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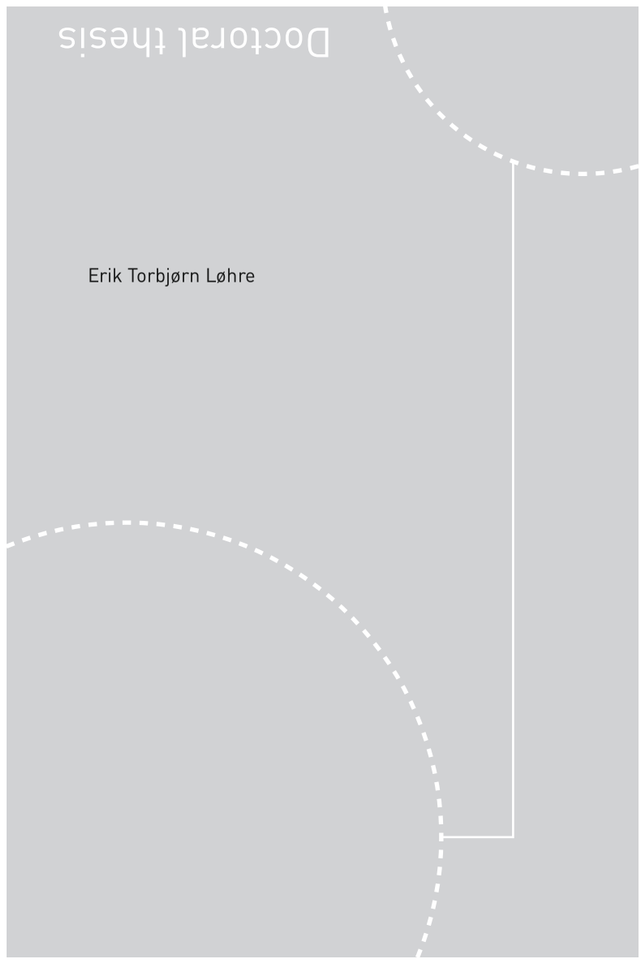
Erik Torbjørn Løhre

Aspects of assessment, classification and treatment of cancer pain



ISBN 978-82-326-4428-5 (printed ver.)
ISBN 978-82-326-4429-2 (electronic ver.)
ISSN 1503-8181

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Trondheim, January 2020

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Printed by NTNU Grafisk senter

Om kartlegging, klassifikasjon og behandling av kreftsmerte

Kreftsmerte forårsakes av skade på bevegelsesapparatet, indre organer eller nervevev, resulterer i somatisk, visceral eller nevropatisk smerte og oppleves som både kontinuerlig bakgrunnssmerte og forbigående smertetopper. Gjennombruddssmerte er en type forbigående smerte som «bryter gjennom» den regelmessig doserte smertebehandlingen.

Forskere med flest publikasjoner om gjennombruddssmerte deltok i en anonym spørreundersøkelse. De var enige om at begrepet gjennombruddsmerte ikke dekket alle forbigående smertetopper og så behovet for en egnet samlebetegnelse. Videre var de enige om at informasjon om smertetoppenes årsak kan påvirke valg av behandling og at vurdering av pasienttilfredshet er viktig i smertekartlegging.

Ekspertoppfatningene fra spørreundersøkelsen ble etterprøvd i et eksisterende datasett. Informasjon fra nesten sju hundre kreftpasienter viste at begrepet gjennombruddssmerte bare var dekkende for halvparten av de forbigående smertetoppene. Dataene viste også at rapportert forekomst av gjennombruddssmerte er helt avhengig av hvor intens bakgrunnssmerte som aksepteres, og hvor intense smertetopper som kreves for at definisjonskriteriene for gjennombruddssmerte anses oppfylt.

Pasienter med kreftsmerter og som ble innlagt ved SLB, Kreftklinikken, St. Olavs hospital, ble et halvt år fulgt ekstra tett med spørsmål om bakgrunnssmerte, smertetopper og i hvor stor grad de var tilfredse med smertebehandlingen. Basert på pasientopplysningene ble legene spurt om de fant grunnlag for endringer i behandlingen av bakgrunnssmerten eller de forbigående smertetoppene. Legene måtte også vurdere behovet for spesifikk behandling av somatisk, visceral eller nevropatisk smerte. I denne perioden var gjennomsnittlig bedring av bakgrunnssmerte under sykehusoppholdet 3.4 poeng (på en 0-10 skala) for pasienter innlagt med kreftsmerter. Bedringen av de forbigående smertetoppene var enda større, med en reduksjon på 4.1 poeng fra innleggelse til utskrivelse for de 41 pasientene som ble fulgt.

Name of the candidate: Erik Torbjørn Løhre

Department: Department of Clinical and Molecular Medicine

Cancer Clinic, St. Olavs hospital, Trondheim University Hospital

Main supervisor: Pål Klepstad

Co-supervisors: Stein Kaasa and Anne Kari Knudsen

This thesis is found to be worthy of public defence for the degree of Philosophiae Doctor in palliative medicine.

The public defence takes place at the MTA Auditorium, 27.02.20.

Avhandlingen er funnet verdig til å forsvares offentlig for graden ph.d. i palliativ medisin.

Disputas finner sted i Medisinteknisk forskningssenter 27.02.20.

Table of Contents

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (1).

Pain must be appreciated to be adequately treated, and pain of which the severity is underestimated will not be treated aggressively enough (2).

Acknowledgements

The presented work was conducted at the Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology (NTNU) and at the Palliative Care Unit, Cancer Clinic, St. Olavs hospital, Trondheim University Hospital. The work was funded by the Norwegian Cancer Society, NTNU, and the Cancer Clinic.

I want to thank the study participants for their time and helpful cooperation.

Without the sharp-mindedness and fast-track structured responses of my main supervisor, Pål Klepstad, this work could not have been conducted within the planned timeline. I have very much appreciated our discussions and your advice on scientific writing.

Stein Kaasa introduced me to palliative care and the necessity of a scientific approach to the topic. Your encouragement and support over the years has been essential for the thesis. I also would like to thank Anne Kari Knudsen for her contributions. The input is always valuable, and your eye for linguistic details is impressive.

During the entire PhD project period, scientific work has been combined with clinical activity, both at the Regional Advisory Unit for Palliative Care, Department of Research and Education, and at the Palliative Care Unit, Cancer Clinic. This combination was only possible with the kind cooperation from the respective leaders, Signe Danielsen and Morten Thronæs. The Cancer Clinic, St. Olavs hospital, has provided possibilities for, and encouraged, a combination of clinical activity and research. For this I am grateful and want to thank the head of the clinic, Arne Solberg.

The scientific work was conducted at the Research Group for Cancer and Palliative Care, Department of Clinical and Molecular Medicine. Thank you to the head, Bjørn Henning Grønberg, and the rest of the research group for providing the possibility and a nice scientific environment.

Over the years, I have shared a lot of moments, and frustrations, with my colleagues at the Palliative Care Unit: Morten, Anne, Elisabeth, and Robin. Especially, I have valued the discussions about the important, and not so important, aspects of life.

Cinzia Brunelli is a co-author of all the three publications, and for several years she has shared her expertise on statistics and scientific stringency. Marianne Jensen Hjermstad provided a possibility for using the data set for paper II and contributed largely to the paper. I am also grateful to Ragnhild Green Helgås for her expertise and opinions throughout the PhD project.

Without the support from my life companion for three decades, Gjertrud, this work could not have been accomplished.

Abbreviations

BTP	breakthrough pain
PI	pain intensity
EPCRC-CSA	European Palliative Care Research Collaborative-Computerized Symptom Assessment
NRS	numeric rating scale
PROMs	patient-reported outcome measures
DS	decision support
LOS	hospital length of stay
CI	confidence interval
IQR	interquartile range
ICD-11	11th revision of the World Health Organization's International Classification of Diseases
PMI	Pain Management Index
ECS-CP	Edmonton Classification System for Cancer Pain
EAPC	European Association for Palliative Care
BPI	Brief Pain Inventory
MPQ	McGill Pain Questionnaire
ESAS	Edmonton Symptom Assessment System
ABPAT	Alberta Breakthrough Pain Assessment Tool
BAT	Breakthrough Cancer Pain Assessment Tool

LANSS	Leeds Assessment of Neuropathic Symptoms and Signs
DN4	Douleur Neuropathique en 4
PDQ	painDETECT
PSG	personalized symptom goal
WHO	World Health Organization
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ESMO	European Society for Medical Oncology
ATC	around the clock
PRN	on demand (pro re nata)
SD	standard deviation
ECOG	Eastern Cooperative Oncology Group
SQUIRE	Standards for QUality Improvement Reporting Excellence
VRS	verbal rating scale

Summary in English

Cancer pain is undertreated in about one out of three patients. The pain can be caused by the cancer itself or by cancer therapy. Tissue damage may occur in several different sites such as bone, viscera, and nerve structures. Different cancer pain conditions often call for specific treatment strategies. Cancer pain can be described as continuous background pain and intermittent spikes of higher intensity, occurring episodically. Breakthrough pain (BTP) is an episode of severe pain that “breaks through” a constant pain at least partly controlled by a stable opioid regimen. The definition of BTP includes an adequately controlled and stable background pain and transient exacerbations of pain, which are pain flares well distinguished from the background pain. Despite agreement on these basic characteristics, controversies about the definition of BTP continue. Differences in definitional criteria complicate both the clinical diagnosis and the comparison of epidemiological data between studies.

In the first study, the most frequent authors on BTP literature were identified and invited to participate in a two-round Delphi survey. Fifty-two authors had published three or more papers on BTP over the past ten years. Twenty-seven responded in the first round and 24 in the second round. Topics with a low degree of consensus on BTP classification were refined into 20 statements. The participants rated their degree of agreement with the statements on a numeric rating scale (NRS 0-10). Consensus was defined as a median numeric rating scale score of ≥ 7 and an interquartile range of ≤ 3. Consensus was reached for the following: 1) Transient cancer pain exacerbations can occur without background pain, when background pain is uncontrolled, and regardless of opioid treatment. 2) There exist cancer pain exacerbations other than BTP, and the term "episodic pain" could serve as an umbrella term for all clinically relevant pain flares. 3) Patient-reported treatment satisfaction is important with respect to assessment. 4) Subclassification according to pain pathophysiology can provide treatment guidance.

The second study examined BTP prevalence variability due to use of different cutoffs for controlled background pain, different assessment periods for background pain, and difference between worst and average pain intensity (PI). Patients from the international cross-sectional EPCRC-CSA study with episodic pain flares the past 24 hours were potential BTP cases. BTP prevalence was calculated for different cutoffs for background PI (NRS 0-10) for the past week, past 48 and past 24 hour periods. Furthermore, BTP cases were categorized based on the difference between worst and average PI past 24 hours (range 0 to > 2 points, NRS 0-10). Of 696 respondents, 43.4% reported episodic pain flares the past 24 hours. The BTP prevalence, when using a defined background PI ≤ 4 (NRS 0-10) for the past week, was 19.8%. This percentage varied for different cutoffs for background PI. Actual background PI and BTP prevalence also varied between the assessment periods "past week", "past 48 hours", and "past 24 hours" (PI 4.0, 3.6, and 3.4; BTP prevalence 19.8 %, 22.7 % and 24.9 % for background PI ≤ 4). For patients with background PI ≤ 4 past week, 105 had a difference between worst and average PI ≥ one point and 48 had a difference > two points.

In the third study, a care pathway for pain management in a palliative care unit was studied. Mandatory use of patient-reported outcome measures (PROMs) and physician-directed decision support (DS) were integrated parts of the pathway. Adult cancer patients with PI ≥ 5 (NRS 0-10) when admitted to the Palliative Care Unit, Cancer Clinic, St. Olavs hospital, Trondheim University Hospital, were eligible. The patients reported average PI, worst PI, and treatment satisfaction at admission, day four, and discharge. The physicians completed the DS at admission and day four. The DS presented potential needs for treatment changes based on PI, patient-reported treatment satisfaction, and pain pathophysiology. The physicians reported treatment changes due to input from the DS system. The two primary outcomes were average and worst PI changes from admission to discharge. Hospital length of stay (LOS) was registered. Of 52 included patients, 41 were discharged alive. For those, the mean average PI at admission and at discharge was 5.8 and 2.4, respectively, a reduction of 3.4 points (CI 95% 2.7-4.1). The corresponding worst pain intensities were 7.9 and 3.8, a reduction of 4.1 points (CI 95% 3.4-4.8). Fifty-five percent (CI 95% 41-69) of

the patients had pain intervention changes based on the DS. A significant reduction in LOS (4.4 days, CI 95% 0.5-8.3) was observed during the study period.

