VOLUME 23 · NUMBER 25 · SEPTEMBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Prognostic Factors in Advanced Cancer Patients: Evidence-Based Clinical Recommendations—A Study by the Steering Committee of the European Association for Palliative Care

Marco Maltoni, Augusto Caraceni, Cinzia Brunelli, Bert Broeckaert, Nicholas Christakis, Steffen Eychmueller, Paul Glare, Maria Nabal, Antonio Viganò, Philip Larkin, Franco De Conno, Geoffrey Hanks, and Stein Kaasa

From the Palliative Care Unit, Department of Medical Oncology, Morgagni-Pierantoni Hospital, Forlì; Istituto Scientifico Romagnolo per lo Studio e Cura dei Tumori, Forlì-Meldola; Palliative Care Unit, National Cancer Institute, Milan, Italy; Faculty of Theology, Catholic University, Leuven, Belgium; Department of Health Care Policy, Harvard Medical School, Boston, MA; Department of Palliative Care, Kantonsspital, St Gallen, Switzerland; Department of Palliative Care, Royal Prince Alfred Hospital, Sidney, Australia; Hospital Universitario Arnau de Vilanova, Valencia, Spain; Palliative Care Division, McGill University, Montreal, Quebec, Canada; Centre for Nursing Studies, National University of Ireland, Galway, Ireland; Department of Palliative Medicine, University of Bristol, Bristol Hematology and Oncology Centre, Bristol, United Kingdom; and Department of Oncology and Radiotherapy, Trondheim University Hospital, Trondheim, Norway.

Submitted November 23, 2004; accepted April 19, 2005.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Marco Maltoni, MD, Palliative Care Unit, Department of Medical Oncology, Morgagni-Pierantoni Hospital, Via Forlanini, 34, 47100 Forlì, Italy; e-mail: ma.maltoni@ausl.fo.it.

0732-183X/05/2325-6240/$20.00

DOI: 10.1200/JCO.2005.06.866

ABSTRACT

Purpose
To offer evidence-based clinical recommendations concerning prognosis in advanced cancer patients.

Methods
A Working Group of the Research Network of the European Association for Palliative Care identified clinically significant topics, reviewed the studies, and assigned the level of evidence. A formal meta-analysis was not feasible because of the heterogeneity of published studies and the lack of minimal standards in reporting results. A systematic electronic literature search within the main available medical literature databases was performed for each of the following four areas identified: clinical prediction of survival (CPS), biologic factors, clinical signs and symptoms and psychosocial variables, and prognostic scores. Only studies on patients with advanced cancer and survival ≤ 90 days were included.

Results
A total of 38 studies were evaluated. Level A evidence-based recommendations of prognostic correlation could be formulated for CPS (albeit with a series of limitations of which clinicians must be aware) and prognostic scores. Recommendations on the use of other prognostic factors, such as performance status, symptoms associated with cancer anorexia-cachexia syndrome (weight loss, anorexia, dysphagia, and xerostomia), dyspnea, delirium, and some biologic factors (leukocytosis, lymphocytopenia, and C-reactive protein), reached level B.

Conclusion
Prognostication of life expectancy is a significant clinical commitment for clinicians involved in oncology and palliative care. More accurate prognostication is feasible and can be achieved by combining clinical experience and evidence from the literature. Using and communicating prognostic information should be part of a multidisciplinary palliative care approach.

J Clin Oncol 23:6240-6248. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Besides being one of the core skills in the practice of medicine,[1,2] prognostication in advanced cancer has special importance. In advanced phases of the disease, prognostication cannot be based on the same information as in earlier stages, when it is typically based on tumor stage.[3-5] However, accurate prediction of survival is still necessary for clinical, organizational, and ethical reasons, especially in helping to avoid harm, discomfort, and inappropriate therapies in vulnerable patients[6] and, conversely, in planning specific care strategies. Additionally, important personal decisions are influenced by

Table 1. Literature Search Strategy

Limits: human full article studies and English language publications
1. Strategy used to search for articles on advanced cancer patients
(Neoplasms (MesH term all subheadings) OR cancer (tw+) OR tumor (tw) OR tumour (tw) OR oncolog* (tw)) AND (terminal care (MesH term all subheadings) OR terminally ill (MesH term all subheadings) OR palliative care (MesH term all subheadings) OR hospices (MesH term all subheadings)
2. Strategy used to search for articles on prognosis
incidence (MesH term) OR mortality (MesH term all subheadings) OR follow-up studies (MesH term) OR mortality (subheading) OR prognosis* (tw) OR predict (tw) OR course (tw)
3. One of the following strategies used to search for articles on a specific topic
Prediction (Mesh term and tw)
Symptoms (Mesh term and tw)
Performance status tw
Biological factors (Mesh term and tw)
Prognostic score (tw) OR prognostic index (tw)
1 AND 2 AND 3

Abbreviation: tw, text word.

prognostic information, and therefore, patients' autonomy can be enhanced by providing better prognostication within the context of appropriate communication.[7-9]

Prognostic accuracy in this population seems to be the exception rather than the rule. A large prospective cohort study, involving 343 doctors and 468 hospice outpatients, found that only 20% of prognoses were accurate and that, overall, doctors overestimated survival by a factor of approximately 5.[10] Therefore, the Research Network of the European Association for Palliative Care decided to establish a Working Group (WG) with the aim of providing evidence-based recommendations on the use of prognostic factors to determine length of survival in advanced cancer patients.

