Prognostic Factors for Survival in Advanced Cancer Patients in Iceland

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Thesis for the degree of Master of Science
University of Iceland
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HÁSKÓLI ÍSLANDS

Forspárþættir fyrir lifun sjúklinga með langt genginn krabbameinssjúkdóm á Íslandi

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Ritgerð til meistaragráður í læknisfræði

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Ritgerð þessi er til meistaragráðu í læknisfræði og er óheimilt að afrita ritgerðina á nokkurn hátt nema með leyfi rétthafa.

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Abstract

Introduction: Over 150 different factors have been evaluated with regard to prognostication in cancer in various studies. The most common are performance status, cognitive function, quality of life (QoL), physical symptoms and signs, concomitant diseases and biochemical related factors. The aim of this thesis is to investigate the prognostic value of cancer characteristics, prevalent physical symptoms (e.g. pain, fatigue and dyspnoea), opioid treatment, mobility, falls, nutrition, cognitive function and QoL. The objective was also to compare the two datasets used in relation to prognostication and to evaluate survival prediction by health care professionals. A comparable study has not been conducted among Icelandic cancer patients before.

Materials and methods: Data consisted of material from two prospective cohort studies, including 266 patients. Firstly, data from Icelandic participants in the European Pharmacogenetic Opioid Study (EPOS) were used (N=150). These patients, who all received opioid treatment due to pain, had cancer and were either on palliative care and/or life-prolonging cancer therapy. Secondly, assessments of patients in palliative care service evaluated with the interRAI Palliative Care (PC) assessment tool, were included (N=116). Statistical analysis was performed with Kaplan Meier survival and Cox regression analyses.

Results: Median survival of the patients in the EPOS part of the study was 101 day. In a multivariate Cox regression, variables that significantly predicted shortened survival were greater number of metastases (HR 1.24) and presence of fatigue (HR 1.82). Higher score on Mini Mental State Examination (MMSE) (HR 0.86), the role function scale (HR 0.99) of the EORTC questionnaire and the Brief Pain Inventory (BPI) interference scale (HR 0.91) was significantly related to longer survival. In the study using the interRAI PC assessment tool the median survival was 41 day. The variables significantly associated with shorter survival in a multivariate Cox regression were increased age (HR 1.02), shortness of breath on exertion (HR 2.53), and falls in the last 30 days (HR 2.73). Health care professionals were most accurate in their prediction of survival when survival time was short.

Conclusion: The group of cancer patients on opioids lived longer than the group of patients on first admission to palliative care. Shorter survival in advanced cancer patients on opioids was associated with more metastases, fatigue, lower cognitive function and lower role function as well as decreased interference of pain. Shorter survival in patients with advanced cancer on first admission to palliative care is associated with higher age, dyspnoea and falls. These results are in accordance with previous studies on prognostic factors in advanced cancer patients. The datasets were different especially regarding survival which could explain the different results from survival analyses.

Ágrip

Inngangur: Yfir 150 mismunandi þættir í ýmsum rannsóknum á krabbameinum hafa verið metnir m.t.t. forspárgildi fyrir lifun. Algengustu þættirnir eru líkamleg færni, vitræn geta, lífsgæði, líkamleg einkenni og tákn, aðrir sjúkdómar og lífefnafræðilegir þættir. Tilgangur þessarar rannsóknar var að athuga forspárgildi ýmissa krabbameinsþátta, algengustu einkenna (s.s. verkja, þreytu og mæði), ópíóíða meðferðar, hreyfigetu, byltna, næringar, vitrænnar getu og lífsgæða. Einnig var markmið að bera saman gagnagrunnina tvo sem voru notaðir í þessari rannsókn m.t.t. forspáþætti fyrir lifun og meta hversu vel spá heilbrigðisstarfsfólks, lækna og hjúkrunarfræðinga, um lifun samræmdist raunlifun. Sambærileg rannsókn hefur ekki verið gerð hjá íslenskum krabbameinssjúklingum.

Efniviður og aðferðir: Gögn úr tveimur framsýnum hóprannsóknum, með 266 sjúklingum, voru rannsökuð. Í fyrsta lagi, voru gögn frá íslenskum þátttakendum í European Pharmacogenetic Opioid Study (EPOS) rannsökuð (N=150). Þeir sjúklingar voru allir með krabbamein á ópíóíðum við verkjum og fengu líknar – og/eða lífslengjandi krabbameinsmeðferð. Í öðru lagi, þá var notast við möt á sjúklingum í líknarþjónustu gert með interRAI Palliative Care (PC) mælitækinu (N=116). Tölfræðilegir útreikningar voru gerðir með Kaplan Meier lifunargreiningu og Cox aðhvarfsgreiningu.

Niðurstöður: Miðgildi lifunar sjúklinga í EPOS hluta rannsóknarinnar var 101 dagur. Í fjölþátta Cox aðhvarfsgreiningu þá var aukinn fjöldi meinvarpa (HR 1.24) og þreyta (HR 1.82) sjálfstæður áhættuþáttur fyrir skemmri lifun. Hærra skor á Mini Mental State Examination (MMSE) (HR 0.86) og hlutverkakvarðanum á EORTC QLQ-C30 tengdist marktækt lengri lifun (HR 0.99). Meiri áhrif verkja á daglegt líf mælt með Brief Pain Inventory (BPI) tengdist einnig marktækt lengri lifun (HR 0.91). Í seinni rannsókninni, þar sem möt frá interRAI PC mælitækinu voru notuð, var miðgildi lifunar sjúklinga 41 dagar. Hærri aldur (HR 1.021), áreynslumæði (HR 2.529) og byltur síðustu 30 daga (HR 2.725) voru marktækt tengd skemmri lifun í fjölþátta Cox aðhvarfsgreiningu. Heilbrigðisstarfsfólk var nákvæmara í spá sinni á lifun þegar raunlifun var styttri.

Ályktun: Þegar niðurstöður gagnagrunnanna tveggja voru bornir saman þá kom í ljós að sjúklingar með langt genginn krabbameinssjúkdóm á ópíóíðum virtust lifa lengur en þeir sem voru metnir við fyrstu komu í líknarþjónustu. Styttri lifun hjá krabbameinssjúklingum á ópíóíðum, tengdist fleiri meinvörpum, þreytu, lægri vitrænni getu, minnkun á hlutverki og minni áhrifa verkja á daglegt líf. Hjá sjúklingum með krabbamein, metnir í fyrstu komu í líknarþjónustu, tengdist styttri lifun hærri aldri, mæði og byltum. Þessar niðurstöður eru sambærilegar fyrri rannsóknum á forspáþáttum fyrir lifum hjá sjúklingum með langt gengið krabbamein. Gagnagrunnarnir eru ólíkir, sérstaklega varðandi lifun, sem gæti útskýrt mismunandi niðurstöður lifunargreininganna.

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Abbreviations

ADL	Activities of Daily Living
BPI	Brief Pain Inventory
CI	Confidence Interval
CPS	Cognitive Performance Scale
CRP	C - Reactive Protein
EAPC	European Association for Palliative Care
EORTC QLQ–C30	European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire 30
EPOS	European Pharmacogenetics Opioid Study
HR	Hazard Ratio
interRAI PC	international Resident Assessment Instrument Palliative Care
KPS	Karnofsky Performance Scale
LDH	Lactate dehydrogenase
LSH	Landspitali – The National University Hospital of Iceland
MMSE	Mini Mental State Examination
po	Per os, by mouth
PPI	Palliative Performance Index
PaP	Palliative Prognostic Score
PPS	Palliative Performance Score
QoL	Quality of Life
TIQ	Therapy Impact Questionnaire

1 Introduction

In this introduction, the incidence of cancer and the need for distribution of health care resources in the near future is explored. Then definition and history of palliative care as well as research within the field is reviewed. At last several factors related to prognosis is presented e.g. why prognostication is important, how well it is assessed by health care professionals and which factors have shown to have predictive value for survival.

1.1 Cancer incidence

In 2008, about 12.7 million new cancer cases and 7.6 million cancer deaths were registered in the world, but incidence between countries varies greatly (1). The incidence in Iceland is around 300:100.000 and the prevalence about 10%. A nearly twofold increase in 5-year survival rate has been seen during the past 50 years, resulting in an increased prevalence, but the incidence has also risen, around 50% in the last 50 years (2). According to populations Statistics Iceland (i.Hagstofa Íslands) an 8% increase in the population of Iceland is expected between the years 2011 and 2021, mainly due to a greater number of people 65 years and older, or an increase of 38% the next 10 years. With increasing age of the population, cancer risk will increase, but currently the mean age at cancer diagnosis is 68 years for women and 64 years for men (3). The incidence in the Nordic countries is estimated to increase by 49% in men and 34% in women between 1993-97 and 2018-22 (4). In addition to the ageing of the population this rise is also attributed to enlarged population size due to bigger birth cohorts, the so called baby boomers after the Second World War.

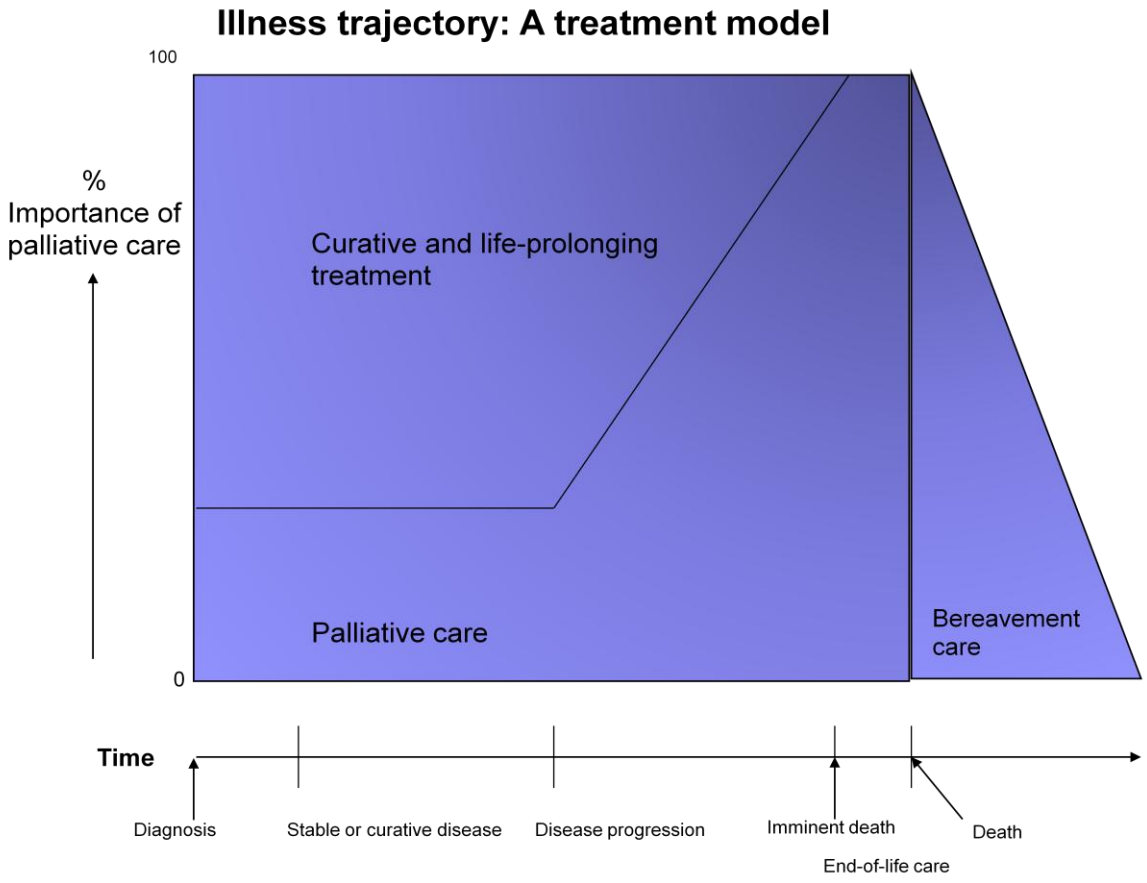
A greater number of older people in the population and a rise in cancer prevalence along with earlier diagnosis and better treatment, leads to longer survival of cancer patients who in turn live with a chronic condition rather than an acute terminal one. This trend is seen in other diseases as well, e.g. chronic pulmonary and heart disease, where people survive through the acute phases to live with a chronic condition (5). With age, therefore, people will have more diseases and symptom load than earlier generations and the focus of treatment will shift from the curative to symptom management or palliative care. This puts an increased strain on an otherwise taxed health care system and especially the palliative care system. Since medical treatment will be more centred on symptom management, such as pain management and psycho-social support (6), it is imperative to make accurate survival predictions. The idea of prognostication in palliative care is not to predict recovery but to provide patients and their families with useful information about prognosis so they can set their goals and priorities for the limited time left of life. This will then help with advanced care planning, appropriate use of resources and allocation of services in the palliative care system and, therefore, will be more financially prudent.

1.2 Palliative care

1.2.1 Definitions

The definition of palliative care originates from the World Health Organization (WHO), which first defined palliative care in the 1990s, and modified the definition in 2002. Changes in the definition reflect evolution of palliative care from being exclusively treatment used after curative treatment failed to treatment used early in the disease process and parallel with a curative treatment throughout the disease trajectory (7). In the end, when death approaches, the importance of palliative care increases together with bereavement service/care (figure 1).

Figure 1. A treatment model in illness trajectory (8)



Palliative treatment is an active treatment where the purpose is not to cure but to improve quality of life (QoL) and well-being of patients with life-threatening illness and their families. Emphasises is on providing pain and symptom relief, spiritual and psychosocial support from diagnosis to end of life and to offer support to the family during the illness and in their bereavement after death of the patient. The palliative care model uses a team approach to address these various needs and the intention is neither to hasten or postpone death but to affirm life and regards dying as a normal process. Palliative care can be applied early in the course of illness along with other therapies that are intended to

prolong life and includes investigations that are needed to better understand and manage distressing clinical symptoms (7).

Palliative care is supposed to be an inseparable part of the patients' comprehensive management and based on the patient's needs not diagnosis. The message is: "you matter because you are you, and you matter until the last moment of your life. We will do all we can, not only to help you die peacefully, but also to live until you die" as Dame Saunders said in 1976 (9). In cases of chronic diseases and when the chance for recovery is none "hope remains for a moment without suffering, an hour of dignity, a day without pain, a week of bonding with family and friends, and a good death" as Patricia Bomba M.D. said in her article about transition to hospice care (10).

1.2.2 History

The perception of death and dying in Western countries during the last centuries has changed dramatically. From being a natural part of life, death became shameful and a taboo. Following the First World War the tendency was not to inform the dying patient about the truth of his/her situation and people often died alone in hospitals. With advancing medical technology, over last decades, the emphasis has been on curing instead of symptom control and palliation. With increased awareness of the multiple needs of patients and their families this has again gradually changed (5, 11).

The first modern hospice, St.Christopher's Hospice in England, was opened in 1967. It was the first research and teaching hospice that included home care and family support throughout illness and the bereavement period. St.Christopher's was founded by Dr. Cecily Saunders, the pioneer of modern palliative medicine with new approach to pain and symptom management and appreciation for the multi-dimensional need and nature of suffering. In the beginning palliative care centred on cancer patients but the concept has evolved into care based on need regardless of diagnosis (5, 12, 13).

Palliative care is most often provided by general health care professionals but specialised palliative care is appropriate when patients have difficult, complex and diverse physical, emotional, social, spiritual and existential problems (8) Specialisation in palliative medicine was acknowledged in the 1980s in England and is now a recognised specialty in medicine in many countries (13).

Palliative care in Iceland, as elsewhere, evolved along with oncology where in- and out-patient oncology units opened in the 1980s. The hospice model was introduced in 1986 and in 1987 the first home palliative care unit was established in Reykjavik. By the year 2001, two in-patient palliative care units, one general, the other geriatric, with a total of 21 beds, had been established within Landspitali – The National University Hospital of Iceland (LSH) (14). A hospital-based palliative consultation team and three palliative home-care teams, two serving in Reykjavik metropolitan area and one in Akureyri and surroundings, were established. Unfortunately, the geriatric palliative care unit was closed early in 2012 due to financial constraints at the hospital but the general unit will expand in the autumn of 2012.

1.2.3 Research in palliative care

At St. Christopher's, research was a priority and many of the first studies on pain control were conducted there (5). In spite of enthusiasm and urgency in the beginning, the research efforts began

to wane because of the prevalent view that a scientifically clinical research was incompatible with palliative care (5, 6).

A major objection to palliative care research has been based on the notion that palliative care population is too vulnerable, frail and with such a complex symptom burden and distress that it is not ethically sound to conduct research on this group of patients. This has been repudiated by many palliative care clinicians by referring to, among other things, the Declaration of Helsinki (15), which is an ethical code of practice for clinical research and applies also for the palliative care population (16). Palliative care should, therefore, like any other medical care, be grounded on evidence. The opinion, that frailty and complexity of the palliative care population should preclude clinical studies, has greatly affected research in palliative care. This view has gradually changed over the last two decades as the palliative care movement has expanded.

An important milestone in the evolution of palliative care research was the establishment of European Association for Palliative Care (EAPC) and subsequently their first congress in 1990. EAPC research meetings developed later and so did collaboration between professionals in Europe, Canada, Australia and the USA (6). In 2009, a European Palliative Care Research Centre was established in Norway in close collaboration with EAPC (17).

Research in palliative care faces many challenges, however, palliative care is based on a multi-professional approach and, therefore, many different treatments may be offered to patients simultaneously. In order to get a comprehensive view of the patient, information from different sources needs to be gathered. Interviewing patients and/or their families, collecting information from patient records and/or using specialised questionnaires are all accepted methods. Patients can be frail and many tolerate poorly lengthy questions and investigations. This puts a strain on the investigator to find balance between optimising the scientific rigor while ensuring that the patient's limits are honoured. It is, therefore, often difficult to get adequate numbers of patients to participate and attrition is even more of a problem than in other clinical studies (5).

The quantity of palliative care research is now expanding through arrangement of research congresses and formation of collaborations around the world, and the possibilities of research within the field are plenty. There is a need for greater emphases on national strategies for research in palliative care and funding with larger multi-centre, randomised, clinical studies on treatment and treatment techniques (16).

1.3 Prognosis

Diagnosing, treating and predicting survival of patients is a role of the physician. The importance of prognosis had in some ways diminished in the 19th century, with better diagnostic tools and treatment options and main emphases on curative therapies. This has since changed, as previously described, and more attention is now being paid to symptom control and quality of life.

Palliative care is mostly provided by health care professionals who are not specialised in palliative care. Many clinicians, e.g. surgeons, geriatricians, oncologists and haematologists, will frequently see,

non-curative patients and some of those clinicians may not feel competent or confident enough to communicate with patients about terminal illness and treatment options (18, 19).

To predict time of death can be difficult and requires clinical skills. It is challenging for health care professionals, who have been trained to fight death by all means, to address the possibility of death. Higgs et al (20) suggested that when, diagnosis of a progressive non-curable disease is made and the patient is no longer responsive to treatment, it is appropriate to confront the issue. In clinical practice, it can be useful for health care professionals to ask themselves whether it would surprise them if their patient would still be alive after one year and if so, palliative approach should be considered (21).