The following conclusions can be drawn from the three studies:

Significant transient cancer pain exacerbations include more than just BTP. A traditional BTP definition includes only approximately half of all episodes of intermittent spikes of pain.

The reported BTP prevalence is dependent on the cutoff for background PI in the BTP definition, the population background PI during the assessment period, and cutoff for the difference between worst and average PI.

Structured pain assessment, reflecting available treatment options for both background pain and episodic pain and including the patient perspective, can result in significantly reduced PI, provided the information is utilized systematically.

Norsk sammendrag

Kreftsmerte er ikke godt nok behandlet hos omtrent en av tre pasienter. Både selve kreftsykdommen og kreftbehandlingen kan gi smerter og vevsskade i eksempelvis skjelett, indre organer og nerver. Forskjellig typer kreftsmerte må ofte behandles forskjellig. Kreftsmerter kan være en kontinuerlig bakgrunnssmerte, men også forbigående smertetopper. Gjennombruddssmerte (på engelsk «breakthrough pain», forkortet BTP) er en kortvarig intens smerte som «bryter gjennom» smertelindringen den faste dosen opioider gir. Definisjonen av BTP omfatter en godt behandlet og stabil bakgrunnssmerte samt forbigående smertetopper som er mer intense enn bakgrunnssmerten. Til tross for internasjonal enighet om disse grunnleggende karakteristika er det fortsatt mange kontroverser rundt definisjonen av BTP. Mangel på standardisering kompliserer både den kliniske diagnosen og sammenligningen av epidemiologiske data.

I den første studien ble forfatterne med flest publiserte BTP studier identifisert og invitert til å delta i en to runders Delphi undersøkelse. Femtito forfattere hadde publisert tre eller flere artikler om BTP de ti foregående årene. Tjuesju av disse deltok i den første runden av Delphi undersøkelsen og 24 i den andre runden. Områder med liten grad av konsensus innen BTP terminologi ble formulert i 20 utsagn. Studiedeltakerne rapporterte på en numerisk skala (NRS 0-10) i hvor stor grad de var enige i utsagnene. En median score ≥ 7 med en variasjonsbredde i kvartiler (IQR) ≤ 3 ble definert som konsensus blant deltakerne. Det ble konsensus for at: 1) Forbigående smertetopper kan forekomme uten bakgrunnssmerte, når bakgrunnssmerten er ukontrollert, og uavhengig av om pasienten behandles med opioider eller ikke. 2) Det forekommer smertetopper utover det BTP definisjonen inkluderer, og begrepet "episodisk smerte" kan passe som en samlebetegnelse for alle smertetopper av klinisk betydning. 3) Pasientrapportert behandlingstilfredshet er en viktig del av kartleggingen. 4) Patofysiologiske smertemekanismer kan påvirke behandlingsvalg.

Den andre studien undersøkte variasjon i BTP prevalens relatert til bruk av forskjellige grenseverdier for kontrollert bakgrunnssmerte, forskjellige kartleggingsperioder for bakgrunnssmerten og relatert til forskjellige differanser mellom verste og gjennomsnittlig smerteintensitet. Kreftpasienter som rapporterte forbigående smertetopper de siste 24 timene i den internasjonale EPCRC-CSA tverrsnittsstudien ble definert som mulige BTP pasienter. BTP prevalenser ble beregnet med forskjellige grenseverdier for bakgrunnssmerteintensitet (NRS 0-10), rapportert for den foregående uken og de foregående 48 og 24 timene. Videre ble BTP pasienter kategorisert basert på differansen mellom verste og gjennomsnittlig smerteintensitet de foregående 24 timene (fra 0 til > 2 poeng, NRS 0-10). Av 696 pasienter rapporterte 43,4% forbigående smertetopper de siste 24 timene. BTP prevalens, med grenseverdi for bakgrunnssmerteintensitet ≤ 4 (NRS 0-10) den siste uken, var 19,8%. Denne prosenten varierte med forskjellige grenseverdier for bakgrunnssmerten. Rapportert intensitet av bakgrunnssmerte og tilhørende BTP prevalens varierte også mellom kartleggingsperiodene "siste uke", "siste 48 timer" og "siste 24 timer" (bakgrunnssmerteintensitet 4.0, 3.6 og 3.4; BTP prevalens 19,8%, 22,7% og 24,9% med grenseverdi ≤ 4 for intensitet av bakgrunnssmerten). Av pasientene med bakgrunnssmerteintensitet ≤ 4 siste uke hadde 105 en differanse mellom verste og gjennomsnittlige smerteintensitet ≥ ett poeng, og 48 hadde en differanse > to poeng.

I det tredje arbeidet studerte vi et pasientforløp for smertebehandling av pasienter innlagt i en palliativ enhet. Obligatorisk bruk av pasientrapporterte utfallsmål og beslutningsstøtte for leger var integrert i pasientforløpet. Vi fulgte voksne kreftpasienter med smerteintensitet ≥ 5 (NRS 0-10) ved innleggelse Seksjon lindrende behandling, Kreftklinikken, St. Olavs hospital. Pasientene rapporterte gjennomsnittlig og verste smerteintensitet samt tilfredshet med smertebehandlingen ved innleggelse, dag fire og ved utskrivelse. Legene brukte beslutningsstøtten ved innleggelse og dag fire. Beslutningsstøtten sensibiliserte legene på eventuelle behov for endring av smertebehandlingen på grunnlag av smerteintensitet, pasientrapportert tilfredshet med smertebehandlingen, samt smertepatofysiologi. Legene anga om de endret behandlingsopplegget basert på beslutningsstøtten. De to primære utfallsmålene var endring i intensitet av gjennomsnittlig og verste smerte fra innleggelse til

utskrivelse. Vi undersøkte også hvor lenge pasientene var innlagt. Av de 52 pasientene som ble inkludert i studien ble 41 utskrevet i live. For pasientene som ble utskrevet i live var gjennomsnittlig smerteintensitet ved innleggelse og utskrivelse henholdsvis 5,8 og 2,4, en reduksjon på 3,4 poeng (CI 95% 2,7-4,1). Verste smerteintensiteter for disse pasientene var henholdsvis 7,9 og 3,8, en reduksjon på 4,1 poeng (CI 95% 3,4-4,8). For 55% (CI 95% 41-69) av pasientene endret legene smertebehandlingen basert på beslutningsstøtten. Vi observerte en signifikant reduksjon i lengden av sykehusoppholdene (4,4 dager, CI 95% 0,5-8,3) under studien.

Følgende konklusjoner kan trekkes fra de tre studiene:

Det finnes andre forbigående smertetopper av betydning enn BTP. En tradisjonell BTP definisjon omfatter bare halvparten av alle forbigående smertetopper.

Målt BTP prevalens vil variere med grenseverdien for bakgrunnssmerte, bakgrunnssmerten i populasjonen i kartleggingsperioden og grenseverdien for differansen mellom verste og gjennomsnittlig smerteintensitet.

Strukturert smertekartlegging, som gjenspeiler tilgjengelige behandlingsmuligheter for både bakgrunnssmerte og forbigående smertetopper og hvor pasientens perspektiv er vektlagt, kan resultere i betydelig redusert smerteintensitet hvis informasjonen utnyttes systematisk.

List of papers

Paper I

From ‘‘Breakthrough’’ to ‘‘Episodic’’ Cancer Pain? A European Association for Palliative Care Research Network Expert Delphi Survey Toward a Common Terminology and Classification of Transient Cancer Pain Exacerbations

Erik Torbjørn Løhre, Pål Klepstad, Michael I. Bennett, Cinzia Brunelli, Augusto Caraceni, Robin L. Fainsinger, Anne Kari Knudsen, Sebastiano Mercadante, Per Sjøgren, Stein Kaasa

Journal of Pain and Symptom Management Vol. 51 No. 6, June 2016

Paper II

Pain Intensity Factors Changing Breakthrough Pain Prevalence in Patients with Advanced Cancer: A Secondary Analysis of a Cross-Sectional Observational International Study

Erik Torbjørn Løhre, Marianne Jensen Hjermstad, Cinzia Brunelli, Anne Kari Knudsen, Stein Kaasa, Pål Klepstad

Pain and Therapy 7:193–203, 2018

Paper III

An in-hospital clinical care pathway with integrated decision support for cancer pain management reduced pain intensity and needs for hospital stay

Erik Torbjørn Løhre, Morten Thronæs, Cinzia Brunelli, Stein Kaasa, Pål Klepstad

Supportive Care in Cancer First Online: 23 May, 2019

1. Background

1.1. Pain pathophysiology and classification

1.1.1. Basic pain pathophysiology

Pain is a complex sensation involving both the peripheral and the central nervous system (3). The pain process usually originates in the periphery, initiated by a trauma, disease or lesion (3). In the presence of a noxious stimulus, the basic pain mechanisms include the three events transduction, transmission, and modulation of the pain impulse (4). Transduction is the conversion of a noxious stimulus into electrical energy by a peripheral nociceptor (5). The electrical signal is transmitted along the neuronal pathways, with neurotransmitters providing the signal transmission in the synaptic clefts connecting the ascending sensory neurons (4). The modulation of pain involves both the central and the peripheral nervous system, and includes both up- and downregulation (6). Central sensitization plays an important role in persistent pain (7). In fact, all types of pain and all chronic painful conditions can be influenced by central factors, whether the pain is acute or chronic, widespread or local (8).

1.1.2. Classification based on pathophysiology

Based on the primary pathophysiological mechanisms, pain can principally be classified into nociceptive pain, neuropathic pain, and inflammatory pain (4). Nociceptive pain can be divided into somatic and visceral pain, based on the localization of the tissue injury (9). Some authors further subdivide somatic pain into deep somatic pain (e.g. pain from skeletal lesions) and superficial somatic pain (e.g. pain from cutaneous lesions) (10).

The first step in processing nociceptive pain is the transduction (11). Once the receptors have been stimulated and have reached the pain threshold, the resulting impulses are propagated along afferent fibers to the central nervous system. In addition to the peripheral mechanisms of nociception, there are nociceptive mechanisms at the spinal cord level, spinocortical nociceptive pathways, and cortical detection of nociceptive information.

Furthermore, the afferent passage of nociceptive information is either suppressed or enhanced by the activity in descending nociceptive pathways (11).

Neuropathic pain can develop after nerve injury, when deleterious changes occur in injured neurons along nociceptive pathways and descending modulatory pathways (12). In neuropathic pain, there is no transduction process (12). On the other hand, central sensitization is considered an important contributor to the pain phenotype (7). In addition, the large amount of neurotransmitters and other substances involved in the development and maintenance of neuropathic pain also play a role in other neurobiological disorders, implicating a reason for high comorbidity rates for chronic pain, sleep disorders and depression (12).

In an inflammatory response, tissue wounding induces the rapid recruitment of leukocytes, followed by the release of other chemical mediators (13). The acute localized inflammatory response induces pain that normally occurs for a short period of time (4). In prolonged inflammation, the pain lasts beyond the expected period of healing. Inflammatory pain causes an increase of afferent input and leads to the development of central sensitization (4). In chronic inflammatory conditions like rheumatoid arthritis, also systemic inflammation might contribute to the central pain augmentation (8). Even in multifactorial conditions like tendinopathy, there is an inflammatory phenotype including key inflammatory mediators like cytokines, nitric oxide and prostaglandins, despite the absence of classical clinical inflammation (14).

1.1.3. Classification based on temporal characteristics

Acute pain is the normal physiological response to an adverse chemical, thermal or mechanical stimulus (15). Acute pain provides a warning signal for body injury. The self-limiting nature of acute pain finally results in the resolution of pain as the healing process occurs (15).

Chronic pain was previously defined as pain that persists past normal healing time, and hence lacks the acute warning function of physiological nociception (16). Although applicable for conditions like persistent pain after surgery, such a definition does not

include situations as chronic musculoskeletal or neuropathic pains (16). Because of this, a definition of chronic pain according to pain duration has been preferred, with the advantages of being both clear and operationalized (17). In the 11th revision of the World Health Organization's International Classification of Diseases (ICD-11), chronic pain is defined as pain that lasts or recurs for longer than three months (16). In ICD-11, chronic pain is classified as chronic primary pain or chronic secondary pain syndromes, of which chronic cancer-related pain is an entity (16).

1.2. Chronic cancer-related pain

The expression "cancer pain" is often a poorly described concept (18). The term is not equivalent to pain in a cancer patient, and even less so to pain in a cancer survivor (18). Cancer-related pain includes pain caused by the tumor or its metastases, or pain caused by the cancer treatment (17). As patients diagnosed with cancer frequently are older individuals with a high prevalence of comorbid conditions causing pain, pain in a cancer patient also may be unrelated to the cancer (18). The fact that the cancer patient reports a mean of two different pains further complicates the picture (19). In addition, the three months duration criterion for chronic pain may be challenging to apply in cancer patients with progressive disease and limited survival. A study of opioid prescription in 6000 cancer patients reported a median interval between first prescription of a strong opioid and death of nine weeks (20).