METHODS

The WG reviewed several sources describing the clinical guidelines development process,[11-14] and the following steps were adopted: (1) defining group membership; (2) identifying the target population; (3) defining the key questions; (4) systematically searching the literature; (5) assigning the level of evidence to the selected literature; and (6) formulating and grading the final recommendations.

Defining Group Membership

WG members were identified on the basis of their clinical experience in palliative care and in prognostic cancer studies (M.M., A.C., N.C., S.E., P.G., M.N., and A.V.). Members with epidemiologic and statistical expertise were also enlisted (C.B., P.G., and A.V.), and the contribution of an experienced nursing person was ensured (P.L.). Practical and ethical considerations determined the exclusion of patients. Sociologic and philosophical points of view were available (B.B. and N.C.). Finally, the group conclusions were submitted to external reviewers (F.D.C., G.H., and S.K.) and to the Steering Committee of the European Association for Palliative Care Research Network.

Identifying the Target Population

Accepted criteria for staging advanced cancer patients are lacking. Some authors have attempted to describe, with subjective criteria, inception cohorts,[15-19] whereas others have examined patient populations referred to a palliative care program.[20,21] However, many studies have shown that the median survival in populations of advanced cancer patients undergoing palliative care is less than 90 days.[15,22-24] For these reasons, only populations homogeneous by survival (survival cohort)[25] were included by selecting studies in which the median survival of the group was $\leq$ 90 days, excluding surgical series.

Defining the Key Questions

The WG defined six key questions, which developed into recommendations, that were assigned to different pairs of group members to carry out a literature search and analyze the available evidence about the usefulness of an accurate prognostication of life expectancy in advanced cancer patients, the prognostic role of clinical signs and symptoms, psychosocial characteristics, laboratory parameters, and prognostic scores.

Systematic Literature Search

Systematic reviews were performed for each area of interest. The search for relevant articles was performed on the Medline and Embase databases. The search strategy is presented in Table 1. A hand search of the References section of electronically identified articles was also performed. Articles not based on original data (unless formal meta-analyses) were excluded.

Table 2. Checklist of Quality Criteria for Study Evaluation*

Checklist
1. Prospective study design
2. Well-defined cohort of patients assembled at a common point in the course of their disease
3. Random patient selection
4. Percentage of patients lost to follow-up $\leq$ 20%
5. Ratio between the number of events (death) and the number of potential predictors $\geq$ 10
6. Prognostic variables fully defined, accurately measured, and available for all or a high proportion of patients
7. Reliable measurement of outcome (date of death)

*High quality (or low probability of bias) is attributed to studies fulfilling at least five of seven criteria.

Table 3. Classification of Study Type

1.	Impact studies: studies aiming at evaluating the clinical benefit of implementing a prognostic strategy; these studies should have a randomized controlled design
2.	Formal meta-analysis of cohort studies
3.	Confirmative cohort studies: the main aim is to evaluate the agreement between actual and predicted survival by the prospective application of indices and/or to test if a prognostic model still maintains its strength in a different sample of patients
4.	Explorative cohort studies: the main aim is to examine how the predictive power of a new prognostic factor relates to those factors already available and/or to estimate the magnitude of its effect
5.	Investigative cohort studies: the main aim is to investigate the association of putative new factors with survival
6.	Nonanalytic studies (case reports/case series)

A formal meta-analysis was not conducted because of the great heterogeneity of the combinations of different prognostic factors examined,[17,26,27] poor quality of published studies, and frequent lack of minimal standards in reporting results. The prognostic strength of each predictor examined was described considering the hazard ratios and their CIs. A detailed report of all the hazard ratios and their CIs will be presented elsewhere.

Assigning the Level of Evidence to the Selected Literature

The level of evidence attributed to the results from each study was based on the methodologic quality of the study and on the study type.[11-13] A quality assessment checklist, based on the existing literature,[12,28-35] was formulated (Table 2). When evaluating meta-analyses, homogeneity of results was required to ensure quality. The study type classifications are listed in Table 3.[12,29,31] Quality and study type classification levels were combined to give the final level of evidence (Table 4, modified from the Centre for Evidence Based Medicine Web site).[12] Each study was evaluated independently by at least two group members.

Formulating and Grading the Final Recommendations

The evidence available for each topic, graded as shown in Table 4, was developed into draft recommendations by a writing committee, circulated to the full WG and to the external reviewers, and finalized into the present format.

RESULTS

The literature review produced a list of publications, which are listed in Table 5, that show the quality and characteristics of the evidence that was used to formulate the following recommendations (listed in brief in Table 6).

Recommendations

Recommendation 1. In the management of the patient with advanced cancer, physicians should base their decisions about therapeutic interventions and the place and type of care on the preferences and expectations of patients and their care givers as well as the life expectancy of the patient. Prognosis will sometimes determine access to specialist services, and an accurate estimate of life expectancy will generally facilitate decision making both for professional care givers and for patients and their families (grade D).

There is no study on prognostic factors aimed at evaluating whether an accurate prediction of survival can improve actual clinical care; that is, there is no impact study concerning the role of prognostic tools in improving decision making in the palliative care of advanced cancer. Despite this, it is the opinion of the WG that increased prognostic accuracy would assist health professionals to improve their care strategy and help patients and families to make more informed choices.[10,22,23,65]

Recommendation 2. The Clinical Prediction of Survival (CPS) is a generally useful and valid tool but is subject to a series of factors that limit its accuracy. The CPS should not be used alone but in conjunction with other prognostic factors (grade A).

