 (34)
Liver	24 (14)
Lower gastro-intestinal	24 (14)
Upper gastro-intestinal	16 (9)
Breast	5 (3)
Gynaecological	5 (3)
Haematological	3 (2)
Nasopharyngeal	2 (1)
Prostate	2 (1)
Unknown	7 (4)
Others	24 (14)
No. of involved metastatic sites	
0	28 (16)
1	75 (44)
2	49 (29)
≥3	18 (11)
Religious support	
Yes	63 (37)
No	107 (63)
Comprehensive Social Security Assistance scheme†	
Yes	47 (28)
No	122 (72)

* Data are shown in No. (%) of patients, except otherwise indicated

† Data were missing in one patient

hazard model, setting the significance level at $P<0.05$.

Patients with missing data for an item and/or for a scale were eliminated from the analyses involving that scale or item. All the analyses were performed using the Statistical Package for the Social Sciences (Windows version 11.0; SPSS Inc, Chicago [IL], US).

Results

Patient characteristics

Of the 188 advanced cancer patients enrolled into the service during the study period, five patients refused to participate in the initial assessments, seven could not communicate adequately, and six died shortly after admission, leaving 170 whose baseline characteristic were analysed. A total of 167 patients were followed up until death, while three were censored cases—one survived to the end of study, whilst two were lost to follow-up in public hospitals so their date of death could not be retrieved from computer records.

Table 1 shows the demographic characteristics of the recruited patients. The mean age of the sample was 69 (standard deviation, 12) years. The median duration of advanced malignancy before enrolment into the palliative care service was 74 (interquartile range [IQR], 37-210) days, while after enrolment the median survival of the overall group in this cohort was 77 (IQR, 31-160) days. Most of the patients were male (62%); lung (34%), liver (14%), and lower gastro-intestinal tract (14%) malignancies accounted for almost two thirds of the primary cancers. Common sites of metastasis at entry were lung (36%), lymph nodes (32%), and liver (24%). Of the 170 patients, the majority (44%) had one site of metastasis, while 28 (16%) had none, and only 18 (11%) involved three or more sites.

In the univariate analysis of demographic and clinical data (Tables 2 and 3), variables more discriminating for worse survival were peritoneal metastasis, skin metastasis, tachycardia, younger age, higher number of involved metastatic sites, higher total white cell count, higher HDS score, higher ESAS score, lower serum albumin level, lower KPS score, and lower QOL (HK)–single item score. Multivariable analysis with the forward stepwise Cox proportional hazard model demonstrated that only age (hazard ratio=0.84; 95% confidence interval, 0.73-0.96), number of involved metastatic sites (1.33; 1.13-1.56), serum albumin (0.95; 0.92-0.98), KPS score (0.86; 0.78-0.96), and ESAS score (1.22; 1.05-1.41) were independent predictors of survival (Table 4).

Discussion

A more accurate prediction of survival is important because it is relevant to the quality of care patients receive at the end of life. First, with a better understanding of survival, both patients and clinicians can make better treatment choices, avoiding futile aggressive interventions. Second, the clinician may provide a better answer to the question "How long have I got, doctor?" While the response needs to be tactful and empathetic, there is no certainty about exact survival in individual cases, a more accurate prediction is an important advance for clinician-to-patient communication. This enables patients and families to develop better insight into the terminal phase of the illness, facilitating the setting of goals, priorities, and expectations. Third, a more accurate prediction of survival may also help clinicians refer the patients to hospice/palliative care with more

TABLE 2. Univariate survival analysis for categorical variables by Kaplan-Meier method (n=170)

