Some Elements of Prognosis in Terminal Cancer

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ABSTRACT

Predicting the survival of terminal cancer patients is a difficult task. To better understand this difficulty, we divide prognostication into two distinct elements: foreseeing and foretelling. Foreseeing is a physician's silent cognitive estimate about a patient's illness. Foretelling is the physician's communication of that prediction to the patient or significant others. In this article, we review the impact of each element of prognosis on physicians' overall prognostic accuracy. We show that physicians often make unwitting, large, and generally optimistic errors in foreseeing patients' prognoses. They also may make more conscious, but equally large, optimistic errors in foretelling prognoses to patients. The net effect is that patients may become twice removed from the truth about their illness, both times toward a falsely optimistic prognosis. We also describe the possible consequences of these optimistic prognostic errors. Finally, we review techniques that may improve physicians' prognostic accuracy. We conclude that part of the challenge of providing humane, compassionate end-of-life care to cancer patients may involve accurately foreseeing and foretelling their prognoses.

A *prognosis* is a physician's prediction about a patient's future. This prediction may be divided into two distinct elements: foreseeing and foretelling. Foreseeing is a physician's silent, cognitive estimate about a patient's illness. Foretelling is the physician's communication of that prediction to the patient. In this article, we will consider both aspects of prognostication as they relate to physicians' care of cancer patients as they near death. We will review the findings on the significant inaccuracy of physicians' predictions and then offer hypotheses to explain the sources of this inaccuracy. We will describe techniques that may improve physicians' prognostic accuracy. Through this review, we hope to show that part of the challenge of providing humane, compassionate end-of-life care to cancer patients may entail accurately foreseeing and foretelling their prognoses.

Foreseeing the Prognosis

Because the success of novel anticancer therapies is measured primarily by their ability to extend life, prognosis is a central element of oncologic research. Technologic advances now allow cancer patients to be scrutinized, even to the level of gene expression, for factors that may explain a comparatively long or short survival. Typically, researchers create statistical models that integrate such factors to predict outcomes, and published results may assist physicians in making predictions and treatment decisions about their own patients.

For example, in a paper from the National Surgical Adjuvant Breast and Bowel Project's first prevention trial (NSABP P-01), Fisher and colleagues developed a risk model, a variant of the Gail model, that integrates a number of proven breast cancer prognostic factors (age, age at menses, age at first parity, personal history of breast disease and/or biopsy, family history of breast disease, and race) to quantify an individual's lifetime risk of developing the disease.[1,2] They used the model to select individuals at high risk of developing breast cancer, and then randomized those individuals to receive daily tamoxifen (Nolvadex) or placebo. Models, such as this one, that rely on multivariate regression analysis are found in all aspects of cancer research, including translational and basic science research.[3-5]

Although prognosis is a central element of oncologic research, such formal and explicit prognostication is

Table 1

Studies of Physicians' Prognostic Accuracy

Investigator	Number of Doctors	Number of Patients	Median Estimated Survival	Median Survival	Estimated Survival/ Actual Survival	Percentage Correct	Percentage Error	Optimistic Error/ Total Error
Evans	3	42	—	—	3.17[a]	54%	46%	.86
Heyse-Moore	NR	50	8 wk	2 wk	4	22%	78%	.92
Forster	3	108	7 wk[b]	3.5 wk	2	—	—	—
Maltoni	4	100	6 wk	5 wk	1.2	70%	30%	.63
Parkes	NR	168	4.5 wk	2.5 wk[c]	1.8	47%	53%	.86

NR = not reported.

[a]Ratio of mean estimated survival/mean survival

[b]7 weeks calculated based on statement in paper that survival was overestimated by 3.4 weeks on average

[c]Values estimated from graph in paper

seldom required in the clinical care of cancer patients. There are at least two situations in the care of advanced cancer patients, however, in which physician's need to formally foresee the prognosis: (1) enrollment into experimental phase I (dose-determining) chemotherapy protocols; and (2) referral to hospice programs. Both settings have discrete eligibility requirements pertaining to survival.

Typically, to be considered for entry into phase I trials, patients must have an estimated survival of at least 2 to 3 months, and for entry into a hospice program, patients must have an estimated survival of at most 6 months. Because of these formal requirements, physicians' ability to determine fine gradations in survival among cancer patients in their last 6 months of life may mean the difference between aggressive and palliative care.

How Good Are Physicians at Prognostication?

