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Anne Kari Knudsen

Cancer pain classification

Doctoral Thesis

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Norwegian University of Science and Technology
Thesis for the degree of Philosophiae Doctor
Faculty of Medicine
Department of Cancer Research
and Molecular Medicine

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Trondheim, April 2012

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På vei

Veien er lang, det er langt til mål,
det er bare å gå.
Gi tål!
Når du er fremme,
vil du forstå,
på vei er vandreren hjemme.

Arnulf Øverland

Name of candidate:	***Anne Kari Knudsen***
Department:	***Institutt for kreftforskning og molekylær medisin/ Department of Cancer Research and Molecular Medicine, European Palliative Care Research Centre***
Supervisors:	***Pål Klepstad, Nina Aass and Peter Fayers***
Funding:	***Samarbeidsorganet Helse Midt-Norge og NTNU/ Liaison Committee between the Central Norway Regional Health Authority and the NTNU***

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This thesis has been assessed to be worthy of being defended
for the doctoral degree of PhD in Palliative Care, philosophiae doctor.
The public defence takes place at the Auditorium,
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Friday 20 April 2012 at 12.15 pm

NTNU – Trondheim
Norwegian University of
Science and Technology

EPCRC

Contents

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The work presented in this thesis was carried out from 2008 to 2011 at the European Palliative Care Research Centre (PRC), Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology (NTNU) and at the Palliative Care Unit, Cancer Clinic, St. Olav's Hospital, University Hospital of Trondheim. The primary financial support for this thesis was a grant from the Liaison Committee between the Central Norway Regional Health Authority and the NTNU.
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Trondheim, January 2012
Anne Kari Knudsen

Abbreviations

BPI	Brief Pain Inventory
BTP	Breakthrough pain
CI	Confidence interval
CPACS	Cancer pain assessment and classification system
CPOR	Cancer Pain Outcome Research (Study Group)
CPPS	Cancer Pain Prognostic Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders fourth edition
EAPC	European Association for Palliative Care
ECS-CP	Edmonton Classification System for Cancer Pain
EORTC	European Organization for Research and Treatment of Cancer
EORTC-QLQ-C30	EORTC Cancer Core Quality of Life Questionnaire-C30
EPCRC	European Palliative Care Research Collaborative
EPOS	European Pharmacogenetic Opioid Study
ESAS	Edmonton Symptom Assessment System
ESS	Edmonton Staging System
FACT-G	Functional Assessment of Cancer Therapy-general
FDA	U.S. Food and Drug Administration
HRQOL	Health related quality of life
IASP	International Association for the Study of Pain
ICD-10	International Classification of Diseases 10^{th} edition
IP	Incident pain
KPS	Karnofsky Performance Status score
MEDD	Total oral morphine equivalent daily dose
MMSE	Mini Mental Status Exam
MPQ	McGill Pain Questionnaire
NCCN	The National Comprehensive Cancer Network

NeuPSIG	Neuropathic pain Special Interest Group (IASP)
NICE	National Institute for Health and Clinical Excellence
NRS-11	Numerical rating scale (ranging from 0 to 10)
OEI	Opioid Escalation Index
PMI	Pain management index
PRC	European Palliative Care Research Centre
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROs	Patient reported outcomes
QOL	Quality of life
rESS	Revised Edmonton Staging System
SD	Standard deviation
TIQ	Therapy Impact Questionnaire
TNM	The TNM classification of malignant tumours; T: Extent of the primary tumour, N: Regional lymph node metastasis, M: Distant metastasis.
VAS	Visual analogue scale
VRS	Verbal rating scale
WHO	World Health Organization

Summary in Norwegian

Klassifikasjon av kreftsmerte

Kreftsmerte – hva skal et fremtidig klassifikasjonssystem inneholde?

Smerte er et subjektivt, sammensatt og plagsomt symptom som forekommer hyppig hos kreftpasienter. Til tross for eksisterende retningslinjer, er det mange kreftpasienter som ikke får god smertebehandling, særlig ved langkommet sykdom. En av mange årsaker til dette, er mangelen på et allment akseptert klassifiseringssystem for kreftsmerte – et verktøy for å stille en korrekt diagnose.

På bakgrunn av ovennevnte forhold ble den internasjonale EU-finansierte forskningsgruppen 'European Palliative Care Research Collaborative' (EPCRC) dannet. En av gruppens hovedmålsettinger var å utvikle klassifikasjonssystem for tre vanlige symptomer hos kreftpasienter med langtkommet sykdom: smerte, depresjon og ufrivillig vekttap. Arbeidene i denne avhandlingen har vært utført i nær tilknytning til EPCRC. Det overordnete målet med avhandlingen er å bidra i utviklingsprosessen av et internasjonalt klassifikasjonssystem for smerte hos kreftpasienter blant annet ved å finne frem til noen faktorer som er avgjørende for å kunne beskrive en smertetilstand og derved å kunne stille en korrekt smertediagnose.

Hovedfunnene i avhandlingen er:

- Det foreligger flere systemer for klassifisering av smerte hos kreftpasienter, men ingen av disse er i utstrakt bruk, verken i forskning eller klinisk praksis. Smertens intensitet og patofysiologi, forekomst av gjennombruddssmerte, psykisk stress og respons på behandling inngår i to eller flere av de seks formelle systemene som ble funnet ved systematisk litteraturgjennomgang.
- Pasienter bekreftet i intervju at faktorer påvist å være viktige for kreftsmerte i tidligere studier, også var relevante for deres smerteopplevelse. De vektla fysiske og psykiske aspekter ved det å ha smerte, og søvn ble ansett som en viktig faktor.

- I en europeisk studie hvor mer enn 2000 kreftpasienter som brukte sterke smertestillende (opioider) deltok, ble følgende faktorer funnet å ha betydning for grad av smerteintensitet og/eller smertelindring: gjennombruddssmerte, smertens lokalisasjon, opioiddose, bruk av svake smertestillende, søvn, psykisk stress, smertens patofysiologi, misbruk av alkohol/narkotika, kreftdiagnose og lokalisasjon av spredning av kreftsykdommen.
- I en italiensk studie hvor 1800 kreftpasienter deltok, ble de fem førstnevntes relevans bekreftet. Videre ble det i den samme studien påvist at smerteintensitet og opplevd smertelindring målt ved studiens oppstart samt forekomst av gjennombruddssmerte, smertens lokalisasjon, alder og kreftdiagnose var faktorer som kunne predikere smerte etter to uker.

Minst tre hovedutfordringer må løses for å komme nærmere et internasjonalt klassifikasjonssystem for kreftsmerte: å velge de mest relevante faktorene for inklusjon i systemet, inkludert å velge et tilstrekkelig antall faktorer, å oppnå enighet om hvilke endepunkt som skal brukes og til slutt å innføre det fremtidige klassifikasjonssystemet i klinisk praksis.

Summary in English

Cancer pain classification – what should be the content of a future system?
Pain is a subjective, complex and burdensome symptom which is very common in cancer patients. Despite existing treatment guidelines, several cancer patients still do not receive optimal pain treatment, in particular patients with advanced disease. The lack of a common classification system for cancer pain – a diagnostic tool – has been identified as one of several causes for this undertreatment.

Motivated by these considerations, the international EU-funded 'European Palliative Care Research Collaborative' (EPCRC) was established. One of the main aims was to develop a classification system for three common symptoms in cancer patients with advanced disease: pain, depression, and cancer related weight loss.

The papers included in this thesis have been performed in close collaboration with the EPCRC. The overall aim of the thesis is to contribute in the development process of an international classification system for pain in cancer patients by for example to identify factors that are important for describing pain and thus improve diagnostics and treatment of cancer pain.

The main results in this thesis are:

- There are several systems for pain classification in cancer patients, but none of these are widely used in research or in clinical practice. Pain intensity and pathophysiology, the presence of breakthrough pain, psychological distress, and response to treatment are included in two or more of the six formal systems that were identified by systematically reviewing existing literature.
- Patients confirmed in interviews that the factors identified to be important for cancer pain in previous studies, were relevant also for their experience of pain. They emphasised physical and psychological aspects of being in pain, and sleep was considered important.

- In an European study where more than 2000 cancer patients using strong pain medication (opioids) participated, the following factors were identified to be of importance for the degree of pain intensity and pain relief: breakthrough pain, localisation of pain, opioid dose, use of weak pain medication, sleep, psychological distress, pathophysiology of pain, substance abuse, cancer diagnosis, and localisation of metastases.
- In an Italian study where 1800 cancer patients participated, the relevance of the five first factors listed above was confirmed. Furthermore, results from the same study showed that pain intensity and pain relief measured at study start as well as the presence of breakthrough pain, localisation of pain, age, and cancer diagnosis were factors that could predict pain after two weeks.

At least three major challenges for the further development a future international classification system for cancer pain: to choose the most relevant factors (and how many) to include in the system, to achieve agreement on what outcomes to use, and finally to start using the classification system in clinical practice.

List of papers

This thesis is based on the following original publications, which are referred in the text by Roman numerals, paper I to IV.

Paper I

Knudsen AK, Aass N, Fainsinger R, Caraceni A, Klepstad P, Jordhoy M, Hjermstad MJ, Kaasa S. Classification of pain in cancer patients -a systematic literature review. Palliative Medicine 2009;23(4):295-308.

Paper II

Knudsen AK, Aass N, Klepstad P, Heitzer E, Schippinger W, Brenne E, Kaasa S, Wasteson E. Interviews with patients with advanced cancer - another step towards an international cancer pain classification system. Supportive Care in Cancer 2012; Jan 18. DOI: 10.1007/s00520-011-1361-z. [Epub ahead of print].

Paper III

Knudsen AK, Brunelli C, Kaasa S, Apolone G, Corli O, Montanari M, Fainsinger R, Aass N, Fayers P, Caraceni A, Klepstad P. Which variables are associated with pain intensity and treatment response in advanced cancer patients?-Implications for a future classification system for cancer pain. European Journal of Pain 2011;15(3):320-327.

Paper IV

Knudsen AK, Brunelli C, Klepstad P, Aass N, Apolone G, Corli O, Montanari M, Caraceni A, Kaasa S. Which domains should be included in a cancer pain classification system? Analyses of longitudinal data. PAIN® 2012; 153(3):696 703.

1. Background

1.1 Preface

Pain is one of the most prevalent, burdensome and feared symptoms among cancer patients. Despite analgesic pain treatment and tumour directed therapy, as many as 50% of cancer patients in general and about 70% of patients with incurable disease, experience pain [34, 185]. The lack of standardised diagnostic procedures has been identified as one important reason for the under treatment of pain [20, 80, 106, 187].

Motivated by multiple problems seen in cancer patients receiving palliative care, international palliative care researchers, many of them connected to the European Association for Palliative Care (EAPC) Research Network[47], launched the European Palliative Care Research Collaborative (EPCRC) [50] in 2006. The EPCRC was funded by a three-year grant from the European Union's 6th framework. EPCRC aimed at establishing an international arena for palliative care research. The overall aims were to study genetic variations relevant for response to opioid treatment, to develop an international and computer based assessment and classification system for pain, cachexia, and depression in cancer patients, and to develop evidence based guidelines for these symptoms [106]. This thesis has been performed as a part of the EPCRC. It aims at contributing to the development of an international classification system for cancer pain.

1.2 Cancer

Worldwide, the incidence of cancer is estimated to increase from 11.3 million cases in 2007 to 15.5 million cases in 2030 [191]. In Norway, there were in 2009 27 500 new cases of cancer, a number that is expected to increase to 30 500 in 2020 [28]. Also the survival rates for many cancers are increasing. Therefore, in the future, patients are expected to live longer with the malignant disease, and even more patients will risk experiencing distressing symptoms including pain [46].

1.3 Palliative care

The World Health Organization (WHO) defines palliative care as follows: «Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. [Palliative care] provides relief from pain and other distressing symptoms» [(168)]. Palliative care is offered to patients with any life-threatening diseases. However, the majority of patients receiving specialised palliative care are suffering from a malignant disease. The EAPC has defined palliative care as «the active, total care of the patient whose disease is not responsive to curative treatment» and points out that palliative care is interdisciplinary and that «palliative care affirms life and regards dying as a normal process; it neither hastens nor postpones death. It sets out to preserve the best possible quality of life until death» [(46)].

Due to therapeutic refinements the patients receive anti-cancer treatment for a longer period of time during the disease trajectory with the intention of life prolongation. Furthermore, symptom relief is also an important aspect of the oncological treatment. In general oncology, patients with incurable disease are offered both tumour directed and symptom specific treatment, and are also often in need of a comprehensive, broad and patient-centred multi professional diagnostic and therapeutic approach [(182)]. A recent randomised controlled study in patients with metastatic non-small cell lung cancer compared standard oncologic care with standard oncologic care plus early integrated palliative care. The ‘palliative care’ group had longer survival and significantly better quality of life and mood compared to the ‘oncology group’ [(177)]. Recognising the importance of integrating palliative care into oncology, the WHO revised its definition of palliative care by also adding the following: «Palliative care is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical

complications» [168]. This approach was also recently supported in a commentary by the EAPC [107] and in a review [175].

Despite existing definitions of palliative care, the terminologies used worldwide for this medical field are heterogeneous [46]. The descriptions 'palliative care patients', 'patients with advanced cancer' and 'patients with incurable cancer' have commonly been used to describe cancer patients with metastases and a complex disease burden. Patients in palliative care often suffer from many symptoms at the same time. These symptoms usually are fluctuating in presence and intensity [116]. In a systematic literature review among patients with incurable cancer, 37 symptoms were identified as occurring in more than 10 % of the patients [178]. Pain, fatigue, lack of energy, weakness, and appetite loss were experienced by > 50% of the patients. Similar results were found in an earlier study at our institution [102]. Improved diagnostics and treatment of these symptoms, including pain, is important.

1.4 Cancer pain

The International Association for the Study of Pain (IASP) defines pain as «an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage» and points out that pain is always subjective [94]. Pain is a complex and multifactorial symptom which is experienced differently due to inter-individual differences. Pain influences most aspects of a person's life and is considered to be a major threat to good function and quality of life [62 ,63 ,155 ,159 ,198]. Pain due to a malignant disease is common; about 90% of cancer patients experience pain at some point during the disease trajectory [34]. Pain in cancer patients may be caused by the cancer disease itself, by the anti-cancer treatment or may occur due to other conditions [63]. The term 'cancer pain' refers mainly to pain caused directly by the cancer disease. A meta-analysis on prevalence of cancer pain reported prevalence rates to be 33% in cancer patients after curative treatment and 64% in patients with metastatic disease [185].

Pain is prevalent even in cancer patients treated with opioids. In a review of 26 publications on analgesic treatment of cancer pain, nearly half of the patients were identified as being undertreated [44]. In a pan-European cross-sectional multicentre study performed by the EAPC including 3030 patients receiving analgesic pain treatment (94% with cancer), 32% reported moderate to severe pain [111]. In a Norwegian multicentre prevalence study 52% of 857 included hospitalised cancer patients receiving anti-cancer treatment reported to have pain, and scored mean pain on average the last 24 hours to be 3.99 on an 11-point numerical rating scale ranging from 0 to 10 (NRS-11)[90].

1.4.1 Guidelines for treatment of cancer pain

Opioids are considered the cornerstone of analgesic treatment of cancer pain [155,159].The WHO three step pain relief ladder was introduced in the 1980's. These guidelines, that are widely accepted and used for treatment of cancer pain, recommend that a cancer patient with pain should be offered oral administration of analgesic drugs in the following order: step I non-opioids (for example paracetamol/non-steroidal anti-inflammatory drugs); step II mild opioids (codeine); and step III strong opioids such as morphine, until the patient is free of pain [190].

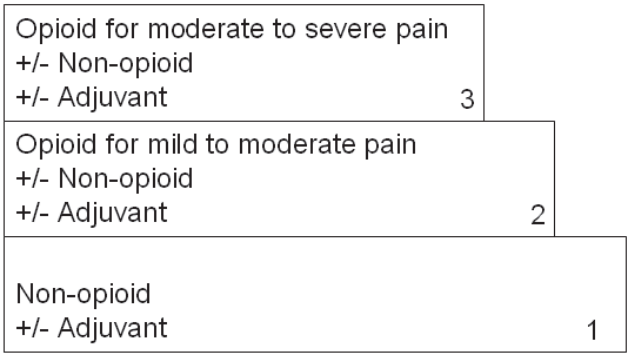

Figure 1: World Health Organisation's (WHO) three step pain relief ladder for treatment of cancer pain [195].

Based upon these treatment principles, the EAPC Research Network in 1996 published guidelines for the use of opioids in cancer pain [45] which were updated in 2001 [78]. Sixteen new recommendations are given in a review of the evidence base for the EAPC guidelines and other aspects of cancer pain treatment which is in the process of being published[31]. In summary, most of current recommendations for cancer pain treatment are based on low levels of formal scientific evidence.

In addition to opioids, several different approaches are applied for the treatment of cancer pain [155]. Neuroaxial treatment of cancer pain including such as spinal, epidural and intrathekal administration of opioids and local anesthetics may be necessary to apply in some patients to achieve pain control [133], and tumour directed therapy, such as surgery, radiotherapy, and systemic therapy (endocrine treatment, chemotherapy and 'targeted therapy') should be considered for the treatment of cancer pain [175].

1.4.2 Barriers to optimal cancer pain management

Several barriers to optimal treatment of cancer pain have been identified, and can be related to patients, physicians and to the health care system.

Patients' barriers

Several patients' beliefs and misconceptions regarding the use of opioids for cancer pain have been identified [73]. Patients fear side-effects and development of tolerance as well as addiction and are therefore reluctant to take analgesics. Patients' reluctance to report pain was recently stated as one important reason for the under treatment of pain [20]. There may be several reasons for this. The patients may fear that pain represents disease progression; they may be fatalistic thinking that 'pain is an inevitable part of having cancer'; they may think that 'good patients' do not complain about pain, and they may think that the report of pain would distract the physician from treating the cancer disease [73].

Professionals' barriers

Physicians' and nurses' insufficient knowledge about the underlying malignant disease, the pathophysiology of cancer pain, and principles of pain treatment are important barriers to correct pain diagnosis and appropriate pain treatment [146]. Physicians' reluctance to prescribe opioids was in 1993 described as 'opiophobia' [199] and is still stated as an important barrier to optimal pain management by medical oncologists [20].

Barriers of the health care system

Accessibility of opioids is limited in many European countries due to excessive regulatory barriers which cause poor pain treatment [37]. A lack of standardised and evidence based education of health care professionals as well as a lack of available specialists in pain management and palliative care have also been identified as important barriers to optimal pain management [20 ,199].

Finally, the lack of standardised and systematic assessment and classification tools for cancer pain has by several authors been stated as an important barrier to optimal pain management [20 ,35 ,80 ,106 ,187].

1.4.3 Why is an international cancer pain classification system needed?

Several arguments for an international consensus on a classification system for cancer pain have been proposed. An international cancer pain classification system can:

In the clinic [35 ,55 ,64 ,85]

- Improve the management of pain in the individual patient
- Guide the information to assess
- Guide the use of standardised and efficient assessment methods
- Guide treatment decisions
- Predict the level of complexity of needed interventions for pain
- Predict response to pain treatment

Research [17 ,18 ,55 ,85]

- Guide the inclusion of patients into clinical studies
- Facilitate comparison of effects between studies
- Improve the quality of meta-analyses
- Facilitate the translation of research results into clinical practice

Health care system / policy making [42 ,148]

- Tool for quality assurance of cancer pain treatment
- Tool for conducting comparisons between institutions

1.5 What is classification?

1.5.1 Classification in general

Taxonomy is the science and practice of classification. A classification divides objects into subclasses. Each of the subclasses is defined by «certain characteristics essential for membership in that subclass» [82]. Aristotle (384-322 BC) developed a 'classification of living things', placing plants, animals and humans in a hierarchy according to structure, function and skills [11]. Carl Linnaeus (1707-1778) established conventions for the naming of organisms; the Linnaean taxonomy is a scientific hierarchical classification system widely used in biology [164] . In medicine, the concept of diagnosis is the assignment of individual cases to particular classes in a taxonomic system of diseases and is identical to classification in other areas of biological science [82].

1.5.2 Classification in medicine

A diagnostic procedure is an essential part of clinical practice, and much medical research is performed aiming at improving methods of diagnostics. A classification system in medicine summarises all relevant information from the patient's medical history, the clinical examination and supplementary examinations into a short and useful description and is a guide to which information to assess and how to assess it. The diagnosis or the classification of a condition is a summary and a conclusion of information gathered from different sources (e.g. the results of x-ray or a biopsy, or the presence or absence of a symptom or sign); it constitutes the basis for medical treatment decisions and guides prognostic considerations [115]. In clinical practice, the diagnostic process usually contains the following steps:

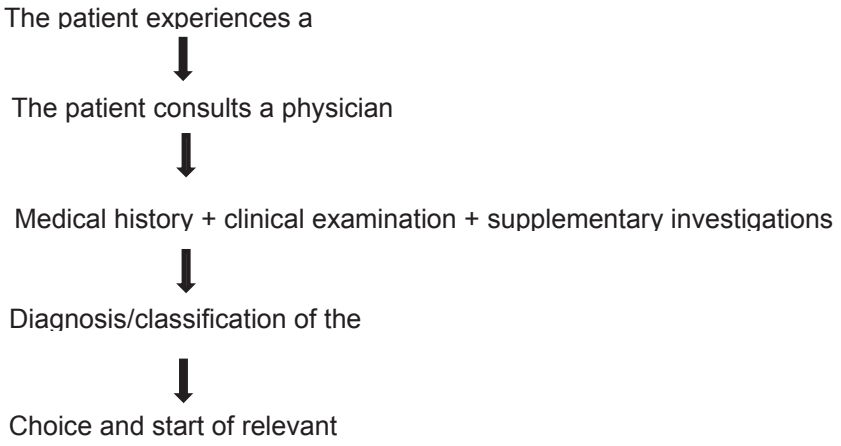

Figure 2: The diagnostic process

1.5.3 Examples of classification systems in medicine

International Classification of Diseases

The International Classification of diseases,10th edition, the ICD-10, is the international standard diagnostic classification for general epidemiological and health management purposes as well as clinical use. The first edition of this classification system was the International List of Causes of Death from 1893. The WHO has been responsible for the ICD since 1948. The ICD is widely used to classify diseases and other health problems, it provides the basis for national mortality and morbidity statistics, and is an important tool for administrative health care planning [193]. The field of cancer pain is poorly reflected in the ICD-10 and has been addressed as a part of the revision, which is planned to be finalised by 2015 [165].

International Classification of Diseases for Oncology

The international Classification of Diseases for Oncology (ICD-O) is a multi-axial classification of the site, morphology, behaviour, and grading of cancer diseases. It is used in cancer registries for coding of site (topography) and histology (morphology), information usually obtained from a pathology report and is not used for cancer pain [193].

Diagnostic and Statistical Manual of Mental Disorders

The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, the DSM-IV, is published by the American Psychiatric Association and is the standard classification of mental disorders. It can be used in various clinical settings e.g. for inpatients as well as in primary care, it can be used by health care providers of different professions and is an important tool for public health statistics. It contains five axes: clinical syndromes, developmental disorders and personality disorders, physical conditions, severity of psychosocial stressors, and highest level of functioning, none of these related to cancer pain [7].

TNM Classification of Malignant Tumours

The TNM classification of malignant tumours is the gold standard for describing the anatomical extent of malignant diseases. It is based on the assessment of three components: T: the extent of the primary tumour, N: the absence or presence and extent of regional lymph node metastasis, and M: absence or presence of distant metastasis. The TNM classification divides the patients into four prognostic stages. The TNM system was developed in the 1940s by Prof. Pierre Denoix and first published in 1953 [183]. In 1987 this and two other approaches to classification tumours (from the International Federation of Gynecology and Obstetrics (FIGO) and the American Joint Committee for Cancer (AJCC)) were unified as the Union for International Cancer Control (UICC) TNM Classification of Malignant Tumours 4th Edition, which has been revised and developed continuously. For instance in brain tumours, testicular cancer and lymphomas other classification systems are applied. The TNM system does not address cancer pain.

1.5.4 Examples of classification systems for cancer pain

A comprehensive review by Caraceni and Weinstein summarised in 2001 that there have been several attempts to define a cancer pain classification system during the last decades. For example, cancer patients experience pain with different pathophysiological mechanisms in multiple sites and described existing approaches to cancer pain classification as temporal, etiologic, anatomic, pathophysiologic, or syndromic [35].

International Association for the Study of Pain: Classification of Chronic Pain

The International Association for the Study of Pain (IASP) Classification of Chronic Pain is a descriptive coding system for chronic pain syndromes which was first presented in 1986 and later revised in 1994 [135]. The included list of pain terms was also revised in 2011 [94]. This classification system consists of five axes: I, anatomical region or site affected by pain; II, organ systems whose abnormal functioning produces pain; III, temporal characteristics of pain; IV, pain intensity and time since pain onset; and V, etiology, where cancer is listed among several other causes of pain. The patients report intensity and duration of pain. Further assessments consisting of medical history, clinical examinations and supplementary investigations are performed by a health care provider. A code number is given to every clinical pain syndrome.

Edmonton Classification System for Cancer Pain

The Edmonton Classification System for Cancer Pain (ECS-CP) is a tool for prediction of treatment response and was initially launched in 1989 as the Edmonton Staging System for Cancer Pain (ESS) [23]. Since then, thorough research has been performed and the ECS-CP has been developed and revised [55]. The ESS [23] consisted of seven domains: mechanism of pain (visceral, bone or soft tissue, neuropathic, mixed, unknown); incidental pain (presence or absence); daily opioid dose; cognitive function (impaired or normal); psychological distress (present or absent); tolerance (present according to an average daily increase in opioid consumption of more than 5% over the first three weeks of follow-up); and past history of drug or alcohol addiction (positive or negative). Depending on the

assessment of these domains, the patients were classified as having good, intermediate, or poor prognosis for pain control. In 1995 the number of prognostic groups were reduced to two (good and poor) and the two domains daily opioid use and cognitive function were removed from the system [25].

Due to difficulties with the definitions, its practical use and the relatively poor predictive properties of the ESS, a revised version was presented in 2005 (rESS) [145]. In the rESS the domain cognitive function was reintroduced based upon literature review and expert opinion. Tolerance was excluded due to difficulties in clinical interpretation and practical implementation of the calculations [55]. To classify patients into different prognostic groups was left as most patients achieved pain control [56]. A Delphi process among palliative care and pain experts resulted in: the change of the name 'incidental pain' to 'incident pain'; an "unable to classify" category was added to all domains; the domains 'psychological distress' and 'addictive behaviour' were re-separated into two domains; and the name was changed to the Edmonton Classification System for Cancer Pain [145].

