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Prognostication in Advanced Cancer: Update and Directions for Future Research

David Hui[1], **Carlos Eduardo Paiva**[2], **Egidio G. Del Fabbro**[3], **Christopher Steer**[4,5], **Jane Naberhuis**[1], **Marianne van de Wetering**[6], **Paz Fernández-Ortega**[7], **Tatsuya Morita**[8], **Sang-Yeon Suh**[9], **Eduardo Bruera**[1], and **Masanori Mori**[8]

[1]Department of Palliative Care, Rehabilitation and Integrative Medicine, MD Anderson Cancer Center, Houston, TX, USA [2]Department of Clinical Oncology, Barretos Cancer Hospital, Barretos, SP, Brazil [3]Division of Hematology/Oncology and Palliative Care, Massey Cancer Center, Virginia Commonwealth University, Richmond, VA, USA [4]Border Medical Oncology, Albury Wodonga Regional Cancer Centre, Albury, NSW 2640 [5]UNSW Rural Clinical School, Albury Campus, Albury 2640 [6]Department of Pediatric Oncology, Emma Children's Hospital, Academic Medical Center, Amsterdam, the Netherlands [7]Institut Català d'Oncologia - ICO, Nursing University of Barcelona, Barcelona, Spain [8]Department of Palliative and Supportive Care, Palliative Care Team and Seirei Hospice, Seirei Mikatahara General Hospital, Shizuoka, Japan [9]Department of Family Medicine, Dongguk University Ilsan Hospital, Goyang, South Korea; Department of Medicine, School of Medicine, Dongguk University, Seoul, South Korea

Abstract

The objective of this review is to provide an update on prognostication in patients with advanced cancer, and to discuss future directions for research in this field. Accurate prognostication of survival for patients with advanced cancer is vital, as patient life expectancy informs many important personal and clinical decisions. The most common prognostic approach is clinician prediction of survival (CPS) using temporal, surprise, or probabilistic questions. The surprise and probabilistic questions may be more accurate than the temporal approach, partly by limiting the time frame of prediction. Prognostic models such as the Glasgow Prognostic Score (GPS), Palliative Performance Scale (PPS), Palliative Prognostic Score (PaP), Palliative Prognostic Index (PPI), or Prognosis in Palliative Care Study (PiPS) predictor model may augment CPS. However, care must be taken to select the appropriate tool since prognostic accuracy varies by patient population, setting, and time frame of prediction. In addition to life expectancy, patients and caregivers often desire that expected treatment outcomes and bodily changes be communicated to them in a sensible manner at an appropriate time. We propose the following 10 major themes for future prognostication research: 1) enhancing prognostic accuracy; 2) improving reliability and reproducibility of prognosis; 3) identifying the appropriate prognostic tool for a given setting; 4) predicting the risks and benefits of cancer therapies; 5) predicting survival for pediatric

Corresponding author: David Hui, MD, MSc, Palliative Care, Rehabilitation and Integrative Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 1414, Houston, TX 77030, Tel: (713) 794-1803, dhui@mdanderson.org.

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populations; 6) translating prognostic knowledge into practice; 7) understanding the impact of prognostic uncertainty; 8) communicating prognosis; 9) clarifying outcomes associated with delivery of prognostic information; and 10) standardizing prognostic terminology.

Keywords

prognostication; cancer; survival; clinical decision making

Introduction

Accurate prediction of survival for patients with advanced cancer is critical since many personal and clinical decisions are driven by patient life expectancy. Complex decisions regarding initiation, intensity, or termination of palliative systemic therapies, palliative procedures or surgery, artificial nutrition or hydration, and hospice care are all dependent on a patient's prognosis [1,2]. Prognostication of survival is a challenging task, however. Clinician intuition (ie, clinician prediction of survival [CPS]) is often inaccurate, and prognostic uncertainty decreases clinician confidence in communicating prognosis with patients [3]. Inaccurate prognostic understanding may also contribute to more aggressive end-of-life care [4,5].