Predictor	No. of patients	Median survival (95% CI) [days]	P value
Gender			
Male	106	70 (46-94)	0.219
Female	64	102 (58-146)	
Primary site of malignancy			
Carcinoma of lung			
Yes	58	72 (42-102)	0.173
No	112	77 (39-115)	
Carcinoma of liver			
Yes	24	85 (5-165)	0.697
No	146	76 (51-101)	
Site of metastases			
Lung secondary			
Yes	61	60 (45-75)	0.249
No	109	93 (66-120)	
Liver secondary			
Yes	40	60 (17-103)	0.243
No	130	85 (57-113)	
Brain secondary			
Yes	12	87 (29-145)	0.440
No	158	76 (48-104)	
Peritoneal secondary			
Yes	21	36 (18-54)	0.009
No	149	92 (68-116)	
Bone secondary			
Yes	26	61 (0.07-122)	0.534
No	144	77 (51-103)	
Lymph node secondary			
Yes	55	70 (54-86)	0.079
No	115	93 (52-134)	
Skin secondary			
Yes	7	29 (26-32)	0.011
No	163	85 (60-110)	
Religious support			
Yes	63	71 (33-109)	0.992
No	107	85 (57-114)	
Herbal medicine			
Yes	35	56 (31-81)	0.491
No	135	87 (62-112)	
Tachycardia			
Yes	11	46 (26-67)	0.009
No	159	87 (64-110)	

confidence. Although patients may have derived benefit from short stays in hospice/palliative care units, in some cases earlier referral might have even greater benefits.[19] In our programme, though patients can be referred when the predicted survival is less than 6 months, the majority were not enrolled early enough; median survival after enrolment being only 77 (IQR, 31-160) days, and median time of 74 (IQR, 37-210) days after diagnosis of advanced disease till enrolment to the programme. Hence, if there was a more accurate predictor of survival at the time of diagnosis of advanced disease, this median time could have been shortened and the referrals made earlier.

Within clinical oncology and palliative care, there is a growing literature focusing on identifying clinical predictors of survival for advanced cancer patients, so much so that the Steering Committee of the European Association for Palliative Care in 2005 made evidence-based clinical recommendations.[20] Performance status has been studied in great depth, and undoubtedly proved to be an independent prognosticator in advanced cancer patients.[4,15,20-25] The KPS score is the most commonly used measure for this purpose. Recently a new performance status, Palliative Performance Status was developed, which also appears to have prognostic value.[9,26] Generally, a low performance status is considered a reliable prognostic factor predicting shorter survival. However, high scores do not invariably indicate longer survival, whereas a deteriorating score is a serious indication of worsening prognosis.[15] Our study showed that for any two patients enrolled into the palliative care service, the one whose KPS score was 10 points higher was 14% less likely to die on the following day. Most studies showed that for advanced cancer patients enrolled in a palliative care programme, a KPS score of less than 50% consistently suggested a life expectancy of less than 8 weeks.[1,4,9,21,27]

Our study demonstrated that serum albumin was a prognostic factor, as suggested by others,[13,24,28] but not in all studies.[25,29] Such differences could be related to heterogeneous populations with different median survival durations. For a population with short median survival, serum albumin appears not to be an independent predictor, as in the latter it was closely correlated with the anorexia-cachexia syndrome, whilst in others it exerted its significance nearer the end of life.

Regarding age, survival time was generally independent of this parameter according to other studies.[4,19,21,22,24,27,28,30] In our study, it appeared that the younger the age, the worse the prognosis. We postulated that performance status was naturally lower in older age-groups, whereas a similarly low performance status in the young indicates much more severe disease. More research is needed to confirm this.

In 1966 Feinstein[31] first described the utility of clinical symptoms as independent prognostic

factors. To date, many individual symptoms have been found to have prognostic value. They include: dyspnoea, anorexia, delirium, dysphagia, and dry mouth,[4,20,21,26,30,32] whilst other symptoms (eg nausea,[28] asthenia[27]) have occasionally been incriminated. In most clinical scenarios, patients nearly always suffer from clustering of symptoms, though of different severity. In a few studies, overall symptom severity was also found to be a survival predictor,[33,34] though none had shown different combinations of symptoms of differing severity to be associated with differing prognoses. Our study indicated that the ESAS, which can help to quantify the number and severity of symptoms, could also be an independent prognosticator. To our knowledge, this is the first demonstration of such a finding.

