

Predicting life expectancy in patients with advanced incurable cancer: a review

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Oncologists frequently face the difficult task of estimating prognosis in patients with incurable malignancies. Their prediction of prognosis informs decision-making ranging from recommendations of cancer treatments to hospice enrollment. Unfortunately, physicians' estimates of prognosis are often inaccurate and overly optimistic. Further, physicians often fail to disclose their prognosis estimates, despite patient wishes to the contrary. Several studies have examined patient factors that might improve physicians' prognostic accuracy, including performance status, clinical symptoms and laboratory values. Prognostic models have been developed and validated but, to date, none are able to provide accurate estimates throughout the spectrum of advanced illness. This review examines tools utilized to predict life expectancy for patients with advanced, incurable cancer.

Estimating prognosis is one of the most difficult tasks the oncologist encounters, particularly for patients with incurable malignancies whose life expectancies may vary between days and years. A physician's ability to formulate an accurate estimate of prognosis among patients with advanced, incurable cancers is essential to medical decision-making, such as whether to pursue chemotherapy, clinical trials, or hospice care. In the United States, Canada, and many European countries, hospice referrals require a physician-predicted prognosis of 6 months or less. Furthermore, advanced cancer patients who hold overly optimistic perceptions of their prognosis are more likely to want futile, aggressive care.¹ When physicians provide prognostic information during end-of-life discussions, advanced cancer patients are more likely to avoid aggressive medical care that is associated with lower quality of life near death, greater medical care costs, and worse caregiver bereavement outcomes.²⁻⁴

This review discusses data informing prognostication in patients with advanced, incurable solid tumors, including physician assessment of life expectancy, prognostic factors, and prognostic models in this patient population.

Physician prediction of prognosis

Physician assessment of prognosis—drawing upon clinical experience and comprehensive knowledge of the patient—is frequently utilized to assess prognosis. This mechanism of predicting prognosis among advanced cancer patients has been investigated in multiple studies demonstrating these estimates to be largely unreliable, with accuracy ranging from 20%-60%.⁵⁻¹⁰ Glare et al reviewed 8 studies investigating the accuracy of physicians' survival estimates in over 1500 terminal cancer patients; physicians' prognostic estimates were correct 25% of the time to within 1 week of actual survival time, 43% to within 2 weeks, and 61% to within 4 weeks.⁸ Studies suggest that physicians tend to overestimate life expectancy among advanced cancer patients. Vigano et al prospectively evaluated 210 advanced cancer patients and asked physicians to provide survival estimates based upon their clinical evaluations (median of 15 weeks before death).¹⁰ Physicians overestimated patients' survivals by a median of 1.1 months. In a

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systematic review by Chow et al, clinicians' estimates of survival tended to be in the overly optimistic direction in 9 of the 12 studies included.⁵ Furthermore, length of the patient-physician relationship has been shown to be associated with reduced accuracy of physician predictions. Each year a physician has known a patient has been shown to increase the likelihood of making an erroneous prediction by 12%.¹¹ Additionally, accuracy of prediction has not been found to be dependent on length of clinical experience. In the aforementioned study by Gripp et al, both a young physician and a senior physician (greater than 10 years experience) demonstrated similar accuracies in predicting survival (accuracy of 60%).¹² Hence, a key next step in better estimating prognosis in advanced cancer patients is equipping physicians with prognostic tools that improve upon physician accuracy in life expectancy predictions.

Prognostic factors

Although factors such as tumor size, stage, grade, and genetics are important in determining prognosis for patients with nonmetastatic cancers, they do not appear to play as significant a role in predicting prognosis among cancer patients with incurable disease.^{13,14} Several other potential prognostic factors have been studied in patients with incurable cancers, including performance status, symptoms, and laboratory values.

