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Predicting survival in patients with advanced disease

Chapter: Predicting survival in patients with advanced disease
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Introduction to predicting survival in patients with advanced disease

Diagnosis, treatment, and prognosis have long been recognized as the three cardinal skills of clinical medicine (Hutchinson, 1934). Prior to the twentieth century, when few effective treatments were available for any disease, offering a prognosis was about all the physician could do. Due to progress in diagnosis and treatment in the twentieth century, the need for this kind of prognostication has—thankfully—largely disappeared (Christakis, 1997). In the twenty-first century, the growth of palliative medicine has led to a renaissance of interest in predicting survival in patients with fatal diseases. But nowadays they are chronic, incurable conditions such as advanced cancer, end-organ failures, and dementia, and not acute, medical diseases such as pneumonia.

There are many reasons why palliative care clinicians need to be proficient at prognosis:

- It provides patients and their families with information on what to expect so they can set

meaningful goals, priorities, and expectations for care.

- ◆ It is a key technical prerequisite for many clinical decisions.
- ◆ It determines eligibility for the hospice benefit in the United States and admission to inpatient units in other countries.
- ◆ It is important for the design and analysis of clinical trials.

Despite the importance of prognosis as a clinical skill in palliative care, most clinicians are not trained how to do it well. Prognostic issues may be covered in a class on 'breaking bad news' which typically uses disclosure of a poor prognosis as an example of difficult physician–patient communication. But most students are not taught how to formulate a prognosis or how to use it appropriately. Being poorly trained in the prognosis skills, it is not surprising that physicians find it difficult to prognosticate and do not like doing it (Christakis and Iwashyna, 1998). They also find it stressful because they believe patients desire too much certainty and accuracy from their predictions. They also feel intimidated by being judged by patients and other clinicians if their prognosis is wrong—although not as badly as for getting the diagnosis wrong. As a result, various norms of prognostication have evolved within mainstream clinical medicine:

- ◆ Avoid prognosticating.
- ◆ Wait to be asked rather than volunteering a prediction, especially if the clinical situation is atypical.
- ◆ Be optimistic, especially if the patient is also optimistic.
- ◆ Avoid being specific.
- ◆ Do not use prognostication for survival in treatment decision-making.

These behaviours emphasize the need to improve both education and clinical research in prognosis. There have been advances in the science of prognostication in the past 10 years that are teachable to physicians to improve their confidence to make predictions. Palliative care specialists should have special expertise in this area because it will guide care planning, diagnostic and treatment decisions, as well as communication with patients and families.

In *The Book of Prognostics*, Hippocrates wrote that the physician who was a good prognosticator was highly esteemed among his colleagues and trusted by his patients. This secular perspective contrasts with many religious traditions which insist that only God knows the hour of an individual's death. As a result, in many non-English-speaking cultures, such discussions have traditionally been avoided, although this situation may be gradually changing (Bruera et al., 2000). Patients, family, and staff who wish to defer discussing prognosis to the idea 'God only knows' may use it as a way to culturally identify the acknowledged uncertainty of prognostication.

Even in cultures that accept that predicting survival is allowable, questions are asked about the importance of prognostication. Unlike modern diagnosis and treatment, prognostication remains inherently inaccurate. Nevertheless, we believe prognostication is necessary and inevitable, and in the best interests of all involved. There may even be a moral duty for clinicians to prognosticate (Broeckaert and Glare, 2008), striving to formulate as accurate a prediction as possible, and to communicate it and use it appropriately. This means deeply embedding the clinical acts of prognostication in an open, flexible, dialogical, patient-centred approach (Glare, 2011).

Scientific principles of prognostication

Domains of prognosis

Although the focus of this chapter is on predicting survival, it is important to remember that the word prognosis is defined more broadly by clinical epidemiologists as the 'relative probabilities of the various outcomes of the natural history of a disease' (Sackett et al., 1991). To categorize the many different outcomes of a disease which can be predicted, the '5Ds of prognostication' has been proposed (Fries and Ehrlich, 1981):

- disease progression/recurrence
- death
- disability/discomfort
- drug toxicity
- dollars (costs of health care).

All five of the 'Ds' are relevant to palliative care, and patients may be more interested in predictions other than survival, such as response rates and side effects of palliative therapies (Steinhauser et al., 2000). However, because remaining survival time is so central to establishing patient-centred goals, making decisions about treatment and end-of-life decision-making, the focus of this chapter is on predicting death.

Three components of prognostication

The clinical act of prognostication is in fact a composite of three skills that palliative care clinicians should be competent in. These are formulating the prognosis, communicating the prognosis, and using the prognosis when making clinical decisions. To date, prognosis research has focused on good formulation and communication. With the exception of the Study to Understand Prognosis and Preferences for the Outcomes and Risks of Treatment (SUPPORT) study (The SUPPORT Principal Investigators 1995), there have been few studies of how clinicians use prognostic information when making decisions.

Formulating the prognosis: two approaches

A prognosis can be formulated in one of two ways. The first, called clinical prediction of survival (CPS), involves the use of subjective judgement and formulation of the prognosis in the clinician's head. The other way, referred to as actuarial judgement, relies on statistical data such as median survivals and hazard ratios and eliminates the need for the human judge (Dawes et al., 1989). Research from clinical psychology indicates actuarial judgement is generally superior to clinical judgement in predicting human behaviour (Steyerberg and Harrell, 2002), but this is not yet the case for predicting survival.

Irrespective of how the prognosis is formulated, it may be expressed as a temporal prediction or a probabilistic one. A temporal prediction estimates the time to the event (that is, death) and is normally expressed as a continuous variable (i.e. actual number of days, weeks, or months) but may also be a categorical variable (e.g. < 3 weeks, < 6 months, > 1 year). A probabilistic prediction estimates the chance of surviving to a certain time point, for example, percentage chance of being alive in 6 months.

The question of which is the best way to formulate and express the prognosis raises the topic of research in prognosis and the methodological challenges that are encountered when designing or appraising a prognostic study, and they are very different to the methodological issues arising in a clinical trial of a therapy (Laupacis et al., 1994; Altman, 2009). There are many different research questions in prognosis, including evaluation of predictive factors, development and validation of prognostic models, and systematic reviews of the two. Some of the characteristics of a well-designed study to evaluate the association of a prognostic factor with survival are shown in Box 2.3.1.

Box 2.3.1 Characteristics of well-designed studies to evaluate the association of prognostic factors with survival

- A well-defined study population
- Inception cohort design
- Prognostic factors selected are appropriate and clearly defined
- Sample size is adequate for sufficient statistical power
- Clearly defined end point
- Complete follow-up of all patients
- Data analysis is appropriate to test associations between the study factors and survival
- A measure of agreement between the predicted and actual survival
- The definition of accuracy is explicit and appropriate
- The prediction tested mirrors clinical language or practice (i.e. not hazard ratios).

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Subjective judgement: clinical prediction of survival

Little is currently known about what goes through a clinician's head when they are using subjective judgement. Are they being truly subjective, are they recalling previous patients similar to the one before them, or are they using a kind of actuarial judgement and weighing clinical and other factors? A survey of Italian oncologists found they mainly utilized tumour-related factors when formulating the prognosis in advanced disease (Tannenberger et al., 2002), even though factors such as performance status, symptom burden, and laboratory tests are more relevant in this setting (Hauser et al., 2006). For the clinician who wishes to be more systematic with their CPS, a semi-structured approach has been posited (Mackillop, 2006), beginning with the general prognosis which is based on the clinical and pathological findings (e.g. median survival of 6 months for stage 4 lung cancer). This is then customized to the patient's clinical situation, taking into account their co-morbidities, symptoms, and laboratory abnormalities, as well as their psychosocial issues.

Studies of the accuracy of CPS in advanced cancer indicate that temporal CPS are typically inaccurate, with less than one-quarter of predictions falling within 33% either side of the actual survival, and most being in the over-optimistic direction (Christakis and Lamont, 2000; Glare et al., 2003). Probabilistic CPS are often more accurate (typically in the 60–75% range) and have less of an optimistic bias. Factors influencing the accuracy of CPS have been evaluated. Improvements may be achieved with repeated estimates or asking multiple clinicians to predict. Few differences have been found between disciplines, although physicians may make better initial predictions and nurses may be better in the last few days of life—perhaps because of the amount of time they spend with the patient (Oxenham and Cornbleet, 1998). Experience matters, but a strong physician–patient relationship has been shown to lower prognostic accuracy (Christakis and Lamont, 2000). The accuracy of CPS in non-malignant diseases is less well studied, but clinicians may be less likely to overestimate prognosis in these populations. Other terminology from the science of measurement, such as calibration and discrimination are also relevant to survival predictions. Predictions discriminate well if the patients in one prognostic group have a different survival to those in another prognostic group. Predictions are well calibrated if patients with better prognoses live longer than patients with worse prognoses.

In an attempt to improve CPS, national organizations in the United Kingdom and the United States have offered clinicians guidance on this subject. In the United Kingdom, the National Health Service's Gold Standards Framework prognostic indicator guidance consists of general 'triggers' for identifying patients and then some more specific guidance for individual diseases (Gold Standards Framework, 2011). In the United States, where incorrectly recommending hospice can result in charges of fraud, the National Hospice and Palliative Care Organization (NHPCO) has developed guidelines to help physicians determine if American patients meet the 6-month prognosis rule 'if the disease follows its usual course' to be eligible for the hospice benefit. These guidelines have been shown to be not very accurate, especially for patients with non-cancer diagnoses (Fox et al., 1999).

For physicians facing difficulties with formulating a CPS, an alternative approach is to ask oneself the 'surprise question', namely 'Would I be surprised if the patient died in the next . . . ?'. Rather than needing to definitely conclude that the patient is dying, asking if they would be surprised if the patient died before some future time point may be more intuitive and feasible. In a study of 826 patients with breast, lung, or colon cancer being followed at a US university cancer centre, 41% of the 'No, I would not be surprised' patients had died at 12 months, while only 3% of the 'Yes, I would be surprised' group had died (Moss et al., 2010). Patients in the 'No' group in this study were older, more likely to have stage IV disease, more likely to have lung cancer, and more likely to have completed an advance directive.

