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SPECIAL ARTICLE

Prognostic evaluation in patients with advanced cancer in the last months of life: ESMO Clinical Practice Guideline☆

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INTRODUCTION

Patients with cancer may have potentially curable disease or may live for many years despite incurable cancer. However, these guidelines specifically relate to patients with advanced incurable cancer who are expected to live for a few months or less. Distinction is made between patients with a few months to live, who may or may not be receiving anticancer therapies, and those thought to be imminently dying (i.e. within days or weeks). This guideline focuses on the prediction of death or length of survival and not other clinically-important outcomes such as response to treatment, preferred place of death or length of inpatient stay. Recommendations are provided to health care professionals (HCPs) who care for patients with advanced cancer in the last months of life regarding the best way to prognosticate and to communicate prognoses to patients and their families or caregivers. A proposed algorithm for prognostication and communication is shown in Figure 1.

Importance of prognosis

Prognostic information is important to patients, their families and HCPs. Prognoses help to inform future care and provide opportunities for patients and their families to focus on the things that are most important to them when time is short. Prognostic information can also facilitate access to services and benefits. At an organisational level, prognoses can be helpful for describing the case mix of services or for summarising the health status of patients in different arms of a clinical trial. At an individual level, prognoses can provide information about when a particular patient is likely to die.

Prognostic research methodology

The PROGnosis RESearch Strategy (PROGRESS) partnership describes a four-stage hierarchy of prognostic research.[1] In the context of cancer care, fundamental prognosis research employs epidemiological methods to understand the natural history of cancers under different conditions. Prognostic factor research identifies specific factors associated with length of survival. Statistical models use a combination of prognostic factors to predict an individual's survival risk and such models need to undergo development, validation and assessment for impact. Finally, stratified medicine research uses prognostic information to tailor treatments to individuals or groups with specific prognostic features. Most research in cancer palliative care has been at the level of identifying and validating individual prognostic factors or developing and validating multivariable prognostic models. There have not yet been any studies to evaluate the impact of prognostic models on clinical care. Prognostication in advanced cancer is also somewhat unusual in that, in

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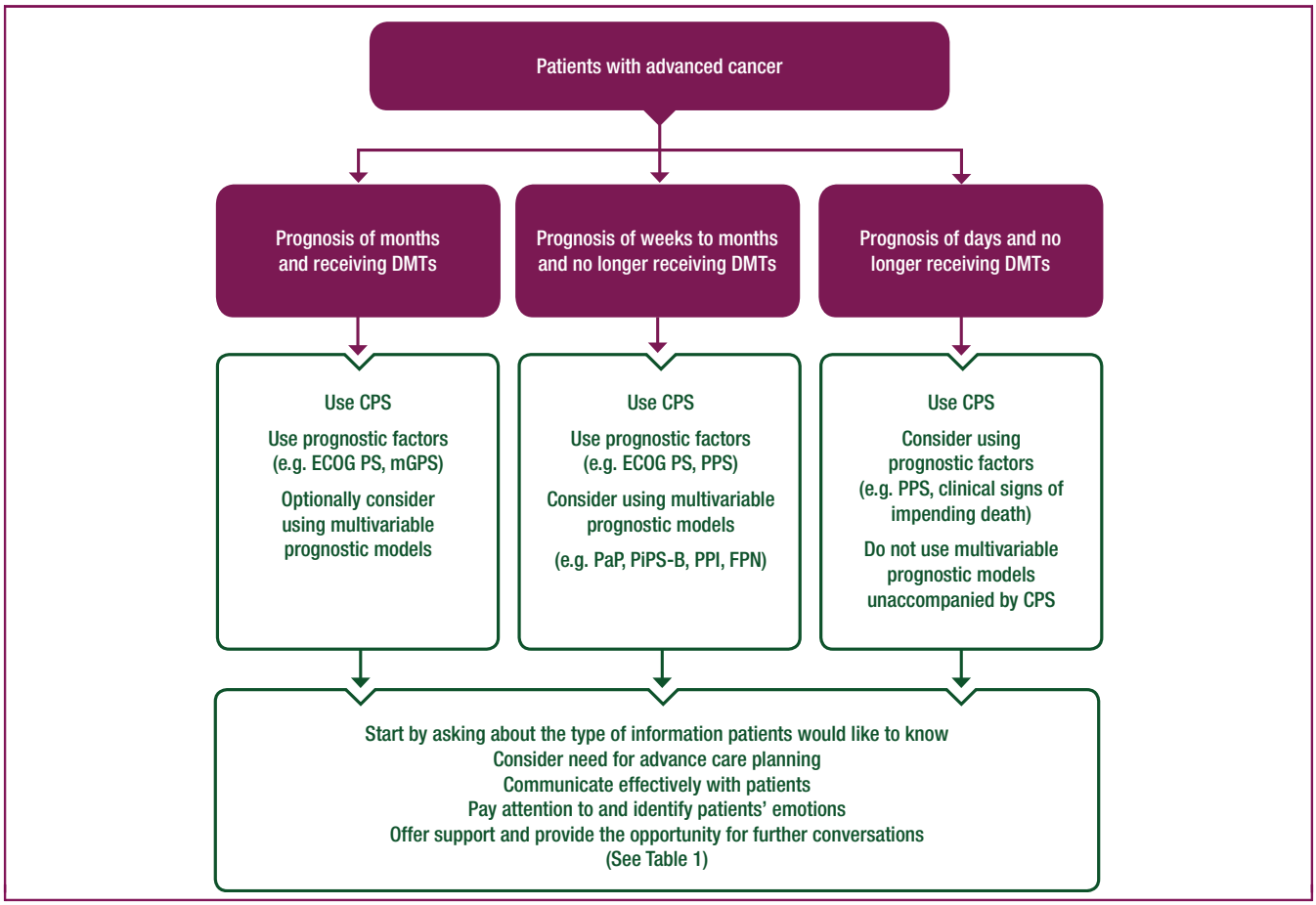