1.2.1. Chronic cancer pain

Chronic cancer pain is defined as chronic pain caused by the primary cancer or metastases (18). The pain is caused by tumor expansion, which induces tissue damage and release of inflammatory mediators. In addition, the cancer may compress and destroy sensory nerves. Described by temporal characteristics, the pain is a continuous background pain with intermittent flares of episodic worsening (18).

1.2.2. Chronic post-cancer treatment pain

Chronic post-cancer treatment pain is pain caused by any treatment given to treat the cancer (18). The most common forms are chronic peripheral neuropathic pain caused by chemotherapy, and chronic pain caused by delayed local damage to the nervous system after radiotherapy. Chronic post-surgical pain is particularly common after treatment for breast and lung cancer, but can follow any surgical procedure. Post-cancer treatment pain is distinct from pain caused by tumor recurrence or co-morbid diseases (18).

1.3. Cancer pain epidemiology

1.3.1. Cancer pain prevalence

Despite increased attention to cancer pain, pain prevalence in cancer patients has not changed significantly during the past decade compared to the preceding ones (21). A systematic review, published more than ten years ago, reported pain prevalence over the previous 40 years for cancer patients after curative treatment, for patients on anticancer treatment, and for patients with advanced cancer (22). The prevalence of pain for the three groups were 33%, 59%, and 64 %, respectively. In an updated review, published in 2016 and including 117 studies and more than 60.000 patients, 39% of the patients reported pain after curative treatment, 55% during anticancer treatment, and 66% of the patients reported pain in advanced, metastatic, or terminal disease (23). For the 18 studies that included patients with all stages of cancer, the prevalence of pain was 51%. The corresponding percentage for the previous decades was 53 (22). A Norwegian study, which compared cancer pain prevalence in 2008 and 2014, found similar percentages (24). That study reported cancer pain in 55% of the cancer inpatients in 2008, and cancer pain in 53% of the cancer inpatients in 2014.

1.3.2. Cancer pain intensity

Comparing the two above-mentioned systematic reviews, the oldest review reported pain intensity based on information from 18 studies (22). More than one third of the patients with pain reported pain of moderate or severe intensity. In the updated review, covering

more than 32.000 patients in 52 studies published between 2005 and 2014, moderate to severe pain (NRS ≥ 5 on the eleven point numeric rating scale (NRS 0-10)) was reported by 38 % of the patients (23). For the approximately 7.500 patients with advanced, metastatic, or terminal disease, 52% reported pain of moderate or severe intensity (23).

1.3.3. Cancer pain site and characteristics

Cancer pain characteristics and cancer pain syndromes were described in an international survey, where the 51 participating physicians categorized cancer pain in a total of 1095 patients (9). The major pain syndromes comprised bone or joint lesions, found in 42 % of the patients, peripheral nerve injuries, visceral lesions and soft tissue infiltration. The three latter categories were all found in approximately 28% of the patients (9). A study performed almost two decades earlier also found bone metastases, nerve compression, visceral involvement, and soft tissue infiltration to be the most common causes of pain in cancer patients (25).

1.3.4. Undertreatment of cancer pain

Two systematic reviews, published in 2008 and 2014 respectively, investigated undertreatment of cancer pain (26, 27). The oldest review covered studies from 1994 to 2007 and reported undertreatment of pain in 43% of the patients (26). The most recent review, covering 20 studies published from 2007 to 2013, reported undertreatment in 32% of the patients (27). The decrease represented a relative reduction in undertreatment of 25% (27). A commentary was published in the aftermath of the most recent review, criticizing the methodology for measuring undertreatment of pain (28). Both reviews used the Pain Management Index (PMI) as an indirect measure for quality of pain management, a tool originally developed to measure the health care provider's response to a patient's pain (29). The commentary argued that the PMI score will provide an excessively optimistic view of the situations, and asserted that PMI cannot be considered as a tool to assess adequacy or to monitor changes in cancer pain management (28).

1.4. Cancer pain pathophysiology

The mechanisms of cancer pain is a complex pathological process that comprises cellular, tissue, and systemic changes that occur during the proliferation, invasion, and metastasis of cancer (30). The different patterns of chemical and electrical events that transfer the painful messages pass activity to many parts of the brain through a series of increasingly complex pathways (3). In broad terms, also nociceptive pain can be considered a form of inflammatory pain, where the pain arises from chemical or natural stimuli from damaged tissue (3). Neuropathic pain is predominantly initiated by changes in the ion channels that produce action potentials within the nerves (3). Chronic cancer pain consists of both inflammatory and neuropathic mechanisms as a direct effect of tissue response to the primary tumor or metastases (18). Given these traits, cancer pain can be considered a type of mixed pain, but increasing amount of evidence suggest additional unique features indicating that it should be regarded as a separate pain state (3).

1.4.1. Cancer-induced bone pain

The primary tumor or metastases may invade and damage the bony skeleton, and cancer-induced bone pain is the most common type of chronic cancer pain (18, 31). Cancer-induced bone pain includes elements from both inflammatory and neuropathic pain, with cancer-specific mechanisms contributing to the modifications of tissues, including nerves, in the periphery and the neurochemical changes at the spinal cord level (3, 32). The inflammation is caused by both direct tissue damage and release of pain mediators by the cancer cells, whereas the neuropathic component can be caused by both tumor-induced hyperinnervation and denervation, in addition to the cancer-related nerve compression and infiltration (3). The variability in cancer-induced bone pain intensity, not necessarily dependent on size or number of the skeletal lesions, is likely related to both peripheral and central mechanisms, including central downregulation of peripheral neuronal activity (3).

1.4.2. Cancer-induced neuropathic pain

The cancer can compress and destroy sensory nerves, and the pain is typically perceived in the distribution area of the affected nerves (18). Nerve damage leads to pathological

interaction, other than synaptic activity, between neurons (30). This feature is caused by the development of aberrant points of contact, called ephapses, permitting interaction between the somatic and the autonomous nerve system (30). Mutual excitation may occur directly or indirectly, and the peripheral nerve damage can result in a sympathetically maintained pain component (30). The mixed-mechanisms pain often seen in cancer patients (32), may contribute to the limited effect observed from co-analgesics for chronic cancer pain (33, 34). On the other hand, chronic post-cancer treatment pain is considered more similar to classic neuropathic pain in mechanisms and characteristics (33).

1.4.3. Cancer-induced visceral pain

The cancer-induced damage to internal organs in the head and neck region or within the thoracic, abdominal, or pelvic cavities can result in visceral pain (18). The pain mechanisms of cancer-induced visceral pain include compression, distension, inflammation, and ischemia (18). The pain may be poorly localized or even presented as referred pain in a somatic region (18). In comparison to somatic pain, the often more diffuse nature of visceral pain is conditional to both the more limited number of peripheral receptors and more scarce representation within the somatosensory cortex (30). In addition, the convergence of visceral and somatic afferent neurons in the spinal cord contributes to its referral to superficial structures (30). Visceral afferent neurons are called polymodal since they generate excitatory responses when influenced by different stimuli like inflammation, ischemia, compression, and distension (30). Organ distension is typically associated with episodic worsening of the cancer-induced visceral pain (18).

1.5. Cancer pain classification

Cancer pain is a complex symptom affecting physical and psychological functioning, daily activities, and emotional and social life (35, 36). The cancer patients experience their pain individually and heterogeneously, contributing to the challenges of cancer pain classification (37).

1.5.1. Previously developed classification systems

A systematic literature review published ten years ago identified six standardized classification systems for pain in cancer patients, of which three were systematically developed and partially validated (36):

1. The Edmonton Classification System for Cancer Pain (ECS-CP) has demonstrated value in predicting pain management complexity (38). As a standardized guide for clinical management, the physician evaluates pain mechanisms, psychological distress, addictive behavior, and cognitive function (39). In addition, the physician evaluates a feature named incident pain, describing a temporal increase in pain intensity (39). According to the ECS-CP administration manual, 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 (40). Incident pain usually has a rapid onset and often a known trigger (40).
2. The International Association for the Study of Pain classification system for chronic pain is intended both for malignant and non-malignant pain syndromes and includes evaluations of pain etiology, pathophysiology, intensity, localization, and temporal characteristics (36, 41).
3. The Cancer Pain Prognostic Scale was developed as a prognostic tool for prediction of pain relief in cancer patients based on information of pain characteristics, worst pain intensity, daily opioid dose, and emotional well-being (36, 42).

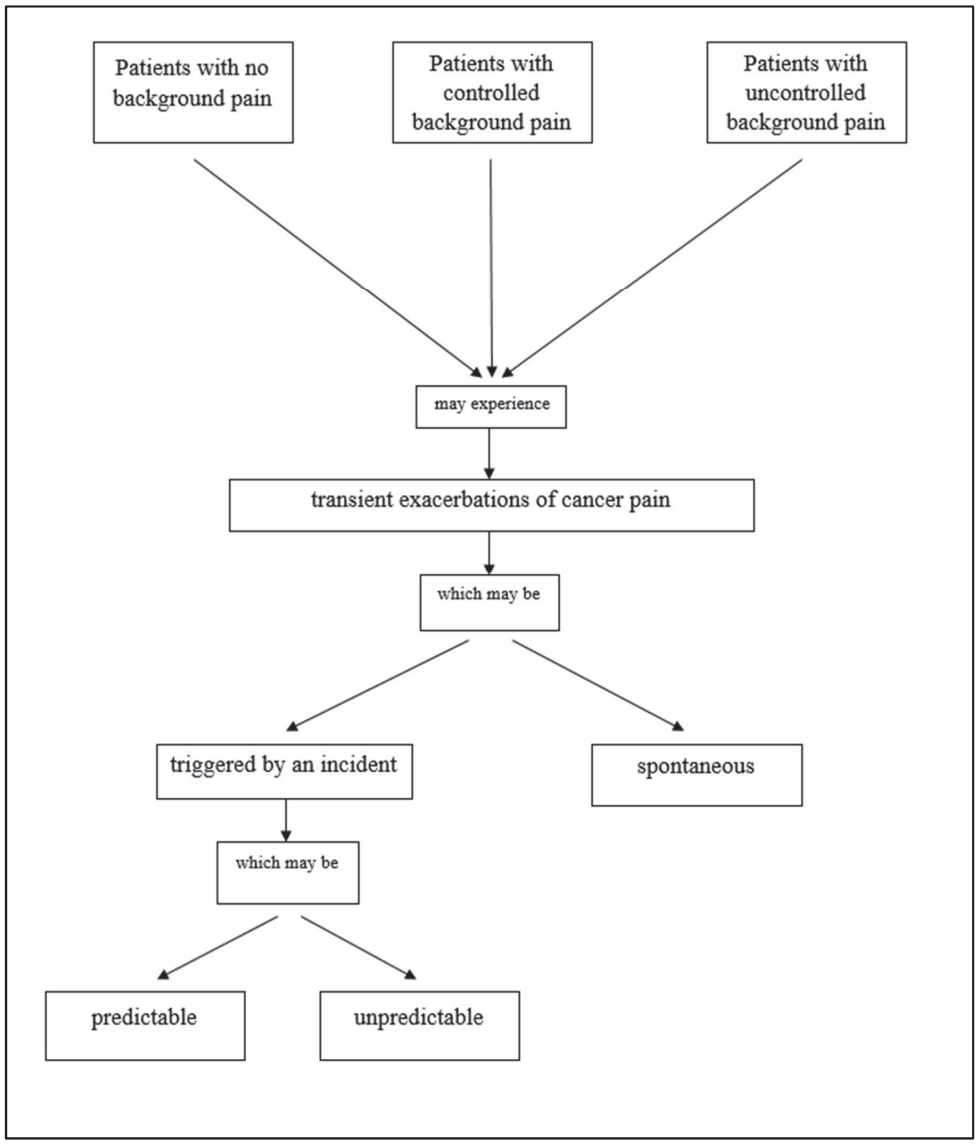
The systematic review on classification systems for cancer pain expressed the need for a shorter and more convenient system with the potential to become a standard for cancer pain

classification (36). A follow-up paper on the ECS-CP also advocated a simplification of the system for more successful adoption in clinical practice (38).