In 2005, a Working Group of the Research Network of the European Association for Palliative Care identified evidence-based recommendations regarding prognostication in advanced cancer [6]. Since then, a growing body of research has aimed to improve the accuracy of CPS as well as of prognostic factors and models. In June 2018, a panel of prognostic researchers and clinicians convened an international prognostication workshop at the Multinational Association for Supportive Care in Cancer annual meeting in Vienna, Austria. This manuscript summarizes the workshop, provides an update on prognostication in patients with advanced cancer, and proposes future directions for prognostication research in this population.

Current prognostic factors and models

Clinician prediction of survival.

CPS is the most common approach to estimating survival of patients with cancer [1]. The three general forms of CPS are 1) the temporal approach (How long will this patient live?); 2) surprise questions (Would I be surprised if this patient died in [specific time frame]?); and 3) the probabilistic approach (What is the probability of survival of this patient in [specific time frame]?). The tendency of the temporal approach to overestimate survival was first identified in a cardinal study conducted at St. Christopher's Hospice over 40 years ago [7], and has since been well established [8–10]. In contrast, the binomial nature (yes or no) of the surprise question may improve prognostic accuracy. Indeed, the surprise question performs relatively well as a survival prediction tool, with a C-index of 0.75 in a meta-analysis of studies in the oncology setting [11]. Interestingly, accuracy of the surprise question may be higher in oncology patients than in other disease groups [12,11]. Probabilistic CPS may also outperform the temporal approach, as demonstrated by a

systematic review of 42 studies in which probabilistic estimates performed modestly (C-index of 0.74–0.78), while both categorical (overall accuracy 23–78%) and continuous (difference between predicted and actual survival ranged from −86 to +93 days) temporal approaches yielded wide variation [8]. Thus, by limiting the time frame of prediction, both the surprise and probabilistic questions appear to predict survival more accurately than temporal CPS; however, further research is needed.

Prognostic factors.

Clinical signs and symptoms may improve the accuracy of CPS, the most significant of which include deterioration in performance status (PS), dyspnea, delirium or cognitive failure, and cancer anorexia-cachexia syndrome [13,14,6]. The systemic inflammatory response, as evidenced by high C-reactive protein (CRP), low albumin, and leukocytosis, among other markers, also has independent prognostic value in patients with advanced cancer [15]. Phase angle (PA), a marker of nutritional status obtained via bioelectrical impedance analysis, is also significantly associated with overall survival [16–19].

Prognostic models.

A recent systematic review identified seven distinct prognostic tools of varying objectivity and utility for use in patients with advanced cancer [20]. Of these, the Glasgow Prognostic Score (GPS), Palliative Performance Scale (PPS), Palliative Prognostic Index (PPI), and Palliative Prognostic Score (PaP) were the most widely used. These models incorporate a combination of clinical (subjective) and biomarker (objective) parameters. Of note, the GPS includes only two parameters, both of which are objectively measured, and has prognostic value complementary to that of PS [21,22]. Other potentially useful prognostic tools include nomograms [23,24], the Objective Palliative Prognostic Score (OPPS) [25], the Objective Prognostic Score (OPS) [26,27], the Prognosis in Palliative Care Study (PiPS) predictor model [28,29], and PRONOPALL [30,31].

Accuracy of prognostic models.

The accuracy of the PaP, Delirium-PaP (D-PaP), PPI, and PPS were directly compared in 549 patients admitted to Italian hospices [32]. All tools achieved adequate discrimination, but the C-index was greater for PaP and D-PaP versus PPI and PPS. The PaP, D-PaP, PPI, and PiPS (modified forms A and B) were also compared in patients with advanced cancer in various clinical settings [33]. All tools discriminated patients with distinct survival times and achieved accuracy (true positive + true negative / total cases) of ≥ 69%; however, PPI had a lower C-index as compared to PaP and D-PaP. Table 1 summarizes common prognostic models and highlights the varied methods used to assess their accuracy, including area under the curve (AUC) within a specified time frame, C-index, and overall accuracy. Future trials should focus on consistency of reporting to facilitate direct comparisons between studies. Future trials should also investigate novel prognostic strategies and refine existing prognostic tools so as to increase their utility in clinical practice.

Diagnosis of impending death.