Figure 1. An algorithm for appropriate use of clinical predictions, prognostic factors and multivariable risk prediction models.
Purple: general categories or stratification; white: other aspects of management.
CPS, clinician predictions of survival; DMT, disease-modifying treatment; ECOG, Eastern Cooperative Oncology Group; FPN, Feliu Prognostic Nomogram; mGPS, modified Glasgow Prognostic Score; PaP, Palliative Prognostic Score; PiPS-B, Prognosis in Palliative care Study-Blood; PPI, Palliative Prognostic Index; PPS, Palliative Performance Scale; PS, performance status.

practice, it often relies on subjective clinician predictions of survival (CPS).

REVIEW OF CPS

CPS may be required to inform decisions as part of routine medical care, such as the continuation or cessation of treatments, referral to specialist services, access to benefits or insurance cover. Although other survival prediction methods have been developed, CPS remains the standard of care against which new innovations should be judged.

Accuracy of CPS

CPS is often considered to be inaccurate and excessively optimistic. It has been highlighted, however, that heterogeneous methods have been used to obtain CPS[2] and assess their accuracy. For instance, CPS can be reported as a continuous estimate (e.g. number of days), a categorical estimate (e.g. 0-2 weeks; 3-4 weeks) or as a probability estimate (e.g. the probability of surviving for 3 months). The accuracy of CPS has been defined as an estimate ±30% actual survival, within a maximum time window (e.g. within 30 days) or within a threshold range (e.g. within 7-14 days). A systematic review of the accuracy of CPS in palliative care reported the accuracy of categorical estimates of survival as ranging between 23% and 78%, continuous estimates as ranging between an average underestimation of 86 days to an average overestimation of 93 days and probability estimate discrimination (as measured using the C-statistic) as ranging between 0.74 and 0.78.[2] Nonetheless, such predictions may be accurate enough to guide practice at the very end of life. For example, if accuracy is defined as a margin of error of 1 week, then clinicians' predictions of imminent death (i.e. death within 1 week) have a positive predictive value (PPV) of 88%.[3]

Another approach to prognosticating is the so-called 'surprise question (SQ)', i.e. 'Would I be surprised if this patient were to die within the next year (or other specified time period)?' The SQ requires clinicians to reflect on whether or not death should be considered a likely outcome and then to plan care accordingly. In effect, the SQ can be considered a categorical CPS with just two categories as the patient either will or will not survive to the specified timepoint. In a meta-analysis of studies evaluating the SQ, its overall accuracy was found to be 75%.[4] This was principally because the SQ was good at identifying patients who

lived longer than 1 year and most patients in most studies did so. The PPV of the SQ for identifying patients who would die within the next year, however, was low (33%), meaning that the SQ was better at identifying patients who were not in the last year of life rather than those who were. In 2021, Ermers and colleagues[5] reported that the PPV of the SQ for 1-year survival could be improved (from 55% to 74%) by including a second SQ, i.e. 'Would I be surprised if this patient is still alive…?' The improved PPV, however, came at the cost of creating a third category of patients about whom clinicians would neither be surprised nor unsurprised if they died within 12 months. Among palliative care inpatients with an expected survival of <6 weeks, the SQ and temporal predictions are reported to have similar accuracies, suggesting that they may both be useful for predicting death in the short term.[6]

Differences in accuracy between HCPs

Some studies have shown that the prognostic estimates of palliative care physicians are more accurate than those of junior doctors[7] and oncologists.[8] Furthermore, a study reported that the prognostic estimates of palliative care nurses were slightly more accurate than those of palliative care doctors.[9] The available evidence for the superiority of prognostic prediction by any particular group of HCPs, however, is currently inconsistent.[2]

Factors affecting accuracy of CPS

Individuals who frequently make CPS (experts) are expected to be more accurate at this task than those who make such predictions less often. Experts, however, are not always able to articulate the processes underlying their judgements. White et al.[10] used judgment analysis to understand subconscious factors underlying clinical intuitions about imminent death and provided preliminary evidence that it may be possible in principle to teach the relevant skills to less experienced HCPs.[11] It appears that neither profession, years of experience nor the age of the HCP is associated with prognostic accuracy,[2] whereas a shorter duration of the pre-existing HCP—patient relationship and a longer time since the patient's last review were associated with more inaccuracies.[12] The European Association of Palliative Care has recommended that a second opinion may improve CPS.[13] One study reported limited evidence in support of this recommendation; however, although statistically significant, the magnitude of improvement was very small (accuracy of nurse prediction 55.2%, accuracy of doctor prediction 56.3%, accuracy of team prediction 57.5%).[14] There is also evidence to support the existence of the so-called 'horizon effect', the phenomenon whereby CPS is more accurate when death is more imminent,[3,15] although not all studies have observed this phenomenon.[16]

Recommendations

- Clinicians should use their experience to predict the survival of patients with advanced incurable cancer (i.e. a prognosis of a few months or less), but should be aware of their limitations and understand that, in general, there is a tendency to overestimate survival [III, A].
- It is suggested that clinicians might use estimates of survival based on input from multiple professionals to supplement their own clinical judgement [III, C].