Karnofsky Performance Status

Numerous studies have suggested that Karnofsky Performance Status (KPS) is a prognostic indicator in patients with advanced cancer.¹⁵⁻²⁴ In a retrospective study, Evans demonstrated a moderate correlation between KPS and survival in 42 patients seeing a terminal care support team.²⁵ Change in performance status has also been shown to inform prognosis; in a study of patients admitted to a palliative care unit by Chan et al, greater magnitude of decrement in the palliative performance scale ([PPS] a modified version of the KPS) was associated with poorer prognosis.²⁶ In addition, the prognostic utility of KPS has been shown to increase when combined with clinical symptoms.¹⁴ Morita et al examined both KPS and clinical symptoms in 95 patients referred to hospice and found that the symptoms most associated with 3- and 6-week survival were edema, dyspnea at rest, delirium and a KPS of 10 or 20.²⁷ In summary, KPS status and change is an important predictor of prognosis, particularly in the lower range and when combined with clinical symptoms.

Symptoms

The clinical symptoms evaluated most frequently in studies examining factors that influence the physicians' ability to estimate prognosis are dyspnea, anorexia, nausea, fatigue and weight loss. The cachexia-anorexia syndrome (CACS) is loosely defined as anorexia and involuntary weight loss, though there is no consensus regarding the precise definition. CACS is theorized to arise from imbalanced interactions between inflammatory cytokines, neuropeptides, hormones and tumor-derived products.²⁸ Lasheen investigated the correlation between CACS and survival in 484 patients with metastatic cancer receiving palliative care consults. He found that longer survival was seen among patients with neither anorexia nor weight loss as compared to patients having anorexia and/or weight loss.²⁹ Teunissen et al assessed clinical symptoms as prognostic indicators in a prospective study of 181 hospitalized patients referred to a palliative care team.³⁰ A multivariate analysis showed nausea, dysphagia, dyspnea, confusion and absence of a depressed mood to be independent prognostic factors for worse survival. Patient survival time decreased as their risk factors increased; patients with 4 risk factors had a 60% absolute increased risk of dying at 1 month compared to those with no risk factors.

While symptoms have been shown to correlate with survival, they must be used cautiously, particularly as they can be subjective and difficult to accurately assess at the end of life. Further research is required to establish the most predictive and reliably assessable symptoms that inform prognosis.

Laboratory values

Laboratory values have also been used to aid in survival prediction in advanced cancer. Numerous types of cancer have been associated with an elevated lactate dehydrogenase (LDH).^{31,32} Given LDH's known elevation in cancer,³³⁻³⁶ it has been theorized that it could be a marker for higher disease burden and potentially a prognostic indicator in patients with metastatic disease. Suh et al investigated the correlation between median split LDH (low < 313, high \geq 313) and survival in 93 terminal cancer patients.³⁷ The median survival time in the low LDH group was 27 days compared with 14 days in the elevated LDH group ($P < .001$). In a retrospective evaluation of 154 advanced cancer patients, performance status and LDH > 600 were the 2 factors that significantly predicted patients' survival in a multivariate analysis.²⁴

C-reactive protein (CRP) is an acute phase reactant that responds to inflammation, injury and cancer. It has been investigated as an independent predictor of survival in pancreatic cancer, colorectal cancer, esophageal cancer and hematologic malignancies.³⁸⁻⁴² Suh and Ahn inves-