How good are physicians at determining which patients are in their last 6 months of life? Janisch and colleagues analyzed survival data from 349 advanced cancer patients after enrollment in phase I therapies.[6] They found that the median survival was 6.5 months, well above the requisite 2 months described in their eligibility requirements. Overall, approximately 10% of patients died within 2 months, although very few of those with a Karnofsky performance status greater than 70 died before 2 months. Given the low clinical response rates associated with phase I therapies, it is unlikely that survival was enhanced by the therapies themselves. Therefore, results from this study suggest that physicians who enroll patients in phase I protocols are generally able to predict which patients have more than 2 to 3 months to live. An alternate explanation is that other eligibility requirements, such as performance status and laboratory tests, select patients with more than 2 to 3 months to live, obviating the need for the input of physicians. Since the study was not designed to test the prognostic accuracy of physicians, however, it is difficult to draw strong conclusions about the actual role of physician prognostication.

Within the palliative oncology literature, a few studies were specifically designed to determine physicians' accuracy in predicting the survival of cancer patients admitted to hospice programs.[7-12] Investigators in these studies measured physicians' prognostic accuracy by comparing patients' observed survival to their predicted survival. Results of the studies, summarized in Table 1, show that, in aggregate, physicians' overall survival estimates tended to be incorrect by a factor of approximately two, always in the optimistic direction.[7-10,12]

Another method for measuring physicians' prognostic accuracy is to determine the percentage of patients dying within a calculated interval surro. ing their predicted date of death. example, Parkes identified extrem: rors in prediction by noting that *pe mistic errors* occur when patients at least twice as long as their predi survival and *optimistic errors* oc when patients live less than half as l as their predicted survival.[12] Acc ing to this system, physicians wh patients do not fall into *either* error egory have made *correct* prognoses though, admittedly, this is a gene definition of correct). Table 1 also c tains a summary of the results of s ies using this method of measu physicians' prognostic acc cy.[7,9,10,12] Even with this gene definition of correct, physicians predict the survival of hospice pati are correct only half of the time. thermore, the results show that the rection of these extreme error predominantly positive.

Studies of physicians' abilities to dict cancer patients' survival are limited to patients in palliative care tings. Physicians' prognostic accu also has been evaluated with gre mathematical rigor in ambulatory tients undergoing anticancer th py.[13] Mackillop and Quirt meas oncologists' prognostic accuracy by ing them to first predict ambulatory cer patients' likelihood of cure and to estimate the duration of surviva patients whose likelihood of cure zero. At the 5-year point, patients

were alive and disease-free were termed "cured"; the dates of death of the incurable patients also were determined. Although oncologists were quite accurate in predicting cure, they had difficulty in predicting the length of survival of incurable patients. They predicted survival "correctly" for only one-third of patients, with the errors divided almost equally between optimistic and pessimistic.

In summary, physicians asked to foresee gradations of survival in advanced cancer patients enrolling in certain therapies (either aggressive or palliative) are able to do so accurately much less than half the time, and, when in error, they tend to overestimate survival. Although clinicians appear to be adept at foreseeing the likelihood of cure in cancer patients, they are not skilled at foreseeing the length of survival in incurable patients.

Challenges to Accurately Foreseeing the Prognosis

Two factors may hinder physicians in their attempts to accurately predict survival of advanced cancer patients: the method of prediction used and forecaster bias.

Method of Prediction

There are two general methods of prediction: actuarial prediction and clinical prediction. With the actuarial method, a prediction is made using empirical data contained in life tables.

For example, an oncologist might consult Surveillance, Epidemiology and End Results (SEER) tables of patients with non-Hodgkin's lymphoma to predict a given patient's 5-year survival. Alternatively, the oncologist might use the International Prognostic Index to determine the likelihood of 5-year survival of a 45-year-old patient with an aggressive stage IV lymphoma and an elevated lactate dehydrogenase (LDH) level.[14] Models of greater complexity may provide the physician with greater prognostic precision.

In the clinical method, a prediction arises out of human intuition alone, without the benefit of explicit precedent data from similar patients or optimal weighting of patient and disease variables through mathematical formulas.

Although the actuarial method has been shown in many disciplines, including medicine, to be superior to the purely clinical method,[15,16] few actuarial models are designed explicitly to aid physicians in predicting the survival of terminal cancer patients. However, several studies have correlated performance status[7,10,17] and symptoms (eg, dysphagia, dyspnea)[17-19] with the survival of terminal cancer patients.

