PART A: DEFINITIONS AND MODELS

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PROGNOSTICATION IN ADVANCED DISEASE

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One meaning of *prognosis* is that it is a physician's estimate of the future course of a patient's disease and especially of their survival. Prognoses are important to physicians and patients in all phases of cancer care, and they inform both medical and nonmedical decisions. In early-stage disease, prognoses help physicians and patients to weigh the likely benefit of given therapies (e.g., adjuvant chemotherapy). In advanced stage disease, prognoses may be of additional importance, as they may herald a switch from primarily curative or life-prolonging care to primarily palliative care and in so doing set off a cascade of both clinical and personal decisions. Despite its importance and ubiquity, reliable prognostication in advanced disease is not straightforward. Numerous studies have revealed substantial optimistic bias in physicians' prognoses for their terminally ill cancer patients. It seems likely that this optimistic bias may contribute to the short survivals observed in patients referred for hospice care and to other types of decisions doctors and patients make near the end of life. Research that is focused on improving physicians' prognostic abilities is therefore of critical importance to palliative care.

PROGNOSTIC INACCURACY

Although prognosis is a central element of a significant amount of oncologic research, formal and explicit prognostication is not often required in the clinical care of cancer patients. Nevertheless, there are two instances in the care of advanced cancer patients where physicians are asked explicitly to prognosticate: (a) when they are enrolling patients on experimental chemotherapy protocols, and (b) when they are referring patients for hospice care. Each therapy has discrete and opposite eligibility requirements pertaining to survival—that is, to be considered for enrollment on phase I experimental chemotherapy protocols, patients typically must have an estimated survival of longer than 3 months. To be considered for enrollment for hospice care under the Medicare Hospice Benefit, patients must have an estimated survival of less than 6 months. Because of these formal requirements, physicians' ability to determine fine gradations in survival among patients in their last 6 months of life may mean the difference between aggressive and palliative care.

Optimism in Formulating Prognoses

How good are physicians at determining which patients are in their last 6 months of life? The answer may be found in literature pertaining to aggressive and palliative therapies for advanced cancer patients. From the experimental chemotherapy literature, Janisch and colleagues analyzed survival data from 349 advanced cancer patients after enrollment in phase I therapies (1). Overall, they found that the median survival was 6.5 months, well above the requisite 3 months described in most eligibility requirements. However, 25% died within 3 months (i.e., inconsistent with the prognostic standard), although very few of those with a performance status of more than 70 died before 3 months. Given the low clinical response rates associated with phase I therapies, it is unlikely that survival was

TABLE 42-1. SUMMARY OF STUDIES COMPARING PHYSICIANS' ESTIMATED SURVIVAL TO PATIENTS' ACTUAL SURVIVAL

Primary investigator	Reference	Year	Number of doctors	Number of patients	Median estimated survival (wk)	Median actual survival (wk)	Estimated survival/actual survival
Parkes	2	1972	NR	168	4.5[a]	2.5[a]	1.8
Evans	3	1985	3	42	NR	NR	3.2[c]
Heyse-Moore	4	1987	NR	50	8	2	4
Forster	5	1988	3	108	7[b]	3.5	2
Maltoni	6	1994	4	100	6	5	1.2
Christakis	7	2000	343	468	NR	3.4	5.3[c]

NR, not reported.
[a]Values estimated from graph in paper.
[b]Seven weeks calculated through statement in paper that survival was overestimated by 3.4 weeks on average.
[c]Ratio of mean estimated survival/mean survival.

enhanced by the therapies themselves. Therefore, results from this study suggest that physicians enrolling patients on phase I protocols are generally able to predict which patients have longer than 3 months to live. An alternate explanation is that other eligibility requirements, like performance status and laboratory tests, select for patients with longer than 3 months to live, obviating the utility of the physicians' prognostic assessment. Because the study was not designed to test physician prognostic accuracy, it is difficult to draw strong conclusions about the actual role of physician prognostication.

Within the palliative oncology literature, there are several studies specifically designed to determine physicians' prognostic accuracy in predicting survival of patients admitted to hospice programs (2–7). Investigators in these studies have measured physicians' prognostic accuracy by comparing patients' observed survival to their predicted survival (these predictions are not necessarily ones communicated to patients; rather, they are ones physicians formulate for themselves). Results of the studies, summarized in Table 42-1, show that, in aggregate, physicians' overall survival estimates tended to be incorrect by a factor of approximately three, always in the optimistic direction (2–7).

