



# Can oncologists predict survival for patients with progressive disease after standard chemotherapies?

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## ABSTRACT

### Background

Prediction of prognosis is important for patients so that they can make the most of the rest of their lives. Oncologists could predict survival, but the accuracy of such predictions is unclear.

### Methods

In this observational prospective cohort study, 14 oncologists treating 9 major adult solid malignancies were asked to complete questionnaires predicting survival based on performance status, oral intake, and other clinical factors when patients experienced progressive disease after standard chemotherapies. Clinically predicted survival (CPS) was calculated by the oncologists from the date of progressive disease to the predicted date of death. Actual survival (AS) was compared with CPS using Kaplan–Meier survival curves, and factors affecting inaccurate prediction were determined by logistic regression analysis. The prediction of survival time was considered accurate when the CPS/AS ratio was between 0.67 and 1.33.

### Results

The study cohort consisted of 75 patients. Median CPS was 120 days (interquartile range: 60–180 days), and median AS was 121 days (interquartile range: 40–234 days). The participating oncologists accurately predicted AS within a 33% range 36% of the time; the survival time was overestimated 36% of time and underestimated 28% of the time. The factors affecting the accuracy of the survival estimate were the experience of the oncologist, patient age, and information given about the palliative care unit.

## Conclusions

Prediction of CPS was accurate for just slightly more than one third of all patients in this study. Additional investigation of putative prognostic factors with a larger sample size is warranted.

## KEY WORDS

Survival prediction, cancer patient survival, chemotherapy

## 1. INTRODUCTION

Prediction of survival is important for patients with advanced cancer so that they can make the most of the rest of their lives. Many cancer patients want to obtain information about their prognosis in a direct and honest manner<sup>1–3</sup>. Nevertheless, clinicians are often averse to predicting survival<sup>4</sup> and divulging prognostic information<sup>5</sup>, possibly because breaking bad news to a patient can be stressful for the physician.

A physician's level of experience in estimating survival might affect how prognosis is formulated. For example, an inexperienced physician might guess or use "intuition," ask an "expert," consult a textbook, search the electronic literature for prognostic studies, rely on their own judgment, or use a prognostic index<sup>6</sup>. However, even experienced oncologists find it difficult to predict survival time. Indeed, previous studies reported that clinically predicted survival (CPS) by oncologists was uncertain<sup>7</sup> and optimistic in terminally ill patients with cancer<sup>8–11</sup>. A systematic review of eight studies reported that CPS for terminal ill cancer patients was accurate for only 25%, 43%, and 61% within, respectively, 1, 2, and 4 weeks of actual survival (AS)<sup>11</sup>. Some studies reported that only 20%–25% of predictions were accurate (within  $\pm 33\%$  of AS); others reported that survival was overestimated in 63%–83% of terminally ill patients<sup>8–10,12</sup>.

Prediction of survival for patients before terminal illness is more important than that for the terminal stage, because a prediction 1–4 weeks ahead of death might be too late for patients to make the most of their remaining life.

In previous studies, predictions of survival were limited to terminally ill patients with cancer, except in work by Stockler and colleagues<sup>7</sup>. No reports have addressed CPS in patients who finished standard chemotherapies and experienced progressive disease. Predictors of prognosis have to be determined to improve the accuracy of CPS estimates for such patients. In this prospective study, we examined the accuracy of CPS estimates for patients who experienced progressive disease after standard chemotherapies.

## 2. METHODS

This single-centre prospective study was based on a questionnaire (Table I). The study was approved by the institutional review board.

### 2.1 Patients

At the National Cancer Center Hospital in Japan, between October 2010 and October 2011, our study recruited patients with advanced unresectable cancer and patients with progressive disease after standard chemotherapies (Table II). This observational cohort consisted of adult patients with various solid malignancies, including those of breast, lung, pancreas, colon and rectum, stomach, cervix, endometrium, and ovary, and sarcoma. The attending oncologists ( $n = 14$ ) were asked to complete the CPS questionnaire for patients who had acquired resistance to standard chemotherapies. The CPS was estimated by the attending doctor within 7 days (at most) after the diagnosis of progressive disease after standard chemotherapy. Doctors were asked to write the predicted survival as a number of months, weeks, or days at the time of prediction. All completed questionnaires were sent to the clinical trials office. The patients were all followed until death.