Actuarial judgement: predictive factors in advanced disease

Performance status

Performance status has long been recognized as a predictor of various oncological outcomes, including survival. Multiple studies in the 1980s and 1990s confirmed that cancer patients with a low score on the Karnofsky Performance Status (KPS) scale—developed in the 1940s to assess the effects of chemotherapy on functional level in cancer patients—had a short survival.

One limitation of the KPS scale is that the definitions for scores below 50 depend on the patient's need for hospitalization. The rapid development of community-based palliative care and home hospice programmes over the past 30 years that strive to keep the patient at home has made the KPS scale difficult to apply in these settings. To overcome this problem, the Palliative Performance Scale (PPS) was developed. Multiple studies have shown that the PPS score is a strong predictor of survival in cancer patients already identified as palliative. A meta-analysis of four studies demonstrated that each PPS level is distinct and without grouping (Downing et al., 2007). A large study of PPS scores in ambulatory cancer patients found that the average PPS score declined slowly over the 6 months before death, starting at approximately 70 and ending at 40, declining more rapidly in the last month (Seow et al., 2011). Prognostat is a web-based tool for survival prediction in palliative care patients which is based on the PPS (Health Terminology Group, n.d.). It includes a calculator, survival tables, and a nomogram for cancer and non-cancer patients.

Symptoms

Most of the research on the impact of symptoms and survival has involved cancer patients. Various individual symptoms have been consistently associated with poor survival in multiple studies (Vigano et al., 2000). The strongest association is with the anorexia-cachexia complex, which has been called the 'final common pathway of terminal cancer'. Dyspnoea and confusion are also associated with a short survival in most studies. In hospice patients with a better performance status (above 40 on the KPS scale), a high symptom burden helps identify the subset with a worse survival outlook (Reuben et al., 1988).

Somewhat surprisingly, pain is not usually identified as one of the predictors of a poor survival in studies of prognostic factors, even though it is known to be a progressive problem in cancer patients. This discrepancy is likely to be explained by lead time bias. Most of the studies of prognostic factors in advanced cancer do not utilize a true, disease-based inception cohort. Instead they study patients who have been referred to palliative care services or hospice, in whom pain is usually the trigger for referral. In a recent study, the use of strong opioids, rather than pain per se, was shown to be prognostic (Gripp et al., 2007).

Various symptom scores have also been shown to be associated with survival, including the Symptom Distress Score (Degner and Sloan, 1995), Rotterdam Symptom Checklist (Earlam et al., 1996), the Memorial Symptom Assessment Scale (Chang et al., 1998), and the Edmonton Symptom Assessment Scale (Seow et al., 2011). In ambulatory cancer patients with end-stage disease, more than one-third of the cohort reported moderate to severe Edmonton Symptom Assessment Scale scores (i.e. 4–10) for most symptoms in the last month of life. Average scores for pain, nausea, anxiety, and depression scores remained relatively stable over the final 6 months. Conversely, shortness of breath, drowsiness, well-being, lack of appetite, and tiredness increased in severity over time, particularly in the month before death.

The association between symptoms and survival is less well studied in non-cancer patients. A systematic review of the prevalence of 11 common symptoms among end-stage patients with cancer, acquired immunodeficiency syndrome, heart disease, chronic obstructive pulmonary disease (COPD), or renal disease found that symptoms were widely and homogeneously spread across the five diseases (Solano et al., 2006). Pain, breathlessness, and fatigue were found among more than 50% of patients, for all five diseases. The authors concluded that the concept of a 'final common pathway' towards death featuring fatigue, anorexia, weight loss,

and dyspnoea applies as much to non-malignant diseases as it does to cancer.

Mood, quality of life, and self-rated health

While several physical symptoms are associated with a poor survival, the impact of psychological symptoms is less clear. A systematic review of depression, cancer, and survival identified 25 relevant studies and concluded that mortality rates were significantly higher in depressed patients, but the effect size was small. Mortality rates were up to 25% higher in patients experiencing depressive symptoms and up to 40% higher in patients diagnosed with major or minor depression. The effect of depression remains after adjustment for other prognostic factors, suggesting that depression may play a causal role (Satin et al., 2009). Intriguingly, accelerated cellular aging as indexed by short telomere length has emerged as a potential common biological mechanism linking various forms of psychological stress and diseases of aging, including cancer (O'Donovan et al., 2012).

Quality of life (QOL) scores generally are not associated with survival, especially when measured with instruments developed for palliative care that focus largely on non-physical domains. The Therapeutic Impact Questionnaire developed in Italy for use in hospice/palliative care, rates four major components of QOL—physical symptoms, function, psychological state, and family and social relationships (Tamburini et al., 1996). Global well-being is also evaluated. Only the patient-rated perception of cognitive function and global well-being showed independent prognostic value. Patients had median survivals of 137, 50, and 17 days for impairment of neither, one, or both scales, respectively.

Self-rated health (SRH) is increasingly being recognized as a valid measure for predicting future health outcomes, including survival. Global SRH, the most commonly used measure to rate overall health, is an important predictor of mortality. An unfavourable assessment of overall health has been associated with increased risk of death, even after controlling for socioeconomic status, physical health, functioning, chronic conditions, and health risk behaviours. In a study of ambulatory advanced cancer patients with a median survival time of 10 months, SRH was the strongest predictor of survival from baseline (Shadbolt et al., 2002). The risk of dying was greatest for patients rating their health as 'poor', intermediate if they rated it 'fair', and lowest if they rated it 'good' or better.

Co-morbidities

Cancer patients often have other diseases or medical conditions in addition to their cancer, especially when they are older. Multiple studies have shown that early-stage cancer patients with co-morbid conditions have worse outcomes than patients without co-morbid ailments. The prognostic impact of co-morbidities is greatest for patients with cancers associated with a long natural history, such as prostate cancer, and least in patients with aggressive cancers, such as lung cancer (Read et al., 2004). Co-morbidities have been shown to influence the survival of critically ill cancer patients (Soares et al., 2005), but have rarely been evaluated in studies of prognostic factors in less severely ill palliative care patients. A notable exception is the SUPPORT prognostic model (Knaus et al., 1995), which included cancer as a co-morbidity in patients with other diagnoses (see later section).

Biomarkers

The possibility of taking a single blood sample to provide a precise, accurate, objective estimate of prognosis is tantalizing to clinicians. Pro-inflammatory cytokines such as interleukin-6 (IL-6) are implicated in the genesis of the anorexia-cachexia syndrome (Lee et al., 2004), and C-reactive protein (CRP) is a readily available, inexpensive blood test that is highly correlated with IL-6 levels for inflammation. Other parameters that have been evaluated include elevations of serum alpha-1-acid glycoprotein, alkaline phosphatase, lactate dehydrogenase, and pseudocholinesterase.

Several simple, objective prognostic scores incorporating CRP levels have been developed in advanced cancer. The Glasgow Prognostic Score uses CRP and albumin levels, with elevated CRP levels and hypoalbuminaemia being awarded prognostic points. It has been shown to predict survival in patients with advanced lung cancer (Forrest et al., 2005) and gastric cancer. The vitamin B_{12}/CRP Index (BCI) takes the product of the serum vitamin B_{12} (in pmol/L) and CRP (mg/mL). A retrospective analysis of BCI scores in Swiss geriatric cancer patients who were terminally ill showed that a high score (> 40,000) was associated with a poor survival, that is, less than a 10% chance of surviving 3 months (Geissbuhler et al., 2000). This finding has been validated by others (Kelly et al., 2007; Tavares, 2010), and shown to be as accurate as CPS (Tavares, 2010).

Biomarkers may be prognostic in other diseases. In heart failure, brain natriuretic peptide (BNP) levels may indicate an increased risk of sudden death (Tannenberger et al., 2002), either alone or combined with troponin levels and CRP. In 44 patients dying suddenly versus 89 other patients who died more slowly within 3 years of first diagnosis of heart failure and ejection fraction less than 35%, multivariate analysis showed that log BNP level was the only independent predictor of sudden death ($P = 0.0006$), with a cut-off point of log BNP less than 2.11 (130 pg/mL) (Berger et al., 2002).

Prognostic tools and models

Models for cancer patients

There is the potential to combine the simple clinical and laboratory factors described above to provide physicians with accurate information about prognosis. Yet caution is needed in interpreting any studies or systematic reviews on survival prediction and prognostic models. Firstly, it is important to distinguish those based on the general population at large from ones within a defined palliative or hospice population. A strong consideration must be given to the inception cohort issue, which requires patients to be at a uniform, disease-based point in time when the measurements of survival begin. Secondly, even in a defined palliative population, attempting to compare published data to one's own palliative programme requires attention to the demographics and inclusion/exclusion criteria. There is often a difference between patients admitted directly to an acute tertiary palliative care unit and those cared for at home or admitted to a hospice facility. The former admissions are usually for urgent symptom assessment and management and as such, may have shorter survival data due to patient complications and difficult symptoms. Hospices will have a somewhat more stable population at least on admission. Thirdly, prognostic scores with statistical significance will follow a Kaplan–Meier curve for the subset analysed but the location on that curve for each individual's death is less obvious, and is in fact indeterminate without other factors being taken into consideration.

Models for terminally ill cancer patients

Many studies over the past decade have developed multiple regression models to determine the association between prognostic factors and survival in patients with far advanced cancer, but few have tested the predicative accuracy of their final models, a key step in prognostic model building. Some of the better developed models are discussed in more detail here.

The SUPPORT study

The SUPPORT study (Knaus et al., 1995) was designed to identify deficiencies in the care of hospitalized patients with various eventually fatal illnesses. The SUPPORT model was developed for this study, with the aim of providing prognostic information as the cornerstone of improved decision-making about end-of-life care in hospitals. Based on the APACHE system for prognostication in critically ill patients in intensive care units (ICUs), individuals' clinical and physiological parameters were utilized in a complex algorithm that was computer generated and gave a probability for the hospitalized patient being alive in 2 and 6 months' time. Only some of them had cancer, making it difficult to compare this model with others developed in patients with terminal cancer. The mathematical model is complex and not suitable for routine use by the clinician at the bedside. The information provided (chance of being alive in 6 months) is relevant to only a small minority of cancer patients referred to hospice/palliative care. Nevertheless, the SUPPORT study is important because it was the first large study to demonstrate the potential of using actuarial judgement to provide the clinician with accurate prognostic data.