The models above were designed to differentiate among patients with months, weeks, and days of survival, whereas factors predictive of death within three days consist largely of physical signs. The Investigating the Process of Dying study assessed the frequency, onset, and diagnostic performance for death in three days of 62 physical signs in 357 patients admitted to acute palliative care units. Multiple highly specific “tell-tale” signs of impending death were identified, including pulselessness of the radial artery, hyperextension of the neck, grunting of vocal cords, Cheyne-Stokes breathing, and death rattle [34–37]. In a subsequent prognostic model, patients were classified into prognostic categories based on PPS and drooping of the nasolabial folds. These skin folds, which can be assessed with a high degree of interrater reliability [38–40], run from the nose to the corners of the mouth and become less prominent in the last days of life due to loss of facial muscle tone [36]. The four prognostic categories (3-day mortality rate) included: 1) PPS score ≤ 20% and drooping of nasolabial folds present (94%); 2) PPS score ≤ 20% and drooping of nasolabial folds absent (42%); 3) PPS score of 30–60% (16%); and 4) PPS score ≥ 70% (3%), with an accuracy of 79–86% [34].

Important principles of prognostication.

For all of the approaches above, it is important to note that prognostic accuracy varies by 1) patient population and setting; 2) individual clinician making the prediction; 3) prognostic approach and time frame of prognostication; and 4) method used to assess accuracy. Thus, findings from individual studies may not be generalizable to others, and it is critical that confounding variables be adequately controlled or described. Meta-analyses should also pay particular attention to only combine studies examining similar populations.

The role of anorexia-cachexia in prognostication

Cancer anorexia-cachexia is driven by a variable combination of reduced food intake and abnormal metabolism. The resulting negative protein and energy balance precipitates weight loss not corrected by conventional nutrition support, leading to functional impairment. Several facets of anorexia-cachexia are associated with poor prognosis, including poor appetite, nutrition impact symptoms (NIS), weight loss, changes in body composition, and sarcopenia [41]. Inflammation and low testosterone have also been associated with decreased survival in patients with cancer cachexia [42].

Changes in body weight and composition.

Weight loss of > 5% is significant in determining prognosis of patients with cancer [43], particularly in patients with a lower body mass index (BMI) [44]. Prognostic accuracy of weight loss and BMI in patients with advanced cancer is improved when PS, anorexia, and physical and emotional functioning are also considered [45]. Changes in body composition and depletion of skeletal muscle mass are also associated with decreased survival in patients with cancer [46–50]. In both early and late stage cancer, sarcopenia increases risk of overall mortality [51,47,52,53].

Anorexia and NIS.

Poor appetite is a pervasive problem in oncology that increases in severity over the disease course [54]. A systematic review of 30 randomized controlled trials (RCTs) of patients with cancer demonstrated that inclusion of three health-related quality of life parameters (appetite loss, physical functioning, and pain) in prognostic models increased accuracy of overall survival prognosis by 6% relative to sociodemographic and clinical characteristics alone [55]. A recent pooled analysis of 17 RCTs also confirmed appetite loss to be a significant independent prognostic factor in patients with cancer [56]. In addition to poor appetite, NIS such as nausea may also decrease energy intake and further exacerbate the catabolic processes associated with cachexia [57]. Indeed, NIS are independently prognostic of survival in patients with cancer [58].

Combining cachexia domains and other factors.

Preliminary studies incorporating anorexia, markers of inflammation, and weight loss failed to distinguish between stages of cancer cachexia based on survival [59,60]. More recent studies have developed cachexia staging scores which correlate with Eastern Cooperative Oncology Group (ECOG) PS [61], as well as discriminate between stages of cachexia and predict survival [62]. Sample sizes of these studies were relatively small, however, and larger studies are needed to develop a more robust prognostic model that combines the various cachexia domains with other biomarkers such as lymphocyte count, albumin, or CRP [63,64].

Predictive models of treatment toxicity

General principles.

The ability to predict toxicity of therapy in patients with advanced cancer is vital for appropriate treatment selection. Toxicity prediction is dependent on treatment-related factors as well as general patient characteristics such as age, genetics, and metabolism. In many settings, PS is predictive of chemotherapy-related toxicity [65], and treatments are generally avoided in patients with poor PS. However, high-level evidence of the utility of PS to predict treatment-related toxicity from newer regimens is lacking, partly because PS-based subgroup analysis for toxicity is generally not reported [66].

Geriatric oncology setting.