TABLE Models for predicting prognosis in patients with advanced cancer

Study/model name	Patient population (N)	Factors in model (estimated life expectancy)	Strengths/weaknesses
Pirovano, 1999/Palliative Prognostic Score (PaP) ¹⁹	Advanced solid tumors no longer considered suitable for anti-cancer therapies and determined unlikely to live >6 months (N = 519)	Anorexia, dyspnea, KPS, total WBC, lymphopenia, physician's survival prediction in weeks (30 d)	External validation ⁴⁸ /Requires physician prediction of survival, limited applicability for longer survivals (>30 days), study population limited to advanced cancer patients no longer receiving anti-cancer therapies
Morita, 1999/Palliative Prognostic Index (PPI) ¹⁸	Terminally-ill cancer pts admitted to a palliative care unit and determined unlikely to live >6 months (N = 150)	Palliative performance score, oral intake, edema, dyspnea at rest, delirium (3 wk, 6 wk)	External validation ⁴⁹ /Limited applicability for longer term survival (>6 weeks), study population limited to advanced cancer patients admitted to a single palliative care unit
Chow, 2008/Number of Risk Factors (NRF) ¹⁵	Advanced cancer patients referred for palliative radiation therapy (N = 395)	Primary tumor, site of metastasis, KPS (9 wk, 26 wk, 60 wk)	External validation, ease of use (3 clinical factors)/Study population limited to those receiving palliative radiation therapy, limited applicability to patients with shorter survivals (<9 weeks)
Zhou, 2009/Chinese Prognostic Scale (ChPS) ¹⁶	Advanced cancer patients referred to a palliative home care service (N = 1019)	Weight loss, nausea, dysphagia, dyspnea, edema, cachexia, dehydration, gender, KPS, QOL (3 mo)	Large patient population/Not externally validated, study population limited to cancer patients in a palliative care home setting
Chiang, 2010 ⁵⁰	Terminal cancer patients in an inpatient hospice setting (N = 727)	Gender, intervention tubes, grade 3 edema, ECOG PS, mean muscle power, hemoglobin, BUN, SGOT, respiratory rate, heart rate (7 d)	Large patient population/No external validation, study population limited to cancer patients in a hospice setting, limited utility among patients with longer survivals (>7 days)
Hyodo, 2010 ⁵¹	Inpatient advanced cancer patients in cancer centers or hospice (N = 201)	Physicians' survival prediction (in weeks), consciousness, pleural effusion, WBC, lymphocyte % (2 wk, 5 wk, 7 wk)	Internal validation/No external validation, requires physician prediction of survival, limited utility among patients with longer survivals (>30 days), study population limited to inpatient advanced cancer patients
Martin, 2010 ⁵²	Patients with metastatic cancer referred to a palliative care center (N = 1164)	Primary tumor, PS, short-term weight change, dietary intake, dysphagia (1 mo, 2 mo, 4 mo)	Large patient cohort, internal validation/Not externally validated, study population limited to cancer patients in a palliative care center
Ohde, 2011 ⁵³	Terminally-ill cancer pts in a palliative care unit (N = 158)	Anorexia, dyspnea, edema, BUN, platelet count (2 wk)	Ease of use/Not externally validated, small study population from single palliative care site, limited utility among patients with longer survivals (>2 weeks)
Suh, 2010/Objective prognostic score (OPS) ²⁰	Terminally-ill cancer patients (N = 209)	Reduced oral intake, dyspnea at rest, ECOG performance status, leukocytosis, elevated bilirubin, elevated creatinine, elevated LDH (3 wk)	Multicenter study/Not externally validated, limited utility among patients with longer survivals (>3 weeks)
Feliu, 2011 ⁵⁴	Terminally-ill cancer pts in oncology and palliative care units no longer receiving anti-cancer therapies (N = 406)	ECOG PS, LDH, albumin, lymphocyte count, time from initial diagnosis to terminal cancer diagnosis (15 d, 3 d, 60 d)	External validation, ⁵⁴ ease of use/Limited utility among patients with longer survivals (>60 days), study population limited to patients no longer receiving anti-cancer therapies
Tredan, 2011 ²¹	Patients with locally advanced or metastatic cancer who had received at least one line of systemic therapy for metastatic disease (N = 299)	KPS, LDH, lymphocyte count, IL-6, albumin, platelets (4 mo, 5 mo, 18 mo)	Dichotomous variables used to make clinical interpretation easier and less subjective/Not externally validated, limited utility among patients with shorter survivals (<4 months)
Gwilliam, 2011/Prognosis in palliative care study (PiPS-A) ⁵⁵	Patients with advanced, incurable cancers from palliative care centers (N = 1018)	Mental test score, pulse rate, presence of metastases, site of metastases, ECOG performance score, global health score, loss of appetite, dyspnea, dysphagia, primary cancer, weight loss (2-8 wk)	Large population from multiple centers, compared to accuracy of physician estimates/Not externally validated, study population limited to those seen at palliative care centers, limited utility among patients with longer survivals (>2 months)