The Palliative Prognostic Index (PPI)

This model was originally developed in Japanese cancer patients enrolled in palliative care programmes (Morita et al., 1999). The PPI is calculated by attributing partial scores to five clinical variables (performance status, oral intake, dyspnoea, delirium, and oedema). In the initial study, the total PPI score was used to define three groups with differing prognoses and these results were subsequently replicated in an independent validation sample. A PPI greater than 4 predicted death within 6 weeks with a positive predictive value (PPV) of 83% and a negative predictive value (NPV) of 71%. A later study by the same group confirmed the effectiveness of the PPI at predicting 6-week survival and also demonstrated that the accuracy of clinicians' estimates was improved if they were provided with PPI scores prior to making a prediction (Morita et al., 2001). Further evidence for the validity of this instrument has been provided by Stone and colleagues (Stone et al., 2008) who reported that among patients referred to their palliative care service in Ireland, the PPI had a PPV for predicting death within 6 weeks of 91% and a NPV of 64%.

The Palliative Prognostic (PaP) score

The predictive model from which the PaP score is derived was developed in Italian home hospice patients with advanced cancer (Pirovano et al., 1999). The model consists of six variables that are easily measured at the bedside, namely Karnofsky performance status, anorexia, dyspnoea, total white blood count, and lymphocyte percentage plus the CPS measured in 2-week intervals out to 12 weeks. These factors were independently predictive of survival, and the model is able to split a heterogeneous sample of patients with far advanced cancer into three groups with differing probabilities of being alive at 30 days (group A > 70%,

group B 30–70%, and group C < 30%). To calculate the PaP score, points are allocated for each of the six factors, the points for each being based on their parameters in the model. The individual points are then summed to give a final score, which can range from 0 to 17.5, with higher scores representing worse survival. In the original clinical validation study, group A had a score of 0–5, group B 5.5–11, and group C, 11.5–17.5 (Maltoni et al., 1999).

The PaP score is the most robust prognostic model in hospice and palliative care, having been validated in a variety of populations and settings (Glare and Virik, 2001; Glare et al., 2003, 2004; Naylor et al., 2010; Tarumi et al., 2011). The largest validation study, in a mixed cancer and non-cancer palliative care population at a Canadian acute care hospital, involved 958 patients, 18% of whom had non-cancer diagnoses (Tarumi et al., 2011). In this population, PaP group A had a 78% probability of 30-day survival, group B had a 55% probability, and group C had an 11% probability. These results are in keeping with the original development studies for the PaP and generally support its validity as a prognostic tool in palliative care patients. Although the PaP is the most widely validated of the palliative prognostic scales some investigators have expressed dissatisfaction with its over-reliance on subjective clinician estimates (the clinician's intuitive guess accounts for approximately 50% of the total PaP score) and with the omission of cognitive function (which is known to be a poor prognostic factor) from the scoring algorithm

Prognosis in Palliative care Study (PiPS) models

The PiPS models attempt to address the limitations of the PaP score. A large, prospective, multi-centre study involving over 1000 advanced cancer patients newly referred to palliative care services in England identified 11 core variables (pulse rate, general health status, mental test score, performance status, presence of anorexia, presence of any site of metastatic disease, presence of liver metastases, CRP, white blood count, platelet count, and urea) which independently predicted both 2-week and 2-month survival (Gwilliam et al., 2011). Four other variables had prognostic significance only for 2-week survival (dyspnoea, dysphagia, bone metastases, and alanine transaminase), and eight further variables had prognostic significance only for 2-month survival (primary breast cancer, male genital cancer, tiredness, loss of weight, lymphocyte count, neutrophil count, alkaline phosphatase, and albumin). Separate prognostic models were created for patients without (PiPS-A) or with (PiPS-B) blood results.

These models were able to reliably identify those patients with expected prognoses of 'days', 'weeks', or 'months/years' (St George's, University of London, 2011). The median survival across the PiPS-A categories was 5, 33, and 92 days and survival across PiPS-B categories was 7, 32, and 100.5 days. All four PIPs models performed as well as, or better than, CPS. The area under the curve for all models varied between 0.79 and 0.86. Absolute agreement between actual survival and PiPS predictions was 57.3% (after correction for over-optimism). The models can be used in either competent or incompetent patients and in circumstances when blood results are available and when additional investigations would be inappropriate. The prognostic models were shown to be at least as good as a multi-professional clinical estimate of survival; when blood results were available, the models were significantly better than either a doctor's or a nurse's prediction (but not a multi-professional estimate). The instruments have not yet been independently validated, nor has the performance of the PiPS been compared to the performance of the PaP score or the PPI.

Feliu prognostic nomogram

Feliu and colleagues (Feliu et al., 2011) have developed a nomogram to predict survival of terminally ill cancer patients at 15, 30, and 60 days. The prognostic index is generated from a weighted combination of Eastern Cooperative Oncology Group (ECOG) performance status, albumin, lactate dehydrogenase, lymphocyte counts, and time elapsed between initial diagnosis and development of a terminal disease. The nomogram correctly classified survival in 70% of patients in the development study and in 68% of the validation cohort. The authors tested their nomogram against the PaP score and found the nomogram to be significantly more accurate. A potential limitation of the Feliu nomogram is its reliance on the concept of the 'time to terminal diagnosis'. This is a very subjective concept, potentially open to the same limitations as using CPS in the PaP. To assist validation studies of the nomogram, standardized definitions of the onset of a terminal diagnosis, for example, progression through third-line chemotherapy, are needed.

Prognostic tools for less seriously ill cancer patients receiving palliative care

There is currently no prognostic model for predicting survival from cancer that has been validated in the setting of an outpatient palliative care clinic, where patients often don't have many of the symptoms and other problems incorporated in the above models and often survive for several years. A vast amount of prognostic information is available for individual cancers within the oncology literature but is not easily accessible; PubMed has no single MeSH term for 'prognostic index' (Yourman et al., 2012). A tool that is applicable to the heterogeneous patient population seen in the palliative care outpatient clinic is urgently needed. As more palliative care programmes offer ambulatory clinics for patients with months–years to live, a tool for predicting their survival is an important innovation.

A prognostic tool has been developed for ambulatory patients receiving palliative radiotherapy (Chow et al., 2002). It has subsequently been simplified (Chow et al., 2008), the simplified model utilizing just three variables—primary cancer type, site of metastases, and performance status—to divide patients into three independent prognostic groups with median survivals of 12, 6, and 3 months, respectively. This simple prognostic model may be applicable to the broader palliative care population (Vij et al., 2012).

Prognostic tools and models for other life-limiting diseases

End-organ failures

Congestive heart failure (CHF)

The prognosis of CHF may be as bad, if not worse, than many cancers (see Chapter 15.3). Overall, 1-year and 5-year survival rates in the Framingham Heart Study were 57% and 25% in men and 64% and 38% in women, respectively (Ho et al., 1993). The New York Heart Association (NYHA) classification category is the major gauge of disease severity in CHF, and is the cornerstone of the criteria for hospice admission for CHF in the United States. Based on data from the Framingham Heart Study and other studies, NYHA Class IV (severe symptoms) CHF has a 1-year mortality of 30–40%. However, providing more accurate predictions of 6–12-month mortality has been nearly impossible, due to the unpredictable disease trajectory of CHF. On the one hand it is highly mutable by application of evidence-based therapies, yet it is also marked by a high incidence of sudden death, in the vicinity of 15–20%.

A limitation of the current US hospice admission criteria for CHF is that they are outdated. Written by the NHPCO in 1996, 'optimal treatment' is specified as angiotensin-converting enzyme inhibitors, diuretics, and vasodilators when contemporary optimal treatment includes beta blockers, aldosterone antagonists, and device therapies. The increased use of left ventricular assist devices as 'destination therapy', that is, until death in patients who are non-eligible for transplants, also makes prognostication in CHF increasingly challenging, as do the placement of pacemakers and intra-cardiac defibrillators.

Although it does not predict 6-month mortality, the Seattle Heart Failure Model is a well-validated model that provides an accurate estimate of 1-, 2-, and 3-year survival with the use of easily obtained clinical, pharmacological, device, and laboratory characteristics (Levy et al., 2006; Mozaffarian et al., 2007). Caution should be noted in application in the very elderly, as it is given to greatly overestimating prognosis in this group. A dynamic web version is available which shows changes in Kaplan–Meier survival curves as various parameters are inserted (University of Washington, n.d.). Enhanced Feedback for Effective Cardiac Treatment (EFFECT), a Canadian consortium, has validated another online prognostic model (Canadian Cardiovascular Outcomes Research Team, n.d.).

The prognosis for survival to discharge after cardiopulmonary resuscitation (CPR) is also important, as it is the typical starting point in a discussion of code status. The outcome of in-hospital arrest has not changed since the early 1990s, even though there have been major improvements in the outcome of out-of-hospital cardiac arrest during this period. For the general hospitalized patient experiencing an in-hospital cardiac arrest, a return of spontaneous circulation can be achieved with CPR approximately 50% of the time, but less than 20% of patients survive to discharge (Ehlenbach et al., 2009). The neurological outcomes of those who survived to discharge were generally good, and most patients admitted from home pre-arrest were able to return there. Having multiple co-morbidities pre-arrest is associated with a worse outcome, as are extreme age, poor functional status, and admission from a nursing home.

Chronic obstructive pulmonary disease

COPD also has a poor prognosis with men aged 65 with stage 3 or 4 COPD who continue to smoke dying 10 years before non-smokers without COPD (Shavelle et al., 2009) (see Chapter 15.2). Traditionally, the two most important prognostic factors in COPD have been forced expiratory volume in 1 second (FEV_1) and age. More recently, the level of dyspnoea, graded by the Medical Research Council (MRC) dyspnoea scale, has been found to be a better predictor of survival than the FEV_1 (O'Donnell et al., 2007). For example, a Japanese study of mortality predictors in 227 outpatients with COPD of whom 73% were alive at 5 years found that dyspnoea was significantly correlated to the 5-year survival rate and the level of dyspnoea had a more significant effect on survival than disease severity based on FEV_1 (Oga et al., 2003).