It is of importance for patients to receive information in order to make appropriate plans and to utilize the time they have left. Physicians have to be careful of not being too ambiguous about results and plans because this can easily mislead patient's regarding their prognosis (18, 19).

In the following subchapters several aspects of prognosis are reviewed. The importance of prognosis for patients and the health care system and an overview of prognostic factors for survival that have earlier been investigated and studied. The need of patients and their families for information about prognosis will also be reviewed and how too little information can affect this group.

1.3.1 Why prognostication is important

Most physicians, at some time, treat and care for dying patients. Being able to predict outcome and survival is, therefore, important for most physicians, though especially for oncologists and palliative care physicians. This has significance for many reasons. Many patients and their families want to know how long patients have so they can make plans and decisions about their final time together. Health care professionals want to improve care of those who are dying and to utilise and organize available resources of the health care system equally (22).

According to a British study, professionals and the patients' families/relatives found good symptom control, QoL, dignity and relationships, to be the most important factors in the last months and weeks of life. However, patients themselves focused more on communication, dignity, access to services and co-ordination and continuity within and between clinical specialties and services (23). To meet these needs of patients, their families and health care professionals, it is important to have access to as accurate survival predictions as conceivable.

Resource management is highly important in the health care system and prognosis can influence appropriate use of those resources. If prognostication is made, suitable arrangements for example can be made with regards to location of care. Studies examining individual preferences about medical care at the end of life show that patients, families and health care professionals focus more on home-based care and good symptom-control with minimally invasive means than hospital based care with focus on extension of life by invasive techniques (24).

1.3.1.1 Awareness time

Prognostication is also important for the health of future widows and widowers. The length of time that a spouse is aware of an impending death is called awareness time and has been extensively investigated, especially by Swedish researchers. A Swedish study indicated that a short awareness

time may result in additional anxiety and use of sedatives in widows (25). Another Swedish study of widowers showed that men who had not had an end-of-life discussion with their wife during the last 3 months of her life had a greater risk of experiencing feelings of guilt and regret as widowers than men who did discuss these matters with their dying wife (26). In addition, they also had increased risk of psychological morbidity and other symptoms such as anxiety, a heightened startle response, emotional numbness and sleep disorders (27). One of the most important factors that predicted the preparedness of the widower in this study was the awareness time (28).

1.3.2 "How long do I have, doctor?"

Physicians frequently address the question "how long do I have, doctor?" Despite its prevalence, many physicians try to avoid prognostication and think they should avoid being too specific when asked. Nearly half do not offer information on prognosis voluntarily but wait to be asked (29). According to the Icelandic Patients' Rights law (30) the patient has a right to be informed about his or her health, including information about his/her condition, prognosis, planned treatment, other options and the possibility to seek a second opinion. This negates the view of physicians about their patients' wishes concerning disclosure of information.

A large British study showed that 87% of cancer patients and other palliative care patients want to know everything about their disease and prognosis, good or bad, something that physicians tend to underestimate. Those few (13%) who preferred that the physician decides about disclosure of information tend to be older than 70 years. Women, rather than men, seem to prefer more detailed knowledge about their disease (18). An American study based on interviews with physicians regarding deaths of their patients, revealed that 86% of physicians knew that their patients were dying but only 11% spoke personally with patients about the possibility. Most of them discussed prognoses with the relatives or the medical team. Those physicians who recognised early approaching death and spoke with the patient about it reported higher satisfaction with the end-of-life care they delivered (31) .In another American study on physicians' experiences and attitudes towards prognostication, over half of physicians felt they had an inadequate training to predict survival and found it a stressful process. Most believed that their patients expected too much certainty regarding prognostication and were concerned about being adversely judged for their prognostic errors, both by their colleagues and patients (29). An international study by Bruera et al analysed the attitudes and beliefs of palliative care specialists in Europe, Canada and South America towards communication with the dying. They all reported that they would like to be told the truth if they themselves were diagnosed with terminal illness, yet 93% of the Canadian, and only 26% of the European and 18% of the South American palliative care specialists thought that most of their patients would like to know. Cultural differences may influence this type of communication between physicians and patients, and though often an overrated aspect it has to be acknowledged in clinical settings (32). These studies emphasises that patients both want and need information regarding their condition. However, physicians tend to avoid talking to patients about their imminent death and speak instead with the family and relatives or to the medical team, mainly because of perceived stress and inadequate training.

The medical literature reveals no evidence that terminally ill patients die more happily in blissful ignorance or that they will lose all hope if told the truth and sink into depression. End-of-life discussions were not associated with higher rates of major depression or more worry in patients according to a study on association between end-of-life discussions and aggressive interventions. End-of-life discussions were associated with lower rates of assisted ventilation, resuscitation and ICU admission and earlier hospice enrollment. Aggressive medical treatments were furthermore related to worse patient's QoL and higher risk of major depression with the bereaved caregiver (33).

Patients need to make plans for their death, decide where and even how they want to die and say their final fare-wells to family and friends. A failure to prognosticate can lead to patients dying in places they dislike, enrolling into clinical trials of experimental treatment that have not shown benefit and seeking noxious chemotherapy rather than good palliative care.

In spite of this, patients have the right to refuse to be informed of their health and prognosis and it is, therefore, imperative to take into account the ethical, cultural, religious and psychological aspects when communicating with the patient to avoid inflicting additional harm. The important clinical point is to ascertain the preferences of the patient regarding knowledge about their terminal illness regardless of his/her cultural background and not make assumptions about their wishes (19).

1.4 Prognostic factors for survival

Many papers have suggested prognostic factors for survival and most of those included end-stage cancer patients. Some studies have investigated other palliative care disease groups e.g. heart failure, respiratory diseases and dementia. Few studies have been performed in open palliative care service (34) and no comparable studies have been conducted in Iceland.

Over 150 different factors have been evaluated with regard to prognostication in various studies. Factors most commonly studied are performance status, cognitive function, OoL, physical symptoms and signs and concomitant diseases and biochemical measures (35). In the next chapters several factors shown to have a relationship with survival in cancer patients in earlier studies will be reviewed.

1.4.1 Physical performance and cognitive function

Several studies have evaluated prognostic value of physical performance in palliative and cancer care and performance status is frequently used for selection of patients entering clinical trials and/or aggressive oncological regimens. These studies have shown strong connection to survival (36).

Different performance scales and measurements have been used to quantify performance status. The Karnofsky Performance Scale (KPS) is most often used for this purpose but also activities of daily living (ADL) scales which measures various activities during the day. KPS is a scale from 0 to 100 where 100 is "perfect" health and 0 signifies death (36-38). ADL is a term used to refer to daily self-care activities such as personal hygiene and grooming, dressing, eating, transfer, bowel and bladder management and ambulation (5).

Studies have confirmed that poor performance status is related to shorter survival but good performance status is not necessarily related to longer survival (22, 39-41). An American study, on

hospitalised older people, showed that those who were dependent in all aspects of ADL had a higher hospital and one-year mortality and use of nursing homes within 90 days than those who were independent in ADLs. This relationship was unchanged even when controlled for acute illness, co-morbidity and demographical characteristics (42).

Delirium and worsening cognitive function have been found to predict shorter survival in many studies (22, 43). One of the most prevalent measurements of cognitive function is the Mini-Mental State Examination (MMSE). It is used as a brief screening of cognitive function and can be used to document changes, for e.g. when delirium is assessed (44). Cognitive impairment, where MMSE was less than 24 out of 30, was independently associated with shorter survival in a study by Bruera et al in patients with advanced cancer (45). An Italian study by Caraceni showed that diagnosis of delirium significantly worsened life expectancy. Delirium was found in nearly a third of the study population of advanced cancer patients who had been referred to palliative care. Median survival for delirious patients was 21 days compared with 39 days for those not affected ($p<0.0001$) (46).

1.4.2 Physical symptoms and signs

Various physical symptoms and signs are related to shortened survival in advanced cancer patients (22). Symptoms like pain, fatigue, anorexia-cachexia and dyspnoea have been related to shorter survival in many studies but results are inconclusive. Several studies show an independent relationship when entered into multivariate analyses but others do not.

Pain is a very common symptom in final stages of diseases and is often the reason for patients to be referred to palliative care services. Neither pain, nor use of pain medications has been shown to have an independent relationship to survival (22, 47, 48).

Fatigue and anorexia are two of the symptoms most frequently associated with shortened survival. In a recent systematic review, it was established, in univariate and multivariate analyses that presence of anorexia, weight loss or cachexia affected survival negatively but fatigue seemed only to affect survival when the disease was advanced (48). However, fatigue is the most common symptom in patients with advanced cancer (49). Anorexia is a part of the anorexia-cachexia syndrome which is connected to „the final common pathway“, a pathway that patients with various end-stage diseases go through, before death. These symptoms may reflect consequences of cancer cachexia and progress of the underlying terminal disease. Many other symptoms have been connected to this pathway, such as fatigue, difficulty with swallowing, nausea and xerostomia, although a statistically independent association of these latter symptoms to survival has not been confirmed (41, 50-52).

Dyspnoea has been studied in connection with survival. Most authors have confirmed a relationship between increased dyspnoea and shortened survival (43, 53), especially in final stages of palliation (48).

Other signs and symptoms i.e. many gastrointestinal symptoms, dizziness, anxiety, depression, fever and tachycardia have been associated with shortened survival in univariate analysis but not conclusively in multivariate analyses. The same applies for many demographical factors like sex, age and marital status (22, 43, 53-55).

The site of primary cancer and presence of metastases are predictive of survival at early stages of cancer. In a Canadian study survival was examined in two cohorts of cancer patients, where the first cohort was seen at the onset of terminal phase and the second cohort at a later stage. The presence of liver metastases, lung tumour and total tumour burden predicted worsened survival in the earlier cohort but functional performance and quality of life seemed to affect survival most in later stages (41). This finding has been demonstrated in other studies in advanced cancer, i.e. the cancer type or dissemination is less important than in earlier stages of disease (54, 55).

Recently, a study from Taiwan found results from various symptom scales to be associated with survival. An independent relationship between survival and the severity and number of symptoms was found (56). This was also shown in a Canadian study, where total symptom burden, lack of appetite, drowsiness, dyspnoea and fatigue were significantly associated with length of time to death (52).

Various biochemical measures have been studied in relation to survival. In multi-factorial analyses, increased white cell count and decreased neutrophil count, have shown association to shortened survival and seems to indicate a dysfunction of the immune response. Lactate dehydrogenase (LDH), interleukin-6 and C-reactive protein (CRP) (35, 57) are of greatest interest. A South Korean study of LDH levels in palliative care patients with cancer showed that high LDH was an independent risk factor for shortened survival. Because of the involvement of LDH in basic physical chemical reactions it has been suggested to be a marker of tumour aggressiveness and is related to damage of multiple organs (58). This has been confirmed in an another study by the same group where anorexia, resting dyspnoea, low physical function, leukocytosis, elevated s-bilirubin, s-creatinine and s-LDH were all independently related to shortened survival (59). Increased CRP and B12 have shown an independent relationship to shortened survival. An elevated B12 in relation to shortened survival probably reflects hepatic involvement and inflammation (60). All these factors are difficult to analyse statistically because of a likely interaction between them.

1.4.3 Quality of life

Various QoL questionnaires, like the EORTC QLQ-C30, have been evaluated for prognostic value for cancer patients but with mixed results. QoL is a very important aspect of the terminal process. Evaluation of these aspects ensures better care (23). However, studies have not found an independent relationship between QoL and survival with the exception of the physical measures included in the QoL instruments or questionnaires such as nausea, dyspnoea and fatigue (41, 61-63).

One study on women with breast cancer showed that loss of appetite and physical and role performance assessed with the EORTC QLQ-C30 questionnaire were related to survival. Only loss of appetite though, was independently related to shorter survival in a multivariate analysis (64). A Scandinavian study on a comparable patient group and using the same instrument did, however, not find any importance of QoL assessment in predicting clinical outcome (65). The prognostic value of EORTC QLQ questionnaire was not confirmed in an American study of patients with advanced lung cancer. In that study, the authors found that pain assessed by the patients themselves had the best predictive value, after clinical factors had been accounted for in multivariate analysis (66).

Other QoL questionnaires have been designed, e.g. Therapy Impact Questionnaire (TIQ), which is constructed especially for the palliative care setting (67). A large Italian study on prognostic power of clinical variables and QoL measures in terminal cancer patients using TIQ, demonstrated that clinical variables predicted survival better than QoL. In spite of a comprehensive model based on several physical symptoms and signs and functional performance that model accounted only for about 30% of the variance (68).

1.4.4 Opioids and survival

It is a common belief that opioids hasten death and the principle of double effect has in the past undermined the appropriate use of opioids to relieve pain. The principle of double effect states that an action with two or more possible effects, including at least one possible good effect and others that are not, is morally permitted if: 1) the action is not immoral, 2) is undertaken only with the intention of achieving the good effect and possible bad effect may be foreseen but not intended, 3) the action must not achieve the good effect through the bad effect and 4) the action must be undertaken for grave reasons. In palliative care this applies for example when giving opioids to patients with pain and dyspnoea risking sedation and respiratory depression (69). Physicians have been reluctant to administer high doses of opioids to relieve severe pain in terminally ill patients because of the risk of harm to the patient. Recent studies based on adequate opioid management have not confirmed this relationship. Opioid use is more common at the end of life and in high doses, but no evidence is documented indicating that initiation of opioids or sedatives or increase in doses according to need is related to shortened survival. For this reason the principle of double effect does not hold (47, 70, 71). Studies have also revealed that those receiving high morphine doses do not have shorter survival than those receiving low doses (70).

A review article from 2003, revising 17 studies on opioid and sedative use in the final stages of life, showed that opioid dosages increased closer to death but had no relationship with shortened survival (47). A large American study on opioid use and survival at the end of life did, on the other hand, reveal in multivariate models that there is a significant association between higher opioid use and shortened survival. The models did, however, not explain more that 10% of the variance and the authors reflected on whether the association was influenced by other factors not measured. The authors emphasised that these results do not justify withholding opioid treatment (72).

1.4.5 Physician's clinical prediction

It is difficult for health care professionals to predict survival and one needs to be highly skilled to do it accurately (22). An audit was conducted in a British hospital on whether deaths that occurred could have been anticipated and whether those impending deaths had been diagnosed and documented as such. The results showed that nearly 50% of patients were diagnosed as dying within 24 hours prior to death and only 13% greater than 72 hours prior to death. Most of the anticipated deaths were recorded as such (73).

A study on physician's prognostic accuracy in terminally ill patients showed that medical specialists, excluding oncologist, are three times more likely than general internists to make overly

unfavourable estimates of prognosis and physicians with the most experience are the most accurate (74). Studies have also revealed that when the physician-patient relationship is good and long-standing and duration between visits short, prognostic ability of the physician worsens (54, 74). This over-estimation of survival is around 40%. Even though physicians over-estimate survival their prediction is associated with actual survival, i.e. the prediction differentiates between those that live longer and shorter but the calibration of the estimate is often inaccurate (75, 76).

According to clinical recommendations from EAPC (39), clinical prediction of survival should be used in conjunction with other prognostic factors. As it has greater accuracy in short-term predictions than in long-term predictions, repeated evaluations may be suitable.

Physician‘s clinical prognostication is important for the over-all prediction of a patient‘s survival. The factors mentioned above, e.g. functional and cognitive performance, physical signs and symptoms, have an impact on the prognostication of physicians. Clinical prediction of survival is usually regarded as a separate predictor of survival because it has been shown to provide more prognostic information beyond those of performance status and other markers (24). The predictive power of a prognostic model improves when physicians’ clinical prediction is added (77, 78). Many models have been designed to combine scores from various factors shown to be predictive of survival to construct a single, final score.

1.4.6 Prognostic Tools

Various prognostic tools have been developed which are easy to use and categorize patients into groups according to survival (34, 39). The tools are based on various factors that have been shown to have statistical relevance in multi-factorial survival analysis (39) and improve on clinical prediction alone (22, 77, 78). They are highly inter-correlated with each other and with physician’s clinical prognostication but the association is only moderately correlated with actual survival (79) so clinicians should be careful in relying only on prognostic tools and be aware of their clinical shortcomings.

The Palliative Prognostic Score (PaP), Palliative Performance Scale (PPS) and the Palliative Performance Index (PPI) are prognostic tools that have been tested and validated in various clinical circumstances (34, 39).

The PaP consists of 6 factors (presence of dyspnoea and anorexia, KPS, clinical prediction of survival, total white blood cell count and lymphocyte percentage) and constructs three specific risk classes, built on the likelihood of 30 day survival (78). Pirovano et al described the construction of the PaP where group A, had a 30 day survival of >70%, group B 30-70% and group C <30%. A statistical difference was found between the groups (80). The PaP score was originally constructed for cancer patients. It has though been found to have prognostic value for both cancer and non-cancer patients and within different settings (81, 82). Limitations of the PaP are the use of laboratory tests and questionable ranges of clinical prediction of survival and short survival of 30 days (34). Because of the biological markers used it is unsuitable for haematological malignancies (78).

The PPS was first developed as a physical performance measurement in palliative care and is derivative of the KPS (83) but was later validated for prognostication for both cancer and non-cancer patients (84, 85). It includes ambulation, activity and evidence of disease, self care, intake and

conscious level. It scores from 0-100% in increments of 10% where 0% is death and 100% is normal condition. Survival estimates are based on the score (84, 85). Low score on PPS is highly predictive for short survival but mid-range score is ambiguous with regards to prognosis (34). Patient's functional status is fundamental to PPS, so for patients with aggressive disease, but who are not yet experiencing functional decline, the score might not reflect actual prognosis (85).

The PPI has only been validated for cancer patients and combines the results from the PPS, oedema, dyspnoea and delirium. It calculates three risk groups based on median survival of >6 weeks, 3-6 weeks and <3 weeks. The sensitivity and specificity of the index is about 80% (86).

1.5 Scientific value

In Iceland, research on prognostic factors in patients with advanced cancer is lacking. Increased knowledge of prognostic factors is a basis for better clinical assessment of prognosis and survival of patients. Prognostication is important for meeting patients' and their families' needs and for resource management. It also helps physicians to be more secure in their prognoses.

Numerous international studies have examined prognostic factors in advanced cancer patients but their results are inconclusive and sometimes contradictory. Many studies are small and their statistical analyses superficial which may explain mixed results. Therefore, further research is needed.

In the current study, two different databases were used to evaluate prognostic factors. The study populations are at different stages in their disease trajectory and different factors and study instruments are examined in each dataset. This study gives a more comprehensive view of an otherwise, fragile and changing study population. The study highlights importance of the process of the disease trajectory and how various symptoms and sign can differ in importance according to timing of the trajectory process. To this day, few studies have examined this process in detail.

2 Objective

The primary objective of this study was to examine prognostic factors for survival in advanced cancer patients in Iceland. For that purpose, two sets of data were used.

The first dataset was an Icelandic data from an international study, the European Pharmacogenetics Opioid Study (EPOS). The participants were cancer patients on strong opioids either receiving life-prolonging cancer treatment and/or palliative care from palliative care settings. In this dataset the predictive value for survival was evaluated for number of metastases, symptoms, pain severity and interference, physical mobility, cognitive function, quality of life, opioid use and demographical variables.