Studies of physicians' abilities to predict terminally ill cancer patients' survival are not limited to patients in palliative care settings but have also been evaluated in ambulatory patients undergoing anticancer therapy. Mackillop and Quirt measured oncologists' prognostic accuracy in the care of their ambulatory cancer patients by asking them to first predict patients' likelihood of cure and then to estimate the duration of survival for those whose likelihood of cure was zero (8). At the 5-year point, patients who were alive and disease-free were termed "cured"; the dates of death of the incurable patients also were determined. The researchers reported that oncologists were highly accurate in predicting cure. That is, for subgroups of patients (not individual patients) the ratio of the observed cure rate at 5 years to the predicted cure rate was quite high, at 0.92. However, the same oncologists had difficulty predicting the length of survival of individual incurable patients. They predicted survival "correctly" for only one-third of patients, with the errors divided almost equally between optimistic and pessimistic.

Optimism in Communicating Prognoses

Once a prognosis has been formulated, a physician must decide how to communicate it. This is the distinction between foreseeing and foretelling the patient's future (9). Although, as noted above, there is unconscious optimism in the prognoses physicians formulate regarding their advanced cancer patients' survival, there is also additional—and conscious—optimism in the prognoses physicians subsequently communicate to their patients. For example, one study asked physicians referring terminally ill cancer patients for hospice care how long they thought the patient had to live and also what prognosis, if any, they would provide to their patient if the patient inquired (10). It found that the median survival the physicians would communicate to patients was 90 days, their median formulated survival was 75 days, and the median observed survival was 24 days. This study revealed that the prognoses patients hear from their physicians may be more optimistic than what their physicians actually believe, which again is more optimistic than what actually occurs. Figure 42-1 shows the relationship between these three types of prognoses (communicated, formulated, and observed).

In sum, although physicians are asked to foresee gradations of survival in advanced cancer patients enrolling in certain therapies (either aggressive or palliative), they are able to do so accurately less than a third of the time and, when in error, they generally tend to overestimate survival. This overestimation in formulated survival is compounded by an overestimation of communicated survival. Therefore, through their physicians' step-wise prognostic errors, advanced-stage cancer patients may become twice removed from the reality of their survival, both times toward a falsely optimistic prognosis.

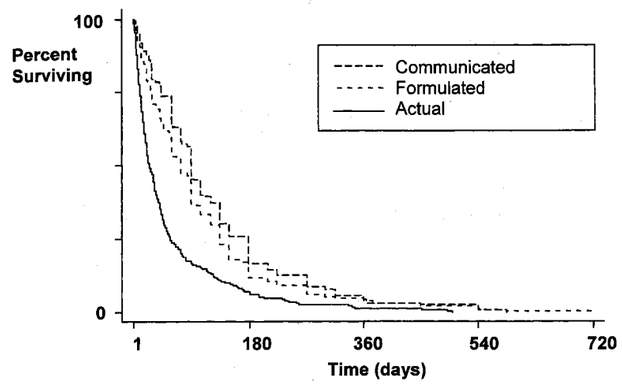

FIGURE 42-1. Relationship between physicians' communicated and formulated prognoses and their advanced cancer patients' actual survival after referral to hospice palliative care. [From Lamont EB, Christakis NA. Prognostic disclosure to patients with cancer near the end of life. *Ann Intern Med* 2001;134(12):1096–1105, with permission.]

PROGNOSTIC ACCURACY

Within palliative oncology, there is a growing literature focused on identifying predictors of survival of advanced cancer patients that might aid physicians in their prognostic estimates for similar patients. This literature is motivated not only by the centrality of prognosis to the care of such patients but also by physicians' inability to prognosticate accurately and their discomfort in doing so. Multiple prospective and retrospective cohort studies have consistently identified three broad classes of survival predictors: patients' performance status, patients' clinical signs and symptoms, and physicians' clinical predictions. New research seeks to increase the predictive yield of these clinical factors through models of increasing complexity that integrate these elements with each other and with new elements into easy-to-use composite measures. Additional new research in the broader oncologic arena of translational research seeks to exploit survival aspects of new biological markers [i.e., molecular (e.g., p53 [11], Her-2/neu [12])], although the extent to which these will aid in clinical prognostication in advanced disease is not yet established.