1.5.2. The concept of transient cancer pain exacerbations

Pain fluctuates, and cancer pain fluctuates, peaks and aggravates both due to treatment and disease factors (43-45). Information on the temporal pattern of pain is essential for adequate pain management, and evaluations of both worst pain intensity and background pain intensity are considered important (2, 43, 46-48). Transient pain exacerbations are defined as temporary pain flares that passes with time (49, 50). Transient cancer pain exacerbations are described in patients with both high and low background pain intensity and may even occur in patients without background pain (40, 49, 51, 52) (Fig.1.5). The episode may be spontaneous and not related to an identifiable precipitant, or the episode may be triggered by an identifiable incident, like walking, abdominal spasms, or wound dressing (45, 49). Thus, incident transient cancer pain exacerbations may be both predictable and unpredictable (45). Pain exacerbation at the end of an opioid dosing interval, and when the background pain increases, is described as end of dose failure (45, 49).

Fig.1.5 **Transient cancer pain exacerbations regardless of background pain intensity**



Different terminologies have been used to describe transient cancer pain exacerbations in cancer patients (43). Partly for linguistic reasons, in 2002 an Expert Working Group of the European Association for Palliative Care (EAPC) suggested the wording "episodic pain" (49, 53). However, breakthrough pain (BTP) is by far the most commonly used term (43).

1.5.3. Breakthrough pain

BTP is an episode of severe pain that "breaks through" the persistent and controlled chronic pain (45). The definition, prevalence and characteristics of BTP was described in 41 patients almost three decades ago (54). In the original definition, BTP was described as a transitory increase in pain to greater than moderate intensity, superimposed on a background pain intensity of moderate intensity or less (54). The description of incident pain in the ECS-CP shows great similarity with the original definition of BTP (40, 54). In more recent literature, adequately controlled background pain is defined as "mild", or specified as ≤ 4 (NRS 0–10) (49, 55). Furthermore, BTP is not considered a single entity, but a spectrum of very different entities (49). In addition, a mixture of different terms and subgroupings have been used, not necessarily contributing to clarity when interpreting the literature (43).

Ever since the first definition of BTP (54), most definitions are based on criteria of a controlled background pain, ruling out pain fluctuations in patients with inadequately controlled background pain and pain episodes occurring without background pain (43, 49). Still, there is a lack of consistency in the use of the term "BTP" in both literature and medical practice, varying from any exacerbation of pain, to pain peaks within the context of stringent BTP definitions (56). The level of basic analgesic treatment needed for diagnosing breakthrough pain also has been a matter of debate (51, 53).

1.5.4. The need for improved cancer pain classification

One aim of medical terminology is logical and accurate descriptions of symptom complexes and pathological processes in order to facilitate diagnostic precision, and in turn, logical and effective treatment. In the aftermath of a systematic review underlining the lack of a widely accepted classification system for BTP (43), a commentary pinpointed the need

for a classification system that reflects the different therapeutic approaches relevant for treating cancer pain (57). Furthermore, in a subsequent commentary on a review of BTP, the question whether BTP in fact is to be considered a separate entity was raised (44, 45).

1.5.5. ICD-11 classification for cancer pain

A recently published narrative review describes cancer pain classification in the 11th revision of the World Health Organization's International Classification of Diseases (ICD-11) (18). In ICD-11, chronic cancer pain is classified based on etiology and pathophysiology into bone pain, neuropathic pain and visceral pain, based on the logic that correct identification of the nature and cause of cancer pain will facilitate tailored treatment and hence optimal pain control. By temporal characteristics, cancer pain is described as continuous background pain and intermittent episodic pain (18).

1.6. Cancer pain assessment

Symptom assessment is pivotal in palliative care throughout the disease trajectory (58), and might even have a positive impact on survival (59). Patients with a history of cancer should routinely be screened for pain-related symptoms in the follow-up (60). Those identified with cancer-related pain should receive a pain assessment when seen by a health care professional, which as a minimum classifies the cause of pain based on the ICD-11 criteria (60). In addition, at least the intensity of pain and its impact on quality of life must be established (60).

The patient perspective and patient involvement are important elements in cancer pain care (58, 61). The use of patient-reported outcome measures (PROMs) and shared decision-making can facilitate this process (58). PROMs is an umbrella term covering the patient's perspective on physical and psychological wellbeing, including symptom severity, symptom impact, and treatment effects (62). Systematic use of PROMs in cancer pain assessment can provide information on factors such as pain intensity, duration and frequency, pain localization and quality, and the impact of pain on physical functioning and quality of life (58).

Pain assessment might be part of the general symptom assessment, or constitute a separate assessment of pain only (60). Furthermore, the assessment may be designed for evaluating pain subgroups such as bone pain, neuropathic pain, and visceral pain (60).

Visual analogue scales, numeric ratings scales, and verbal rating scales are all considered valid to assess pain intensity (63). Among the multidimensional questionnaires designed to assess pain, The Brief Pain Inventory (BPI) and the McGill Pain Questionnaire (MPQ) are valid in many multilingual versions (63).

1.6.1. The Edmonton Symptom Assessment System

The Edmonton Symptom Assessment System (ESAS) was developed almost thirty years ago as a clinical tool to document the symptom burden in patients with advanced cancer admitted to a palliative care unit (64). The initial version included eight predefined symptoms, pain included, and was intended to examine symptom intensity at the moment of assessment (64). The most updated version includes ten items and evaluates average symptom intensity over the past 24 hours (65). The symptoms are rated numerically (NRS 0-10), and for pain, zero represents no pain and ten represents worst pain intensity.

1.6.2. The Brief Pain Inventory

The BPI is a widely used tool that assesses the severity of pain and its impact on functioning (46). The BPI is available in two formats, the short form and the long form. The BPI long form contains additional descriptive items such as pain quality. Both the short and the long form include a pain body map and rates pain intensity numerically (NRS 0-10), with the assessment periods “last 24 hours” and “last week”, respectively. Both forms include questions on average and worst pain intensity. In addition to subjective pain intensity, the BPI measures different impairments caused by pain, such as influence on mood, walking ability and sleep (46). Hence, the BPI may be especially suited when the impairment caused by pain is considered an important outcome (47). Furthermore, the BPI also provides a measure for pain relief provided by the pain intervention.

1.6.3. The McGill Pain Questionnaire

The MPQ is a frequently used questionnaire for the multidimensional assessment of pain (66). The MPQ assesses three separate components of the pain experience: the sensory intensity, the emotional impact, and the cognitive evaluation of pain (67). The MPQ includes a pain body map, and hence, in addition to information on pain intensity and quality, also supplies information on pain localization (67).

1.6.4. Assessment tools for breakthrough pain

A systematic review performed almost a decade ago identified ten assessment tools for BTP in cancer patients, of which seven had been used in only one publication (43). Nine of the ten tools were for self-report, and all the tools included the domains pain intensity and treatment-related factors. Treatment-related factors include exacerbating and relieving factors, response to treatment, and treatment satisfaction (43). The Alberta Breakthrough Pain Assessment Tool (ABPAT) for cancer patients, developed for research purposes, includes questions on pain intensity, duration and frequency, and pain localization and quality (68). The ABPAT also contains questions on pain relief and treatment satisfaction with pain medication. Additionally, the ABPAT includes the health care provider's evaluation of pain etiology and pathophysiology (68). In a later validation study, the ABPAT was found to be well-accepted tool for BTP assessment and characterization in cancer patients (69). A more recently developed Breakthrough Cancer Pain Assessment Tool (BAT) includes questions on pain intensity, duration, frequency, and localization as well (70). The BAT also comprises questions on effects and side-effects of pain medication, and pain interference (70). According to the systematic review, the pain descriptors and treatment-related factors used in these two assessment tools are important in BTP assessment (43). Tools used for assessment of episodic pain worsening in patients regardless of background pain intensity also have been studied (51, 71).

1.6.5. Assessment of cancer-induced bone pain

A diagnostic work-up attempting to verify the mechanistic basis of the suspected bone pain needs to be done (2). In addition, pain intensity at rest and during activity, interference with

function, and pain localization will provide important information for tailoring pain treatment interventions (2).

1.6.6. Assessment of cancer-induced neuropathic pain

Rigorous pain assessment, followed by a diagnostic work-up, is needed to identify the presence of neuropathic pain in cancer patients (72, 73). The most widely used neuropathic pain screening tools are the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Douleur Neuropathique en 4 (DN4), and painDETECT (PDQ) (72). Concordance between clinical diagnosis and screening tool outcomes has been demonstrated for all three of them (72). Recently, a new algorithm has been proposed for diagnosing neuropathic pain in cancer patients, where the diagnosis is based on patient history, clinical examination, and a subsequent confirmation of the findings (73).

1.6.7. Assessment of cancer-induced visceral pain

Visceral pain both might be poorly localized and even referred to a somatic region, and these facts must be taken into consideration during assessment (18). The assessment must also include the temporal variations with episodic worsening due to organ distension (18). In addition to the necessary pain descriptors, the assessment of visceral pain must capture the often accompanying neurovegetative symptoms like nausea and vomiting (74).

1.6.8. Personalized symptom goals

The intrinsic subjectivity of the NRS 0-10 scale can result in significant variations with regard to how individual patients interpret the scale and express their symptom intensity (75). For example, one patient may consider a pain score of 6 (NRS 0-10) to be agonizing, whereas another patient may appear to be comfortable with the same pain score (65). In the era of personalized cancer care, personalized symptom goals (PSGs) are novel measures that may help to individualize symptom treatment (75). PSGs are determined by asking the patient “At what level of symptom intensity would you feel comfortable?” (75). In a study where 722 patients reported PSG for pain, the median PSG intensity for pain was 3, with an interquartile range (IQR) of 1-4 (NRS 0-10) (75).

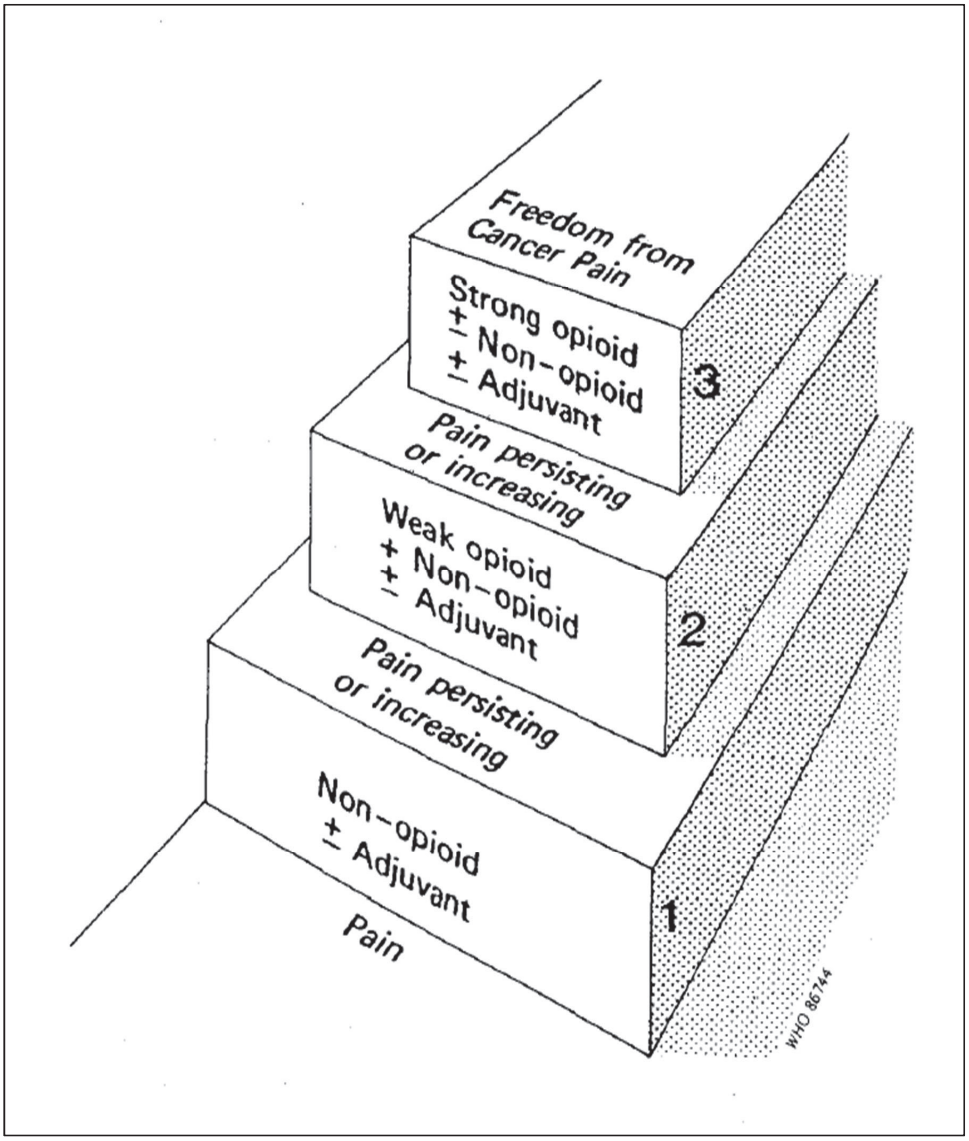
1.7. Cancer pain treatment

The treatment of chronic cancer-related pain should be individualized and balance benefits and burdens (76). The feasibility, appropriateness, and potential effects of systemic disease-modifying treatment should be considered in the overall strategy for pain management (76). The emerge of novel treatment modalities like immune checkpoint inhibitors and molecularly targeted therapies emphasizes the importance of this approach (77). If the pain is focal and related to mass effect or local destruction by a tumor, radiotherapy can be highly effective (76). Single fraction radiation treatment regimens provide similar outcomes related to pain control and toxicity compared with fractionated regimens (78). The goals of cancer-related pain management should be to reduce the pain and its impact on daily living through tailored treatment, and to increase each patient's ability for self-management (60).