Although several studies had demonstrated that quality-of-life measurements could have prognostic significance,[32,35,36] the tools used differed, and there was no confirmative study showing psychosocial parameters as prognostic determinants of survival. Toscani et al[37] compared the relative prognostic power of clinical variables and quality-of-life measure and concluded that in terminal cancer patients, the former were better predictors of survival, and our findings concur with this view. In our study, no psychosocial parameters appeared to have prognostic significance. However, our investigation was not designed to examine this issue in depth; possible influence of these factors could have been overwhelmed by other aspects in the biology of these patients with malignant diseases.

The selection of symptoms and functional characteristics permitted the development of a prognostic model that was objective, easy to measure, and independent of the physician's previous experience. A few integrated prognostic scores or indices have been developed that permit a rapid estimate of life expectancy, and place patients into broad groups that differ significantly in survival. Examples were the Palliative Prognostic Score (PaP[38-40]) and Palliative Prognostic Index (PPI[10]). The PaP includes the following variables: clinical prediction of survival, the KPS, anorexia, dyspnoea, total white cell count, and lymphocyte percentage. Based on the total score, validated cut points have been established that categorise patients into three prognostic groups for survival to 30 days. For scores of 0-5.5, the probability of 30-day survival was higher than 70%; for scores of 6-11, the probability was 30 to 70%; for scores of 11.5-17.5, the probability was less than 30%. The PPI does not include the physician's clinical prediction but does entail the following: the KPS, oral intake, oedema, dyspnoea at rest, and delirium. For a PPI of 2 or less than 2, median survival was 90 days; for a PPI of 2.1-4, it was 61 days; for a PPI of higher than 4, it was 12 days. Further study is suggested to develop prognostic instruments applicable in local clinical settings.

TABLE 3. Univariate survival analysis for continuous variables by Cox proportional hazard model

Predictors	Hazard ratio (95% CI)	P value
Age (n=170)	0.987 (0.975-0.999)	0.040
No. of involved metastatic sites (n=170)	1.294 (1.111-1.507)	0.001
Maximum dose of morphine (n=170)	1.000 (0.998-1.002)	0.909
Total white cell count (n=165)	1.053 (1.020-1.090)	0.002
Lymphocyte percentage (n=162)	0.998 (0.970-1.007)	0.214
Albumin (n=165)	0.943 (0.919-0.968)	<0.001
Calcium (n=156)	0.398 (0.133-1.189)	0.099
Sodium (n=165)	0.994 (0.985-1.003)	0.183
Haemoglobin (n=165)	0.957 (0.887-1.031)	0.246
Mini-mental State Examination (n=152)	0.982 (0.951-1.015)	0.289
Karnofsky Performance Status (n=170)	0.797 (0.727-0.874)	<0.001
Hamilton Depression Scale (n=162)	1.030 (1.009-1.050)	0.004
Edmonton Symptom Assessment System (n=166)	1.210 (1.067-1.373)	0.003
Quality of Life–single item (n= 147)	0.880 (0.812-0.953)	0.002
Charlson's co-morbid score (n=170)	0.955 (0.863-1.056)	0.366

TABLE 4. Positive findings of multivariable survival analysis by Cox proportional hazard model

Predictors	Regression coefficients	Hazard ratio (95% CI)	P value
Age	-0.17	0.84 (0.73-0.96)	0.013
No. of involved metastatic sites	0.28	1.33 (1.13-1.56)	<0.001
Albumin	-0.05	0.95 (0.92-0.98)	0.001
Karnofsky Performance Status	-0.15	0.86 (0.78-0.96)	0.007
Edmonton Symptom Assessment System	0.20	1.22 (1.05-1.41)	0.008

In our study, we did not include the physician's clinical prediction in the analysis. This was because such predictions are largely subjective and dependent on experience. We preferred instead to look at objective, measurable, and quantifiable parameters to assist the clinician in offering a prognosis in this patient group.

The main limitation of our study was that it was confined to a single centre study, hence its findings might be difficult to generalise to other centres. In future, a larger group of patients could be sampled from multiple centres for a prospective study.

Conclusion

Prognostication is a significant clinical commitment for physicians and oncologists. In this cohort, age, number of involved metastatic sites, serum albumin, the KPS and ESAS scores were found to

be independent prognosticators. Further study is suggested to provide physicians with prognostic instruments that are more applicable in local clinical settings.

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