At present the ECS-CP consists of five domains: mechanism of pain (mainly nociceptive or neuropathic), incident pain (present/absent), psychological distress (present/absent), addictive behaviour (present/absent), and cognitive function (impaired/normal). A health care provider performs the assessment and summarise it into a 'code' [52].

In 2010 the results from a prospective international validation study of the ECS-CP including 944 cancer patients with pain was published [54]. The primary outcome was time (in days) to achieve stable pain control, defined as «receiving less than three breakthrough analgesic doses per day and a patient self-reported pain score of less than or equal to 3/10 for three consecutive days». The final opioid dose and the number of adjuvant analgesics use were also outcome measures. In multivariate analysis, younger age (< 60 years), neuropathic pain, incident pain, psychological

distress, and pain intensity (moderate and severe), were associated with longer time to achieve stable pain control [54]. Pain intensity has been stated to be an important domain to add to the ECS-CP [53]. Both the ESS from 1989, the rESS from 2005, and the ECS-CP are presented in appendix.

Cancer Pain Prognostic Scale

The Cancer Pain Prognostic Scale (CPPS) is a tool for the prediction of pain relief in cancer patients [92]. Seventy-four cancer patients were included in a prospective study defining pain relief $\geq$ 80% measured by the Brief Pain Inventory (BPI) (0% no relief, 100% complete relief) as the primary endpoint. Worst pain intensity (NRS-11) and emotional well-being (the Functional Assessment of Cancer Therapy-general (FACT-G)) were identified as predictors at week 1 and daily opioid dose and mixed pain mechanism predictors at week 2.

1.5.5 Definitions and understanding of concepts

To improve cancer pain management, there is a need for a comprehensive, accurate and simple diagnostic tool for cancer pain [85]. A cancer pain classification system should combine a series of information about the patient and the pain to a common description, a pain diagnosis. It may be comparable with the use of the term 'phenotype' in genetic studies [68]. The standardised and systematic description might be used for grouping of patients. Different groups or subclasses in a classification system may represent different levels of probability for achieving pain control or may give information about the expected level of complexity of offered pain treatment, for example as suggested in the first version of the ECS-CP [21 ,23]. Prediction of expected response to pain therapy is an important aim of a cancer pain classification system [35].

Some theoretical terms are useful for the evaluation of a systems' quality: If 'positive' and 'negative' refer to the presence or absence of the condition of interest 'sensitivity' is defined as «the proportion of positives that are correctly identified by a test» and 'specificity' as «the proportion of negatives that are correctly identified by a test».

'Positive predictive value' is the proportion of patients with positive test results who are correctly diagnosed with a condition, and 'negative predictive value' is the proportion of patients with negative test results who are correctly diagnosed [6].

Several terms have been used to describe symptoms and signs within cancer pain classification, for example 'covariates'/'attributes' [30], 'features' [52], and dimensions [88]. For the improvement of diagnostic tools, clear definitions of the domains to include are necessary [106 ,143]. The EPCRC agreed upon a conceptual framework using the terms 'symptom', 'domain', and 'item' [85] a framework which has been used in this thesis with the following definitions:

Symptom

A 'symptom' is defined as «a physical or mental feature which is regarded as indicating a condition of disease, particularly such a feature that is apparent to the patient» [147]. Pain and dyspnoea are examples of symptoms.

Domain

A 'domain' is a word which origins from old French '*demeine'* meaning «belonging to a lord» [147] and is a concept used in every field of human activity. Regarding cancer pain, pain localisation and breakthrough pain are examples of domains. A sub-domain has been used for one of more characteristics of a domain. Sub-domains of pain mechanism are for example nociceptive and neuropathic pain.

Item

An 'item' is «an individual article or unit, especially one that is part of a list, collection, or set» [147]. Items may be used for more detailed assessment of pain domains. The number of pain episodes and their duration are examples of items of the domain breakthrough pain.

1.5.6 Patient reported outcomes

Patient reported outcomes (PROs) has become a commonly used ‘umbrella’ term for the description of patients’ self-report of subjective symptoms, health related quality of life (HRQOL) and effect of treatments [189], defined by the U.S. Food and Drug Administration (FDA) as «any report coming directly from patients about a health condition and its treatment» [184].

1.5.7 Quality of life

There is no generally agreed definition of quality of life (QOL), however, many agree that QOL is a multidimensional construct defining all aspects of a patient’s well-being including e.g. physical, psychological, social, spiritual, and economic aspects [57]. The WHO defines health as follows: «Health is a state of complete physical, mental and social well being and not merely the absence of disease or infirmity» [192]. The general term QOL has been narrowed into ‘health related quality of life’ (HRQOL) for use in clinical research, covering the aspects of QOL that are most relevant to medicine and health care: physical, psychological, role, cognitive, and social function as well as pain and other subjective symptoms [105]. HRQOL is widely assessed in cancer care by the EORTC-QLQ-C30 [122,172]. In addition, several other questionnaires for the assessment of PROs and HRQOL exist [57].

1.6 Cancer pain domains

Pain is a complex and multifactorial symptom. Thus, to be able to classify cancer pain properly, several aspects of the pain condition and the patient should be considered and assessed. In a systematic literature review on cancer pain assessment, the following domains ('dimensions') of pain were identified [88]: pain intensity, breakthrough pain, neuropathic pain, pain localisation, duration, pain history, treatment and exacerbating/relieving factors, interference, psychological distress/pain affect, and beliefs/coping. Other domains considered relevant for cancer pain classification are pain etiology - as one approach to classification presented in a comprehensive review by Caraceni and Weinstein [35] - and cognitive function and addiction, which were additional domains included in the ECS-CP [52,56].

1.6.1 Pain intensity

Intensity has in several publications been presented as the clinically most important domain of cancer pain [29,36,53,87,88,98]. Pain intensity is essential for describing and reporting the subjective pain experience [39], it is an indicator of impact on several aspects of life [150] and crucial as a guide for treatment decisions[53]. Unidimensional scales such as NRS, VRS, and VAS are recommended used for the assessment of pain intensity, preferably an 11-point NRS where 0 corresponds to "no pain" and 10 to "pain as bad as you can imagine" [103]. The categorisation of pain intensity is commonly used for clinical decision making using the cut-points 0 to 3 for mild, 4 to 6 for moderate, and 7 to 10 for severe pain [150]. More severe pain indicates that the patient is undertreated [44] and/or the pain is difficult to treat [53].

1.6.2 Breakthrough pain

Several terms have been used to describe temporal variations of intensity and quality of pain. Haugen et al. conclude in a systematic literature review [81] that the majority of authors used the term 'breakthrough pain' and thus this term will be used in the following, even if other terms has been used in the papers included in this thesis (for

example ‘incident pain’ in paper IV). There is no universally accepted definition of breakthrough pain [200]. Most definitions include that the background or baseline pain needs to be adequately treated [81] as Portenoy and Hagen did in 1990: «Breakthrough pain is a transitory exacerbation of pain that occurs on a background of otherwise stable pain in a patient receiving chronic opioid therapy» [157]. Breakthrough pain is often experienced as recurrent episodes of pain characterised by rapid onset and short duration. It varies if it is predictable or not, and if the pain is different from the baseline pain. These aspects were considered in the definition by Hagen et al. in 2008 [75]: «A transitory exacerbation of pain experienced by a patient who has relatively stable and adequately controlled baseline pain. Breakthrough pain can be an exacerbation of the baseline pain OR it can be a pain with a different cause from that of the baseline pain. Breakthrough pain can be evoked, spontaneous, predictable, or unpredictable. It is difficult to characterize breakthrough pain when baseline pain is not controlled».

The ECS-CP includes the domain ‘incident pain’, a term mainly used to describe one of several subtypes of breakthrough pain [81]. In the ECS-CP pain is defined as incident when «a patient has background pain of no more than moderate intensity with intermittent episodes of moderate to severe pain, usually having a rapid onset and often a known trigger» [52].

Ten different assessment tools for breakthrough pain were identified in a systematic literature review [81], nine of them for patients’ self-report. The Breakthrough Pain Questionnaire [157] has been used in several clinical studies [93 ,202], it contains four screening questions to identify the presence of breakthrough pain and 12 questions related to characteristics of the breakthrough pain, such as frequency, relation to fixed analgesic dose, and precipitating events. The Alberta Breakthrough Pain Assessment Tool has been developed for the use in clinical studies. It consists of 15 questions to the patient, in addition, a health care provider assesses the pathophysiology, the etiology, descriptions of the baseline and the breakthrough pain as well as current medications[75].

Depending on the population studied, study methodology, and definition used, the prevalence of breakthrough pain varies considerably. Thirty-nine per cent [152], 52% [160], 65% [32], and 89% [202] are examples of numbers reported. The lack of a common definition and assessment of breakthrough pain, and the lack of a common description of the patient populations included in studies, may be reflected in the major variability in reported prevalences. Breakthrough pain is a domain shown to be associated with more severe pain, an increased risk of pain-related adverse outcomes, and greater cost of care [200].

1.6.3 Pain mechanism

Pathophysiology of cancer pain has been thoroughly studied and different terms are in use also for this domain, for example 'pain mechanism' and 'pain quality' [15]. In the original ESS [23], 'pain mechanism' was assessed by the following sub-domains: 'visceral', 'bone-soft tissue', 'neuropathic', 'mixed', and 'unknown' pain. This was later revised in the ECS-CP to mainly distinguish between nociceptive and neuropathic pain as it was shown that neuropathic pain was clinically most relevant [56]. The importance of neuropathic pain in cancer patients has been recognised in several publications [15, 35, 130, 154, 156, 181]. Thus, throughout the text in this thesis mainly the term 'neuropathic pain' will be used to cover the clinically most important aspect of mechanisms and pathophysiology of pain, even if for example 'pain mechanism' was the term mainly used in paper I, II and III.

The definition of neuropathic pain was in 2008 revised by the Neuropathic Pain Special Interest Group (NeuPSIG) of IASP to: «Pain caused by a lesion or disease of the somatosensory nervous system». Neuropathic pain can be peripheral or central and is usually further classified according to anatomical site and disease [94, 179]. These studies have mainly focused on non-cancer pain. Cancer patients may experience neuropathic pain due to several causes; for example direct infiltration of peripheral nerves by the cancer, tumours or metastases in brain or spinal chord, side-effects after anti-cancer therapy (surgery, chemotherapy and radiotherapy), and due to other co morbidities [72, 154]. Neuropathic pain is a burdensome and

increasingly common symptom in cancer patients which represents a therapeutic challenge [16].

Several screening tools exist for neuropathic pain for use in both non-cancer and cancer pain [14], five of them will briefly be presented in the following. The 'Leeds Assessment of Neuropathic Symptoms and Signs' was the first tool to be developed; it contains five items regarding pain for self-report and two clinical examination items [13]. The 'Neuropathic Pain Questionnaire' consists of 10 items related to sensations or sensory responses, and two related to affect [113]. The 'Douleur Neuropathique en 4 questions' consists of seven items related to symptoms and three related to clinical examination [19]. 'painDETECT' is a questionnaire for patient's self-report. Seven questions address the quality of pain and are scored on a six-point verbal rating scale ranging from never to very strongly. Temporal course of the pain and radiated pain are addressed with one item each [66]. Finally, the 'ID-Pain' is also a questionnaire not requiring clinical examination, consisting of five sensory descriptor items and one item relating to whether pain is located in the joints [153]. All of these five screening tools for neuropathic pain have been developed in a chronic pain population and not in cancer patients. In the new IASP guidelines for neuropathic pain it is underlined that the clinical examination, including accurate sensory testing, is crucial for neuropathic pain diagnosis [74].

A recent systematic review of 22 studies of neuropathic pain including a total of nearly 13700 cancer patients reported a prevalence of neuropathic pain to be 19% and a prevalence of 39% if mixed pain also was included [15].

1.6.4 Pain localisation

The site of pain influences the degree of interference with functions as e.g. pain in a finger may cause less practical problems than pain in a leg hampering walking. Many cancer pain patients experience pain at more than one site. A study including 2266 cancer patients reported that 30% had pain at one site, 39% at two sites and that 31% had pain at three or more sites [72]. A figure representing the body where the patient can shade the area corresponding to the localisation of the actual pain, a

body map, has been used for the assessment of pain localisation for the last 30-40 years in both non-cancer [121] and cancer pain patients [43].

1.6.5 Duration

How long the pain has lasted was identified as one relevant pain domain in a combined systematic literature review and expert survey [88]. In textbooks pain is usually divided into acute and chronic. Acute pain is characterised by a well-defined onset whereas chronic pain is defined as pain that persists for more than three months, often with a less well-defined temporal onset. Chronic pain may be associated with changes in personality, lifestyle, and physical functions [63]. In the IASP Classification of Chronic Pain, the duration of pain is assessed as time since onset 'less than one month', 'one to six months', and 'more than six months' [135].

1.6.6 Pain history

Previous pain experiences regardless of non-cancer or cancer pain, may influence the present pain condition, and how the patient is coping. Information regarding previous pain treatments and the response is important to include in general medical history [63], however, this domain has not been emphasised in existing approaches to cancer pain classification [35].

1.6.7 Etiology

It has been usual to divide cancer pain into pain caused directly by the cancer disease (cancer pain), caused by treatment (for example radiotherapy induced osteonecrosis), and pain unrelated to cancer (e.g. arthritis or fractures) [63]. Etiology is included as the fifth axis in the IASP Classification of Chronic Pain, listing nine different causes of pain, among these malignant disease, infections, and degenerative diseases [135].

1.6.8 Treatment and exacerbating/relieving factors

As presented in section 1.4.1, the management of cancer pain includes analgesic pain treatment with opioids, non-opioids and adjuvant analgesics, as well as tumour directed therapy. In addition, other treatment modalities are available such as

neuroaxial, anaesthetic, surgical, neurostimulatory, physiatric, and psychological interventions as well as complementary procedures such as acupuncture [155]. Other exacerbating and relieving factors of pain may be for example movement, swallowing, or stretching. This domain was ranked as number three of ten by experts in pain and palliative care in two expert surveys [87,88]. For the use of different opioids in different administration forms it is common to calculate the equipotent dose of morphine taken orally during the last 24 hours in mg as the 'total morphine equivalent daily dose' (MEDD), in this thesis mainly referred to as 'opioid dose'.

1.6.9 Interference

Interference is one important domain of pain as pain is a complex symptom that influences most aspects of a person's life [87]. BPI measures interference by asking to what extent pain has interfered with the following seven domains: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life [43]. Fayers et al. recently investigated pain intensity and pain interference closely in both palliative care cancer patients and patients with chronic pain [59]. They conclude that intensity and interference should be regarded as two separate measures. In general, it may be difficult for patients with a complex pain condition to identify if it is their pain or other aspects that are influencing their functions [59,112,173].

1.6.10 Psychological distress

Psychological distress is an 'umbrella' concept used in different meanings. Originally, it was introduced as a term for the stress not buffered by coping [167]. No common agreed-upon definition exists, and the term is used with quite different meanings in clinical practice and in research. The National Comprehensive Cancer Network (NCCN) in 1999 introduced the term in relation to oncology in their first published guidelines for the management of distress in cancer patients [141]. This was done in order to gain increased focus on the psychological aspects of patient-care in oncology without making the patients psychiatric cases. In these guidelines, distress in cancer patients is defined as «a multifactorial unpleasant emotional experience of a psychological, social and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment. Distress

extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis» [141].

In oncology and palliative care, the term 'psychological distress' is used in different meanings covering a wide range of psychological states from normal stress responses to psychiatric disorders like depression and delirium. Different overlapping terms are also in use without being clearly defined such as 'stress', 'problems', and 'suffering' as well as 'psychological', 'psychosocial', 'emotional', and 'pain affect'. In the ECS-CP 'psychological distress' is defined as «a patient's inner state of suffering resulting from physical, psychological, social, spiritual and/or practical factors that may compromise the patient's coping ability and complicate the expression of pain and/or other symptoms» [52]. 'Pain affect' was identified as one of several pain domains related to cancer pain in a systematic literature review [88]. It was described as an «emotional component of pain, the unpleasantness and significance of pain», and has earlier been described to express an affective response related to being in pain [2]. Several studies have reported a close relationship between cancer pain and psychological distress [140 ,198], however, the question of causality remains unsolved [114].

The prevalence of psychological distress among cancer patients vary depending on definitions, populations studied and assessment method used. In a study including nearly 4500 cancer patients the prevalence of psychological distress as measured by the 'Brief Symptom Inventory' (a measure of distress with nine subscales and three global scales) was 35.1% [197] and a recent literature review reported the prevalence of distress to be 20-40% [89].

Depression and anxiety

Cancer patients receiving palliative care being distressed, for example due to pain, often suffer both from depression- and anxiety- related symptoms [89]. In the DSM-IV, the criteria for a depressive disorder are: depressed mood (such as feelings of sadness or emptiness), reduced interest in activities that used to be enjoyed, sleep

disturbances (either not being able to sleep well or sleeping to much), loss of energy or a significant reduction in energy level, difficulty concentrating, holding a conversation, paying attention, or making decisions that used to be made fairly easily, and suicidal thoughts or intentions [7]. These criteria might be problematic in patients with advanced cancer because some symptoms, such as tiredness and loss of appetite, may be present just due to the cancer disease itself. However, it is important to recognise and diagnose major depression in patients in palliative care as this is a treatable condition [95]. The prevalence of depression in palliative care is stated to vary between 3% and 58% [174]; a recent study of 300 patients receiving care reported a prevalence of depression according to the DSM-IV criteria in 19% of the patients [163].

Both depression and anxiety are assessed in Edmonton Symptom Assessment System (ESAS) and in the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire-C30 version 3.0 (EORTC-QLQ-C30): In ESAS by use of single items scored on an NRS-11 [22], and in the EORTC-QLQ-C30 by the emotional functioning scale consisting of the four questions: 'did you feel tense?', 'did you worry?', 'did you feel irritable?', and 'did you feel depressed?' scored on a four point verbal rating scale (VRS-4) and transformed into a 0-100 scale where lower scores mean poorer emotional functioning [1].
Taking the prevalence rates, treatments available for depression and the patients' suffering related to psychological distress into consideration, it is of importance to cover these emotional aspects in the everyday clinical assessment of cancer pain patients.

1.6.11 Pain beliefs

Patients' beliefs about causes and consequences of pain, attitudes to living with cancer and pain as well as ways of coping were identified as a commonly assessed domain in a systematic literature review [88]. Beliefs and misconceptions about opioid treatment identified as patients' barrier to optimal pain management are presented in section 1.4.2.

1.6.12 Cognitive function

Cognitive function is one domain included in the ECS-CP [52]. Attention, concentration, intelligence, learning, judgment, memory, orientation, perception, problem solving, and psychomotor ability are cognitive functions[84]. Loss of one or more of these functions is often described as cognitive impairment or failure. Several reasons for cognitive impairment or failure in advanced cancer patients have been identified, for example metabolic disturbances, brain metastases, infections, dehydration, and opioid use. According to the DSM-IV Text Revision, cognitive failure includes three separate conditions: delirium, dementia, and amnestic disorders [8] [84]. A review of 22 studies concerning cognitive failure in patients receiving palliative care summarised the reported prevalence rates to range from 10% to 83% for general cognitive impairment, from 20% to 88% for delirium and from 50% to 68% for confusion [84]. Cognitive failure is observed in the majority of advanced cancer patients before death [118 ,151].

Despite the high prevalence rates, health care professionals are often under- or misdiagnosing cognitive failure [84 ,151]. The MMSE has been identified as the most frequent used assessment tool for cognitive function, but several tools exist [84]. The assessment of pain in the cognitively impaired patients represents an additional challenge; in 2002 the EAPC recommended the use of a VRS-4 (none, mild, moderate, severe) [30]. For the nonverbal patient the NCCN guidelines recommend a combination of direct observation, family/caregiver input, and evaluation of treatment responses and list different tools to use [141].

1.6.13 Addiction

The WHO defines addiction as “repeated use of psychoactive substance(s) to the extent that the user is periodically or chronically intoxicated, shows a compulsion to take the preferred substance, has great difficulty in voluntarily ceasing or modifying substance use, and exhibits determination to obtain psychoactive substances almost by any means. Typically, tolerance is prominent and a withdrawal syndrome frequently occurs when substance use is interrupted”. The term ‘addiction’ is not

included in the ICD-10 and was replaced by the term ‘dependence’ in 1964, however still widely used [194].

Both alcohol and drug addiction are relevant to consider in a cancer pain setting. Three sub-groups of patients with cancer pain and a history of drug addiction have been described: 1. patients actively using drugs with a drug-seeking behaviour; 2. patients receiving methadone as maintenance; and 3. patients who have not used drugs for several years [63]. The management of pain in these patients requires special attention as a drug-seeking behaviour may interfere with pain related symptoms and as patients in group 2 and 3 may be at risk for relapse when experiencing cancer pain [63]. Case reports have exemplified the complexity of opioid treatment in patients with addiction [117,139].

Among patients admitted to acute care hospitals an overall prevalence of alcoholism has been reported between 12% and 30% [138]. In a retrospective study of 100 advanced cancer patients 28% were diagnosed with alcoholism [24]. The CAGE questionnaire was used in that study as a simple tool for screening of alcoholism; it includes the following four questions, where a score of two of four was defined as alcoholism: [24]:

1. Have you ever felt you should **c**ut down on your drinking?
2. Have people **a**nnoyed you by criticizing your drinking?
3. Have you ever felt bad or **g**uilty about your drinking?
4. Have you ever had a drink first thing in the morning or to get rid of a hangover (**e**ye-opener)?

1.7 Assessment

Assessment constitutes the basis for correct classification of a phenomenon. To assess is to evaluate or estimate the nature, ability, or quality of a certain phenomenon [147]. Assessment can be described as the process of collecting and documenting relevant information which may be relied upon for decision making.

In medicine, accurate, appropriate and standardised assessment is crucial for classifying the condition or the patient; that is making a diagnosis. Assessment in medicine may include medical history, clinical examinations, x-rays, other supplementary investigations, and patients' self-report of symptoms. For subjective symptoms, the use of patients' self-report has been recommended as gold-standard [61,105] and the assessment should ideally be brief, precise, multi-dimensional and specifically targeted to the patient population [85].

In a recent survey among palliative care professionals more than 100 different tools for assessment of health related quality of life (HRQOL) and symptoms were identified used in clinical practice and in research [80]. A systematic literature review covering 1966 to 2003 identified 80 different assessment tools for cancer pain in palliative care [88], and in a new search from 2003 to 2008 11 new cancer pain assessment tools were identified [87]. What tools that are used differ across studies and there is no consensus on which background information and which symptom specific domains to include in different tools [85,103]. Some of the most commonly used assessment tools in oncology and palliative care will be presented in the following and in the appendix, all of these have been applied in the papers included in this thesis.

1.7.1 Visual analogue, verbal rating, and numerical rating scales

Visual analogue scales (VAS), categorical verbal rating scales (VRS), and categorical numerical rating scales (NRS) are commonly used and well validated unidimensional measurement tools for intensity of symptoms in cancer patients [30,86]. An 11-point NRS (NRS-11) with 'no pain' and 'pain as bad as you can imagine' as anchor words for the extreme values was recently recommended used for assessment of cancer pain intensity by an international group of pain and palliative care experts [103].

1.7.2 Edmonton Symptom Assessment System

The ESAS was first presented in 1991 [22] and is a well validated and widely used tool for patient's self-report of subjective symptoms [188]. Ten NRS-11 are included; eight for assessment of common symptoms (including pain), one for general well-being

and one for a patient-specific symptom. ESAS was recently revised, among the suggested changes were: change of order of items, using the time frame 'now', and inclusion of short definitions of the symptoms [188].

1.7.3 Brief Pain Inventory and McGill Pain Questionnaire

As cancer pain is a multi-dimensional and complex symptom, the EAPC Expert Working Group in 2002 [30] recommended the use of the following two multi-dimensional assessment tools: Short Form of the Brief Pain Inventory (BPI) [43] or the McGill Pain Questionnaire (MPQ) [126]. The BPI is a tool for self-report of pain that is easy to administer and to understand [30] which has gained widespread recognition and that has been translated and validated in many different languages, for example in Italian [33] and Norwegian [112]. It records information about medical history, pain and interference. Pain intensity is measured by an NRS-11 for each of the following items: 'right now', 'on average', 'at its worst', and 'at its least'. 'Pain relief provided by pain treatments' is recorded on an NRS-11 from 0% (no relief) to 100% (complete relief). Pain's interference with functions is assessed by seven items by using NRS-11: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The time frames 'the last month' [43], 'the last week' [30] and 'the last 24 hours' [30 ,112] have been used. The MPQ is widely used tool for self-report that has been validated in cancer patients [71] assessing localisation, quality, temporal pattern, and intensity of pain [126]. A list of pain descriptors is provided and the patients are asked to mark the words that best describe their pain and its temporal pattern, the patients are asked to list exacerbating and relieving factors, and intensity is assessed by a VRS-5 using the words mild, discomforting, distressing, horrible, and excruciating.
A body map is included both in the BPI and in the MPQ.

1.7.4 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30

The EORTC-QLQ-C30 version 3.0 is a multidimensional instrument for self-reported assessment of function, symptoms and quality of life (QOL) in cancer patients [1]. The questionnaire consists of 30 items incorporated in five functional scales (physical,

role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health/QOL scale, five singe items regarding common symptoms (dyspnoea, loss of appetite, insomnia, constipation, and diarrhoea) as well as one item regarding financial difficulties. Except for the items 'overall physical condition' and 'overall QOL' that are scored by seven-point scales (from 'very poor' to 'excellent'), all items have four level response categories (from 'not at all' to 'very much'). Using standardised scoring methods, the measures are transferred into a 0 to 100 scale. A high score for a functional scale represents a high level of functioning, whereas a high score for a symptom scale/item means more symptoms/more problems [58]. The EORTC QLQ-C30 has been translated into several languages [48], is widely used in clinical trials, and has been shown to be sensitive to differences between patients, treatment effects and changes over time [57,101].