PROGNOSTICATING IN PATIENTS STILL RECEIVING PALLIATIVE DISEASE-MODIFYING THERAPIES WITH AN EXPECTED SURVIVAL OF MONTHS

Patients with advanced cancer in the last few months of life sometimes start or continue treatment with disease modifying therapies (DMTs),[17] including immunotherapies,[18] to improve quality of life (QoL), increase survival or both. Patient and treatment selection, however, are vital as poorly targeted DMTs may lead to a reduced QoL and other negative outcomes.[19] In patients with a poor prognosis, chemotherapy (ChT) is associated with increased hospital admissions, a decreased likelihood of dying at home and reduced survival.[20] DMTs in the last 30 days of life have also been suggested as an indicator of poor quality care[21] and are associated with delayed referral for palliative care.[22]

Prognostic factors

Performance status. Performance status (PS), commonly measured using the Karnofsky performance score (KPS)[23] or Eastern Cooperative Oncology Group (ECOG)[24] scale, is the cornerstone of prognostication in day-to-day oncology practice. Worsening PS is associated with increased 30-day mortality in patients with advanced incurable cancer receiving systemic anticancer therapy (SACT).[25] Worsening PS is also firmly established as the most reliable survival predictor in advanced cancer, either alone or in conjunction with other prognostic markers, and is associated with deteriorating QoL.[26] As a result, it is not routine practice to treat patients with an ECOG PS >2 with DMT.

Biomarkers of systemic inflammatory response. Biomarkers of systemic inflammatory response have been extensively studied as prognostic factors in patients with advanced cancer. One of the most studied is the Glasgow Prognostic Score (GPS) combining serum C-reactive protein (CRP) and albumin levels with equal weighting. The GPS was subsequently modified (mGPS), supported by data showing that allocating CRP levels a higher weighting than albumin levels provided greater prognostic accuracy (CRP <10 mg/l, mGPS 0; CRP >10 mg/l, mGPS 1; CRP >10 mg/l and albumin <35 g/l, mGPS 2). GPS and mGPS have been assessed in >150 000 patients with cancer in 300 studies across all tumour types, and have been found to be reliable prognostic factors that are able to distinguish between patients with varying survival prospects.[27] mGPS has also been incorporated into clinical guidelines for cancer nutrition.[28,29]

Increased systemic inflammation measured using neutrophil count along with mGPS predicts survival in patients with advanced cancer receiving DMT, including

immunotherapies.[30,31] A large systematic review and meta-analysis has demonstrated a significant association between GPS/mGPS and survival in patients with advanced cancer [hazard ratio 1.93, 95% confidence interval (CI) 1.76-2.13, $P < 0.00001$].[32] The systemic inflammatory response, as measured by the neutrophil to lymphocyte ratio (NLR) and mGPS, has been shown to be prognostic in patients undergoing immunotherapy treatment of lung and renal-cell cancers.[31,33] Furthermore, increased inflammation has been associated with weight loss and reduced PS and may be an important contributing factor in the nutritional and functional decline seen in patients with advanced cancer.[26,28,34]

Combination of PS and systemic inflammatory response. ECOG PS and mGPS are individually prognostic, but they can also work synergistically to improve survival prediction in patients with advanced cancer receiving DMT (as part of the so-called ECOG PS/mGPS framework).[26,34-36] As such, their use in patients with advanced cancer would seem appropriate.[34,37,38] There is now strong evidence that the presence of a systemic inflammatory response, as evidenced by mGPS, is associated with loss of lean tissue, anorexia, weakness, fatigue, reduced QoL and poor survival in patients with advanced cancer.[26,30,32]

Prognostic factors in older patients. In older patients, additional prognostic factors to consider include poor nutritional status and prolonged timed 'get-up-and-go'.[39] For this reason, a comprehensive geriatric assessment may help with the estimation of prognosis in these patients.

Individualised risk prediction models

Whereas there is good evidence for the role of individual or simple combinations of prognostic factors, there has been relatively little research into the development and validation of multivariable prognostic models or individualised risk stratification scores for patients with cancer and a prognosis of a few months or less who are still receiving DMT.

One study used routinely collected laboratory data in patients receiving ChT to develop six adaptable prognosis prediction models.[40] The combination of albumin, lactate dehydrogenase (LDH) and neutrophil count was predictive of death at every month within the last 6 months of life (each of the six models utilised a different set of coefficients in the same general regression equation). The area under the curve (AUC) for each model ranged from 0.852 to 0.713 for 1-month and 6-month models, respectively. External validation ($N = 367$) supported the performance of all six models, albeit with lower AUC values (0.698-0.803).

Bourgeois et al.[41] evaluated the performance of a previously developed prognostic score (combination of PS, number of metastatic sites, serum albumin and LDH) in patients with a variety of advanced incurable cancers who were about to start palliative treatment with ChT, tyrosine kinase inhibitors or monoclonal antibodies.[42] The score effectively divided patients into three risk groups. Calibration of the score, however, was different from the original study, particularly in the worst risk group.