TABLE Models for predicting prognosis in patients with advanced cancer (*continued*)

Study/model name	Patient population (N)	Factors in model (estimated life expectancy)	Strengths/weaknesses
Gwilliam, 2011/Prognosis in palliative care study (PiPS-B) ⁵⁵	Patients with advanced, incurable cancer from palliative care centers (N = 1018)	Same as PiPs-A with WBC, platelets, urea, CRP, Alanine transaminase, neutrophils, lymphocytes, alkaline phosphatase, albumin (and not dyspnea or dysphagia) (2-8 wk)	Large population from multiple centers; compared to accuracy of physician estimates/Not externally validated, study population limited to those seen at palliative care centers

Abbreviations: BUN, blood urea nitrogen; CRP, C-Reactive Protein; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LDH, lactate dehydrogenase; NPV, negative predictive value; PPV, positive predictive value; PS, performance status; QOL, quality of life; SGOT, serum glutamic oxaloacetic transaminase; WBC, white blood cell count.

tigated the use of CRP (dichotomized as low < 2.2 and high \geq 2.2) as a prognostic indicator in a prospective study of 44 advanced cancer patients admitted to a palliative care unit.⁴³ Survival of the high CRP group was significantly shorter than that of the low CRP group with a hazard ratio of 3.22 ($P = .001$). Ishizuka et al investigated the use of an inflammation-based score (modified Glasgow Prognostic Score, mGPS) for predicting survival in 112 patients with advanced or recurrent colorectal cancer.⁴⁴ The score included the patient's CRP level and hypoalbuminemia; modified Glasgow Prognostic Score was found to be an independent predictor of survival.

Both leukocytosis and lymphopenia have been implicated as poor prognostic markers in non-hematologic malignancies.^{17,45,46} In a retrospective review of 252 hospitalized patients with non-hematological malignancies,⁴⁷ leukocytosis was present in 30.6% of patients. Of the patients with leukocytosis, 70.1% presented with metastatic disease, and had a shorter mean survival time (5.3 months vs. 16.6 months). Lymphopenia is also associated with poorer prognosis among advanced cancer patients. In a retrospective analysis of 1051 cancer patients receiving chemotherapy, performance status > 1 and lymphocyte count < 700/uL were independent risk factors for early death (death within 31 days of chemotherapy).²³

While laboratory values appear to inform prognosis for advanced cancer patients, studies done to date are small and insufficient to establish the key laboratory predictors of prognosis. Further research is required to establish what the key laboratory predictors of prognosis are and their role along with other identified prognostic factors in prognostication.

Clinical models for predicting prognosis

Using the above factors, several models have been created to aid physicians in predicting prognosis in patients with solid tumors. A comprehensive literature search was undertaken in PUBMED using the words, "Prognosis," "Model," "Palliative" and "Cancer." Inclusion criteria

were as follows: prognostic model predicting life expectancy in adult patients with advanced or incurable cancer; and multiple factors used in prediction of prognosis. Studies were excluded if they were not written in English or if they were limited to one cancer type or a single advanced cancer clinical scenario (eg, malignant spinal cord compression). From the inclusive dates of July 1985 to June 2012, the search yielded 332 studies. Inspection of these abstracts yielded a total of 13 studies that met the inclusion and exclusion criteria, summarized in the Table. The Figure illustrates the breakdown of the aforementioned categories of prognostic factors with respect to the proportion of predictive models in which they are included. We will provide greater description of the 4 prognostic models that have undergone external validation in this review.