1.7.5 Therapy Impact Questionnaire

The Therapy Impact Questionnaire (TIQ) is a quality-of-life questionnaire developed for advanced cancer patients measuring common symptoms and side effects of medications, consisting of 36 items rated on a VRS-4 from 1 = absent to 4 = very much referring to the previous week [176]. In more details the following is assessed: common physical symptoms (24 items: pain is one and headache is one), functional status (3), emotional and cognitive factors (6), social interaction (2), and one global item worded as 'have you been feeling ill?'.

1.7.6 Performance Status

Patients' performance status is commonly assessed within oncology and palliative care as a measure of the patients' well-being and daily life activities. The Karnofsky Performance Status score (KPS) was published in 1948, an 11-point 0% to 100% scale where 0% corresponds to death and 100% to a normal situation with «no complaints and no evidence of disease» [108]. The KPS has been recognised as a negative prognostic factor for survival in cancer patients [51] and it has been demonstrated that patients with a lower KPS ($\leq$ 80) have more symptoms and more severe pain than patients with higher KPS [158].

1.7.7 Mini Mental State Exam

The Mini Mental State Exam (MMSE) from 1975 is a valid and reliable tool that has proven to record changes in cognitive function [65]. It consists of 20 items and has a total score of 30 points, with higher scores representing higher levels of cognitive functioning. A score of less than 23-24 of 30 is a commonly used as cut-off to indicate cognitive impairment [136]. A set of four items from the MMSE (current year, date, backward spelling, and copy of a design; with a total score of five) has been identified as an appropriate screening tool for cognitive impairment and delirium in palliative care patients [60].

2. Aims of the thesis

The overall aim of this thesis is to contribute to the development of an international classification system for cancer pain.

Paper I

The overall aim of paper I was to identify existing approaches to cancer pain classification, thus the following research questions were raised:

- Which classification systems for pain in cancer patients exist in the published literature?
- How are the classification systems developed and validated?
- Which domains and items are included and what assessment methods are used in cancer pain classification systems?
- Are the classification systems used in clinical studies?

Paper II

In paper II the overall aim was to gain detailed knowledge about advanced cancer patients' experiences of pain. The following research questions were asked:

- Can patients verify the relevance of cancer pain domains identified in previous studies?
- Can patients identify additional domains relevant for cancer pain classification?
- How do patients describe their experience of cancer pain?

Paper III and IV

For both paper III and IV the overall aims were to verify known domains and to explore new domains for cancer pain classification.

In **paper III** the research question were:

- To what extent are the 'established' candidate domains breakthrough pain, neuropathic pain, and psychological distress associated with pain intensity and/or pain relief?

- To what extent are cancer pain domains identified in the literature, by patients, and by experts associated with pain intensity and/or pain relief?

The research questions in **paper IV** were:

- Can the associations with pain intensity and/or pain relief of domains previously identified in a cross-sectional study be confirmed in another patient population?
- Can previously identified domains relevant for cancer pain and/or new candidate domains be identified as predictors of pain intensity and/or pain relief in a population of cancer patients followed prospectively?

3. Materials and methods

In 2008 a systematic and stepwise research strategy to be used by the European Palliative Care Research Collaborative (EPCRC), consisting of systematic literature reviews, expert evaluations, patients' involvement, and empirical data collections was presented [106]. The designs of the four papers in this thesis have been guided by this stepwise research strategy which is summarised in nine steps described in table 1. The papers in this thesis have contributed in step 1, 5, and 8.

Step	Description
1	Definition of content and selection of items based on systematic literature review. Determine the content of the measure based on the literature, the content of widely used forms, the clinical expert experience, and advice from an expert panel. Generate an item pool for pain assessment, primarily based on existing pain assessment tools and reflecting the recommended dimensions
2	Data collection I
3	Analyses of data leading to functional specification of a computerized pain assessment tool
4	International expert evaluation II
5	Patient involvement, qualitative interview, and focus groups to document qualitative evidence of content and face validity
6	Development of a computerized analyses model (software based on collected data)
7	International data collection II
8	Data analysis
9	Programming of first version of the computer-based pain assessment tool

Table 1: The stepwise research approach of the European Palliative Care Research Collaborative [106].

3.1 Systematic literature review

A systematic literature review aims at identifying, evaluate and interpret all available knowledge of a certain topic. It differs from a traditional review as systematic procedures for searching and selection of papers and information to include are used, and thus being repeatable and transparent research methodology [70 ,137]. Aiming at the development of an international assessment and classification system for cancer pain, the identification of existing approaches to cancer pain classification was considered an important first step.

3.1.1 Systematic literature search

The design of the systematic literature review (paper I) was based upon the present knowledge in the study group as well as on findings from hand search of textbooks and relevant peer reviewed journals. The search strategy was to reflect the aim of identifying all existing approaches to cancer pain classification, in all stages of a malignant disease. The searches were performed in MEDLINE and Embase using OVID as search engine. Both free text and MeSH/EMTREE search terms were used. The following terms were covered: 'classification', 'categorisation', 'characterisation', 'staging' and 'grading' in studies of cancer patients in general. The initial searches resulted in more than 7000 hits that mainly included clinical studies of effectiveness of anti-tumour treatment. To narrow the search, we defined that it should be a maximum of five words between the word 'pain' and for example 'classification'. The search string used in MEDLINE is presented in the appendix.

3.1.2 Selection of relevant papers

The titles and abstracts of all hits were screened by four of the authors, independently. When at least two of the authors identified a hit as relevant, it was included for further evaluation. If only one author recognised a hit as relevant, it was discussed in the group to achieve consensus whether to include or exclude. For all hits identified as relevant, the full-text papers were retrieved and reviewed by three of

the authors. Papers of all methodological categories were included. Exclusion criteria were: Papers published before 1986, non-English papers, papers on non-malignant pain, papers addressing children or adolescents, and papers exclusively addressing development or validation of pain scoring instruments.

3.1.2. Contents and quality

For each paper the following information was recorded:

- All details of a classification system if used
- Domains and items of cancer pain applied in the papers (for example pain intensity, pain mechanism, temporal variations, localisation of pain, etiology, pain syndromes and pain treatment) – based upon knowledge presented in section 1.6.
- Other subjective symptoms and signs (for example psychological distress, physical functioning and interference)
- Patient related information: patients' demographics, primary cancer disease, stage and localisation of disease and tumour directed treatment.
- Study design and methodology, country of origin of the study, and assessment methods.

After systematically extraction of information from the papers, the main findings were categorised and synthesised by the authors as
1) Formal classification systems; systematically developed and partially validated, or not validated, and
2) Characteristics not formally described as part of a classification system ('informal approaches').

3.2 Patients

Paper II, III, and IV in this thesis are based upon data from three cohorts of mainly advanced cancer patients (an overview of the samples are presented in table 2 in this section). Patients were included for qualitative interviews at the cancer

department in Trondheim, Norway and Graz, Austria (paper II). The second cohort consists of patients included in the European Pharmacogenetic Opioid Study (EPOS) (paper III), and the third cohort consists of patients included in the Cancer Pain Outcome Research Study Group (CPOR) study (paper IV).

3.2.1 Interview sample

Patients with advanced cancer, with a pain history, and receiving treatment with opioids at the Department of Oncology, St. Olav's Hospital, University Hospital in Trondheim, Norway and at the Division of Oncology, Medical University of Graz, Austria were approached. Cognitive status was examined by a short version of the Mini Mental Status Exam (MMSE) [60]. Only cognitively intact patients (defined as score = 5) were included. All patients completed the ESAS. [22]. Information regarding socio-demographic data and medical history was obtained from the medical records.

3.2.2 European Pharmacogenetic Opioid Study

The European Pharmacogenetic Opioid Study (EPOS) was an international, multicentre, cross-sectional, observational study of cancer patients treated with opioids for moderate to severe pain from 2004 to 2008 [110]. Patients $\geq$ 18 years with verified malignant disease and on regularly scheduled opioid treatment (step III at the WHO pain ladder) for at least three days were included.

The following information was assessed by a health care provider: Medical history and consumption of opioids and other medication, functional status assessed by the KPS [108] and cognitive function by the MMSE [65]. Breakthrough pain was evaluated as a dichotomised yes/no- question focusing on pain with a known trigger. Pain mechanism was categorised according to the Edmonton Staging System [25]: visceral, bone / soft tissue, neuropathic, mixed, and unknown pain. Addiction was evaluated by answering yes or no to the question of previous or present known abuse of either alcohol or drugs. The patients completed the BPI [43] and EORTC-QLQ-C30 version 3.0 [1]. The following items from the BPI were included as outcomes: 'pain on the average', 'pain at its worst', and 'pain relief', all referring to the last 24 hours and measured by an NRS-11. Additionally, pain localisation was

recorded by using a body map. The following scales and items from the EORTC-QLQ-C30 were included in the analyses: emotional functioning (measuring psychological distress), physical functioning, social functioning, sleep disturbances, nausea/vomiting, and constipation.

3.2.3 Cancer Pain Outcome Research Study Group

The Italian Cancer Pain Outcome Research (CPOR) Study Group performed a multicentre, prospective, non-randomised observational study during 2006 and 2007 [9,10]. The CPOR study was initiated motivated by undertreatment of pain [44]. It aimed at gathering data on the epidemiology of cancer pain and of its treatments, to assess the efficacy of pain treatment measured by patient reported outcomes, and to evaluate safety profile of the treatments. Patients with advanced cancer, persistent pain of any intensity, requiring or already on analgesic treatment, age $\geq$ 18 years, with a life expectancy longer than one month, and able to provide informed consent to participate were included. Patients with impaired cognitive function or substance abuse were excluded.

Two samples from these data were used for study IV: sample A consisted of cross-sectional data from cancer patients using opioids at the day of inclusion and sample B consisted of longitudinal data from cancer patients newly referred to palliative care. Reasons for this were for sample A to replicate the design of EPOS and for sample B to achieve a homogenous sample as possible for the longitudinal analyses.

After inclusion, the patients were examined weekly for four weeks as well as at week 12. Only data from study entry and day 14 were analysed in paper IV. At each visit a health care provider registered: medical history including cancer history, physical examination data, medications and recent therapies including analgesic consumption, and functional status assessed by the KPS [108]. Furthermore, a health care provider completed the ECS-CP (version rESS from 2005) [56] assessing neuropathic pain, breakthrough pain, psychological distress and/or addiction, and cognitive function (appendix).

The patients completed a questionnaire assessing pain, other symptoms, and common side effects of opioids at each visit. Pain was measured by an Italian version of the BPI [33]. Symptoms and side effects of medications were evaluated using a list of 23 items from the TIQ [176]. Each item was rated on a four-point verbal rating scale (VRS) from 1 = absent to 4 = very much. The previous week was used as time frame for all questions (appendix).

Patient's characteristics		Paper II Qualitative study	Paper III EPOS	Paper IV CPOR	
Study design		Semi-structured interviews and quantitative ranking of domains	Cross-sectional	Longitudinal	
Time period for patient inclusion		2008 to 2009	2004 to 2006	2006 to 2007	
Number of participating centres		2	17	110	
Number of included patients		N = 33	N = 2278	N = 1801	
				CPOR Sample A N= 1529	CPOR Sample B N =352
Age Mean (range) / S.d.[1]		63.4 (38-85) / 11.7	62.2 (18-96) / 12.3	63.8 (22-92) / 12.2	64.8 (26-88) / 11.9
Gender	Male: N (%)	17	1193 (52.4)	808 (52.8)	216 (61.4)
	Female: N (%)	16	1085 (47.6)	721 (47.2)	136 (38.6)
Karnofsky Performance Status Mean (range) / s.d.		64.9 (40-90) / 14.2	59.2 (10-100) / 17.2	64.5 (20-100) / 16.3	62.8 (20-100) / 17.1
Time since diagnosis: Mean (range) / s.d. (months)		43.4 (1-196) / 52	31.5 (0-401) / 45.5	33.6 (0-42.6) / 47.2	23.7 (0-30.6) / 34.2
Treatment setting	Inpatients	32	1850 (81.2%)	Not evaluable	Not evaluable
	Outpatients	1	428 (18.8%)	Not evaluable	Not evaluable
Main diagnoses	Breast	4 (12.1%)	303 (13.3%)	254 (16.6%)	32 (9.1%)
	Gastro intestinal	11 (33.3%)	523 (23.0%)	430 (28.1%)	95 (27.1%)
	Lung	4 (12.1%)	418 (18.3%)	342 (22.4%)	97 (27.6)
	Prostate	5 (15.2%)	264 (11.6%)	119 (7.8%)	22 (6.3%)
Metastatic or locally advanced disease		33 (100%)	1908 (83.8%)	1426 (93.3%)	315 (89.5%)

Table 2: Overview of patient samples investigated in paper II-IV

1 S.D: standard deviation

2 EORTC-QLQ-C30 functioning scale 0-100: high score represents a high level of functioning

3 MEDD: Daily oral morphine equivalent dose in mg

N.A. = Not assessed

Patient's characteristics	Paper II Qualitative study	Paper III EPOS	Paper IV CPOR	
Pain intensity (average): Mean (range) / s.d.	1.8 (0-8) / 2.1	3.50 (0-10) /	4.4 (0-10) / 2.0	5.0 (0-9) / 1.9
Pain intensity (at its worst): Mean (range) / s.d.	8.8 (5-10) / 1.3	5.25 (0-10) /	6.8 (0-10) / 2.3	7.5 (0-10) / 2.0
Pain relief Mean (range) / s.d.	N.A.	74 (0-100) /	57.5 (0-10) / 25.4	43.0 (0-10) / 26.6
Breakthrough pain Present: N (%)	19 (57.8%)	1322 (58.0)	803 (52.2)	201 (57.1)
Absent: N (%)	14 (42.2%)	947 (41.6)	726 (47.5)	151 (42.9)
Pain mechanism				
Neuropathic pain: N (%)	N.A.	110 (4.8)	388 (25.9)	86 (24.7)
Mixed pain: N (%)	N.A.	778 (34.2)	N.A.	N.A.
Nociceptive pain: N (%)	N.A.	N.A.	1108 (74.1)	262 (75.3)
Bone/soft-tissue pain: N (%)	N.A.	1011 (44.4)	N.A.	N.A.
Visceral pain : N (%)	N.A.	358 (15.7)	N.A.	N.A.
Unknown: N (%)	N.A.	18 (0.8)	33 (2.2%)	4 (1.1%)
Psychological distress Present: N (%)	N.A.	N.A.	550 (36.0)	131 (40.2)
Emotional functioning EORTC-QLQ-C30 scale 0-100[2] / s.d.	N.A.	64.5 / 26.4	N.A.	N.A.
Opioid dose (MEDD) [3] Miligram (range) / s.d.	139 (7.6-640) / 164	341 (0-9090) / 550.2	86.7 (1.5-1050) / 94.5	66.1 (0-1050) / 110.7

Table 2 continued

3.3 Patients' involvement

The involvement of patients in the process of development of clinical instruments (for example questionnaires evaluating symptoms and clinical guidelines) has been recommended by the European Organisation for Research and Treatment of Cancer (EORTC) [172], the National Institute for Health and Clinical Excellence (NICE)[142], and the U.S. Food and Drug Administration (FDA) [184]. Thus, the EPCRC also involved patients in the develpoment process of the new classification system for cancer pain [106]; this was done in paper II.

3.3.1 Semi-structured interviews

The aims of paper II were to gain more in-depth understanding of pain domains according to patients' self report and to explore if any domains were missing among the previously identified. Thus, qualitative semi-structured interviews guided by a general method first presented by Giorgi [69], and later modified and applied by Malterud [120], using phenomenology as the theoretical framework, i.e. focusing on how phenomena are experienced, was considered as the appropriate methodology.

The interview guide (appendix) consisted of one open-ended introductory question asking 'Can you please describe what it is like to have pain?' with clarification probes like 'how is it?' and 'what do you think about having pain?' as well as general open-ended questions about the 12 predefined candidate pain domains. If needed, follow-up questions were used in order to reveal the patients' thoughts, experiences and opinions about cancer pain [149]. The patients were then asked if they could think of other domains relevant for their pain experience. At both sites one researcher performed all interviews, respectively. The complete interviews were audio-recorded and transcribed word-by-word by one person at each site. The analyses of the interviews started during data collection, and were analysed according to the below presented procedure by two of the authors. Comments deepening the quantitative scoring were transcribed as part of the interview and included in the qualitative analyses. Patient quotations relevant for publication were translated into English by the authors.

The Giorgi/Malterud method (for analysis) consists of four steps:
1. «Getting a total impression of the data»; the transcribed interviews were read several times to identify relevant descriptions of cancer pain reported by the patients.
2. «Identifying 'meaning units' in each interview»; sentences and paragraphs from each interview were collected as meaning units in a dialogue excerpt for each interview.
3. «Abstracting the content of individual meaning units across all interviews»; the meaning units were labelled and grouped together with similar descriptions across all interviews.
4. «Summarising their importance»; summarising of the findings (Paper II).

3.3.2 Patients' ranking of domains

A mixed method approach was chosen as the use of diverse methods may enrich the understanding of a complex phenomenon such as cancer pain [41,120]. In the quantitative part, the patients were asked to score the relevance of the 12 previously identified pain domains by using a 0 to 10 Numerical Rating Scale (NRS-11); 0 = not important, 10 = very important, similar to a ranking previously done by experts [87,88].

3.4 Expert survey

An expert survey was performed per e-mailing in January 2009 aiming at gathering advice on which domains to choose as the dependent variables (paper III and IV). Thirty experts within oncology, pain and palliative care were asked to rank the clinical relevance of five variables from the BPI on an NRS-11 (0= not relevant, 10 = highly relevant): 'pain relief provided by pain treatments or medications'; 'pain at its worst'; 'pain at its least'; 'pain on the average' (all in the last 24 hours); and 'pain right now' [43].

3.5 Assessment tools used in paper II-IV

Patients' performance status was assessed by the KPS in paper II, III and IV. ESAS was used in paper II (German and Norwegian versions, appendix). An NRS-11 was

used in paper II for the patients' scoring of the relevance of each domain, where 0 referred to 'not important' and 10 to 'very important'. Cognitive function was assessed by the MMSE in paper III and by the short version of the MMSE in paper II. BPI was used in paper III and in paper IV with the time frame 'last 24 hours' and 'last week', respectively. EORTC-QLQ-C30 and 23 items from TIQ were completed in paper III and IV, respectively.

3.6 Statistics

The statistical software SPSS (Statistical Package for Social Science) for Windows version 16.0 was used for the analyses in paper II and for the descriptive analyses in paper III. For the bivariate and multiple regression analyses in paper III, and for all analyses in paper IV, the statistical software STATA (StataCorp. STATA Statistical Software: Release 11. College Station, TX: StataCorp LP 2009) version 11.0 was used.

3.6.1 Bivariate analysis

Bivariate analyses were performed in paper III and IV to investigate possible associations between a series of candidate domains (independent variables) and the outcomes. In paper III the Spearman's rank correlation was used for continuous variables. This is a non-parametric measure of statistical dependence between two variables, resulting in values from -1 to +1 [(4)]. For the categorical variables, the Kruskall-Wallis test was used which is a non-parametric method for comparison of more than two independent samples [(3)]. In paper IV, the Pearson correlation coefficient (r) ranging from -1 to +1 was used for all variables. For both paper III and IV all correlation coefficients and the belonging p-values were calculated; the p-values were reported in paper III and the correlation coefficients reported in paper IV. In paper III the correlations were presented as p-values; the cut-off for inclusion was defined as p-value $\leq$ 0.001, and in paper IV the correlation coefficients were reported and the cut-off for inclusion was defined as Pearson correlation coefficient $\geq$ 0.1.

3.6.2 Multivariate regression analysis

As one aim of a cancer pain classification system is to predict response to treatment and the course of pain, we aimed at investigating possible relationships between different domains and the pain measured as pain intensity and pain relief. In both paper III and IV, regression analysis was chosen as the most appropriate and feasible method. Regression analysis is a method for describing the relation between the values of two or more variables allowing for to see how much of the variability in the dependent variable (outcome) can be attributed to different values of the independent variables (predictors) [(5)]. The explained variance is expressed as 'R square' (R^2) and is ranging from 0 to 1. Standardised betas obtained as results in a regression analysis allow for comparison of the impact of the independent variables on the outcomes regardless of assessment scales used.

In paper III a linear regression model was used due to continuous outcomes, in paper IV both linear and non-linear relationships (by using fractional polynomials) were investigated. A backward stepwise model was used both in paper III and IV. The cut-off p-value for removing domains/variables was 0.01 and 0.05 in paper III and IV, respectively. Reasons for having a higher p-value in the longitudinal sample were the smaller sample size and the explorative aim of the study in paper IV. Standard diagnostics on for example residuals and interactions of the models were tested.

3.7 Ethics

All studies used in this thesis were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki [(196)]. All patients in all studies used in this thesis gave written informed consent prior to study participation.
In paper II the study protocol and interview guide was approved by the Regional committee for medical research ethics at each site and by the Norwegian Data Inspectorate. The transcripts contained no person-identifiable information.
The EPOS protocol (paper III) was approved by the committee for medical research ethics of each study centre and the CPOR study (paper IV) complied with Italian

requirements for observational studies. The protocol was approved by each Local Research Ethics Committee of participating centres.

4. Results and summary of papers

4.1 Paper I

«Classification of pain in cancer patients - a systematic literature review»
Despite several efforts to develop common criteria for the diagnosis and classfication of cancer pain, no internationally widely accepted cancer pain classification system exists. Standardised assessment and classification would improve cancer pain management. As a starting point for the development process of an international, robust, and clinically useful assessment and classification system for cancer pain, a systematic literature review was performed. The aims were to identify and describe existing systems; their development, the included domians/items, assessment methods used, and impact on clinical studies.

A systematic literature search in the MEDLINE and Embase databases was performed using ‘pain’, ‘cancer’ and classification’/‘characterisation’/’categorisation’/ ‘staging’/ ‘grading’ as search terms for the time period 1986 to 2006. Titles, abstracts, and fulltext articles in English concerning pain classificaiton in adult patients were reviewed sytematically by in total four of the authors. The main findings were divided into two main categories: 1. formal classification systems (either systematically developed and partially validated, or not validated), and 2. characteristics not formally described as part of a classifcation system.

The search yielded 692 hits, of these were 92 full text papers included for further reading. 55 were clinical studies and 37 were defined as educational papers. Three formal, systematically developed and partially validated systems were identifed: the International Association for the Study of Pain (IASP) Classification of Chronic Pain, the Edmonton Classification System for Cancer Pain (ESC-CP), and the Cancer Pain Prognostic Scale (CPPS). None were widely applied in the clinic or in research. Another three formal, however not validated systems, were also identified: the Opioid Escalation Index (OEI), a prognostic tool for pain treatment, and the Pain Management Index (PMI), mainly tools for prognostication and evaluation of pain

treatment. Fourty-three clinical studies applied common characteristics of pain and patients not formally desrcibed as part of a classification system. Five domains were identified in two or more of the formal systems: pain intensity, breakthrough pain, neuropathic pain, psychological distress, and treatment response. The assessment of these and other domains varied across studies.

4.2 Paper II

«Interviews with patients with advanced cancer - another step towards an international cancer pain classification system»
About 50 % of cancer patients in general and about 70 % of the advanced cancer patients experience pain during their disease trajectory. Pain is a highly subjective and complex experience influencing several aspects of a patient's life.

Patients' self report is the gold standard for reporting subjective symptoms. For the development of assessment tools regarding subjective symptoms, the involvement of patients has been recommended. Thus, the present study was performed to investigate if patients in palliative care could verify the relevance of selected pain domains and to explore if any domains were missing.

Results from systematic literature reviews, experts' opinion, as well as the content of the ECS-CP were used as basis for which domains to include in the interview guide and for the quantitative ranking of domains, which were the following 12: pain intensity, duration, etiology, pain localisation, previous pain experience, interference (with function), coping, breakthrough pain, neuropathic pain, psychological distress, cognitive function, and addiction. In the quantitative part of the study, the patients were asked to score the relevance of the 12 predefined pain domains on an NRS-11. In the qualitative part, semi-structured interviews were performed and analysed word-by-word. The interview guide is included in appendix 2 of paper II.

Thirty-three Norwegian and Austrian patients were interviewed, 16 females and 17 males. All were advanced cancer patients using opioids for pain; their mean age was 63 and the mean Karnofsky performance score was 65. The patients ranked the domains according to their relevance as follows: 1. etiology (most relevant), 2. duration, 3. intensity, 4. coping, 5. localisation, 6. physical functioning, 7. psychological distress, 8. breakthrough pain, 9. cognitive function, 10. neuropathic pain, 11. previous pain experience, and 12. addiction. The patients emphasised

aspects related to having pain such as poor physical functioning and psychological distress. Sleep was identified as a new domain to consider for inclusion in a future cancer pain classification system.

In summary, based upon the patients' descriptions of their pain experiences, the relevance of previously identified pain domains was confirmed, however, the ranking of their importance differed from experts' ranking in a previous study. Except for sleep, no new domains relevant for cancer pain classifcation were identifed.

4.3 Paper III

«Which variables are associated with pain intensity and treatment response in advanced cancer patients? - Implications for a future classification system for cancer pain»

A lack of a shared language and a diagnostic tool for cancer pain has been recognised by several authors as one barrier to improved cancer pain management. Using existing knowledge from systematic literature reviews, view of experts in pain and palliative care as well as patients' opinion, consensus has been reached on some of the content of an international cancer pain classification system. However, this knowledge has not been widely empirically tested. The aim of the present study was thus to apply empirical data from a large European cohort of cancer patients treated with opioids to investigate which domains to include in such a system.

EPOS is a cross-sectional study recruiting 2294 cancer patients treated with opioids from 17 centres in 11 European countries. Clinical data from EPOS were used in paper III. 'Pain on average', 'pain at its worst', and 'pain relief', all from the BPI measured on an NRS-11 and referrring to the last 24 hours, were chosen as outcomes based upon resuts from an expert survey and findings in the literature.

Data from 2278 patients were used in the present analysis; 52 % males, mean age 62 years, mean Karnofsky Performance status 59 %, mean opioid dose (MEDD) 341 mg. The mean pain scores were: average pain 3.5, worst pain 5.3, and pain relief 74%. Breakthrough pain was present in 58%. Fourty-six candidate domains were identified through previous studies. Of these, 21 domains were shown to be associated with at least one of the outcomes, and thus included in multivariate linear regression analyses.