Paiva et al.[43] developed and validated a prognostic nomogram for use in ambulatory patients with advanced cancer. A substantial proportion of patients in the development (47.5%) and validation (67.8%) cohorts were still receiving DMT. Median survival was 166 and 124 days for patients in the development and validation cohorts, respectively. Their prognostic score (based on sex, presence of distant metastasis, KPS, white blood cell count and serum albumin level) showed acceptable discrimination (C-index 0.70) and calibration for predicting survival at 30, 90 and 180 days.

Some scores have specifically been developed to predict risk of death in older patients with cancer, and these include variables such as PS, nutritional status, activities of daily living and gait speed.[44,45]

Many other prognostic scores have been developed for use in patients with advanced cancer who are no longer receiving DMT (see section 'Prognosticating in patients with an expected survival of weeks to months'). However, two large prospective studies have evaluated the performance of these tools in cohorts with a significant proportion of participants who were still receiving treatment.[46,47] In both studies, the tools performed well and were able to distinguish between patients with differing survival prospects. It is notable that these prognostic scores were not assessed in patients receiving newer therapies such as immunotherapy or targeted therapies and so their utility in these patient groups is unknown.

Conclusions

There is good evidence for the use of certain prognostic factors to reliably stratify patients with advanced cancer receiving DMT according to their survival risk. This is particularly true of ECOG PS and mGPS, and preferably a combination of the two. Caution should be exercised with the interpretation of prognostic factors in patients receiving DMT since variables such as PS, CRP levels and NLR may be temporarily affected by the therapy itself and may not accurately reflect the patient's underlying condition. It is also clear that other prognostic factors (e.g. epidermal growth factor receptor mutation in lung cancer, neurotrophic tyrosine receptor kinase translocation or microsatellite instability) may dramatically influence prognosis, particularly if genotype-directed therapy is employed.

Whereas there is good evidence for the value of individual or simple combinations of prognostic factors, data on the development and validation of multivariable prognostic models in patients with advanced cancer receiving DMT are limited. The models that have been developed typically rely heavily on PS, markers of systemic inflammation and a few other prognostic factors.

Recommendations

- In patients with advanced cancer and a prognosis of months who are undergoing palliative DMT:
  - Clinicians should use PS and/or measures of systemic inflammatory response as prognostic factors to

discriminate between groups of patients with advanced cancer and differing survival prospects [III, A].
- o It is suggested that clinicians use PS and/or measures of systemic inflammatory response to inform decisions and discussions regarding the goals of care [V, C].
- o Optionally, clinicians might consider using multivariable individual risk prediction models to discriminate between patients with differing survival prospects [III, C].

PROGNOSTICATING IN PATIENTS WITH AN EXPECTED SURVIVAL OF WEEKS TO MONTHS

Prognostic factors

Prognostic factors such as PS and systemic inflammatory response markers, which are important for patients with advanced cancer receiving palliative DMT, are also important for patients with more advanced disease and a likelihood of survival of weeks to months. In this population, however, traditional measures of PS (such as ECOG PS and KPS) may lack discrimination. The Palliative Performance Scale (PPS),[48] which was developed as a modification of KPS,[23] focuses on patients with poorer mobility and self-care abilities and includes other potentially relevant prognostic indicators (e.g. oral intake and consciousness level). PPS has been shown to reliably distinguish between patients with differing survival outcomes, regardless of tumour type, setting and geographical location.[49] It should be noted that although PPS consists of several potentially important prognostic factors, it was not constructed as a multivariable individualised risk prediction model, but rather as a refined measure of PS, which has subsequently been found to be a reliable prognostic factor in this patient population.

Individualised risk prediction models

A variety of multivariable individualised risk prediction models have been developed to predict survival in patients with an expected survival of weeks to months (at least one of which incorporates PPS as a prognostic factor).[50] Clinicians need to understand the characteristics and limitations of these tools for appropriate use.

The most widely used and/or well-researched models are described below.

Palliative Prognostic Score and modifications. The Palliative Prognostic score (PaP)[51] was one of the first multivariable prognostic models developed for use in patients with advanced cancer (see Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.101195). Scores are generated from partial scores across six domains: dyspnoea, anorexia, KPS, total white blood count, lymphocyte percentage and clinical estimated survival (2-week categories up to >12 weeks), with total scores ranging between 0 and 17.5. Rather than provide an individualised risk score, PaP stratifies patients into one of three broad risk groups according to their 30-day survival probability: group A (score 0.0-5.5, >70% probability), group B (score 5.6-11.0, 30%-70% probability) and group C (score 11.1-17.5, <30% probability). PaP has also been modified to include an additional domain related to delirium (D-PaP), with total scores ranging from 0.0 to 19.5 and the same risk groups as those used for PaP but with different scoring boundaries.[52]

Although both PaP and D-PaP divide patients into three prognostic groups with varying 30-day survival probabilities, importantly, clinicians' predictions are equally able to do so.[53,54] Although not designed to be used as a continuous variable, when PaP is treated as such, it shows good-to-excellent ability to discriminate between patients with different survival prospects [C-statistics range from 0.64 (95% CI 0.54-0.74) to 0.90 (95% CI 0.87-0.92)].[54]

Some groups have investigated the effect of separating the subjective (i.e. CPS) and objective (i.e. symptoms and laboratory data) elements in PaP to evaluate their prognostic performance independently. An initial study undertaken at a tertiary palliative care unit suggested that PaP without CPS was more accurate than the original PaP.[55] A more recent, large cohort study, however, failed to confirm this finding and found that both elements were necessary for maximum accuracy.[56]

A nomogram version of the PaP score, which aimed to improve the individualised estimate of survival, has now been published.[57] The nomogram had a concordance index of 0.74 (0.72-0.75). The accuracy of the nomogram at 15, 30 and 60 days was 74% (70-77), 89% (85-92) and 72% (68-76), respectively.

