Clinical Trials at the End-of-life

Schrijvers D* and Teurfs W

Ziekenhuisnetwerk Antwerpen (ZNA)-Middelheim, Lindendreef 1, B-2020 Antwerp, Belgium

Abstract

Although clinical trials are the basis where daily clinical practice should be based on, such evidence is scarce at the end-of-life of cancer patients. Research in this patients population is hampered by the lack of clear definition of the study population, the study design, the definition of meaningful endpoints and ethical consideration.

This review addresses problems at the end-of-life of cancer patients and proposes some solutions.

Keywords: Research; end-of-life; palliative care; study design.

Introduction

At the end of their disease trajectory, cancer patients have a multitude of problems, that have to be addressed to ensure their quality of life (QoL). End-of-life (EoL) issues, that this patient population encounters, are not only related to physical symptoms, but consists also in the social, psychological and spiritual field, and the scope of interventions shifts from survival to QoL [1].

In addition, the family becomes the aim of care, since they are suffering together with the patient.

It has been difficult to get evidence-based information from classical designed randomized trials with progression-free or overall survival or even QoL endpoints to guide the clinician dealing with this patient population, that is not well studied due to their poor general condition and the short duration (some days or weeks) of this phase of the disease.

Nevertheless, some improvement has been made in the research in patients with advanced incurable disease and the value of palliative treatments and care has been demonstrated in studies with endpointsofprogression-free or overall survival. Also a positive influence on QoL has been shown for certain anti-cancer treatments such as chemotherapy, hormonal treatment or targeted therapies in patients with advanced incurable cancer. However, the prognosis of patients included in these trials was in most instances more than 3 months, and data on patients at the EoL are scarce.

Due to the nature of the EoL, classical methods focusing on outcome measures are difficult to perform and other approaches should be developed. This review reflects on the problems with current trial design at the EoL such as definition of this stage of the disease, study design, study population, interventions, study endpoints and minimal criteria for therapeutic efficacy.

Definition of End-of-Life

There is no clear definition of the EoL. The European Society for Medical Oncology defines EoL care as palliative care given in the period when death is imminent [2], while the National Cancer Institute defines it as the period when the cancer patient's health care team determines that the cancer can no longer be controlled, medical testing and cancer treatment stops while the person's care continues, with an emphasis on improving their QoL and that of their loved ones, making them comfortable for the following weeks or months [3].

Other organizations use other definitions of the EoL such as the General Medical Council, which considers patients to be approaching the EoL when they are likely to die within the next 12 months, including patients who are expected to die within the next few hours or days, and those with advanced incurable conditions [4]. For clinical studies, such a wide time range is difficult to use.

A similar problem did arise at the start of the palliative care movement, in which palliative care was defined as the care during the last 3 months of a patient's life while it is now considered to be the period when the patient is confronted with a life-threatening incurable disease. This period may extend over years in case of certain cancers (e.g. distant metastatic disease in hormone-sensitive breast cancer patients), while the intensity of palliative care may vary.

In clinical studies, the period of the EoL could be considered as the period where the patient has a high probability of dying within 30 days/4 weeks, as projected by predictive indicators.

Definition of Patient Population

In most oncology trials, life expectancy has always been an important inclusion criterion and most trials, even in studies evaluating palliative care interventions in patients with advanced-stage cancer, require a minimal survival duration of around 12 weeks.
weeks [5]. However, it remains difficult to determine life expectancy in patients with advanced cancer and drop out due to death has been a problem because of the over-estimation by physicians of survival [6].

There are some predictive indicators (e.g. Palliative Prognostic Score (PaP) [7], palliative prognostic index (PPI) [7], Chuang prognostic score (CPS) [7], terminal cancer prognostic (TCP) [7] score, Bruera poor prognostic indicator [7], Prognosis in Palliative care Study predictor (PiPS) [8], and one nomogram [9]) to predict the survival probability of patients with advanced cancer, which can be used to define patient populations for developing studies at the EoL (Table 1). However, their accuracy varies and they should be used with caution.

There have also been described some signs that indicate that the patient will die in the next 3 days, including non-reactive pupils, a decreased response to verbal and visual stimuli, the inability to close eyelids, drooping of the nasolabial fold, hyperextension of the neck, grunting of vocal cords, and upper gastrointestinal bleeding with a specificity of more than 95% and a high positive likelihood ratio [10].