The second dataset consisted of data from advanced cancer patients on first admission to palliative care in Iceland and the international Resident Assessment Instrument for Palliative Care (interRAI PC) was used as a data source. The interRAI PC instrument is a part of a family of assessment tools and is still under development at the time of this study. Hence, its prognostic value has not been explored before. Number of symptoms, presence of pain and other symptoms, nutritional and fluid status, falls, cognitive and functional performance were tested as predictors for survival.

A secondary objective of the study was to compare the prognostic value of each dataset.

Thirdly, nurses' and physicians' assessments of cancer patients' survival, at first admission to palliative care, were examined.

3 Materials and methods

In this chapter the basic methodology of the two datasets is introduced. Both datasets are illustrated and study design and sample, demographical and clinical data and instruments used in the datasets are described. The details of the present study, “Prognostic factors for survival in advanced cancer patients in Iceland”, is explained and which variables and methods are used for analysis.

3.1 Part 1: Data from the European Pharmacogenetic Opioid Study (EPOS)

3.1.1 EPOS dataset

The European Pharmacogenetic Opioid Study (EPOS) (87) was an international, multicentre study with prospective cohort design, which collected information on clinical characteristics, measured serum concentrations of opioids, and gathered biological material for pharmacogenetic analysis to answer several research questions. The primary aim was to study the pharmacogenetics of opioids, brands and dosages of opioids, patients’ assessment of pain and quality of life and the relationship between these factors. It was also a survey of prevalence of symptoms and clinical practices in Europe.

The inclusion criteria were: patients with a verified malignant disease, 18 years and older, no known contraindications, able to give a blood sample, on regularly scheduled strong opioids with duration of treatment not less than three days and a signed informed consent.

Exclusion criteria were: patients did not consent to participate, not capable of the language used at the study centre and had cognitive failure due to dementia or neurological disease (other than those caused by cancer).

Patients were still receiving life-prolonging cancer treatment and/or palliative care. Total of 2294 patients were included in the international study.

3.1.1.1 Demographical and clinical data in EPOS

Demographical and clinical data, collected in EPOS, are reviewed in table 1.

Table 1. An overview of demographical and clinical data in EPOS

Demographical and clinical data	**Specifications**
Patient characteristics	Name, age, gender, weight, height and ethnicity Concomitant diseases Previous known history of alcoholism or drug abuse Principle indication for referral to hospital and department category Category of department when the patient is recruited into the study
Medications	All medications and dosages including opioids for the previous 24 hours Duration of opioid treatment, time since last change in scheduled opioid dose, use of rescue opioids last 24 hours, route of opioid administrations, date of first opioid treatment and date of last change in opioid dose Observed status of present opioid treatment Previous unsuccessful trials with other opioids
Non-proven treatments	Acupuncture, homeopathic, healing/praying, diet/herbal/vitamin/zone therapy or other
Cancer disease	Cancer diagnosis, time since cancer diagnosis, localization of metastases
Pain	The mechanism of pain registered as recommended in the Edmonton Staging System for cancer pain
Blood samples	Not used

3.1.1.2 Study instruments in EPOS

Instruments in the international study are the Symptom checklist, Karnofsky Performance Scale (KPS), Mini Mental State Examination (MMSE), Brief Pain Inventory (BPI) and EORTC QLQ-C30. They are further explained in table 2.

Table 2. An overview of study instruments in EPOS

Variable	Study instrument	
Symptoms	Symptom Checklist (88)	17 symptoms and their severity assessed the last 24 hours by a research nurse Grading from none (0) to mild (1), moderate (2) and severe (3) Symptoms assessed: pain, fatigue, generalised weakness, anxiety, anorexia, depression, constipation, poor sleep, dyspnoea, focal weakness, nausea, confusion, vomiting, diarrhoea, itch, hallucinations and hiccups
Physical function	Karnofsky Performance scale (KPS) (36-38, 89) (see appendix 1)	Physical performance rated on 1-100% scale, in steps of ten, where 0 = death, 50% = considerable assistance and frequent medical care; out of bed greater than 50% of the time, and 100% = no evidence of disease on performance The KPS has been documented to have good predictive validity
Cognitive function	Mini Mental State Examination (MMSE) (44)	Cognitive function test that tests orientation, memory, attention, recall, language, repetition and complex commands. Based on scores between 1 and 30. Scores 23 and under indicate cognitive impairment
Pain	Brief Pain Inventory (BPI) (90-92)	14 item self-assessment scale on pain the last 24 hours, assesses the presence of pain and pain severity (6 items; 0=no pain to 10=worst pain imaginable), pain management (1 item; 0%=no relief from pain and 100%=total relief of pain) and interference with life activities (7 items, daily activities, mood, walking, working, social communication, sleeping and enjoyment of life; 0=no interference to 10=total interference with daily living) This scale has been used in numerous studies in palliative care and has shown to be both sensitive and reliable
Quality of life	EORTC QLQ-C30, version 3.0. (93, 94)	A 30 item quality of life questionnaire developed by the European Organization for Research and Treatment of Cancer (EORTC). Cancer specific and measures general aspects of health related quality of life. Consists of one global scale for health status and quality of life, five functional scales (physical, emotional, social, role and cognitive) and nine symptom items (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties) A high score for the global health status and the functional scales represents a high QoL or a high/healthy level of functioning. A high score for a symptom scale/item represents a high level of symptoms or problems The global scale have a response format from 1=very poor to 7=excellent. Other scales and items have a Likert response choices, 1=not at all to 4=very much. Assessment refers to the last 7 days

3.1.2 Prognostic Factors for Survival in Advanced Cancer Patients in Iceland

The present study was a secondary analysis of data from the Icelandic part of EPOS. A descriptive analysis was given for multiple variables from the original dataset and prognostic value was estimated. The variables were age, gender, department category, time since diagnosis, number of medication taken in the last 24 hours, survival, cancer type and number of metastases, number of symptoms, presence of physical symptoms the last 24 hours, physical mobility, cognitive function, quality of life and opioid use.

Some variables in EPOS were not used for survival analyses. A few were irrelevant for this study and excluded. Others were inappropriate for direct survival analyses and had to be transformed. This is explained further in table 3 and the chapter “Statistical analysis”.

3.1.2.1 Participants and sample

Of EPOS participants, 150 patients were from Iceland, and they were all included in the present study. The study sample was a convenience sample of patients, recruited by a research nurse at LSH i.e. from the general and geriatric in-patient palliative care wards in Kópavogur and Landakot, the oncology, haematology and surgical wards and from out-patient clinics. The two palliative home-care services in Reykjavik, one within LSH *(Heimahlynning)* and the other privately run Karítas (*Hjúkrunar- og ráðgjafaþjónusta Karítas)* were included with the patients from the out-patient clinics.

Data were collected from October 1st, 2005 to February 29th, 2008. All data were transferred to Trondheim, Norway, entered into a database and the Icelandic data became accessible in the spring of 2008. The Death Registers in Iceland was used to determine date of death and the information was collected until August 1st, 2009.

Responsible investigators were Valgerður Sigurðardóttir and Sigríður Gunnarsdóttir. Informed consent was provided and permission obtained from the National Bioethics Committee (VSN 05-041-S2), the Data Protection Authority (2005030131) and the Chief Medical Executive of LSH (04.03.2005). An additional approval, regarding the survival analysis, was obtained from the National Bioethics Committee (see appendix 4).

3.1.2.2 Data analysis

Table 3 illustrates the variables from demographical and clinical data together with instruments studied with respect to descriptive and survival analysis. A thorough descriptive analysis was done to compare the two datasets.

Table 3. Analysed factors for EPOS

Variable	
Demographical data	Age and gender analysed descriptively and entered into a survival model Time from diagnosis to enrollment into study in months and analysed descriptively Number of medication taken last 24 hours excluding opioids was counted and analysed descriptively
Survival	Days from enrollment to death or end of study time, i.e. August 1st, 2009
Cancer characteristics	
- **Cancer diagnosis**	Grouped in eight groups according to the location of the primary tumour, breast, prostate, lung and GI cancer (including pancreas, stomach and colon), cancer of the female reproductive organs, haematological cancer, urological cancer and of other sites Analysed descriptively
- **Number of metastatic sites**	Localization of metastases was converted to a number of different sites Analysed descriptively and entered into a survival model
Opioid treatment	Time since start of opioid treatment to enrollment into the study in months Observed status of present opioid treatment. Grouping was transformed, from 6 groups to 3 - 1=recently initiated, still undergoing titration - 2= stable dosing, good or partial relief (stable dosing, good relief + stable dosing, partial relief, no significant side effects + stable dosing, partial relief, but with side effects) - 3= stable dosing but inadequate relief (stable dosing, inadequate relief, no significant side effects + stable dosing, inadequate relief, but with side effects) Total scheduled opioid dose and total break-through dose during the last 24 hours, converted to oral morphine equivalent doses in milligrams (see appendix 2) All items were analysed descriptively and total scheduled opioid doses entered into a survival model
Number of symptoms	Number of symptoms from the symptom checklist were analysed descriptively and entered into a survival model
Instruments	
- **Symptom Checklist**	Grouping transformed to present the last 24 hours (group 0) vs. not (groups 1-3) All symptoms were analysed descriptively according to their frequency Some, but not all symptoms, were entered into the survival model – see in more detail in "Statistical analysis"
- **KPS**	Descriptive statistics applied and entered into a survival model
- **MMSE**	Descriptive statistics applied and entered into a survival model
- **BPI**	Pain severity and interference score used and entered into a survival model
- **EORTC QLQ-C30**	The global health and quality of life scale and 3 of 5 functional scales (role, emotional and social function scale) were entered into a survival model Other scales were excluded from the survival analysis – see in more detail in "Statistical analysis"

3.1.2.2.1 Missing Data

The EPOS dataset had minimal missing data. No missing data was on age, gender, cancer type, number of metastases, department category, time since diagnosis, Karnofsky Performance Scale score, status of present opioid treatment and morphine and medication specifics. Five out of 150 had missing data from MMSE, BPI interference score and the EORTC QLQ-C30 scales. Only one person had missing data from the physical symptoms and three from the BPI severity score.

3.1.2.3 Statistical analysis

Descriptive statistics were used to analyse demographical and clinical data including KPS and MMSE. Categorical data were summarized as frequencies and percentages but continuous variables reported with mean, standard deviation (SD) and median. Total survival was analysed using the Kaplan-Meier method. Survival was calculated from date of admission into the study until death or end of study time, whichever came first. Death from all causes was the outcome variable.

3.1.2.3.1 Variable selection

For statistical analyses some variables had to be excluded or transformed. Transformation of variables was done to enable statistical analysis and comparison with interRAI PC data. According to Vittinghoff et al (95) a small number of events (deaths) in each subgroup of variables does not reach statistical relevance and lack power for further analyses. The aim is to have more than 15-25 events per subgroup. To achieve power for regression analyses, grouping was transformed for some variables where events were lower than 15. Grouping was transformed in the symptom checklist to present the presence of symptoms in the last 24 hours and then compared with interRAI PC data where presence of symptoms was observed in the last 3 days. This was also done for “status of present opioid treatment”. Both transformations were made because of lack of events in each subgroup of variables and for comparable reasons. In the EPOS dataset, metastases were described according to their location. This was transformed into number of different sites of metastases to simplify analysis.

To avoid type 1 error (where the null hypothesis is true, but is rejected) by measuring the effect of two or more similar variables on the same outcome (95) some variables are excluded from regression analyses. In EPOS were two physical measures (KPS and the physical function scale in EORTC QLQ-C30), two cognitive measures (MMSE and the cognitive function scale in EORTC QLQ-C30), three measures of pain (BPI, pain symptom item in EORTC QLQ-C30 and pain in Symptom Checklist) and finally two measures on symptoms other than pain (Symptom Checklist and symptom items in EORTC QLQ-C30). Analysis was done on KPS, MMSE, BPI regarding pain and Symptom Checklist regarding other symptoms. Each has strong validity and is widely known and accepted for prognostic purposes (38, 44, 90, 92). Other symptoms in the Symptom Checklist were chosen for statistical analyses because the results are in a form comparable to interRAI PC data whereas the form of the symptom items in EORTC QLQ-30 is not.

A survival model is based on a total number of variables. If the number of variables in the model exceeds 10% of the total number of events in the model (the number of deaths in this study) a loss of

power occurs in the study (95). In EPOS, 144 patients died out of 150, therefore only 15 variables were selected for further analyses in the current study.

The selection of variables was based on former knowledge of factors that have shown relationship with survival. Because proportional hazard did not hold for general weakness and cancer diagnosis (see later) the final 15 selected variables were the following: age, gender, number of metastases, number of symptoms, two of the most common symptoms in the symptom checklist (fatigue and dyspnoea, excluding pain and general weakness), morphine equivalent of total daily oral dose, KPS, MMSE, BPI severity and interference score and at last four scales on the EORTC QLQ-C30 (global health status, role, emotional and social function scales).

3.1.2.3.2 Final analyses

The data were right censored (death) with left truncation (study time). For survival estimation, log-minus-log survival plots in Kaplan-Meier analysis were used to estimate whether proportional hazard held and, if so the variables were entered into univariate and multivariate Cox regression models.

Proportional hazard on categorical variables was assessed unchanged using Kaplan-Meier survival curves but the continuous variables were grouped into tertiles and then assessed by the same method. If the survival curves crossed and were not proportional to each other, the variable was not used in further analyses (95). The variables, cancer diagnosis and presence of weakness, broke the proportional hazard and were therefore not included into the final model (95).

Cancer site and type have been shown to affect survival in other studies (41, 54, 55), so even though cancer diagnosis did not hold proportional hazard a model was run including cancer diagnosis. The final results did not change (results not shown).

Univariate analyses with categorical and continuous variables were performed by Cox Regression model with adjustment for age and gender. All the variables were then entered into a multivariate Cox regression model. With a stepwise backward selection method the final model was completed. The significance level was set at 0.05 for all statistical tests. Statistical analysis was done in SPSS, version 19 (96).

3.2 Part 2: Data from the study "Comprehensive assessment of patients' well-being in palliative care" using the interRAI PC assessment tool

3.2.1 interRAI PC dataset

"Comprehensive assessment of patients' well-being in palliative care" with the interRAI PC dataset was a longitudinal, quantitative study performed within palliative care in Reykjavik, Iceland. The interRAI PC assessment tool (version 8.0), which at the time was in the final phase of development, was used to gather information. The primary objective of this study was to assess symptoms and needs of the palliative care population in Iceland and take part in development of the interRAI PC assessment tool.

During a six month period, from October 15th, 2003 to April 15th, 2004, data were collected. Patients were evaluated by a health care professional, either a responsible nurse or a physician at three time points; first admission to palliative care, two weeks later and upon discharge or death.

Responsible investigators were Valgerður Sigurðardóttir and Ingibjörg Hjaltadóttir. Informed consent was provided and permission obtained by the National Bioethics Committee (VSN 02-160-V1), the Data Protection Authority (2002120589) and the Chief Medical Executive of LSH (18.12.2002).

3.2.1.1 Participants

All new patients, over 18 years of age, with incurable, advanced diseases and enrolled in palliative care in the greater Reykjavik area were approached for recruitment in the study. The participating palliative care services were; the general and geriatric palliative care in-patient wards in Kópavogur and Landakot and the hospital-based palliative consultation team at LSH together with the two palliative home-care teams in Reykjavik, one within LSH *(Heimahlynning)* and the other privately funded Karitas (*Hjúkrunar- og ráðgjafaþjónusta Karítas)*. Information on those who denied participation was not gathered. In the study, 124 patients were included, resulting in total of 421 assessments from all three assessment points.

3.2.1.2 interRAI Palliative Care Assessment Tool

The international Resident Assessment Instrument Palliative Care (interRAI PC) is an assessment tool which documents well-being and care of palliative care patients. The first interRAI tool was developed in the USA in 1987 to standardise quality of care of nursing home residents. The interRAI Nursing Home (NH) is now being used in over 30 countries and has evolved into a family of assessment tools like interRAI Home Care, interRAI Long Term Facility and interRAI Palliative Care. InterRAI NH has been used in nursing homes in Iceland since 1994 (97). The interRAI assessment tools contain comprehensive information about health, function and nursing care needs of people in various health and social care situations. The objective of the assessment is to analyse strengths, wishes and needs of patients and to give a comprehensive view of the person. The assessment of patients' condition refers to the last three days prior to assessment (98).

Every interRAI tool has a common core of variables in addition to specific items related to the individual measurement tool. InterRAI PC is designed for palliative care to document symptoms in patients near end of life. In addition to core items for the interRAI assessment tools, it adds an item of estimated survival, psycho-social items and treatment and procedural items. InterRAI PC emphasises various symptoms in advanced diseases i.e. pain, dyspnoea, nausea in addition to cognitive function and physical function in activities of daily living. InterRAI PC comprises 16 sections and 62 items, see table 4 and appendix 3.

Table 4. An overview of interRAI PC contents

Section	Content
A. Identity information	Name, gender, year of birth, marital status, location of treatment, date of death, reasons for assessment, type of palliative care program, ICD codes of diseases, estimated prognosis, date of assessment, zip code of the patients' address, date of the beginning of PC program, ethnicity/race, primary language, living status, living arrangement and time since last hospital stay
B. Health conditions (as observed the last 3 days by the health care professional)	Various pain symptoms and sources of the pain (e.g. frequency, strength and pattern) Frequency of falls Frequency of various symptoms e.g. GI, cardiac and pulmonary problems. Ascites, pleural effusion, fatigue, dry mouth, hiccups, offensive odour, muscle cramps, oedema and sleep disturbance Lifestyle questions regarding smoking and alcohol consumption
C. Oral/nutritional status	Mode of nutritional and fluid intake and whether sufficient or not
D. Skin condition	Highest current pressure ulcer stage and number. Presence of stasis ulcer, major skin problems, skin tears or cuts or other skin conditions or changes in skin condition. Number of current pressure ulcers. Presence of foot problems that interfere with gait
E. Cognition	Cognitive skills for daily decision making and memory/recall ability. Experiences of fluctuating states of consciousness or periodic disordered thinking/awareness
F. Communication	The ability to communicate and understand others
G. Mood and behaviour	Indicators of possible depression, anxiety and sad mood
H. Psychosocial well-being	Relationship with the family and the patient's coping skills and spirituality
I. Physical functioning	ADL-self performance and ADL functional rehabilitation potential
J. Continence	Bladder and bowel continence and the presence of urinary collection device
K. Medications	List of medications and allergy
L. Treatments and procedures	Treatments and programmes received or scheduled
M. Responsibility/directives	Various wishes and directives of the patient
N. Social relationships	Social interaction with friends and family
O. Discharge	Date and place of discharge
P. Assessment information	Signature

3.2.2 Prognostic Factors for Survival in Advanced Cancer Patients in Iceland

In this study only data from patients with cancer were used and the assessment made on first admission to palliative care. Of a total of 124 patients in the original study, 116 had cancer, but eight patients had non-cancer diagnoses.

Numerous variables were collected in the dataset but not all were analysed in this study. The variables included in analysis are: gender, age, cancer type, self-reported pain control, number of and observed presence of many physical symptoms in the last three days, survival, physical and cognitive function, falls in the last 30 days and nutritional and fluid intake. The variables chosen for analysis were those that have been shown previously to be relevant. This is further described in the chapter on statistical analysis.

The Death Registers in Iceland is used to determine date of death. The information was collected on September 1st, 2008.