Prognosis in Palliative care Study models. Prognosis in Palliative care Study (PiPS) models were developed and validated in patients with advanced incurable cancer both currently receiving and no longer receiving DMT.[46,58-60] PiPS-A is calculated using clinical observations, PS and disease status, and PiPS-B additionally requires blood test results (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101195). Both versions of PiPS provide probability estimates of 14- and 56-day survival and use a 'decision rule' to allocate patients to one of three prognostic risk categories; those predicted to survive for days (0-13 days or <2 weeks), weeks (14-55 days or 2-<8 weeks) or months (>55 days or ≥2 months). In validation studies, survival of patients in each risk category was found to fall within the expected range for both PiPS-A and PiPS-B.[59,60]

The initial PiPS development study[58] compared the accuracy of models against CPS in terms of predictions of days, weeks or months. PiPS-B showed significantly better accuracy than CPS by physicians or nurses (62% versus 53% and 52%, respectively) and non-significant superiority to multidisciplinary team (MDT) estimates (54%). PiPS-A was as accurate as physician, nurse or MDT estimates (60% versus 56%, 55% and 58%, respectively). A subsequent validation study found that PiPS-A risk categories performed less well than MDT CPS (56% versus 62% accuracy) whereas PiPS-B once again demonstrated similar accuracy to MDT CPS (61% versus 62%).[47,53,59]

When constituent PiPS scores (for 14- and 56-day survival) are used as standalone continuous variables (rather than by being combined using a 'decision rule' to categorise patients into three risk groups), they show good-to-excellent ability to discriminate between patients with different survival prospects. C-statistics ranged from 0.776 (95% CI 0.755-0.797) for PiPS-A predicting 56-day survival to 0.837 (95% CI 0.810-0.863) for PiPS-B predicting 14-day survival.[59]

Palliative Prognostic Index and its modifications. Palliative Prognostic Index (PPI) was originally developed and validated to predict 3- and 6-week survival in patients with advanced cancer.[50] PPI comprises partial scores in five domains: PPS, oral intake, oedema, dyspnoea and delirium. Scores range between 0 and 15; scores >6 indicate survival for <3 weeks and scores >4 indicate survival for <6 weeks (see Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101195).

PPI has been validated in various settings and has undergone some modifications. There are, however, no universally established cut-offs.[61] In initial evaluations, PPI predicted 3-week survival with a sensitivity of 83% and specificity of 85%, and 6-week survival with a sensitivity of 79% and specificity of 77%.[62] Subsequent studies confirmed that survival for PPI risk groups falls within expected ranges[53] and that risk categories show good discrimination.[63] However, a large prospective study ($N = 1833$) reported that PPI risk categories were less accurate than CPS (54.2% versus 62.5%, $P < 0.001$).[59] In contrast, a smaller, single-centre study involving 18 physicians reported that PPI scores showed greater discrimination at predicting 30-day survival than CPS.[64] In this study, PPI score was treated as a continuous variable and this was used to predict 30- or 100-day survival (rather than evaluating the previously created 3-week and 6-week cut-off points). In another study, three physicians working at one centre reported that the routine use of PPI improved the accuracy of CPS.[62]

Other prognostic tools. Feliu Prognostic Nomogram (FPN) is a multivariable risk prediction model[65] that uses readily available clinical and analytical information to predict probabilities of survival in patients with advanced cancer at 15, 30 and 60 days. The nomogram comprises ECOG PS, LDH, lymphocyte count, albumin level and time from initial diagnosis to diagnosis of terminal disease (see Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.101195). In the original validation studies, FPN discriminated between patients with 15-, 30- and 60-day survival probabilities with AUCs of 0.776, 0.778 and 0.774, respectively. Both clinicians and FPN made similar predictions about the probability of surviving 15, 30 or 60 days, which were compatible with observed proportions of patients surviving for these lengths of time.[59]

Comparative accuracy of prognostic tools

Studies comparing the accuracy of prognostic tools are limited and there is no consensus on the most appropriate methods to compare tools using different formats to predict survival (e.g. probabilities versus lengths of survival). A common metric is to compare discrimination using C-statistics or AUC values;[46,66] however, this does not always reflect the ways in which the prognostic scores were designed to be used, nor is it established what represents a clinically significant and important difference in prognostic discrimination.[54]

Two large multicentre cohort studies reported that PiPS and PaP may be superior to PPI[46,59] when compared using the same measures of discrimination. Where direct comparisons were possible,[59] PiPS-B performed better than PiPS-A and PPI. AUCs for PaP/D-PaP were significantly better than for PPI[46] and overall accuracy of short-term (e.g. death within 3 weeks) and long-term (e.g. death after >1 month) survival were generally similar (69%-81%).[46] Other (smaller) studies have also reported that the accuracy of PaP is superior to that of PPI, PPS and Objective Prognostic Score.[66-68] In contrast, a single institution study indicated that there was no significant difference in C-index between PaP, PPI and PPS scores.[69] Another study suggested that the Chinese Prognosis Scale had a significantly higher AUC than PPI,[70] and a validation study reported that FPN had a higher AUC than PaP scores.[65] Several small studies have suggested that the accuracy of prognostic tools depended on the circumstances in which the tools were used. For example, repeated use of PPI was found to be superior to single use on admission, and combined use of both PPI and changes in PPI score improved accuracy.[63,71]