A large proportion of patients with cancer are over age 65 and have multiple comorbidities. Geriatric assessment is recommended for all older adults under consideration for anticancer therapy [67–69], as assessment enables more nuanced prediction of chemotherapy toxicity [70–72]. The Cancer and Aging Research Group (CARG) chemotherapy toxicity prediction score (Table 2) is more sensitive than PS and has been studied in patients with a variety of solid tumours [73,74]. The score is available as an online tool [75], but its use is limited to patients receiving conventional chemotherapy. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score is a similar prediction tool that utilizes geriatric variables in addition to PS and the estimated risk of hematological toxicity of the individual chemotherapy regimen [70]. Two recent systematic reviews confirmed the use of various

patient factors for prediction of chemotherapy toxicity [76,77], highlighting the need to consider multiple geriatric assessment domains when caring for older adults with cancer.

Multi-targeted agents.

The ability to predict chemotherapy toxicity has led to creation of similar algorithms for use in patients on non-cytotoxic therapy such as epidermal growth factor receptor, vascular endothelial growth factor receptor, and proteasome inhibitors [78,79]. The heterogeneous mechanisms of action of these agents, combined with additional factors such as decreased creatinine clearance, PS, age, and comorbidities makes prediction of treatment toxicity difficult, though a predictive nomogram has been developed [79].

Immunotherapies.

Unlike conventional cytotoxic chemotherapy, immunotherapy with checkpoint inhibitors, particularly programmed cell death protein 1 (PD-1) or PD-1 ligand (PD-L1) inhibitors, has a relatively low rate of toxicity. However, patients with established autoimmune diseases such as rheumatoid arthritis or psoriasis are more likely to experience exacerbations of these conditions due to immune activation [80,81]. A recent systematic review found flare of existing autoimmune disease to be common in patients receiving immune checkpoint inhibitor therapy, but that this flare can typically be managed without discontinuing therapy [80]. Further research is needed to identify additional predictors of immunotherapy toxicity since these reactions may be severe or fatal [82].

Prognostication in pediatric oncology

Approximately 1% of all cancer diagnoses are in children, with leukemia, brain and central nervous system tumors, and lymphoma the most commons cancers of childhood [83]. The death rate of pediatric cancer has declined over the past four decades. Over 80% of children diagnosed with cancer before age 20 now survive at least five years [84]. Cancer remains the second leading cause of death in children, but survival rates vary widely among cancer types. For example, the 5-year survival rate for children with Hodgkin lymphoma is over 95%, but median survival of children with diffuse intrinsic pontine glioma is less than one year from the time of diagnosis [85,83].

Accurate prognostication of survival in children with advanced malignancies, as well as effective communication of this prognosis, is paramount as these efforts can ease parental distress, provide hope, and improve patient quality of life and advanced care planning (ACP) [86,87]. Similar to adults, prognosis of children with advanced cancer is often driven by a combination of disease- and patient-related factors [88]. A number of prognostic studies of childhood cancer have been conducted, but few have specifically identified prognostic factors in the advanced disease setting. Reasons for this dearth of research may include the relative rarity of pediatric cancer, the possibility of cure even for some patients with advanced pediatric malignancies, and challenges in assessing symptoms and patient-reported outcomes in children. As such, objective measures such as body weight and laboratory values have traditionally been used for prognostic purposes in this population [89,90]. Pediatric cancer patient databases such as the Children’s Oncology Group childhood cancer

registry (Project:EveryChild) systematically collect demographic and epidemiologic information as well as laboratory values and outcome data regarding treatment effectiveness and survival [91]. This type of large database of individual patient data may allow for development of prognostic models for advanced pediatric malignancies.

Patient preference for prognostic communication

What patients want to know.

Approximately 80% of patients with advanced cancer want to be informed of their prognosis [92,93]. In addition to life expectancy, patients often want information regarding expected treatment outcomes, adverse effects, and bodily changes in the last weeks to days of life [94,95]. Caregivers also have a strong desire for information [96], which, in contrast to the patients' declining need for prognostic information, typically increases over the disease course [97]. Despite the overwhelming majority of both patients and caregivers expressing a desire to be informed of their prognosis, physicians must be aware that a small proportion of patients prefer not to know their prognosis. Reasons for this preference may stem from cultural differences [98] or the fact that uncertain prognosis may increase patient anxiety [99] or precipitate treatment or ACP decisions that are contrary to the patient's own well-being [100,101].