3.2.2.1 Data clearance

At the start of this study, the interRAI PC dataset was crude. Therefore, data clearance became necessary in order to take out repeated data as some patients had been repeatedly assessed when they were moved between service settings.

3.2.2.2 Data analysis

Table's 5-8 show demographical and clinical variables that were entered into descriptive and survival analysis.

Tables 6 and 7 explain pain control and physical symptoms and nutrition, fluid intake and falls respectively. The scaling was transformed for survival analysis and comparison with EPOS (95).

Variables on pain, cognitive performance and ADL were combined in the interRAI PC dataset to get comprehensive scales for analysis (99, 100). These scales are shown in table 8 and for statistical testing they were simplified as is demonstrated.

Table 5. Analysed factors for interRAI PC: Demographical and clinical factors

Item	
Demographical data	Age and gender analysed descriptively and entered into a survival model
Number of symptoms	Number of observed physical symptoms analysed descriptively and entered into survival model
Survival	Days from enrollment to death or end of study , i.e. September 1, 2008
Cancer type	Cancer types registered as ICD numbers in the dataset, grouped into eight types, breast, prostate, lung and GI cancer (including pancreas, stomach and colon), cancer of the female reproductive organs, haematological cancers, urological cancer and other cancers Analysed descriptively

Table 6. Analysed factors for interRAI PC: Pain control and physical symptoms in the last 3 days. Transformation of scaling for descriptive and survival analysis

Item	Scaling	Transformed scaling
Pain control (ability of current therapeutic regime to control pain adequately, self-reported)	0. No pain 1. Controlled adequately by therapeutic regime 2. Controlled when therapeutic regime followed, but not always followed as ordered 3. Therapeutic regime followed, but pain control not adequate 4. No therapeutic regime being followed for pain, pain not adequately controlled	0. No pain (0) 1. Satisfactory results (1,2) 2. Unsatisfactory results (3,4)
Physical symptoms (observed): - Pain - Constipation - Faecal impaction - Diarrhoea - Vomiting and nausea - Difficulty coughing or clearing airway secretion - Shortness of breath with exertion (=dyspnoea) - Inability to lie flat due to shortness of breath - Tires easily and poor task endurance (weakness) - Various sleep problems - Ascites - Pleural effusion - Fatigue - Dry mouth - Hiccups - Offensive odour - Muscle cramps - Oedema	0. Not present 1. Present but not exhibited in last 3 days 2. Exhibited on 1-2 of last 3 days 3. Exhibited daily last 3 days	0. No symptom the last 3 days (0,1) 1. Symptom the last 3 days (2,3)

Table 7. Analysed factors for interRAI PC: Nutrition, fluid intake and falls. Transformation of scaling for descriptive and survival analysis

Item	Scaling	Transformed scaling
Sufficient nutritional intake	0. Intake sufficient, not losing substantial weight 1. Losing 2+ pounds (1kg) a week, most likely not water loss 2. Evidence of wasting	0. Sufficient intake (0) 1. Insufficient intake (1,2)
Sufficient fluid intake: More than 1000ml per day	0. Yes 1. No	Unchanged
Falls	0. No falls in the last 90 days 1. No fall in the last 30 days, but fall reported in 31-90 days 2. One fall in the last 30 days 3. Two or more falls in the last 30 days	0. No fall in the last 30 days (0,1) 1. Falls in the last 30 days (2,3)

Table 8. Analysed factors for interRAI PC: Items combined and transformation of scaling for descriptive and survival analysis.

	Items combined from interRAI PC assessment tool	Scaling (used for descriptive analysis)	Simplified scaling (used for survival analysis)
Pain scale (101)	Pain frequency (self-reported) Pain intensity (self-reported)	0. No pain 1. Less than daily pain 2. Daily pain but not severe 3. Daily severe pain 4. Daily excruciating pain	0. Less than daily pain (0,1) 1. Daily pain (2-4)
Cognitive performance scale (CPS) (99)	Cognitive skills for daily decision making Short-term memory Making self understood ADL self-performance: eating	0. Intact 1. Borderline intact 2. Mild impairment 3. Moderate impairment 4. Moderate/severe impairment 5. Severe impairment 6. Very severe impairment	0. Intact (0,1) 1. Impaired (2-6)
The ADL hierarchy scale (100)	ADL self-performances: personal hygiene, wheeling, toilet use and eating	0. Independent 1. Supervision required 2. Limited impairment 3. Extensive assistance required–1 4. Extensive assistance required–2 5. Dependent 6. Total dependence	0. Independent or assistance (0-4) 1. Dependency (5,6)

3.2.2.2.1 Missing Data

The interRAI PC dataset had no missing data on gender, age and from cancer type, other variables had <10% of missing data.

3.2.2.3 Predictions of survival

One variable from the interRAI PC dataset was an estimation of prognosis. The health care professionals were asked to estimate the patient's survival. The grouping according to time left of life was: 1) death is imminent, 2) less than six weeks, 3) six weeks to six months or 4) more than six months. The accuracy of this estimation was calculated.

3.2.2.4 Statistical analysis

Demographical and clinical data and prediction of survival were analysed with descriptive analysis. Categorical data were summarized as frequencies and percentages but continuous variables reported with mean, standard deviation (SD) and median. Total survival was analysed using the Kaplan-Meier method. Survival was defined from date of admission into the study until death or end of study time, whichever came first. Death from all causes was taken as an outcome.

3.2.2.4.1 Variable selection

Some variables had to be transformed or excluded for statistical analysis. In statistical analyses a small number of events (deaths) or under 15-25 events per subgroup of variables in a study does not

reach statistical relevance and lack power for more analyses (95). Therefore, some variables (see below), where events were lower than 15, were transformed to increase statistical power for regression analyses and also for comparison reasons with results from the EPOS dataset. The transformation is shown in detail in tables 6-8. Pain control (no pain, satisfactory result of therapeutic regime and unsatisfactory results) was compared with status of present opioid treatment in EPOS (recently initiated, stable dosing and good or partial relief and stable dosing but inadequate relief). Physical symptoms, as observed in the last 3 days, were compared with the Symptom Checklist in EPOS which is a self-assessment of symptoms in the last 24 hours. The items on nutritional intake and falls were transformed for regression analysis because number of events in each subgroup was very small. The EPOS dataset contained no comparable variables. InterRAI PC scales on pain, cognitive performance and ADL hierarchy also had many subgroups so transformation for regression analysis was made.

Similar to what had been conducted in the EPOS dataset, some variables were excluded from survival analyses in the interRAI PC dataset. The exclusion was done to avoid type 1 error but the risk of type 1 error increases when effects of two or similar variables are measured on the same outcome (95). Two variables were about presence of pain in the dataset, pain in the physical symptom category and the pain scale. The pain scale was included because it is a more comprehensive measurement on pain and it measures not only the presence of pain but also the intensity. Nutritional and fluid intake was selected because of their relation to anorexia and cachexia. Falls in the last 30 days were included because in pilot analysis, not shown in this paper, it revealed repeated effect on survival.

The interRAI PC part of the study had 111 events (i.e. deaths) so total variable selection for final survival model was limited to 11 to 12 as explained previously (95). Age, gender, cancer diagnosis, number of symptoms, presence of fatigue and dyspnoea in the last 3 days, ADL hierarchy, cognitive performance and pain scale, falls in the last 30 days and nutritional and fluid intake were selected.

Of 19 physical symptoms, only two were chosen for analyses, fatigue and dyspnoea. Fatigue and dyspnoea are two out of five most frequent symptoms in the interRAI PC dataset and are comparable with results in the EPOS part. The other three most frequent symptoms were weakness, which was excluded from EPOS because it did not hold proportional hazard, pain, which was estimated by other means and sleep dysfunction which was too poorly defined. Other factors, not selected for analyses, were either irrelevant for this study or too complex for statistical analyses.

3.2.2.4.2 Final analyses

These data were right censored (death) and truncated left (study time). Survival estimation was done with log-minus-log survival plots in Kaplan-Meier analysis and tested to see if proportional hazard held or not. If the variables held, they were entered into univariate and multivariate Cox regression models.

The proportional hazard was assessed using Kaplan-Meier survival curves on the categorical variables. The continuous variables were grouped into tertiles to get categories and then assessed by same method. If the survival curves crossed and were not proportional to each other, the variable was

not used in further analyses (95). The cancer type variable broke the proportional hazard estimate and was not included in the final model.

Univariate analyses with categorical and continuous variables were performed with the Cox Regression model with adjustment for age and gender. The variables were then entered into a multivariate Cox regression model. With a stepwise, backward selection method the final model was completed. The significance level was set at 0.05 for all statistical tests. Statistical analysis was done in SPSS, version 19 (96).

3.3 Comparison between the two datasets

This study, Prognostic factor for Survival in Advanced Cancer in Iceland, is a study conducted on two datasets which are different in many ways. One of the objectives of this study was to explore the observed differences of these datasets, both in regards to demographics and results of regression analyses but no statistical analyses were made on these observations.

4 Results

4.1 Part 1: The Icelandic EPOS data

4.1.1 Demographical data

Included in the Icelandic EPOS database were 150 patients, 88 women (59%) and 62 men (41%) with a mean age of 65 years (SD 12.7). Most common cancer type was gastrointestinal, followed by breast and lung cancer. Majority (91%) of patients had metastases. Most patients were recruited through an out-patient clinic (67%). The average time since diagnosis was 36 months (SD 55.1). Mean KPS value was 53% (SD 14.0) and 27 (SD 2.6) on the MMSE (table 9).

Mean number of symptoms in the last 24 hours were six (SD 2.5), with most frequent symptoms being fatigue (85%), pain (82%) and general weakness (81%) (table 10).

Table 9. Patients' characteristics for EPOS.

Variable	N (%)	Mean	SD	Median
Gender				
Women	88 (59)			
Men	62 (41)			
Age (years)		65	12.7	66
Cancer type				
Breast	27 (18)			
Prostate	23 (15)			
Lung	26 (17)			
Gastrointestinal	33 (22)			
Gynaecological	18 (12)			
Haematological	3 (2)			
Urological	7 (5)			
Other	13 (9)			
Metastases				
No	13 (9)			
Yes	137 (91)			
Service Category				
In-Patient	50 (33)			
Out-Patient	100 (67)			
Time since diagnosis (months)		36	55.1	16
Karnofsky Performance scale (KPS) (%)		53	14.0	50
Mini Mental State Examination (MMSE)		27	2.6	28

Table 10. Patients' characteristics for EPOS cont.: Number of symptoms and presence of symptoms in the last 24 hours

Variable	N (%)	Mean	SD	Median
Number of symptoms (last 24 hrs.)		6	2.6	6
Presence of physical symptoms (last 24hrs) (as measured by the Symptom Checklist – observed)				
Fatigue	127 (85)			
Pain	123 (82)			
General weakness	122 (81)			
Dyspnoea	81 (54)			
Anorexia	77 (51)			
Local weakness	63 (42)			
Constipation	53 (35)			
Nausea	52 (35)			
Anxiety	49 (33)			
Depression	43 (29)			
Poor sleep	32 (21)			
Itch	29 (19)			
Diarrhoea	26 (17)			
Confusion	20 (13)			
Vomiting	9 (6)			
Hiccups	10 (6)			
Hallucination	8 (5)			

Most patients received a stable morphine dose with adequate relief (67%). Mean morphine equivalent scheduled total daily oral dose was 179 mg (SD 228.0) and as needed 45 mg (SD 86.5). The number of medication taken 24 hours before study time (excluding opioids) was nine (SD 3.4) (table 11).

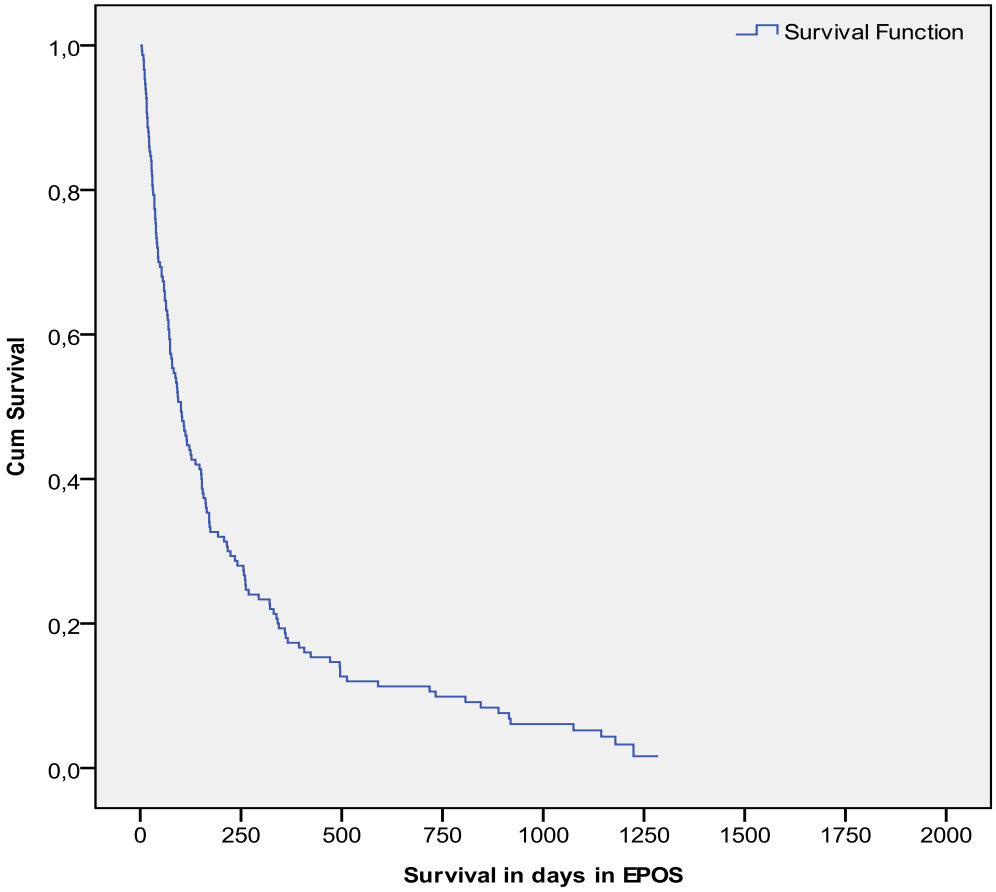
Table 11. Patients' characteristics for EPOS cont.: Status and time since start of present opioid treatment, number of medications and morphine equivalent use (po).

Variable	N (%)	Mean	SD	Median
Observed status of present opioid treatment				
Recently initiated, still undergoing titration	21 (14)			
Stable dosing, adequate relief	101 (67)			
Stable dosing, inadequate relief	28 (19)			
Time since start of opioid treatment (months)		4	6.0	2
Total daily oral dose of morphine equivalent (mg)		179	228.0	120
Total daily oral dose of morphine equivalent as needed (mg)		45	86.5	29
Number of medications taken last 24 hrs (excl. opioids)		9	3.4	9

4.1.2 Total survival

Six patients (4%) of the study group were alive on August 1, 2009. Mean survival was 235 days (SD 26.0) and the median survival was 101 day (SD 14.1) (figure 2) from admission to study to death or end of study.

Figure 2. Kaplan Meier survival curve: Total survival for EPOS, in days from admission to death or end of study (August 1st, 2009).



4.1.3 Univariate analysis

Table 12 shows all studied variables included in a univariate Cox regression model, adjusted for age and gender. The statistically significant variables for survival in a univariate Cox regression model were as follows; higher number of metastases increased the risk of death (HR 1.240), higher score on KPS (HR 0.984), MMSE (HR 0.860) and the role function scale in the EORTC QLQ-C30 (HR 0.991) decreased the risk of death.

Table 12. Univariate Cox regression model for EPOS (adjusted for age and gender)

Variables	Hazard Ratio (95% CI)	p-value
N of metastases	*1.240 (1.033-1.489)	0.021
N of symptoms	1.063 (0.997-1.133)	0.063
Presence of symptom in the last 24 hours		
Fatigue	1.556 (0.957-2.527)	0.074
General weakness	1.263 (0.821-1.944)	0.287
Dyspnoea	1.339 (0.938-1.910)	0.108
Morphine equivalent of total daily oral dose (mg)	1.000 (1.000-1.001)	0.217
Karnofsky Performance scale (KPS)	*0.984 (0.972-0.996)	0.007
MMSE	*0.860 (0.799-0.926)	<0.001
BPI severity score	0.982 (0.888-1.086)	0.727
BPI interference score	1.006 (0.944-1.071)	0.862
EORTC QLQ-C30		
Global health status scale	0.996 (0.989-1.004)	0.344
Role function scale	*0.991 (0.986-0.996)	<0.001
Emotional function scale	1.001 (0.993-1.010)	0.761
Social function scale	0.998 (0.993-1.003)	0.498

***significant, value <0.05**

4.1.4 Multivariate analysis

The results of multivariate analysis (table 13) showed that number of metastases was independently related to survival where every new site of metastasis was estimated to increase the risk of death by 24%. Each additional point on MMSE independently decreased the risk of death by an estimation of 14%. The same applied for role function scale where one increased point on the role function independently decreased the risk of death by about 1%. Increased interference of pain with daily living seemed to be independently significant and related to longer survival (HR 0.915). Presence of fatigue during the last 24 hours was significantly related to worse prognosis (HR 1.823). Of note is that the doses of opioids were not related to survival.

Table 13. Final multivariate Cox regression model for EPOS

Variables	Hazard Ratio (95% CI)	p-value
N of metastases	1.242 (1.028-1.501)	0.024
MMSE	0.860 (0.798-0.927)	<0.001
Role function scale	0.991 (0.986-0.997)	0.002
BPI interference	0.915 (0.846-0.990)	0.027
Fatigue (last 24hours)	1.823 (1.065-3.120)	0.029

4.2 Part 2: InterRAI PC data

4.2.1 Demographical data

This part of the study included 116 patients with advanced cancer. Women were 61 (53%) and men 55 (47%). The mean age was 72 years (SD 12.6). Most common cancer type was gastrointestinal followed by lung and breast cancer (table 14). All patients had advanced disease. Patients had a high score on the ADL hierarchy scale, a mean of four (out of six), and were thus quite dependent. CPS score was low or one (out of six), which translates into a more intact cognitive function. The pain scale showed a mean of one (out of four) (table 14).

The mean number of physical symptoms in the last 3 days was six. Pain control was satisfactory in 47 patients (42%) of all patients but unsatisfactory in 35 (32%). Pain was not reported by 26% of patients. The most common symptoms were fatigue, weakness, pain and sleep dysfunction (table 15).

Over 60% of patients had sufficient nutrition and fluid intake and most had not fallen in the last 30 days (83%) (table 16).