CPS could be defined as clinical prognostic judgment;

Table 4. Classification of the Level of Evidence and Grading of the Strength of the Recommendations

Level of evidence	
I	Impact studies with low risk of bias* or homogeneous† meta-analyses
II	Heterogeneous meta-analyses or confirmatory studies with a low risk of bias*
III	Exploratory studies with a low risk of bias
IV	Any type of study with a high risk of bias, or investigative studies or nonanalytic studies
V	Experts' opinion
Grading of the strength of the recommendations	
A	Consistent level I or II studies
B	Consistent level III studies or one level II study
C	One level III study or consistent level IV studies
D	Level V evidence or inconsistent or inconclusive studies of any level

*Low risk of bias means at least five of seven quality criteria listed in Table 2 are satisfied.
†See text.

Table 5. Results of the Literature Review Used for Developing the Recommendations

Prognostic Factor Area Considered	No. of Articles Selected	% of Total No. of Articles Identified	Selected Studies		No. of Patients	No. of Quality Criteria Points Fulfilled*	Study Type	Level of Evidence
			Reference	Year				
Clinical prediction	16	59	Christakis and Lamont[10]	2000	468	6	Inv	IV
			Llobera et al[15]	2000	200	6	Expl	III
			Faris[16]	2003	162	4	Expl	IV
			Maltoni et al[18]	1995	503	6	Expl	III
			Bruera et al[20]	1992	47	4	Inv	IV
			Parkes[36]	1972	42	5	Inv	IV
			Evans and McCarthy[37]	1985	45	6	Inv	IV
			Heyse-Moore and Johnson-Bell[38]	1987	50	6	Inv	IV
			Forster and Lynn[39]	1988	108	5	Inv	IV
			Maltoni et al[40]	1994	100	6	Inv	IV
			Oxenham and Cornbleet[41]	1998	41	5	Inv	IV
			Pirovano et al[42]	1999	519	7	Expl	III
			Glare and Virik[43]	2001	100	7	Conf	II
			Morita et al[44]	2001	150	5	Conf	II
			Tanneberger et al[45]	2002	269	5	Inv	IV
			Higginson and Constantini[46]	2002	275	6	Inv	IV
Physical and psychological symptoms and signs	20	25	Llobera et al[15]	2000	200	6	Expl	III
			Faris[16]	2003	162	4	Expl	IV
			Maltoni et al[18]	1995	503	6	Expl	III
			Bruera et al[20]	1992	47	4	Expl	III
			Evans and McCarthy[37]	1985	45	6	Inv	IV
			Maltoni et al[40]	1994	100	6	Inv	IV
			Forster and Lynn[47]	1989	111	5	Expl	III
			Heyse-Moore et al[48]	1991	303	5	Inv	IV
			Hardy et al[49]	1994	107	6	Expl	III
			Vitetta et al[50]	2001	102	4	Expl	IV
			Mor et al[51]	1984	685	6	Expl	IV
			Reuben et al[52]	1988	1,592	6	Expl	III
			Schonwetter et al[53]	1989	172	5	Inv	IV
			Rosenthal et al[54]	1993	148	6	Expl	III
			Allard et al[55]	1995	1,081	6	Inv	IV
			Tamburini et al[56]	1996	100	5	Inv	IV
			Morita et al[57]	1999	150/95	5	Conf	II
			Caraceni et al[58]	2000	393	6	Expl	III
			Pasanisi et al[59]	2001	76	3	Inv	IV
Biologic factors	9	28	Rodrigus et al[60]	2001	250	4	Expl	IV
			Faris[16]	2003	162	4	Expl	IV
			Pirovano et al[42]	1999	519	7	Expl	III
			Forster and Lynn[47]	1989	111	5	Expl	III
			Rosenthal et al[54]	1993	148	6	Expl	III
			Pasanisi et al[59]	2001	76	3	Inv	IV
			Maltoni et al[61]	1997	530	7	Expl	III
			Maltoni et al[62]	1999	451	7	Conf	II
			Geissbuhler et al[63]	2000	161	6	Expl	III
			McMillan et al[64]	2001	404	5	Expl	III
Prognostic score	8	33	Yun et al[19]	2001	91	6	Expl	III
			Bruera et al[20]	1992	47	4	Inv	IV
			Morita et al[21]	1999	150/95	5	Expl	III
			Pirovano et al[42]	1999	519	7	Expl	III
			Glare and Virik[43]	2001	100	7	Conf	II
			Morita et al[44]	2001	108	5	Conf	II
			Caraceni et al[58]	2000	393	6	Conf	II
			Maltoni et al[62]	1999	451	7	Conf	II

NOTE. Some articles have a certain level of evidence for a given parameter and another level for a different factor.
Abbreviations: Inv, investigative; Expl, explorative; Conf, confirmative.
*There are seven quality criteria points (listed in Table 2). Five of seven points is considered to be the minimum level acceptable for a low risk of bias.

Table 6. Recommendations Synopsis

Recommendation 1
In advanced cancer patient management, physicians should base their decisions about therapeutic interventions and settings of care considering both quality of life and life expectancy (grade D)
An accurate prognostication of life expectancy will facilitate decision making both for professional careers and for patients and their families (grade D)
Recommendation 2
The clinical prediction of survival is a valid tool to obtain a general prognostic evaluation of patients (grade A), but it is subject to a series of factors that limits its accuracy (see text); its use is recommended together with other prognostic factors (grade A)
Recommendation 3
Clinicians can use a number of clinical signs and symptoms that have proven to be associated with life expectancy in this patient population: performance status (grade B), cancer anorexia-cachexia syndrome signs and symptoms (grade B), dyspnea (grade B), and cognitive failure or delirium (grade B)
Recommendation 4
Clinicians can use some laboratory variables associated with life expectancy: leukocytosis (grade B), lymphocytopenia (grade B), and high C-reactive protein (grade B).
The need for a blood sample should be balanced with the clinical advantage that is envisaged and never taken lightly (grade D)
Recommendation 5
Clinicians can make use of some easily applicable prognostic scores to make a rapid prediction capable of identifying classes of patients with significantly different life expectancies (grade A)
At the moment, the Palliative Prognostic Score is the more readily available system including most of the factors (grade A)
Recommendation 6
Establishing a prognosis is part of the therapeutic alliance; patients have the right to be informed or not to be informed about their prognosis
Using and communicating prognostic information should be within the context of a comprehensive, individualized, patient-centered approach (grade D)