Performance Status

A performance status is a global measure of a patient's functional capacity. Because it has been consistently found to predict survival in cancer patients (13), it is frequently used as a selection criteria for patients entering clinical trials and also as an adjustment factor in the subsequent analyses of treatment effect. Several different metrics have been developed to quantify performance status, and among them, the Karnofsky performance status (KPS) is the most often used. The KPS ranges from values of 100, signifying normal functional status with no complaints nor evidence of disease, to zero, signifying death. The complete spectrum of values for the KPS scale is reproduced in Table 42-2.

Multiple studies (1,3,6,14–27) have reported associations between cancer patients' survival and their performance status. The direction of the association is positive—that is, as a patient's performance status declines, so, too, does their survival. The magnitude of the association is described differently in different studies depending on the statistical methods used, but several studies report that among patients enrolled in palliative care programs, a KPS of less than 50% suggests a life expectancy of fewer than 8 weeks (3,6,14,16,27,28). The association between KPS value and survival in advanced cancer patients enrolled in palliative care programs is described in Table 42-3.

Patients' Signs and Symptoms

Patients' clinical signs and symptoms have also been studied with respect to survival in advanced cancer. The usefulness

TABLE 42-2. KARNOFSKY PERFORMANCE STATUS SCALE

Value	Level of functional capacity
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity, minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self, unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization is indicated although death is not imminent
20	Hospitalization is necessary, very sick, active supportive treatment necessary
10	Moribund, fatal processes progressing rapidly
0	Dead

TABLE 42-3. PREDICTORS OF SURVIVAL WITH ADVANCED CANCER UNDER PALLIATIVE CARE

Index	Value	Median survival (d)	References
Karnofsky performance status	10–20	7–16	3,6,14,16,27,28,
	30–40	8–50	35
	≥50	50–90	
Anorexia	Present	≤58	14,28,35
Confusion	Present	≤38	28,35
Dysphagia	Present	<30	14
Dyspnea	Present	<30	14
Xerostomia	Present	<50	35
Leukocytosis	>8500 cells/μl	≤30	37
Doctor estimate	3 mo	30	2,4,7

of such indicators, even in preference to biological details of a patient's condition, was first outlined in a classic paper by Alvan Feinstein in 1966 (29,30). Recently, Vigano and colleagues engaged this topic in their qualitative systematic review of prognostic factors in advanced cancer (31). In examining 136 different variables from 22 studies, they found that, after performance status, specific signs and symptoms were the next best predictors of patient survival. The presence of dyspnea, dysphagia, weight loss, xerostomia, anorexia, and cognitive impairment had the most compelling evidence for independent association with patient survival in these studies. Table 42-3 contains the range of median survivals for the various symptoms reported in univariate analyses from these and other studies.

For example, numerous investigators have documented that dyspnea is inversely associated with survival in this patient population (14,16,26,33). The presence of dyspnea is associated with a survival of fewer than 30 days according to work by Maltoni et al. (14). Other investigators have described dyspnea as doubling the hazard of death (32). Similarly, others have shown inverse associations between dysphagia and survival (14,16,33,34), with Maltoni et al. describing an associated median survival of fewer than 30 days (14). Anorexia, confusion, and xerostomia are also inversely associated with survival (14,28,35), with median survival times of fewer than 60 days. These findings suggest that for advanced cancer patients such as those referred to palliative care programs, the presence or absence of these symptoms may help physicians to estimate patient survival.

Several groups of investigators have evaluated associations between biological markers (i.e., laboratory values) and survival in advanced cancer patients. For example, in their retrospective analysis of 339 phase I chemotherapy patients with advanced cancer at the University of Chicago, Janisch and colleagues found that among routine pretreatment laboratories, only platelet count elevation and serum albumin depression were associated with shorter survivals in a multivariate model that included KPS (1). Among a sample of 207 consecutive advanced non–small cell lung patients, Muers and colleagues found that in addition to performance status and symptoms, lymphocyte count, albumin, sodium, and alkaline phosphatase were all predictive of survival (36). Similarly, Maltoni and colleagues examined 13 hematological and urinary parameters at baseline and every 28 days in a group of 530 patients in Italian palliative care centers (37). In a multivariate model that included performance status, the investigators describe high total white blood cell count, low lymphocyte percentage, and low pseudocholinesterase as associated with diminished survival. Their Kaplan-Meier curves suggest that patients with elevated white blood cell counts (>8500 cell/μl) had median survivals of 1 month or less. The Janisch, Meurs, and Maltoni results are consistent; Janisch et al. found a strong correlation between platelet count and absolute neutrophil count and therefore dropped absolute neutrophil count from the final model. There may be a similar degree of correlation between albumin and pseudocholinesterase, both serum proteins. From these studies one can conclude that there appear to be negative associations between survival and bone marrow parameters (e.g., platelets, white blood cells) as well as positive associations between survival and synthetic parameters (e.g., serum proteins) in this patient population.