The domains breakthrough pain, neuropathic pain, localisation of pain, opioid dose, use of non-opioids, psychological distress, sleep, addiction, cancer diagnosis, and localisation of metastases were results in the final regression models. Breakthrough pain and psychological distress were the most important domains as they they

contributed significantly to all three final regression models and showed the highest standardised betas. The identifed domains explained 12% to 19% of the variablility of the pain outcomes.

4.4 Paper IV

«Which domains should be included in a cancer pain classification system?
- Analyses of longitudinal data»

To ensure that a cancer pain classification system groups the patients correctly and predicts the course of pain properly, such a system should be evaluated in longitudinal studies. Thus, aiming at deciding upon which domains to include in a cancer pain classification system, data from the longitudinal CPOR study were used to verify the relevance of previously identified domains relevant for cancer pain classification, and to explore the value of other domains.

Data from a multicentre, observational longitudinal study of 1801 Italian cancer patients were analysed. Analyses were carried out in two samples. A: cross-sectional data from patients on opioids at inclusion, and B: longitudinal data from patients just admitted to palliative care. Outcome measures in the investigated models were: 'pain on average', 'worst pain', and 'pain relief' at study entry, and at day 14, respectively, all measured on an NRS-11. Uni- and multivariate regression models were applied to test the explicative power on pain outcomes of a series of known pain domains, among which breakthrough pain, neuropathic pain, pain localisation, opioid dose, psychological distress, sleep disturbances, and cancer diagnosis.

In the two analyses, 1529 (sample A) and 352 (sample B) patients were included, respectively. The sample characteristics were: males 53% in A and 61% in B, respectively, mean age 64/65 years, mean Karnofsky performance status 65%/63%. Mean pain scores were: average pain 4.4/5.0, worst pain 6.8/7.5, and pain relief 58%/43%. Mean opioid dose (MEDD) was 87/66 mg. Breakthrough pain was present in 52%/57% of the patients, and 26%/25% of the patients had neuropathic pain.

In the cross-sectional analysis (A), the domains breakthrough pain, localisation of pain, opioid dose, use of non-opioids, and sleep were associated with one or more of

the pain outcomes. In the longitudinal analyses (B), pain intensity at study entry, pain relief at study entry, breakthrough pain, localisation of pain, age, and cancer diagnosis were predictors. Identified domains explained 16 to 24 % of the variability of the pain outcomes.

In summary, the following nine domains were identified to be of significance from the CPOR analyses: Pain intensity, pain relief, breakthrough pain, pain localisation, opioid dose, use of non-opioids, sleep disturbances, age, and cancer diagnosis. Pain intensity at study entry emerged as the strongest predictor of the pain outcomes after two weeks.

5. Discussion

5.1 Discussion of main findings

The principle idea of this thesis was to contribute to the process of improvement of cancer pain classification and thereby improve treatment of pain for the large number of cancer patients experiencing pain. A stepwise approach was applied, based upon recommendations given in the EU-funded research collaborative EPCRC[50], including one systematic literature review, one study of mainly qualitative design, and two studies applying empirical data, of cross-sectional and longitudinal design, respectively. This thesis is to be considered as an integrated part of the research planned and conducted in this community of researchers at eight European centres as well as from Canada and Australia, with the European Palliative Care Research Centre (PRC)[49] at the Norwegian University of Science and Technology (NTNU) in a leading position.

5.1.1 Paper I

The first step of this approach was to get an overview of the field of cancer pain classification. The systematic literature review identified a lack of international consensus regarding cancer pain classification, but also several attempts to classify cancer pain were identified. Of these were three defined as formal and formally validated classification systems: the IASP Classification for Chronic Pain, the ECS-CP, and the CPPS. Furthermore three formal, however not systematically validated, were identified: the PMI, the OEI and a prognostic tool for pain treatment. Several other 'informal' approaches were also identified. The ECS-CP was identified as the most comprehensive cancer pain classification system, also due to a long lasting validation and development process. Five domains were in paper I identified in two or more of the six formal systems: pain intensity, breakthrough pain, neuropathic pain, psychological distress, and treatment response.

International Association for the Study of Pain Classification of Chronic Pain

When evaluating the IASP Classification of Chronic Pain in relation to cancer pain, two aspects seem to be relevant: it does not aim at providing prognostic information, and it was mainly developed for non-cancer pain. Pain due to malignant diseases is included only as one of several etiologies. Details about the cancer diagnosis are not included neither in this system nor in the ECS-CP or in the CPPS, this will be further discussed in section 5.1.4.11.

Edmonton Classification System for Cancer Pain

At expert meetings in Lofoten [76], Milan [103] and Edmonton [27], one of the conclusions was that the Edmonton Classification System for Cancer Pain (ECS-CP) is to be regarded as a template and starting point for further development of a cancer pain classification system. However, the system has limitations. First, some important information is not included, such as pain intensity and cancer disease, however, pain intensity is now considered for inclusion [53]. Second, even if the ECS-CP has performed a thorough work to develop a manual with definitions and instructions for use [52], the definitions may be subject to discussion. For example, the definition of psychological distress is limited to patients experiencing psychological distress only in relation to pain. However, distress of other causes is also of importance for the pain experience as distress in general may increase the level of reported pain intensity (and vice versa) [198]. Furthermore, the definition suggests that psychological distress may impair a patients' coping ability, however, a more commonly accepted view is that psychological distress occurs when the coping abilities are exceeded [167].

Third, all assessments are provided by a health care provider and not by patients' self-report which is the recommended method for the assessment of PROs [61 ,105]. Finally, the inclusion of a category of 'unknown'/'insufficient information to classify' for each domain represents a challenge when analysing data statistically. When allowing researchers and clinicians to not to decide upon a category/domain/diagnose, this will be similar to a problem of handling missing data.

Cancer Pain Prognostic Scale

The Cancer Pain Prognostic Scale (CPPS) is in opposite to the IASP system a prognostic tool and it was developed in a population of advanced cancer patients. However, different domains were identified as predictors of pain relief at different points in time. Furthermore, the CPPS was only identified used in the development study [92] and to our knowledge it has not been used in later publications.

Systems for prognostication and evaluation of treatment response

The three other formal systems identified in paper I are mainly tools for prognostication and/or evaluation of pain treatment. The 'Pain Management Index' (PMI) [40] assesses the adequacy of pain treatment by combining the potency of the prescribed analgesic drug and the level of worst pain intensity (assessed by NRS-11); the 'Opioid Escalation Index' (OEI) evaluates opioid responsiveness based upon the patient's opioid requirement and the level of pain intensity (assessed by VAS) [128]; and a tool predicting the effect of pharmacological pain treatment based upon time to achieve pain relief, breakthrough pain ('incident') and opioid dose [132]. The latter has not been identified used in other studies, but studies applying the PMI [10] and the OEI [134] have been identified.

5.1.2 Paper II

Paper II represents an additional input to the experts' opinions and the findings from the literature. The semi-structured interviews gave in-depth insight into the patients' experiences of having cancer pain and revealed that the patients emphasise the consequences of being in pain such as poor physical functioning and psychological distress, and that poor sleep was closely connected to pain. Etiology, duration, and intensity of pain were in the quantitative part of paper II ranked as the most important domains to the patients. Of importance for the development process of the classification system was that we, except for sleep, did not reveal further new domains – this was interpreted as a confirmation that we were 'on the right track'. The value of including patients in this process was questioned; this issue will be further discussed in section 5.2.2.

5.1.3 Paper III and IV

In this thesis, and in the stepwise research procedure within the EPCRC, several cancer pain domains have been investigated and some have been eliminated. The findings from paper I and II and from further publications on cancer pain assessment and classification, for example [56,76,87,88], as well as clinical patient-, disease-, and treatment related information (for example age, cancer diagnosis, and common side effects) guided which domains to include in the analyses performed in paper III and IV. We applied large cohorts of advanced cancer patients with pain to empirically investigate the content of the classification system. In both papers we chose an explorative approach in the sense that we started with a broad perspective, that is several pain domains, and then eliminated domains in order to end up with a smaller set of domains highly relevant for cancer pain classification. Also the findings from paper III contributed to conclusions drawn at the expert meeting in Milan [103]. Considering the results from paper III and IV together, the following domains have been identified as relevant for cancer pain classification: pain intensity, pain relief, breakthrough pain, neuropathic pain, localisation of pain, opioid dose, use of non-opioids, psychological distress, sleep disturbances, addiction, age, cancer diagnosis, and localisation of metastases, and all of these domains will be discussed in the following.

5.1.4 Cancer pain domains

5.1.4.1 Pain intensity

Pain intensity has a key role in cancer pain management guiding clinical decision making [29,53]. Paper I demonstrated that pain intensity was included as a domain in the IASP Classification of Chronic Pain [135], in the CPPS [92] and in the three tools for prognostication/evaluation of pain treatment [40,128,132] and that it was the most frequently applied domain in the clinical studies reviewed. Pain intensity has until now not been a part of the ECS-CP [55]. However, the Edmonton group has identified moderate and severe pain intensity to be a predictor of length of time to achieve stable pain control, the need for higher final opioid doses and more complex

analgesic treatments in two large study samples [54,56], and thus considers to include this important domain in a future revision of the ECS-CP. In paper II the advanced cancer patients first described the intensity of pain when asked about what it was like to have pain and they ranked pain intensity as the third most important domain. In the cross-sectional analyses in paper III and IV, pain intensity was used as outcome, measured both as 'pain on average' and 'pain at its worst' (NRS-11). In the longitudinal part of paper IV, the pain intensity at study entry was identified as the most important predictor of pain intensity after two weeks. The Milan 2009 consensus meeting regarded pain intensity to be one of four 'core domains' to be included in a classification system for cancer pain as well as among the three domains most relevant as outcomes in clinical practice and in research. Additionally, it was reached consensus to recommend to assess pain intensity on an 11-point NRS with the following anchoring points: 'no pain' and 'pain as bad as you can imagine' [103].

5.1.4.2 Pain relief

The CPPS was developed as a prognostic tool for pain relief, using pain relief > 80% measured on an NRS-11 as the outcome. None of the remaining formal classification systems reviewed in paper I included pain relief. In the systematic literature review twelve studies focused on treatment response, which mainly was assessed as a decrease in self-reported pain intensity. In paper II, the patients described pain relief as «getting a new life» and they reported considerable improvement of physical and psychological functioning after analgesic treatment. Pain relief was used as one of the outcomes in both paper III and IV. Pain relief at study entry was identified as the most important predictor of pain relief after two weeks in paper IV. At the Milan 2009 consensus meeting pain relief was among the three most relevant domains considered used as outcomes in clinical pain management and in cancer pain research [103].

In the two large multicenter studies validating the ECS-CP [54,56], time to achieve stable pain control was used as main outcome. Stable pain control was defined as «receiving less than three breakthrough analgesic doses per day and a patient self-reported pain score less than or equal to 3/10 for three consecutive days» [54].

The use of pain relief as an outcome measure in patients with both non-cancer and cancer pain has a longstanding tradition [91]. Pain relief has been shown to be related to pain intensity, but also to be different from a change in pain intensity, in pain studies with cancer [98] and non-cancer [99] patients. Pain relief is considered as a concept that can offer additional information to change in pain intensity, such as psychological aspects [99]. Pain relief is one of the items included in the BPI, asking the question: «In the last week / in the last 24 hours, how much pain relief have pain treatments or medications provided?». It is measured on a 0 % to 100 % NRS where 0% corresponds to no relief and 100% complete relief. Thus, pain relief is assessed by asking the patients to in retrospect evaluate an eventual relief of a subjective symptom. In general, it has been argued that patients should be followed prospectively since a retrospective report may be influenced by recall bias [119].

5.1.4.3 Breakthrough pain

In paper I, breakthrough pain was identified as a domain in three of the formal systems, however all used different terminologies: 'temporal characteristics' [135], 'incident pain' [54], and 'incidental pain' [132]. The terminologies used, the assessed information, and assessment tools used, varied across the investigated studies; a finding consistent with a systematic literature review on breakthrough pain [81]. The patients in paper II were able to identify and describe breakthrough pain episodes different from their baseline pain; however, they did not regard breakthrough pain as an important domain.

In paper III, the patients with and without breakthrough pain scored pain intensity on average (mean NRS-11) as 3.9 versus 2.9, respectively, and breakthrough pain was the domain most strongly associated with pain intensity and pain relief. In paper IV, breakthrough pain was the domain most strongly associated with pain intensity in the cross-sectional analyses, and was identified as one of four predictors of pain intensity in the longitudinal sample. In paper III and IV the presence of breakthrough pain was assessed by a health care provider using the definition from the rESS [56]: «pain aggravated suddenly because of movements, swallowing, defecation, or urination».

Despite this 'narrow' definition, breakthrough pain was among the main findings in these papers, demonstrating its robustness and underlining its relevance for cancer pain classification.

Also in the ECS-CP multicentre studies, breakthrough pain ('incident pain') has been identified as an important domain by being a predictor of time to achieve pain control, the need for higher opioid doses and adjuvant analgesics [54,56]. Several further studies have demonstrated breakthrough pain as a common and significant domain in cancer patients and that breakthrough pain is a predictor of more complex pain [32,129,160,201].

5.1.4.4 Neuropathic pain

Paper I revealed that pathophysiology of pain was included in the ECS-CP ('pain mechanism', mainly distinguishing between nociceptive and neuropathic pain) [52] and in the CPPS ('mixed pain', meaning patients having some element of neuropathic pain) [92]. Among the characteristics not formally described as part of a classification system, pathophysiology/pain mechanism was described in several studies, often using the sub-domains nociceptive, somatic, visceral, neuropathic, psychogenic, and mixed pain. In paper II, pain mechanism was scored as one of the three less important domains to the patients, and was, as expected, one of few domains that the patients had little to tell about during the interviews. In EPOS (paper III), 'mixed pain' was among the final results, interpreted to represent neuropathic pain due to the assessment method (rESS) [25] and because of the medications used by the patients classified to have mixed pain (gabapentin/pregabalin). Unexpectedly, neuropathic pain was not among the results in paper IV despite that pain mechanism was assessed by the rESS from 2005 mainly distinguishing nociceptive from neuropathic pain [56], and despite that about 25% of the included patients had neuropathic pain.

In the 2010 multicentre study of the ECS-CP neuropathic pain was a predictor of time to achieve stable pain control and patients with neuropathic pain used higher doses of opioids and needed more adjuvant pain treatments [54], confirming the findings

from the 2005-study [56]. A prospective study of 167 cancer patients in palliative care reported similar results; patients defined as having 'definite neuropathic pain' had higher pain intensity and required higher doses of opioids than patients without a neuropathic pain component [130].

To recognise and diagnose a neuropathic pain condition is important as this may have therapeutic consequences [15]. One recent attempt to further investigate different assessment methods of neuropathic pain in cancer patients by comparing four different assessment tools reported that the 'Leeds Assessment of Neuropathic Symptoms and Signs' (LANSS) showed the highest specificity [130]. The IASP Neuropathic Pain Special Interest Group has proposed a grading system for the diagnosis of non-cancer neuropathic pain [179]. The four criteria of this system are: 1. Pain with a distinct neuroanatomically plausible distribution; 2. A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system; 3. Demonstration of the distinct neuroanatonically plausible distribution by at least one confirmatory test (as part of the neurologic examination); and 4. Demonstration of the relevant lesion or disease by at least one confirmatory test (as part of the neurologic examination). If the patient satisfies the first two criteria, the presence of neuropathic pain is 'possible'. To confirm the diagnosis of neuropathic pain, confirmatory testing is necessary; if either criteria three or four are satisfied, the diagnosis of neuropathic pain is 'probable', and if all four are satisfied, the diagnosis is 'definite' [179]. Only eight of 22 studies in a systematic literature review of studies of neuropathic pain in cancer patients met at least three of the NeuPSIG criteria [15]. Thus, the NeuPSIG system needs to be validated in large unselected cohorts of cancer patients, the four criteria need to be further developed, and an international agreement on the assessment methods of neuropathic pain in cancer patients needs to be achieved [15].

5.1.4.5 Pain localisation

Pain localisation is included in the IASP Classification of Chronic pain, however neither in the ECS-CP nor in the CPPS (paper I). In paper II the patients reported changes in pain sites during the disease trajectory, but did not emphasise the

localisation. Pain localisation was among the results in both paper III and IV, however with variable sites. The repeated finding of the relevance of pain localisation in this thesis, suggests that the assessment, for example by a pain body map, should be included in a cancer pain classification system. Within the EPCRC, a computerised version of a pain body map has been developed allowing also for indication of pain intensity in the marked painful area, a tool which has been shown to be feasible and well accepted by patients receiving palliative care [67] and research is on-going to further develop and validate this tool [96].

5.1.4.6 Pain treatment

Paper I identified that the CPPS [92] includes opioid dose as one of four domains. Opioid dose ('previous narcotic exposure') was included in the original ESS [23], however later excluded as it was not found to be associated with the probability of obtaining good pain control [25]. In later validation studies of the ECS-CP, opioid dose has been used as an outcome measure [54,56]. The three formal, although not validated classification systems identified in paper I are mainly to consider as tools for prognostication and/or evaluation of pain treatment and are not really classification systems. Both the 'Pain management Index' (PMI) and the 'Opioid Escalation Index' (OEI) were identified as dynamic tools useful for assessing response to opioid treatment in paper I, and were also recently applied in clinical studies [10,131].

The patients in paper II emphasised mainly the positive effect of pain treatment, but also mentioned to have common side-effects. The patients reported to initially have fears of dependency and tolerance. These were eliminated after experiencing the treatment effect and after repeatedly getting relevant information about the medication. Even if clinically useful, these results, however, do not contribute to the decision on the content of a future classification system. Opioid dose and the use of non-opioids were associated with the pain outcomes in paper III and in the cross-sectional part of paper IV, confirming previous findings and the clinical experience that patients with more complex pain conditions often require higher opioid doses, adjuvant analgesics as well as other treatment approaches [54,56,127,155].

5.1.4.7 Psychological distress

Psychological distress was one of five domains identified in two or more of the formal cancer pain classification systems identified in paper I, however differently defined and assessed. In the semi-structured interviews (paper II), the patients reported different aspects of being psychological distressed influencing their lives significantly, but did not rank it higher than number seven. In paper III, psychological distress was assessed by patients' self-report using the emotional functioning scale of the EORCT-QLQ-C30. It was among the domains associated with all three outcomes and next after breakthrough pain the one contributing mostly to the explained variance. These findings confirm the results from the ESC-CP validation studies [54,56] and other studies showing that pain and psychological distress are closely related [114,140,198]. In contrast, psychological distress was not among the significant domains in paper IV. One reason for this may be that psychological distress was measured by a health care provider using the rESS [56] and not by the patients, and that training in the use of this tool was not given in CPOR. The experts at the Milan meeting 2009 regarded psychological distress as one of the four core domains to be included in a cancer pain classification system for cancer pain [103].

5.1.4.8 Sleep disturbances

Disturbed sleep was not among the identified domains/items in paper I, however emphasised by the patients in paper II and thus included for further investigation in paper III and IV. Both in paper III and the cross-sectional part of paper IV, sleep disturbances was a domain being associated with all three outcomes and contributed significantly to changes in the outcomes. This is in concordance with findings of sleeping problems being associated with pain in more than 2800 cancer patients [169] and observations that poor sleep may cause more pain [166]. Sleep was assessed by patients' self-report in both studies; in paper III with the question 'have you had trouble sleeping?' from the EORTC-QLQ-C30, and in paper IV with the question 'have you had problems sleeping?' from the TIQ [176], which could be simple to implement in a classification system without being a burden to the patients. More

detailed information about sleep quality can be obtained by using sleep questionnaires such as the Pittsburgh Sleep Quality Index [26], however such a tool would probably be too comprehensive to include in a cancer pain classification system for clinical use.

5.1.4.9 Addiction

Addiction ('addictive behaviour') is included in the ECS-CP, but was not identified in any of the other formal classification systems nor among the 'informal' approaches (paper I). Only two of the patients in paper II reported to have any experience with addiction, and these two did not regard this as relevant for their pain experience. In paper III, addiction was assessed by a simple question if alcohol and/or drug abuse was present or not. Addiction was only included in the regression model for pain relief, and its impact on the outcome was limited. In paper IV, substance abuse was among the exclusion criteria and thus not available for investigation. In the last multicentre validation study of the ECS-CP, addiction was not among the domains associated with longer time to achieve pain control in the multivariate analysis [54]. It may therefore be questionable if addiction is a relevant domain to include in a general diagnostic tool; even it is an important condition to be aware of in clinical practice.

5.1.4.10 Age

In paper I patients' demographics such as age, gender, and performance status were identified as investigated and commonly reported domains in the field of cancer pain. Age was not among the results in paper II or III, but was one of six domains identified as predictors of pain in the longitudinal part of paper IV; indicating that younger patients may have more complex pain conditions than older patients. Similar results were reported for the ECS-CP [54] and have been reported earlier as well [124]. On the other hand, another study by Hill et al. reported that age did not influence level of reported pain intensity, but that older patients seemed to require lower opioid doses [186]. It seems reasonable to include a number of patients' demographics in the further development process of a cancer pain classification system (as usual in clinical

practice). However, the predictive value of these domains and thus their role in a future cancer pain classification system is still unclear.

5.1.4.11 Cancer diagnosis and localisation of metastases

Tumour biology plays an important role in pain pathophysiology [12 ,100 ,162]. For example prostate, breast and lung cancer often cause bone metastases, whereas head and neck cancer seldom results in distant metastases, but often leads to complex and burdensome local pain conditions [109] Pain caused by tumour directed treatments such as surgery, radiotherapy and chemotherapy is also common. Furthermore, radiotherapy for painful bone metastases has been shown to cause pain relief even with one single fraction [104]. Considering these facts, information about the cancer disease, the pattern of metastases and the anti-cancer treatments given should be mandatory also when classifying or diagnosing cancer pain, and cancer disease and oncologic treatments should be an integrated part of the management of cancer pain. In paper I, cancer diagnosis and stage of disease were reported in the majority if the included clinical studies, but cancer diagnosis was not a part of any of the formal classification systems. Based upon the considerations above, this may be considered as a major limitation. The patients in paper II were not asked about this issue as we regarded this to be too 'medical'. However, the patients' experiences of pain were closely related to the fact that they were suffering from an incurable disease. These patients as well as patients in other studies often believe that pain is a sign of disease progression [125]. Cancer diagnosis was confirmed to be of importance in paper III and in the longitudinal part of paper IV.

5.1.5 Do the models explain the variation in pain?

Multivariate regression analysis was chosen as analytical method in both paper III and IV, giving an explained variance (R square/R^2) as one important indicator of comprehensiveness [5]. The R square was moderate to low in both papers (12-19% in paper III and 16-26% in paper IV), meaning that the independent domains included in the models, explained only a minor part of the variability of the pain outcomes. This may have several reasons such as: 1. Lack of accurate assessment methods as well

as the use of crude methods to assess complex pain domains (for example breakthrough pain, neuropathic pain and psychological distress were all assessed dichotomously in paper IV), and 2. The low explained variance indicate that several other aspects than the investigated ones may influence cancer pain. By including for example genetic variability, differences in tumour biology, and variability in patients' pain perception and susceptibility into a future system, the explained variance may be increased. Similar results for explained variance (14%-35%) [83], but also higher (39%-48%) [97] have been reported by others. In the last validation study of the ECS-CP [54] multivariate Cox regression analysis was applied. The Nagelkerke pseudo-R square [123] for their final model was 21%, which also was low, however not directly comparable with our results [144].

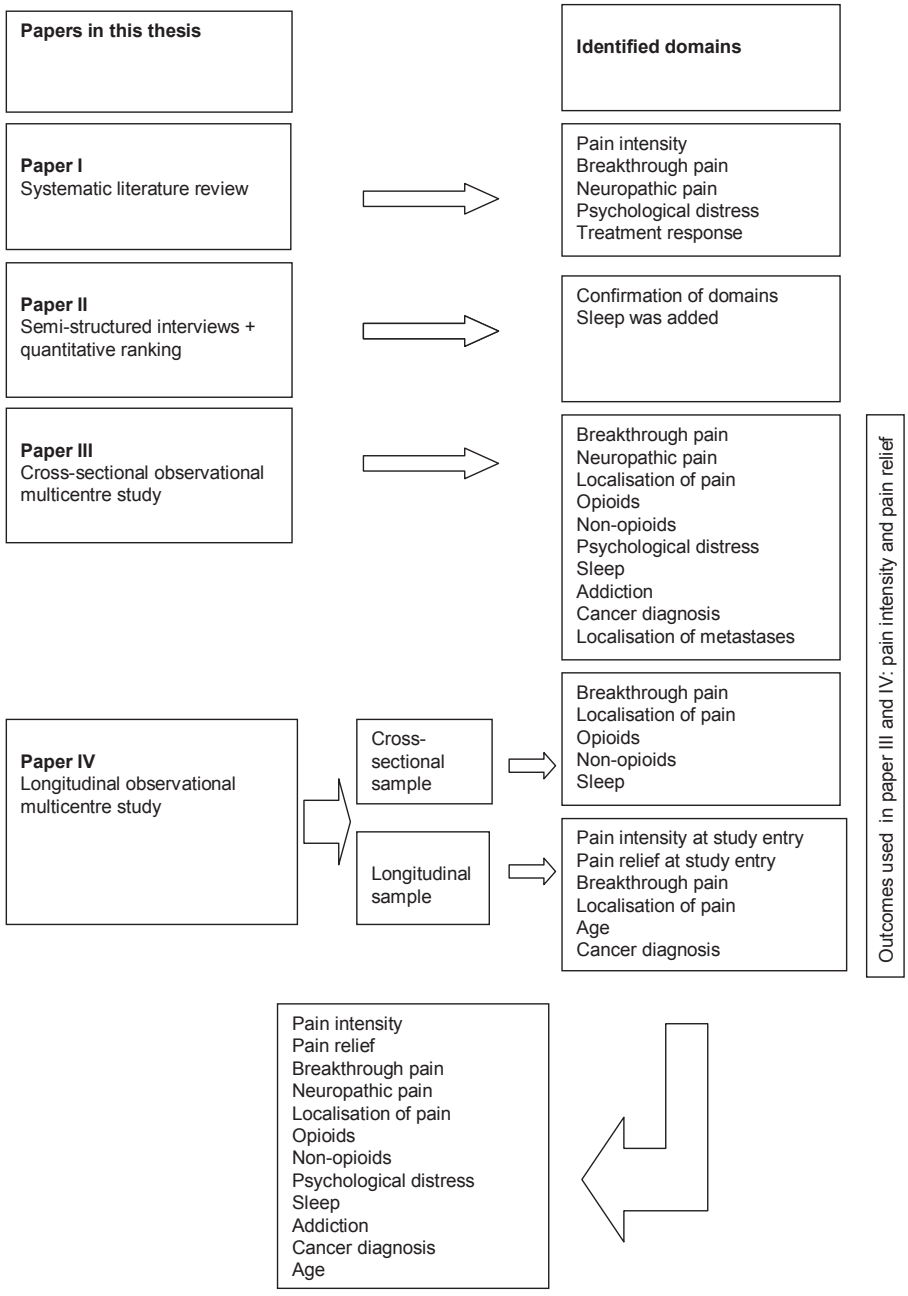

Figure 3: Summary of the results obtained in this thesis

5.2 Methodological considerations

In general, awareness of the methodological limitations is necessary to evaluate for example internal and external validity of scientific studies. Internal validity refers to whether the results are representative for the cohort studied and external validity concerns if the results are applicable in other populations (generalisability) [180]. Limitations related to the papers included in this thesis will be discussed in the following.