it is subjective and depends on the clinician's assessment of the individual patient at the bedside or in the clinic. The prognostic value of CPS has received a great deal of criticism in the literature because of the characteristics previously mentioned and because of its inherent nonreproducibility.

Our systematic review of the literature on CPS resulted in the selection of 27 articles, 11 of which were excluded. In the 16 eligible studies,[10,15,16,18,20,36-46] the correlation coefficient of CPS/actual survival varied between 0.2 and 0.65. In all the studies examined in a review published in 2000, CPS was reported as having an independent effect when used with most other prognostic factors or tools.[5] When using CPS, physicians need to be aware that it is subject to a series of features and shortcomings that limit its prognostic capacity. CPS is more than twice as likely to be overoptimistic versus overpessimistic and to overestimate the length of actual survival by a factor of between 3 and 5 (grade A).[26] CPS is subject to the Horizon Effect[24,66,67] (grade B), which is a term taken from the language of weather forecasting and used in clinical prognostication to mean the greater accuracy of short-term predictions over long-term predictions. Therefore, repeated evaluations of CPS at fixed intervals may be opportune (grade A). Considering CPS as a probability rather than a temporal value would ensure a greater accuracy (grade A). Lack of experience in oncology and palliative care reduces accuracy, and thus, a second opinion by a more experienced professional could be useful (grade D). A second opinion could also be worth obtaining if the first physician has a close relationship with the patient (grade B).

Clinicians should consider using CPS in combination with other prognostic factors or scores to improve the accuracy of their predictions (grade A). Training in prognostication could improve the accuracy of CPS (grade D).

Recommendation 3. Certain clinical signs and symptoms have proven to be prognostically significant in this patient population, the most important of which are performance status (grade B), some symptoms of the cancer anorexia-cachexia syndrome (CACS; grade B), dyspnea (grade B), and delirium or cognitive failure (grade B). Factors linked to the patient or to the primary/metastatic site and biologic characterization of the tumor do not seem to be prognostically important in advanced cancer, as defined in this review.[15,16,18,47-50] Conversely, a correlation between some clinical signs and symptoms and survival has been confirmed in numerous multivariate analyses. In this section, of the 80 works analyzed, the 20 studies considered[15,16,18,20,37,40,47-60] show that performance status[18,37,40,47,51,52,54,57,59] and various indices of activity and functional autonomy[15,16,49,50,53,55] are prognostically significant. In particular, low performance status is considered a reliable prognostic factor to predict short-term survival. However, initially high scores are not necessarily predictive of a long survival, whereas their deterioration often indicates a serious worsening of the prognosis.[18,20-22,40,42,47,51-56]

Signs and symptoms characterizing a clinical condition that is often termed the common terminal pathway,[54,69,70] including nutritional status and CACS, anorexia,[18,21,53,54,56] weight loss,[17,18,20,52,57] dysphagia and difficulty in swallowing,[18,20,21,52] and xerostomia,[18,20,52,56] have a prognostic impact. Finally, there is significant evidence of the prognostic importance of dyspnea[18,48-50,52,57] and delirium or cognitive impairment.[20,47,57,58,60]

Other signs and symptoms (nausea, constipation, dizziness, anxiety, depression, fever, pain, diarrhea, hemorrhage,

pulse, and respiratory rate), polymorbidity, opioid therapy, and therapeutic and diagnostic interventions[18,20,47,50,52,54,59] have occasionally proven to be significant, mainly in less advanced stages of the disease. However, these symptoms have not been confirmed in multivariate analysis, especially in the far advanced patient population.

The prognostic capacity of subjective indicators of quality of life or other psychological parameters is somewhat contradictory. Although they are certainly relevant in the earlier stages of disease,[71-78] the prognostic relevance of multidimensional tools in patient populations with a median survival of 90 days or less seems to be attributable to the physical-symptomatic component of the test.[15,56]

Recommendation 4. There is some evidence that abnormalities in certain laboratory tests (particularly leukocytosis, lymphocytopenia, and elevated C-reactive protein) have prognostic significance (grade B). The need for a blood sample also needs to be weighed against the likely clinical advantage for the individual patient (grade D). Biologic parameters have not been as widely investigated as clinical parameters in this population of patients,[5] and a more accurate evaluation of these variables in relation to prognosis is undoubtedly warranted.

In the present review, a total of 23 biologic factors were studied in the nine works[16,42,47,54,59,61-64] selected for assessment. Laboratory parameters that proved significant in at least one multivariate analysis were low pseudocholinesterase,[61] high vitamin B_{12},[63] and high bilirubin.[54] Statistical significance in more than one study was observed for elevated C-reactive protein,[63,64] lymphocytopenia,[42,61] and leukocytosis.[42,61] The same biologic parameters also proved to be prognostically valid in other heterogeneous populations of patients with less advanced disease. This positive relationship was, conversely, lost by some factors, such as low serum albumin, in the patient population evaluated in the present study. For some factors, such as albumin and prealbumin levels, this could be attributed to a close correlation with other CACS characteristics that maintain their significance, to the detriment of weaker factors.