### 2.2 Definition of Terms

All primary cancers were diagnosed by pathology examination. The AS was defined as the time from the date of diagnosis of progressive disease after standard chemotherapy to the date of death. The CPS was defined as the time from the date the questionnaire was completed to the predicted date of death.

Oral intake was judged mainly by the attending doctor using a simple open-ended question: How do you feel about your appetite? The answer was then scored: 1, normal or good; 2, more than 50% of normal oral intake; or 3, less than 50% of normal oral intake. A palliative care unit (PCU) was defined as a place for palliation and residency without

chemotherapy and included inpatient or outpatient PCUS and home-based hospices. Best supportive care referred to hospice care based in a hospital or at home without any intensive chemotherapy<sup>13</sup>.

### 2.3 Statistical Analysis

We calculated the Spearman correlation coefficient between the AS and the CPS. The ratio of the CPS to the AS was calculated for each patient to examine the concordance between the variables. The prediction of survival time was considered accurate when the ratio was in the range 0.67–1.33 (that is, a concordance of  $\pm 33\%$ )<sup>8</sup>. Survival analysis was performed using the Kaplan–Meier method. Using multivariate regression analysis, we assessed factors affecting the difference between AS and CPS. Putative factors affecting successful prediction of survival were examined using multivariate logistic regression analysis. In all statistical analyses, values of  $p < 0.05$  were considered significant. The statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC, U.S.A.).

## 3. RESULTS

### 3.1 Patient and Physician Characteristics

The study enrolled 75 patients who met the eligibility criteria. Oncologists were stratified according to professional experience: less than 10 years' experience ( $n = 7$ ) and 10 or more years' experience ( $n = 7$ ). Table III shows patient and oncologist characteristics, and Table IV shows the decisions of the oncologists based on patient factors. Nearly 70% of the study patients had a performance status of 0–1 at the time of progressive disease. At that time, approximately 60% were considered preferable for best supportive care by their oncologist, but 70% of all patients did not receive any information about their prognosis. The main reason for that information not being conveyed was uncertainty about the survival prediction or lack of a request for the information. Although the patients had experienced progressive disease after standard chemotherapy, 35% were supposed to receive further chemotherapy. In cases of progressive disease after standard chemotherapies, 80% of patients were referred to hospice before death, and 80% of referred patients died at hospice.

### 3.2 Survival Estimates

In the 75 patients, median CPS was 120 days (interquartile range: 60–180 days), and the median AS was 121 days (interquartile range: 40–234 days). Figure 1 shows the Kaplan–Meier curves for CPS and AS. The median difference between CPS and AS (CPS – AS) was –5 days (interquartile range: –74 to 43 days). The Spearman correlation coefficient indicated a highly

TABLE 1 The questionnaire

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1 Oncologist's name: \_\_\_\_\_

2 Malignancies

Lung cancer       Breast cancer       Gastric cancer       Colorectal cancer

Sarcoma       Ovarian cancer       Pancreatic cancer       Endometrial cancer

3 Performance status (ps)

1       2       3       4

4 Patient's oral intake

Normal       Moderately reduced       Severely reduced

5 Clinical prediction survival (cps), defined as the period between the date of questionnaire completion and the predicted date of death

\_\_\_\_\_ month(s)      \_\_\_\_\_ week(s)/day(s)

6 Main factor for cps

ps       Metastatic lesion       Other \_\_\_\_\_

Clinical symptoms

( dyspnea       oral intake       edema       delirium)

7 Disclosure

Did you communicate the cps?

To the patient       To the family       To neither

If you did NOT communicate the cps ("to neither"), why?

Uncertainty       They did not ask       You dared not tell

Other \_\_\_\_\_

8 Ways in which you treated the patient

Best supportive care       Chemotherapy       Alternative medicine       Second opinion

Other       Surgery       Clinical trial       Palliative radiation

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9 If you did NOT refer to palliative care unit (pcu), why?