Although discrimination (as measured using AUC or C-statistics) is an important consideration, there are other characteristics which are important for the evaluation of prognostic tools, particularly how well calibrated the tools are for use in the population for which they are intended. Another consideration is the feasibility of use in clinical practice (e.g. difficulty of calculating scores, obtaining CPS or collecting blood for analysis). It is also important to consider what the end users of prognostic scales actually want. Patients or HCPs may prefer qualitative or quantitative information, probabilistic or temporal predictions, with or without confidence limits (best-case and worst-case scenarios). Furthermore, prognostic models that are less accurate than CPS are unlikely to be of clinical use. Risk prediction models which have been shown to perform at least as well as CPS, however, may have other advantages. For example, they may be more objective, more reproducible and/or be capable of being calculated by non-experts. Thus, they may improve communication between health care teams, act as training aids for less experienced HCPs or act as a spur to improve communication regarding prognosis with patients or relatives. Future studies should therefore assess the impact of prognostic tools on clinical practice and decision making.

Recommendations

- In patients with advanced cancer who are no longer receiving DMT and with a prognosis of months to weeks:

- o Clinicians should use PPS or other measures of PS as a prognostic factor to distinguish between patients with advanced cancer and an expected survival of weeks to months, with varying survival prospects [III, A].
- o It is suggested that clinicians could preferentially use validated prognostic models (e.g. PaP, PiPS-B, FPN), which have been shown to be as accurate as predictions of survival by expert clinicians, to calculate individualised levels of risk [III, C].
- o The use of other prognostic tools may be considered in certain circumstances (e.g. when expert CPS is not available, when scores can be calculated using routinely available data or for research purposes) [V, C].
- o It is suggested that the choice of prognostic model should be influenced by the type of prognostic estimate desired (e.g. how long or how likely), the availability of required data (e.g. blood test results) and timeframe being predicted [III, C].
- o The authors conditionally advise against the use of individualised risk prediction models in isolation unaccompanied by clinician judgement of prognosis [V, D], and models should not be used by patients without guidance from an oncology or palliative care clinician [V, D].

PROGNOSTICATING IN PATIENTS WITH AN EXPECTED SURVIVAL OF DAYS

Patients often develop physiological changes when death is imminent,[72] and being able to identify imminent death may help clinicians to make appropriate care recommendations. In addition, for family members, knowing how long the dying process is likely to last and what changes to expect has practical implications.[73] For example, family members may want to know whether to stay another night so that the patient does not die alone.

Clinician predictions of impending death

In one study, palliative care nurses were reported to be highly accurate at predicting impending death (91% and 86% for 24-h and 48-h predictions, respectively).[74] In contrast, palliative care physicians were significantly less accurate (71% and 66% for 24-h and 48-h predictions, respectively). However, another study reported that predictions of death within the next 7 days were similarly accurate (79% and 77% for nurses and physicians, respectively).[3] The 3-day SQ is reported to have a sensitivity of 84%, specificity of 26%, PPV of 54%, negative predictive value (NPV) of 84% and overall accuracy of 59% ($N = 1411$ patients with PPS $\leq$20%).[75]

Prognostic factors

Many symptoms and signs increase in frequency as death approaches. A recent study ($N = 2131$) conducted in 38 palliative care units in three East Asian countries observed patients in the last 3 days of life.[76] The authors reported that fatigue, dry mouth, drowsiness and dyspnoea were the most frequent symptoms and lower body oedema was the most common sign as death approached. In a study of palliative cancer patients ($N = 178$), 'death rattle' was found to be a prognostic factor for death within 48 h with a PPV of 74% and NPV of 77%; altered level of consciousness was less predictive (PPV of 64% and NPV of 67%).[77] The observational Investigating the Process of Dying Study[78] systematically documented frequency and onset of 62 physical signs in 357 consecutive patients with cancer receiving palliative care from admission until death or discharge. Several 'early' signs (including PPS $\leq$20%, Richmond Agitation Sedation Scale ≥ -2 and dysphagia of liquids) had higher prevalence, relatively early onset (>3 days before death), moderate sensitivity and low positive likelihood ratio (LR) for impending death within 3 days. In contrast, multiple 'late' signs (physiological changes in neurological, neuromuscular, cardiovascular and respiratory systems) were identified with relatively low frequency, late onset (<3 days before death), high specificity and high positive LR for impending death within 3 days. When present, these signs suggested a high probability of death within the next 3 days; however, they had a low negative LR and thus their absence could not rule out impending death. Moreover, it is not clear whether these signs were better predictors than CPS. The same study reported a significant decrease in blood pressure and oxygen saturation and an increase in heart rate starting 2-3 days before death.[79] Many patients continued to have normal vital signs even on the last day of life, limiting the predictive utility of vital signs. One study reported that the typical sequence preceding death was for patients to stop eating and drinking (6 days before death), develop impaired consciousness (1.3 days before death) and then exhibit respiration with mandibular movement (12 h before death).[80]