Recommendation 5. A number of prognostic scores or indices have been developed that are easy to use and permit a rapid estimate of life expectancy by placing patients into broad groups that differ significantly in survival (grade A). Some authors have built and validated prognostic scores for patients in palliative care programs. These scores are constructed on the basis of prognostic factors that have proven to be significant in multivariate analysis and have been validated quantitatively on the basis of their individual prognostic weight.

Only eight of the 24 studies identified satisfied the review requirements. Of these studies, four involved construction and development of scores,[19-21,42] whereas four concerned the validation of two of the scores, the Palliative Prognostic (PaP) Score and the Palliative Prognostic Index (PPI).[43,44,58,62] The PaP Score (Table 7) was built and validated in two independent multicenter population studies and is the only measure to include some simple biologic factors that require a blood sample. It has been validated in several countries, in various settings, and in different disease phases.[23,42,43,58,62] This score includes CPS, which means that it is used together with, rather than instead of, clinical judgment. The PaP Score was not constructed to include hematologic malignancies and, therefore, cannot be used in this patient population. Furthermore, the score does not include delirium, which was subsequently demonstrated to subdivide each population categorized by the PaP Score into two further prognostic subgroups.[58]

Table 7. Palliative Prognostic Score*

Prognostic Factor	Partial Score
Dyspnea	
Absent	0
Present	1
Anorexia	
Absent	0
Present	1.5
Karnofsky performance status	
≥ 50	0
30-40	0
10-20	2.5
Clinical prediction of survival	
> 12 weeks	0
11-12 weeks	2.0
9-10 weeks	2.5
7-8 weeks	2.5
5-6 weeks	4.5
3-4 weeks	6.0
1-2 weeks	8.5
Total WBC count (cell/mm^3)	
Normal: 4,800-8,500 cells/μL	0
High: 8,501-11,000 cells/μL	0.5
Very high: > 11,000 cells/μL	1.5
Lymphocyte percentage	
Normal: 20.0%-40.0%	0
Low: 12.0%-19.9%	1.0
Very low: 0%-11.9%	2.5

NOTE. The risk groups and total scores were as follows: group A: 30-day survival probability of > 70%, score = 0 to 5.5; group B: 30-day survival probability of 30% to 70%, score = 5.6 to 11.0; and group C: 30-day survival probability of < 30%, score = 11.1 to 17.5.

*Palliative Prognostic Score = dyspnea score + anorexia score + Karnofsky performance status score + clinical prediction of survival score + total WBC count score + lymphocyte percentage score.

The PPI does not include CPS, and one study specifically aimed at evaluating the impact of PPI on CPS[44] showed a significant improvement in prognostication. No studies have ever been conducted to compare the efficacy of different scores.

Recommendation 6. Establishing an accurate prognosis is part of the therapeutic alliance. Patients have a right to be informed of their prognosis or, if they prefer, not to be informed. Using and communicating prognostic information

Table 8. Factors Subdivided on the Basis of Level of Evidence Obtained by a Correlation With Actual Survival and, Therefore, According to Their Prognostic Capacity in the Selected Population

Factors for which a definite correlation with prognosis has been identified
Clinical prediction of survival
Performance status
Signs and symptoms of cancer anorexia-cachexia syndrome (anorexia, weight loss, dysphagia, and xerostomia)
Delirium
Dyspnea
Some biologic factors (leukocytosis, lymphocytopenia, and C-reactive protein)
Prognostic scores
Factors for which a correlation has been indicated but not confirmed or for which a statistical significance has been identified in patient populations with less advanced disease or for which contradictory data have emerged
Pain
Nausea
Tachycardia
Fever
Neoplastic pattern (primary and secondary sites)
Comorbidity
Anemia
Hypoalbuminemia
Prehypoalbuminemia
Proteinuria
Serum calcium level
Serum sodium level
Lactate dehydrogenase and other enzymes
Patient characteristics (age, sex, and marital status)
Factors with controversial indications
Multidimensional quality-of-life questionnaires; it is possible that their prognostic capacity is a result of the identifying component of physical symptoms contained within them

should be within the context of a comprehensive, individualized, patient-centered approach (grade D).

A number of principles should be applied to this clinical situation. First, do not be a burden to the patient. From an ethical point of view, it is important that prognostic tools do not impose an additional burden on the patient, be it directly or indirectly (ie, by being time consuming and, thus, leaving less time for other aspects of patient care).

Second, use prognostic information within an ethically valid approach. It is important to understand that a prognosis is established, used, and communicated. Although our recommendations concentrate on establishing a prognosis, we should not forget that, once established, a prognosis should be used in an appropriate way. Treatment decisions should be based on a number of variables, including prognosis, and all these variables should receive due attention. The fact that prognostic information is, by definition, probabilistic, and that even the best prognostication will be dramatically inaccurate for a significant number of patients provides an additional reason for never losing sight of the patient and his or her individual trajectory and personal history. Prognostication that is not deeply embedded in an open, flexible, patient-centered, and dialogic approach is potentially dangerous.

Third, communicate prognosis when requested and in an appropriate way. Patients have a right to be informed about their prognosis, but they also have the right to refuse to be informed. When prognosis is communicated, ethical, cultural, religious, and psychological considerations are of fundamental importance to avoid inflicting additional harm to the patient.