Factors other than age, dyspnoea, and FEV_1 have been evaluated in prognostic models of dyspnoea. The BODE Index incorporates *b*ody mass index (BMI), *o*bstruction (FEV_1 %), *d*yspnoea (MRC dyspnoea scale), and *e*xercise capacity (6-minute walk distance) (Celli et al., 2004). Similarly, the HADO score includes *h*ealth (5-point self-assessment), *a*ctivity (self-reported), *d*yspnoea, and *o*bstruction (FEV_1 %) (Esteban et al., 2006). The BODE Index and the HADO Score have both been identified as good predictors of all-cause and respiratory mortality

in COPD. In patients with severe COPD (FEV_1 < 50%) the BODE Index may be more accurate (Esteban et al., 2010).

Two major clinical issues related to prognosis in COPD are the identification of patients who are eligible for hospice and the outcomes of mechanical ventilation. COPD patients most likely to die within 6–12 months include those with severe, irreversible airflow obstruction, severely impaired and declining exercise capacity and performance status, older age, concomitant cardiovascular or other co-morbid disease, and a history of recent hospitalizations for acute care (Hansen-Flaschen, 2004). Clinicians' predictions in COPD found underestimation of survival after admission to the ICU. For example, the quintile of patients with the lowest expected prognosis (10% probability to survive 6 months) had a group survival of 40% at 6 months (Wildman et al., 2007). The reason for the underestimate is not elucidated in this study but the issue is important for further study as it may impact decisions to admit to the ICU that may be overweighted towards futility arguments. This is an excellent illustration for how prognostication can have profound impacts on policy and utilization of resources, and should be a critical area for more research to serve patients best.

Prognostic models for the frail elderly

Prognosis in the general geriatric population

Failure to consider prognosis in the context of clinical decision-making in the elderly can lead to poor care (see Chapter 16.3). Healthy older patients with good prognosis have low rates of cancer screening, while hospice is underutilized for patients with non-malignant yet life-threatening diseases. Guidelines increasingly incorporate life expectancy as a central factor in weighing the benefits and the burdens of tests and treatments, but prognostic indices offer a potential role for moving beyond arbitrary, age-based cut-offs in clinical decision-making for older adults.

Many geriatric prognostic indices have been published. An excellent recent systematic review of this literature has identified 16 indices that predict risk of mortality from 6 months to 5 years for older adults who do not have a dominant terminal illness such as CHF or dementia, and who are in a variety of clinical settings (Yourman et al., 2012). The review focuses on the accuracy, generalizability, potential for bias, and usability of these indices. To enable clinicians to find the right tool from the 16 available that best fits their patient's situation, the review's authors have created a website which provides an online repository of each of the indices in the review and advice about when to use them (Yourman et al., n.d.).

Dementia patients

The illness trajectory for Alzheimer's dementia follows a generally predictable decline in functional and cognitive status (see Chapter 15.4). The onset of inability to walk unaided indicates the patient is entering the final phase of the illness. However, the final phase of the illness can be protracted and the event that precipitates the death is often unclear. The current NHPCO hospice admission criteria for dementia requires the patient to be stage 7C on the FAST (Functional Assessment Staging Tool; Reisberg 1988) classification system—defined as dementia with impaired activities of daily living (ADLs), incontinence and loss of ambulation—plus the onset of a major medical complication such as aspiration pneumonia, urinary tract infection, or decubitus ulcers in the previous 12 months. Two small studies (Luchins et al.,

1997; Hanrahan et al., 1999) have reported that the NHPCO guidelines did appear to identify patients at higher risk of dying within 6 months, but in one study, 30% patients with dementia aged more than 90 years who had been referred to a US hospice programme were still alive 3 years later (Aguero-Torres et al., 1998). Several other studies have found the guidelines had a predictive ability 'no better than chance' (Schonwetter et al., 1998, 2003; Mitchell et al., 2004). Furthermore, many bed-ridden dementia patients do not progress through the earlier stages of the FAST system in an orderly fashion. They are not technically at stage 7C and therefore not hospice eligible. Hospice has been shown to benefit people dying with dementia (Teno et al., 2011), but these studies indicate that prognostication is difficult and may be a barrier to hospice enrolment (Jayes et al., 2012).

In view of the inaccuracy of the NHPCO criteria, several other tools have been developed to improve on them. Of them, the Advanced Dementia Prognostic Tool (ADEPT) has been specifically developed to be more accurate than the FAST 7C criteria used for hospice eligibility, and validated against them (Mitchell et al., 2010). Unlike FAST, ADEPT includes scores for age, male gender, weight loss/BMI, performance status, ADLs, symptoms, and continence. When benchmarked against FAST, it performed slightly better (58% vs 51% accuracy).

Communicating a prognosis

Multiple surveys show most patients with cancer want information about their prognosis (Kutner et al., 1999; Butow et al., 2002; Hagerty et al., 2004, 2005; Parker et al., 2007; Innes and Payne, 2009), whether it be good news or bad (Fallowfield et al., 2002) (see Chapter 6.1). But talking to patients about prognosis is difficult and clinicians are poor at this type of communication. There are large discrepancies between patients' and healthcare professionals' perceptions about how much information is needed, how much information has been given, and what such information means (Hancock et al., 2007). Clinicians tend to underestimate patients' prognostic information needs and overestimate how much they had understood about their illness and its likely outcome (Beadle et al., 2004).

Giving patients prognostic information is also important in terms of the effects it can have on patient outcomes. Advance care planning for patients at the end of life requires frank disclosure about prognosis. In one large cohort study (Wright et al., 2008), explicit discussion of end-of-life issues was associated with less aggressive medical care near death, earlier hospice referrals, and improved outcomes for bereaved family members. Without such explicit prognostic information patients may find themselves being managed in the acute care setting at the end of life rather than a more appropriate environment (Innes and Payne, 2009; Mack and Smith, 2012).

Physicians and patients may, to some extent, enter into a level of collusion about avoiding any discussion of prognosis (The et al., 2000). Consultations tend to focus on treatment options and the results of investigations rather than on questions of prognosis, often involving 'false optimism' about the prospects of recovery. This optimism may be fostered both by doctors' reluctance to give clear information about prognosis and patients' avoidance of asking direct questions.

What prognostic information do patients want?

Patients both crave and dread prognostic information. They are caught between wanting to know what is going on and fearing the answers they might receive. Therefore, they want the prognosis to be given by someone whom they perceive to be an expert, and they find inconsistent information or evasiveness on the part of the professional to be distressing and unhelpful. Patients also want hopeful messages, even when they accept the terminal phase of the illness (Kutner et al., 1999; Kirk et al., 2004). Strategies clinicians may use to facilitate hope when discussing prognosis include retaining professional honesty, avoiding being blunt or giving more detailed information than desired by the patient, pacing of information, respecting patients' need to follow alternative paths/treatments, and exploring and facilitating realistic goals and wishes where appropriate.

Many studies have stressed the importance of individualizing the content of prognostic discussions, but few patient characteristics have been identified to predict how much information patients want or how such information should be delivered (Kutner et al., 1999). Patients have different needs from one another and individual patients' information needs and preferences can change during the course of their illness. While many want to discuss prognosis when they were first diagnosed with metastatic disease, others want to negotiate with the clinician about when such issues were discussed. In one study, more than half the patients wanted the physicians to initiate discussions about prognosis, less than a quarter only wanted the physician to tell them about survival 'if asked', and approximately 10% of patients never wanted to discuss likely duration of survival (Hagerty et al., 2004). In general, women want more information than men (Fallowfield et al., 2002) and older patients request less information than younger patients. Cultural differences may also be important (Parker et al., 2007). Likewise patients tend to want less information as their underlying disease progresses and they approach the terminal phase of their illness.

How to communicate the formulated prognosis to the patient?

Although patients generally indicate they want information about prognosis, it is not always clear what is the best way to communicate such information. Guidelines and other recommendations for the best way to deliver the information are available (Clayton et al., 2007; Back et al., 2009; Kiely et al., 2010). They stress the importance of communication occurring within the context of a caring, trusting relationship, consistency of information within the multiprofessional team, and the need to communicate prognostic information to other members of the family. As highlighted above, not all patients want to be provided with an estimation of their life expectancy. Hence it is very important to first clarify the person's understanding of their medical situation and the information they desire. Any information provided about prognosis should then be tailored to the individual needs of patients and their families.

Most patients want to be informed of their likely survival duration in a straightforward and clear manner. For patients who would like to be provided with a numerical estimation of their life expectancy the following approach has been advocated for patients with advanced cancer (Kiely et al., 2010). The first step is to use a prognostic tool to estimate the median survival of a group with similar characteristics. The survival curve of patients with a variety of advanced cancers typically approximates an exponential function—as would be predicted for a heterogeneous population (see Fig. **2.3.1**) (Stockler et al., 2006). In the case that follows, assume that the median survival is 6 months.

◆ Explain that a median survival of 6 months means that 50% will live longer than 6 months.

◆ Use simple multiple of the median to estimate and explain the typical, best case, and worst case scenarios:

• Typical—about half of similar patients would live for somewhere between 3 and 12 months (half to double the predicted median).

• Best case—about 10% of patients could expect to live beyond 2 years (three to four times the predicted median).

• Worst case—about 10% of patients will experience more rapid decline and will die within 1 month (1/6 of the predicted mean).

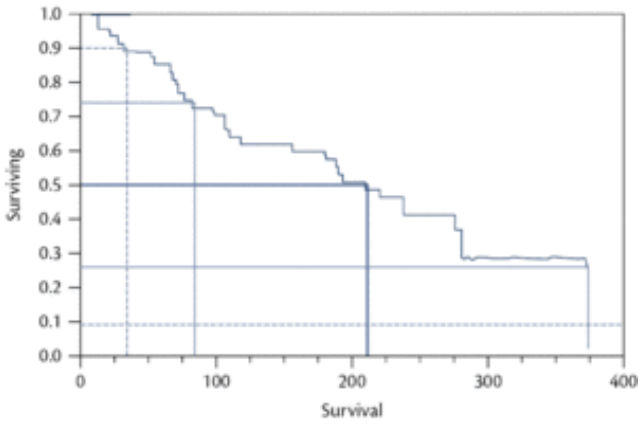

Fig. 2.3.1
Using the median survival to make other probabilistic survival predictions.