Inappropriate time       You dared not suggest the pcu       Other \_\_\_\_\_

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10 Final decision

Best supportive care       Chemotherapy       Alternative medicine       Second opinion

Other       Surgery       Clinical trial       Palliative radiation

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TABLE II Development of drug resistance by malignancy

<i>Malignancy</i>	<i>Progressive disease after ...</i>
Breast cancer	Anthracycline, taxane, or capecitabine
Colorectal cancer	Fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, tyrosine kinase inhibitors with wild-type EGFR
Gastric cancer	Tegafur, gimeracil, and oteracil potassium with or without cisplatin
Pancreatic cancer	Gemcitabine
Lung cancer	Second- or third-line regimens with EGFR mutation
Ovarian cancer	Platinum resistance
Cervical cancer	Cisplatin-containing regimen
Endometrial cancer	Doxorubicin or cisplatin
Sarcoma	Anthracycline- or ifosfamide-containing regimens (excluding Ewing sarcoma and rhabdomyosarcoma)

EGFR = epidermal growth factor receptor.

TABLE III Oncologist and patient characteristics

<i>Characteristic</i>	<i>Value</i>
Oncologists ( <i>n</i> )	14
Career [ <i>n</i> (%)]	
>10 Years	7 (50)
<10 Years	7 (50)
Patients ( <i>n</i> )	75
Age (years)	
Median	60
Range	26–78
Sex [ <i>n</i> (%)]	
Men	26 (35)
Women	49 (65)
Site of malignancy [ <i>n</i> (%)]	
Breast	11 (15)
Colorectum	15 (20)
Stomach	4 (5)
Pancreas	15 (20)
Lung	11 (15)
Ovary	5 (7)
Cervix	3 (4)
Endometrium	3 (4)
Sarcoma	8 (11)
Performance status	
0–1	51 (68)
≥2	24 (32)
Oral intake	
Normal	41 (55)
Moderately reduced	25 (33)
Severely reduced	9 (12)

significant correlation between CPS and AS (0.70,  $p < 0.001$ , Figure 2.).

The survival estimation was accurate (CPS within  $\pm 33\%$  of AS) in 36.0% of patients [95% confidence interval (CI): 25.2% to 47.9%], overestimated in another 36.0% of patients (95% CI: 25.2% to 47.9%), and underestimated in 28.0% of patients (95% CI: 18.2% to 39.6%).

### 3.3 Multivariate Analyses

We examined independent factors correlated with the difference between CPS and AS (Table v). These variables were significant in multivariate regression analysis for inaccurate survival estimations:

- Oncologists with less than 10 years' experience tended to estimate shorter survival times (72.2 days; 95% CI: 8.4 to 136.0 days;  $p = 0.027$ ).
- In patients more than 65 years of age, oncologists tended to underestimate survival times (54.7 days; 95% CI: 6.9 to 102.4 days;  $p = 0.025$ ).
- In patients who did not receive information about PCUS, oncologists overestimated survival times (78.6 days; 95% CI: 15.7 to 141.4 days;  $p = 0.014$ ).

## 4. DISCUSSION

In the present study, we investigated the accuracy of CPS estimates in patients with advanced cancer who had experienced progressive disease after standard chemotherapy. Survival was accurately predicted in only 36% of cases, although the CPS estimate was highly correlated with AS overall. The professional experience of the oncologist, patient age, and referral to a PCU were independent factors for a difference between CPS and AS.

Giving information as needed to patients, including expected survival, is important even though patients might not ask doctors for that information. In the present study, more than half the patients had a performance status of 0 or 1 at detection of progressive disease after standard chemotherapies. Prediction of survival might have been more difficult for doctors in that setting than in the terminally ill setting. Previous studies reported that only 20%–25% of predictions are accurate in terminally ill cancer patients<sup>8,9</sup>. In our study, 36% of the predictions were in the accurate range, and more than 80% of the predictions were based either on performance status or metastatic lesions (Table iv). As seen in earlier studies, survival predictions for the near future were more accurate than those for more than 6 months into the future (Figure 1 and 2). A report on the association between the professional experience of the oncologist and prediction shows that prognostic accuracy increases with the experience of the doctor<sup>8</sup>; however, another study reported contradictory findings<sup>10</sup>. Of the oncologists who did not disclose