Timing and means of communication with patients.

Although patients with advanced cancer often desire prognostic information, many hesitate to ask about it directly and instead expect clinicians to initiate such a conversation [102]. Some patients prefer to discuss their prognosis immediately after diagnosis [103], while others may prefer to wait. Furthermore, prognosis is a process rather than a single event, and a patient's prognosis may change over time based on treatment response, development of complications, or competing comorbidities [2]. Communication techniques such as the six-step SPIKES [104] or ask-tell-ask approaches [105] help determine the patient's values, increase patient understanding, and increase physician confidence in disclosing potentially distressing information. These flexible techniques facilitate communication and help ensure patients receive adequate follow-up, including referral to palliative care. Referral to palliative care may further encourage patient-clinician prognostic discussions and ease subsequent care planning [106].

Communication aids.

In addition to communication skills training for healthcare professionals, communication aids such as question prompt sheets and decision aids may enhance patient understanding of prognostic information and facilitate decision-making [107,108]. These aids improve patient-clinician interaction and encourage conversations related to prognosis, quality of life, treatment options, ACP, and concerns regarding end-of-life. Importantly, these tools can minimize patient anxiety in discussing these topics without significantly prolonging the duration of clinic visits [107,109,110]. In addition to question prompt sheets and decision aids, patient understanding of prognostic information may be augmented by discussing typical as well as best-case and worst-case scenarios [111–113]. However, as there is currently no established best practice for communicating prognostic information, clinicians

should aim to provide as much accurate information as possible for patients and families desiring prognostic information.

Future of prognostication

Future prognostic research should address 10 major themes (Table 3).

1. Enhancing prognostic accuracy.

Efforts to improve prognostic accuracy should focus on incorporating all relevant data, including existing variables (eg, PiPS [28,29,33]), novel prognostic factors (eg, phase angle [16,17]), and any signs of impending death (eg, Cheyne-Stokes breathing or drooping of the nasolabial folds [34–37]). Prognostic tools should utilize appropriate statistical models such as fractional polynomial modeling [114,115], or alternatively, may be built by machine learning, which can utilize big data from the electronic health record (EHR) to build prognostic algorithms from a vast array of variables. Using a deep neural network model, Avati et al. were able to predict 3–12 month survival with high accuracy (AUC 0.93 overall and 0.87 for admitted patients) among adult and pediatric patients at two hospitals [116]. More recently, using data from 216,221 adult patients admitted to two hospitals, Rajkomar and colleagues also reported their deep neural network models were able to predict in-hospital mortality (AUC 0.93–0.94), prolonged hospitalization (AUC 0.85–0.86), and 30 day readmission (AUC 0.75–076) [117]. These machine learning algorithms already appear to outperform more traditional predictive models and may be further refined with real-time data feedback through cognitive learning algorithms. With further validation, such machine learning approaches have the potential to transform the future of prognostication.

2. Improving reliability and reproducibility.

Objective variables such as laboratory values and vital signs should be used to further improve the reliability and reproducibility of prognostication tools such as the OPPS [25] and six adaptable prognosis prediction (SAP) models [118]. While widely used prognostic tools such as PaP, PPI, and PiPS models have acceptable predictive accuracy [33,119–121], their major limitations include the use of subjective variables such as patient symptoms or conditions as well as CPS. As subjective variables could be influenced by evaluators' experiences and competence [122,123], use of objective variables is recommended [124,125].

3. Identifying the appropriate prognostic tool for a given setting.

As prognostic models are often calibrated for particular populations, it is essential to identify the tool that best fits each clinical setting and specific patient's needs. Doing so requires understanding the clinical utility of each prognostic tool in regards to balancing sensitivity versus specificity and feasibility versus accuracy. For example, if a rough estimation of prognosis is needed in daily care of patients with advanced cancer, or laboratory values are not readily available (such as in home hospice or many situations in low- or middle-income countries), then prognostic tools utilizing easily evaluable variables such as PPI may be sufficient. Conversely, if the most accurate prognostication is highly desired (eg,

chemotherapy use at the end-of-life), then prognostic tools with many variables, yet higher accuracy may be more useful [33,121,32].