Using multiples of the median to estimate and provide typical, best, and worst case scenarios as outlined above may offer a way of conveying more realism and hope than a single point estimate of the median survival. Finally after providing patients with information about life expectancy it is important to explore and acknowledge the patient's and family's emotional reaction to the news and to check their understanding about what has been discussed.

Conclusion

Prognostication remains a challenging topic in palliative care. In the past 20 years, much research has been undertaken to identify ways of improving the accuracy and precision of clinicians' estimates and as presented here many tools are now available to improve prognostication.

While we are now in a better position to give the patient 'x % chance of surviving for y weeks/months', we are not yet able to posit any of the existing tools as the ideal one to be recommended for widespread use. Most of the existing tools focus on performance status, symptoms, and simple laboratory markers; while these are helpful, they are no more accurate than the subjective judgements of experienced clinicians. Novel objective prognostic factors need to be identified, and biomarkers such as CRP and the proinflammatory cytokines are the

main focus of current research.

Clinical judgement remains important, in our opinion. The clinical data needed to use a tool to calculate the prognosis (e.g. recent laboratory parameters) may not be available, tools may not provide the prognostic information required, and they may not have been validated in the population to which the individual patient belongs. Clinical judgement alone may be sufficient if the issue is acknowledging a probability of dying from an illness in the foreseeable future. The SUPPORT study showed patients will change their planning behaviour once they understand the chance of surviving beyond 6 months is small. Furthermore, models predicting survival should be thought of like any diagnostic test, that is, they should not be interpreted in isolation but as a way of improving the pre-test probability of survival, which is based on clinical judgement.

Even if precise and accurate predictions of survival duration become available, this alone should never drive treatment plans. What ultimately is needed is not so much an accurate prediction of time but an acknowledgement of the possibility of dying, communicated carefully by the compassionate and skilful physician.

Online materials

Additional online materials for this chapter are available online at <http://www.oxfordmedicine.com>.

References

Aguero-Torres, H., Fratiglioni, L., Guo, Z., Viitanen, M., and Winblad, B. (1998). Prognostic factors in very old demented adults: a seven-year follow-up from a population-based survey in Stockholm. *Journal of the American Geriatrics Society*, 46(4), 444–452.

Altman, D. (2001). Systematic reviews of studies of prognostic variables. *BMJ*, 323(7306), 224–228.

Altman, D.G. (2009). Prognostic models: a methodological framework and review of models for breast cancer. *Cancer Investigation*, 27(3), 235–243.

Bachmann, P., Marti-Massoud, C., Blanc-Vincent, M.P., *et al.* (2003). Summary version of the Standards, Options and Recommendations for palliative or terminal nutrition in adults with progressive cancer (2001). *British Journal of Cancer*, 89(Suppl. 1), S107–110.

Back, A., Arnold, R.M. and Tulsky, T.J. (2009). *Mastering Communication with Seriously Ill Patients—Balancing Honesty with Empathy and Hope*. New York: Cambridge University Press.

Bao, Y., Dalrymple, L., Chertow, G.M., Kaysen, G.A., and Johansen, K.L. (2012). Frailty, dialysis initiation, and mortality in end-stage renal disease. *Archives of Internal Medicine*, 172(14), 1071–1077.

Beadle, G.F., Yates, P.M., Najman, J.M., *et al.* (2004). Beliefs and practices of patients with advanced cancer: implications for communication. *British Journal of Cancer*, 91(2), 254–257.

Berger, R., Huelsman, M., Strecker, K., *et al.* (2002). B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation*, 105(20), 2392–2397.

Brechtl, J.R., Patrick, P.A., Visintainer, P., and Brand, D.A. (2005). Predictors of death within six months in patients with advanced AIDS. *Palliative & Supportive Care*, 3(4), 265–272.

Brody, K.K., Perrin, N.A., and Dellapenna, R. (2006). Advanced illness index: predictive modeling to stratify elders using self-report data. *Journal of Palliative Medicine*, 9(6), 1310–1319.

Broeckaert, B. and Glare, P. (2008). Ethical perspectives. In P. Glare and N. Christakis (eds.) *Prognosis in Advanced Cancer*, pp. 88–94. Oxford: Oxford University Press.

Bruera, E., Miller, M.J., Kuehn, N., MacEachern, T., and Hanson, J. (1992). Estimate of survival of patients admitted to a palliative care unit: a prospective study. *Journal of Pain & Symptom Management*, 7(2), 82–86.

Bruera, E., Neumann, C.M., Mazzocato, C., Stiefel, F., and Sala, R. (2000). Attitudes and beliefs of palliative care physicians regarding communication with terminally ill cancer patients. *Palliative Medicine*, 14(4), 287–298.

Butow, P.N., Dowsett, S., Hagerty, R., and Tattersall, M.H.N. (2002). Communicating prognosis to patients with metastatic disease: what do they really want to know? *Supportive Care in Cancer*, 10(2), 161–168.

Canadian Cardiovascular Outcomes Research Team (n.d.). *Enhanced Feedback for Effective Cardiac Treatment (EFFECT) Study*. [Online] Available at: <http://www.ccort.ca>.

Capitani, E., Cazzaniga, R., Francescani, A., and Spinnler, H. (2004). Cognitive deterioration in Alzheimer's disease: is the early course predictive of the later stages? *Neurological Sciences*, 25(4), 198–204.

Celli, B.R., Cote, C.G., Marin, J.M., *et al.* (2004). The body-mass index, airflow obstruction, dyspnoea, and exercise capacity index in chronic obstructive pulmonary disease. *The New England Journal of Medicine*, 350(10), 1005–1012.

Chang, V.T., Thaler, H.T., Polyak, T.A. Kornblith, A.B., Lepore, J.M., and Portenoy, R.K. (1998). Quality of life and survival: the role of multidimensional symptom assessment. *Cancer*, 83(1), 173–179.

Chiang, J.-K., Cheng, Y.-H., Koo, M., Kao, Y.-H., and Chen, C.-Y. (2010). A computer-assisted model for predicting probability of dying within 7 days of hospice admission in patients with terminal cancer. *Japanese Journal of Clinical Oncology*, 40(5), 449–455.

Chow, E., Abdolell, M., Panzarella, T., *et al.* (2008). Predictive model for survival in patients with advanced cancer. *Journal of Clinical Oncology*, 26(36), 5863–5869.

Chow, E., Fung, K., Panzarella, T., Bezjak, A., Danjoux, C., and Tannock, I. (2002). A predictive model for survival in metastatic cancer patients attending an outpatient palliative radiotherapy clinic. *International Journal of Radiation Oncology, Biology, Physics*, 53(5), 1291–1302.

Christakis, N.A. (1997). The ellipsis of prognosis in modern medical thought. *Social Science & Medicine*, 44(3), 301–315.

Christakis, N.A. and Iwashyna, T.J. (1998). Attitude and self-reported practice regarding prognostication in a national sample of internists. *Archives of Internal Medicine*, 158(21), 2389–2395.

Christakis, N.A. and Lamont, E.B. (2000). Extent and determinants of error in doctors' prognoses in terminally ill patients: prospective cohort study. *BMJ*, 320(7233), 469–472.

Chuang, R.-B., Hu, W.-Y., Chiu, T.-Y., and Chen, C.-Y. (2004). Prediction of survival in terminal cancer patients in Taiwan: constructing a prognostic scale. *Journal of Pain & Symptom Managemen*, 28(2), 115–122.

Clayton, J.M., Hancock, K.M., Butow, P.N., *et al.* (2007). Clinical practice guidelines for communicating prognosis and end-of-life issues with adults in the advanced stages of a life-limiting illness, and their caregivers. *Medical Journal of Australia*, 186(Suppl. 12), S77, S79, S83–108.

Dawes, R.M., Faust, D., and Meehl, P.E. (1989). Clinical versus actuarial judgment. *Science*, 243(4899), 1668–1674.

Degner, L. and Sloan, J. (1995). Symptom distress in newly diagnosed ambulatory cancer patients and as a predictor of survival in lung cancer. *Journal of Pain & Symptom Management*, 10(6), 423–431.

Downing, G.M., Lau, F., Lesperance, M., *et al.* (2007). Meta-analysis of survival prediction with the Palliative Performance Scale. *Journal of Palliative Medicine*, 23(4), 245–252.

Earlam, S., Glover, C., Fordy, C., Burke, D., and Allen-Mersh, T.G. (1996). Relation between tumor size, quality of life, and survival in patients with colorectal liver metastases. *Journal of Clinical Oncology*, 14(1), 171–175.

Ehlenbach, W.J., Barnato, A.E., and Curtis, J.R. (2005). Epidemiologic study of in-hospital cardiopulmonary resuscitation in the elderly. *The New England Journal of Medicine*, 361(1), 22–31.

Esteban, C., Quintana, J.M., Aburto, M., Moraza, J., and Capelastegui, A. (2006). A simple score for assessing stable chronic obstructive pulmonary disease. *Quarterly Journal of Medicine*, 99(11), 751–759.

Esteban, C., Quintana, J.M., Moraza, J., *et al.* (2010). BODE-Index vs HADO-score in chronic obstructive pulmonary disease: which one to use in general practice? *BMC Medicine*, 8, 28.

Fallowfield, L.J., Jenkins, V.A., and Beveridge, H.A. (2002). Truth may hurt but deceit hurts more: communication in palliative care. *Palliative Medicine*, 16(4), 297–303.

Feliu, J., Jimenez-Gordo, A.M., Madero, R., *et al*. (2011). Development and validation of a prognostic nomogram for terminally ill cancer patients. *Journal of the National Cancer Institute*, 103(21), 1613–1620.