5.2.1 Paper I

The PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [137,161] was published in 2009 to guide researchers in planning, completing, and reporting systematic literature reviews. According to these new guidelines our search could have been improved. We chose to use only MEDLINE and Embase databases, but could have expanded the search in other databases, for example the Cochrane library, the date of the searches should have been reported, and the eligibility criteria and the detailed checklist for data extraction could have been reported.

In the final searches we ended up with 692 hits, a low number when considering the number of studies published on cancer pain in general. A relevant question is whether we identified all relevant domains/items and classification systems in the systematic literature review. It would, however, be a 'too big task' to explore all existing papers on cancer pain to address the question about its classification and the achieved results were regarded sufficient to conclude.

5.2.2 Paper II

To involve the patients in the process of deciding upon the content of a cancer pain classification system was planned as a part of the stepwise research strategy of the EPCRC [106] and based upon recommendations regarding assessment tool development from the FDA [184], NICE[142] and EORTC [172]. Patients' experience of disease and symptoms in paper II, however, contributed marginally with new

information in the development process of a classification system. Considering this, one may question the appropriateness of using recommendations developed for symptom assessment also for symptom classification. In order to achieve completeness of a comprehensive symptom assessment for example in cancer survivors, it is intuitively understandable that various methodologies, including in-depth interviews, should be applied in order to include all relevant domains. However, a diagnostic procedure (that is classification) is basically different from assessment of symptoms or patient reported outcomes. The content of a classification system is a combination of domains related to pathophysiology, clinical examination, imaging, laboratory tests, and PROs and thus a complex task for patients to evaluate. For the future it may therefore be questioned whether patients' perspectives need to be recommended included in a development process of a classification system for symptoms in palliative care specifically and in cancer care in general.

We may not have explored all possible domains due to the methodology applied in paper II. With another approach for example by more open patients' interviews or by using focus groups interviews including both experts and patients and hereby opening for an interaction between health care providers and patients, we might have obtained more relevant and comprehensive information.

The qualitative analyses were performed according to a general method by Giorgi [(69)] and Malterud [(120)]. From the presentation of the results it might be claimed that the analysis is more reflective of a content analysis. Content analysis has been presented as one method of text analysis with two different approaches: a) a quantitative approach counting the frequency distribution of words/codes identified in the text, and b) a qualitative approach in which extracts from the text are reported to illustrate particular themes or categories, referred to as 'thematic analysis' [(171)]. The analysis we performed may be reflective to a thematic content analysis as in (b), however to avoid confusion regarding terminologies and as we did not apply the

quantitative approach described as (a), we did not use the term ‘content analysis’ in the paper.

The population studied was narrow, as intended, including patients with advanced cancer and pain. However, this may hamper the generalisability of the findings into general oncology as other aspects of pain may be regarded as more relevant to for example long-term survivors or patients receiving curative treatment.

5.2.3 Paper III and IV

The empirical studies are both large multicentre studies consisting of data from rather heterogeneous patients populations. The heterogeneity may be considered as a strength with regard to generalizability of the findings. It may however also be a limitation since small effect sizes may be diluted in such heterogeneous samples. Considering this, we chose in paper IV to analyse data only from patients recently admitted to palliative care in the longitudinal part and thus achieved a more homogenous sample.

The cross-sectional design (paper III) has limitations. Such a study design allows only for the study of associations/correlations between the dependent and independent variables and thus does not allow for any answers regarding prediction or causality. An ideal cancer pain classification system should guide treatment by classifying patients into subgroups of patients with different needs for treatment and/or different chance for effect of various treatments. To show such a clinical validity, a prospective intervention study is needed. The strength of paper IV was the prospective design, however, this is also only an observational study. Furthermore, paper III and IV were not planned and designed for the development and validation of a cancer pain classification system, which limits their value in this development process.

Another limitation is the outcomes applied. Pain intensity and pain relief can be considered as not representative for the patients’ global pain experience. We aimed at studying a complex phenomenon, but had to choose outcomes applicable for

research purposes. To minimalise this limitation, the choice of outcome was guided by findings in the literature and by an expert survey (paper III), and three outcome measures were used.

Regression analysis was chosen as the most appropriate method to study which and to what extent a series of domains were influencing or were related to pain intensity and/or pain relief. Taking the complexity of pain and all aspects influencing cancer pain, and also the need for investigating causality into consideration, it could be claimed that the use of a more complex method such as structural equation modelling would provide additional and important insights. The explained variance (R^2) was low in both paper III and IV indicating that several other aspect than those investigated contribute to cancer pain. This aspect has been discussed in section 5.1.5.

6. Conclusions

Pain is a common and often undertreated symptom in cancer patients. The lack of an international cancer pain classification system has been identified as one reason for this. This thesis has contributed with four studies to the on-going development process of a cancer pain classification system; one systematic literature review, one qualitative study, and two studies of empirical data from large cohorts of cancer patients with cross-sectional and longitudinal design, respectively. The four papers demonstrate that several aspects are contributing to the complexity of pain in patients with advanced cancer; both pain-, patient- and cancer related information.

The following conclusions indicate the answers to the research questions raised in this thesis:

Paper I

Six formal classification systems for cancer pain were identified:

- Three were systematically developed and partially validated: the International Association for the Study of Pain Classification of Chronic Pain, the Cancer Pain Prognostic Scale, and the Edmonton Classification System for Cancer Pain.
- Three further formal systems were identified as mainly being tools for prognostication and evaluation of pain treatment, namely: the Opioid Escalation Index, a prognostic tool for pain treatment, and the Pain Management Index.
- In addition, several other domains/items not formally described as part of a classification system were identifed.

The domains pain intensity, breakthrough pain, neuropathic pain, psychological distress, and treatment response were included in two or more of the formal systems, and the assessment methods used differed across studies. None of the approaches were widely applied in research or in clinical practice.

Paper II

Previously identified domains relevant for cancer pain classification were confirmed to be relevant to the patients. These were (ordered due to the patients' scoring of their importance): Etiology, duration of pain, pain intensity, coping, localisation of pain, physical functioning, psychological distress, breakthrough pain, cognitive function, neuropathic pain, previous pain experience, and addiction. Except for sleep disturbances, no new domains were identified. In semi-structured interviews the patients emphasised aspects related to being in pain, such as poorer emotional and physical functioning.

Paper III and IV

In paper III, breakthrough pain and psychological distress were confirmed as important domains of a cancer pain classification system. Neuropathic pain, pain localisation, opioid dose, use of non-opioids, sleep, addiction, cancer diagnosis, and localisation of metastases were identified as candidate domains.
In the cross-sectional analysis in paper IV, breakthrough pain, pain localisation, opioid dose, use of non-opioids, and sleep were associated with one or more of the pain outcomes. Furthermore, in the longitudinal analysis of paper IV, the domains pain intensity and pain relief at study entry, breakthrough pain, localisation of pain, age, and cancer diagnosis were identified as predictors. Identified domains/items explained from 12% to 26% of the variability of the pain outcomes.

7. Future directions

An international cancer pain classification system is needed to improve cancer pain management. At the expert meeting in Milan in 2009 it was proposed to name an upcoming classification system the 'Cancer Pain Assessment and Classification System' (CPACS) [103]. The major future challenges are to choose the most appropriate and the optimal number of domains for inclusion, to reach a consensus on how to assess these domains, to reach consensus on the appropriate outcomes, and to implement the future CPACS into research and clinical practice.

At the Milan meeting it was recommended to include the following domains as 'core domains' in the future CPACS: pain intensity, breakthrough pain, neuropathic pain, and psychological distress [103]. The results obtained in this thesis suggest to also considering the following domains for inclusion: pain relief, localisation of pain, analgesic pain treatment, sleep disturbances, and cancer diagnosis.

For assessment consensus has been reached to use a 0 to10 numerical rating scale for pain intensity (NRS-11) [103]. Which assessment methods and tools to use for other domains are not decided, and need to be clarified through further research and collaboration.

Efforts have been made to standardise what information to assess in clinical studies in palliative care research. The EU-funded 'PRISMA project' initiated by the EAPC Research Network has completed a systematic literature review and a collected experts' opinions regarding what is the appropriate information needed for describing a palliative care population [38 ,79]. A publication proposing a general 'basic data set' to include in all palliative care studies that can be expanded with symptom specific assessment appropriate for different studies is in preparation [170].

Finally, large studies are required to investigate the feasibility and effectiveness of a future cancer pain assessment and classification system. Studies can investigate the

clinical benefit of using a cancer pain classification system for categorising patients according to their pain condition and for guiding treatment decisions in individual patients. The performance of such studies is facilitated by international collaboration [77]. The international network of palliative care researchers within the EPCRC is now continued within the EAPC Research Network [47] and the European Palliative Care Research Centre (PRC) [49].

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Paper I

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Paper III

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Which variables are associated with pain intensity and treatment response in advanced cancer patients? – Implications for a future classification system for cancer pain

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ABSTRACT

Background: This study is part of a research program to reach consensus on an international cancer pain classification system. A confirmative and explorative approach was applied to investigate which of the variables identified in the literature, by experts and patients that are associated with pain.
Methods: Data from an international, multicentre, cross-sectional study of cancer patients treated with opioids were investigated. Dependent variables were: average pain, worst pain, and pain relief (11-point Numerical Rating Scales). Forty-six independent variables were chosen based upon previous studies. Bivariate analyses identified independent variables associated with at least one of the dependent ones; 21 were included in multivariate linear regression analyses.
Results: Two thousand two hundred and seventy-eight patients were investigated; 52% males, mean age 62 years, mean Karnofsky Performance Status 59%, mean daily opioid oral equivalent dose 341 mg. Fifty-eight percent had breakthrough pain. Mean pain scores were: average pain 3.5, worst pain 5.3 and pain relief 74%. Variables most strongly associated with these three dependent variables were: breakthrough pain, psychological distress, sleep, and opioid dose.
Conclusions: Breakthrough pain and psychological distress were confirmed as key variables of a future classification system. Candidate variables were: sleep, opioid dose, pain mechanism, use of non-opioids, pain localisation, cancer diagnosis, location of metastases, and addiction.

1. Introduction

There is no agreement on which cancer pain classification system that should be used in research and clinical practice (Caraceni and Weinstein, 2001; Fainsinger and Nekolaichuk, 2008). Consensus on a shared language for cancer pain would facilitate the translation of results from research into clinical practice, make comparison between studies possible (Borgsteede et al., 2006), and be a tool for quality assurance of cancer pain treatment (Pasman et al., 2009). A cancer pain classification system can improve treatment of cancer pain (Fainsinger and Nekolaichuk, 2008).

The European Palliative Care Research Collaborative (EPCRC) was funded by the EU's 6th framework program to develop an international, consensus based and feasible classification system for prevalent symptoms in patients with advanced cancer. The research strategy is a stepwise process including literature reviews, input from experts, input from patients and empirical studies (Kaasa et al., 2008).

A systematic literature review identified six existing formal classification systems for cancer pain (Knudsen et al., 2009). Three

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were systematically developed and partially validated; the Classification of Chronic Pain of the International Association for the Study of Pain (Merskey and Bogduk, 1994), the Edmonton Classification System for Cancer Pain (ECS-CP) (Fainsinger and Nekolaichuk, 2008) and the Cancer Pain Prognostic Scale (CPPS) (Hwang et al., 2002). Except for the ECS-CP, none of the systems have been widely used. Five variables were common: pain intensity, breakthrough pain (BTP), pain mechanism, response to treatment, and psychological distress (PD) (Knudsen et al., 2009). Experts in pain and palliative care recommended additionally the variables pain localisation, interference, duration, previous pain experience, and pain beliefs for inclusion in a future assessment and classification system for cancer pain (Hjermstad et al., 2008). A qualitative study on advanced cancer patients' experiences with pain and their opinion of its assessment and classification proposed to add sleep and social functioning (Knudsen et al., 2010).

The process of development and validation of a clinically useful cancer pain classification system requires definition of which variable to be the dependent one. A series of dependent variables have been applied in previous cancer pain studies such as pain intensity (Caraceni et al., 1999), opioid dose (Mercadante et al., 2000), treatment response (Cleeland et al., 1994), and time to achieve pain control (Fainsinger et al., 2005). Pain intensity is by many clinicians regarded as a key variable since it guides treatment decisions and influences pain experience (Chow et al., 2006; Hjermstad et al., 2008).

The overall aim of the present study was to apply empirical data to investigate which variables to include in an international cancer pain classification system. Data from the European Pharmacogenetic Opioid Study (EPOS) (Klepstad et al., 2010) was applied in a confirmative and explorative approach to answer the following research questions:

1. To what extent are the variables pain mechanism, breakthrough pain (BTP) and psychological distress (PD) associated with pain intensity and/or response to pain treatment?
2. Are other previously identified variables relevant for cancer pain classification associated with pain intensity and/or response to pain treatment?

2. Methods

2.1. Patients

EPOS is an international, multicentre, cross-sectional, observational study of cancer patients treated with opioids for moderate to severe pain (Klepstad et al., 2010). Patients $\geqslant$18 years with verified malignant disease and on regularly scheduled opioid treatment for at least three days were included.

2.2. Assessment

The following information was assessed by a health care provider: Medical history and consumption of opioids and other medication, functional status assessed by the Karnofsky Performance Status (KPS) (Karnofsky et al., 1948) and cognitive function by the Mini Mental Status Exam (MMSE) (Folstein et al., 1975). BTP was evaluated as a dichotomised yes/no-question focusing on pain with a known trigger. This was similar to the question of incident pain in an early version of the Edmonton Classification System for Cancer Pain and the only question addressing this domain in EPOS (Bruera et al., 1989, 1995b). Pain mechanism was categorised as follows: visceral, bone/soft tissue, neuropathic, mixed, and unknown pain; not further defined in EPOS (Bruera et al., 1995b). Addiction was evaluated by answering yes or no to the question of previous or present known abuse of either alcohol or drugs.

The patients completed the Brief Pain Inventory (BPI) (Daut et al., 1983) and the European Organisation for Research and Treatment of Cancer quality-of-life core questionnaire (EORTC-QLQ-C30) version 3.0 (Aaronson et al., 1993). Variables included in the present analyses were from BPI: pain localisation (body map), 'pain on the average', 'pain at its worst' and 'pain relief'; all referring to the last 24 h (11-point Numerical Rating Scales (NRS-11)), and from EORTC-QLQ-C30: the physical, emotional and social functioning scales, and the symptom scales/items for nausea and vomiting, constipation and insomnia ('have you had trouble sleeping?'). Hence, PD was assessed by use of the emotional functioning scale in the EORTC-QLQ-C30 questionnaire, consisting of the four questions: 'did you feel tense?', 'did you worry?', 'did you feel irritable?', and 'did you feel depressed?'. All scales and single-item measures were calculated following the EORTC guidelines into a score ranging from 0 to 100. A high score for a functional scale represents a high level of functioning whereas a high score for a symptom scale/item represents a high level of symptomatology (Aaronson et al., 1993).

2.3. Stepwise analytical process

The analytical approach in this paper consists of four steps (Fig. 1).

Step 1 was performed as an expert survey with the aim to advise on dependent variables to be applied. In January 2009, 30 experts within oncology, pain and palliative care were asked to rank the clinical relevance of five variables from the BPI on an NRS-11 (0 = not relevant, 10 = highly relevant). The variables chosen for ranking were: Pain relief provided by pain treatments or medications; pain at its worst; pain at its least; pain on the average (all in the last 24 h); and pain right now.

Step 2 was conducted in order to decide upon which variables to include as dependent ones in the analyses. These were defined based upon results from: (1) a systematic literature review on cancer pain classification (Knudsen et al., 2009); (2) a combined systematic literature review and expert survey on cancer pain assessment (Hjermstad et al., 2008); and (3) data from a qualitative study on 33 advanced cancer patients exploring the patients' experiences and view upon variables identified in (1) and (2) (Knudsen et al., 2010). Additionally, the common opioid side effects nausea/vomiting and constipation were included.

In step 3 bivariate analyses were performed in order to decide which of the examined variables to include in the multivariate analyses. For each of the dependent variables, the Kruskal–Wallis test was used for the categorical independent variables and the Spearman's correlation coefficient for the continuous ones. All variables from step 2, showing a statistically relevant association with at least one of the dependent variables were included in the multivariate analyses.

In step 4 multivariate regression analyses were conducted. Backward elimination was chosen for selecting the relevant variables, as a lack of high correlations between independent and dependent variables is one of the assumptions under which this is considered a good method (Sauerbrei et al., 2007). A p-value = 0.01 was applied for removing variables. As the data showed between country differences in mean pain intensity and pain relief scores, country was used as an adjustment factor in all the regression analyses, choosing Norway as reference country. The adjustment was performed forcing nine dichotomous variables in each model, one for each of the remaining countries. Due to collinearity between physical functioning and Karnofsky Performance Status, only the latter was included in the model. Common assumptions in regression analysis were investigated without identifying conditions weakening the models.

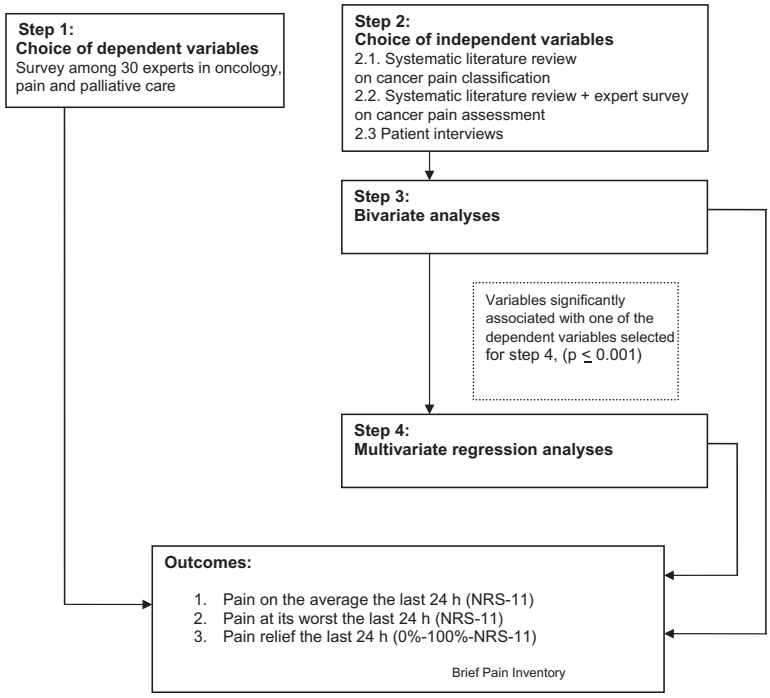

Fig. 1. Flowchart of the stepwise analytic process of the EPOS data described in the methods part.

2.4. Ethics

The protocol was approved by the committee for medical research ethics of each study centre. All patients gave written informed consent to participate in the study.

3. Results

Two thousand two hundred and ninety-four patients were included in the present analyses; the patients were recruited from 17 centres in 11 European countries from February 2004 to April 2008 (Klepstad et al., 2010). Greek patients were not included due to a low number of patients. Eleven patients withdrew from the study. Hence, the final study sample included 2278 patients. As shown in Table 1, 1193 were male and 1085 female, mean age was 62 years, and mean KPS was 59. The majority was inpatients (81%). The most common cancer diagnoses were gastrointestinal, lung, breast and prostate cancer, and 45% of the patients had bone metastases. The characteristics of pain and other symptoms are presented in Table 2. Average pain was 3.5 and pain at its worst was 5.3. Pain relief was 74%, and 58% of the patients had BTP. The most common pain mechanism was 'bone/soft-tissue pain'. The average oral morphine daily equivalent dose was 341 mg.

Sixteen experts (53%) responded and scored the items from the BPI in the following order of importance: 'pain right now' (median score 9), 'pain at its worst' (9), 'pain on the average' (8.5), 'pain relief' (8) and 'pain at its least' (4). Three dependent variables were chosen for the present study: '**pain on the average**', '**pain at its worst**' and '**pain relief**'.

Based upon the studies in step 2, 46 independent variables were included in the present analyses (Table 3). Bivariate analyses showed that six variables were significantly associated with all three dependent variables: BTP, pain localisation (lower extremities), opioid dose, physical functioning, PD and sleep. Eight variables showed significant association with two of the dependent ones: pain mechanism (bone/soft-tissue and mixed pain), pain localisation (upper extremities), the use of non-opioids, the use of gabapentin/pregabalin, KPS, social functioning, and constipation. Seven variables (back pain, use of corticosteroids, cognitive functioning, addictive behaviour, nausea/vomiting, prostate cancer, liver metastases and gender) were significantly associated with only one of the dependent variables (Table 3).

In Fig. 2 box plots for the dependent variable 'pain on the average' and the three hypothesised key variables are presented. Patients with and without BTP reported average pain as 3.9 vs. 2.9. Patients with PD had average pain of 4; patients without scored 3.2. With visceral pain the average pain was 3.1, with bone/soft-tissue pain 3.3, with neuropathic pain 3.8, with mixed pain 3.9 and with unknown pain, the average pain score was 2.5. Similar results were observed for the two other dependent variables 'pain at its worst' and 'pain relief'.

The regression analyses included 21 variables (Table 3), of which 13 variables constituted the final models (Table 4). Two of the three hypothesised variables, BTP and PD, were confirmed to be associated with pain. In addition, sleep disturbances and the use of non-opioids were included in all three models. The third hypothesised variable, pain mechanism, was included in two of the models, so were also opioid dose, cancer diagnosis and location of metastases. Pain localisation was included in all three models, however with different sites for each model. BTP, PD, sleep and opioid dose showed the highest standardised betas among the included (Table 4). The adjusted explained variance (R^2) for the regression models varied from 0.12 to 0.19.

Table 1
Patient characteristics.

Patient characteristics	*N* (%)	Mean (range)	S.d.[a]
Age		62.2 (18–96)	12.3
Gender			
Male	1193 (52.4)		
Female	1085 (47.6)		
Country			
Norway	565		
Italy	462		
Germany	452		
United Kingdom	295		
Iceland	150		
Sweden	135		
Switzerland	115		
Lithuania	54		
Denmark	31		
Finland	30		
Greece	5		
Karnofsky Performance Status		59.2 (10–100)	17.2
Time since diagnosis (months)		31.5 (0–401)	45.5
Cancer diagnosis			
Gastro intestinal	523 (23.0)		
Lung	418 (18.3)		
Breast	303 (13.3)		
Prostate	264 (11.6)		
Gyneacological	173 (7.6)		
Urological	166 (7.3)		
Hematological	133 (5.8)		
Head and neck	125 (5.5)		
Unknown origin	62 (2.7)		
Sarcoma	58 (2.5)		
Skin	50 (2.2)		
Location of metastases[b]			
Bone	1020 (44.8)		
Liver	562 (24.7)		
Lung	502 (22.0)		
CNS	132 (5.8)		
Other	911 (40.0)		
None	370 (16.2)		
Treatment setting			
Inpatients	1850 (81.2)		
Outpatients	428 (18.8)		

[a] S.d. = standard deviation.
[b] Patients may have more than one site of metastases.

Table 2
Characteristics of pain and other symptoms.

Pain and other symptoms	*N* (%)	Mean (range)	S.d.[a]
Pain intensity			
Pain on the average last 24 h[b]		3.50 (0–10)	2.2
Pain at its worst last 24 h[c]		5.25 (0–10)	2.8
Pain relief			
Pain relief provided by pain treatments last 24 h[d]		74 (0–100)	22.3
Breakthrough pain			
Present	1322 (58.0)		
Absent	947 (41.6)		
Pain mechanism			
Bone/soft-tissue pain	1011 (44.4)		
Mixed pain	778 (34.2)		
Visceral pain	358 (15.7)		
Neuropathic pain	110 (4.8)		
Unknown	18 (0.8)		
Localisation of pain[e]			
Back	868 (38.1)		
Pelvic front	835 (36.7)		
Thorax front/abdomen	700 (30.7)		
Lower extremities	535 (23.5)		
Upper extremities	300 (13.2)		
Head	193 (8.5)		
Pharmacological pain treatment			
Total oral morphine equivalent opioid dose (mg)		341 (0–9090)	550.2
Time on opioids (months)		4.9 (0–132)	10.9
Previously treated with another opioid	761 (33.4)		
Systemic corticosteroids	1107 (48.6)		
Non-opioids (NSAIDs, paracetamol)	1212 (53.2)		
Gabapentin, pregabalin	399 (17.5)		
Other subjective symptoms			
Physical functioning[f]		40.3	25.8
Psychological distress[f]		64.5	26.4
Social functioning[f]		46.0	33.2
Sleep[g]		35.0	33.8
Nausea/vomiting[g]		23.7	28.2
Constipation[g]		45.0	37.1
Cognitive functioning[h]		26.9 (9–30)	3.4
Addictive behaviour present	142 (6.2)		

[a] S.d. = standard deviation.
[b] 11-point Numerical Rating Scale (NRS-11 from 0 to 10).
[c] NRS-11.
[d] NRS-11 0–100%: 0% = no relief, 100% = complete relief.
[e] Patients may have more than one localisation of pain.
[f] EORTC functioning scale 0–100; high scores represents a high level of functioning.
[g] EORTC symptom scale/single item 0–100; high score represents a high level of symptomatology or problems.
[h] Mini Mental Status Exam (MMSE): score range 0–30; higher scores mean better cognitive function.