Table 14. Patients' characteristics for interRAI PC

Item	N (%)	Mean	SD	Median
Gender				
Women	61 (53)			
Men	55 (47)			
Age (years)		72	12.6	74
Cancer type				
Breast	16 (14)			
Prostate	12 (10)			
Lung	28 (24)			
Gastrointestinal	33 (28)			
Gynaecological	3 (3)			
Haematological	3 (3)			
Urinary tract	10 (9)			
Other	11 (9)			
ADL hierarchy scale (from 0-6)		4	1.7	5
Cognitive Performance Scale (CPS) (from 0-6)		1	1.7	0
Pain Scale (from 0-4)		1	1.2	1

Table 15. Patients' characteristics for interRAI PC cont.: Pain control and presence of symptoms in the last 3 days

Item	N (%)	Mean	SD	Median
Pain control (self-reported)				
No pain	29 (26)			
Satisfactory pain control	47 (42)			
Unsatisfactory pain control	35 (32)			
Number of physical symptoms (last 3 days)		6	2.7	6
Presence of physical symptom (last 3 days) (observed)				
Fatigue	97 (83)			
Weakness	92 (78)			
Pain	70 (60)			
Sleep dysfunction	55 (47)			
Shortness of breath with exertion (dyspnoea)	44 (38)			
Nausea	44 (38)			
Dry mouth	40 (34)			
Constipation	33 (28)			
Vomiting	27 (23)			
Difficulty coughing	25 (21)			
Oedema	23 (20)			
Diarrhoea	21 (18)			
Inability to lie flat due to shortness of breath	20 (17)			
Faecal impaction	8 (7)			
Ascites	6 (5)			
Pleural effusion	5 (4)			
Muscle cramps	2 (2)			
Hiccups	1 (1)			
Offensive odour	1 (1)			

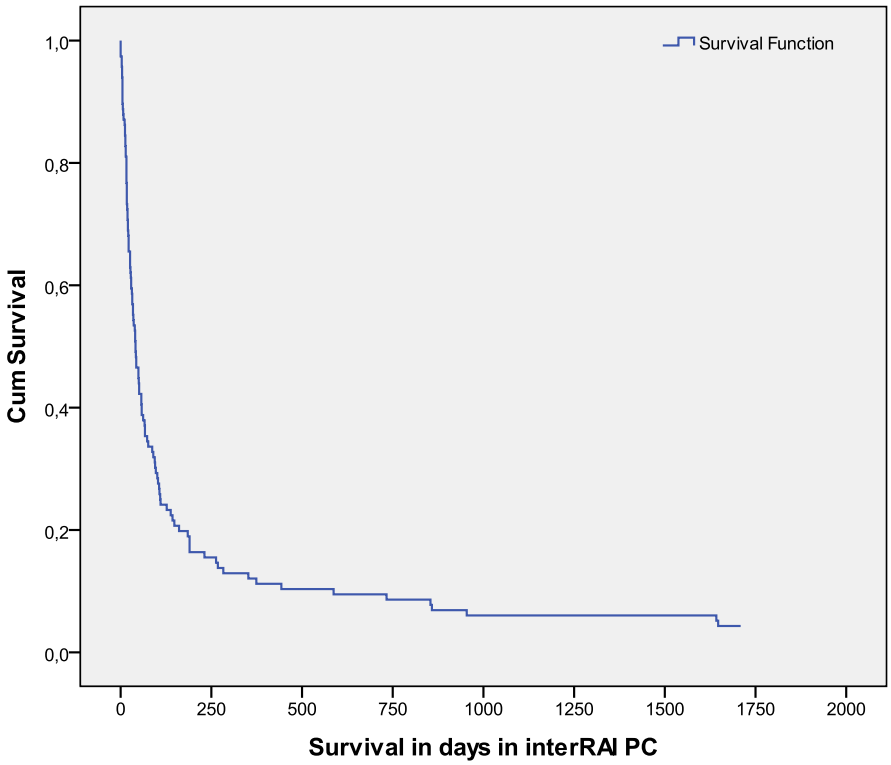
Table 16. Patients' characteristics for interRAI PC cont.: Nutrition, fluid intake and falls

Item	N (%)
Insufficient nutritional intake	
Yes	37 (38)
No	61 (62)
Insufficient fluid intake	
Yes	36 (33)
No	72 (67)
Falls in the last 30 days	
No	91 (83)
Yes	18 (17)

4.2.2 Total survival

Five patients (4%) in this study were alive on September 1st, 2008. Mean survival was 196 days (SD 38.5) from date of admission to September 1st, 2008 and median survival was 41 day (SD 6.7) (fig. 3).

Figure 3. Kaplan Meier survival curve: Total survival for interRAI PC, in days from admission to death or end of study (September 1st, 2008)



4.2.3 Univariate analysis

In an univariate analysis the analysed variables were number of symptoms, the presence of fatigue and shortness of breath with exertion in the last 3 days, ADL hierarchy scale, CPS, pain scale, falls, nutrition and fluid intake. When adjusted for age and gender, increased number of symptoms (HR 1.117), presence of shortness of breath with exertion in the last 3 days (HR 2.248), falls in the last 30 days (HR 2.324) and insufficient nutritional intake (HR 1.544) was related to shortened survival (table 17).

Table 17. Univariate Cox regression model from interRAI PC (adjusted for age and gender)

Variables	Hazard Ratio (95% CI)	p-value
N of symptoms	*1.117 (1.039-1.202)	0.003
Presence of symptom in the last 3 days		
Fatigue	1.291 (0.757-2.202)	0.348
Shortness of breath with exertion (dyspnoea)	*2.248 (1.448-3.492)	<0.001
ADL hierarchy scale	0.876 (0.557-1.377)	0.566
Cognitive Performance scale (CPS)	1.505 (0.955-2.371)	0.078
Pain scale	1.399 (0.942-2.079)	0.097
Falls in the last 30 days	*2.324 (1.372-3.936)	0.002
Insufficient nutritional intake	*1.544 (1.013-2.354)	0.043
Insufficient fluid intake (less than 1L per day)	1.137 (0.753-1.718)	0.542

***significant, value <0.05**

4.2.4 Multivariate analysis

When entered into a final model of Cox regression, the presence of shortness of breath with exertion in the last 3 days and falls in the last 30 days, continued to be independently related to survival. With each year of age, the risk of death rose by an estimation of 2%. The presence of shortness of breath increased risk of death, of about 2.5 times when compared with those without shortness of breath. A history of falls in the last 30 days increased the risk 2.7 times more than those who did not have a history of falls.

Table 18. Final multivariate Cox regression model from interRAI PC

Variables	Hazard Ratio (95% CI)	p-value
Age	1.021 (1.002-1.040)	0.033
Shortness of breath with exertion (dyspnoea)	2.529 (1.601-3.994)	<0.001
Falls in the last 30 days	2.725 (1.563-4.752)	<0.001

4.2.5 Survival predictions by health care professionals

Very few patients in the present study were imminently dying. Health care professionals were more accurate in estimation of survival when prognosis was short (table 19). Accuracy decreased, the longer the survival prediction was and for those who were estimated to survive longer than six months, only four did, the other ten died within six months.

Table 19. Prediction of survival by health care professionals in palliative care.

Predicted survival	Number of correctly estimated deaths / total number of estimated deaths	Accuracy of predicted survival (%)
Death imminent	2/3	67
Death in less than six weeks	21/25	84
Death between six weeks and six months	19/58	33
Death after six months	4/14	29

4.3 Comparison between the two datasets

In the EPOS part of the study, patients were on opioids, were younger with a mean age of 65 years vs. 72 years in interRAI PC and were slightly more often women. Gastrointestinal, breast, prostate and lung cancer were the most common cancers in both datasets. However, lung cancer was relatively more common in the interRAI PC part.

Number of symptoms was the same in both datasets, a mean of 6 symptoms. The physical symptoms in the two datasets differed, however. The same symptoms were not featured in both datasets and the assessments were different. In both datasets symptoms were assessed by a health care professional but in EPOS the presence of the symptom in the last 24 hours was assessed vs. 3 days in interRAI PC. Fatigue was the most common symptom in both groups, with a prevalence of over 80%. Dyspnoea and constipation were more common in EPOS while weakness, sleep problems and vomiting were rarer than in interRAI PC. Pain was more common in EPOS or 82% vs. 60% in interRAI PC when the Symptom Checklist was compared for presence of pain in the last 3 days. An estimation on pain control was conducted in both datasets. In interRAI PC three groups were analysed, those with no pain and those with satisfactory and unsatisfactory pain control, but in EPOS status of opioid treatment was viewed. Opioid treatment was grouped into recently initiated, stable dosing with adequate relief and stable dosing with inadequate relief. The former is self-assessed while the latter is based on observed results and therefore, comparison is difficult. The majority in both groups seem to have either satisfactory pain control or adequate relief, however, unsatisfactory pain control is more common in interRAI PC than inadequate relief in EPOS. Both groups scored low on physical performance but high on cognitive function. The most important variable that differentiated the two groups was survival. In EPOS, the median survival was 101 days while in interRAI PC it was 41 days.

In univariate analyses differences were also found. In EPOS, the number of metastases, KPS, MMSE and the role function scale in EORTC QLQ-C30 seemed to relate to survival. Comparable

variables would be ADL hierarchy and CPS, for KPS and MMSE respectively, in interRAI PC and neither was significantly related to survival. In interRAI PC, the number of symptoms, presence of dyspnoea in the last 3 days (both of which were not significant in EPOS), falls in the last 30 days and insufficient nutritional intake significantly affected survival. Multivariate analysis also revealed a marked difference between these two groups.

5 Discussion

In this chapter the results of the present study will be discussed. A short summary of the results will be presented followed by answers to the research questions. A comparison to other studies in the field will be made and also between the two datasets in this study. In the end the strengths and limitations of the study is examined and further research suggested.

5.1 Summary of results

Patients with advanced cancer on opioids, still receiving life-prolonging oncological therapy and/or palliative care were more often women and the vast majority had metastases (the EPOS part). Mean age was 65 years and they had on average six symptoms in the past 24 hours. Their cognitive function was good with MMSE score on average 27 but their physical function was relatively less preserved with a mean KPS score of 50. The most common symptoms were fatigue, pain and general weakness. Most had stable dosing of opioids and adequate pain relief. Average survival was 235 days with median survival 101 day. Significant factors in multivariate analysis for shorter survival were higher number of metastases and presence of fatigue. Higher score on MMSE, role function scale on the EORTC QLQ-C30 and BPI interference scale was statistically significant in relation to longer survival.

Patients with advanced cancer entering into a palliative care program were slightly more often women and a mean age of 72 years (the interRAI PC part). On average, they had six symptoms in the last 3 days. Cognitive function was good but physical performance was impaired. About 30% had unsatisfactory pain control. Most frequent symptoms were fatigue, weakness and pain. Mean survival was 196 days and median 41 days. Significant factors in multivariate analysis for shorter survival were increased age, falls in the last 30 days and presence of dyspnoea in the last 3 days. Survival prediction, made by health care professionals, were more accurate when prognosis was short or when death was occurred in less than six weeks compared to death after six months.

The EPOS part of the study had younger patients and longer survival. Cognitive function was good in both study groups and physical performance low. Both groups had similar number of symptoms. However, results of survival analyses were different between the datasets.

5.2 Prognostic factors for survival in patients with advanced cancer on opioids

In the EPOS dataset, for patients with advanced cancer and on opioids, increased number of metastases was significantly related to shortened survival. How number of metastases or the presence of metastases affect survival in advanced cancer has been extensively investigated with mixed results. Lam et al studied advanced cancer patients in an in- and out-patient clinic with regards to prognostic factors for survival. The median survival was 77 days, and in a multivariate analysis, the number of metastatic sites was an independent prognosticator with HR 1.33 (62). In another study, which focused on patients admitted to hospice care, the median survival was 12 days, metastatic disease was related to shorter survival in a univariate analysis but not when entered into a multivariate

analysis (55). In comparison, the difference between these two studies seems to be the median survival of the groups, 77 days vs. 12 days, respectively. It appears that metastases loose it's predictive power when survival is short. This is further confirmed by Vigano et al who examined two groups of advanced cancer patients. The first group had a median survival of 101 days and the second group 42 days. The presence of liver metastases, lung tumour and total tumour burden was associated with survival in the first group but not the second (41). This is in accordance with results of the current study.

As previous studies have established (22, 43, 46), impaired cognitive function is significantly linked to shortened survival in patients with advanced cancer. This is seen in the EPOS part of the present study. Cognitive failure or delirium has shown a significant prognostic power and it has been incorporated into several scales used to assess quality of life and prognosis for e.g. the PPI (86). In a multicentre study of terminal cancer patients in home-care units in Italy, using quality of life scores measured by the Therapy Impact Questionnaire (TIQ), confusion and cognitive status showed an independent prognostic value together with global health status (102).

Of the four scales tested from the EORTC QLQ-C30 questionnaire, only the role function scale was independently related to survival. In this study increased role function was related to lengthened survival. The role function scale measures the degree of difficulty of working or enjoying hobbies, hence, a high score represents high level of physical functioning. QoL indicators have been well studied. These questionnaires are usually grouped into functional and health-related symptom subscales. Studies have shown that less function on the health-related subscales is mostly associated with shortened survival in univariate analyses (63, 66, 68). If functional subscales, including the role function scale in EORTC QLQ-C30, show a relationship with survival it is more often in univariate analyses (61, 64). This is in contrast to the present study where the role function scale significantly affected survival in both univariate and multivariate analyses. Other QoL factors, besides role function, were however, not related to survival. The reason for this may lie in the sensitivity of the scales.

Surprisingly, greater interference of pain, as measured by BPI, on daily activities is significantly related to longer survival i.e. more interference of pain means longer survival. Previous studies have revealed contradicting results regarding pain. Most have not found a relationship between pain and survival except in univariate analyses (22, 48, 53) but a couple of studies have found a negative relationship in multivariate analyses (58, 65, 66). In the present study, interference of pain as measured by BPI was not significant in an univariate analysis. Arguably, patients in pain, where pain interferes with daily activities, get more attention from medical professionals and therefore other life-threatening symptoms or problems might be recognised and treated earlier than would be otherwise. This relates to the original objective of this study which was to examine patients on opioids. Various reasons could be partly responsible for this result such as interaction between different factors and symptoms which were not analysed in this study and could therefore be a part of type 1 error, even though measures were made to minimize the risk of that.

In the EPOS part of present study, patients were all on opioids as a treatment for pain, hence pain was a common symptom in the study group. The total daily dose of morphine was high with a mean of 180mg which is higher than is seen in rest of Europe according to Klepstad et al (87). Higher doses of

morphine did not affect survival in the present study. This has been supported by other studies (53, 70) which have shown that health care professionals traditionally have been afraid of harming patients by giving high dosages of morphine. Nothing supports that fear when pain management is according to recommendations. Pain has been underappreciated and undertreated, partly because of this fear (90, 103-105), hence, it is important to get this message across.

The relationship between shortened survival and fatigue was an expected finding as several previous studies have confirmed this (52, 68). Fatigue is a common symptom in patients with advanced cancer and has been linked to the anorexia-cachexia syndrome which marks the final stage of various types of neoplasm.

Patients in the EPOS part of the present study had on average six symptoms which is less than studies have shown where 8 to 11 symptoms on average have been documented (106, 107). However, this was in accordance with the number of symptoms in the interRAI PC part of the present study. Number of symptoms did not affect survival in multivariate analysis. Recent studies have demonstrated the opposite, where increased number of symptoms is associated with shortened survival (52, 56). Those studies were performed on patient groups with advanced disease and with short median survival. The number of symptoms has been found to play a greater role as the terminal phase progresses. Patients in the current study are assumed to be in early terminal phase. However, few studies have been conducted on number of symptoms and its effect on survival in patients with different types of neoplastic disease.

Physical performance, as measured by KPS, was associated with survival in an univariate analysis, but not in a multivariate analysis. The prognostic value of physical performance has been repeatedly established (43, 64, 68) and studies have shown the relationship between decreased physical performance and shortened survival. Current results can partly be explained by the fact that the present study assessed physical performance at one time-point only but shorter survival has been found to be more connected to worsening of performance (22, 39) than the actual state of physical performance.

5.3 Prognostic factors for survival in patients with advanced cancer at first admission to palliative care

Patients with advanced cancer entering into palliative care services were at a heightened risk of death with increased age. The relationship between age and survival has been established in some earlier studies but the results have been contradictory. Some have shown no relationship (52, 53) while others have. Lam et al (62) found that higher age was significantly associated with longer survival but Schonwetter (108) et al, the opposite. One of the differences between these studies is median survival, which is 77 days in the former study but 48 days in the latter. Different factors may be relevant for survival at different time periods in the disease trajectory. In the present study, median survival was 41 days which is comparable to the study done by Schonwetter et al. This may indicate that as the terminal phase progresses, age or age-related co-morbid diseases start to matter for survival.

No published studies were found on the effect of falls on survival. Present study was the first one to confirm such a relationship. Falls are indicative of worse physical performance and impaired cognitive function which have repeatedly been recognised as important prognostic factors (43, 64, 68). Falls can also have serious consequences which can affect survival. This result indicates that the presence of recent falls should be considered for prognostication and needs to be investigated further.

In line with other studies, shortness of breath (dyspnoea) is related to shortened survival in the current study. Many studies have found a relationship between dyspnoea and survival (53, 109, 110) and the dyspnoea has been included into prognostic tools such as PaP and PPI. Shortness of breath has most often been found to be related to shortened survival in terminal patients (48, 59) which is in accordance with our results.

Number of symptoms, fatigue in the last 3 days and pain had no relationship with survival in a multivariate analysis in this part of the study. Recent studies have demonstrated a relationship between increased number of symptoms and shortened survival (52, 56) especially in groups where survival is short. Few studies, up to now, have been conducted to illuminate this aspect but with increased interest further results on this matter are to be expected. Surprisingly, fatigue did not affect survival in this study. Fatigue has been revealed to have a significant effect on shortened survival in early stages of the terminal phase but also and particularly in latter stages (48, 68). The reason is unclear but can be explained in part that fatigue was a very common symptom both in early stages of cancer disease and latter. Furthermore, pain did not have an effect on survival which is in accordance with prior studies (22, 48, 53).

Patients who were dependent in ADL or cognitively impaired, measured by the ALD hierarchy scale and the cognitive performance scale, respectively, did not have shortened survival compared with those who were independent in ADL or cognitively intact. Low cognitive function and especially delirium, has repeatedly been found to have a relationship with shortened survival (22, 43, 46, 48). An explanation for this difference could be that few patients in the interRAI PC dataset had impaired cognition. Physical function has also been extensively investigated and decreased mobility is closely associated with shortened survival (39). A possible interaction with unmeasured variables could also explain this.

A relationship between insufficient nutritional intake and fluid intake with shortened survival was not found in multivariate analyses. Nutrition and hydration are related to weight loss or anorexia which have an established connection to shorter survival (22, 39), especially in latter stages of advanced cancer (48). In an univariate analysis, however, insufficient nutritional intake did significantly affect survival. To our knowledge, fluid intake has not been examined in association with survival before.

5.4 Survival predictions of health care professionals for cancer patients at first admission to palliative care

Results from the estimated survival by health care professionals were in line with earlier studies (75). The estimations were most accurate when actual survival was short or within 6 weeks. In the first group, those who were predicted imminent death, accuracy was 67%. This can be explained by the fact that only three patients were in the group and one of them survived for eight days. In the group

with patients whom were predicted death between six weeks and six months, accuracy was only 33%. Of those, with inaccurately estimated death, two out of three died earlier than predicted, making an over-estimation of survival by health care personnel which has been established in previous studies (75, 76).

5.5 Differences between the two datasets

The two datasets were in many aspects similar. Gender ratio was similar and also the cancer type and number of symptoms. The EPOS part of the study had a slightly younger patient group. All patients in the EPOS part received opioids due to pain so it might, therefore, skew the results towards higher prevalence of pain but 82% of patients in EPOS were observed to be in pain in the last 24 hours as opposed to 60% in the last 3 days in interRAI PC.