Fourth, place emphasis on a holistic therapeutic approach beyond time limits. It is only by working within the realms of multidisciplinary palliative care and by continuing to consider the individual value of the patient's residual life that life expectancy prognostication can improve and further personalize the care of advanced cancer patients.

DISCUSSION

The recommendations made here are confined to a population of patients with advanced cancer and a median survival of no more than 90 days. The WG demonstrated that, given the available literature evidence, prognostication of life expectancy in advanced cancer patients is feasible and facilitated by the use of clinical tools such as signs and symptoms, laboratory examinations, and prognostic scores. In particular, strong evidence of prognostic significance has emerged for CPS, performance status, clinical symptoms of CACS (anorexia, weight loss, dysphagia, and xerostomia), dyspnea, delirium, some biologic factors (leukocytosis,

lymphocytopenia, and C-reactive protein level), and prognostic scores (Table 8).

More research is needed to deepen our understanding of the processes leading to clinical prediction and of how it can be improved and refined by the help of other explicit, objective evaluations.[79,80] The lack of evidence from impact studies supporting the usefulness of better prognostic tools for advanced cancer patients should also be underlined as an urgent area for research. Therefore, health workers involved in the care of advanced cancer patients are encouraged to use their clinical skills, together with evidence-based recommendations, to elaborate their own prediction of individual patient survival. The systematic use of prognostic scores can teach clinicians to focus their attention on prognosis and, at the same time, help in the clinical management of the patient. Therefore, these scores can be considered useful tools for health workers in clinical practice.

It is important to point out that prognostic information should not be limited to palliative care populations, but it can also be used to gain a better understanding of patient survival before referral for palliative care. More studies on well-defined inception cohorts are needed to improve our knowledge in this field.

Finally, it is clear to the WG that ethical considerations regarding prognostication at the end of life are indeed of fundamental importance. The failure to prognosticate or to prognosticate accurately can, in some circumstances, be as harmful as a mistaken diagnosis or therapy. The fallibility of prognosis alone highlights its moral dimensions.

Acknowledgment

We thank Gráinne Tierney for editing the manuscript.

Appendix

Members of the Steering Committee of the Research Network of the European Association of Palliative Care who also contributed to this study include the following: F. De Conno (Chair), H. Huyer Abu-Saad, A. Caraceni, N. Cherny, C.J. Furst, J. Ferraz Gonçalves, G.W. Hanks, S. Kaasa, P. Klepstad, M. Lloyd Williams, S. Mercadante, J.M. Nunez Olarte, P. Poulain, L. Radbruch, C. Ripamonti, F. Strasser, and A. Tuca i Rodriguez.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

REFERENCES

1. Hippocrates: Hippocrates, With an English Translation by WHS Jones. London, United Kingdom, William Heinemann Ltd, 1931

2. Christakis NA: Death Foretold: Prophecy and Prognosis in Medical Care. Chicago, IL, University of Chicago Press, 1999

3. Lamont EB, Christakis NA: Complexities in prognostication in advanced cancer. JAMA 290: 98-104, 2003

4. Surveillance Epidemiology and End Results: SEER cancer statistics review, 1975-2001. http://seer.cancer.gov/csr/1975_2001/

5. Viganò A, Dorgan M, Buckingham J, et al: Survival prediction in terminal cancer patients: A systematic review of the medical literature. Palliat Med 14:363-374, 2000

6. Earle CC, Neville BA, Landrum MB, et al: Trends in the aggressiveness of cancer care near the end of life. J Clin Oncol 22:315-321, 2004

7. Parkes CM: Commentary: Prognoses should be based on proved indices not intuition. BMJ 320:473, 2000

8. Weeks JC, Cook EF, O'Day SJ, et al: Relationship between cancer patients' predictions of prognosis and their treatment preferences. JAMA 279:1709-1714, 1998

9. Fischer GS, Tulsky JA, Arnold RM: Communicating a poor prognosis, in Portenoy RK, Bruera E (eds): Topics in Palliative Care, Vol 4. Oxford, United Kingdom, Oxford University Press, 2000, pp 75-89

10. Christakis NA, Lamont EB: Extent and determinants of error in doctors' prognoses in terminally ill patients: Prospective cohort study. BMJ 320:469-472, 2000

11. Scottish Intercollegiate Guideline Network: SIGN 50: A guideline developers' handbook. http://www.sign.ac.uk/guidelines/fulltext/50/index.html

12. Centre for Evidence Based Medicine: Levels of evidence and grades of recommendation. http://www.cebm.net/levels_of_evidence.asp

13. Programma Nazionale Linee Guida: Manuale Metodologico Istituto Superiore di Sanità 2004. http://www.pnlg.it/doc/manuale.htm

14. Shekelle PG, Woolf SH, Eccles M, et al: Clinical guidelines: Developing guidelines. BMJ 318:593-596, 1999

15. Llobera J, Esteva M, Rifa J, et al: Terminal cancer: Duration and prediction of survival time. Eur J Cancer 36:2036-2043, 2000

16. Faris M: Clinical estimation of survival and impact of other prognostic factors on terminally ill cancer patients in Oman. Support Care Cancer 11:30-34, 2003

17. Viganò A, Bruera E, Jhangri GS, et al: Clinical survival predictors in patients with advanced cancer. Arch Intern Med 160:861-868, 2000

18. Maltoni M, Pirovano M, Scarpi E, et al: Prediction of survival of patients terminally ill with cancer: Results of an Italian prospective multicentric study. Cancer 75:2613-2622, 1995

19. Yun HY, Heo DS, Heo BY, et al: Development of terminal cancer prognostic score as an index in terminally ill cancer patients. Oncol Rep 8:795-800, 2001