Palliative prognostic score

The palliative prognostic score (PaP) was developed in a prospective, multicenter study of 519 patients with advanced solid tumors who were no longer receiving chemotherapy.¹⁹ The aim of the study was to create a model that simultaneously employed independent predictors of survival to classify patients into distinct prognostic categories. The final model included anorexia, dyspnea, KPS, total WBC, lymphopenia, and the physician's survival prediction in weeks. A numerical score was given to each variable, based upon the relative weight of the independent prognostic significance. Patients were divided into 3 groups based on probability of surviving 1 month (Group A [$>70\%$, score 0-5.5], Group B [30-70%, score 5.6-11.0], and Group C [$<30\%$, score 11.1-17.5]). No measure of accuracy was given for the model. The model was validated in a population of 451 patients entering hospice programs,⁴⁸ with 1 month survivals of 86.6%, 51.6% and 16.9% in the 3 groups, respectively. The PaP was also validated with similar results by Glare et al in 100 patients with advanced cancers being cared for by oncologists.⁵⁶

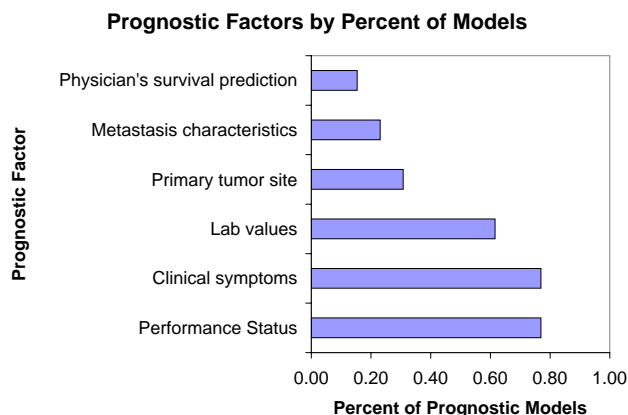


FIGURE Prognostic factors by proportion included in prognostic models.*

*See Table for prognostic models.

The PaP model has been externally validated and is a useful tool for predicting survival at 30 days. But it may not be as useful to predict survival in patients with longer life expectancies. The model also includes the physician's estimate of survival, which as previously discussed is often inaccurate.

Palliative prognostic index

The palliative prognostic index (PPI) was developed in a prospective study of 150 terminally ill cancer patients admitted to a palliative care unit and expected to live ≤ 6 months.¹⁸ The study examined the utility of the palliative performance score (PPS, a modified version of the KPS for patients with advanced illness) and 20 other clinical symptoms in predicting prognosis. The final model consisted of PPS, oral intake, edema, dyspnea at rest, and delirium. Based on the weight of each predictor in determining prognosis in the model, a partial score was assigned to each variable. These partial values were then summed to create the PPI. Patients were categorized according to 3 PPI score groups: (1) Group A (PPI < 2.0), (2) Group B (2.0 < PPI < 4.0) and (3) Group C (PPI > 4.0). Mean survivals for each group were estimated to be, 155 \pm 20 days; 89 \pm 7.7 days; and 18 \pm 2.9 days, respectively ($P < .01$). The authors examined the utility in predicting survival < 3 weeks and < 6 weeks using scores of 6 and 4 as cut-off points, respectively. They found a sensitivity of $\sim 70\%$ and a specificity of $\sim 85\%$ for both time points. Accuracy was 0.84 at 3 weeks and 0.78 at 6 weeks. Morita et al validated the model in 2 prospective studies of hospice patients.⁴⁹ In the first series, physicians predicted survival based on clinical experience alone; and in the second series, physicians predicted survival using the PPI. The number of instances where the difference between actual and pre-

dicted survival was 28 days or longer was significantly smaller in the second study compared with the first (42% vs. 23%, $P < .0001$).

The PPI's strengths lie in its ability to predict survival for patients with short survivals (eg, < 3 weeks or < 6 weeks) and its external validation. However, it has limited applicability for estimation of long-term survival (> 6 weeks) in advanced cancer patients.