1.7.1. The World Health Organization Guidelines for cancer pain relief

More than thirty years ago the World Health Organization (WHO) published guidelines for cancer pain relief (79). The guidelines acknowledged that cancer pain could be a result of the cancer and the cancer treatment, and be related to tumor growth in bone, nerves and visceral structures. The treatment principles included a step-wise intensification of analgesics, based on a "three-step analgesic ladder" for cancer pain management, administered on a regular, "by the clock", basis (Fig 1.7). Step one includes non-opioid drugs, step two the addition of weak opioids, which at the third step of the ladder are replaced with strong opioids, with or without the addition of non-opioids. Adjuvant drugs might be relevant at any step of the ladder (79). In the subsequent years, the WHO guidelines for cancer pain relief were evaluated and validated (80, 81).

Fig.1.7 **The original World Health Organization analgesic ladder for cancer pain** (79)



1.7.2. EAPC Guidelines on opioids for treatment of cancer pain

In 2012, the European Association for Palliative Care (EAPC) published updated recommendations on the use of opioids for the treatment of cancer pain (82). By a formalized expert consensus process, a list of 16 evidence-based recommendations were developed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (83). The EAPC opioid guidelines supplies recommendations on different aspects of cancer pain treatment ranging from the role of different opioids and alternative routes of administration to relative opioid analgesic potencies and management of opioid-related side effects (82).

1.7.3. ESMO Clinical practice guidelines for management of cancer pain

The European Society for Medical Oncology (ESMO) has provided guidelines for management of cancer pain in adult patients, last updated in 2018 (84). As described in the guidelines, a recent Cochrane review found no high-quality evidence to support or refute the use of paracetamol alone or in combination with opioids for the first two steps of the three-step WHO cancer pain ladder (84, 85). It was not clear whether any additional analgesic benefit of paracetamol could be detected in the available studies (85). The ESMO guidelines for the treatment of cancer pain recommends oral morphine as the first choice for moderate to severe cancer pain. Recommendations are made for different opioid routes and opioid rotation, alongside with recommendations for invasive management of refractory pain. Furthermore, the guidelines provide treatment recommendations for bone pain and cancer-related neuropathic and visceral pain (84).

1.8. Factors limiting improvement in cancer pain treatment

There are several reasons for the lack of improvement in cancer pain management. To be adequately treated, cancer pain needs to be identified, assessed, classified, and managed appropriately (27). Pain is a subjective symptom, and the physicians have to rely on patient self-reports (86). Inadequate cancer pain management is a multidimensional problem, and several authors have addressed barriers in cancer pain management and suggested

approaches for improvements (23, 58, 86-88). Barriers can be related to the patient, the health care professional, and the health care system (86). A recent study confirmed that patients show reluctance to discuss their symptoms with the health care professional (89), and misconceptions about pain and analgesic use are described (21). Furthermore, inadequate pain assessment is prevalent, and numeric and visual scales are used by only 7% to 43% of physicians (86). Moreover, there is a continuing deficit in health care professionals' knowledge with regard to cancer pain management (90). Barriers related to the health care system may include limited accessibility and collaboration (86). Suggested strategies to overcome barriers to cancer pain management include repeated self-assessments (NRS 0-10) for screening and monitoring, management according to pain guidelines and pain pathophysiology, and educational approaches directed towards the patients, the physicians, and their interaction (86).

1.9. Health care improvement and implementation

Health care interventions must be proven appropriate and not wasteful (91, 92). Purposeful efforts to secure positive changes have gained focus, and the study of improvement interventions has been promoted as a science (92-94). Adoption of a more scientific approach will help ensure validity and generalizability of care quality efforts (94), as standards for reporting will facilitate dissemination of results from health care improvement (95). Improvement science aims to create practice that can make a timely difference to patient care (94), with a primary goal to determine which improvement strategies work in the strive to ensure effective and safe patient care (92). Implementation research addresses the gap between available knowledge and real-world practice (96), with a focus on carrying an intention into effect (92).

1.10. Clinical care pathways and bundles of care

The optimization of patient safety and quality in health care remains the primary focus of quality improvement initiatives (97). Clinical care pathways and care bundles are both structured interventions aiming to improve patient outcomes and the process of care (98, 99).

1.10.1. Clinical care pathways

Clinical pathways aim to link best available evidence to clinical practice for specific health problems, and thus optimize patient outcomes and maximize clinical efficiency (100). Inspired by the systematic approach in production industries, clinical care pathways are structured interventions that describe essential steps in patient treatment (58). Important elements are a multidisciplinary plan, a translation of evidence into local structures by a detailed and standardized stepwise intervention, and time-frames or criteria-based progression (100). A care pathway is a complex intervention intended for decision-making and organization of the care processes for a well-defined group of patients during a well-defined period of time (101). Clinical care pathways may be applicable in many areas of health care (58). The Lancet Oncology Commission on integration of oncology and palliative care endorsed the use of clinical care pathways as a systematic approach to standardize care for cancer patients with needs for palliative care (58).

1.10.2. Bundles of care

Bundles of care are a composite of synergistic interventions intended to improve the clinical outcome for a condition (102). In addition, they ensure that the application of all relevant interventions is consistent for all patients at all times (102). Bundles of care are evidence-based practices that are grouped together to encourage the consistent delivery of these practices (103). Usually, they constitute a small, straightforward set of practices, that when performed collectively and reliably, improve patient outcomes (98). Care bundles are used widely across healthcare settings with the aim of preventing and managing different health conditions (104).

1.11. Clinical decision support systems

While the knowledge base regarding effective medical therapies continues to improve, the practice of medicine continues to lag behind, and errors are distressingly frequent (105). A time lag of approximately five years for guidelines to be adopted into routine practice has been demonstrated (105). Decision support addresses the gap between optimal and actual practice (105). Classic clinical decision support systems include alerts, reminders, order sets, or care summary dashboards that remind the clinician of a specific action, or provide feedback on quality indicators (106). In addition to the traditional clinical decision support systems, there is a continuum of information support for clinical care (106). A recently published cluster randomized trial described the effect of adding a clinician-delivered bedside pain assessment and management tool (107).

1.12. Rationale for the thesis

Cancer pain is prevalent and undertreated (23, 27), despite the potential for pain relief for the majority of the patients (86). The diversity and complexity of existing pain assessment tools has not resulted in pain assessment applied in the recommended manner (46, 64, 67, 68, 70, 86, 87). Furthermore, the lack of a universally accepted classification system hampers classification reflecting available treatment options (18, 36). In addition, there is a great variability in familiarity with and adherence to pain treatment guidelines and in knowledge on cancer pain pathophysiology (86, 87, 90). Practice variations and inconsistencies may further add to the observed variability (108).

We hypothesized that pain assessment and classification, reflecting the patient perspective and available treatment options, would result in improved pain control, provided systematic pain treatment according to established principles and guidelines.

2. Aims, objectives, research questions and outcomes

2.1. The aims of the thesis

The overall aims of the thesis were twofold: 1. To improve cancer pain assessment and classification, suitable for both research and clinical practice. 2. To improve cancer pain management by rigorous use of available knowledge.

2.2. The objectives of the thesis

The overall objectives of the thesis were threefold: 1. To reach a higher degree of international expert consensus on definitions, terminology and subclassification of transient cancer pain exacerbations. 2. To study the support for the expert opinions and BTP prevalence variability using data from a previous cross-sectional study. 3. To examine the effect of implementing scientific evidence into practice by the means of a clinical care pathway, including the patient perspective and integrated decision support, for cancer pain management.

2.3. Research questions paper I

1. How should transient cancer pain exacerbations be defined? 2. How should transient cancer pain exacerbations be termed? 3. How could transient cancer pain exacerbations be subclassified to guide treatment?

2.4. Research question paper II

How is the assessed BTP prevalence affected by different definitions for cutoffs for controlled background pain intensity, assessment periods for background pain, and cutoffs for the difference between worst and average pain intensity past 24 hours?

2.5. Aim and outcomes paper III

The overall aim of paper III was to investigate effects and use of an intervention based upon a care pathway structure, including systematic and repeated use of PROMs and a mandatory use of a physician-directed decision support, for cancer pain management in a specialized palliative care unit. The two primary outcomes were average and worst pain intensity reductions from admission to discharge. In addition, the number of eligible patients included and reporting PROMs, if and how the physicians used and based their decision-making on the PROMs and decision support, and development in hospital length of stay (LOS) during the study period, were secondary outcomes.

3. Materials and methods

Due to differences in study populations and study methodology, each study of the thesis is described separately.

3.1. Materials and methods paper I

3.1.1. The Delphi technique

The Delphi technique is widely used for the development of guidance in palliative care (109). A Delphi study is a survey where the judgement of experts is collected and distilled through an iterative group facilitation technique (110). The Delphi method is especially applicable where unanimity of opinions does not exist, and when the goal is improved understanding of problems and solutions (111). The feedback process allows and encourages the selected participants to reassess their initial judgements based on information provided in the previous iteration (112). Most Delphi studies are run for a prespecified number of rounds, and two rounds are most frequently used (110). Questionnaire research is notorious for its low response rates (113), and Delphi studies may have response rates below fifty percent (114, 115). A systematic review identified that most Delphi surveys include from 11 to 25 participants in the final round (110).

3.1.2. Study design and participants

Paper I is a Web survey performed in 2015 (116). The study included the most frequently published authors on BTP literature over the past ten years and was designed as a two-round international Delphi expert survey. The authors were identified by a literature search performed in PubMed, using the same strategy as in a previous systematic review on BTP (43). A predefined initial number of approximately 50 experts was chosen to ensure a final sample size large enough for valid results (114).

3.1.3. Selection of issues to be addressed

The issues addressed in the Delphi survey were based on areas with low degree of consensus identified in a systematic literature review on assessment and classification of

BTP (43). These included opioid medication as a prerequisite for the diagnosis of BTP, controlled background pain and how to measure it, and the lack of a formal classification system. The authors of the paper discussed these issues and formulated 20 statements included in the Delphi survey. The work was done on behalf of the European Association for Palliative Care Research Network.

3.1.4. Ratings, analysis and consensus definition

The study participants were asked to rate their degree of agreement with the statements (NRS 0-10, with the anchors ‘‘do not agree at all’’ and ‘‘completely agree,’’ respectively). The median consensus score (NRS 0-10) and the IQR were calculated for each statement, the latter being a measure of agreement among experts (73). Based on previous research and in accordance with the study protocol (73, 110), the statements reaching a median score of less than seven (NRS 0-10) or an IQR of more than three were reassessed, except for statements where the participants universally did not agree with the statement (median NRS 0). The median NRS rating and the IQR for each statement in the previous round were disclosed to the participants in the second round. According to a priori agreement and in line with recently published research (73, 115), consensus was defined as a median NRS (0-10) score of seven or more and an IQR of three or less. The results were reported as medians and IQRs of the agreement with the statements (111).

3.2. Materials and methods paper II

Paper II is a secondary analysis of the previously published European Palliative Care Research Collaborative-Computerized Symptom Assessment (EPCRC-CSA) study, which originally was designed to assess the feasibility of computer-based symptom assessment (117, 118).

3.2.1. Study Design and Patient Population

The EPCRC-CSA is a cross-sectional observational international study conducted in 17 centers within eight countries and was completed in 2009 (117). Adult patients with

incurable cancer and able to complete a computer-based symptom assessment were eligible for the EPCRC-CSA study. Patients who rated their worst pain intensity ≥ 1 (NRS 0–10) for the previous 24 hours were subject to further pain assessment and eligible for paper II.

3.2.2. Measurement Tools and Data Collection

The measurements used in the secondary analysis included: 1. A simplified item from the ABPAT (68), where all patients with worst pain intensity ≥ 1 (NRS 0–10) for the past 24 hours were introduced to the concept of BTP as characterized in the ABPAT instructions (68). They were then presented with the question: ‘‘Have you had flare-ups of BTP in the last 24 hours?’’ (Yes/No). 2. Elements from the BPI, where each pain intensity scale ranges from 0 (no pain) to 10 (pain as bad as you can imagine) (46). BPI questions on worst pain intensity past 24 hours and past week were supplemented with questions on worst pain intensity past 48 hours, and average pain intensity specified for the time periods ‘‘past 24 hours’’, ‘‘past 48 hours’’, and ‘‘past week’’.