Forecaster Bias

A distinct reason that oncologists may be inaccurate in their predictions about the survival of terminal cancer patients may relate to their own biases. Within the literature on prognostication, certain forecaster biases are well-described impediments to accurate prediction.[20] For oncologists, optimistic bias may be the most germane type of forecaster bias. Optimistic bias about personal risk occurs when a person believes that he or she is less likely than others to experience an adverse outcome.[21]

Optimistic bias is pervasive and well studied. A classic example is the uniform optimism held by cigarette smokers about their health.[22-24] In study after study, cigarette smokers rate their personal risk of developing a smoking-related illness far lower than the average smoker, even if they can accurately forecast the risk of smokers in general.

In his review of optimistic bias about personal risk, Weinstein postulates three reasons for such bias that may be applied to physicians caring for patients.[21] First, by employing optimistic bias, physicians invoke denial to shield themselves from a painful reality, perhaps, in this case, the imminence of a patient's death. Second, they may think that they are better than their peers (ie, that they take better care of their patients) and, therefore, may believe that their patients will live longer than a survival curve would suggest. Third, optimistic bias may occur because of simple cognitive errors, eg, that a terminal cancer patient's performance status of 90 simply means that they cannot die of their cancer in the next 3 months

Foretelling the Prognosis

Although almost all cancer patients are now informed of their diagnoses, it is unclear how many cancer patients are informed of their prognoses.[25] The few studies that compare physicians' estimates of patients' prognoses to the estimates of patients themselves reveal a disparity between the two. In a study of 100 cancer patients undergoing cancer treatment, Mackillop and colleagues found that one-third of those with metastatic cancer thought that they had local or regional disease for which they were being treated for cure.[26] Similarly, Eidinger and colleagues studied 190 patients being treated for metastatic cancer and found that 37% thought the treatment would cure them.[27]

Recently, Weeks and colleagues, in their analysis of 917 patients with either advanced non–small-cell lung cancer or metastatic colon cancer in the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT), found that patients with such optimistic prognostic misperceptions often request medical therapies that most physicians would consider futile.[28] For example, almost half (43%) of patients who were estimated by their physicians to have less than a 10% chance of surviving 6 months believed that they had at least a 90% chance of living that long. These same patients were 8.5 times as likely to favor receiving aggressive, life-extending medical care than were patients whose estimates of their 6-month survival were more accurate.

Given the natural histories of these cancers and the limits of available treatment, it is not surprising that the patients who chose maximally aggressive care did not live any longer than those receiving palliative therapy. It is disturbing to note, however, that those with incorrectly optimistic views of their prognoses were more likely to die in the hospital on mechanical ventilation than were patients with more realistic estimates of their survival potential. The paper at least suggests that terminal cancer patients' optimistically miscalibrated prognostic estimates may lead them to choose highly aggressive, invasive, and futile medical care rather than (probably more beneficial) palliative care.

The reason for the discrepancy between patients' comparatively optimistic estimates of their prognoses and their physicians' estimates is not clear from these studies. Is it that patients misinterpret or deny the poor prognoses that their physicians give them? Alternatively, do physicians think one thing about