When performing research at the EoL, the study population should be exactly defined with the help of these instruments.

The inclusion of patients with a specific cancer or previous anticancer treatments seems to be of lesser importance in this stage of the disease, since symptoms pairs or clusters seem to be similar in cancer and non-cancer patients at the EoL [11]. This may facilitate the accrual of large patient groups including those presenting with rare tumors.

**Research Methods**

Different study designs can be used as research methods to evaluate problems at the EoL (Table 2) [12].

**Quantitative research** uses techniques, in which phenomena are explained by collecting numerical data that are analyzed using mathematically-based methods in particular statistics. This type of research uses experimental (e.g. clinical studies) and non-

---

**Table 1. Prognostic scoring systems to predict end-of-life**

| Scoring system                              | Predictive variables                                                                 | End point               |
|---------------------------------------------|--------------------------------------------------------------------------------------|-------------------------|
| PaP                                         | Clinician prediction survival, Karnofsky PS, anorexia, dyspnea, total white blood count, lymphocyte percentage | 30-day survival         |
| PPI                                         | PS, oral intake, edema, dyspnea at rest, delirium                                    | 6-week survival         |
| CPS                                         | Lung metastasis, liver metastasis, tiredness, ascites, edema, cognitive impairment, weight loss, ECOG PS | 2-week survival         |
| TCP                                         | Anorexia, diarrhea, confusion                                                       | Median survival > 28 days |
| Bruera’s poor prognostic indicator          | Dysphagia to solids or liquids, cognitive failure, weight loss >10 kg in the last 6 months | 4-week survival         |
| PiPS                                        | Dyspnea, dysphagia, bone metastases, alanine transaminase Primary breast cancer, male genital cancer, tiredness, loss of weight, lymphocyte count, neutrophil count, alkaline phosphatase, and albumin | 2-weeks survival        |
|                                             |                                                                                       | 2-month survival        |
| Angelo (33)                                 | Lung or bladder cancer, ECOG PS 3-4, low hemoglobin, opioid analgesic use, steroid use, known progressive disease outside radiotherapy volume | 30-days survival        |
| Nomogram                                    | ECOGPS, lactate dehydrogenase levels, lymphocyte levels, albumin levels, time from initial diagnosis to diagnosis of terminal disease | 15-, 30-, 60 day survival |

ECOG: Eastern Cooperative Oncology Group; PS: performance status; PaP: Palliative Prognostic Score; PPI: palliative prognostic index; CPS: Chuang prognostic score; TCP: terminal cancer prognostic (TCP) score; PiPS: Prognosis in Palliative care Study
Typical experimental studies in medicine are randomized trials, in which 2 or more treatment strategies are compared, with endpoints of progression-free or overall survival or patient-reported outcome measures (PROM). They are used for the registration and use of new anti-cancer medications, radiotherapy or surgical techniques and are considered an important tool to demonstrate benefit of one treatment over another one. Recently other study designs have been explored especially in orphan diseases with limited numbers of patients such as double-blind randomized discontinuation studies or enrichment of the study populations based on predictive targets. At the EoL, this kind of experimental studies are difficult to perform because of the high drop-out rate of the patients due to impending death or inability to apply to PROM tools.

Non-experimental studies have been used, for instance to study the place of death, and they can be applied even in patients with a short life expectancy. However, they have mostly a descriptive character and are difficult to use for showing a benefit of one intervention compared to others.