3.2.3. Terminology and Statistical Analysis

Average pain was used as a measurement for background pain and, unless stated otherwise, with the assessment period ‘‘past week’’ (49). Patients answering ‘‘yes’’ to the ABPAT-based BTP screening question were classified as ‘‘ABPAT+’’. The ABPAT-positive patients were grouped according to background pain intensity past week, and the cumulative percentages of ABPAT-positive patients within each potential level of maximal background pain intensity were computed. Subsequently, the procedure was repeated for the assessment periods for background pain ‘‘past 48 hours’’ and past ‘‘24 hours’’. Kappa statistic was used to compare agreement beyond chance between the cumulative percentages of ABPAT-positive patients with background pain ≤ 4 (NRS 0–10) for the three different assessment periods for background pain. Kappa values 0.61–0.80 indicate substantial agreement, and kappa values 0.81–1.0 indicate almost perfect agreement (119). Finally, the ABPAT-positive patients grouped according to background pain intensity past week were further categorized based on the difference between reported worst and average pain intensity past 24 hours. The chosen categories were: A difference of at least one point,

a difference of at least two points, and a difference of more than two points (NRS 0–10) between worst and average pain intensity past 24 hours. Hypothetical BTP prevalences were calculated from percentages of ABPAT-positive patients satisfying specified criteria for background pain intensity and difference between worst and average pain intensity past 24 hours.

3.2.4. Compliance with Ethics Statement

Paper II is based on a previously conducted clinical study. All procedures performed in the primary study were in accordance with the ethics committees at the respective study sites and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the primary study.

3.3. Materials and methods paper III

3.3.1. Context

The study was performed among inpatients at the Palliative Care Unit, Cancer Clinic, St. Olavs hospital, Trondheim University Hospital (120). The Regional Committee for Medical and Health Research Ethics classified the project as quality assurance, and the hospital Data Protection Supervisor endorsed the study. The study was designed as a phase II interventional prospective uncontrolled trial, where the intervention represented measures to accomplish pain treatment according to recommended standards.

As part of the routine symptom screening, pain intensity is assessed for all admitted patients. Patients with a pain score ≥ 5 (NRS 0-10) at admittance are in specific need of attention, as their pain is more intense than “mild” (121, 122). In the period September 2016 to March 2017, all patients with locally advanced and/or metastatic cancer and with a pain score ≥ 5 (NRS 0-10) on admittance were screened for inclusion in the study. Exclusion criteria were patients < 18 years of age, patients with severe cognitive

impairment, patients admitted for planned radiotherapy, and patients unwilling or unable to fill in symptom self-assessment reports.

3.3.2. Interventions

PROMs were collected at admission, at day four of the hospital stay, and at planned discharge. The patients rated the average pain intensity the past 48 hours (NRS 0-10), the worst pain intensity the past 24 hours (NRS 0-10), and the degree of treatment satisfaction with both the around the clock (ATC) and the on demand (PRN) pain medication (NRS 0-10, 10 representing completely satisfied) (116, 118).

The physicians had access to the collected PROMs when presented with a decision support paper form. The decision support was filled in by the physicians at admission and at day four of the hospital stay. It was formulated as ten questions with the response options “yes”, “no”, and “uncertain”. By nature, the decision support represented “reminders” on possible needs for changes in opioid dose, administration route or opioid rotation, or needs for additional treatment for neuropathic, visceral, or bone pain. In addition, the physicians were asked to report whether the pain treatment was changed based on the PROMs and/or the decision support.

3.3.3. Primary outcome measures

Comparison of patient-reported average pain intensity and worst pain intensity at admission and discharge, respectively, were primary outcomes. A pain intensity difference of two points (NRS 0-10) was considered clinically relevant for both primary outcomes (123, 124).

3.3.4. Secondary outcome measures

The number of patients with pain intensity ≥ 5 (NRS 0-10) at admittance, the number of eligible patients included in the study, and the number of patients formally reporting PROMs were secondary patient-related outcomes.

The number of physicians who filled in the decision support at admission and at day four was a secondary physician-related outcome. Further physician-related outcomes were the percentages of treatment revisions based on the PROMs and decision support at admission,

respectively, and changes in the percentage of treatment revisions based on decision support information during the study period. Finally, to which degree the physician-reported need for treatment changes at admission were verified when the patient charts were searched for actual treatment changes at discharge, also constituted a secondary physician-related outcome measure.

Besides the secondary outcomes related to the patients and the physicians, change in LOS during the study period was a secondary health care service-related outcome.

3.3.5. Analysis

Recently published research reported a standard deviation (SD) of 2.1 for average pain intensity and an SD of 2.7 for worst pain intensity for cancer in-patients (24). Power analysis based on two primary outcomes (reduction in average and worst pain intensity), an SD of 2.7, and an alpha error of .025, indicate that a one-sided paired t-test carried out on 40 patients will have a minimum power of .9 to detect a two point (NRS 0-10) pre-post pain intensity difference, allowing for repeated measurements correlation of .1 or higher. As varying and high attrition rates are reported in supportive care and palliative oncology trials (125), the study was run until the necessary number of consecutive patients with complete data was obtained.

Patients who died during the hospital stay resulted in missing data. Single imputations with last value carried forward were performed for the patients with missing data. Mean average pain intensity and mean worst pain intensity at discharge for all included patients were computed for comparison with the complete cases. The subgroup not able to fill in the PROMs constituted patients in need of end-of-life care, and they were not included in the subsequent effect outcome analyses.

For the patients discharged alive, mean pain intensities at admission and discharge were compared using a paired sample t-test.

The number of patients filling in PROMs at admission, at day four of the hospital stay, and at planned discharge were compared to the number of available patients at the respective points of time, and completion rates were calculated.

The completion rate of the decision support forms by the physicians at admission and at day four was computed. The percentages of physician-reported treatment changes based on PROMs and decision support at admission, respectively, were calculated with 95 % confidence intervals (CI). In addition, the percentages of physician-reported treatment changes based on the decision support were computed for patients enrolled early, in the mid-phase, and late in the study period. Finally, the percentage of concordance between physician-reported need for treatment changes at admission and documented treatment changes recorded from the medical charts was calculated for each item in the decision support. For these calculations, decision support responses were dichotomized into “yes” and “no/uncertain”, and treatment changes were dichotomized into “increased” and “decreased/unchanged”.

LOS was reported for patients enrolled early, in the mid-phase, and late in the study period. The difference between early and late enrolment was calculated with 95% CI.

4. Results related to objectives, research questions and outcomes

4.1. Results with respect to the overall objectives of the thesis

Despite persisting controversies and disagreement regarding basic definitions of transient cancer pain exacerbations (43), the expert Delphi survey provided consensus on several key statements. The existence of transient cancer pain exacerbations outside the definition of BTP was agreed upon. Moreover, the experts agreed that an overarching concept for all significant transient cancer pain exacerbations will contribute to standardization in assessment and classification, and the suggestion that the term “episodic pain” could serve the purpose was endorsed. In addition, consensus was reached for the importance of identifying pathophysiological pain mechanisms, and for the importance of assessing patient-reported treatment satisfaction.

Expert opinions from the Delphi study were verified in paper II, which demonstrated that episodic pain outside the definition of BTP is prevalent. Estimated BTP prevalence is dependent on definitional criteria and population background pain intensity during the assessment period. The study also demonstrated that assessment of worst and average pain intensity recalled from the past one or two days, and hence reflecting the most recent changes in pain medication, are appropriate.

The third paper demonstrated effect with the standardized and repeated use of PROMs and decision support. The reduction in average and worst pain intensities was in the range of three to four points (NRS 0–10). The PROMs included worst and average pain intensity, recalled from the past one and two days, respectively, and treatment satisfaction with both ATC and PRN pain medication. The decision support explored the need for pain treatment changes based on patient-reported worst and average pain intensity and pain treatment satisfaction, and the need for specific treatment interventions based on pathophysiological pain mechanisms. The concordance between the responses indicated in the decision support and actual pain treatment changes made during the hospital stay was high.

4.2. Results paper I

Fifty-two authors had published three or more articles on BTP over the past ten years and were eligible for the study. The contact details were unavailable for four authors; therefore, an invitation mail was sent to 48 potential participants. Two authors declined participation because of lack of clinical experience, leaving 46 potential respondents. After two reminders, 27 respondents provided complete answers to the first round and 24 respondents provided complete answers to the second round. Consensus was reached for 13 of 20 statements (Table 4.2).

Regarding the statements on definitions, consensus was reached in the first round for: ‘‘Transient cancer pain exacerbation is possible without significant background pain’’ (NRS 9.0, IQR 3.0), ‘‘Significant transient cancer pain exacerbation is possible without background pain being controlled’’ (NRS 10.0, IQR 3.0), and ‘‘Significant transient cancer pain exacerbation can occur in patients currently not on opioids’’ (NRS 10.0, IQR 2.0). Consensus was also reached in the first round for the statements: ‘‘Background pain is best described as controlled when the patient is satisfied with the overall pain control the around the clock pain medication provides’’ (NRS 8.0, IQR 3.0), and ‘‘A significant transient cancer pain exacerbation can best be assessed by the patient’s wish/need for rescue medication’’ (NRS 7.0, IQR 3.0).

For statements on terminology, consensus was reached in the first round for the statements: ‘‘An overarching concept for all significant transient cancer pain exacerbations will contribute to standardization in assessment and classification’’ (NRS 7.0, IQR 3.0), and ‘‘The term episodic pain could serve as an overarching concept for all significant transient cancer pain exacerbations’’ (NRS 7.0, IQR 3.0).

Consensus was reached in the first round for all the statements on subclassification: ‘‘A subgrouping of transient cancer pain exacerbations will provide better opportunities for a more precise diagnosis and better tailored treatment’’ (NRS 8.0, IQR 3.0), ‘‘Identification

of transient cancer pain exacerbations due to bone metastases can affect treatment choices'' (NRS 9.0, IQR 2.0), ''Identification of transient cancer pain exacerbations due to neuropathic pain can affect treatment choices'' (NRS 9.0, IQR 2.0), and ''Identification of transient cancer pain exacerbations due to visceral pain can affect treatment choices'' (NRS 9.0, IQR 3.0).

Two statements on definitions and terminology reached consensus after reassessment in the second round (ratings from 1. and 2. round, respectively): ''The increase in pain intensity on an NRS scale (0-10) has to be more than two points for the transient cancer pain exacerbation to be significant'' (NRS 7.0, IQR 5.0 and NRS 7.0, IQR 3.0), and ''There are significant cancer pain exacerbations other than breakthrough pain''(NRS 9.0, IQR 5.0 and NRS 8.0, IQR 2.75).

For five statements, consensus could not be reached, and there was a unanimous disagreement with two of the statements (Table 4.2).

Table 4.2 **Statements and consensus ratings** (116) *

Consensus Reached in Favor of the Statement	1. Round		2. Round	
	NRS	IQR	NRS	IQR
Definitions				
Significant transient cancer pain exacerbation can occur in patients currently not on opioids	10.0	2.0		
Significant cancer pain exacerbation is possible without the background pain being controlled	10.0	3.0		
Transient cancer pain exacerbation is possible without significant background pain	9.0	3.0		
Background pain is best described as controlled when the patient is satisfied with the overall pain control the around the clock medication provides	8.0	3.0		
A significant transient cancer pain exacerbation can best be assessed by the patient's wish/need for rescue medication	7.0	3.0		
The increase in pain intensity on an NRS scale (0–10) has to be more than two points for the transient cancer pain exacerbation to be significant	7.0	5.0	7.0	3.0
Terminology				
An overarching concept for all significant transient cancer pain exacerbations will contribute to standardization in assessment and classification	7.0	3.0		
The term episodic pain could serve as an overarching concept for all significant transient cancer pain exacerbations	7.0	3.0		
There are significant cancer pain exacerbations other than breakthrough pain	9.0	5.0	8.0	2.75
Subclassification				
Identification of transient cancer pain exacerbations due to bone metastases can affect treatment choices	9.0	2.0		
Identification of transient cancer pain exacerbations due to neuropathic pain can affect treatment choices	9.0	2.0		
Identification of transient cancer pain exacerbations due to visceral pain can affect treatment choices	9.0	3.0		
A subgrouping of transient cancer pain exacerbations will provide better opportunities for a more precise diagnosis and better tailored treatment	8.0	3.0		
No consensus in favor of the statement				
Background pain is best described as controlled when the background pain intensity is 3 or less on an NRS scale (0–10)	7.0	5.0	7.5	6.75
Background pain is best described as controlled when the background pain intensity is 4 or less on an NRS scale (0–10)	7.0	6.0	6.0	3.0
A significant transient cancer pain exacerbation can best be assessed by an increase in NRS score to a certain predefined number	5.0	6.0	5.0	3.0
A significant transient cancer pain exacerbation can best be assessed by a percentage increase in NRS score	5.0	6.0	5.0	5.0
An increase in pain intensity of two point on an NRS scale (0–10) is a significant transient cancer pain exacerbation	4.0	4.0	5.0	3.75
An increase in pain intensity of one point on an NRS scale (0–10) is a significant transient cancer pain exacerbation[a]	0.0	2.0		
Background pain is best described as controlled when the background pain intensity is 6 or less on an NRS scale (0–10)[a]	0.0	2.0		

NRS = numeric rating scale; IQR = interquartile range.
[a]Statement not reassessed in the second round.