Physicians' Clinical Predictions

As noted previously, numerous studies suggest that physicians' predictions regarding patients' survival in palliative care programs are frequently incorrect and that the direction of the error is almost always optimistic. However, the overly optimistic estimates *are* correlated with actual survival (6,7,38). That is, although physicians are not well-calibrated with respect to survival (i.e., they are systematically optimistic), they nevertheless have discriminatory abilities (39). They are able to order patients in terms of how sick they are or how long they have to live. This fact suggests that physicians' clinical predictions may be a useful, but not exclusive, source of information regarding patient survival. Thus, integration of clinical predictions with other known prognostic factors may be beneficial in predicting patient survival. For example, Muers and colleagues found that the addition of physician clinical prediction to their previously mentioned prognostic model (that contained performance status, symptoms, and laboratory values) improved the model's predictive power (36). This suggests that physicians are able to measure and quantify factors relevant to survival that are unmeasured by the previously mentioned factors. Similarly, Knaus and colleagues, in their Study to Understand Prognoses and Preferences for Outcomes and Risks for Treatments patients, found that multivariate regression models that included physicians' prognostic estimates were more accurate than the models without the physician input (40). Hence, although it is true that statistical models can be more accurate than human intuition alone (36,40,41), it is also true that physicians provide valuable prognostic information that, thus far, has not been captured in the objective models. Such integrated models hold the greatest promise for improving physicians' predictive accuracy in advanced cancer patients. Maltoni et al. explicitly combined this information with other known predictors of patient survival in their predictive tool (42).

Integrated Models

Investigators have also sought to model patient survival by combining and interacting these previously identified clinical predictors. Bruera and colleagues described a parsimonious model that combined three independently predictive elements (dysphagia, weight loss, cognitive failure) (34). They reported that the presence of all three poor prognostic factors among advanced cancer patients admitted to palliative care predicted death within 4 weeks, with a sensitivity of 0.74 and a specificity of 0.71. In this study, this measure performed better than physicians' clinical estimates of survival.

Using data from the National Hospice Study, Reuben and colleagues evaluated the initial performance status and symptomatology of 1592 terminal cancer patients admitted to hospice care and found that interacting the two survival predictors led to better prognostic modeling (16). That is, the survival associated with a given performance status depended on the number and type of additional symptoms. For example, patients with an initial KPS of 50% or more and no symptoms had a median survival of 172 days. This survival decreased to 125 days when dyspnea was also present at the initial evaluation. The survival decreased to 67 days when dyspnea, dysphagia, weight loss, and xerostomia were all present at the initial evaluation.

The most recent generation of studies describe integrated models that combine these and other prognostic variables into a single prognostic score. For example, Morita and colleagues developed a regression model predicting survival from performance status and certain clinical signs and symptoms (33). Coefficients from the regression were then transformed into partial scores, and summing the values of each partial score led to a final score termed the *Palliative Prognostic Index* (PPI). After developing the PPI in a sample of 150 patients, the investigators then tested the approach on a second sample of 95 patients, finding that the PPI predicted 3-week survival with sensitivity of 83% and a specificity of 85% and 6-week survival with sensitivity of 79% and a specificity of 77%. Table 42-4 contains a description of the PPI scoring system and Table 42-5 a summary of predictive relevance of PPI scores. Several other groups have developed similar scoring systems that rely on integration of all or some of the previously described classes of prognostic indicators of patients with advanced cancer and under palliative care (25,35,42). Such scoring systems need to be sensitive to a variety of methodological concerns (30,39,43–45). Further research is needed to determine if these scoring systems are useful in the clinical care of cancer patients and if they are applicable to patients who are not yet enrolled in palliative care programs or who are dissimilar from such patients. With respect to the clinical usefulness of the scoring systems, treating physicians will need to determine if the tools' test characteristics (e.g., sensitivity and specificity) fall above certain minimum thresholds for use in clinical decisions. Because of the issue of "zero time" (30,46) (i.e., the analytical impact of the selection of the time at which measurement of survival begins), many of the algorithms that rely on KPS, symptoms, or laboratory values obtained *after* referral to hospice may not be applicable to advanced cancer patients *before* referral to hospice.