4. **Predicting the risks and benefits of cancer therapies.**

   Given the unique adverse effects often associated with cancer treatments, models that accurately estimate the risk of grade 3 or 4 toxicities could be highly informative for clinical decision making. In the era of big data, machine learning algorithms may allow identification of novel predictive factors beyond traditional biomarkers.

5. **Predicting survival for pediatric populations.**

   Additional research is acutely needed to identify key prognostic factors in advanced pediatric malignancies.

6. **Translating knowledge into practice.**

   The ability to translate research knowledge to clinical practice is vital. Better understanding of clinicians' prognostic decision-making process as well as research regarding how best to educate trainees and junior faculty in this critical task is essential. Various prognostic models may aid clinicians in predicting patient survival, but cumbersome calculations or ambiguous interpretation may limit their clinical utility. The issue of cumbersome calculations may be partially addressed through the use of web-based tools such as www.predictsurvival.com, which provides survival prediction based on multiple prognostic scores. Similarly, confidence in prognostic determination may be augmented through the use of multiple models, taking the point of convergence to be indicative of relative confidence in the prediction. Regarding interpretation of prognostic information for patients and their families, visual or graphical formats may facilitate translation of information, improve patient understanding, and enhance the quality of patient-clinician interaction [126–128]. However, more extensive validation of web-based prognostic models, as well as further assessment of the impact of graphical presentation of prognostic data, is necessary. Furthermore, regardless of whether CPS or prognostic models are used, and regardless of the manner in which predictions are shared with the patient's family, there is a need to consider the clinical impact of prognostication on clinical decision making, patient outcomes, and cost [129].

7. **Understanding the impact of prognostic uncertainty.**

   Death is a probabilistic event, with increasing likelihood as patients get sicker and weaker, but by definition, there is always some degree of uncertainty when predicting the future. Prognostic accuracy is associated with prognostic confidence, and a more confident estimate is likely to facilitate prognostic discussions and care planning [130–132]. More research is needed to examine the relationship between prognostic accuracy, confidence, and patient-clinician discussions.

8. **Communicating prognosis.**

   In the era of personalized medicine, it is important to tailor the timing and format of prognostic information delivery. Face-to-face discussion may be augmented by customized printed material from prognostic websites or the EHR. Some patients may prefer general

time frames (eg, months, weeks, or days), while others may prefer probabilistic information. Regardless, communication of prognostic information should convey explicit information as well as maintain hope [93,133]. Few studies have explored the effects of different verbal and nonverbal communication skills [134,135], but RCTs of actual prognostic disclosure may not be practical or ethical. Thus, video-vignette randomized trials may be appropriate [134,136,137]. Such qualitative studies in patients with advanced cancer would help identify optimal outputs of prognostication that meet patients' needs for information and facilitate ACP.

9. Clarifying outcomes associated with delivery of prognostic information.

It is important to link prognostic information to clinical decision making, such as treatment selection and ACP. Prognostic information should be communicated and interpreted in light of the patient's and family's values to ensure that that decisions are made accordingly [138]. For patients and families, improving communication and decision making in the last days to weeks of life is a high priority [139]. Accordingly, an ongoing Australian ACP study of patients with advanced cancer is investigating the effects of prognostic information on whether patients' end-of-life wishes will be discussed and met [140]. Future studies should examine how effective communication of prognostic information may maximize patient outcomes and improve end-of-life care.

10. Standardizing prognostic terminology in reporting.

Much inconsistency exists in how both authors and readers interpret commonly used prognostic descriptors such as "terminally ill," "end-of-life," and "end-stage" [141]. Such terms are rarely defined when used, which may contribute to mischaracterization and misinterpretation of study findings [142]. For example, among reports of overall survival, median survival was 114 days for "advanced cancer," 63 days for "end-of-life," 42 days for "terminally ill," 25 days for "end-stage," and 4 days for "dying" [143]. Further complicating the lack of existing consensus definitions of these prognostic terms is the frequently inadequate characterization of study subjects and settings in manuscripts. A review of 742 original articles in palliative oncology found that 67% did not provide overall survival, and it was impossible to determine where patients fell along the disease trajectory in 49% of studies [143]. It is imperative that future trials avoid this ambiguity, explicitly define prognostic descriptors, and provide sufficiently detailed descriptions of study subjects and methodology. International consensus on the definition of these commonly used terms, as well as standardization of statistical techniques used to assess accuracy (eg, AUC, C-index), would facilitate more ready comparison across studies.