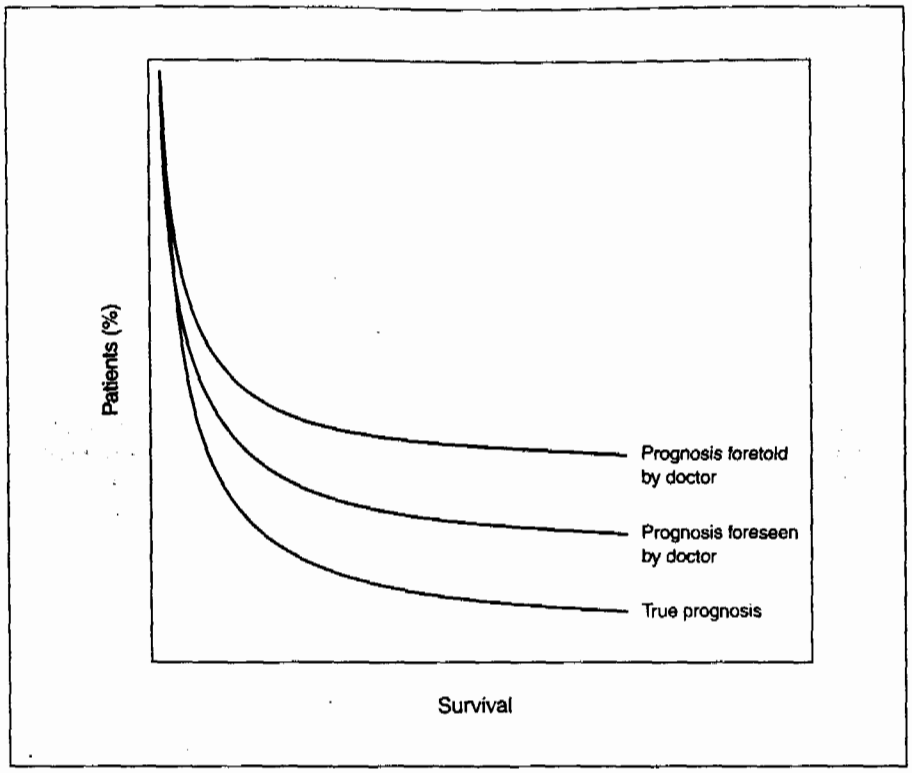

Figure 1: Theoretical Survival Curves illustrating the effects of physicians' optimistic prognostic errors

a patient's prognosis, but tell the patient something more positive? Although it may be that both pressures operate independently, recent work suggests that at least part of disparity between the prognostic estimates of patients and physicians may be due to purposely inaccurate and generally optimistic prognostic estimates that physicians give their patients.[29]

Challenges to Accurately Foretelling the Prognosis

The reason that some physicians may provide patients with deliberately overly optimistic prognoses is unknown. However, it may relate to physicians' concerns about prognostications' dual iatrogenic potential. Positive iatrogenesis from prognostication occurs when the revelation of a good prognosis causes a better outcome than would have happened otherwise. Conversely, negative iatrogenesis from prognostication occurs when the revelation of a bad prognosis causes a worse outcome than would have happened alone.

Two studies have documented physicians' belief in the positive iatrogenic potential of prognostication. Through structured interviews with 51 oncologists (from Harvard teaching hospitals), Delvecchio Good and colleagues reported that oncologists believe that hope and optimism can modify disease.[30] Almost three-quarters of the oncologists interviewed thought that a "positive attitude" affected the outcomes of both early- and late-stage cancers. Although most of these oncologists did not believe that patients who were hopeful or optimistic would live longer, they did believe that they would live better and tolerate the complications of treatment better. Having said this, 88% of the physicians interviewed admitted that they tried to make their patients' attitudes more optimistic.

In her study of truth-telling among 32 American physicians caring for dying patients, Miyaji documented how physicians' concerns for maintaining their patients' hope may interfere with truth-telling.[31] She reported that physicians are often purposely vague in the prognostic estimates that they give to dying patients in order to maintain hope, and that two-thirds portray information optimistically to patients when the true clinical course is uncertain to them.

If physicians believe that report favorable, but inaccurate, prognoses improve cancer patients' lives throu optimism and hope, do they believe t reporting unfavorable, albeit accur prognoses can compromise patier lives? Physicians' belief in the dam ing power of unfavorable prognose at least implied by Miyaji's finding t two-thirds of physicians *modify* inf mation to patients when they think t the truth "will have a seriously l outcome."

Other work examining physicia beliefs in this area has shown that tl believe in the self-fulfilling prophe and that this belief attenuates th willingness to offer unfavorable pr noses.[29] The results of these stuc suggest that physicians believe that favorable predictions can have a ne tive iatrogenic effect, or that unfavor predictions can compromise patie survival.

It may be physicians' concern a prognostication's dual iatrogenic po tial that has led to the evolution of rent professional norms regar communication of prognoses to can patients, which mostly stress the av ance of prognostication.[32,33] B implicitly and explicitly, oncologists instructed to provide staged, optimi and temporally nonspecific progn to cancer patients.[34,35] This typ communication both acknowledges cultivates the ambiguity inherer medical knowledge. Ambiguity ma seen as optimal and beneficial whe comes to prognostication, in large n sure because it is seen as a predicate hope. In adhering to these norms, p sicians may actually communicate accurate information, and, thus, t are costs as well as benefits to practice.[35]

The Difficulty of Making a Prognosis

Predicting the survival of te cancer patients is difficult. To beg understand the difficulty better, we l divided prognostication into two ments: foreseeing prognosis and telling prognosis. In foreseeing ter cancer patients' survival, physic especially with the relative pauci easy-to-use actuarial models, often extreme (usually optimistic) er

prediction. In foretelling survival, oncologists may make equally extreme, and usually consciously optimistic, errors. They may do so in an attempt to enhance patient survival.

The net result is that patients become twice separated from "the truth" about their survival, both times toward a falsely optimistic prognosis. Figure 1 contains theoretical survival curves that illustrate the effects of these stepwise optimistic prognostic errors.