4. Discussion and conclusions

The present study aimed at verifying three key variables and at exploring other variables relevant for cancer pain classification in a cohort of cancer patients on opioids. BTP and PD were confirmed to be relevant as they contributed significantly to all three final regression models and showed the highest standardised betas. Sleep disturbances and opioid dose were important as well, contributing significantly to three and two of the final regression models, respectively. Pain mechanism was included in two of the final models. Identified candidate variables were: The use of non-opioids, which was included in all three models; pain localisation, cancer diagnosis and location of metastases, all included in two of the final models; and finally addiction, only included in one model.

In a treatment decision making process, one important step is to group or classify the patients according to expected treatment effects. This may also provide a better understanding of patient cohorts in clinical studies. A classification system should be based upon simple, but robust variables. Our primary hypothesis was based upon a systematic literature review where BTP, PD and pain mechanism were identified as key variables (Knudsen et al., 2009). Interestingly, BTP and PD were confirmed to also be important in this large sample of cancer patients recruited from 11 countries and 17 institutions across Europe. This strengthens the value of these variables for inclusion in a future cancer pain classification system. Similar variables have been shown to be important in the validation studies of the Edmonton Classification System for Cancer Pain (ECS-CP) (Fainsinger et al., 2005, 2010); a system consisting of the five variables: incident pain or BTP, pain mechanism, PD, addiction and cognitive function, and which is regarded as a template and a starting point for further development of an international pain classification system (Hagen et al., 2008; Kaasa et al., 2010).

In the ECS-CP all variables are assessed by a health care provider using definitions and guidelines developed through an international construct validation study (Nekolaichuk et al., 2005). In EPOS, BTP and pain mechanism was assessed similarly as in the ECS-CP. Despite the narrow definition of BTP used in EPOS

Table 3
Bivariate analyses: overview independent and dependent variables.

Dependent variables	'Pain on the average'		'Pain at its worst'		'Pain relief'	
	Mean complete sample = 3.5 (NRS 0–10)		Mean complete sample = 5.3 (NRS 0–10)		Mean complete sample = 74% (0% = no relief, 100% complete relief)	
Independent variables	Kruskal–Wallis	Spearman's coefficient	Kruskal–Wallis	Spearman's coefficient	Kruskal–Wallis	Spearman's coefficient
	p-Value	*p*-Value	*p*-Value	*p*-Value	*p*-Value	*p*-Value
Breakthrough pain	<0.001	–	<0.001	–	<0.001	–
Pain mechanism						
Visceral pain	0.002	–	0.501	–	0.018	–
Bone/soft-tissue pain	**0.001**	–	<0.001	–	0.337	–
Neuropathic pain	0.209	–	0.618	–	0.332	–
Mixed pain	**<0.001**	–	<0.001	–	0.012	–
Localisation of pain						
Head	0.002	–	0.402	–	0.007	–
Thorax front/abdomen	0.002	–	0.003	–	0.628	–
Pelvic front	0.005	–	0.006	–	0.016	–
Back	0.011	–	0.003	–	<0.001	–
Upper extremities	**<0.001**	–	**<0.001**	–	0.003	–
Lower extremities	**<0.001**	–	**<0.001**	–	**<0.001**	–
Opioid dose[a]	–	**<0.001**	–	**<0.001**	–	**<0.001**
Time on opioids[b]	–	0.870	–	0.906	–	0.162
Previous opioid treatment[c]	0.030	–	0.212	–	0.091	–
Adjuvant analgesics						
Steroids	0.024	–	0.721	–	**<0.001**	–
Non-opioids[d]	**0.001**	–	0.023	–	**<0.001**	–
Gabapentin/pregabalin	**<0.001**	–	**<0.001**	–	0.009	–
Karnofsky Performance Status	–	**<0.001**	–	**<0.001**	–	0.386
Physical functioning	–	**<0.001**	–	**<0.001**	–	**<0.001**
Psychological distress	–	**<0.001**	–	**<0.001**	–	**<0.001**
Social functioning	–	0.016	–	**0.001**	–	**<0.001**
Sleep	–	**<0.001**	–	**<0.001**	–	**<0.001**
Nausea/vomiting	–	0.007	–	0.294	–	**<0.001**
Constipation	–	**<0.001**	–	**<0.001**	–	0.005
Body mass index	–	0.495	–	0.284	–	0.332
Cognitive functioning	–	0.002	–	**<0.001**	–	0.180
Addictive behaviour	0.183	–	0.051	–	**<0.001**	–
Cancer diagnosis						
Gastro intestinal	0.093	–	0.161	–	0.169	–
Lung	0.112	–	0.475	–	0.268	–
Breast	0.738	–	0.513	–	0.195	–
Prostate	0.003	–	**<0.001**	–	0.649	–
Gyneacological	0.018	–	0.315	–	0.356	–
Urological	0.529	–	0.168	–	0.049	–
Hematological	0.624	–	0.917	–	0.812	–
Head and neck	0.036	–	0.188	–	0.293	–
Unknown origin	0.167	–	0.108	–	0.674	–
Sarcoma	0.380	–	0.154	–	0.251	–
Skin	0.659	–	0.922	–	0.750	–
Time since diagnosis[b]	–	0.316	–	0.245	–	0.919
Location of metastases						
Bone	0.998	–	0.196	–	0.239	–
Liver	**<0.001**	–	0.003	–	0.019	–
Lung	0.226	–	0.198	–	0.392	–
CNS	0.355	–	0.271	–	0.584	–
Other	0.750	–	0.573	–	0.016	–
Age	–	0.105	–	0.005	–	0.495
Gender	**<0.001**	–	0.026	–	0.019	–

Variables in bold print were included in the regression analyses (step 4).
[a] Daily oral morphine equivalent dose in mg.
[b] In months.
[c] Number of previous opioids used.
[d] Paracetamol and NSAIDs.

(presence of a known trigger), this was the variable most strongly associated with pain. The assessment of pain mechanism in EPOS was based on the revised Edmonton Staging System (rESS) from 1995 (Bruera et al., 1995b); an assessment later revised in the

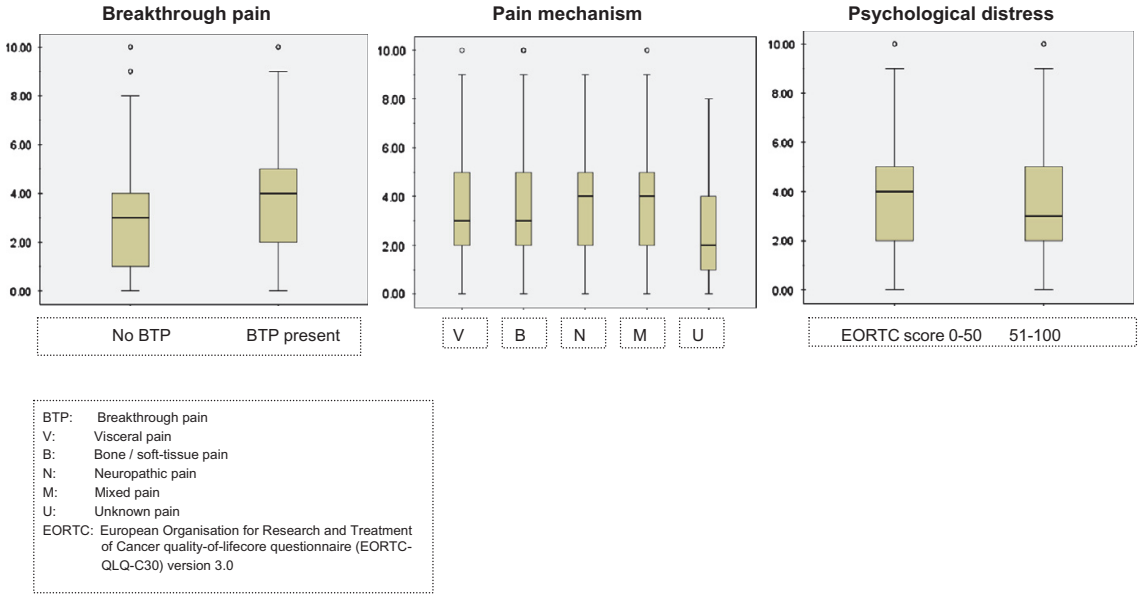

Fig. 2. Box plots of the hypothesised key variables with 'pain on the average' as the dependent variable.

Table 4
Multivariate regression analyses: the final models for all three dependent variables.

Independent variables	Dependent variables	'Pain on the average'			'Pain at its worst'			'Pain relief'		
		N = 1870			N = 1883			N = 1843		
		R^2 adj. = 0.17			R^2 adj. = 0.19			R^2 adj. = 0.12		
		β[a]	CI[b]	Stand. β[c]	β	CI	Stand. β	β	CI	Stand. β
Const.		2.22	1.63, 2.80	–	2.72	1.96, 3.50	–	76.1	71.9, 80.4	–
Breakthrough pain		0.87	0.68, 1.06	0.20	1.29	1.04, 1.53	0.23	−6.1	−8.1, −4.0	−0.13
Psychological distress		−0.01	−0.01, −0.006	−0.12	−0.01	−0.02, −0.007	−0.11	0.1	0.05, 0.14	0.11
Pain mechanism	Mixed	0.34	0.14, 0.54	0.07	–	–	–	–	–	–
	Bone soft-tissue	–	–	–	−0.47	−0.72, −0.22	−0.08	–	–	–
Sleep		0.47	0.27, 0.68	0.10	0.58	0.31, 0.84	0.10	−4.0	−6.3, −1.8	−0.08
Non-opioids		0.32	0.14, 0.51	0.07	0.42	0.18, 0.66	0.07	−3.1	−5.1, 1.1	−0.07
Pain localisation	Upper extremities	0.42	0.17, 0.68	0.07	–	–	–	–	–	–
	Lower extremities	–	–	–	0.44	0.18, 0.71	0.07	–	–	–
	Back	–	–	–	0.38	0.15, 0.62	0.07	−3.0	−4.9, −1.0	−0.07
Opioid dose (lg)		0.23	0.14, 0.31	0.12	0.34	0.23, 0.44	0.14	–	–	–
Cancer diagnosis	Prostate cancer	−0.44	−0.72, −0.16	−0.07	−0.51	−0.88, −0.14	−0.06	–	–	–
Location of metastases	Liver metastases	−0.39	−0.61, −0.18	−0.08	−0.54	−0.81, −0.27	−0.08	–	–	–
Addictive behaviour		–	–	–	–	–	–	−6.8	−11.0, −2.6	−0.07

[a] Regression coefficient.
[b] 95% confidence interval.
[c] Standardised beta.

ECS-CP as the distinction between nociceptive and neuropathic pain has been shown to be the clinically most relevant (Fainsinger et al., 2005). The different pain mechanisms were not defined in EPOS. Only 110 patients were categorised to have neuropathic pain and 788 to have mixed pain. Four hundred and two patients used gabapentin/pregabalin, medication often used for treatment of neuropathic pain. This indicates that more than 110 patients had neuropathic pain; most probably categorised as having mixed pain. As mixed pain was included in the final regression model (for 'average pain' as dependent variable), this may still be regarded as a confirmation of previous findings defining neuropathic pain as a key variable for cancer pain classification (Caraceni et al., 1999; Fainsinger et al., 2005).

Our results show that more PD is associated with more severe pain, confirming previous results (Wilson et al., 2007). PD was assessed by the patients, applying one of the most widely used health related quality of life instruments, the EORTC QLQ-C30 (emotional functioning scale) (Aaronson et al., 1993). Such a rater-independent confirmation of a key variable may be regarded as a further strengthening of its importance.

In the present study, addiction was only included in the regression model with 'pain relief' as a dependent variable. This may be explained by the fact that pain relief is a concept covering other and more complex aspects of pain than the measurement of pain intensity (Jensen, 2003). In EPOS, only 142 patients (6.2%) with addiction were recognised. In ECS-CP the screening tool

'CAGE'-questionnaire (Fainsinger et al., 2005) can be applied; recently identifying addiction in 11% of the patients (Fainsinger et al., 2010). This may suggest that a more comprehensive assessment is needed to recognise patients with addiction, e.g. by use of the 'CAGE'-questionnaire (Bruera et al., 1995a).

The fifth variable of the ECS-CP, cognitive functioning, was not included in the present regression models. However, pain management and research in cognitively impaired patients requires attention in the further development of a classification system.

Sleep disturbances were identified as associated with pain and may reflect some of the underlying complexity of a pain patient (Knudsen et al., 2010). Sleep, therefore, may be an important and feasible candidate variable for identifying patients with poorly controlled pain. In the present study sleep was assessed by one simple question from the EORTC QLQ-C30 ('have you had trouble sleeping?') (Aaronson et al., 1993). Perhaps more detailed information about sleep quality such as in designated sleep questionnaires (e.g. Pittsburgh Sleep Quality Index) (Buysse et al., 1989) could add further information; however, these instruments are too comprehensive to be used for general assessment of sleep in a pain classification system.

Different variables have been applied as the dependent ones in different cancer pain studies. Pain intensity may be the most crucial variable for classification and treatment decisions (Fainsinger et al., 2009) and therefore chosen as dependent variable in the present study. Two different measures of pain intensity from the BPI were applied; 'pain on the average' and 'pain at its worst' The experts ranked 'pain right now' and 'pain at its worst' to be the most relevant items followed by 'pain on the average', 'pain relief' and 'pain at its least'. In order to keep the number of dependent variables low, only 'pain on the average' and 'pain at its worst' were chosen by the authors for the assessment of pain intensity; a choice guided by findings in previous studies and by experts' opinions. As 'pain on the average' is more adequate for guidance of long term pain treatment this was chosen in preference to 'pain right now'; the latter regarded as more useful for assessment of acute pain or by i.v. titration of opioids (Elsner et al., 2005). 'Pain at its worst' may reflect the presence of fluctuating pain and to be more associated with interference (Paul et al., 2005). The third dependent variable, response to pain treatment measured as 'pain relief', was chosen to strengthen the analysis. The use of multiple dependent variables for our analyses and the fact that many variables showed a significant association with more than one of them, strengthens the face validity of our results. However, an international pain classification system should use one standardised clinically relevant dependent variable.

The independent variables investigated explain up to 19% of the variation of the dependent ones. This indicates that several other factors influence the level of pain intensity and the experience of treatment response; e.g. genetic variation, differences in tumour biology and differences in the patients' perception. Similar results have been published in previous cancer pain studies. The differences in the scores between categories on an NRS, e.g. with or without BTP or history of addiction, were all below 1, which is below what is usually considered as clinically significant (Sloan et al., 2003). However, the differences in the EPOS data were shown in a population of more than 2000 patients, which make the findings interesting. In comparison, meta-analysis of more than 30,000 patients with hypertension have shown that a reduction of blood pressure of 5–6 mm Hg, i.e. not relevant on an individual level, significantly reduce the risk of stroke and coronary heart disease at a group level (Collins et al., 1990).

The most important limitation of EPOS is the cross-sectional design. In the cross-sectional sample, only possible associations between independent and dependent variables can be described. The associations shown in the present study do not explain how the variables are related, e.g. if PD causes more severe pain or vice versa, and the findings do not equals causality. New studies should be conducted with a longitudinal design in order to find which variables that predict pain complexity and variability in response to treatment.

The present study emphasises the importance of well-defined and standardised assessment and classification tools. However, complex time consuming assessments may limit the user friendliness of a classification system. This suggests the need to consider combinations of the classification system; one basic to be used as core questions in all studies and in clinical practice and one specialised for symptoms or variables to be used in clinical research.

Based upon the findings of the present study, the previous EPCRC studies, the ECS-CP as well as the consensus achieved among experts, pain intensity, treatment response, breakthrough pain and psychological distress are key variables to be included in a future classification system for cancer pain. Several other candidate variables have been identified and need further investigation.

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Appendix A. Research collaboratives

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A.2. EPCRC

The European Palliative Care Research Collaborative is funded by the European Commission's Sixth Framework Programme (Contract No. LSHC-CT-2006-037777) with the overall aim to improve treatment of pain, depression and fatigue through translation research. *Core scientific group/work package leaders:* Stein Kaasa (project coordinator), Frank Skorpen, Marianne Jensen Hjermstad, and Jon Håvard Loge, Norwegian University of Science and Technology (NTNU); Geoffrey Hanks, University of Bristol; Augusto Caraceni and Franco De Conno, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; Irene Higginson, King's College London; Florian

Strasser, Cantonal Hospital St. Gallen; Lukas Radbruch, RWTH Aachen University; Kenneth Fearon, University of Edinburgh; Hellmut Samonigg, Medical University of Graz; Ketil Bø, Trollhetta AS, Norway; Irene Rech-Weichselbraun, Bender MedSystems GmbH, Austria; Odd Erik Gundersen, Verdande Technology AS, Norway. *Scientific advisory group:* Neil Aaronson, The Netherlands Cancer Institute; Vickie Baracos and Robin Fainsinger, University of Alberta; Patrick C. Stone, St. George's University of London; Mari Lloyd-Williams, University of Liverpool. *Project management:* Stein Kaasa, Ola Dale, and Dagny F. Haugen, NTNU.

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Paper IV

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Which domains should be included in a cancer pain classification system? Analyses of longitudinal data

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ABSTRACT

The overall aim of the present study was to further develop an evidence-based platform for the content of an international cancer pain classification system. Data from a multicentre, observational longitudinal study of cancer patients were analysed. Analyses were carried out in 2 samples: (A) Cross-sectional data of patients on opioids at inclusion, and (B) patients just admitted to palliative care. Outcome measures in the models we investigated were pain on average, worst pain, and pain relief at inclusion, and at day 14, respectively. Uni- and multivariate regression models were applied to test the explicative power on pain outcomes of a series of known pain domains, including incident pain, psychological distress, neuropathic pain, pain localisation, sleep disturbances, total morphine equivalent daily dose (MEDD), and cancer diagnosis. In the 2 analyses, 1529 (A) and 352 (B) patients were included, respectively. Incident pain, pain localisation, MEDD, use of nonsteroidal antiinflammatory drugs, and sleep were associated with one or more of the pain outcomes in analysis A, while initial pain intensity, initial pain relief, incident pain, localisation of pain, cancer diagnosis, and age were predictors in the longitudinal analysis. Identified domains explained 16% to 24% of the variability of the pain outcome. Initial pain intensity emerged as the strongest predictor of pain outcome after 2 weeks, and incident pain was confirmed to be a relevant domain. The regression models explained only a minor part of the variability of pain outcomes.

1. Introduction

In order to choose the optimal treatment of a symptom such as cancer pain, knowledge of expected treatment response is fundamental. Most medical classification systems are grouping patients based upon a prediction of treatment response and/or the natural course of the disease. A diagnostic tool for cancer pain may consist of host factors (e.g., age, gender, genetics), disease factors (e.g., cancer diagnosis), pain factors (e.g., intensity), comorbidities, and susceptibility (e.g., previous psychological/somatic experiences). For optimal management of cancer pain and for comparison of research results, standardised approaches for assessment and classification are needed [5,14], but there is no international consensus on the content of a cancer pain classification system [22,33].

The Edmonton Classification System for Cancer Pain (ECS-CP) is extensively studied [33]. It includes the following domains: incident pain, neuropathic pain, psychological distress, addiction, and cognitive function [14,15,35], and has been recommended as a starting point for the development of an international system for cancer pain classification [29]. In the cross-sectional European

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Pharmacogenetic Opioid Study (EPOS) including 2278 cancer patients, incident pain, psychological distress, neuropathic pain, pain localisation, sleep disturbances, opioid dose, the use of nonsteroidal antiinflammatory drugs (NSAIDs), cancer diagnosis, localisation of metastases, and addiction were considered potential domains in a new system [32]. Pain intensity is also recognised as a key domain for prognostication and management of cancer pain [13,29] and is a predictor of time needed to achieve stable pain control in cancer patients [14].

Standardised assessment of key domains is crucial for the correct classification of cancer pain. However, assessment methods used in clinical practice and in research vary considerably [23]. Haugen et al. recently addressed this for incident pain [20]. For neuropathic pain, the International Association for the Study of Pain (IASP) recently published assessment recommendations aiming at standardisation [19]. To agree upon who is to assess which domain is also important. Patients' self report is recommended for pain intensity and other subjective pain domains [16,45], whereas clinical examination is stated to be a crucial part of the diagnostic process of neuropathic pain [19].

A system's ability to predict the course of pain should be evaluated prospectively. In 2006 the Italian Cancer Pain Outcome Research Study Group (CPOR) initiated a longitudinal observational study of cancer pain patients [3]. Aiming at deciding upon which domains to include in a first version of an international cancer pain classification system, data from the CPOR study are used to answer the following research questions:

1. Can the domains/items associated with cancer pain in the cross-sectional EPOS study [32] be confirmed in an independent patient population?
2. Can previously identified domains relevant for cancer pain classification and/or new candidate domains be identified as predictors of pain intensity and/or pain relief in a population of cancer patients followed prospectively?

2. Material and methods

2.1. Patients

During 2006 to 2007, the CPOR Study Group performed an Italian multicentre, open-label, prospective, nonrandomised observational study [2,3]. Patients with advanced cancer, persistent pain of any intensity, requiring or already on analgesic treatment, age $\geqslant$ 18 years, with a life expectancy longer than 1 month, and able to provide informed consent to participate, were included. Patients with impaired cognitive function or substance abuse were excluded. Two samples from these data were used for the present study:

- Sample A: cross-sectional data from patients using opioids at the day of inclusion.
- Sample B: longitudinal data from patients newly referred to palliative care.

2.2. Assessment

After inclusion, the patients were examined weekly for 4 weeks as well as at week 12. Only data from inclusion and day 14 were analysed in the present study. At each visit a health care provider registered: medical history including cancer history, physical examination data, medications and recent therapies including analgesic consumption, and functional status assessed by the Karnofsky Performance Status (KPS) [30]. Furthermore, a health care provider completed the ECS-CP (version rESS from 2005) [15] assessing pain mechanism, incident pain, psychological distress and/or addictive behaviour, and cognitive function.

The patients completed a questionnaire assessing pain, other symptoms, and common side effects of opioids at each visit. Pain was measured using 5 questions from the Italian version of the Brief Pain Inventory [7,10], assessing intensity of worst, actual, least, and average pain, and pain relief, all referring to the previous week (11-point numerical rating scales [NRS-11]). Symptoms and side effects of medications were evaluated using a list of 23 items from the Therapy Impact Questionnaire, a quality-of-life questionnaire developed for advanced cancer patients [46]. Each item was rated on a 4-point verbal rating scale from 1 = absent to 4 = very much. The previous week was used as time frame for all questions.

2.3. Analysis design – part A

Part A of the present study was a cross-sectional analysis aiming at verifying the findings from the EPOS [32] in an independent population of advanced cancer patients included in the CPOR study

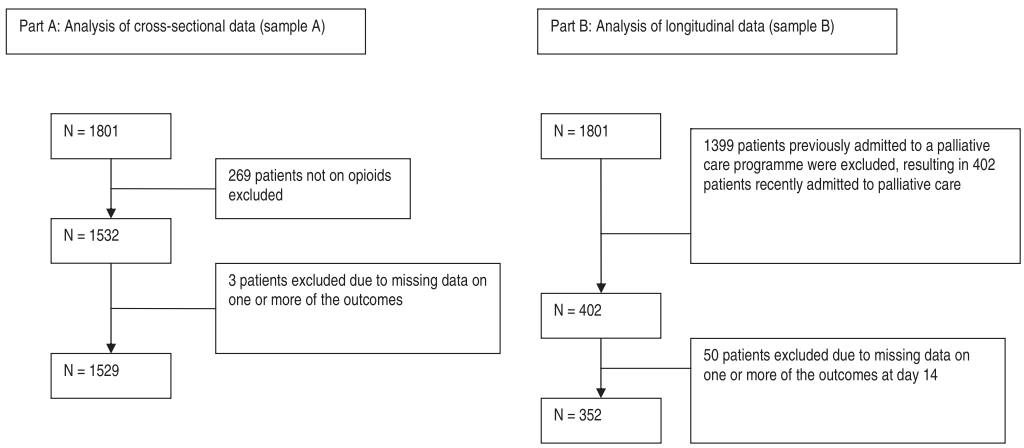

Fig. 1. Flow chart presenting the analysis plan.

[2,3]. Only patients on opioid treatment were considered in order to replicate the design of EPOS. The following domains/items were included as independent variables: incident pain, psychological distress, neuropathic pain, pain localisation (back, upper and lower extremities), sleep disturbances, total morphine equivalent daily dose (MEDD), use of NSAIDs, addiction, cancer diagnosis (prostate cancer), and localisation of metastases (liver), as these were the results from EPOS [32]. The following domains/items were added: 3 other prevalent cancer diagnoses (breast, lung, and gastrointestinal cancer), bone metastases as this most often causes pain, and further localisations of pain.

The choice of outcomes was based upon the results from an expert survey [32] and from other previous studies and included pain intensity assessed as "pain on average" (NRS-11) and "pain at its worst" (NRS-11) as well as "pain relief" (0% = no relief to 100% = complete relief), all referring to the previous week. Pain intensity is regarded as a key domain for pain classification and for clinical decision-making [13]. Assessment of pain relief might reflect further information about the pain and the patient's experience [28] and was therefore added as a third outcome to strengthen the analysis. Multivariate linear regression analysis adjusted by centre was carried out. Backward elimination was chosen for selecting domains/items, as a lack of high correlations between independent and dependent domains/items is one of the assumptions under which this is considered a good method [43]. A *P*-value = 0.01 was applied for removing domains/items.

Table 1
Patient characteristics.