Conclusion

There has been steady progress over the past few decades to improve the science and art of prognostication. Moving forward, our panel has outlined 10 fertile areas for further research. Given the number and diverse nature of important unanswered questions, the development of an international consortium on prognostication in advanced cancer would greatly augment data collection and further research collaboration in this area.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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61–143. See supplementary material.

Table 1.

Accuracy of clinician prediction of survival (CPS) using different prognostic models.

Prognostic tools	Ref.	Population	Median survival	Accuracy measures
BPN	[24]	All cancer, ambulatorial	166 days (development); 124 days (validation)	C-index 0.71; AUC 30 days 0.84
CPS, probabilistic	[8]	Systematic review	NA	AUC 6 months 0.74–0.78
CPS, temporal	[8]	Systematic review	NA	Overall acuracy 23–78%
CPS, surprise question	[12]	Systematic review	NA	AUC 6–18 months 0.83
CPS, surprise question	[11]	Systematic review	NA	C-index 0.76
CPS, PaP	[124]	All cancer, inpatient	109 days	AUC 30 days 0.57 for PaP-CPS, 0.78 for PaP without CPS, 0.73 for PaP-total score
CPS, PPI	[123]	All cancer, inpatient	109 days	AUC 30 days 0.58 for CPS, 0.76 for PPI
OPS	[26]	All cancer, inpatient	26 days	3-week survival overall accuracy 76%
OPS	[27]	Mix of hospital- and home- based palliative care settings	25–35 days, depending on setting	3-week survival overall accuracy 70–78%; C-statistic 0.74–0.81
OPPS	[25]	All cancer, inpatient	Not described	AUC 7 days 0.82
PaP	[144]	Mix of outpatient and inpatient hospice	22 days	C-index 0.72
PaP	[33]	All cancer, various settings	25–48 days	C-index 0.79–0.89
D-PaP	[144]	All cancer, admitted to hospice	22 days	C-index 0.73
D-PaP	[33]	All cancer, various settings	25–48 days	C-index 0.79–0.88
PiPS-A	[33]	All cancer, various settings	25–48 days	Overall accuracy 73% to 87%
PiPS-A	[29]	All cancer, newly referred to a palliative care service	34 days	C-index 0.69
PiPS-B	[33]	All cancer, various settings	25–48 days	Overall accuracy 74% to 86%
PiPS-B	[29]	All cancer, newly referred to a palliative care service	34 days	C-index 0.68
PPI	[144]	Mix of outpatient and inpatient hospice	22 days	C-index 0.62
PPI	[120]	All cancer, admitted to inpatient hospice	~26 days	< 3 weeks survival overall accuracy 84%; < 6 weeks survival overall accuracy 76%
PPI	[33]	All cancer, various settings	25–48 days	C-index 0.75–0.85
PRONOPALL	[30]	All cancer, ambulatorial	Not described	AUC 2 and 6 months 0.81 and 0.78, respectively
PRONOPALL	[31]	All cancer, inpatient	58 days	AUC 2 months 0.86
Spanish nomogram	[23]	All cancer, oncology and palliative care units	29.1 days (development); 18.3 days (validation)	C-index 0.70

Abbreviations: AUC, area under the curve; BPN, Barretos Prognostic Nomogram; CPS, clinician prediction of survival; D-PaP, Delirium Palliative Prognostic Score; NA, not applicable; OPPS, Objective Palliative Prognostic Score; OPS, Objective Prognostic Score; PaP, Palliative Prognostic Score; PiPS-A, Prognosis in Palliative Care Study A; PiPS-B, Prognosis in Palliative Care Study B; PPI, Palliative Prognostic Index.

Table 2.

Prediction model and scoring accuracy for chemotherapy toxicity [70].