20. Bruera E, Miller MJ, Kuehn N, et al: Estimate of survival of patients admitted to a palliative care unit: A prospective study. J Pain Symptom Manage 7:82-86, 1992

21. Morita T, Tsunoda J, Inoue S, et al: The Palliative Prognostic Index: A scoring system for survival prediction of terminally ill cancer patients. Support Care Cancer 7:128-133, 1999

22. McCusker J: The terminal period of cancer: Definition and descriptive epidemiology. J Chronic Dis 37:377-385, 1984

23. Glare P, Christakis N: Predicting survival in patients with advanced disease, in Doyle D, Hanks G, Cherny N, et al (eds): Oxford Textbook of Palliative Medicine (ed 3). Oxford, United Kingdom, Oxford University Press, 2004, pp 29-42

24. Viganò A, Dorgan M, Bruera E, et al: The relative accuracy of the clinical estimation of the duration of life for patients with end of life cancer. Cancer 86:170-176, 1999

25. Altman DG: Systematic reviews of evaluations of prognostic variables, in Egger M, Davey Smith G, Altman DG (eds): Systematic Reviews in Health Care: Meta-Analysis in Context (ed 2). London, United Kingdom, BMJ Books, 2001, pp 228-247

26. Glare P, Virik K, Jones M, et al: A systematic review of physicians' survival predictions in terminally ill cancer patients. BMJ 327:195-200, 2003

27. Chow E, Harth T, Hruby G, et al: How accurate are physicians' clinical predictions of survival and the available prognostic tools in estimating survival times in terminally ill cancer patients? A systematic review. Clin Oncol (R Coll Radiol) 13:209-218, 2001

28. Riley RD, Abrams KR, Sutton AJ, et al: Reporting of prognostic markers: Current problems and development of guidelines for evidence-based practice in the future. Br J Cancer 88:1191-1198, 2003

29. McGinn TG, Guyatt GH, Wyer PC, et al: Users' guides to the medical literature: XXII. How to use articles about clinical decision

rules—Evidence-Based Medicine Working Group. JAMA 284:79-84, 2000

30. Altman DG, Lyman GH: Methodological challenges in the evaluation of prognostic factors in breast cancer. Breast Cancer Res Treat 52: 289-303, 1998

31. Drew PJ, Ilstrup DM, Kerin MJ, et al: Prognostic factors: Guidelines for investigation design and state of the art analytical methods. Surg Oncol 7:71-76, 1998

32. Altman DG: Systematic reviews of evaluations of prognostic variables. BMJ 323:224-228, 2001

33. Randolph AG, Guyatt GH, Calvin JE, et al: Understanding articles describing clinical prediction tools: Evidence Based Medicine in Critical Care Group. Crit Care Med 26:1603-1612, 1998

34. Simon R, Altman DG: Statistical aspects of prognostic factor studies in oncology. Br J Cancer 69:979-985, 1994

35. Laupacis A, Wells G, Richardson WS, et al: How to use an article about prognosis: Evidence-Based Medicine Working Group. JAMA 272:234-237, 1994

36. Parkes CM: Accuracy of predictions of survival in later stages of cancer. BMJ 2:29-31, 1972

37. Evans C, McCarthy M: Prognostic uncertainty in terminal care: Can the Karnofsky index help? Lancet 1:1204-1206, 1985

38. Heyse-Moore LH, Johnson-Bell VE: Can doctors accurately predict the life-expectancy of patients with terminal cancer? Palliat Med 1:165-166, 1987

39. Forster LE, Lynn J: Predicting life span for applicants to inpatient hospice. Arch Intern Med 148:2540-2543, 1988

40. Maltoni M, Nanni O, Derni S, et al: Clinical prediction of survival is more accurate than the Karnofsky performance status in estimating life span of terminally-ill cancer patients. Eur J Cancer 30A:764-766, 1994

41. Oxenham D, Cornbleet MA: Accuracy of prediction of survival by different professional groups in a hospice. Palliat Med 12:117-118, 1998

42. Pirovano M, Maltoni M, Nanni O, et al: A new palliative prognostic Score: A first step for the staging of terminally ill cancer patients—Italian Multicenter and Study Group on Palliative Care. J Pain Symptom Manage 17:231-239, 1999

43. Glare P, Virik K: Independent prospective validation of the PaP Score in terminally ill patients referred to a hospital-based palliative medicine consultation service. J Pain Symptom Manage 22:891-898, 2001

44. Morita T, Tsunoda J, Inoue S, et al: Improved accuracy of physicians' survival prediction for terminally ill cancer patients using the Palliative Prognostic Index. Palliat Med 15:419-424, 2001

45. Tanneberger S, Malavasi I, Mariano P, et al: Planning palliative or terminal care: The dilemma of doctors' prognoses in terminally ill cancer patients. Ann Oncol 13:1320-1322, 2002

46. Higginson IJ, Costantini M: Accuracy of prognosis estimates by four palliative care teams: A prospective cohort study. BMC Palliat Care 1:1-5, 2002

47. Forster LE, Lynn J: The use of physiologic measures and demographic variables to predict longevity among inpatient hospice applicants. Am J Hosp Care 6:31-34, 1989

48. Heyse-Moore LH, Ross V, Mullee MA: How much of a problem is dyspnoea in advanced cancer? Palliat Med 5:20-26, 1991

49. Hardy JR, Turner R, Saunders M: Prediction of survival in a hospital-based continuing care unit. Eur J Cancer 30A:284-288, 1994