**Table 2. Characteristics of different research methods**

| Type of research | Quantitative                                    | Qualitative                              | Mixed                                      |
|------------------|-------------------------------------------------|------------------------------------------|--------------------------------------------|
| Research philosophy | Positivistic knowledge claims                    | Constructivist, advocacy, participatory knowledge claims | Pragmatic knowledge claims                 |
| Strategies of inquiry | Experimental design                             | Narratives                               | Sequential                                 |
|                   | Non-experimental design                         | Phenomenologies                           | Concurrent                                 |
|                   |                                                 | Ethnographies                             | Transformative                             |
|                   |                                                 | Grounded theory                           |                                            |
|                   |                                                 | Case studies                              |                                            |
| Research methods | Predetermined                                   | Emerging methods                          | Both predetermined and emerging methods    |
|                   | Instrument-based questions                      | Performance data, interview data,observation data, document data, and audiovisual data | Both open- and closed-ended questions      |
|                   |                                                 | Text and image analysis                   | Multiple forms of data drawing on all possibilities |
|                   | Performance data, attitude data,                |                                          | Statistical and text analysis              |
|                   | observational data, and census data             |                                          |                                            |
|                   | Statistical analysis                            |                                          |                                            |
| Research instruments | Closed-ended questions, predetermined approaches, numeric data | Open-ended questions, emerging approaches, text or image data | Both open-and closed ended questions       |
|                   |                                                 |                                          | Rationale for mixing                      |
|                   |                                                 |                                          | Integrates data of different stages of inquiry |
|                   |                                                 |                                          | Presents visual aids of the procedures of the study |
|                   |                                                 |                                          | Employs the practices of both quantitative and qualitative research |
Qualitative research involves any research that uses data that do not indicate ordinal values. This type of research uses other strategies of inquiry like narratives; descriptive accounts of a setting or practice; phenomenology, which describes the subjective reality of an event as perceived by the participants; ethnographies, that rely on observation, and the use of research methodologies that enable the researcher to describe how those being studied understand their world; grounded theories; and case studies.

**Mixed Design Research** uses both quantitative and qualitative research methods to evaluate pragmatic knowledge claims by collecting both quantitative and qualitative data sequentially.

Although in medicine and in clinical oncology, most value is given to results from randomized trials as basis for daily clinical practice, many of the conclusions of these randomized trials are for specific ‘study’ populations and the results cannot always be extrapolated to other populations, making them of limited value for patients at the EoL.

Therefore, mixed research designs may be more adapted to the situation for studies at the EoL combining qualitative with quantitative data to obtain the best insight in a specific problem and to formulate research questions, which can be studied by means of this research approach.

**Study Intervention**

Many studies in oncology and especially in advanced cancer are medication-driven. They evaluate the effect of a certain drug (e.g. anti-cancer drug, palliative care drug such as analgesics) in relation to a certain parameter (e.g. progression-free survival, overall survival, pain score). The relationship between treatment and effect is relatively easy to evaluate by validated instruments and outcome measures, considering patient compliance to treatment.

However, at the EoL other interventions may be of importance such as specific care measurements or professional caregivers interventions, complementary measures, psychological and spiritual support of both patient and family.

Unless with the administration of medications, which have to fulfill quality criteria to be used in a clinical trial, definition of these quality criteria is less easy for non-medication interventions and attempts have been made to standardize surgical [13] and radiotherapeutic techniques [14] in clinical studies.

For interventions at the EoL, standardization will be a problem because the intervention should be the same by all participating health care professionals, which may pose a difficult problem as already shown in studies in palliative care with different types of care interventions and a wide variation of interventions all defined as palliative care interventions [15,16]. Therefore, if care interventions are the scope of a study, they should be specifically described and a training should be available for the caregivers to standardize and harmonize these interventions.

**Outcome Measures**

Different outcome measures can be used to study EoL issues. They depend on the study design and may differ in quantitative, qualitative and mixed research setting.

In quantitative research, descriptive outcomes, that do not burden the patient and the family should be preferred (e.g. place of death, number of health care professional involved). They may give in insight in the problems that are encountered at the EoL to be addressed in other types of research.

Experimental designs such as clinical trials, are in most instances looking at the effect on progression-free or overall survival and sometimes impact on patient-reported QoL. While the length of survival does not really apply to EoL patients, the patient’s and families QoL are important issues to be considered.

Several validated instruments by which health-related QoL can be measured are used including the “European Organisation for the Research and Treatment of Cancer” (EORTC) Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) and the Functional Assessment of Cancer Therapy—General (FACT-G) in QoL research and different disease- or symptom-specific modules have been developed [17]. Specific QoL instruments in palliative care (e.g. EORTC QLQ-C15-PAL [18] Functional Assessment of Chronic Illness Therapy - Palliative Care (FACIT-Pal)[19]) are also available to perform QoL research at the EoL. The choice of instrument depends on the field that is addressed by the research question.

These instruments use patient-reported outcome measures and at the EoL this may be difficult to obtain data due the weak general condition of the patient. Therefore, the outcome (e.g. pain, dyspnea, discomfort) of an intervention can be difficult to evaluate in very ill patients.

Different approaches (e.g. proxy-based instruments) can be used to evaluate the effect of an intervention, and there are some data that these evaluations reflect the patient’s QoL in oncology [20].