Variable	Value/response	Score
Patient age	≥ 72 years	2
	< 72 years	0
Cancer type	GI or GU	2
	Other	0
Planned chemotherapy dose	Standard	2
	Reduced	0
Planned number of chemotherapy drugs	> 1 (polychemotherapy)	2
	1 (monochemotherapy)	0
Hemoglobin	< 11 g/dL (male); < 10 g/dL (female)	3
	≥ 11 g/dL (male); ≥ 10 g/dL (female)	0
Creatinine clearance (Jelliffe, ideal weight)	< 34 mL/min	3
	≥ 34 mL/min	0
How is your hearing (with a hearing aid, if needed)?	Fair, poor, or totally deaf	2
	Excellent or good	0
Number of falls in the past 6 months	≥ 1	3
	None	0
Can you take your own medicine?	With some help/unable	1
	Without help	0
Does your health limit you in walking one block?	Somewhat limited/limited a lot	2
	Not limited at all	0
During the past four weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?	Limited some of the time, most of the time, or all of the time	1
	Limited none of the time or a little of the time	0

Total CARG risk score	% of patients with grade 3–5 chemotherapy toxicity
0–3	25
4–5	32
6–7	50
8–9	54
10–11	77
12–19	89

Abbreviations: CARG, Cancer and Aging Research Group; GI, gastrointestinal; GU, genitourinary.

Table 3.

Recommendations for future prognostication research.

Theme		Potential strategies	Examples of study design, methods and contents
1.	Enhance prognostic accuracy	Increase the number of variables	Inclusion of more variables at one point
			Use of time trend
		Identify novel prognostic factors	Phase angle
			Physical signs of impending death
		Utilize advanced statistical models	Machine learning
			Fractional polynomial model
2.	Improve reliability and reproducibility	Use objective variables only	Laboratory values and/or vital signs
3.	Identify the appropriate prognostic tool for the setting	Explore the clinical utility of prognostic tools, balancing sensitivity vs. specificity	Mapping the accuracy of different prognostic tools in different settings
		Balancing feasibility vs. accuracy, depending on clinical scenario	Qualitative interview with clinicians on how prognostic tools with different psychometric features have been useful in various clinical settings
4.	Predict the risks and benefits of cancer therapies	Identify variables that inform risk of grade 3–4 toxicity	Treatment-related factors, patient age and reserve, novel biomarkers
5.	Predict survival for pediatric populations	Use objective variables	Laboratory values and/or body weight
		Develop large databases or individual patient data	Project:EveryChild
6.	Translate knowledge to practice	Educate trainees, junior faculty	Assessment of knowledge, prognostic accuracy, attitudes and beliefs before and after training
		Develop web-based tools to facilitate calculations	www.predictsurvival.com
		Utilize graphical presentation of prognostic information	Qualitative interview with patients and families on effect of visual/graphic information on prognostic
		Assess impact of prognostication	understanding
			Assess patient outcomes and cost
7.	Understand the impact of prognostic uncertainty	Identify optimal approaches to improve prognostic confidence and address prognostic uncertainty	Improve accuracy of current prognostic tools
			Use of multiple prognostic tools
			Use of time ranges (e.g. best and worst case scenarios) instead of specific numbers when communicating prognosis
8.	Communicate prognosis	Clarify the effects of different verbal and nonverbal communication skills in providing prognostic information	Randomized video-vignette studies to evaluate the effects of various verbal and non-verbal communication skills on short-term outcomes (e.g., uncertainty, anxiety, self-efficacy, satisfaction, trust in physician, perception of physician compassion, and willingness to discuss ACP)
9.	Clarify outcomes associated with delivery of prognostic information	Clarify if accurate estimation and effective communication of prognosis improve long-term patient (true) outcomes	A cluster RCT to clarify the effects of routine provision to oncologists of EHR-generated prognostication utilizing most recent data with general ACP suggestions on long-term outcomes (e.g., quality of care and health care utilization)
10.	Standardize prognostic terminology	International congress to establish consensus definitions	Publication of standardized definitions for common terminology Define prognostic terms clearly when they are used

Theme	Potential strategies	Examples of study design, methods and contents
	Standardized statistical techniques	AUC, C-index to describe accuracy

Abbreviations: ACP, advance care planning; AUC, area under the curve; EHR, electronic health record; RCT, randomized controlled trial.