In spite of this, patients in EPOS seemed to have better pain management as only 19% of the patients in EPOS were observed to have inadequate relief of opioids vs. 32% of interRAI PC patients who reported to have unsatisfactory pain control. This difference was even greater if those without pain were excluded from the interRAI PC dataset. One reason for this difference could be that pain management in EPOS is observed while in interRAI PC it is patient-reported. Symptoms are inherently subjective, so patient self-report is most reliable in regards to assessment. Studies have shown that observer and patient assessments are not highly correlated and observer assessment is often under-rated (5). One could also argue that the focus was on pain management in EPOS as the patients were all on opioids due to pain and the study's main focus was on opioid pharmacogenetics. This, however, does not hold as the treating physicians were not a part of the study. Another theory relates to the difference of the study time of the two datasets. EPOS was performed in the years of 2005 to 2008 while interRAI PC in the years 2003 and 2004. Although, advances have been made in improving pain management, this difference in time is slight. Still another explanation could be that pain severity was less in EPOS than interRAI PC. The current study did not analyse descriptively the severity of pain in EPOS. In interRAI PC, the pain scale, which assesses the severity and frequency of pain, showed a mean of one so the probability of patients in EPOS having less severe pain than that is low. Prevalence of other frequent symptoms was similar in the two datasets. Physical function was low in both datasets but cognitive function good.

The most important distinction between the two groups was survival. In EPOS, median survival was 101 day while in interRAI, 41 day, respectively. Different inclusion criteria explain the difference in survival but in EPOS, the patients could be receiving life-prolonging therapy and/or palliative care while patients in interRAI PC exclusively received palliative care. This difference in survival, however, could explain the dissimilar results in survival analyses. In EPOS, factors that are known to be related to survival in earlier stages of advanced cancer were shown to be significant, such as number of metastases, but in interRAI PC factors associated with very advanced stages of terminal disease were relevant, such as age and dyspnoea (41, 48).

The different assessments of physical function did not show a statistical difference between groups but cognitive assessment by MMSE was relevant in EPOS while CPS did not show an association in interRAI PC. The reasons for this could lie in the strength of the measurements. MMSE has an

established use in cognitive measurements in dementia and delirium while CPS is relatively new and few studies published. CPS has although been shown to have some prognostic value in one study and has been included into a mortality index risk using interRAI (111).

5.6 Strengths and limitations

The strength of the EPOS part lies especially in rigorous data collection with few missing data. Data collection was consistently and studiously done by a single research nurse. The advantages of the interRAI part are the fact that all patients in palliative care in the greater Reykjavik area were offered participation and the investigators, although several, were trained for data collection. On average, about 500 persons die each year of cancer in Iceland (3). It is therefore safe to assume that datasets, such as interRAI PC or EPOS, with over 100 patients each is a fair representation of the actual population.

The limitation of both EPOS and interRAI PC datasets lies in their secondary data analyses as the objective of the original researches was not to predict survival. Both datasets were convenience samples, which is, however, often the only research sample that can be obtained in advanced cancer populations and in small communities like Iceland.

Medical records had to be used sometimes to obtain information. There were no records regarding the number of patients declining participation in either study. The interRAI PC assessment tool was also under evolution and the latest version emerged some years later with several changes (latest version 9.1) (112).

Prognostic factors were not examined in relation to probable interaction between variables in either study. Both studies had a limited number of patients participating and to compensate for that, various factors and variables were transformed to increase statistical power as has been explained before.

5.7 Future Research

Future research could entail a prospective, multi centred study with a larger cohort, using an international cohort. This could be conducted e.g. in collaboration with EAPC. This would increase power of the study and thereby allow the use of more variables to increase the possibility of generalisation and even allow for analyses on interactions between factors. Hopefully, results from a prognostic study including material from all participating countries of the original EPOS will be released soon. Furthermore, more emphasis should be put on large studies in groups with different survival time in order to get better information on how prognostic factors change over time.

6 Conclusions

This is the first study done in Iceland on prognostic factors for survival in patients with advanced cancer. Many prognostic factors have been found to be related to survival in advanced cancer patients. The relationship is however, often complex. Other factors associated with the study design can influence the results, like how advanced the disease or illness is in the studied patient group and other demographic factors e.g. age and cancer type. In the present study, the two datasets seem to represent in part two different patient groups. One more advanced in their disease than the other as the EPOS dataset consists of patients that could be assumed to be not as far along in their disease as the patients in the interRAI PC dataset. The results from survival analyses supported that as factors related to survival in earlier stages of advanced cancer were significant in the EPOS part while factors associated with survival in latter stages were significant in the interRAI PC part. The main prognostic factors in advanced cancer are clinical factors, such as symptoms and deteriorating function. In the early stages of cancer however, factors related to the cancer itself, such as type, size and dissemination affect survival. This study emphasises the point that predicting survival is very complicated and relies on experience as well as clinical knowledge. It is important to build every prognostication on an individual basis.

7 References

1. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev. 2010 Aug;19(8):1893-907.
2. Krabbameinsskrá. Krabbameinsfélag Íslands. Iceland: 2011.
3. Hagstofa Íslands. Mannfjöldaspá. Reykjavík, Iceland: 2011.
4. Moller B, Fekjaer H, Hakulinen T, Tryggvadottir L, Storm HH, Talback M, et al. Prediction of cancer incidence in the Nordic countries up to the year 2020. Eur J Cancer Prev. 2002 Jun;11 Suppl 1:S1-96.
5. Doyle D, Hanks G, Cherny N, Calman K, editors. Oxford Textbook of Palliative Medicine. 3 ed. New York, USA: Oxford University Press; 2005.
6. Fainsinger RL. Global warming in the palliative care research environment: adapting to change. Palliat Med. 2008 Jun;22(4):328-35.
7. World Health Organization. WHO definition of palliative care. Geneva: 2011.
8. Landspítali. Líknarmeðferð - leiðbeiningar um ákvörðun meðferðar og meðferðarúrræði hjá sjúklingum með lífshættulega og/eða versnandi langvinna sjúkdóma. Klínískar leiðbeiningar. 2009.
9. Saunders C. Care of the dying. 2. The problem of euthanasia-2. Nurs Times. 1976 Jul 8;72(27):1049-51.
10. Bomba P. Enabling the transition to hospice through effective palliative care. Case Manager. 2005 Jan-Feb;16(1):48-52; quiz 3.
11. Perron V, Schonwetter R. Hospice and palliative care programs. Prim Care. 2001 Jun;28(2):427-40.
12. Saunders C. The symptomatic treatment of incurable malignant disease. Prescriber's Journal. 1964;4:68-73.
13. Clark D. From margins to centre: a review of the history of palliative care in cancer. Lancet Oncol. 2007 May;8(5):430-8.
14. Pálsson P. Líf og Líkn. Iceland: 2008. 1 DVD: 27 minutes.
15. World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects: World Medical Association, Inc.; 2011.
16. Kaasa S, Hjermstad MJ, Loge JH. Methodological and structural challenges in palliative care research: how have we fared in the last decades? Palliat Med. 2006 Dec;20(8):727-34.
17. EAPC. European Palliative Care Research Centre 2010 [Internet]. EAPC;[cited 2012 25.06.]. Available from: www.eapcnet.eu.
18. Jenkins V, Fallowfield L, Saul J. Information needs of patients with cancer: results from a large study in UK cancer centres. Br J Cancer. 2001;84(1):48-51.
19. Fallowfield L, Jenkins V, Beveridge H. Truth may hurt but deceit hurts more: communication in palliative care. Palliat Med. 2002 June 1;16(4):297-303.
20. Higgs R. The diagnosis of dying. J R Coll Physicians Lond. 1999 Mar-Apr;33(2):110-2.

21. Palliative Care (Guideline) [Internet]. Institute for Clinical Systems Improvement. 2011.
22. Glare P, Sinclair C, Downing M, Stone P, Maltoni M, Vigano A. Predicting survival in patients with advanced disease. Eur J Cancer. 2008;44(8):1146-56.
23. Aspinal F, Hughes R, Dunckley M, Addington-Hall J. What is important to measure in the last months and weeks of life?: A modified nominal group study. Int J Nurs Stud. 2006 May;43(4):393-403.
24. Lamont E. A Demographic and Prognostic Approach to Defining the End of Life. J Palliat Med. 2005;8(supplement 1):s-12-s-21.
25. Valdimarsdottir U, Helgason AR, Furst CJ, Adolfsson J, Steineck G. Awareness of husband's impending death from cancer and long-term anxiety in widowhood: a nationwide follow-up. Palliat Med. 2004 Jul;18(5):432-43.
26. Jonasson JM, Hauksdottir A, Nemes S, Surkan PJ, Valdimarsdottir U, Onelov E, et al. Couples' communication before the wife's death to cancer and the widower's feelings of guilt or regret after the loss - A population-based investigation. Eur J Cancer. 2011 Jul;47(10):1564-70.
27. Hauksdottir A, Steineck G, Furst CJ, Valdimarsdottir U. Long-term harm of low preparedness for a wife's death from cancer--a population-based study of widowers 4-5 years after the loss. Am J Epidemiol. 2010 Aug 15;172(4):389-96.
28. Hauksdottir A, Valdimarsdottir U, Furst CJ, Onelov E, Steineck G. Health care-related predictors of husbands' preparedness for the death of a wife to cancer-a population-based follow-up. Ann Oncol. 2010 Feb;21(2):354-61.
29. Christakis N, Iwashyna T. Attitude and Self-reported Practice Regarding Prognostication in a National Sample of Internists. Arch Intern Med. 1998 Nov;158(21):2389-95.
30. Lög um réttindi sjúklinga, 74. Sect. 5, 23-24 (1997).
31. Sullivan AM, Lakoma MD, Matsuyama RK, Rosenblatt L, Arnold RM, Block SD. Diagnosing and discussing imminent death in the hospital: a secondary analysis of physician interviews. J Palliat Med. 2007 Aug;10(4):882-93.
32. Bruera E, Neumann C, Mazzocato C, Stiefel F, Sala R. Attitudes and beliefs of palliative care physicians regarding communication with terminally ill cancer patients. Palliat Med. 2000 Jul;14(4):287-98.
33. Wright AA, Zhang B, Ray A, Mack JW, Trice E, Balboni T, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. JAMA. 2008 Oct 8;300(14):1665-73.
34. Lau F, Cloutier-Fisher D, Kuziemsky C, Black F, et al. A Systematic Review of Prognostic Tools for Estimating Survival Time in Palliative Care. J Palliat Care. 2007;23(2):93.
35. Glare P, Sinclair C. Palliative Medicine Review: Prognostication. J Palliat Med. 2008;11(1):84-103.
36. Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. Eur J Cancer. 1996 Jun;32A(7):1135-41.

37. Karnofsky D, Burchenal J. The Clinical Evaluation of Chemotherapeutic Agents in Cancer. In: MacLeod CM, editor. Evaluation of Chemotherapeutic Agents: Columbia Univ Press; 1949. p. 196.
38. Schaafsma J, Osoba D. The Karnofsky Performance Status Scale re-examined: a cross-validation with the EORTC-C30. Qual Life Res. 1994 Dec;3(6):413-24.
39. Maltoni M, Caraceni A, Brunelli C, Broeckaert B, Christakis N, Eychmueller S, et al. Prognostic Factors in Advanced Cancer Patients: Evidence-Based Clinical Recommendations--A Study by the Steering Committee of the European Association for Palliative Care. J Clin Oncol. 2005 September 1;23(25):6240-8.
40. Rosenthal M, Gebski V, Kefford R, Stuart-Harris R. Prediction of life-expectancy in hospice patients: identification of novel prognostic factors. Palliat Med. 1993;7(3):199-204.
41. Vigano A, Donaldson N, Higginson I, Bruera E, Mahmud S, Suarez-Almazor M. Quality of life and survival prediction in terminal cancer patients. Cancer. 2004;101(5):1090-8.
42. Covinsky K, Justice A, Rosenthal G, Palmer R, Landefeld S. Measuring Prognosis and Case Mix in Hospitalized Elders: The Importance of Functional Status. J Gen Intern Med. 1997;12(4):203-8.
43. Vigano A, Dorgan M, Buckingham J, Bruera E, Suarez-Almazor M. Survival prediction in terminal cancer patients: a systematic review of the medical literature. Palliat Med. 2000 July 1;14(5):363-74.
44. Tombaugh T, McIntyre N. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc. 1992 Sep;40(9):922-35.
45. Bruera E, Miller M, Kuehn N, MacEachern T, Hanson J. Estimate of survival of patients admitted to a palliative care unit: a prospective study. J Pain Symptom Manage. 1992 Feb;7(2):82-6.
46. Caraceni A, Nanni O, Maltoni M, Piva L, Indelli M, Arnoldi E, et al. Impact of delirium on the short term prognosis of advanced cancer patients. Cancer. 2000;89(5):1145-9.
47. Sykes N, Thorns A. The use of opioids and sedatives at the end of life. Lancet Oncol. 2003;4(5):312-8.
48. Trajkovic-Vidakovic M, de Graeff A, Voest EE, Teunissen SC. Symptoms tell it all: A systematic review of the value of symptom assessment to predict survival in advanced cancer patients. Crit Rev Oncol Hematol. 2012 Mar 30.
49. Riechelmann RP, Krzyzanowska MK, O'Carroll A, Zimmermann C. Symptom and medication profiles among cancer patients attending a palliative care clinic. Support Care Cancer. 2007 Dec;15(12):1407-12.
50. Wachtel T, Allen-Masterson S, Reuben D, Goldberg R, Mor V. The end stage cancer patient: terminal common pathway. Hosp J. 1988;4(4):43-80.
51. Vigano A, Bruera E, Suarez-Almazor M. Terminal cancer syndrome: Myth or reality? J Palliat Care. 1999 jan 1;15(4):32-9.

52. Cheung W, Barmala N, Zarinehbaf S, Rodin G, Le L, Zimmermann C. The Association of Physical and Psychological Symptom Burden with Time to Death Among Palliative Cancer Outpatients. J Pain Symptom Manage. 2009;37(3):297-304.
53. Hardy J, Turner R, Saunders M, A'Hern R. Prediction of survival in a hospital-based continuing care unit. Eur J Cancer. 1994;30A(3):284-8.
54. Llobera J, Esteva M, Rifà J, Benito E, Terrasa J, Rojas C, et al. Terminal cancer: duration and prediction of survival time. Eur J Cancer. 2000;36(16):2036-43.
55. Vitetta L, Kenner D, Kissane D, Sali A. Clinical outcomes in terminally ill patients admitted to hospice care: diagnostic and therapeutic interventions. J Palliat Care. 2001;17(2):69-77.
56. Chang J, Lin C. A longitudinal study of the role of patient-reported outcomes on survival prediction of palliative cancer inpatients in Taiwan. Support Care Cancer. 2009:1-10.
57. Maltoni M, Pirovano M, Nanni O, Marinari M, Indelli M, Gramazio A, et al. Biological Indices Predictive of Survival in 519 Italian Terminally Ill Cancer Patients. J Pain Symptom Manage. 1997;13(1):1-9.
58. Suh S, Ahn H. Lactate dehydrogenase as a prognostic factor for survival time of terminally ill cancer patients: a preliminary study. Eur J Cancer. 2007 Apr;43(6):1051-9.
59. Suh S, Choi Y, Shim J, Kim Y, Yeom C, Kim D, et al. Construction of a new, objective prognostic score for terminally ill cancer patients: a multicenter study. Support Care Cancer. 2010 Feb;18(2):151-7.
60. Geissbuhler P, Mermillod B, Rapin C. Elevated serum vitamin B12 levels associated with CRP as a predictive factor of mortality in palliative care cancer patients: a prospective study over five years. J Pain Symptom Manage. 2000 Aug;20(2):93-103.
61. Grande G, Farquhar M, Barclay S, Todd C. Quality of life measures (EORTC QLQ-C30 and SF-36) as predictors of survival in palliative colorectal and lung cancer patients. Palliat Support Care. 2009 Sep;7(3):289-97.
62. Lam P, Leung M, Tse C. Identifying prognostic factors for survival in advanced cancer patients: a prospective study. Hong Kong Med J. 2007 December;13(6):453-9.
63. Chang V, Thaler H, Polyak T, Kornblith A, Lepore J, Portenoy R. Quality of life and survival. Cancer. 1998;83(1):173-9.
64. Efficace F, Biganzoli L, Piccart M, Coens C, Van Steen K, Cufer T, et al. Baseline health-related quality-of-life data as prognostic factors in a phase III multicentre study of women with metastatic breast cancer. Eur J Cancer. 2004;40(7):1021-30.
65. Luoma M, Hakamies-Blomqvist L, Sjöström J, Pluzanska A, Ottoson S, Mouridsen H, et al. Prognostic value of quality of life scores for time to progression (TTP) and overall survival time (OS) in advanced breast cancer. Eur J Cancer. 2003;39(10):1370-6.
66. Herndon J, Fleishman S, Kornblith A, Kosty M, Green M, Holland J. Is quality of life predictive of the survival of patients with advanced nonsmall cell lung carcinoma? Cancer. 1999;85(2):333-40.

67. Tamburini M, Rosso S, Gamba A, Mencaglia E, De Conno F, Ventafridda V. A therapy impact questionnaire for quality-of-life assessment in advanced cancer research. Ann Oncol. 1992 Jul;3(7):565-70.
68. Toscani F, Brunelli C, Miccinesi G, Costantini M, Gallucci M, Tamburini M, et al. Predicting survival in terminal cancer patients: clinical observation or quality-of-life evaluation? Palliat Med. 2005 April 1;19(3):220-7.
69. Sulmasy D, Pellegrino E. The rule of double effect: clearing up the double talk. Arch Intern Med. 1999 Mar 22;159(6):545-50.
70. Bercovitch M, Waller A, Adunsky A. High dose morphine use in the hospice setting. A database survey of patient characteristics and effect on life expectancy. Cancer. 1999 Sep 1;86(5):871-7.
71. Sykes N, Nigel P. Morphine kills the pain, not the patient. Lancet. 2007;369(9570):1325-6.
72. Portenoy R, Sibirceva U, Smout R, Horn S, Connor S, Blum R, et al. Opioid Use and Survival at the End of Life: A Survey of a Hospice Population. J Pain Symptom Manage. 2006;32(6):532-40.
73. Gibbins J, McCoubrie R, Alexander N, Kinzel C, Forbes K. Diagnosing dying in the acute hospital setting--are we too late? Clin Med. 2009 Apr;9(2):116-9.
74. Christakis N, Lamont E. Extent and determinants of error in physicians' prognoses in terminally ill patients: prospective cohort study. West J Med. 2000 May;172(5):310-3.
75. Glare P, Virik K, Jones M, Hudson M, Eychmueller S, Simes J, et al. A systematic review of physicians' survival predictions in terminally ill cancer patients. BMJ. 2003 July 26;327(7408).
76. Vigano A, Dorgan M, Bruera E, Suarez-Almazor M. The relative accuracy of the clinical estimation of the duration of life for patients with end of life cancer. Cancer. 1999;86(1):170-6.
77. Muers M, Shevlin P, Brown J. Prognosis in lung cancer: physicians' opinions compared with outcome and a predictive model. Thorax. 1996 Sep;51(9):894-902.
78. Maltoni M, Nanni O, Pirovano M, Scarpi E, Indelli M, Martini C, et al. Successful Validation of the Palliative Prognostic Score in Terminally Ill Cancer Patients. J Pain Symptom Manage. 1999;17(4):240-7.
79. Stiel S, Bertram L, Neuhaus S, Nauck F, Ostgathe C, Elsner F, et al. Evaluation and comparison of two prognostic scores and the physicians' estimate of survival in terminally ill patients. Support Care Cancer. 2009 Apr. doi: 10.1007/s00520-009-0628-0.
80. Pirovano M, Maltoni M, Nanni O, Marinari M, Indelli M, Zaninetta G, et al. A New Palliative Prognostic Score: A First Step for the Staging of Terminally Ill Cancer Patients. J Pain Symptom Manage. 1999;17(4):231-9.
81. 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. 2001 Nov;22(5):891-8.