TABLE 42-4. DESCRIPTION OF THE COMPONENTS OF THE PALLIATIVE PROGNOSTIC INDEX: A SCORING SYSTEM FOR SURVIVAL PREDICTION OF TERMINALLY ILL CANCER PATIENTS

Prognostic domains	Partial score value
Performance status	
10–20	4.0
30–50	2.5
≥60	0
Clinical symptoms	
Oral intake	
Moderately reduced	1.0
Severely reduced	2.5
Normal	0
Edema	1.0
Dyspnea at rest	3.5
Delirium	4.0

The scores from each prognostic domain are added, and the sum total is associated with a likelihood of survival either <3 weeks or <6 weeks. From Morita T, Tsundoa J, Inoue S, et al. The Palliative Prognostic Index: a scoring system for survival prediction of terminally ill cancer patients. *Support Care Cancer* 1999;7:128–133, with permission.

Other Sources of Prognostic Information

Other sources of information regarding survival in advanced cancer are studies that include cancer patients who do not undergo anticancer therapy. Both natural history studies

TABLE 42-5. MEDIAN SURVIVAL OF PATIENTS ACCORDING TO PALLIATIVE PROGNOSTIC INDEX SCORE[a]

Palliative Prognostic Index score	Median survival (d)
0.0–2.0	90
2.1–4.0	61
>4.0	12

[a]Median survival value was estimated from survival curve in paper. From Morita T, Tsundoa J, Inoue S, et al. The Palliative Prognostic Index: a scoring system for survival prediction of terminally ill cancer patients. *Support Care Cancer* 1999;7:128–133.

TABLE 42-6. MEDIAN SURVIVALS FROM STUDIES THAT INCLUDE UNTREATED PATIENTS

Tumor site	Histology	Dx stage	Median survival[a]	N[a]	Reference
Breast	NR	NR	2.3 yr	1022	58
Colon	Adenocarcinoma	IV	5 mo	12	57
Gastric	Adenocarcinoma	IV	5 mo	30	56
Head and neck	Squamous cell	IV/recurrent	4 mo	808	47
Lung	Non–small cell	IIIb/IV	4.1 mo	98	52
			5.3 mo	57	49
			5.9 mo	150	50
Liver	Hepatocellular	NR	1 mo	127	48
Pancreas	Adenocarcinoma	NR	3 mo	39	55

Dx, diagnosis; NR, not reported.
[a]Values pertain to the subset of untreated patients.

and randomized therapy trials that include a "best supportive care" arm describe patients who do not undergo anticancer therapy. Typically, natural history studies are single institution case series of untreated patients with mortality follow-up. For example, Kowalski and Carvalho described the survival pattern of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (47). The median survival they report is 4 months. Others have looked at this issue in breast cancer (58) and hepatocellular cancer (48). Survival information can also be found by examining the survival of patients on the "best supportive care" arms of randomized clinical trials [e.g., trials in advanced non–small cell lung cancer (49–52), hepatocellular cancer (53), 5-fluorouracil refractory stage IV colon cancer (54), stage IV pancreatic cancer (55), stage IV gastric cancer (56)]. Table 42-6 contains a description of results of some of these trials (47–50,52,55–58).

Prognostic Consultations

Another way for physicians to improve the accuracy of their prognostic estimates is to elicit prognostic estimates from disinterested colleagues. Through informal, "curbside" consultations or through more formal avenues such as tumor boards, physicians may find colleagues helpful in determining patient prognoses. This recommendation stems in part from results of several studies revealing that survival predictions averaged across physicians are more accurate than a prediction from a single physician (59,60) and from results of studies that show that disinterested physicians may provide more accurate predictions (7) than physicians with an emotional or other stake in the outcome of a patient's care. This technique may improve predictive accuracy and minimize optimistic bias by enhancing the "signal-to-noise ratio" in predictions or by decreasing "ego bias."

CONCLUSION

Prognostication in advanced cancer is a difficult task that may become easier as physicians become more comfortable with the process and as researchers begin to develop better clinical prediction tools. Such efforts will help abate the pervasive and systematic optimism in both the formulated and communicated prognoses physicians develop near the end of life. Ultimately, such improvement might be evident through increasing survival times after referral to palliative care programs. As physicians' predictive accuracy improves, survival after referral to hospice may approach physicians' ideal of 3 months (61) rather than the current survival of 3 or 4 weeks (7,62). More broadly, however, such improvement may provide patients with a better understanding of their expected survival and thereby allow them to make informed medical and social choices regarding their treatment path at the end of life, whether curative or palliative (63,64).

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