Forrest, L.M., McMillan, D.C., McArdle, C.S., Angerson, W.J., Dagg K., and Scott, H.R. (2005). A prospective longitudinal study of performance status, an inflammation-based score (GPS) and survival in patients with inoperable non-small-cell lung cancer. *British Journal of Cancer*, 92(10), 1834–1836.

Fox, E., Landrum-McNiff, K., Zhong, Z., Dawson, N.V., Wu, A.W., and Lynn, J. (1999). Evaluation of prognostic criteria for determining hospice eligibility in patients with advanced lung, heart, or liver disease. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. *Journal of the American Medical Association*, 282(17), 1638–1645.

Fries, J.F. and Ehrlich, G.E. (1981). *Prognosis. Contemporary Outcomes of Disease*. Bowie, MD: The Charles Press Publishers.

Geissbuhler, P., Mermillod, B., and Rapin, C.H. (2000). Elevated serum vitamin B12 levels associated with CRP as a predictive factor of mortality in palliative care cancer patients: a prospective study over five years. *Journal of Pain & Symptom Management*, 20(2), 93–103.

Glare, P. (2011). Predicting and communicating prognosis in palliative care. *BMJ*, 343, d5171.

Glare, P., Eychmueller, S., and Virik, K. (2003). The use of the palliative prognostic score in patients with diagnoses other than cancer. *Journal of Pain & Symptom Management*, 26(4), 883–885.

Glare, P. and Virik, K. (2001). Independent prospective validation of the PaP score in terminally ill patients referred to a hospital-based palliative medicine consultation service. *Journal of Pain & Symptom Management*, 22(5), 891–898.

Glare, P., Virik, K., Jones, M., *et al.* (2003). A systematic review of physicians' survival predictions in terminally ill cancer patients. *BMJ*, 327(7408), 195–198.

Glare, P.A., Eychmueller, S., and McMahon, P. (2004). Diagnostic accuracy of the palliative prognostic score in hospitalized patients with advanced cancer. [Erratum appears in *Journal of Clinical Oncology*, 2005, 23(1), 248]. *Journal of Clinical Oncology*, 22(23), 4823–4828.

Gold Standards Framework (2011). *The GSF Prognostic Indicator Guidance*. [Online] Available at: <http://www.goldstandardsframework.org.uk/cd-content/uploads/files/General%20Files/Prognostic%20Indicator%20Guidance%20October%202011.pdf>.

Gripp, S., Moeller, S. Bolke, E., *et al.* (2007). Survival prediction in terminally ill cancer patients by clinical estimates, laboratory tests, and self-rated anxiety and depression. *Journal of Clinical Oncology*, 25(22), 3313–3320.

Gwilliam, B., Keeley, V., Todd, C., *et al.* (2011). Development of prognosis in palliative care study (PiPS) predictor models to improve prognostication in advanced cancer: prospective cohort study. *BMJ*, 343, d4920.

Hagerty, R.G., Butow, P.N., Ellis, P.A., *et al.* (2004). Cancer patient preferences for communication of prognosis in the metastatic setting. *Journal of Clinical Oncology*, 22(9), 1721–1730.

Hagerty, R.G., Butow, P.N., Ellis, P.M., Dimitry, S., and Tattersall, M.H.N. (2005). Communicating prognosis in cancer care: a systematic review of the literature. *Annals of Oncology*, 16(7), 1005–1053.

Hancock, K., Clayton, J.M., Parker, S.M., *et al.* (2007). Discrepant perceptions about end-of-life communication: a systematic review. *Journal of Pain & Symptom Management*, 34(2), 190–200.

Hanrahan, P., Raymond, M., McGowan, E., and Luchins, D.J. (1999). Criteria for enrolling dementia patients in hospice: a replication. *American Journal of Hospice & Palliative Care*, 16(1), 395–400.

Hansen-Flaschen, J. (2004). Chronic obstructive pulmonary disease: the last year of life. *Respiratory Care*, 49(1), 90–97.

Hauser, C.A., Stockler, M.R., and Tattersall, M.H. (2006). Prognostic factors in patients with recently diagnosed incurable cancer: a systematic review. *Support Care Cancer*, 14(10), 999–1011.

Health Terminology Group (n.d.). *Prognostat*. School of Health Information Science at the University of Victoria. [Online] Available at: <https://htg.his.uvic.ca/tools/PrognosticTools/PalliativePerformanceScale/Prognostat/index.php>

Ho, K.K., Anderson, K.M., Kannel, W.B., Grossman, W., and Levy, D. (1993). Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation*, 88(1), 107–115.

Hudson, A. (1990). Amyotrophic lateral sclerosis: clinical evidence of differences in pathogenesis and etiology. In A. Hudson (ed.) *Amyotrophic Lateral Sclerosis: Concepts in Pathogenesis and Etiology*, pp. 108–143. Toronto: University of Toronto Press.

Hutchinson, R. (1934). Prognosis. *The Lancet*, i, 697.

Hyodo, I., Morita, T., Adachi, I., Shima, Y., Yoshizawa, A., and Hiraga, K. (2010). Development of a predicting tool for survival of terminally ill cancer patients. *Japanese Journal of Clinical Oncology*, 40(5), 442–448.

Innes, S. and Payne, S. (2009). Advanced cancer patients' prognostic information preferences: a review. *Palliative Medicine*, 23(1), 29–39.

Jayes, R.L., Arnold, R.M., and Fromme, E.K. (2012). Does this dementia patient meet the prognosis eligibility requirements for hospice enrollment? *Journal of Pain & Symptom Management*, 44(5), 750–756.

Kaufmann, P., Levy, G., Thompson, J.L., *et al.* (2005). The ALSFRSr predicts survival time in an ALS clinic population. *Neurology*, 64(1), 38–43.

Kelly, L., White, S., and Stone, P.C. (2007). The B12/CRP index as a simple prognostic indicator in patients with advanced cancer: a confirmatory study. *Annals of Oncology*, 18(8), 1395–1399.

Kiely, B.E., Tattersall, M.H., and Stockler, M.R. (2010). Certain death in uncertain time: informing hope by quantifying a best case scenario. *Journal of Clinical Oncology*, 28(16), 2802–2804.

Kirk, P., Kirk, I., and Kristjanson, L.J. (2004). What do patients receiving palliative care for cancer and their families want to be told? A Canadian and Australian qualitative study. *BMJ*, 328(7452), 1343.

Knaus, W.A., Harrell, F.E., Jr, Lynn, J., *et al.* (1995). The SUPPORT prognostic model. Objective estimates of survival for seriously ill hospitalized adults. Study to understand prognoses and preferences for outcomes and risks of treatments. *Annals of Internal Medicine*, 122(3), 191–203.

Kutner, J.S., Steiner, J.F., Corbett, K.K., Jahnigen, D.W., and Barton, P.L. (1999). Information needs in terminal illness. *Social Science & Medicine*, 48(10), 1341–1352.

Laupacis, A., Wells, G., Richardson, W.S., and Tugwell, P. (1994). Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-Based Medicine Working Group. *Journal of the American Medical Association*, 272(3), 234–237.

Lee, B.N., Dantzer, R., Langley, K.E., *et al.* (2004). A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. *Neuroimmunomodulation*, 11(5), 279–292.

Levy, W., Mozaffarian, D., Linker, D., *et al.* (2006). The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation*, 113(11), 1424–1433.

Low, J.A., Liu, R.K.Y., Strutt, R., and Chye, R. (2001). Specialist community palliative care services—a survey of general practitioners' experience in Eastern Sydney. *Supportive Care in Cancer*, 9, 474–476.

Luchins, D.J., Hanrahan, P., and Murphy, K. (1997). Criteria for enrolling dementia patients in hospice. *Journal of the American Geriatrics Society*, 45(9), 1054–1059.

Mack, J.W. and Smith, T.J. (2012). Reasons why physicians do not have discussions about poor prognosis, why it matters, and what can be improved. *Journal of Clinical Oncology*, 30(22), 2715–2717.

Mackillop, W.J. (2006). The importance of prognosis in cancer medicine. In M.K. Gospodarowicz, B. O'Sullivan, and L.H. Sobin (eds.) *Prognostic Factors in Cancer*, pp. 3–22. Hoboken, NJ: Wiley-Liss.

Maltoni, M., Nanni, O., Pirovano, M., *et al.* (1999). Successful validation of the palliative prognostic score in terminally ill cancer patients. Italian Multicenter Study Group on Palliative Care. *Journal of Pain & Symptom Management*, 17(4), 240–247.

Mandrioli, J., Faglioni, P., Nichelli, P., and Sola, P. (2006). Amyotrophic lateral sclerosis: prognostic indicators of survival. *Amyotrophic Lateral Sclerosis*, 7(4), 211–220.

Martin, L., Watanabe, S., Fainsinger, R., *et al.* (2010). Prognostic factors in patients with advanced cancer: use of the patient-generated subjective global assessment in survival prediction. *Journal of Clinical Oncology*, 28(28), 4376–4383.

Mitchell, S.L., Kiely, D.K, Hamel, M.B., Park, P.S., Morris, J.N., and Fries, B.E. (2004). Estimating prognosis for nursing home residents with advanced dementia. *Journal of the American Medical Association*, 291(22), 2734–2740.

Morita, T., Tsunoda, J., Inoue, S., and Chihara, S. (1999). The Palliative Prognostic Index: a scoring system for survival prediction of terminally ill cancer patients. *Supportive Care in Cancer*, 7(3), 128–133.

Morita, T., Tsunoda, J., Inoue, S., and Chihara, S. (2001). Improved accuracy of physicians' survival prediction for terminally ill cancer patients using the Palliative Prognostic Index. *Palliative Medicine*, 15(5), 419–424.

Moss, A.H., Lunney, J.R., Culp, S., *et al.* (2010). Prognostic significance of the "surprise" question in cancer patients. *Journal of Palliative Medicine*, 13(7), 837–840.

Mozaffarian, D., Anker, S., Anand, I., *et al.* (2007). Prediction of mode of death in heart failure: the Seattle Heart Failure Model. *Circulation*, 116(4), 360–362.