Qualitative research may be important to evaluate patient’s and families perspectives in relation to the EoL. They may be used for the selection of research questions that have to be addressed or the outcome of specific interventions.

Another possibility is to evaluate the process and not the outcome/ effect on a certain parameter. A consensus on the optimal care process can be developed based on discussions with patients, family and professional caregivers (qualitative research) and the implementation of the process can be evaluated according to quality indicators (quantitative research), that have been defined in advance (e.g. adherence to a defined protocol as the Liverpool Care Pathway for the Dying Patient).

The process should then be evaluated by the caregivers and, the patients or their proxy to evaluate its value. This avoids the problem
of missing data due to the death of the patient and may be helpful for the team dealing with this patient population. In addition it enables to evaluate certain processes before their implementation in daily clinical practice.

**Clinical Meaningful Effect**

The magnitude of the effect of an intervention in clinical trials considered to be a meaningful clinical benefit has been a matter of controversy [21]. While small statistical improvements can be demonstrated depending on the sample size (e.g. small differences of 0.1% in survival with large numbers of patients), they not always present a clinical meaningful effect.

A minimal clinically important difference in health-related QoL can be defined as the smallest difference in score in the domain of interest which patients perceived as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management [22].

There are different thresholds of minimal clinically important difference in different study populations [22,23,24] and among evaluation (sub)scales [17] in different evaluation fields (e.g. mean quality of life; pain [25]), which can change during different interventions [26] making interpretations even more difficult (Table 3).

The threshold for a meaningful effect depends thus on the item studied and should be determined before start of the study, in order to get an answer of the research question with a minimum of patients needed to be included.

**Ethical Considerations**

All studies and especially at the EoL should be performed according to the highest ethical principles to protect the patients and ensure their right. Research participation should be on a voluntary basis with understanding the purpose of the research, its risks, and potential benefits.

In order to improve patient care, research is necessary but EoL studies encounter specific ethical problems including their right to participate in research, the vulnerability of this patient population, and their capacity to consent to research [27].

**Right to Participate in Studies**

Patients may want to participate in research for different reasons such as altruism, hope, and self-benefit [28]. Reasons for refusing participation in a clinical trial are concerns with the trial setting, a dislike of randomization, general discomfort with the research process, complexity and stringency of the protocol, presence of a placebo or no-treatment group, potential side-effects, being unaware of trial opportunities, the idea that clinical trials are not appropriate for serious diseases, fear that trial involvement would have a negative effect on the relationship with their physician, and their physician's attitudes towards the trial [29]. From an ethical point of view, the patient should receive the information to participate in a trial in order to respect the patients autonomy.

**Informed Consent**

All entry into a clinical trial should be on a voluntary basis and the informed consent procedure to ascertain that the patient's participation is a well-considered choice.

An informed consent procedure must provide information about the reason for the proposed matter, its risks, its benefits, and alternative options; the person involved must understand, retain, and believe the information provided; and they must deliberate, make a decision, and be able to communicate this decision.

**Table 3. Clinically meaningful differences according to different scales**

| Author | Ref | Scale | Meaningful differences |
|--------|-----|-------|------------------------|
| Hong   | 22  | EORTC-QLQ-C30 | -6 pts, + 3 pts         |
| Osoba  | 34  | EORTC-QLQ-C30 | Little change: 5-10; 10-20 moderate change; > 20 very much change |
| Mathias| 25  | Brief Pain Inventory-Short Form | 2pts |
| Cella  | 35  | FACT-L | 2-3pts |
| Cella  | 35  | TOI of FACT-L | 5-6pts |
| Yost   | 26  | FACT-BRM | TOI: 5-8 pts, SWB: 2 pts, EW: 2-3 pts |
| Webster| 24  | FACT-G | PWB: 2–3 pts; EW 2, FWB 2–3; total FACT-G: 3–7 |
| Bedard | 36  | EORTC QLQ-C15- PAL | Improvement in emotional functioning: + 20.9, pain: 15.6 Decrease in physical functioning: -20.4, fatigue: -24.5, pain: -17.1 appetite loss: 23.0 |

EORTC QLQ-C30: European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; pts: points; FACT-L: Functional Assessment of Cancer Therapy-Lung; TOI: Trial Outcome Index; FACT-BRM: Functional Assessment of Cancer Therapy-Biological Response Modifier; SWB: subjective well-being; EW: emotional well-being; FACT-G: Functional Assessment of Cancer Therapy-Global; PWB: psychological well-being; FWB: functional well-being
At the EoL, patients may not be able to fulfill all conditions and thus may be incapable of providing informed consent. In such circumstances, a legally authorized representative may agree to the study instead of the patient (proxy consent) [30].