Negative consequences may ensue if cancer patients and their physicians think that the patients have longer to live than they actually do. The study by Weeks et al established an association between patients' optimistic misperception of prognosis and their choice of futile aggressive therapy over palliative therapy and subsequent death in the hospital. This study's findings suggest the following questions: Do terminal cancer patients' incorrectly optimistic views of their prognosis lead them to request futile aggressive therapy over palliative care, and then to die in hospitals, sometimes on ventilators, rather than at home with their families? Is it possible that physicians' unconscious or well-intentioned, conscious optimistic errors in foreseeing and foretelling prognosis may paradoxically lead their patients to suffer undignified, painful, and costly deaths?

Ways to Improve Prognostication

Physicians may improve their accuracy in foreseeing the prognosis of terminal cancer patients by relying more on the actuarial method of prediction and by taking steps to minimize their optimistic bias.

Greater Reliance on Actuarial Prediction

Although, as noted above, few studies in the palliative oncology literature identify survival determinants in terminal cancer patients, many studies in other segments of the oncology literature contain valuable survival data that pertain to terminal cancer patients.

For example, in the previously noted article by Janisch and colleagues, the investigators analyzed the survival of 349 cancer patients receiving phase I therapies and developed a multivariate model (incorporating Karnofsky performance status, baseline platelet count, baseline albumin level, tumor histology, and prior chemotherapy) to predict patient survival after entry into phase I studies.[6] Through their model, patients were stratified into poor-, intermediate-, and good-risk prognostic groups, corresponding to median survival durations of 3.5, 7.4, and 12.7 months, respectively. Although the investigators suggested that this model may help physicians optimize patient selection for phase I clinical trials, the model may also at least guide the predictions of other physicians caring for patients who are not enrolled in phase I trials but who are otherwise similar.

Within the oncologic emergency literature, hundreds of studies examine the management and subsequent survival of patients with complications of cancer, such as brain metastases, carcinomatous meningitis, spinal cord compression, and the superior vena cava syndrome. These studies isolate positive and negative prognostic factors that may aid physicians' predictions in this subset of terminally ill cancer patients.

Within the tumor-specific literature, numerous papers identify specific prognostic factors in patients with advanced-stage disease.

Finally, within the oncologic outcomes literature, there is growing interest in combining clinical variables, such as patients' symptoms and comorbidities, with traditional anatomic tumor staging systems to form more informative cancer taxonomies that provide better prognostic clarity. Piccirillo et al have shown that integrating patient symptoms and comorbidities into the existing laryngeal cancer staging system improves prognostic precision.[36]

Such an approach promises to decrease the prognostic heterogeneity captured in survival curves that stratify patients exclusively on the basis of anatomic stage. In all of these cases, however, there may still be significant barriers to physicians applying this information to their own patients.[35,37]

Use of New Models Incorporating Physicians' Prognostic Estimates

Improved prognostic clarity may also be achieved through the use of new types of models that integrate physicians' prognostic estimates with objective patient variables. Both Muers et al, in their study of advanced non–small-cell lung cancer patients, and Knaus et al, in their study of SUPPORT patients, found that multivariate regression models that included physicians' prognostic estimates were more accurate than the models minus the input of physicians.[38,39] Athough it is true that statistical models can be more accurate than human intuition alone,[16,39] it is also true that physicians provide valuable prognostic information that thus far, has not been captured in the objective models. We believe that one way to improve physicians' prognostic accuracy is to develop and use models that combine physicians' prognostic estimates with objective patient variables in multivariate analyses.

Acknowledge and Control Proclivity Toward Optimism

Another step physicians can take to improve the accuracy of their prognostic estimates is to acknowledge their optimistic proclivity and take steps to control it. One way for physicians to do this is by eliciting 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 the results of several studies revealing that survival predictions averaged across physicians are more accurate than a prediction from a single physician.[35,40] This technique may improve predictive accuracy and minimize optimistic bias, by enhancing the "signal-to-noise ratio" (ie, decreasing random error) in predictions or by decreasing "ego bias."

Conclusions

Because of the clear importance of hope and optimism in American oncologic practice, the task of accurately foretelling prognoses to terminal cancer patients is perhaps a greater challenge than is accurately foreseeing those prognoses. Rather than offering algo-

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that they never receive it.[26,27,44-47] Physicians should also remember that cancer patients *need* prognostic information to make informed decisions about therapies and to make choices about how they will live the rest of their lives.[48] Prognosis needs to be determined impartially and communicated sensitively, but truthfully.

This article is reviewed on pages 1172, 1174, and 1179.

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