Individualised risk prediction models

Several individualised risk prediction models for imminent death have been developed, but none has yet undergone independent external validation or comparison against CPS. Kao et al.[81] developed a prognostic model to predict death within 1 week of admission for patients with cancer receiving palliative care ($N = 459$; median survival 16 days). ECOG PS, liver cancer, male sex, lower extremity muscle power, lower systolic blood pressure, higher heart rate, higher haemoglobin and higher blood urea nitrogen were associated with a higher risk of death. Based on these findings, investigators developed an equation to compute the probability of surviving for up to 7 days. Hui and colleagues[82] initially developed a two-variable model (PPS and drooping nasolabial folds) for predicting imminent death. A subsequent, larger ($N = 1396$) prospective study involving palliative care inpatients with PPS $\leq$20 resulted in a three-variable model (urine output, response to verbal stimuli and agitation/sedation score)[83] which produced four prognostic categories for predicting death within 3 days (mortality rates of 80.3%, 53.3%, 39.9% and 20.6%). Nagasako et al.[84] constructed a three-variable model (CRP, albumin and

platelets) for predicting imminent death in patients with advanced cancer ($N = 991$; median survival 13 days). The model had a sensitivity of 18%, specificity of 98%, positive LR of 7.1 and negative LR of 0.84 for predicting death within 3 days of admission.

Conclusions

Studies suggest that certain physical signs, physiological variables and predictive models may inform the identification of imminently dying patients with relatively high accuracy (>80%). More research is needed to validate these findings and to compare them with simple clinician predictions of imminent death.

Recommendations

- In patients with advanced cancer and a prognosis of days:
  - o Clinician predictions should be used to identify patients in whom death is imminent [III, B].
  - o Late signs of impending death (e.g. pulselessness of the radial artery, hyperextension of the neck, respiration with mandibular movement, 'death rattle', drooping of the nasolabial fold) might be considered to aid the identification of impending death within 3 days [III, B].
  - o Clinicians should not use individualised risk prediction models in isolation unaccompanied by clinician judgement of prognosis [V, E].

COMMUNICATION REGARDING PROGNOSIS AND DECISION MAKING WITH PATIENTS

Once an HCP has formulated a prognosis using CPS or a prognostic algorithm, the information needs to be shared with patients and their families or caregivers. Prognostic information may relate to average properties of large groups (e.g. the spread of survival around the median for patients with a similar illness at a similar stage) or may be an individualised prediction about how long a particular patient will survive or how likely they are to survive for a specified time.

Use of prognostic information to inform shared decision making

In addition to a prediction of the length of survival, prognostic discussions may also be viewed as a joint platform where patients and HCPs can communicate and engage in shared decision making[85] and advance care planning.[86] Prognosis is more than raw data communicated by a doctor to a patient, but rather a construct shaped and refined by the patient in collaboration with their health care team. Shared decision making is the process of patients and clinicians establishing a partnership to help them make decisions about care consistent with patients' goals, priorities and preferences, as well as relying on the best information available from evidence-based health care.[87] This process includes different types of conversations which have been described as 'team talk' (setting the ground for working as a team), 'option talk' (comparing the possible options) and 'decision talk' (making decisions based on patient preferences). The conversations rely on adequate communication skills and active listening by clinicians (e.g. paying attention to verbal and non-verbal cues, showing signs of listening, asking for clarification, summarising).[87]

Decision making should not only be viewed as the consequence of available prognostic information. The decisions that patients make (e.g. to start, withhold or discontinue anticancer therapy) may themselves have an impact on future prognosis. This is particularly true for decisions about pain and symptom management, place of care, place of death, and more broadly, about how remaining time is prioritised by patients.[88] Prognosis (like health) does not pertain to characteristics of a disease only but to different ways in which a person might live and die with an illness. Therefore, discussions about prognosis and uncertainty may support patients in expressing what matters most to them and help to restore hope that they will not be subjected to treatments that are not aligned with their priorities.[85,86,88-90]

How to share and use prognostic information collaboratively

It is important to gauge a patient's baseline understanding of their prognosis and to ask about the type of information they would like to discuss. Some patients may prefer to learn about survival estimates for populations of patients with a similar disease, whereas others may be more interested in possible complications, symptoms and disabilities, or about best-case and worst-case scenarios. In addition, people have different preferences regarding how this information should be presented (e.g. numerical data, visual information, leaflets, video or narrative).[88,90-93]

Different models are available to support effective clinician communication with patients, i.e. tactfully, delicately, at the patient's pace, paying attention to emotional cues and allowing room for silence and expression of grief, fears, hopes and priorities.[94,95] Most models are based on active listening so it is important that clinicians limit how much they talk, deliver information in small understandable chunks and regularly pause to allow patients to express their feelings and ensure that they are not overloaded with information.[88] This is particularly important for patients with cognitive impairment and for whom a preliminary assessment of decision-making capacity is crucial. These principles are incorporated into the PREPARED model (Table 1).[93]

Paying attention to the 'emotions in the room' (i.e. taking time to identify, acknowledge and agree on them) requires clinicians to develop particular skills, and a few tools may help them do so.[96] Given the distressing nature of information shared during such conversations, clinicians should develop self-awareness, debrief with colleagues and allow time for 'housekeeping' between consultations.[97] It is also

Table 1. The PREPARED model of discussing prognosis and end-of-life issues with patients with cancer