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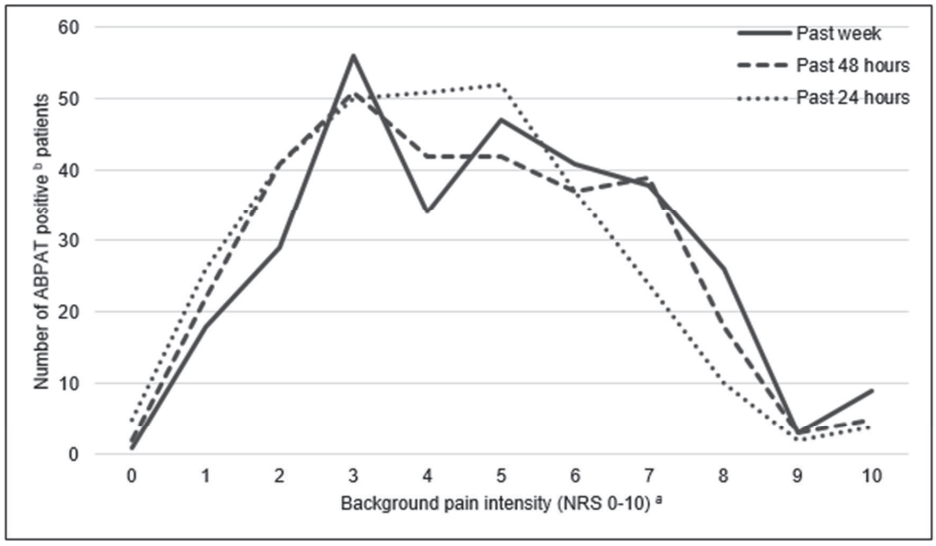
4.3. Results paper II

Among 1017 patients included in the EPCRC-CSA study, 715 persons reported worst pain intensity ≥ 1 (NRS 0–10) past 24 hours. Patient-reported BTP registrations according to the ABPAT-based screening question, and average pain intensity registrations for the three assessment periods ‘‘past week’’, ‘‘past 48 hours’’, and ‘‘past 24 hours’’ were available for 696 patients. The included patients had a mean age of 62 years and a mean Karnofsky status of 69. Eighty-six percent of the patients had metastatic cancer and 58% were inpatients.

Three hundred and two out of 696 patients (43.4%) who answered the APBAT-based screening question reported flare-ups of BTP for the past 24 hours and were classified as ‘‘ABPAT+’’. The distributions of background pain intensity for ABPAT-positive patients are displayed in Fig. 4.3.1 for the three assessment periods ‘‘past week’’, ‘‘past 48 hours’’, and ‘‘past 24 hours’’. The mean average pain intensity scores for the assessment periods ‘‘past week’’, ‘‘past 48 hours’’, and ‘‘past 24 hours’’ were 4.0, 3.6, and 3.4 (NRS 0–10), respectively. Fig. 4.3.1 illustrates that a large proportion of the ABPAT-positive patients had uncontrolled background pain.

Fig.4.3.1 **Distribution of background pain intensity [a] in ABPAT-positive [b] patients** (118) *



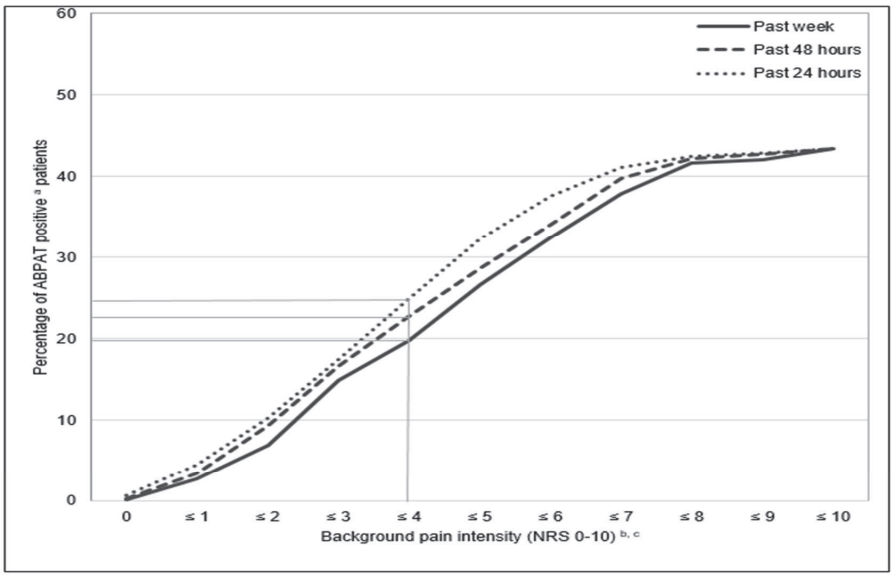
[a] Background pain intensity assessed for the three time periods "past week", "past 48 hours", and "past 24 hours".
[b] Patients answering "yes" to the Alberta Breakthrough Pain Assessment Tool (ABPAT) based breakthrough pain screening question were classified as ABPAT positive.

Defining a cutoff for background pain intensity ≤ 3 (NRS 0–10) in ABPAT-positive patients resulted in a BTP prevalence of 14.9%. The corresponding number for a defined cutoff for background pain intensity ≤ 4 was 19.8%. The assessed BTP prevalence increased when including patients with higher background pain intensity, and reached 43.4 % when including all ABPAT positive patients, irrespective of background pain intensity.

Actual background pain intensity and BTP prevalence varied between the different assessment periods ‘‘past week’’, ‘‘past 48 hours, and ‘‘past 24 hours’’. Different mean average pain intensity scores for the assessment periods (pain intensity 4.0, 3.6, and 3.4,

respectively) result in variable percentages of patients meeting the requirements for having BTP (Fig.4.3.2). Compared to a 19.8% BTP prevalence using background pain intensity ≤ 4 (NRS 0–10) assessed for the past week, the corresponding percentages were 22.7 using background pain intensity the past 48 hours (93% agreement, kappa 0.80), and 24.9 using background pain intensity the past 24 hours (92% agreement, kappa 0.76).

Fig. 4.3.2 **ABPAT positive [a] prevalence variability [b] related to different assessment periods for background pain intensity [c]** (118)

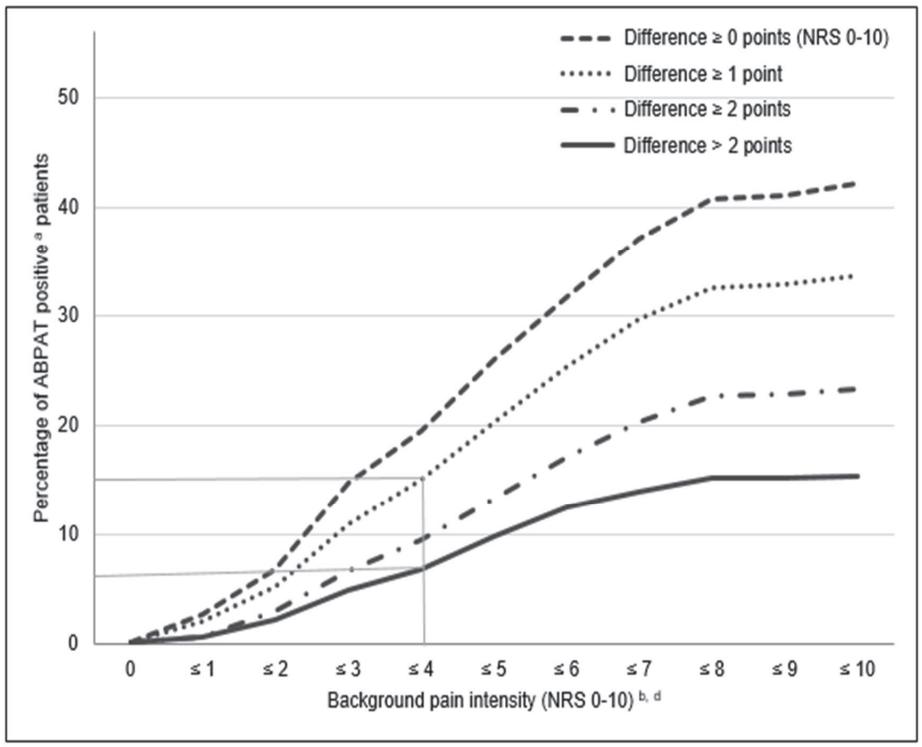


[a] Patients answering "yes" to the Alberta Breakthrough Pain Assessment Tool (ABPAT) based breakthrough pain screening question were classified as ABPAT positive.
[b] ABPAT positive prevalence variability related to different assessment periods for background pain indicated for a cutoff for background pain intensity ≤ 4 (NRS 0-10).
[c] Background pain intensity assessed for the three time periods "past week", "past 48 hours", and "past 24 hours". Mean pain intensity for the three assessment periods were 4.0, 3.6 and 3.4 (NRS 0-10), respectively. All calculations include the cumulative percentages of patients with the respective background pain intensity or less.

Among ABPAT-positive patients, the difference between worst and average pain intensity past 24 hours ranged from zero to more than two points (NRS 0–10). A minimum difference between worst and average pain intensity past 24 hours of one point and background pain intensity ≤ 4 (past week), resulted in a BTP prevalence of 15.1%. A minimum difference of two points between worst and average pain intensity, resulted in a

BTP prevalence of 9.5%. Fig. 4.3.3 illustrates the BTP prevalence variability related to difference between worst and average pain intensity past 24 hours.

Fig. 4.3.3 **ABPAT positive [a] prevalence variability [b] related to difference between worst and average pain intensity [c]** (118)



[a] Patients answering "yes" to the Alberta Breakthrough Pain Assessment Tool (ABPAT) based breakthrough pain screening question were classified as ABPAT positive.
[b] ABPAT positive prevalence variability related to difference between worst and average pain intensity past 24 hours, indicated for a difference of at least one point and a difference of more than two points, and a cutoff for background pain intensity ≤ 4 (NRS 0-10).
[c] Difference between worst and average pain intensity for the past 24 hours, displayed for the differences: ≥ 0 points, ≥ 1 point, ≥ 2 points and > 2 points (NRS 0-10).
[d] Background pain intensity assessed for time period "past week". All calculations include the cumulative percentages of patients with the respective background pain intensity or less.

4.4. Results paper III

In the study period, 246 patients were admitted to the Palliative Care Unit, Cancer Clinic, St. Olavs Hospital. Fifty-two patients with pain intensity ≥ 5 (NRS 0–10) at admission were included. The included patients had a mean age of 67 years and a mean ECOG performance status of III. Ninety-six percent of the patients had metastatic cancer. Mean LOS was 10.6 days for the 52 included patients. Data registrations at discharge were available for 41 patients.

At admission, for all 52 included patients, the mean average pain intensity in the past 48 hours and mean worst pain intensity in the past 24 hours were 5.9 and 7.8 (NRS 0–10), respectively. At discharge, with last value carried forward imputations in the 11 patients who died during the hospital stay, mean average pain intensity in the past 48 hours and mean worst pain intensity in the past 24 hours were 3.0 and 4.3 (NRS 0–10), respectively.

Primary outcomes

For the 41 patients discharged alive, mean average pain intensity in the past 48 hours at admission and at discharge were 5.8 and 2.4 (NRS 0–10), respectively. There was a reduction in average pain intensity during the hospital stay of 3.4 points (CI 95% 2.7–4.1, p = 0.00). For the same group of patients, mean worst pain intensity in the past 24 hours at admission and at discharge was 7.9 and 3.8 (NRS 0–10), respectively. There was a reduction in worst pain intensity during the hospital stay of 4.1 points (CI 95% 3.4–4.8, p = 0.00).