TABLE IV Oncologist decisions about patient factors

Factor	Responses (n)	Decision	Value [n (%)]
Communicate information about CPS	75	No	54 (72)
		Yes (to patients)	13 (17)
		Yes (to family only)	8 (11)
Reason for <i>not</i> communicating CPS	54	Uncertainty	31 (57)
		Information not requested	20 (37)
		Apprehensive about communicating CPS	1 (2)
		Other	2 (3)
		Main factor in CPS	75
Main factor in CPS	75	Metastatic lesion	39 (52)
		Dyspnea	2 (2)
		Other	5 (7)
		Final treatment	75
Final treatment	75	Chemotherapy	26 (35)
		Clinical trial	3 (4)
		Alternative medicine	1 (1)

CPS = clinical prediction of survival.

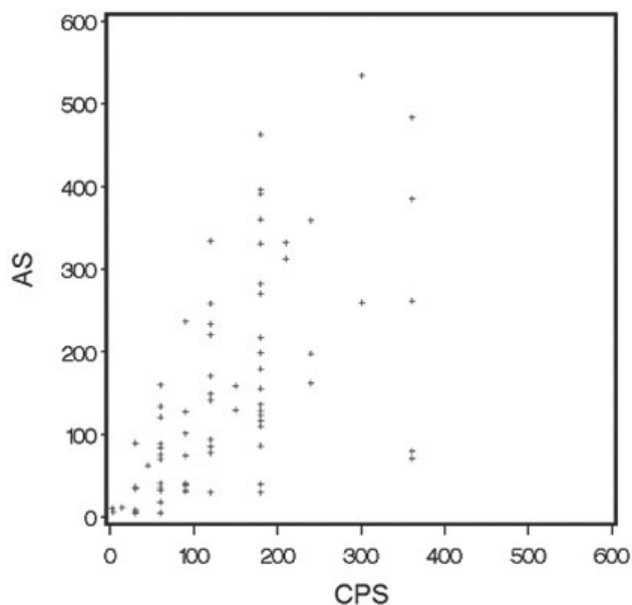


FIGURE 1 The Spearman rank correlation coefficient for clinically predicted survival (CPS) compared with actual survival (AS) was 0.70 ( $p < 0.001$ ), indicating a highly significant association.

the CPS to their patients because the patient did not request that information, 80% had been practicing for less than 10 years. Less-experienced oncologists might tend to build strong doctor–patient relationships, and they might therefore be overly optimistic and unwilling to accept the imminent death of their patients. Alternatively, they might be trying not to scare patients<sup>14</sup>. However, an optimistic CPS can result

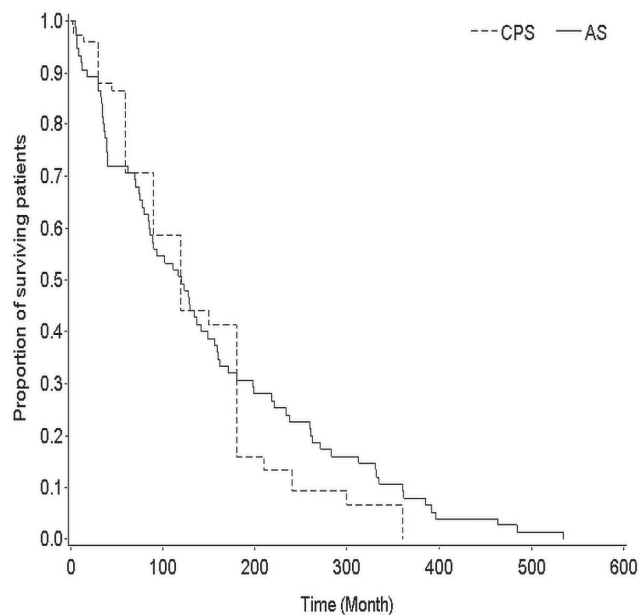


FIGURE 2 Kaplan–Meier curves for clinical predicted survival (CPS) and actual survival (AS). The median difference (CPS – AS) was –5 days (interquartile range: –74 to 43 days).