Patient characteristics	Assessments at study entry	
	Sample A Cross-sectional analysis *n* = 1529	Sample B Longitudinal analysis *n* = 352
Age: mean (range)/SD	63.8 (22-92)/12.2	64.8 (26-88)/ 11.9
Gender: *n* (%)		
Male	808 (52.8)	216 (61.4)
Female	721 (47.2)	136 (38.6)
Karnofsky performance status: mean (range)/SD	64.5 (20–100)/ 16.3	62.8 (20–100)/ 17.1
Time since diagnosis:[a] mean (range)/SD	33.6 (0–42.6)/ 47.2 *n* = 1517	23.7 (0–30.6)/ 34.2 *n* = 350
Cancer diagnosis:[b] *n* (%)		
Gastrointestinal	430 (28.1)	95 (27.1)
Lung	342 (22.4)	97 (27.6)
Breast	254 (16.6)	32 (9.1)
Prostate	119 (7.8)	22 (6.3)
Gyneacological	83 (5.4)	13 (3.7)
Urological	93 (6.1)	31 (8.8)
Head and neck	84 (5.5)	28 (8.0)
Unknown origin	21 (1.4)	6 (1.7)
Sarcoma	9 (0.6)	2 (0.6)
Skin	14 (0.9)	3 (0.9)
Other	79 (5.2)	22 (6.3)
Location of metastases:[c] *n* (%)		
Bone	728 (47.6)	157 (44.6)
Liver	423 (27.7)	79 (22.4)
Lung	431 (28.2)	85 (24.2)
CNS	80 (5.2)	19 (5.4)
Abdominal	240 (15.7)	43 (12.2)
Lymph node	635 (41.5)	135 (38.4)
Other	271 (17.7)	57 (16.2)
None	103 (6.7)	37 (10.5)
Type of recruiting centre		
Oncology centre	911 (59.6)	95 (27)
Palliative care centre	605 (39.6)	256 (72.7)

[a] Months.
[b] For sample A cancer diagnosis is not recorded in 1 patient.
[c] Patients may have more than one site of metastases.

2.4. Analysis design – part B

Part B of the present study aimed at identifying predictors of pain intensity and/or pain relief 2 weeks after initial assessment. Both previously identified and new candidate domains/items were explored in a population of patients admitted to palliative care within 4 days before inclusion in the CPOR study.

Pain on average (NRS-11), pain at its worst (NRS-11), and pain relief (0% = no relief to 100% = complete relief), all at day 14, were defined as outcomes. Titration of opioids is expected to be finalised within 2 weeks and new major symptoms might not occur [31,47].

Table 2
Characteristics of pain, pain treatment, and other symptoms.

Domains/items	Assessments at study entry	
	Sample A Cross-sectional analysis *n* = 1529	Sample B Longitudinal analysis *n* = 352
Pain intensity on the average:[a] mean (range)/SD	4.4 (0–10)/2.0	5.0 (0–9)/1.9
Pain intensity at its worst:[a] mean (range)/SD	6.8 (0–10)/2.3	7.5 (0–10)/2.0
Pain relief:[b] mean (range)/SD	57.5 (0–100)/25.4	43.0 (0–100)/ 26.6
Incident pain: [c] n (%)		
Present	803 (52.5)	201 (57.1)
Absent	726 (47.5)	151 (42.9)
Pain mechanism:[c] n (%)		
Neuropathic pain	388 (25.9)	86 (24.7)
Nociceptive pain	1108 (74.1)	262 (75.3)
Localisation of pain:[d] *n* (%)		
Back	492 (32.2)	109 (31.0)
Pelvis	82 (5.4)	21 (6.0)
Thorax front/abdomen	785 (51.5)	171 (48.6)
Lower extremities	236 (15.5)	55 (15.6)
Upper extremities	143 (9.4)	36 (10.2)
Head	107 (7.0)	29 (8.2)
Psychological distress present:[c] *n* (%)	550 (36.0)	131 (40.2)
Cognitive function limited:[c] *n* (%)	72 (4.7)	16 (4.6)
Addictive behaviour present:[c] *n* (%)	14 (0.9)	5 (1.4)
Sleep disturbances present:[e] *n* (%)	308 (20.2)	110 (31.4)
Pharmacological pain treatment: *n* (%)		
Patients on opioids	1529 (100)	271 (77)
MEDD: mg (range)/SD	86.7 (1.5–1050)/ 94.5	66.1 (0–1050)/ 110.7
Systemic corticosteroids	661 (43.2)	124 (35.2)
NSAIDs	592 (38.7)	156 (44.3)
Anticonvulsants	257 (16.8)	38 (10.8)
Antidepressants	183 (12.0)	27 (7.7)
Anticancer treatment: n (%)		
Ongoing radiotherapy	100 (6.5)	31 (8.8)
Ongoing chemotherapy	754 (49.3)	112 (31.8)
Ongoing hormone therapy	157 (10.3)	16 (4.6)
Other subjective symptoms:[e] *n* (%)		
Nausea	161 (10.5)	29 (8.2)
Vomiting	91 (6.0)	11 (3,1)
Constipation	439 (28.5)	84 (24.1)
Somnolence	295 (19.3)	65 (18.5)
Vertigo	53 (3.5)	19 (5.4)
Difficulties swallowing	138 (9.0)	34 (15.0)
Sweating	233 (15.2)	40 (11.4)

MEDD, total oral morphine equivalent daily dose; NSAIDs, nonsteroidal antiinflammatory drugs.
[a] Brief Pain Inventory: 11-point numerical rating scale (NRS).
[b] NRS-11 0–100%: 0% = no relief, 100% = complete relief.
[c] Edmonton Classification System for Cancer Pain (ECS-CP).
[d] Patients may have more than one localisation of pain.
[e] Therapy Impact Questionnaire (TIQ): assessment on a 4-point verbal rating scale (VRS) from 1 = absent to 4 = very much. Results refer to patients who score 3 or 4 on the VRS-4.

The choice of which domains and items to include as candidate predictors was based upon findings from previous studies and proposed classification systems [15,23,24,29,32,33]. A bivariate correlation analysis (Pearson correlation coefficient $\geqslant 0.1$) was used to decide upon which domains to enter into multivariate linear regression models. Fractional polynomials [42] were applied to investigate possible nonlinear functional relationships for continuous domains/items in the models; the combination of linear and nonlinear domains/items was tested through backward elimination. A *P*-value = 0.05 was applied for removing domains/items, which is different from the *P*-value used in the cross-sectional analysis. Reasons for this were the smaller sample size and the explorative aim of the study. For both parts A and B, standardised regression coefficients from the final regression models were presented with 95% confidence intervals, and adjusted R^2 was used as indicator of the amount of variance in the outcome explained by the included domains/items.

2.5. Ethics

The study complied with Italian requirements for observational studies. The protocol was approved by each Local Research Ethics Committee of participating centres. All patients gave written informed consent to participate in the study.

3. Results

There were 1801 patients from 110 Italian centres included in the CPOR. The samples for the cross-sectional and the longitudinal analyses included 1529 patients on opioids, and 352 patients newly admitted to palliative care, respectively. Flow charts explaining eligibility criteria are shown in Fig. 1. Patients' characteristics are shown in Table 1 and characteristics of pain and other symptoms are shown in Table 2. In both samples the most common cancer diagnoses were gastrointestinal, lung, and breast cancer.

3.1. Sample A

Among the 1529 patients on opioids included in the cross-sectional analysis, 53% were male and 47% female, their mean age was 64 years, and mean KPS was 64.5. Forty-eight percent had bone metastases (Table 1). Pain intensity measured on average was 4.4, pain at its worst was 6.8, and pain relief was 57.5%. Fifty-two percent of the patients had incident pain, and 26% had neuropathic pain. The average oral MEDD was 87 mg. Sixty percent were treated in an oncology department and 40% in a palliative care centre. About 2/3 received tumour-directed treatment (Table 2).

3.1.1. Part A – Cross-sectional analyses

Table 3 shows the results from the cross-sectional multivariate analyses. The domains incident pain, pain localisation (upper extremities and head), MEDD, the use of NSAIDs, and sleep disturbances were statistically significantly associated with one or more of the outcomes. If incident pain was present, pain intensity on average would increase with 0.64 (beta) on an NRS-11, and pain at its worst would increase with 0.87 compared with patients without incident pain. The standardised betas allow for comparison of the impact of the included domains/items on the outcomes regardless of scales used. Incident pain and sleep showed the highest standardised betas (0.16/0.20 and 0.16/0.14/-0.15, respectively), which indicates the highest relevance among the examined domains. The explained variance for the regression models (adjusted R^2) varied from 0.21 to 0.26.

3.2. Sample B

Among the 352 patients on their first visit to palliative care included in the longitudinal analyses, 61% were male and 39% female, the mean age was 65 years, mean KPS was 62.8, and 45% had bone metastases (Table 1). Table 2 shows that pain intensity measured on average was 5.0, worst pain was 7.5, and pain relief 43%. Fifty-seven percent of these patients had incident pain, and 25% had neuropathic pain. The average MEDD was 66 mg. The percentage of patients on opioids at inclusion was 77% and at day 14 it was 94%. In 300 patients (85.2%), a change in the pharmacological treatment was recorded during the first 2 weeks. At day 14 the pain scores were as follows: average pain 3.5, worst pain 5.3, and pain relief 63%. The majority were treated in a palliative care centre (73%). About 45% received tumour-directed treatment.

3.2.1. Part B – Longitudinal analyses – step 1

In the bivariate analysis (Table 4), the domains initial pain intensity, initial pain relief, incident pain, neuropathic pain, pain localisation (thorax/abdomen), sleep disturbances, and ongoing radiotherapy showed a correlation $\geqslant 0.1$ with all 3 outcomes. Lung cancer, abdominal metastases, constipation, and sweating showed a significant correlation with 2 of the outcomes. The following 9

Table 3
Results from cross-sectional analyses (part A).

Domains	Outcomes								
	Pain on average last week NRS-11 (BPI) *n* = 1520			Pain at its worst last week NRS-11 (BPI) *n* = 1480			Pain relief last week NRS-11 (BPI) *n* = 1480		
	Beta [a]	CI	Stand. beta	Beta	CI	Stand. beta	Beta	CI	Stand. beta
Const.	1.73***	1.04–2.41	–	5.39***	4.38–6.41	–	58.1***	48.0–68.2	–
Incident pain	0.64***	0.44–0.84	0.16***	0.87***	0.63–1.11	0.20***	–	–	–
Sleep	0.39***	0.28–0.50	0.16***	0.38***	0.24–0.51	0.14***	−4.7***	−6.2–−3.2	−0.15***
Pain localisation:									
Upper extremities	0.53**	0.21–0.84	0.08**	–	–	–			
Head	–	–	–	–	–	–	−6.1**	−10.6–−1.5	−0.06**
MEDD at inclusion (mg)	–	–	–	0.17**	0.07–0.27	0.08**	–	–	–
Use of NSAIDs	–	–	–	0.36**	0.12–0.60	0.08**	–	–	–
Adjusted R^2	0.26		0.21	0.22					

NRS-11, 11-point numerical rating scale; BPI, Brief Pain Inventory; CI, 95% confidence interval; Stand. beta, Standardised beta (ranging from −1 to +1); MEDD, total morphine equivalent daily dose; NSAIDs, nonsteroidal antiinflammatory drugs.
Table 3 shows the results from the multivariate linear regression analysis of the cross-sectional Cancer Pain Outcome Research Study Group data on advanced cancer patients on opioids, *n* = 1529. It was adjusted by study centre. The *P*-value used for removing domains in the backward procedure was 0.01. R^2 is the variance explained by the domains included in each of the models.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
[a] Regression coefficient.

Table 4
Results from bivariate analysis of longitudinal data (part B).

Outcomes	Pain on average [a] at day 14 $n = 352$	Pain at its worst [a] at day 14 $n = 352$	Pain relief [b] at day 14 $n = 352$
Pain scores at day 14: Mean (range)/SD	3.5 (0–9)/1.9	5.3 (0–10)/2.2	63 (0–100)/24.3
Candidate domains/items			
Pain intensity on average [a] at inclusion	**0.45** [c]	**0.36**	**−0.32**
Pain intensity at its worst [a] at inclusion	**0.26**	**0.33**	**−0.22**
Pain relief at inclusion [b]	**−0.22**	**−0.16**	**0.36**
Incident pain	**0.19**	**0.16**	**−0.15**
Neuropathic pain	**0.18**	**0.12**	**−0.18**
Localisation of pain			
Head	0.07	0.07	−0.07
Thorax/abdomen	**−0.15**	**−0.17**	**0.20**
Pelvic	0.006	−0.04	0.02
Back	0.06	0.08	−0.09
Upper extremities	0.08	0.04	−0.05
Lower extremities	0.07	0.09	−0.05
Age	−0.06	−0.12	0.09
Gender	−0.06	−0.02	0.07
Karnofsky performance status	0.03	−0.0006	−0.03
Physical functioning [d]	−0.03	0.009	−0.03
Psychological distress	0.07	**0.11**	−0.03
Cognitive functioning	0.02	−0.03	−0.02
Addictive behaviour	0.03	−0.008	0.01
Sleep disturbances	**0.15**	**0.14**	**−0.12**
Time since diagnosis	−0.08	**−0.12**	0.07
Cancer diagnosis			
Gastrointestinal	**−0.11**	−0.09	0.06
Lung	0.11	**0.11**	−0.10
Breast	−0.03	−0.02	0.02
Prostate	0.004	−0.03	−0.01
Metastases			
Bone	0.07	0.06	−0.04
Liver	−0.07	0.001	−0.02
Lung	0.05	0.06	−0.03
CNS	−0.006	−0.02	−0.08
Abdominal	**−0.11**	**−0.12**	0.06
Lymph nodes	0.03	0.04	−0.09
Treatment			
MEDD	0.09	**0.10**	−0.03
Steroids	−0.07	−0.05	0.08
NSAIDs	0.05	0.05	−0.07
Anticonvulsants	0.09	0.08	**−0.11**
Antidepressants	0.02	0.04	0.01
Ongoing chemotherapy	−0.02	−0.004	−0.09
Ongoing radiotherapy	**0.13**	**0.10**	**−0.11**
Ongoing hormone therapy	−0.01	−0.4	0.009
Other symptoms (TIQ) [e]			
Nausea	0.03	**0.11**	−0.06
Vomiting	0.03	0.09	−0.05
Constipation	0.08	**0.12**	**−0.04**
Somnolence	0.06	0.07	0.02
Vertigo	0.07	0.09	**−0.10**
Difficulties swallowing	**0.11**	0.09	−0.09
Sweating	**0.11**	**0.11**	−0.08

CNS, central nervous system; MEDD, total morphine equivalent daily dose; NSAIDs, nonsteroidal antiinflammatory drugs.
Table 4 shows the results from the bivariate correlation analysis of the longitudinal Cancer Pain Outcome Research Study Group data on advanced cancer patients just admitted to palliative care; $n = 352$. The Pearson coefficient > 0.1 was used to decide upon which domains to enter into multivariate linear regression models.
[a] From Brief Pain Inventory, assessed on an 11-point numerical rating scale (NRS-11).
[b] From Brief Pain Inventory, assessed on an NRS-11: 0% no relief, 100% complete relief.
[c] Pearson correlation coefficient (r).
[d] Assessed as total score of basic activities of daily living (B-ADL).
[e] Therapy Impact Questionnaire, assessment on a 4-point verbal rating scale (VRS) from 1 = absent to 4 = very much.

domains/items showed significant correlation with only one of the 3 outcomes: psychological distress, MEDD, use of anticonvulsants, age, time since cancer diagnosis, gastrointestinal cancer, nausea, vertigo, and difficulties swallowing. In total, 21 domains/items showed a correlation $\geqslant 0.1$ with one or more of the outcomes. The correlation between initial pain intensity measured as "pain on average" and as "pain at its worst" was 0.72. To avoid multicollinearity, only "pain on average" was used, thus 20 domains/items were included for further investigation.

3.2.2. Part B – Longitudinal analyses – step 2

Table 5 shows the results from the multivariate regression analysis of the longitudinal CPOR data. Six domains were shown to be predictors in one or more of the final regression models: initial pain intensity (on average), initial pain relief, incident pain, localisation of pain (thorax/abdomen), cancer diagnosis (lung cancer), and age (younger). If incident pain was present, pain intensity on average at day 14 would increase with 0.44 (beta) on an NRS-11 compared with patients without incident pain, and patients with

Table 5
Results from multivariate analysis of longitudinal data CPOR (part B).

Domains	Outcomes								
	Pain on average last week NRS-11 (BPI) $n = 348$			Pain at its worst last week NRS-11 (BPI) $n = 351$			Pain relief last week NRS-11 (BPI) $n = 348$		
	Beta [a]	CI	Stand. beta	Beta	CI	Stand. beta	Beta	CI	Stand. beta
Const.	0.81	0.28–1.34	–	4.53	3.19–5.87	–	62.1	50.1–73.2	–
Initial pain intensity [b]	0.44***	0.35–0.54	0.45***	0.44***	0.33–0.55	0.38***	−2.1*	−3.5 to −6.1	−0.16**
Initial pain relief [c]	–	–	–	–	–	–	2.4***	1.4–3.4	0.26***
Incident pain	0.44*	0.08–0.80	0.14**	–	–	–	–	–	–
Localisation of pain: thorax/abdomen	–	–	–	–	–	–	7.2**	2.4–11.9	0.15**
Cancer diagnosis: lung cancer	0.59**	0.20–0.99	0.14**	0.61*	0.13–1.09	0.12*	−7.5**	−12.7 to −2.3	−0.14**
Age	–	–	–	−0.02**	−0.04 to −0.01	−0.13**	–	–	–
Adjusted R^2	0.24			0.16			0.18		

CPOR, Cancer Pain Outcome Research Study Group; NRS-11 = 11-point numerical rating scale; BPI, Brief Pain Inventory; CI, 95% confidence interval; Stand. beta, Standardised beta (ranging from −1 to +1).
Table 5 shows the results from the multivariate linear regression analysis of the longitudinal CPOR data on advanced cancer patients recently admitted to palliative care; $n = 352$. The P-value used or removing domains in the backward procedure was 0.05. No adjustment was performed. R^2 is the variance explained by the domains included in each of the models.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
[a] Regression coefficient.
[b] 11-point NRS.
[c] NRS-11: 0% = no relief, 100% = complete relief.

lung cancer scored pain intensity on average 0.59 (NRS-11) higher than patients without lung cancer. A 1-year increase in age resulted in a reduction of pain intensity (pain at its worst) of 0.02 on an NRS-11, that is, younger age implied higher pain scores. The standardised betas for the longitudinal regression models showed the domains' impact on the outcomes in the following order: initial pain intensity, initial pain relief, pain localisation, cancer diagnosis (lung), incident pain, and age. The explained variance for the regression models (adjusted R^2) varied from 0.16 to 0.24. No evidence of nonlinearity was identified.

4. Discussion

The present study aimed at contributing to the development of an international cancer pain classification system. In the cross-sectional analysis, 5 domains (incident pain, pain localisation, sleep disturbances, initial MEDD, and the use of NSAIDs) were associated with pain in a large population of Italian advanced cancer patients on opioids. Incident pain, sleep disturbances, and pain localisation were associated with 2 or 3 of the outcomes and showed the highest standardised betas. In the longitudinal analysis, 6 domains were identified as predictors of pain intensity and/or pain relief at day 14. Initial pain intensity was the most important domain, contributing significantly to all 3 final models and showing the highest standardised betas. The other domains were initial pain relief, incident pain, pain localisation, cancer diagnosis (lung), and younger age. For all pain outcomes, the identified predictors explained only a minor part of the variability.

Fainsinger et al. [14] recently published an international multicentre study showing that initial pain intensity, psychological distress, incident pain, neuropathic pain, and younger age were associated with longer time to achieve stable pain control. The importance of 3 of these domains was confirmed in the longitudinal part of the present study. Pain intensity has a key role in the management of cancer pain guiding clinical decision-making [12,13]. More severe pain mainly indicates that the patient is undertreated and/or that the pain condition is difficult to treat. Incident pain is a common and problematic domain in cancer patients that also has been shown to predict more complex pain [6,34,40]. To be aware that a patient at younger age may have a more complex pain condition than older patients is of clinical relevance; this may be due to differences in physiology [11] or more difficulties in coping with pain [18].

Initial pain relief was identified as a predictor of improved pain relief after 2 weeks. This domain may contain more information than pure pain, for example, coping ability, and may therefore add relevant information for diagnosing a complex pain condition. Pain localisation was also among the results in both the cross-sectional and the longitudinal analyses of the present study and in the EPOS study [32], however, the sites varied. The repeated finding of the relevance of pain localisation suggests that its assessment, for example, by a body map, should be a part of a cancer pain classification system. Lung cancer was identified as a negative predictor in all 3 longitudinal regression models of CPOR, indicating that different cancer diagnoses may cause different pain features. The ability to associate different pain conditions to different tumour lesions may improve clinical pain diagnosis [4,17]. Poor sleep was associated with all 3 outcomes in the cross-sectional analysis, confirming that sleep disturbances may indicate a poorly controlled pain situation [32] or that poor sleep itself may cause more pain [44]. A higher prevalence of trouble sleeping in cancer patients than in the general population has been reported [37]. This underlines the relevance of assessing sleep disturbances as one aspect of interference in cancer pain patients. Cognitive function and addictive behaviour are 2 of the 5 domains included in the ECS-CP, but because these were related to the exclusion criteria in the CPOR study, further investigation of these domains was not possible.

Unexpectedly, neither neuropathic pain nor psychological distress predicted pain outcomes in this study. Neuropathic pain is considered to be a problematic pain situation needing specific therapeutic strategies [8,19]. For the assessment of neuropathic pain, the previous version of the ECS-CP (rESS) [15] was used, asking the health care provider to state if neuropathic pain was present or not. IASP recently published revised guidelines on neuropathic pain assessment [19] recommending the combination of neuropathic pain screening tools, clinical interview, and clinical examination including sensory examination. To follow the IASP recommendations may have given other results regarding neuropathic pain. Several previous studies have shown a significant association between cancer pain and psychological distress [36,48], and in the last validation study of the ECS-CP, psychological distress was associated with longer time to achieve pain control [14]. Differences in assessment may be one explanation for not

confirming this in the CPOR population. Psychological distress was measured by a health care provider by recording if psychological distress was present or not using the 2005 version of the ECS-CP [15]. However, the researchers in the ECS-CP validation study were systematically trained in the use of the ECS-CP, a training not given in the CPOR study.

Instead of educating the clinicians in measurement of subjective symptoms, the patients can be asked directly. The use of patients' self-report of subjective symptoms may be more reliable and has been recommended as the gold standard [16]. In the EPOS study [32], psychological distress was measured by using the emotional functioning scale of the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire [1], that is, patients' self-report, and was one of the identified key domains. The assessment of incident pain also varies considerably [20]. In CPOR it was evaluated as a dichotomised yes/no-question focusing on pain with a known trigger, as in a previous version of the ECS-CP; the rESS [15]. Even with such a narrow definition and assessment performed by a health care provider, it was shown to be a robust domain for the classification and prognostication of difficult pain conditions.

An important strength of the present study is the longitudinal design of CPOR. Instead of only describing possible associations in cross-sectional data, the longitudinal design allows for analysis of whether domains can predict pain outcomes after a period of time, that is, prognostication, which is the actual purpose of a cancer pain classification system. There are important limitations of the present study. CPOR was initially designed for another purpose, and cancer patients in Italy use less opioids than in many other European countries [9]. There were considerable between-centre differences with regard to pain scores and treatments offered, which may be explained by the fact that more than 100 centres participated in the study. The CPOR patients had higher pain scores and used considerably lower daily oral morphine equivalent doses as compared with the EPOS population. Despite the heterogeneity, 5 of 10 domains from EPOS were confirmed to be of importance in the cross-sectional CPOR population, and 2 of these were also among the longitudinal results, indicating their robustness. Different outcomes are used across cancer pain studies, for example, time to achieve pain control, final opioid dose, number of other modalities to achieve stable pain control [14], pain relief [25], and pain intensity [39], which may be an important reason for differences in domains demonstrating relevance. A recent expert conference recommended the use of pain intensity, pain relief, and temporal pattern of pain as outcomes in clinical practice and research [29].

Our models explained 16% to 26% of the variability of the pain outcomes. This may be explained either by the lack of accurate assessment or by the incomplete relevance of the clinical domains included. The use of crude assessment methods of fluctuating and complex domains in patients with advanced disease is common, for example, incident pain, neuropathic pain, and psychological distress were measured dichotomously. By applying a continuous measure such as a NRS-11, it might have been possible to explain more of the variability. Furthermore, the low explained variance indicates that aspects other than the investigated ones, such as genetic variability or variability in pain perception and susceptibility, may influence cancer pain. Other pain studies have reported similar (14%–35%) [21], but also higher explained variance: 39% to 48%, and 67%, respectively [27,41].

Current knowledge does not result in a diagnostic tool that can be used to precisely predict future outcomes in cancer pain, but points towards some domains that increase the risk for the patients to experience more severe cancer pain in the future. At present, 4 domains are considered core domains of a cancer pain classification system: pain intensity, pain mechanism, incident pain, and psychological distress [29]. The results from the present study suggest that the following further domains may be considered for inclusion in a cancer pain classification system: pain relief, pain localisation, initial MEDD, use of adjuvants, sleep disturbances, age, and cancer diagnosis. One example of clinical utility of such knowledge is: a young patient having severe pain, incident pain, and lung cancer is challenging to treat, and special attention should be given to pain treatment and treatment response. A classification or prognostic system must be considered dynamic. Analogue to the development of the TNM (tumor-nodes-metastasis) system [26,38], new domains should be added when new evidence identifies domains that improve the predictive ability of the cancer pain classification system [29]. Prospective international studies designed for the purpose of pain classification in a well-defined population of cancer patients with standardised assessment and relevant outcomes would be necessary further steps towards achieving consensus on an international cancer pain classification system.

Conflict of interest statement

G. Apolone received consultancy and lecture fees from Grunenthal and Cephalon Italy. O. Corli received consultancy fees from Grunenthal and ProStrakan Italy.

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Appendix A. European Palliative Care Research Collaborative (EPCRC)

The European Palliative Care Research Collaborative was funded by the European Commission's Sixth Framework Programme (contract no LSHC-CT-2006-037777) with the overall aim to improve treatment of pain, depression, and fatigue through translation research. *Core scientific group/work package leaders:* Stein Kaasa (project coordinator), Frank Skorpen, Marianne Jensen Hjermstad, and Jon Håvard Loge, Norwegian University of Science and Technology (NTNU); Geoffrey Hanks, University of Bristol; Augusto Caraceni and Franco De Conno, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; Irene Higginson, King's College London; Florian Strasser, Cantonal Hospital St. Gallen; Lukas Radbruch, RWTH Aachen University; Kenneth Fearon, University of Edinburgh; Hellmut Samonigg, Medical University of Graz; Ketil Bø, Trollhetta AS, Norway; Irene Rech-Weichselbraun, Bender MedSystems GmbH, Austria; Odd Erik Gundersen, Verdande Technology AS, Norway. *Scientific advisory group:* Neil Aaronson, The Netherlands Cancer Institute; Vickie Baracos and Robin Fainsinger, University of Alberta; Patrick C. Stone, St. George's University of London; Mari Lloyd-Williams, University of Liverpool. *Project management:* Stein Kaasa, Ola Dale, and Dagny F. Haugen, NTNU.