An advance consent obtains prospective authorization by the patient for his/her future participation while the patient is still capable to decide [31]. With advanced care planning discussions [32], the participation to a trial at the EoL if the condition of the patient is worsening, can be discussed in advance with the patient, his family, and surrogate. At that moment or later, an informed consent on a specific study can be asked for. This enables the patients to decide for themselves if they want to participate in research.

**Conclusions**

Patients at the end of their lives and their family encounter many problems in the physical, emotional, cultural and spiritual field that should be addressed in an adequate manner. However, research data to base daily clinical practice are lacking and they should be put on the research agenda. There are still many problems to study patients at the EoL such as the definition of the study population, the study design and endpoints, and ethical issues that have to be addressed in near future to improve how we look at this patient group.

**References**

1. Khan SA, Gomes B, Higginson IJ. 2014 End-of-life care—what do cancer patients want? Nat Rev Clin Oncol, 11(2): 100-108.

2. Cherny N, Catane R, Kosmidis P. 2003 ESMO takes a stand on supportive and palliative care. Ann Oncol, 14(9): 1335-1337.

3. National Cancer Institute. 2015 End-of-Life Care for People Who Have Cancer. http://www.cancer.gov/cancertopics/factsheet/Support/end-of-life-care.

4. General Medical Council. Treatment and care towards the end of life: good practice in decision making (2015).

5. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admame S et al. 2010 Early palliative care for patients with metastatic non-small cell lung cancer. N Engl J Med, 363(8): 733-742.

6. Glare P, Virik K, Jones M, Hudson M, Eychmuller S et al. 2003 A systematic review of physicians' survival predictions in terminally ill cancer patients. BMJ, 327(7408): 195-198.

7. Stone PC, Lund S. Predicting prognosis in patients with advanced cancer. 2007 Ann Oncol: 18(6), 971-976.

8. Gwilliam B, Keeley V, Todd C, Matthew Gittins, Chris Roberts, et al. 2011 Development of Prognosis in Palliative Care Study (PIPS) predictor models to improve prognosis in advanced cancer: prospective cohort study. BMJ, 343: d4920.

9. Felle J, Jiménez-Gordo AM, Madero R Rodríguez-Aizcorbe JR, Espinosa E et al. 2011 Development and validation of a prognostic nomogram for terminally ill cancer patients. J Natl Cancer Inst, 103(21): 1613-1620.

10. Hui D, Dos Santos R, Chisholm G, Bansal S, Souza Crovador C, et al. 2015 Bedside clinical signs associated with impending death in patients with advanced cancer: Preliminary findings of a prospective, longitudinal cohort study. Cancer, 121: 960-967.

11. Stiel S, Matthes DM, Seuß D, Walsh D, Lindena G, et al Symptoms and problem clusters in cancer and non-cancer patients in specialized palliative care—is there a difference? J Pain Symptom Manage 2014, 48(1): 26-35.

12. Creswell JW. Research design. Qualitative, quantitative and mixed methods approaches, 2nd edition: SAGE Publications, Thousand Oaks, London New Delhi, 2003.

13. Haase GM. 1994 The implications of surgical quality assurance in cancer clinical trials. Cancer, 74(9 Suppl): 2630-2637.

14. Hurkmans CW, Borger JH, Rutgers EJ, van Tienhoven G, EORTC Breast Cancer Cooperative Group, et al. 2003 Quality assurance of axillary radiotherapy in the EORTC AMAROS trial 10981/22023: the dummy run; Radiother Oncol, 68(3): 233-240.

15. Bakitas M, Lyons KD, Hegel MT, Balan S, Brokaw FC, et al. 2009 Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. JAMA, 302(7): 741-749.

16. Zimmermann C, Swami N, Krzyzanowska M et al. 2014 Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. Lancet, 383: 1721-1730.

17. Luckett T, King MT, Butow P, Oguchi M, Rankin N, et al. 2011 Choosing between the EORTC QLQ-C30 and FACT-G for measuring health-related quality of life in cancer clinical research: issues, evidence and recommendations. Ann Oncol, 22(10): 2179-2190.