in late referral to a PCU<sup>8</sup>. Indeed, our study findings indicated that patients who were not referred to a PCU had optimistic CPS estimates, although the observed relation between PCU referral and CPS is preliminary because of the small sample size. Patients should be given enough time to prepare for a PCU and should be in appropriate physical and psychological condition for referral. In addition, patients who have no



TABLE V Factors independently correlated with differences between clinical predicted survival (CPS) and actual survival in multivariate analysis

Factor	Difference in days		p Value
	Estimate	95% CI	
Oncologist's professional experience			
>10 Years	Reference		
<10 Years	72.2	8.4 to 136.0	0.027
Site of malignancy			
Breast	Reference		
Colorectum	-92.5	-188.6 to 3.7	0.060
Stomach	-38.0	-149.1 to 73.1	0.503
Pancreas	10.2	-69.9 to 90.3	0.803
Lung	37.5	-52.7 to 127.7	0.415
Ovary	4.5	-96.2 to 105.2	0.930
Cervix	-13.5	-135.9 to 108.9	0.829
Endometrium	57.2	-65.2 to 179.5	0.360
Sarcoma	-14.6	-104.3 to 75.1	0.750
Age (years)			
<65 Years	Reference		
>65 Years	-54.7	-102.4 to -6.9	0.025
Performance status			
0-1	Reference		
≥2	0.5	-69.0 to 70.1	0.988
Oral intake			
Normal	Reference		
Moderately reduced	-30.0	-96.9 to 37.0	0.380
Severely reduced	-72.1	-198.0 to 53.9	0.262
Main factor for CPS			
PS	Reference		
Metastatic lesion	-36.3	-85.3 to 12.7	0.146
Dyspnea	-14.8	-153.5 to 124.0	0.835
Other	-14.6	-103.5 to 74.3	0.748
Final treatment			
Best supportive care	Reference		
Chemotherapy	0.6	-62.9 to 64.0	0.986
Clinical trial	-36.1	-155.6 to 83.3	0.553
Alternative medicine	52.1	-131.6 to 235.7	0.579
Referral to palliative care unit			
Yes	Reference		
No	78.6	15.7 to 141.4	0.014

CI = confidence interval.

information about PCUS tend to receive aggressive chemotherapy near the end of life, which can contribute to poor quality of life<sup>13</sup>.

Predicting survival time is difficult, and disclosing the prediction to patients is therefore also difficult. In the present study, the CPS was disclosed in only 28% of cases. Many articles suggest that most patients with incurable cancer are keen on receiving

information regarding their prognosis<sup>1-3,15,16</sup>. Most patients would like to know their predicted survival, although physician and patient predictions are largely discordant<sup>17</sup>. Nevertheless, most physicians remain unwilling to disclose prognosis estimates to patients with incurable cancer. In previous studies, physicians favoured providing frank survival estimates in only 37% of cases<sup>18</sup>. Although disclosing the estimated survival time to a patient is not always necessary, doctors should make a considerable effort to communicate with their patients and to help them decide how they wish to live the remainder of their life<sup>19-21</sup>.

This study has some limitations. First, because of the small sample size, we might have missed some factors affecting the survival prediction other than experience as an oncologist, patient age, and PCU information given. A larger sample would be required to adequately identify other factors. Second, predictive factors that might improve the accuracy of CPS estimates could not be clarified because of variations in patient characteristics and the professional experience of the oncologists. Third, patients might have been told their CPS after the questionnaire was completed, which might have affected subsequent care choices.

## 5. CONCLUSIONS

Although it is difficult to accurately estimate survival for patients who acquire resistance to standard chemotherapies, an earnest attempt should be made to provide as accurate a CPS as possible for patients who wish to have this information so that they can improve their quality of life. Well-planned studies to identify predictive factors that can assist in making an accurate assessment of CPS and to determine how best to deliver that information are warranted.

## 6. ACKNOWLEDGMENTS

We thank all the physicians who took part in this study project. We are also grateful to Ms. Nao Nakamura for secretarial support.

## 7. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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