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Appendix

Appendix

Contents

Search string used for paper I

Ovid MEDLINE 15 February 2007

#	Search History
1	(classif$ adj5 pain).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2	(Cut point$ adj5 pain).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3	(Staging adj5 pain).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4	(Categor$ adj5 pain).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
5	(pain adj5 character$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
6	(grad$ adj5 pain).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7	(1 or 2 or 3 or 4 or 5 or 6) and (cancer.mp. or exp Neoplasms/) Limit to Humans

ESAS (Edmonton Symptom Assessment Scale)

Hvordan har du det i dag?

Smerte - i ro

Ingen 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Smerte - ved bevegelse

Ingen 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Slapphet

Ingen 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Kvalme

Ingen 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Tungpust

Ingen 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Munntørrhet

Ingen 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Matlyst

Meget bra 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Angst/uro

Ingen 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Trist / deprimert

Ingen 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

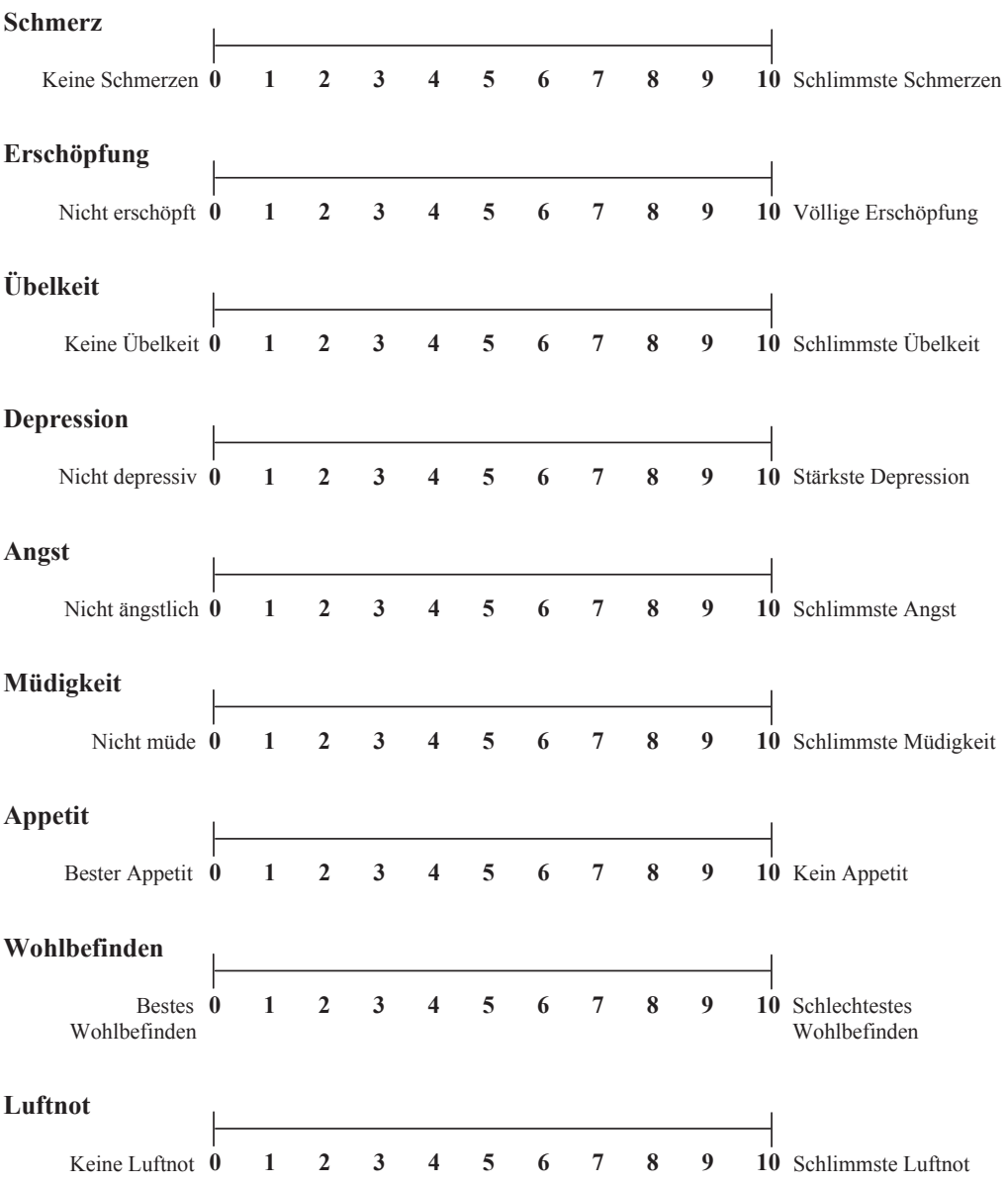
Alt tatt i betraktning, hvordan har du det i dag?

Meget bra 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

ESAS

Edmonton Symptom Erfassung: Numerische Skala

Bitte kreisen Sie die Zahl ein, die Ihre jetzige Sitaution am besten beschreibt:



Brief Pain Inventory

New version

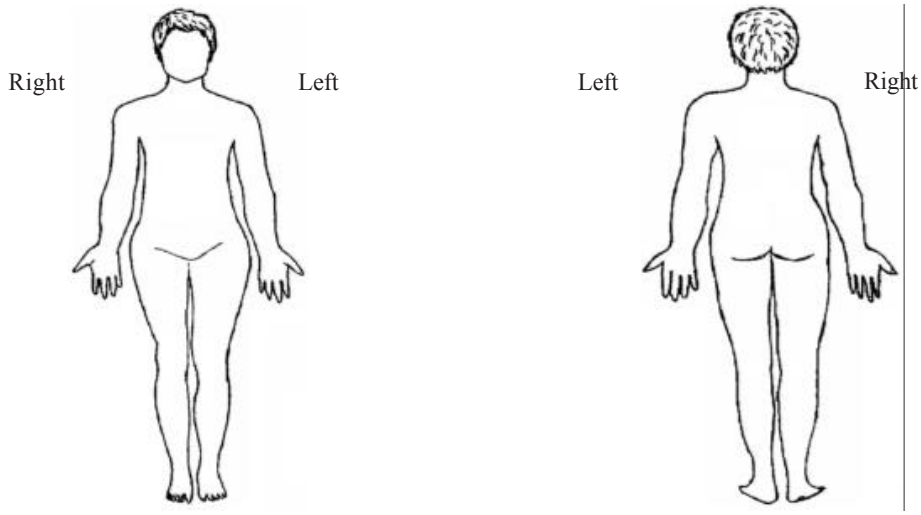
EAPC ONLUS

Projectno.: OPI 03-006

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10

No pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10

No pain — Pain as bad as you can imagine

CRF no: ☐☐☐☐

Please go to the next page

7. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have recieved.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

No Relief **Complete Relief**

Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

8. General Activity

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere Completely Interferes

9. Mood

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere Completely Interferes

10. Walking Ability

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere Completely Interferes

11. Normal work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere Completely Interferes

12. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere Completely Interferes

13. Sleep

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere Completely Interferes

14. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere Completely Interferes

NTNU DMF, IKM

EORTC QLQ-C30
(version 3)
p. 1 of 2

EAPC ONLUS

Projectno.:
OPI 03-006

We are interested in some things about you and your health. Please answer all of these questions yourself by ticking the alternative that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at all	A little	Quite a bit	Very much
1. Do tou have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	☐	☐	☐	☐
2. Do you have any trouble taking a long walk?	☐	☐	☐	☐
3. Do you have any trouble taking a short walk outside of the house?	☐	☐	☐	☐
4. Do you need to stay in bed or a chair during the day?	☐	☐	☐	☐
5. Do you need help with eating, dressing, washing yourself or using the toilet?	☐	☐	☐	☐

During the past week:	Not at all	A little	Quite a bit	Very much
6. Were you limited in doing either your work or other daily activities?	☐	☐	☐	☐
7. Were you limited in pursuing your hobbies or other leisure time activities?	☐	☐	☐	☐
8. Were you short of breath?	☐	☐	☐	☐
9. Have you had pain?	☐	☐	☐	☐
10. Did you need to rest?	☐	☐	☐	☐
11. Have you had trouble sleeping?	☐	☐	☐	☐
12. Have you felt weak?	☐	☐	☐	☐
13. Have you lacked appetite?	☐	☐	☐	☐
14. Have you felt nauseated?	☐	☐	☐	☐

CRF nr: ☐☐☐☐

Please go to the next page

During the past week:

	Not at all	A little	Quite a bit	Very much
15. Have you vomited?	☐	☐	☐	☐
16. Have you been constipated?	☐	☐	☐	☐
17. Have you had diarrhea?	☐	☐	☐	☐
18. Were you tired?	☐	☐	☐	☐
19. Did pain interfere with your daily activities?	☐	☐	☐	☐
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching TV?	☐	☐	☐	☐
21. Did you feel tense?	☐	☐	☐	☐
22. Did you worry?	☐	☐	☐	☐
23. Did you feel irritable?	☐	☐	☐	☐
24. Did you feel depressed?	☐	☐	☐	☐
25. Have you had difficulty remembering things?	☐	☐	☐	☐
26. Has your physical condition or medical treatment interferred with your family life?	☐	☐	☐	☐
27. Has your physical condition or medical treatment interferred with your social activities?	☐	☐	☐	☐
28. Has your physical condition or medical treatment caused you financial difficulties?	☐	☐	☐	☐

For the following question please tick the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

☐ **1** ☐ **2** ☐ **3** ☐ **4** ☐ **5** ☐ **6** ☐ **7**

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

☐ **1** ☐ **2** ☐ **3** ☐ **4** ☐ **5** ☐ **6** ☐ **7**

Very poor Excellent

CRF nr: ☐☐☐☐

8476

QUESTIONARIO PER IL PAZIENTE

Da compilare nel giorno di ingresso nello studio

Data |__|__||__|__||__|__|__|__|
giorno mese anno

Numero di Codice |__|__|__| / |__|__| __|

Nome _____

Cognome _____

1) Nel corso della nostra vita, la maggior parte di noi ha avuto di tanto in tanto qualche dolore (come un leggero mal di testa, uno strappo muscolare, mal di denti). Nell'ultima settimana, ha avuto un dolore diverso da questi dolori di tutti i giorni?

NO SI

2) Valuti il suo dolore facendo un cerchio intorno al numero che meglio descrive l'intensità del suo dolore PEGGIORE nell'ultima settimana

0	1	2	3	4	5	6	7	8	9	10
nessun dolore										il dolore più forte che possa immaginare

3) Valuti il suo dolore facendo un cerchio intorno al numero che meglio descrive l'intensità del suo dolore PIÙ LIEVE nell'ultima settimana

0	1	2	3	4	5	6	7	8	9	10
nessun dolore										il dolore più forte che possa immaginare

4) Valuti il suo dolore facendo un cerchio intorno al numero che meglio descrive l'intensità del suo dolore IN MEDIA nell'ultima settimana

0	1	2	3	4	5	6	7	8	9	10
nessun dolore										il dolore più forte che possa immaginare

5) Valuti il suo dolore facendo un cerchio intorno al numero che meglio descrive quanto dolore ha in questo momento

0	1	2	3	4	5	6	7	8	9	10
nessun dolore										il dolore più forte che possa immaginare

6) Nell'ultima settimana, quanto sollievo ha avuto dalle terapie o medicine? Faccia un cerchio intorno alla PERCENTUALE che meglio descrive quanto sollievo del dolore ha avuto

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

7) Nell'ultima settimana, ha sofferto di qualche SINTOMO tra quelli di seguito elencati?
Se SI, quanto?

	No	Un po'	Molto	Moltissimo
MAL DI TESTA ……...	☐	☐	☐	☐
INSONNIA ……...	☐	☐	☐	☐
PROBLEMI NEL DORMIRE ……	☐	☐	☐	☐
SONNOLENZA ……..	☐	☐	☐	☐
VERTIGINI ……...	☐	☐	☐	☐
TREMORI ……	☐	☐	☐	☐
CONFUSIONE ……	☐	☐	☐	☐
STANCHEZZA ……...	☐	☐	☐	☐
MANCANZA DI APPETITO ……	☐	☐	☐	☐
BOCCA ASCIUTTA ……	☐	☐	☐	☐
DIFFICOLTÀ AD INGHIOTTIRE ……	☐	☐	☐	☐
NAUSEA ……..	☐	☐	☐	☐
VOMITO ……...	☐	☐	☐	☐
DOLORE DI STOMACO ……...	☐	☐	☐	☐
DIFFICOLTÀ A DIGERIRE ……..	☐	☐	☐	☐
DIARREA ……	☐	☐	☐	☐
STITICHEZZA ……	☐	☐	☐	☐
SINGHIOZZO ……...	☐	☐	☐	☐
TOSSE ……..	☐	☐	☐	☐
DIFFICOLTÀ A RESPIRARE ……	☐	☐	☐	☐
SUDORAZIONE ……..……	☐	☐	☐	☐
PRURITO ……...	☐	☐	☐	☐
ALTRO (……..)	☐	☐	☐	☐

8) In generale, qual'è il suo LIVELLO DI SODDISFAZIONE nei riguardi della terapia che sta assumendo per il suo dolore?

DECISAMENTE SODDISFATTO	☐
MOLTO SODDISFATTO	☐
ABBASTANZA SODDISFATTO	☐
NE SODDISFATTO NE INSODDISFATTO	☐
ABBASTANZA INSODDISFATTO	☐
DECISAMENTE INSODDISFATTO	☐

9) In generale, come giudica la QUALITÀ DELLA SUA VITA, nell'ultima settimana? (Indichi con un cerchio il numero che meglio si adatta alla sua opinione)

1	2	3	4	5	6	7
Molto scarsa						Eccellente

NTNU DMF, IKM

Minimental status MMS

EAPC ONLUS

Projectno.:
OPI 03-006

1. ORIENTATION	Score	Maximum score
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5. LANGUAGE		
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TOTAL SCORE	□□	□□

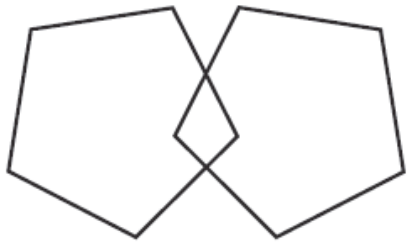
40306

CRF nr: □□□□

Mini Mental Status Exam short version

Patient number: ……..
Date: ……...

	Question	**Score**	**Maximum score**
1.	What year is it?		1
2.	What is today's date?		1
3.	Spell WORLD backwards		2 letters correct = 1 3 or more correct = 2
4.	Copy this design		1
	Total		5



Appendix

Revised Edmonton Staging System for Cancer Pain

The definitions for each of the categories in the rESS are as follows:

Mechanism of Pain

No – No pain syndrome
Nc – Any nociceptive combination of visceral and/or bone or soft tissue pain
Ne – Neuropathic pain syndrome with or without any combination of nociceptive pain
Nx – Insufficient information to classify pain syndrome

Incidental Pain

Pain can be defined as incidental when it is aggravated suddenly because of movements, swallowing, defecation, or urination.
Patients should only be defined as having incidental pain if the incidental pain produces discomfort sufficient to significantly impact on physical and/or psychological function.

I – Used to designate presence of this characteristic

Psychological Distress and Addictive Behavior

Psychological distress is defined as "a major problem assessed as limiting the patient's ability to differentiate physiological and psychological pain accurately, due to the presence of somatization alone or somatization accompanied by symptoms such as depression, anxiety, hostility or neuroticism severe enough to jeopardize the success of the analgesic treatment".

Addictive behavior is defined as "Any lifetime history of alcohol addiction as defined by the CAGE or a strong clinical history of alcohol abuse provided by other sources, and/or any other lifetime history of addiction to prescription or non-prescription drugs."

Po – Psychological distress and addictive behavior not present
Pp – Psychological distress alone present
Pa – Addictive behavior alone present
Ppa – Psychological distress and addictive behavior present

Cognitive Function

Cn – Ability to provide pain history past and present unimpaired (normal cognitive function)
Ci – Sufficient impairment to affect patient's ability to provide accurate pain history for present and/or past
Cu – Patient unable to provide any pain history past or present

INTRODUCTION

The Edmonton Classification System for Cancer Pain (ECS-CP) Quick User Guide provides a brief outline on how to use the ECS-CP.

An initial pain classification assessment, using the ECS-CP, is generally conducted prior to pain management (e.g. on admission to a palliative consultation service). Subsequent assessments may be conducted if the patient's condition changes or as additional information regarding the five pain features is obtained. The classification should be used to guide the interdisciplinary team in using different pharmacological and non-pharmacological approaches to optimize pain control.

The more detailed and complete Administration manual consists of four key sections: (1) *Background*, (2) *Edmonton Classification System for Cancer Pain*, (3) *Case Studies* and (4) *Frequently Asked Questions*. Refer to that resource if you need information beyond what is provided in the Quick User Guide.

Edmonton Classification System for Cancer Pain

Patient Name: _____ Patient ID No:_____

For each of the following features, circle the response that is most appropriate, based on your clinical assessment of the patient.

1. Mechanism of Pain

No No pain syndrome
Nc Any nociceptive combination of visceral and/or bone or soft tissue pain
Ne Neuropathic pain syndrome with or without any combination of nociceptive pain
Nx Insufficient information to classify

2. Incident Pain

Io No incident pain
Ii Incident pain present
Ix Insufficient information to classify

3. **Psychological Distress**

Po No psychological distress
Pp Psychological distress present
Px Insufficient information to classify

4. **Addictive Behavior**

Ao No addictive behavior
Aa Addictive behavior present
Ax Insufficient information to classify

5. Cognitive Function

Co No impairment. Patient able to provide accurate present and past pain history unimpaired
Ci Partial impairment. Sufficient impairment to affect patient's ability to provide accurate present and/or past pain history
Cu Total impairment. Patient unresponsive, delirious or demented to the stage of being unable to provide any present and past pain history
Cx Insufficient information to classify

ECS-CP profile: N__ I__ P__ A__ C__ (combination of the five responses, one for each category)

Assessed by: _____ ***Date:*** _____

DEFINITION OF TERMS

Mechanism of Pain
The ECS-CP classification system is based on a hierarchy of *mechanism of pain* features, in which neuropathic pain represents a greater management challenge than nociceptive pain. If a patient presents with one or more pains involving multiple pain mechanisms, then the default classification would be the one with the greatest management challenge. For example if a patient presents with two different cancer related pains, one of which is neuropathic pain, you would classify the mechanism of pain as neuropathic. This is also addressed in the descriptor for neuropathic pain (Ne), which refers to "neuropathic pain syndrome **with or without** any combination of nociceptive pain." The assessment of the mechanism is a judgment decision made by the clinician, based on history, physical examination and available diagnostic imaging. The use of screening tools such at the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) may enhance accuracy of the classification of the mechanism.

Incident Pain
Pain can be defined as incident pain when a patient has background pain of no more than moderate intensity with intermittent episodes of moderate to severe pain, usually having a rapid onset and often a known trigger.

Guidelines for Use: There are six key characteristics of *incident pain*, as defined in the ECS-CP:

- *Relationship with background pain:* The intensity of incident pain is significantly greater than background pain.
- *Severity:* The intensity of incident pain is moderate to severe.
- *Predictability:* The trigger is often known, such as movement, defecation, urination, swallowing and dressing change. However, clinically significant episodic pain (i.e. no predictable trigger) can be included (e.g. bladder or bowel spasm).
- *Onset:* Its onset is rapid, with intensity often peaking within 5 minutes.
- *Transiency:* Incident pain is transient, and may return to baseline shortly after the trigger is stopped or removed.
- *Recurrence:* It is intermittent, recurring when the trigger returns.

Psychological Distress
Psychological distress, within the context of the pain experience, is defined as a patient's inner state of suffering resulting from physical, psychological, social, spiritual and/or practical factors that may compromise the patient's coping ability and complicate the expression of pain and/or other symptoms.

Guidelines for Use: There are five key characteristics of *psychological distress*, as defined in the ECS-CP:

- *Relationship with pain:* The definition of psychological distress is limited to patients who are experiencing psychological distress within the context of the pain experience and who appear to express their suffering through physical symptoms.
- *Relationship with suffering:* Psychological distress is an expression of suffering, often referred to as *total pain*.
- *Multidimensional:* Psychological distress is multidimensional in nature, influencing many spheres of a patient's experience, including but not necessarily limited to physical, psychological, social, and spiritual factors.
- *Relationship with coping:* Psychological distress may impair a patient's ability to cope with his/her illness.
- *Physical symptom expression:* Psychological distress is often expressed as an exacerbation of pain and/or other symptoms, which may be conceptualized as a form of somatization.

Assessment of psychological distress may include, but is not necessarily limited to, the following:

- Assessment of patient's experience in multidimensional domains
- Patient's behavioral presentation and symptom reporting profile
- Collateral history from primary caregivers

Addictive Behavior
Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Guidelines for Use: There are five key characteristics of *addictive behavior*, as defined in the ECS-CP:

- *chronicity:* It is a chronic disorder, which may have periods of relapse and remission.
- *multidimensional:* It is multidimensional in its development and expression, including genetic, psychosocial and environmental factors.
- *compulsivity*
- *persistent use despite harm*
- *craving*

This definition is limited to the following:

- A remote history of prior alcohol/substance use **may not** be considered relevant as a complicating factor in ongoing pain assessment and management.
- Substances of abuse include alcohol, prescription medications, non prescription medications, and illicit drugs.
- It does not include chronic tobacco use.

Assessment of *addictive behavior* may include, but is not necessarily limited to, the following:

- Use of CAGE as screening tool for possible alcohol abuse
- Patient's behavioral presentation over a series of visits
- A strong clinical history of substance abuse provided by the patient
- Collateral history from primary caregivers

Cognitive Function
The assessment of cognition is at the discretion of the clinician and is focused on the ability to provide a pain history since the ECS-CP is a pain classification system. Other global cognitive assessment measures, such as the Mini-Mental Status Examination (MMSE), SOMCT/BOMCT, Sweet 16, or the Montreal Cognitive Assessment (MOCA), may also be included as part of the screening process, if appropriate.

Dissertations

Dissertations at the Faculty of Medicine, NTNU

1977

1. Knut Joachim Berg: EFFECT OF ACETYLSALICYLIC ACID ON RENAL FUNCTION
2. Karl Erik Viken and Arne Ødegaard: STUDIES ON HUMAN MONOCYTES CULTURED *IN VITRO*

1978

3. Karel Bjørn Cyvin: CONGENITAL DISLOCATION OF THE HIP JOINT.
4. Alf O. Brubakk: METHODS FOR STUDYING FLOW DYNAMICS IN THE LEFT VENTRICLE AND THE AORTA IN MAN.

1979

5. Geirmund Unsgaard: CYTOSTATIC AND IMMUNOREGULATORY ABILITIES OF HUMAN BLOOD MONOCYTES CULTURED IN VITRO

1980

6. Størker Jørstad: URAEMIC TOXINS
7. Arne Olav Jenssen: SOME RHEOLOGICAL, CHEMICAL AND STRUCTURAL PROPERTIES OF MUCOID SPUTUM FROM PATIENTS WITH CHRONIC OBSTRUCTIVE BRONCHITIS

1981

8. Jens Hammerstrøm: CYTOSTATIC AND CYTOLYTIC ACTIVITY OF HUMAN MONOCYTES AND EFFUSION MACROPHAGES AGAINST TUMOR CELLS *IN VITRO*

1983

9. Tore Syversen: EFFECTS OF METHYLMERCURY ON RAT BRAIN PROTEIN.
10. Torbjørn Iversen: SQUAMOUS CELL CARCINOMA OF THE VULVA.

1984

11. Tor-Erik Widerøe: ASPECTS OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS.
12. Anton Hole: ALTERATIONS OF MONOCYTE AND LYMPHOCYTE FUNCTIONS IN REALTION TO SURGERY UNDER EPIDURAL OR GENERAL ANAESTHESIA.
13. Terje Terjesen: FRACTURE HEALING AND STRESS-PROTECTION AFTER METAL PLATE FIXATION AND EXTERNAL FIXATION.
14. Carsten Saunte: CLUSTER HEADACHE SYNDROME.
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16. Bjørn Magne Eggen: STUDIES IN CYTOTOXICITY IN HUMAN ADHERENT MONONUCLEAR BLOOD CELLS.
17. Trond Haug: FACTORS REGULATING BEHAVIORAL EFFECTS OG DRUGS.

1985

18. Sven Erik Gisvold: RESUSCITATION AFTER COMPLETE GLOBAL BRAIN ISCHEMIA.
19. Terje Espevik: THE CYTOSKELETON OF HUMAN MONOCYTES.
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1986

24. Dagfinn Berntzen: ANALYSIS AND MANAGEMENT OF EXPERIMENTAL AND CLINICAL PAIN.
25. Odd Arnold Kildahl-Andersen: PRODUCTION AND CHARACTERIZATION OF MONOCYTE-DERIVED CYTOTOXIN AND ITS ROLE IN MONOCYTE-MEDIATED CYTOTOXICITY.
26. Ola Dale: VOLATILE ANAESTHETICS.

1987

27. Per Martin Kleveland: STUDIES ON GASTRIN.
28. Audun N. Øksendal: THE CALCIUM PARADOX AND THE HEART.
29. Vilhjalmur R. Finsen: HIP FRACTURES

1988

30. Rigmor Austgulen: TUMOR NECROSIS FACTOR: A MONOCYTE-DERIVED REGULATOR OF CELLULAR GROWTH.
31. Tom-Harald Edna: HEAD INJURIES ADMITTED TO HOSPITAL.
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39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
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1989

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1990

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92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
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1996

110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
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117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.

133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
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143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
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154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
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160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.

162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
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169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
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183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
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186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT

192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
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194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
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198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.

217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
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222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
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225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
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227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
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233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
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239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA

244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
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258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
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261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
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267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

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269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT

272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
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283. Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY
284. Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
285. Kristin Gabestad Nørsett: GENE EXPRESSION STUDIES IN GASTROINTESTINAL PATHOPHYSIOLOGY AND NEOPLASIA
286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287. Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OF PATHOLOGICAL GAMBLING IN NORWAY
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289. Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
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294. Lars Fosse: MECHANICAL BEHAVIOUR OF COMPACTED MORSELLISED BONE – AN EXPERIMENTAL IN VITRO STUDY
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