18. Groenwald M, Petersen MA, Aaronson NK, Arraras JI, Blazeby JM, et al. 2006 The development of the EORTC QLQ-C15-PAL: a shortened questionnaire for cancer patients in palliative care. Eur J Cancer, 42(1): 55-64.

19. Lyons KD, Bakitas M, Hegel MT, Hamsom B, Hull J, Ahles TA. 2009 Reliability and validity of the Functional Assessment of Chronic Illness Therapy-Palliative care (FACIT-Pal) scale. J Pain Symptom Manage, 37(1): 23-32.

20. Steinmann D, Vordermark D, Geinitz H, Aschoff R, Bayerl A, et al. 2013 Proxy assessment of patients before and after radiotherapy for brain metastases. Results of a prospective study using the DEGRO brain module. Strahlenther Onkol, 189(1): 47-53.

21. Schrijvers D. 2010 but what, how much and at what cost? Ann Oncol, 21(7): 1562-1563.

22. Hong F, Bosco JL, Bush N, Berry DL. 2013 Patient self-appraisal of change and minimal clinically important difference on the European organization for the research and treatment of cancer quality of life questionnaire core 30 before and during cancer therapy. BMC Cancer, 13: 165.

23. Maringwa J, Quinten C, King M, Ringash J, Osoba D, et al. 2011 Minimal clinically meaningful differences for the EORTC QLQ-C30 and EORTC QLQ-BN20 scales in brain cancer patients. Ann Oncol, 22: 2107-2112.
24. Webster K, Cella D, Yost K. 2013 The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes, 1: 79.

25. Mathias SD, Crosby RD, Qian Y, Jiang Q, Dansey R, et al. 2011 Estimating minimally important differences for the worst pain rating of the Brief Pain Inventory-Short Form. J Support Oncol, 9(2): 72-78.

26. Yost KJ, Cella D, Chawla A, Holmgren E, Eton DT, et al. 2005 Minimally important differences were estimated for the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) instrument using a combination of distribution- and anchor-based approaches. J ClinEpidemiol, 58(12): 1241-1251.

27. Duke S, Bennett H. 2010 Review: a narrative review of the published ethical debates in palliative care research and an assessment of their adequacy to inform research governance. Palliat Med, 24(2): 111–126.

28. Todd AM, Laird BJ, Boyle D, Boyd AC, Colvin LA, et al. 2009 A systematic review examining the literature on attitudes of patients with advanced cancer toward research. J Pain Symptom Manage, 37(6): 1078-1085.

29. Mills EJ, Seely D, Rachlis B, Griffith L, Wu P, et al. 2006 Barriers to participation in clinical trials of cancer: a meta-analysis and systematic review of patient-reported factors. Lancet Oncol, 7(2): 141-148.

30. Sweet L, Adamis D, Meagher DJ, Davis D, Currow DC, et al. 2014 Ethical challenges and solutions regarding delirium studies in palliative care. J Pain Symptom Manage, 48(2): 259-271.

31. Rees E, Hardy J. 2003 Novel consent process for research in dying patients unable to give consent. BMJ, 327: 198.

32. Schrijvers D, Cherny N, ESMO Guidelines Working Group. 2014 ESMO Clinical Practice Guidelines on palliative care: advanced care planning. Ann Oncol, 25 (Suppl 3): 138-142.

33. Angelo K, Norum J, Dalhaug A, Pawinski A, Aandahl G, et al. 2014 Development and validation of a model predicting short survival (death within 30 days) after palliative radiotherapy. Anticancer Res, 34: 877-885.

34. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. 1998 Interpreting the significance of changes in health related quality-of-life scores. J Clin Oncol, 16(1): 139-144.

35. Cella D, Eton DT, Fairclough DL, Bonomi P, Heyes AE. 2002 What is a clinically meaningful change on the Functional Assessment of Cancer Therapy-Lung (FACT-L) Questionnaire? Results from Eastern Cooperative Oncology Group (ECOG) Study 5592. J Clin Epidemiol, 55(3): 285-295.

36. Bedard G, Zeng L, Zhang L, Lauzon N, Holden L, et al. 2014 Minimal important differences in the EORTC QLQ-C15- PAL to determine meaningful change in palliative advanced cancer patients. Asia Pac J Clin Oncol, 10: 109-117.