Number of risk factors model

The number of risk factors (NRF) model was developed in 2008 with the goal of creating a simplified method of predicting prognosis.¹⁵ It was created as part of a retrospective review of 395 patients seen in a radiation oncology department. After examining multiple possible predictive factors (eg, gender, age, tumor site, metastatic site, and symptoms assessed with the Edmonton Symptom Assessment Scale), the final model consisted of the primary cancer site (breast vs non-breast), site of metastasis (bone only vs metastases including non-bone sites) and KPS (> 60 vs < 60). Validation was performed on separate datasets of 467 patients referred for radiation therapy at Princess Margaret Hospital.¹⁵ The concordance-index was 0.65 (ie, the model correctly predicted the order of 2 randomly selected patients 65% of the time). Median survivals were similar in the training and validation sets, with median survivals according to the NRF model estimated to be 60 weeks in Group 1 (0-1 risk factor), 26 weeks in Group 2 (2 risk factors) and 9 weeks in Group 3 (3 risk factors).

The NRF model's ease of use and external validation make it a promising tool. However, it was developed in a select population receiving palliative radiation and is less useful for patients with shorter life expectancies.

Spain prognostic nomogram

Most recently, a prognostic nomogram was developed in a prospective 3-center study in Spain evaluating 406 terminally ill cancer patients.⁵⁴ To be eligible, advanced cancer patients had to be considered no longer candidates for anti-cancer therapies (eg, chemotherapy) and estimated to have a survival of less than 6 months. The study assessed 38 clinical and laboratory variables and the final model consisted of ECOG performance status, LDH level, lymphocyte level, albumin level and time from initial diagnosis to diagnosis of terminal disease. A nomogram was created using these variables. Survival was evaluated at 15, 30 and 60 days. The concordance index was 0.70. The model was externally validated in 474 patients from 8 centers, with a concordance index of 0.68.

The Spain nomogram was created from a large patient cohort and has been externally validated. It has also been converted into a nomogram, increasing its ease of use. However, it requires laboratory data that is not always readily available. Additionally, it has limited applicability in patients with longer survival times (ie, greater than 60 days).

Comparison of models

The aforementioned prognostic tools demonstrated prognostic accuracy in the patient populations examined and have been externally validated. Data comparing these tools include a prospective cohort study of 549 advanced cancer patients receiving palliative care comparing the PaP model, a variant of the PaP that includes delirium (D-PaP),⁵⁷ the PPI, and the palliative prognostic scale (PPS).⁵⁷ This study demonstrated all tools to significantly discriminate between survival groups, though the PaP model (and D-PaP) had the highest accuracy. Further data are required that compare the performance of prognostic tools. As shown in the Table, models frequently are developed within populations of patients with life expectancies limited to a few months (eg, PaP, PPI and Spain nomogram). Others (eg, NRF model) are developed among patients having longer life expectancies. While these tools are useful if the lifespan of a patient can be estimated to fit into one of these categories, the ideal model would function across the spectrum of prognosis for advanced cancer patients.

Conclusions

Physician estimates of prognosis to inform clinical decision-making in advanced cancer patients is important; but the task remains difficult. There are several tools available to improve physicians' prognostic abilities. But further studies are needed to refine which factors and models are the most accurate predictors of survival. In addition, future research should identify a prognostic model that can accurately estimate life expectancies for advanced cancer patients with a wider spectrum of prognoses using an accessible tool, much like the APACHE score to predict mortality in intensive care units.^{58,59} Finally, further research is needed to determine whether prognostic tools will improve end-of-life care for advanced cancer patients by increasing the frequency of goals-of-care discussions, facilitating early referrals to palliative care, or reducing aggressive interventions near death. While tailoring treatment to expected longevity is a promising goal, improving the physicians' ability to formulate these estimates is an important first step in ensuring that patients with advanced cancer receive appropriate care.

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