82. Glare P, Eychmueller S, Virik K. The use of the palliative prognostic score in patients with diagnoses other than cancer. J Pain Symptom Manage. 2003;26(4):883-5.
83. Anderson F, Downing GM, Hill J, Casorso L, Lerch N. Palliative performance scale (PPS): a new tool. J Palliat Care. 1996;12(1):5-11.
84. Olajide O, Hanson L, Usher BM, Qaqish BF, Schwartz R, Bernard S. Validation of the palliative performance scale in the acute tertiary care hospital setting. J Palliat Med. 2007 Feb;10(1):111-7.
85. Head B, Ritchie CS, Smoot TM. Prognostication in hospice care: can the palliative performance scale help? J Palliat Med. 2005 Jun;8(3):492-502.
86. Morita T, Tsunoda J, Inoue S, Chihara S. The Palliative Prognostic Index: a scoring system for survival prediction of terminally ill cancer patients. Support Care Cancer. 1999 May;7(3):128-33.
87. Klepstad P, Fladvad T, Skorpen F, Bjordal K, Caraceni A, Dale O, et al. Influence from genetic variability on opioid use for cancer pain: a European genetic association study of 2294 cancer pain patients. Pain. 2011 May;152(5):1139-45.
88. Klepstad P, Kaasa S, Cherny N, Hanks G, de Conno F. Pain and pain treatments in European palliative care units. A cross sectional survey from the European Association for Palliative Care Research Network. Palliat Med. 2005 Sep;19(6):477-84.
89. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol. 1984 Mar;2(3):187-93.
90. Gunnarsdottir S, Ward S, Serlin RC. Attitudinal barriers to cancer pain management in the Icelandic population. Cancer Nurs. 2008 Mar-Apr;31(2):95-102.
91. Turk DC, Melzack R, editors. Handbook of pain assessment. New York: Guilford Press; 1992.
92. Kumar SP. Utilization of brief pain inventory as an assessment tool for pain in patients with cancer: a focused review. Indian J Palliat Care. 2011 May;17(2):108-15.
93. Aaronson N, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365-76.
94. Fayers PM, Aaronson N, Bjordal K, Groenvold M, Curran D, Bottomley A. The EORTC QLQ-C30 scoring manual (3rd Edition). Brussels: European Organisation for Research and Treatment of Cancer; 2001.
95. Vittinghoff E, Glidden DV, Shiboski SC, McCulloch CE. Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models. NY: Springer; 2005.
96. SPSS. IBM SPSS Statistics. 19.0 ed. USA: SPSS Inc, an IBM Company; 2010.
97. Jónsson P. Rai fjölskyldan á Íslandi. Öldrun. 2003;21(1):4-7.

98. Steel K, Ljunggren G, Topinkova E, Morris J, Vitale C, Parzuchowski J. The RAI-PC: an assessment instrument for palliative care in all settings. Am J Hosp Palliat Care. 2003;20(3):211-9.
99. Morris J, Fries B, Mehr D, Hawes C, Phillips C, Mor V, et al. MDS Cognitive Performance Scale. J Gerontol. 1994 Jul;49(4):M174-82.
100. Morris J, Fries B, Morris S. Scaling ADLs within the MDS. J Gerontol A Biol Sci Med Sci. 1999 Nov;54(11):M546-53.
101. Fries B, Simon S, Morris J, Flodstrom C, Bookstein F. Pain in U.S. nursing homes: validating a pain scale for the minimum data set. Gerontologist. 2001 Apr;41(2):173-9.
102. Tamburini M, Brunelli C, Rosso S, Ventafridda V. Prognostic value of quality of life scores in terminal cancer patients. J Pain Symptom Manage. 1996 Jan;11(1):32-41.
103. Paice JA, Toy C, Shott S. Barriers to cancer pain relief: fear of tolerance and addiction. J Pain Symptom Manage. 1998 Jul;16(1):1-9.
104. Flemming K. The use of morphine to treat cancer-related pain: a synthesis of quantitative and qualitative research. J Pain Symptom Manage. 2010 Jan;39(1):139-54.
105. Gordon DB, Dahl JL, Miaskowski C, McCarberg B, Todd KH, Paice JA, et al. American pain society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force. Arch Intern Med. 2005 Jul;165(14):1574-80.
106. Portenoy RK, Thaler HT, Kornblith AB, Lepore JM, Friedlander-Klar H, Coyle N, et al. Symptom prevalence, characteristics and distress in a cancer population. Qual Life Res. 1994 Jun;3(3):183-9.
107. Chang VT, Hwang SS, Feuerman M, Kasimis BS. Symptom and quality of life survey of medical oncology patients at a veterans affairs medical center: a role for symptom assessment. Cancer. 2000 Mar;88(5):1175-83.
108. Schonwetter RS, Teasdale TA, Storey P, Luchi RJ. Estimation of survival time in terminal cancer patients: an impedance to hospice admissions? Hosp J. 1990;6(4):65-79.
109. Vigano A, Bruera E, Jhangri G, Newman S, Fields A, Suarez-Almazor M. Clinical Survival Predictors in Patients With Advanced Cancer. Arch Intern Med. 2000 Mar;160(6):861-8.
110. Maltoni M, Pirovano M, Scarpi E, Marinari M, Indelli M, Arnoldi E, et al. Prediction of survival of patients terminally ill with cancer. Results of an Italian prospective multicentric study. Cancer. 1995 May 15;75(10):2613-22.
111. Porock D, Oliver DP, Zweig S, Rantz M, Mehr D, Madsen R, et al. Predicting death in the nursing home: development and validation of the 6-month Minimum Data Set mortality risk index. J Gerontol A Biol Sci Med Sci. 2005 Apr;60(4):491-8.
112. Palliative Care [Internet]. interRAI Organization. 2012 [cited 24.6.2012].
113. Dosing and conversion chart of opioid analgesics: American College of Physicians; 2004 [cited 2008 02.10.]. Available from: http://www.acponline.org/clinical_information/journals_publications/acp_internist/dec04/pain/dosing_conv.pdf.

114. Döpfmer UR, Schenk MR, Kuscic S, Beck DH, Döpfmer S, Kox WJ. A randomized controlled double-blind trial comparing piritramide and morphine for analgesia after hysterectomy. Eur J Anaesthesiol. 2001 Jun;18(6):389-93.
115. Ripamonte C, al e. Switching from morphine to oral methadone in treating cancer pain. What is the equianalgesic dose ratio? J Clin Oncol. 1998;16:3216-21.
116. Loseer J, Bonica J, Butler S, Chapman R, Turk D, editors. Bonica's Management of Pain. 3rd ed: Lippincott Williams & Wilkins; 2001.

8 Appendices

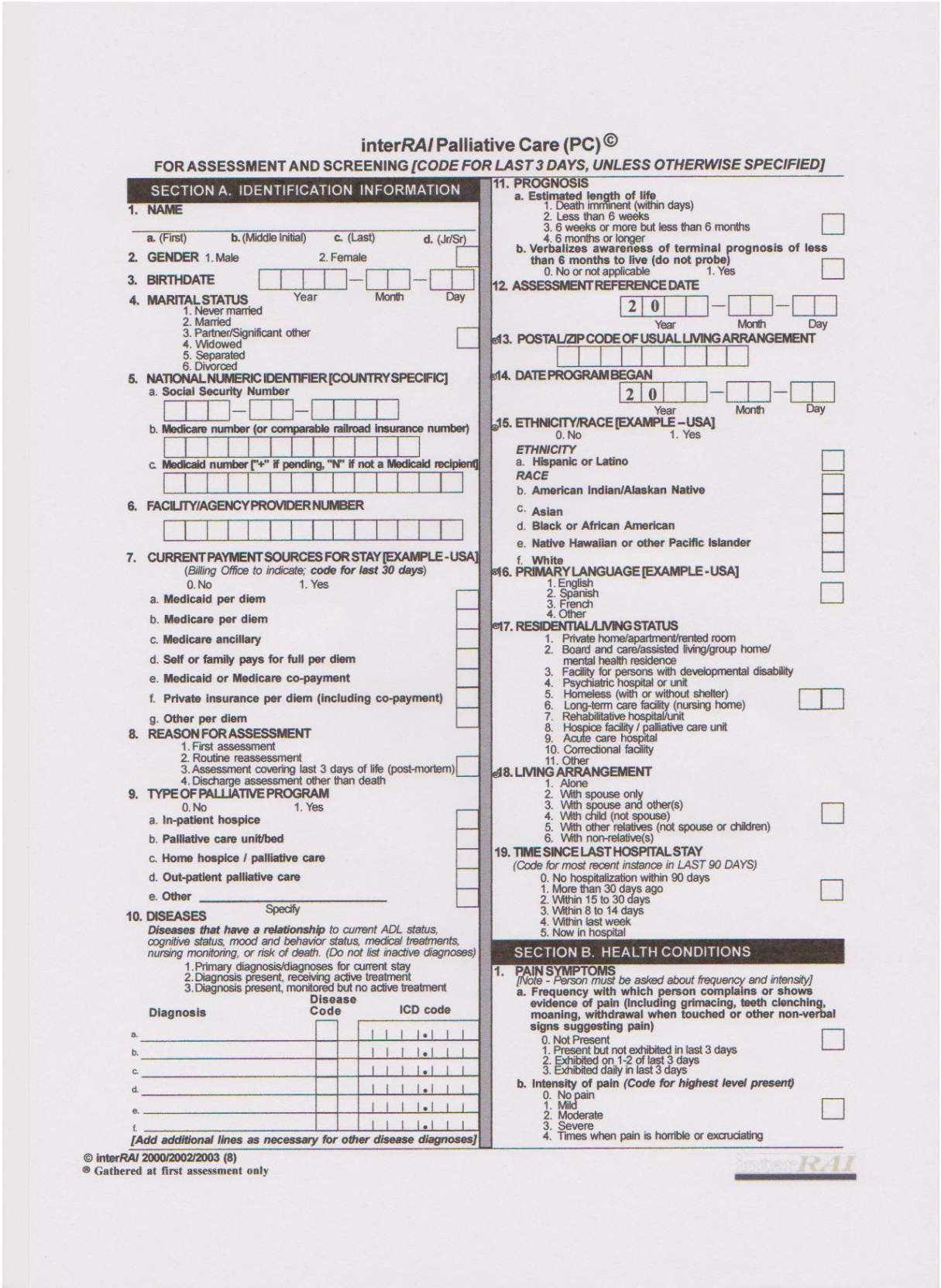
Appendix 1. Equipotency - opioids in the EPOS study (all doses in mg) (113-116)

Opioid	Oral	Sc / IV	Transdermal
Morphine[1]	30	10	-
Fentanyl[1,4]	-	0.1	0.1
Oxycodone[1]	15	10	-
Hydromorphone[1]	7,5	1,5	-
Buphrenorphine[1]	-	0,4	0,4
Ketobemidone[4]	30	10	-
Alfentanil[4]	-	1	-
Pitramide[2]	-	20	-
Methadone[3]	6	4	-
Sufentanil[4]	-	0.05	-
Levomethadone	3	1.5	

Appendix 2. Karnofsky Performance Score (KPS) (5, 37)

Percentage of normal performance score	Karnofsky definitions
100%	Normal, no complaints, no evidence of disease
90%	Able to carry on normal activity, minor signs or symptoms of disease
80%	Normal activity with effort, some signs or symptoms of disease
70%	Cares for self, unable to carry on normal activity or do active work
60%	Requires occasional assistance, but is able to care for most of his needs
50%	Requires considerable assistance and frequent medical care
40%	Disabled, requires special care and assistance
30%	Severely disabled, hospitalization is indicated although death not imminent
20%	Very sick, hospitalization necessary, active supportive treatment necessary
10%	Moribund, fatal process progressing rapidly
0%	Death

Appendix 3. The interRAI PC assessment tool, version 8.0.



interRAI Palliative Care (PC) ©

FOR ASSESSMENT AND SCREENING *[CODE FOR LAST 3 DAYS, UNLESS OTHERWISE SPECIFIED]*

SECTION A. IDENTIFICATION INFORMATION

1. NAME

a. (First) b. (Middle Initial) c. (Last) d. (Jr/Sr)

2. GENDER 1. Male 2. Female

3. BIRTHDATE Year Month Day

4. MARITAL STATUS
1. Never married
2. Married
3. Partner/Significant other
4. Widowed
5. Separated
6. Divorced

5. NATIONAL NUMERIC IDENTIFIER [COUNTRY SPECIFIC]
a. Social Security Number
b. Medicare number (or comparable railroad insurance number)
c. Medicaid number ["+" if pending, "N" if not a Medicaid recipient]

6. FACILITY/AGENCY PROVIDER NUMBER

7. CURRENT PAYMENT SOURCES FOR STAY [EXAMPLE - USA]
*(Billing Office to indicate; **code for last 30 days**)*
0. No 1. Yes
a. Medicaid per diem
b. Medicare per diem
c. Medicare ancillary
d. Self or family pays for full per diem
e. Medicaid or Medicare co-payment
f. Private insurance per diem (including co-payment)
g. Other per diem

8. REASON FOR ASSESSMENT
1. First assessment
2. Routine reassessment
3. Assessment covering last 3 days of life (post-mortem)
4. Discharge assessment other than death

9. TYPE OF PALLIATIVE PROGRAM
0. No 1. Yes
a. In-patient hospice
b. Palliative care unit/bed
c. Home hospice / palliative care
d. Out-patient palliative care
e. Other _____ Specify

10. DISEASES
Diseases that have a relationship *to current ADL status, cognitive status, mood and behavior status, medical treatments, nursing monitoring, or risk of death. (Do not list inactive diagnoses)*
1. Primary diagnosis/diagnoses for current stay
2. Diagnosis present, receiving active treatment
3. Diagnosis present, monitored but no active treatment

	Diagnosis	Disease Code	ICD code
a.			
b.			
c.			
d.			
e.			
f.			

[Add additional lines as necessary for other disease diagnoses]

11. PROGNOSIS
a. Estimated length of life
1. Death imminent (within days)
2. Less than 6 weeks
3. 6 weeks or more but less than 6 months
4. 6 months or longer
b. Verbalizes awareness of terminal prognosis of less than 6 months to live (do not probe)
0. No or not applicable 1. Yes

12. ASSESSMENT REFERENCE DATE
2 0 Year Month Day

®13. POSTAL/ZIP CODE OF USUAL LIVING ARRANGEMENT

®14. DATE PROGRAM BEGAN
2 0 Year Month Day

®15. ETHNICITY/RACE [EXAMPLE – USA]
0. No 1. Yes
ETHNICITY
a. Hispanic or Latino
RACE
b. American Indian/Alaskan Native
c. Asian
d. Black or African American
e. Native Hawaiian or other Pacific Islander
f. White

®16. PRIMARY LANGUAGE [EXAMPLE - USA]
1. English
2. Spanish
3. French
4. Other

®17. RESIDENTIAL/LIVING STATUS
1. Private home/apartment/rented room
2. Board and care/assisted living/group home/ mental health residence
3. Facility for persons with developmental disability
4. Psychiatric hospital or unit
5. Homeless (with or without shelter)
6. Long-term care facility (nursing home)
7. Rehabilitative hospital/unit
8. Hospice facility / palliative care unit
9. Acute care hospital
10. Correctional facility
11. Other

®18. LIVING ARRANGEMENT
1. Alone
2. With spouse only
3. With spouse and other(s)
4. With child (not spouse)
5. With other relatives (not spouse or children)
6. With non-relative(s)

19. TIME SINCE LAST HOSPITAL STAY
(Code for most recent instance in LAST 90 DAYS)
0. No hospitalization within 90 days
1. More than 30 days ago
2. Within 15 to 30 days
3. Within 8 to 14 days
4. Within last week
5. Now in hospital

SECTION B. HEALTH CONDITIONS

1. PAIN SYMPTOMS
[Note - Person must be asked about frequency and intensity]
a. Frequency with which person complains or shows evidence of pain (including grimacing, teeth clenching, moaning, withdrawal when touched or other non-verbal signs suggesting pain)
0. Not Present
1. Present but not exhibited in last 3 days
2. Exhibited on 1-2 of last 3 days
3. Exhibited daily in last 3 days
b. Intensity of pain *(Code for highest level present)*
0. No pain
1. Mild
2. Moderate
3. Severe
4. Times when pain is horrible or excruciating

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c. Consistency of pain
0. No pain
1. Single episode in last 3 days
2. Intermittent, not in cycles
3. Cyclical
4. Constant

d. New pain site or worsening of pain in last 3 days
0. No 1. Yes

e. When pain is present
0. No pain
1. With movement
2. At rest
3. Both

f. Pain control
Ability of current therapeutic regime to control pain adequately (from person's point of view)
0. No issue of pain
1. Controlled adequately by therapeutic regime
2. Controlled when therapeutic regime followed, but not always followed as ordered
3. Therapeutic regime followed, but pain control not adequate
4. No therapeutic regime being followed for pain, pain not adequately controlled

2. PAIN SOURCES
0. No 1. Yes (even if pain is controlled)
a. **Bone**
b. **Muscle**
c. **Neuropathic**
d. **Visceral**
e. **Other**

3. FALLS
0. No fall in last 90 days
1. No fall in last 30 days, but fall reported in 31-90 days
2. One fall in the last 30 days
3. Two or more falls in lst 30 days

4. PROBLEM FREQUENCY
0. Not Present
1. Present but not exhibited in last 3 days
2. Exhibited on 1-2 of last 3 days
3. Exhibited daily last 3 days

GI STATUS
a. **Constipation (no bowel movement in 3 days)**
b. **Fecal impaction**
c. **Diarrhea**
d. **Vomiting**
e. **Nausea**

CARDIAC/PULMONARY
f. **Difficulty coughing or clearing airway secretions**
g. **Shortness of breath with exertion**
h. **Inability to lie flat due to shortness of breath**
i. **Tires easily, poor task endurance**

SLEEP PROBLEMS
j. **Difficulty falling asleep, difficulty staying asleep, waking too early, restlessness, non-restful sleep, too much sleep**

OTHER
k. **Ascites**
l. **Pleural effusion**
m. **Fatigue**
n. **Dry mouth (xerostomia)**
o. **Hiccups**
p. **Offensive odor**
q. **Muscle cramps**
r. **Edema**

5. LIFESTYLE
a. Smokes tobacco daily
0. No
1. Not in last 3 days, but is a daily smoker
2. Yes

b. Alcohol – Highest number of drinks in any "single sitting" in last 14 days
0. None
1. 1
2. 2 - 4
3. 5 or more