Naylor, C., Cerqueira, L., Costa-Paiva, L.H.S., Costa, J.V., Conde, D.M., and Pinto-Neto, A.M. (2010). Survival of women with cancer in palliative care: use of the palliative prognostic score in a population of Brazilian women. *Journal of Pain & Symptom Management*, 39(1), 69–75.

O'Donnell, D. E., Aaron, S., Bourbeau, J., *et al.* (2007). Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease—2007 update. *Canadian Respiratory Journal*, 14(Suppl. B), 5B–32B.

O'Donovan, A., Tomiyama, A.J., Lin, J., *et al.* (2012). Stress appraisals and cellular aging: a key role for anticipatory threat in the relationship between psychological stress and telomere length. *Brain, Behavior, and Immunity*, 26(4), 573–579.

Oga, T., Nishimura, K., Tsukino, M., Sato, S., and Hajiro, T. (2003). Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *American Journal of Respiratory and Critical Care Medicine*, 167(4), 544–549.

Ohde, S., Hayashi, A., Takahasi, O., *et al.* (2011). A 2-week prognostic prediction model for terminal cancer patients in a palliative care unit at a Japanese general hospital. *Palliative Medicine*, 25(2), 170–176.

Oxenham, P. and Cornbleet, M.A. (1998). Accuracy of prediction of survival by different professional groups in a hospice. *Palliative Medicine*, 12, 117–118.

Parker, S. M., Clayton, J.M., Hancock, K., *et al.* (2007). A systematic review of prognostic/end-of-life communication with adults in the advanced stages of a life-limiting illness: patient/caregiver preferences for the content, style, and timing of information. *Journal of Pain & Symptom Management*, 34(1), 81–93.

Piepers, S., van den Berg, J.P., Kalmijn, S., *et al.* (2006). Effect of non-invasive ventilation on survival, quality of life, respiratory function and cognition: a review of the literature. *Amyotrophic Lateral Sclerosise*, 7(4), 195–200.

Pirovano, M., Maltoni, M., Nanni, O., *et al.* (1999). A new palliative prognostic score: a first step

for the staging of terminally ill cancer patients. Italian Multicenter and Study Group on Palliative Care. *Journal of Pain & Symptom Management*, 17(4), 231–239.

Rakowski, D.A., Caillard, S., Agodoa, L.Y., and Abbott, K.C. (2006). Dementia as a predictor of mortality in dialysis patients. *Clinical Journal of the American Society of Nephrology*, 1(5), 1000–1005.

Read, W.L., Tierney, R.M., Page, N.C., *et al.* (2004). Differential prognostic impact of comorbidity. *Journal of Clinical Oncology*, 22(15), 3099–3103.

Reisberg, B. (1988). Functional assessment staging (FAST). *Psychopharmacology Bulletin*, 24(4), 653–659.

Reuben, D.B., Mor, V., and Hiris, J. (1988). Clinical symptoms and length of survival in patients with terminal cancer. *Archives of Internal Medicine*, 148(7), 1586–1591.

Sackett, D.L., Haynes, R.B., Guyatt, G.H., and Tugwell, P. (1991). *Clinical Epidemiology. A Basic Science for Clinical Medicine*. Boston, MA: Little, Brown and Company.

Satin, J.R., Linden, W., and Phillips, M.J. (2009). Depression as a predictor of disease progression and mortality in cancer patients: a meta-analysis. *Cancer*, 115(22), 5349–5361.

Schonwetter, R.S., Han, B., Small, B.J., Martin, B., Tope, K., and Haley, W.E. (2003). Predictors of six-month survival among patients with dementia: an evaluation of hospice Medicare guidelines. *American Journal of Hospice & Palliative Care*, 20(2), 105–113.

Schonwetter, R.S., Soendker, S., Perron, V., *et al.* (1998). Review of Medicare's proposed hospice eligibility criteria for select noncancer patients. *American Journal of Hospice and Palliative Care*, 15(3), 155–8.

Selwyn, P.A. and Forstein, M. (2003). Overcoming the false dichotomy of curative vs palliative care for late-stage HIV/AIDS: "let me live the way I want to live, until I can't". *Journal of the American Medical Association*, 290(6), 806–814.

Seow, H., Barbera, L., Sutradhar, R., *et al.* (2011). Trajectory of performance status and symptom scores for patients with cancer during the last six months of life. *Journal of Clinical Oncology*, 29(9), 1151–1158.

Shadbolt, B., Barresi, J., and Craft, P. (2002). Self-rated health as a predictor of survival among patients with advanced cancer. *Journal of Clinical Oncology*, 20(10), 2514–2519.

Shavelle, R.M., Paculdo, D.R., Kush, S.J., Mannino, D.M., and Strauss, D.J. (2009). Life expectancy and years of life lost in chronic obstructive pulmonary disease: findings from the NHANES III Follow-up Study. *International Journal of Chronic Obstructive Pulmonary Disease*, 4, 137–148.

Shaw, A.S., Ampong, M.A., Rio, A., *et al.* (2006). Survival of patients with ALS following institution of enteral feeding is related to pre-procedure oximetry: a retrospective review of 98 patients in a single centre. *Amyotrophic Lateral Sclerosis*, 7(1), 16–21.

Shoesmith, C.L., Findlater, K., Rowe, A., and Strong, M.J. (2007). Prognosis of amyotrophic

lateral sclerosis with respiratory onset. *Journal of Neurology, Neurosurgery & Psychiatry*, 78(6), 629–631.

Soares, M., Salluh, J.I., Ferreira, C.G., Luiz, R.R., Spector, N., and Rocco, J.R. (2005). Impact of two different comorbidity measures on the 6-month mortality of critically ill cancer patients. *Intensive Care Medicine*, 31(3), 408–415.

Solano, J.P., Gomes, B., and Higginson, I.J. (2006). A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. *Journal of Pain & Symptom Management*, 31(1), 58–69.

Steinhauser, K., Christakis, N.A., Clipp, E., McNeilly, M., McIntyre, L., and Tulsky, J. (2000). Factors considered important at the end of life by patients, family, physicians, and other care providers. *Journal of the American Medical Association*, 284(19), 2476–2482.

Steyerberg, E. and Harrell, F. (2002). Statistical models for prognostication. In M. Max and J. Lynn (eds.) *Symptom Research: Methods and Opportunities*. [Online] Available at: <http://painconsortium.nih.gov/symptomresearch/>.

St George's, University of London (2011). *The PiPS Prognosticator*. [Online] Available at: <http://www.pips.sgul.ac.uk>.

Stockler, M.R., Tattersall, M.H., Boyer, M.J., Clarke, S.J. Beale, P.J., and Simes, R.J. (2006). Disarming the guarded prognosis: predicting survival in newly referred patients with incurable cancer. *British Journal of Cancer*, 94(2), 208–212.

Stone, C.A., Tiernan, E., and Dooley, B.A. (2008). Prospective validation of the palliative prognostic index in patients with cancer. *Journal of Pain & Symptom Management*, 35(6), 617–622.

Suh, S.-Y., Choi, Y.S., Shim, J.Y., *et al.* (2010). Construction of a new, objective prognostic score for terminally ill cancer patients: a multicenter study. *Supportive Care in Cancer*, 18(2), 151–157.

Tamburini, M., Brunelli, C., Rosso, S., and Ventafridda, V. (1996). Prognostic value of quality of life scores in terminal cancer patients. *Journal of Pain & Symptom Management*, 11, 32–41.

Tannenberger, S., Malavasi, I., Mariano, P., Pannuti, F., and Strocchi, E. (2002). Planning palliative or terminal care: the dilemma of doctors' prognoses in terminally ill cancer patients. *Annals of Oncology*, 13, 1319–1323.

Tarumi, Y., Watanabe, S.M., Lau, F., *et al.* (2011). Evaluation of the Palliative Prognostic Score (PaP) and routinely collected clinical data in prognostication of survival for patients referred to a palliative care consultation service in an acute care hospital. *Journal of Pain & Symptom Management*, 42(3), 419–431.

Tavares, F. (2010). Is the B12/CRP index more accurate than you at predicting life expectancy in advanced cancer patients? *Journal of Pain & Symptom Management*, 40(1), e12–13.

Teno, J.M., Gozalo, P.L., Lee, I.C., *et al.* (2011). Does hospice improve quality of care for persons dying from dementia? *Journal of the American Geriatrics Society*, 59(8), 1531–1536.

Teno, J.M., Harrell, F.E.,Jr., Knaus, W., *et al.* (2000). Prediction of survival for older hospitalized patients: the HELP survival model. Hospitalized Elderly Longitudinal Project. *Journal of the American Geriatrics Society*, 48(5 Suppl.), S16–24.

The, A.M., Hak, T., Koeter, G., and van Der Wal, G. (2000). Collusion in doctor-patient communication about imminent death: an ethnographic study. *BMJ*, 321(7273), 1376–1381.

The SUPPORT Principal Investigators (1995). A controlled trial to improve care for seriously ill hospitalized patients. The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). *Journal of the American Medical Association*, 274(20), 1591–1598.

University of Washington (n.d.). *Seattle Heart Failure Model*. [Online] Available at: <http://www.seattleheartfailuremodel.org>.

Vigano, A., Bruera, E., Jhangri, G.S., Newman, S.C., Fields, A.L., and Suarez-Almazor, M.E. (2000). Clinical survival predictors in patients with advanced cancer. *Archives of Internal Medicine*, 160(6), 861–868.

Vij, B., Stabler, S.M., Thaler, H.T., and Glare, P.A. (2012). External validation of the simple prognostic score in a palliative care clinic at a comprehensive cancer center. *Journal of Clinical Oncology, 2012 ASCO Annual Meeting Proceedings (Post-Meeting Edition)* 30(15 Suppl.), e19566.

Walter, L.C., Brand, R.J., Counsell, S.R., *et al.* (2001). Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. *Journal of the American Medical Association*, 285(23), 2987–2994.

Wildman, M.J., Sanderson, C., Groves, J., *et al.* (2007). Implications of prognostic pessimism in patients with chronic obstructive pulmonary disease (COPD) or asthma admitted to intensive care in the UK within the COPD and asthma outcome study (CAOS multicentre observational cohort study. *BMJ*, 335(7630), 1132.