P: prepare for the discussion, where possible	• Review the patient's clinical information, consider your own estimate of their prognosis and appropriate treatment options. Refer to prognostic tools or discuss with other members of the MDT, as appropriate • Try to ensure privacy and uninterrupted time for discussion • Mentally prepare yourself • Negotiate who should be present during the discussion
R: relate to the person	• Introduce yourself at new consultations, explain your role and develop rapport • Show empathy, care and compassion during the entire consultation • Consider cultural and contextual factors that may influence preferences • Use appropriate body language and actively listen
E: elicit patient preferences	• Clarify the patient's or caregiver's understanding of the situation and how much detail they are interested in before providing new medical information • Elicit the patient's goals, values and beliefs relevant to the discussion • Elicit the patient's priorities for care and preferences regarding current and future treatment • Explore the family's concerns and priorities, when applicable • Summarise the patient's and family's most important priorities and check you have understood correctly
P: provide information tailored to the needs of the individual patient and their family	• Ask permission to discuss what they should expect • Pace and tailor the delivery of information about the clinical situation and prognosis to the patient's and family's current understanding and wish for information • Use clear, jargon-free, understandable language • Explain the uncertainty, limitations and unreliability of prognostic information • Consider offering recommendations for the patient's medical care that are clinically appropriate and aligned with the patient's priorities
A: acknowledge emotions and concerns	• Explore and acknowledge the patient's and caregiver's fears and concerns and their emotional reaction to the discussion • Respond to the patient's or caregiver's distress, where applicable, and consider their needs for additional support • Acknowledge your own emotions; discussing prognosis and end-of-life issues is challenging
R: realistic hope should be fostered, e.g. peaceful death and support	• Be honest without being blunt or giving more detailed information than desired • Do not give misleading or false information to try to positively influence a patient's hope • Reassure the patient that all support and care will be provided to control pain and other symptoms • Explore and facilitate realistic goals, wishes and ways of coping on a day-to-day basis, when appropriate
E: encourage questions and additional discussions	• Encourage questions and clarification of information, and be prepared to repeat explanations • Check understanding and if the information provided meets their needs • Leave the door open for topics to be discussed again in the future
D: document	• Assist the patient to document his or her wishes for future care, if desired[a] • Write a summary of what has been discussed in the medical record • Speak or write to other key HCPs who are involved in the patient's care. At a minimum, this should include the patient's general practitioner

HCP, healthcare professional; MDT, multidisciplinary team.
[a]Refer to the rules and legislations pertaining to the capacity to make decisions regarding health care that prevail in each country.
Adapted with permission from Clayton J et al.[92] The complete guidelines can be downloaded from https://onlinelibrary.wiley.com/doi/abs/10.5694/j.1326-5377.2007.tb01100.x.

important to recognise that patients and their families need ongoing support and the opportunity for further conversations after the initial prognostic discussion has taken place.

Conclusions

Sharing information with patients about prognosis is a key component of quality cancer care. It allows for shared decision making and helps patients establish a degree of control by helping them to plan for meaningful ways of living with an incurable illness. Developing effective communication skills about prognosis with patients is a recommended core component of many oncology specialist curricula.

Recommendations

- In patients with advanced, incurable cancer and an expected prognosis of a few months or less:
  - o It is suggested that clinicians should clarify patients' understanding of their condition [V, B].
  - o Clinicians might start by asking patients about the type of information they want to learn about and how it should be presented to them [V, B].
  - o Clinicians might aim to identify, acknowledge and name emotions in response to patients' verbal and non-verbal cues [V, B].
  - o It is suggested that clinicians should allow room for silence during the conversation, control verbal flow and develop self-awareness [V, B].

BARRIERS TO IMPLEMENTATION AND RECOMMENDATIONS FOR FUTURE RESEARCH PRIORITIES

Developing and evaluating prognostic models is complex and time-consuming and is fraught with technical and practical difficulties. As a minimum, prognostic models need to

demonstrate parity with the accuracy of CPS, and several models and scores have already done so.[53,54,59] Additionally, before prognostic models are adopted in clinical practice, they need to demonstrate that they can be used to improve clinically important outcomes. Examples include whether the use of a proposed prognostic model results in greater patient or family satisfaction with communication or care, whether it improves decision making, bed utilisation, identification of patients for referral to palliative care services, the timing of withholding active treatments or the more effective use of palliative treatments. The best way to evaluate these outcomes is in the context of randomised, controlled trials (RCTs) in which new prognostic models are evaluated against standard practice (in this context, CPS). As yet, no such studies have been undertaken.[98]

It is important to recognise that greater accuracy does not necessarily equate to better prognostication. It is possible that some patients or families may regard overly precise survival estimates as being harmful. It is also important to consider how accurate estimates need to be; use of prognostic models without much thought, undue reliance on their accuracy or inappropriate application in populations for which they were not designed or evaluated in, could be potentially detrimental to patient care.

Recommendation

- In patients with advanced, incurable cancer and an expected prognosis of a few months or less, RCTs comparing the effect of different methods of prognostication (including CPS) on clinically important outcomes should be undertaken [V, A].

METHODOLOGY

This Clinical Practice Guideline (CPG) was developed in accordance with the ESMO standard operating procedures for CPG development (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2023.101195.[99] Statements without grading were considered justified standard clinical practice by the authors. Future updates to this CPG will be published on esmo.org as a Living Guideline version or an eUpdate, to be made available at: https://www.esmo.org/guidelines/guidelines-by-topic/supportive-and-palliative-care.

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