50. Vitetta L, Kenner D, Kissane D, et al: Clinical outcomes in terminally ill patients admitted to hospice care: Diagnostic and therapeutic interventions. J Palliat Care 17:69-77, 2001

51. Mor V, Laliberte L, Morris JN, et al: The Karnofsky Performance Status Scale: An examination of its reliability and validity in a research setting. Cancer 53:2002-2007, 1984

52. Reuben DB, Mor V, Hiris J: Clinical symptoms and length of survival in patients with terminal cancer. Arch Intern Med 148:1586-1591, 1988

53. Schonwetter RS, Teasdale TA, Storey P: The terminal cancer syndrome. Arch Intern Med 149:965-966, 1989

54. Rosenthal MA, Gebski VJ, Kefford RF, et al: Prediction of life-expectancy in hospice patients: Identification of novel prognostic factors. Palliat Med 7:199-204, 1993

55. Allard P, Dionne A, Potvin D: Factors associated with length of survival among 1081 terminally ill cancer patients. J Palliat Care 11:20-24, 1995

56. Tamburini M, Brunelli C, Rosso S, et al: Prognostic value of quality of life scores in terminal cancer patients. J Pain Symptom Manage 11:32-41, 1996

57. Morita T, Tsunoda J, Inoue S, et al: Survival prediction of terminally ill cancer patients by clinical symptoms: Development of a simple indicator. Jpn J Clin Oncol 29:156-159, 1999

58. Caraceni A, Nanni O, Maltoni M, et al: Impact of delirium on the short term prognosis of advanced cancer patients: Italian Multicenter and Study Group on Palliative Care. Cancer 89:1145-1149, 2000

59. Pasanisi F, Orban A, Scalfi L, et al: Predictors of survival in terminal-cancer patients with irreversible bowel obstruction receiving home parenteral nutrition. Nutrition 17:581-584, 2001

60. Rodrigus P, de Brouwer P, Raaymakers E: Brain metastases and non-small cell lung cancer: Prognostic factors and correlation with survival after irradiation. Lung Cancer 32:129-136, 2001

61. Maltoni M, Pirovano M, Nanni O, et al: Biological indices predictive of survival in 519 Italian terminally ill cancer patients: Italian Multicenter and Study Group on Palliative Care. J Pain Symptom Manage 13:1-9, 1997

62. Maltoni M, Nanni O, Pirovano, et al: Successful validation of the Palliative Prognostic Score in terminally ill cancer patients: Italian Multicenter and Study Group on Palliative Care. J Pain Symptom Manage 17:240-247, 1999

63. Geissbuhler P, Mermillod B, Rapin CH: Elevated serum vitamin B12 associated with CRP as a predictive factor of mortality in palliative care cancer patients: A prospective study over five years. J Pain Symptom Manage 20:93-103, 2000

64. McMillan DC, Elahi MM, Sattar N, et al: Measurement of the systemic inflammatory response predicts cancer-specific and non-cancer survival in patients with cancer. Nutr Cancer 41:64-69, 2001

65. Maltoni M, Amadori D: Prognosis in advanced cancer. Hematol Oncol Clin North Am 16:715-729, 2002

66. Muers M, Shevlin P, Brown J: Prognosis in lung cancer: Physicians' opinions compared with outcome and a predictive model. Thorax 51:894-902, 1996

67. Mackillop WJ, Quirt CF: Measuring the accuracy of prognostic judgements in oncology. J Clin Epidemiol 50:21-29, 1997

68. Feinstein AR: Symptoms as an index of biological behaviour and prognosis in human cancer. Nature 209:241-245, 1966

69. Wachtel T, Allen-Masterson SA, Reuben D, et al: The end stage cancer patient: Terminal common pathway. Hosp J 4:43-80, 1988

70. Viganò A, Bruera E, Suarez-Almazor ME: Terminal cancer syndrome: Myth or reality? J Palliat Care 15:32-39, 1999

71. Addington-Hall JM, MacDonald LD, Anderson HR: Can the Spitzer Quality of Life Index help to reduce prognostic uncertainty in terminal care? Br J Cancer 62:695-699, 1990

72. Cassileth BR, Lusk EJ, Miller DS, et al: Psychosocial correlates of survival in advanced malignant disease? N Engl J Med 312:1551-1555, 1985

73. Coates A: Quality of life and supportive care. Support Care Cancer 5:435-438, 1997

74. Coates A, Gebski V, Signorini D, et al: Prognostic value of quality-of-life scores during chemotherapy for advanced breast cancer: Australian New Zealand Breast Cancer Trials Group. J Clin Oncol 10:1833-1838, 1992

75. Coates A, Thomson D, McLeod GR, et al: Prognostic value of quality of life scores in a trial of chemotherapy with or without interferon in patients with metastatic malignant melanoma. Eur J Cancer 29A:1731-1734, 1993

76. Earlam S, Glover C, Fordy C, et al: Relation between tumor size, quality of life, and survival in patients with colorectal liver metastases. J Clin Oncol 14:171-175, 1996

77. Chang VT, Thaler HT, Polyak TA, et al: Quality of life and survival: The role of multidimensional symptom assessment. Cancer 83: 173-179, 1998

78. Ringdal GI, Gotestam KG, Kaasa S, et al: Prognostic factors and survival in a heterogeneous sample of cancer patients. Br J Cancer 73:1594-1599, 1996

79. Regehr G, Norman GR: Issues in cognitive psychology: Implications for professional education. Acad Med 71:988-1001, 1996

80. Mandin H, Jones A, Woloschuk W, et al: Helping students learn to think like experts when solving clinical problems. Acad Med 72:173-179, 1997