Wong, C.F., McCarthy, M., Howse, M.L., and Williams, P.S. (2007). Factors affecting survival in advanced chronic kidney disease patients who choose not to receive dialysis. *Renal Failure*, 29(6), 653–659.

Wright, A.A., Zhang, B., Ray, A., *et al.* (2008). Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *Journal of the American Medical Association*, 300(14), 1665–1673.

Yourman, L.C., Lee, S.J., Schonberg, M.A., Widera, E.W., and Smith, A.K. (2012). Prognostic indices for older adults: a systematic review. *Journal of the American Medical Association*, 307(2), 182–192.

Yourman, L.C., Lee, S.J., Schonberg, M.A., Widera, E.W., and Smith, A.K. (n.d.). *ePrognosis. Estimating Prognosis for Elders*. [Online] Available at: <http://www.eprognosis.com>.

Yun, Y.H., Heo, D.S., Heo, B.Y., TYoo, T.W., Bae, J.M., and Ahn, S.H. (2001). Development of terminal cancer prognostic score as an index in terminally ill cancer patients. *Oncology Reports*, 8(4), 795–800.

Appendix Other prognostic indices for far advanced cancer

A number of other prognostic indices have been developed for use in palliative care patients. These include:

- the Chuang prognostic score (Chuang et al., 2004)
- the terminal cancer prognostic score (Yun et al., 2001)
- the poor prognostic indicator (Bruera et al., 1992)
- the Chiang computer-assisted prognostic model (Chiang et al., 2010)
- the Japan palliative oncology study-prognostic index (Hyodo et al., 2010)
- the Suh objective prognostic score (Suh et al., 2010)
- the Ohde prediction model (Ohde et al., 2011).

As with the other models, the population, predictive factors, prognostic outcomes, validity, and accuracy of each model needs to be considered before applying them to individual patients.

The prognostic value of the PG-SGA (Patient-Generated Subjective Global Assessment) of nutritional status has also been evaluated in palliative care patients (Martin et al., 2010).

Prognostication in other life-threatening conditions

Acquired immunodeficiency syndrome (AIDS)

The natural history of HIV/AIDS has been completely altered by the advent of highly active antiretroviral therapy (HAART). However, in some cases of advanced AIDS, there comes a time when continued HAART may no longer be warranted, due to the overall clinical condition of the patient and their anticipated poor short-term prognosis (Selwyn and Forstein, 2003). Survival with AIDS off treatment may still be many months, especially in patients who are otherwise relatively well. Even in patients with AIDS dementia complex the median survival is in the vicinity of 40–80 months from the time of diagnosis, shorter if the CD4 cell count remains lower than 200 cells/mm^3 and the viral load higher than 5000 copies/mL.

Based on experience from the pre-HAART era in the 1980s and 1990s, virtually all patients who die of HIV-related complications have CD4 cell counts less than 50 cells/mm^3. However, patients with advanced HIV infection and very low CD4 cell counts (< 25/mm^3) still have a median survival of 12 months in the absence of antiretroviral therapy. These traditional laboratory markers are less important prognostic indicators than factors such as limited options for further antiviral treatment, poor response to therapy of opportunistic infections, the development of untreatable complications, poor functional status, and poor nutritional status. Therefore an associated life-limiting complication is usually required to fulfil hospice eligibility for an AIDS patient in the United States. There are no prognostic tools or other objective markers to indicate when this time is reached. A study of patients with advanced AIDS admitted to a skilled nursing facility in New York City found that the best combination of predictors of death within 6 months was hypoalbuminaemia, weight loss, and number of co-morbidities at the time of admission (Brechtl et al., 2005). In this study, 40% of patients died within 6 months of enrolment. These findings have not been validated, and a scoring system/prognostic index has

not been developed from these data.

Amyotrophic lateral sclerosis (ALS)/motor neuron disease

The median survival of ALS from diagnosis is 3–5 years but the prognosis varies widely with a range of 6 months to greater than 20 years (Hudson, 1990). The survival curve tends to dip sharply in the first 3 years from diagnosis, followed by a flattening trend, with 50% dying within 2.5 years, and 89% over 7 years in one study (Mandrioli et al., 2006). In this study, the clinical form with lower limb onset was associated with longer survival than the upper limb onset and bulbar forms (median survival: 39, 27, and 25 months, respectively). Survival was also affected by age at onset (median survival: 34, 27, and 23 months for onset < 60, 60–75, and > 75 years, respectively), area of residence (median survival: 24 months in mountainous areas, 32 elsewhere), and type of work (median survival: 25 months in agricultural workers, 33.5 in others).

The Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRSr) may have reasonable predictive value. Patients with a total ALSFRSr score below the median of 38 points had a 4.4-fold increased risk of death or tracheostomy compared to those who scored above the median. It appears an ALSFRSr score at baseline is a strong predictor of death or tracheostomy independently of forced vital capacity (Kaufmann et al., 2005).

Feeding tubes and ventilators are common in ALS patients with advanced disease and may influence survival. In a prospective 7-month study of 55 ALS patients, malnutrition occurred in 16.4%. Survival was worse for malnourished patients ($p < 0.0001$), with a 7.7-fold increased risk of death. The degree of malnutrition was independent of forms of ALS onset (Bachmann et al., 2003). It is unclear whether the use of artificial feeding confers any survival benefit. Ninety-eight ALS patients receiving enteral feeding had a median survival of 6.3 months (range 4.6–8.0) with radiologically placed gastrostomies versus 1.0 months (range 0–2.8 months) with nasogastric tube (Shaw et al., 2006).

A literature review of 12 studies of non-invasive positive pressure ventilation (NIPPV) in ALS included only one randomized trial. However, NIPPV was associated with prolonged survival in patients tolerant of it in seven studies and improved quality of life was reported in five studies (Piepers et al., 2006). NIPPV significantly improved survival compared with those who did not use NIPPV (Shoesmith et al., 2007). This study also showed ALS patients with respiratory onset do not necessarily follow a rapidly progressive course.

End-stage kidney disease (ESKD)

Despite ongoing technological advances in dialysis and other forms of renal replacement therapy, patients with ESKD have a high mortality rate, approximately 25% per year. In having increased mortality (Bao et al., 2012), co-morbid cardiovascular, cerebrovascular, and peripheral vascular disorders often make life on dialysis an ordeal for frail patients. Dementia diagnosed before initiation on dialysis is also an independent risk factor for subsequent death. In a retrospective cohort study of Medicare/Medicaid patients starting dialysis, the average time to death was 2.7 years, but significantly shorter (1.09 years) for patients with dementia. The 2-year survival was also significantly better for patients without dementia (66% vs 24%). Demented patients with ESKD should be considered for time-limited trials of dialysis preceded

by careful discussion about initiation of dialysis or palliative care (Rakowski et al., 2006).

The prognosis in patients with ESKD who decide to discontinue dialysis at the end of life is grim. One study of patients discontinuing dialysis reported median time to death of 7 days (range 0–17 days) (Low et al., 2001). The outlook is different for patients with advanced kidney disease who elect never to be dialysed, and instead choose non-dialytic treatment (NDT). In one study, the median overall survival on NDT was 1.95 years with 65% surviving 1 year (Wong et al., 2007). Co-morbidity was an important independent prognostic factor in this study.

Other prognostic indices for dementia and/or the frail elderly

◆ The Prognostic Index for 1-Year Mortality in Older Adults (PIMOA) assesses 1-year mortality of adults 70 years or older after hospital discharge (Walter et al., 2001) and the HELP survival model which is presented as a nomogram for determining survival in hospitalized patients aged 85 and older (Teno et al., 2000).

◆ The Dementia Mortality Index (DMI) was developed in a community hospice for predicting 6-month mortality (Schonwetter et al., 2003). Significant multivariate predictors of shorter survival include greater age ($p = 0.02$) and anorexia ($p < 0.001$), as well as a combination of anorexia and greater functional impairment ($p = 0.005$). This promising study has never been validated.

◆ A large study of the Resident Assessment Instrument-Minimum Data Set (RAI-MDS) in newly admitted nursing home residents with advanced dementia was conducted in order to identify factors associated with 6-month mortality and to create a practical risk score to predict 6-month mortality in this population (Mitchell et al., 2004). MDS factors were determined in the derivation group, and the resulting mortality risk score was evaluated in the validation cohort. Risk score performance was compared with the cut point of 7c on the FAST scale. Within the study timeframes, 28% of residents died within 6 months of nursing home admission in the derivation cohort, and 35% died in the validation cohort. In the validation cohort, the 6-month mortality rate increased across risk scores (possible range, 0–19): 0 points, 8.9% mortality; 1–2, 10.8%; 3–5, 23.2%; 6–8, 40.4%; 9–11, 57.0%; and at least 12, 70.0%. The area under the receiver operating characteristic (AUROC) curve for predicting 6-month mortality was 0.74 and 0.70 in the derivation and validation cohorts, respectively. This risk score based on 12 variables demonstrated better discrimination to predict 6-month mortality (AUROC, 0.64 for a cut-off of ≥ 6 points vs 0.51 for FAST stage 7c), and also requires further evaluation.

◆ The Milan Overall Dementia Assessment (MODA) scale is used to determine the rate of progression of Alzheimer's disease by repeated administration. Patients with a slow progression rate in the early stage were unlikely to show a subsequent fast progression rate, and vice versa for patients with a fast early progression. A tool is provided for predicting the speed of cognitive decline of patients from a single MODA assessment (Capitani et al., 2004), but its ability to identify patients with less than 6 months to live has not been tested.

◆ The Advanced Illness Index (AII) is a prognostic indicator to identify elders with a higher-than-expected likelihood for death in the next 3 years (Brody et al., 2006). The AII targets a dimension of risk different than frailty alone, utilizing 11 variables of gender (female), poor general health, use of oxygen, organ conditions (heart, lung, pancreas), cancer, more than

five drug prescriptions, help with ADLs, independently active, smoking, proxy-assisted Health Status Questionnaire, and age. In the development study, AII was shown to correctly identify death within 3 years in 74.3% in adults older than 65 years.