SECTION C. ORAL/NUTRITIONAL STATUS

1. MODE OF NUTRITIONAL INTAKE
0. ***Normal***—Swallows all diet consistencies
1. ***Modified independent***—e.g., only sips liquid, takes limited solid food
2. ***Requires mechanical diet (excludes puree)***
3. ***Requires modification to swallow liquids***—e.g, thickened liquids
4. ***Can swallow only pureed solids or thickened liquids***
5. ***Combined oral and parenteral/tube feeding***
6. ***Nasogastric tube feeding only***
7. ***Parenteral (PEG) feeding only***
8. ***No oral intake AND NO parenteral/tube feeding***

2. SUFFICIENT NUTRITIONAL INTAKE
0. Intake sufficient, not losing substantial weight
1. Losing 2+ pounds a week, most likely not water loss
2. Evidence of wasting

3. NUTRITIONAL ISSUES
Insufficient fluid: less than 1,000cc per day (less than four 8oz cups/day)
0. No 1. Yes

SECTION D. SKIN CONDITION

1. HIGHEST CURRENT PRESSURE ULCER STAGE
0. No pressure ulcer
1. Any area of persistent skin redness
2. Partial loss of skin layers
3. Deep craters in the skin
4. Breaks in skin exposing muscle or bone
5. No prior information available, not stageable because necrotic eschar predominant

2. NUMBER OF CURRENT PRESSURE ULCERS (If more than 9, code 9)

3. STASIS ULCER—open lesion caused by poor circulation in the lower limbs
0. No 1. Yes

4. MAJOR SKIN PROBLEMS—e.g., lesions, 2nd or 3rd degree burns, healing surgical wounds
0. No 1. Yes

5. SKIN TEARS OR CUTS—other than surgery
0. No 1. Yes

6. OTHER SKIN CONDITIONS OR CHANGES IN SKIN CONDITION—e.g.,bruises, rashes, itching, mottling, herpes zoster, intertrigo, eczema
0. No 1. Yes

7. FOOT PROBLEMS THAT INTERFERE WITH GAIT—e.g., bunions, hammertoes, overlapping toes, structural problems, infections, ulcers
0. No
1. Yes, but ambulates
2. Yes, does not ambulate

SECTION E. COGNITION

1. COGNITIVE SKILLS FOR DAILY DECISION MAKING
Making decisions regarding tasks of daily life (e.g., when to get up or have meals, which clothes to wear or activities to do)
0. ***Independent*** — Decisions consistent/reasonable/safe
1. ***Modified independence*** — Some difficulty in new situations only
2. ***Minimally impaired*** — In specific situations, decisions become poor or unsafe; cues/ supervision necessary at those times
3. ***Moderately impaired*** — Decisions consistently poor or unsafe; cues/supervision required at all times
4. ***Severely impaired*** — Never/rarely makes decisions.
5. ***No discernable consciousness [Skip to section I]***

2. FLUCTUATING STATES OF CONSCIOUSNESS
0. No 1. Yes

3. MEMORY/RECALL ABILITY
CODE for recall of what was learned or known
0. Yes, memory ok 1. Memory problem
a. **Short-term memory OK**—Seems/appears to recall after 5 minutes
b. **Procedural memory OK**—Can perform all or almost all steps in a multitask sequence without cues for initiation
c. **Situational memory OK—Both**: recognizes caregivers' names/ faces frequently encountered **AND** knows location of places regularly visited (bedroom, dining room, activity room, therapy room)

4. PERIODIC DISORDERED THINKING/AWARENESS

[Note: Accurate assessment requires conversations with staff or others who have direct knowledge of the person's behavior over this time]

0. Behavior not present
1. Behavior present, not of recent onset
2. Behavior present over the last 3 days AND the behavior appears different from usual functioning (e.g., new onset or worsening; different from a few weeks ago)

a. **Easily distracted**—e.g., episodes of difficulty paying attention; gets sidetracked
b. **Episodes of disorganized speech**—e.g., speech is nonsensical, irrelevant, or rambling from subject to subject; loses train of thought
c. **Mental function varies over the course of the day**—e.g., sometimes better, sometimes worse; behaviors sometimes present, sometimes not
d. **Acute change in mental status from person's baseline**—e.g., increased restlessness, lethargy, difficult to arouse, altered environmental perception

SECTION F. COMMUNICATION

1. MAKING SELF UNDERSTOOD (Expression)

Expressing information content—both verbal and non-verbal

0. ***Understood***—Expresses ideas without difficulty
1. ***Usually understood***—Difficulty finding words or finishing thoughts BUT if given time, little or no prompting required
2. ***Often understood***—Difficulty finding words or finishing thoughts, prompting usually required
3. ***Sometimes understood***—Ability is limited to concrete requests
4. ***Rarely/never understood***

2. ABILITY TO UNDERSTAND OTHERS (Comprehension)

Understanding verbal information content (however able) with hearing appliance, if used

0. ***Understands***—Clear comprehension
1. ***Usually understands***—Misses some part/intent of message BUT comprehends most conversation with little or no prompting
2. ***Often understands***—Misses some part/intent of message, with prompting can often comprehend conversation
3. ***Sometimes understands***—Responds adequately to simple, direct communication only
4. ***Rarely/never understands***

SECTION G. MOOD AND BEHAVIOR

1. INDICATORS OF POSSIBLE DEPRESSION, ANXIETY, SAD MOOD

(CODE for indicators observed in last 3 days, irrespective of the assumed cause)

0. Not exhibited in last 3 days
1. Not exhibited in last 3 days but is reported to be present
2. Exhibited on 1-2 of last 3 days
3. Exhibited daily in last 3 days

a. **Made negative statements**—e.g., *"Nothing matters; Would rather be dead; What's the use; Regret having lived so long; Let me die"*
b. **Repetitive verbalizations**—e.g., calling out for help, ("God Help me")
c. **Persistent anger with self or others**—e.g., easily annoyed, anger at care received
d. **Expressions (including non-verbal) of what appear to be unrealistic fears**—e.g., fear of being abandoned, being left alone, being with others; intense fear of specific objects or situations
e. **Recurrent statements that something terrible is about to happen**—e.g., believes he or she is about to die, have a heart attack
f. **Repetitive health complaints**—e.g., persistently seeks medical attention; incessant concern with body functions
g. **Repetitive anxious complaints/concerns (non-health related)**–e.g., persistently seeks attention/reassurance regarding schedules, meals, laundry, clothing, relationships
h. **Insomnia/change in usual sleep patterns**
i. **Sad, pained, worried facial expressions**—e.g., furrowed brow
j. **Crying, tearfulness**
k. **Withdrawal from activities of interest**—e.g., no interest in long standing activities or being with family/friends
l. **Reduced social interactions**
m. **Expressions (including non-verbal) of a lack of pleasure in life**—e.g.,"I don't enjoy anything anymore," anhedonia

2. SELF REPORTED MOOD ITEMS

0. **Not in the last 3 days**
1. Not in the last 3 days, but often feel that way
2. In 1-2 of last 3 days
3. Daily in the last 3 days
8. PERSON COULD NOT (WOULD NOT) RESPOND

a. **Little interest or pleasure in things you normally enjoy**
b. **Anxious, restless or uneasy**
c. **Sad, depressed or hopeless**

SECTION H. PSYCHOSOCIAL WELL-BEING

1. LIFE COMPLETION

0. No 1. Yes

a. **Making progress on unfinished business**
b. **Has strengths that can be fostered**
c. **Minimal unfinished business** (e.g., will, religious rites, personal reconciliations)
d. **Accepting of situation**
e. **Family coping**
f. **Family in conflict**
g. **Family accepting of situation**
h. **Family involved**
i. **Strong and supportive relationship with family**

2. SPIRITUALITY

0. No 1. Yes

a. **Finds guidance in religion or spirituality**
b. **Struggling with meaning of life**
c. **Anger towards God, religion or fate**
d. **Finds meaning in day to day life**
e. **At peace with life**
f. **Consistent positive outlook**

SECTION I. PHYSICAL FUNCTIONING

1. ADL SELF-PERFORMANCE

(CODE for Performance over full 24 hour periods, considering all occurrances of the activity in LAST 3 DAYS)

0. ***Independent***—No help — OR — Help, setup, or supervision provided 1-2 times
1. ***Setup help only***—Article or device provided or placed within reach 3+ times
2. ***Supervision***—Oversight/cuing 3+ times — OR — Oversight/cuing 1+ time and physical assistance 1-2 times
3. ***Limited assistance***—Guided maneuvering of limbs 3+ times — OR — Combination of guided maneuvering and more help 1-2 times
4. ***Extensive assistance***—Weight-bearing support 3+ times by one person
5. ***Maximal assistance***—Weight-bearing support 3+ times by 2+ persons
6. ***Total dependence***—Full performance by others during entire period
8. ***Activity did not occur***—During entire period

a. **Bathing**—How takes full-body bath/shower or sponge bath (EXCLUDE washing of back and hair and transfer). Includes how each part of body is bathed: arms, upper and lower leg, chest, abdomen, perineal area. ***Code for most dependent episode***
b. **Personal hygiene**— How manages personal hygiene, including combing hair, brushing teeth, shaving, applying make-up, washing/drying face and hands [EXCLUDE baths and showers]
c. **Walking**—How walks between locations on same floor
d. **Wheeling**—How moves between locations on same floor indoors when in wheelchair
e. **Transfer toilet**—How moves on and off toilet or commode

f. **Toilet use** —How uses the toilet room (or commode, bedpan/urinal), cleanses self after toilet use or incontinent episode(s), changes pad, manages ostomy or catheter, adjusts clothes [EXCLUDE transfer on/off toilet]

g. **Bed mobility**—How moves to and from lying position, turns side to side, and positions body while in bed

h. **Eating**- How eats and drinks (regardless of skill). Includes intake of nourishment by other means (e.g., tube feeding, total

2. ADL FUNCTIONAL REHABILITATION POTENTIAL

0. No 1. Yes

a. **Person believes he/she is capable of improved performance in physical function**

b. **Care professional believes person is capable of improved performance in physical function**

SECTION J. CONTINENCE

1. BLADDER CONTINENCE

0. ***Continent***—Complete control; DOES NOT USE any type of catheter or other urinary collection device
1. ***Complete control with any catheter or ostomy***
2. ***Infrequent incontinence***—Not incontinent over last 3 days, but does have incontinent episodes
3. ***Episode(s) of incontinence***—On one day
4. ***Occasionally incontinent***—On two days
5. ***Frequently incontinent***—Incontinent daily, but some control present
6. ***Incontinent***—Has inadequate control of bladder, multiple daily episodes all or almost all of time
8. ***Did not occur***—No urine output from bladder

2. URINARY COLLECTION DEVICE

0. None
1. Condom Catheter
2. Indwelling catheter
3. Cystostomy

3. BOWEL CONTINENCE

0. ***Continent***—Complete control
1. ***Control with ostomy***—Complete control with ostomy device
2. ***Infrequent incontinence***—Not incontinent over last 3 days, but does have incontinent episodes
3. ***Episode(s) of incontinence***—On one day
4. ***Occassionally incontinent***—On two days
5. ***Frequently incontinent***—Incontinent daily, but some control present (e.g., during part of day)
6. ***Incontinent***—All days
8. ***Did not occur***—No bowel movement during the period

SECTION K. MEDICATIONS

1. LIST OF ALL MEDICATIONS

List prescribed and nonprescribed medications scheduled in **LAST 3 DAYS** [NOTE: Where possible, use computerized records (e.g., for prescribed medications); hand enter only where absolutely necessary]

a-b. Name and Dose: Record the name of the medication and dose

c. Form: Code the route of administration using the following list:

PO. By mouth	SQ. Subcutaneous	ET. Enteral tube
SL. Sub lingual	R. Rectal	TD. Transdermal
IM. Intramuscular	TOP. Topical	OTH. Other
IV. Intravenous	IH. Inhalation	

d. Freq: Code the number of times per day, week, or month the medication is administered using the following list:

QH. Every hour	QOD. Every other day
Q2H. Every two hours	Q3D. Every 3 days
Q3H. Every three hours	QW. Once each week
Q4H. Every four hours	2W. Two times every week
Q6H. Every six hours	3W. Three times every week
Q8H. Every eight hours	4W. Four times each week
QD. Once daily	5W. Five times each week
BID. Two times daily (includes every 12 hrs)	6W. Six times each week
	1M. Once every month
TID. Three times daily	2M. Twice every month
QID. Four times daily	C. Continuous
5D. Five times daily	O. Other

a. Name	b.Dose	c.Form	d.Freq	e. PRN (✓)	f. ATC or NDC code
1.					
2.					
3.					
4.					
5.					

[Add additional lines as necessary, for other drugs taken]

2. ALLERGY TO DRUGS

0. No 1. Yes

SECTION L. TREATMENTS AND PROCEDURES

1. TREATMENTS AND PROGRAMS RECEIVED OR SCHEDULED DURING LAST 3 DAYS (OR SINCE LAST ASSESSMENT IF LESS THAT 3 DAYS)

0. Did not occur, not ordered
1. Ordered, not yet implemented
2. 1-2 of last 3 days
3. Daily in last 3 days

a. **Alternative non-medication pain therapies (e.g., massage, music)**

b. **Bowel regimen**

c. **Chemotherapy**

d. **Morphine pump**

e. **Oxygen therapy**

f. **Radiation therapy**

g. **Suctioning**

h. **Terminal sedation**

i. **Tracheostomy care**

j. **Ventilator or respirator**

k. **Other** _____ Specify

SECTION M. RESPONSIBILITY/DIRECTIVES

1. LEGAL RESPONSIBILITY

0. No 1. Yes

a. **Living will**

b. **Court appointed guardian**

c. **Durable power of attorney/health care proxy**

2. ADVANCED DIRECTIVES / WISHES

0. No 1. Yes

ADVANCED DIRECTIVES

a. **Do not resuscitate**

b. **Do not intubate**

c. **Do not hospitalize**

d. **Do not send to emergency department**

e. **No tube feeding or hydration**

f. **Medication restrictions**

g. **Other treatment restrictions**

h. **Comfort measures only**

PERSON'S WISHES

i. **To die at home**

j. **To die at current living site**

k. **Terminal sedation**

l. **Other** _____ Specify

3. RESPONSE TO TREATMENT OFFERED

0. Treatment not offered
1. Accepted offered treatment
2. Declined offered treatment

a. **ADL care**

b. **Hospitalization**

c. **IV therapy**

d. **Liquids / solids orally**

e. **Antibiotics**

f. **Medicines other than antibiotics and analgesics**

g. **Alternative therapies**

h. **Oxygen**

i. **Tube feeding**

j. **Other** _____ Specify

4. ACTIVITY PREFERENCES

0. No preference
1. Continue at current level
2. Discontinue or reduce
3. Add or increase

a. **Visits with friends or others**
b. **Telephone calls**
c. **Discuss/reminisce about life**
d. **Be alone**
e. **Recreation**
f. **Spiritual activity**
g. **Bathing– i.e., shower, tub baths**
h. **Massage**
i. **Comfort foods**
j. **Hospice care**
k. **Other** _____ Specify

SECTION N. SOCIAL RELATIONSHIPS

1. TIME WITH PERSON

[In last 24 hours, how long was any family member, significant other or friend with the person?]

0. No contact
1. Less than 1 hour
2. One to four hours
3. More than four hours

2. TWO KEY INFORMAL HELPERS

a. Relationship to person — Helper 1 2

0. Child or child-in-law
1. Spouse
2. Partner/significant other
3. Parent
4. Other relative
5. Friend or neighbour
8. No helper

b. Lives with person — Helper 1 2

0. Yes, more than 6 months
1. Yes, 6 months or less
2. No
8. No helper

c. Has contact with person on a daily or almost daily basis — Helper 1 2

0. Yes, in person
1. Yes, over phone or email
2. No
8. No helper

AREAS OF HELP: — Helper 1 2

0. No 1. Yes

d. IADL care
e. ADL care

3. HOURS OF INFORMAL CARE PROVISION AND ACTIVE MONITORING

*For instrumental and personal activities of daily living received over **LAST 3 DAYS**, indicate total number of hours of help received from family, friends, and neighbors (rounded hours)* — Helper 1 2

SECTION O. DISCHARGE [CODE ONLY AT DISCHARGE]

1. DATE OF DISCHARGE [after discharge only]

2 0 ☐☐ – ☐☐ – ☐☐
Year Month Day

2. DISCHARGED TO

1. Private home/apartment/rented room
2. Board and care/assisted living/group home/ mental health residence
3. Facility for persons with developmental disability
4. Psychiatric hospital or unit
5. Homeless (with or without shelter)
6. Long-term care facility (nursing home)
7. Rehabilitative hospital/unit
8. Hospice facility/Palliative care unit
9. Acute care hospital
10. Correctional facility
11. Other
12. Deceased

SECTION P. ASSESSMENT INFORMATION

SIGNATURE OF PERSON COORDINATING THE ASSESSMENT:

a. Signature (sign on above line)
b. Date signed as complete

2 0 ☐☐ – ☐☐ – ☐☐
Year Month Day

Appendix 4. License from the National Bioethics Committee – an additional licence for the EPOS part of this study

Landspítali, fræðasvið krabbameinshjúkrunar
Sigríður Gunnarsdóttir, lektor og forstöðumaður
Eiríksgötu 19
101 REYKJAVÍK

VÍSINDASIÐANEFND

Vegmúla 3, 108 Reykjavík,

Sími: 551 7100, Bréfsími: 551 1444
netfang: visindasidanefnd@vsn.stjr.is

Reykjavík 24. mars 2009
Tilv.: VSNb2005030002/03.15

Á fundi sínum 24.03.2009 fjallaði Vísindasiðanefnd um umsókn ykkar Valgerðar Sigurðardóttur, yfirlæknis dags. 03.03.2009, vegna viðbótar við ofangreinda rannsóknaráætlun.

Í bréfinu kemur m.a. fram að rannsakendur sækja um leyfi til þess að afla upplýsinga um dánardægur íslensku þátttakendanna í ofangreindri rannsókn. Farið er fram á að leita megi eftir dánardegi í rafrænni sjúkraskrá LSH. Beiðni verður send til lækningaforstjóra LSH til að nálgast gögn úr sjúkraskrám spítalans. Þessar upplýsingar verða síðan sendar til Þrándheims til innsláttar og verða persónugreinanlegu upplýsingarnar kóðaðar eins og áður. Samkvæmt upplýstu samþykki sem þátttakendur skrifuðu undir, var veitt samþykki fyrir frekari rannsóknum tengdum þessu efni. Fyrirhugað er að fá íslensku gögnin og nýta þau sem meistaraverkefni frá læknadeild HÍ fyrir Sigríði Helgadóttur deildarlækni á LSH. Gagnasöfnun á Íslandi lauk í febrúar 2008 og voru öll gögn send til Þrándheims til innsláttar og úrvinnslu lyfjaerfðafræðilegra þátta.

Vísindasiðanefnd hefur farið yfir bréf ykkar og innsend gögn og gerir ekki athugasemdir við tilgreindar breytingar. Viðbót nr. 1 ásamt fylgigögnum við ofangreinda rannsókn, er endanlega samþykkt af Vísindasiðanefnd.

Með kveðju,
f.h. Vísindasiðanefndar,

dr. med., Björn Rúnar Lúðvíksson, læknir, formaður