Secondary outcomes

In the study period, 22% of the admitted patients had pain intensity ≥ 5 (NRS 0–10). Only two eligible patients were not included. All 52 included patients reported PROMs at admission, and all 46 and all 41 available patients reported PROMs at day four and at discharge, respectively. Decision support forms were filled in by the physicians for all 52 and for all 46 available patients at admission and day four, respectively. For 80% (95% CI 69–90%) of the patients, the physicians reported pain intervention revisions at admission

based on the PROMs. For 55% (95% CI 41–69%) of the patients, the physicians reported pain intervention revisions at admission based on decision support information. There was a non-significant increase in physician-reported treatment changes based on the decision support during the study period, from less than 50% to approximately 70% of the patients ($p = 0.17$). The percentages of concordance between the physician-reported need for treatment changes at admission (collected from the decision support forms), and documented treatment changes made during the hospital stay (collected from the charts) was more than 80 % for six items in the decision support. Comparing the first third and the last third of the enrolled patients, mean LOS were 12.9 days and 8.5 days, respectively. There was a significant reduction in LOS of 4.4 days (CI 95% 0.5–8.3 days, $p = 0.03$) from patients enrolled early to late in the study period.

5. Discussion

The Delphi survey established that clinically important cancer pain flares exist outside the definition of BTP. International experts on BTP acknowledged the need for an umbrella term including all clinically relevant pain flares and agreed that the term “episodic pain” would be applicable. Furthermore, the importance of pathophysiological pain mechanisms and the patient perspective was recognized. There were, however, diverging opinions on numerical descriptors of the definitions of controlled background pain intensity and clinically relevant pain flares. Paper II verified that episodic pain outside the definition of BTP is prevalent. Moreover, the importance of strict definitional criteria for controlled background pain intensity and clinically relevant pain flares in BTP research was demonstrated. Study III showed that structured pain assessment, reflecting available treatment options for both background pain and episodic pain and including the patient perspective, ultimately can result in significantly reduced pain intensity. In order to achieve this goal, the collected information was utilized systematically in cancer pain management based on pathophysiological pain mechanisms and evidence-based principles. There was a high level of compliance with the interventions in the study.

5.1. Appraisal of methods

5.1.1. Paper I

In paper I, a Delphi survey was performed among experts on BTP for the predefined two rounds and with definitions of criteria for reassessment and consensus described in the study protocol.

The Delphi technique was initially developed to predict cold war enemy attack probabilities, but it is a relevant source of evidence in health care research and has been employed in palliative care research for defining professional standards and developing guidance on best practices (109, 110). Key features of the method are anonymity between

the participants, controlled feedback provided in a structured manner, and data analysis (110, 112). The credibility of the results depends on the rigorous use of the Delphi technique (109). Still, the results from a Delphi process remain expert opinions, and its outcomes can only be as reliable as the available evidence and the participating experts (109). In the hierarchy of medical evidence, expert opinions are considered the lowest level of evidence (126).

Rationale for the choice of the Delphi technique

One aim of medical terminology is logical and accurate descriptions of symptom complexes and pathological processes in order to facilitate diagnostic precision and in turn, reasonable and effective treatment. BTP is the most commonly applied term for the transient exacerbation of pain in cancer patients, but the variety of definitions with different limitations and terminology reflect the diversity of opinions on this subject (43). Pain is subjective and personal, and although a frequent finding in cancer patient populations, often left untreated (127). Cancer pain fluctuates, peaks and aggravates both due to treatment and disease factors. Based on the question whether the nomenclature captures these variations and enable classification in a logical manner, issues with low degree of consensus identified in a systematic literature review were addressed in an expert Delphi study (43). In addition to the systematic review, the literature was searched to provide more insight on the controversies (9, 39, 49, 51, 128-135).

Study design

The study was a web survey with anonymity between the participants, who were contacted by email. Web surveys can by nature be subject to considerable bias by the non-representative nature of the population and the self-selection of participants (136). Therefore, the participants in the study were selected based on specified criteria, as described below. However, the four missing mail addresses may represent a selection bias (137). Moreover, the low response rates in questionnaire research (113, 115), further contributes to the selection. Also in our study, responses were obtained only from approximately 50% of the potential participants. Aside from the two authors with lack of

clinical experience, the potential risk for selection bias was checked for the eligible authors with respect to number of publications on BTP. For the authors who completed the survey the mean number of publications on BTP was 5.5, and for those who did not the corresponding number was 4.7. For the non-responders, mean time since their previous publication on BTP was 2.7 years (range 0-7 years), indicating recent research activity.

The current study was carried out for two rounds and with twenty predefined statements. The flexibility of the Delphi process allows for adaptation on number of rounds and to which degree the statements evaluated for consensus are specified at the start of the process (111, 138). It might be argued that the chosen design contributed to study rigor and reduced the probability of sample fatigue (109, 138). In addition, for the majority of the statements, consensus was reached in the first round. For the two statements where consensus was reached after reassessment in the second round, the iterative group facilitation technique did not increase the degree of agreement with the statements, only the interrater agreement. However, the chosen design did not allow the participants to provide opinions for discussion and evaluation (111), which in addition to the perception that the process might force consensus are arguments in disfavor of the Delphi technique (109, 138). Thus, the Delphi technique is exposed both to researcher and participant bias (138).

Study participants

The expert panel was selected based on a predefined search in PubMed, originally used in a systematic review on BTP (43). The experts were the most published authors on BTP literature, and to ensure the intended size of the final sample authors with three or more publications the previous decade were addressed. The selection criteria were chosen with the intent to achieve the most appropriate panel for the purpose, reduce selection bias, and provide transparent information on recruitment (109). There are no universally agreed criteria for the selection of experts for a Delphi panel, and little guidance on the number of panelists (109, 112, 113). In line with previous literature (73, 110, 112, 113, 138), we identified stakeholders on BTP research through an objective approach and aimed for a final sample of approximately 25 participants. Considerably smaller sample sizes might not

include participants with representative opinions on the statements, whereas too large sample sizes might result in lower response rates and unnecessary time consumption (112).

Selection of issues to be addressed

A systematic review on BTP identified low degree of consensus on definitions and classification of transient cancer pain exacerbations (43). The authors further discussed these problems based on described cancer pain syndromes, available treatment options, and the need for a taxonomy that promotes good clinical practice and allows research to progress (9, 57, 73, 82, 139, 140). Despite a thorough process, based on disagreements detected in a systematic review, knowledge of relevant literature, and the clinical and research expertise of the authors, the choice of statements to address in a Delphi study ultimately relies on elements of subjective preferences.

Analysis

In accordance with the study protocol, consensus was a priori defined as a median NRS (0-10) score of seven or more and an IQR of three or less. Besides the opinion that agreement should exceed 50 percent, there is no universally agreed upon definition of consensus in Delphi studies (110, 114, 138). However, most authors agree that a consensus definition must be provided prior to the study and include a measure of central tendency and level of dispersion (109, 111, 113, 138). In the current study, the measure of agreement with the statements and to which degree the respondents agreed with each other were defined based on previous research (73, 111, 115). Different cutoffs, of course, would have affected the results.

5.1.2. Paper II

Cross-sectional study design

The EPCRC-CSA study, which constituted the database of paper II, is a cross-sectional observational study (117). Cross-sectional studies are carried out at one time point, or over a short period of time, and hence represent a snapshot of the presence (141). They are usually designed for prevalence estimations, but, due to the study design, different time frames might yield different results (141). Epidemiological studies are prone to systematic

errors like information bias and selection bias (142). Recall bias is one type of information bias, and a selection bias called Neyman bias is a feature and a disadvantage of cross-sectional studies (141, 142). Neyman bias represents the fact that patients with a poor prognosis might be excluded from a study (141). Although patients with transient exacerbations of pain have been associated with a poorer prognosis (143), this is mainly related to time to pain control and opioid dose requirements (144). However, the sample not being representative of the population from which it was drawn is a general problem (145). The facts that the patients in the EPCRC-CSA study were not included consecutively and that the participating centers were not chosen at random, might represent selection biases.

Secondary analysis of existing data

Paper II is a secondary analysis of a data set originally collected to assess the feasibility of computer-based symptom assessment (117). Hence, the available data were not collected primarily to address the research question in paper II (146). Addressing novel research questions based on existing data requires a rationale for the research question and a description of the study population, time frame of the data collection, and assessment tools before conducting the analysis (146). The approach is described in the "Introduction" and "Methods" sections of the paper.

The secondary analysis of existing data has become more common in health care research (146, 147). One advantage in secondary analyses is the availability of large data sets (148). Paper II included 696 patients whose pain was evaluated by several self-reported assessment methods. A potential limitation of the analysis of existing data is that the researchers analyzing the data were not involved in the data collection process (146). Two of the authors of the primary study on computer-based symptom assessment, including the principal investigator, also co-authored paper II and provided access to the original study protocol, questionnaires, and database. Other problems analyzing existing data might be sampling errors and missing data, resulting in bias (149). In paper II, study participants with pain intensity ≥ 1 (NRS 0-10) were subject to further pain assessment, meaning that all patients in the primary study reporting pain the previous 24 hours were eligible in the

secondary analysis. Missing data was present for 19 patients, or 2.7% of the eligible patients. Variables missing less than five percent of the values are deemed acceptable for statistical analysis (149).

Measurement tools

The measurement tools in paper II included a simplified item from the ABPAT and elements from the BPI (46, 68).

According to the ABPAT research definitions, characterizing BTP when baseline pain is not controlled is difficult (68). Controlled baseline pain is defined as "mild" or less, or ≤ 4 (NRS 0-10) (68). In the EPCRC-CSA study, the participants were introduced to the concept of BTP by the two sentences: "BTP can be defined as a brief flare-up of pain. It can be a flare-up of the usual, steady pain you always experience (your baseline pain) OR it can be a pain that is different from your baseline pain". Then, regardless of background pain intensity, the study participants were presented with the screening question: "Have you had flare-ups of BTP in the last 24 hours?" with the response options "yes" or "no". To assess BTP, the patient must have background pain, which also must be adequately controlled (49). If the patient in addition experiences transient exacerbations of pain, the patient has BTP (49). Hence, based on the single screening question, the presence of BTP cannot be detected. However, a patient-reported positive response to the screening question indicates the presence of transient exacerbations of cancer pain.

The pain assessments in the BPI include patient-reported worst and average pain intensity rated numerically (NRS 0-10) (2). For worst pain intensity, the long form of BPI uses "in the last week" as the time reference and the short form uses "in the last 24 hours" as the time reference. For average pain intensity, no time reference is indicated (2). In the EPCRC-CSA study, patient-reported worst and average pain intensity were rated numerically (NRS 0-10) for the assessment periods "last 24 hours", "last 48 hours", and "last week". Previous research has indicated that recall ratings are reliable and valid measures of actual pain and that ratings from different recall periods are highly correlated (150, 151). Moreover, some authors have argued that recalled pain might even better reflect

the overall experience of pain and its impact on function in cancer patients compared to ratings of current pain, even though recalled pain ratings tend to overestimate pain intensity (150, 152).

Average pain intensity as a measure for background pain intensity

For decades, average pain intensity has been used to describe background pain intensity in patients with BTP (51, 54). Background pain is described as more intense in patients with BTP, which seems reasonable considered that BTP is a transient exacerbation of pain, and average pain intensity reflects all variations in pain intensity (132, 153). It may be argued that average pain and background pain are not equivalent terms. Still, given the inherent challenges and complexity of pain assessment, separating the terms might not result in relevant improvements (48).

Difference between worst pain intensity and average pain intensity as a measure for the intensity of transient cancer pain exacerbations

Proxy knowledge on cancer pain may be relevant if firsthand information is lacking (154). Information on the magnitude of transient exacerbations of pain was not available in the current data set. To compensate this lack of information, the difference between worst pain intensity and average pain intensity was computed. This difference may be different from the difference in peak pain intensity during a transient pain exacerbation and the background pain intensity at that point in time. However, to illustrate that the prevalence of pain flares is dependent on the definition of the phenomenon, this approach was found acceptable.

Kappa statistic

If the possibility of chance agreement is neglected, misleading conclusions might be the result (119). The kappa statistic is frequently used to test interrater reliability and compares agreement beyond chance (155). In paper II, kappa statistic was used to compare the cumulative percentages of patients with background pain ≤ 4 (NRS 0-10), recalled from different assessment periods, in patients responding “yes” to the ABPAT BTP screening

question. Measuring only the degree of agreement between the ratings overestimates the concordance, as chance agreement is not accounted for (155).

5.1.3. Paper III

Study III is an interventional prospective uncontrolled trial, performed within the framework of a health care improvement project (95).

Randomized controlled trials and "pragmatic" study designs

Randomized trials provide robust evidence about the effects of interventions because they can be designed to create groups that are balanced, with the intention to remove systematic errors like bias and confounders (156, 157). Concerns that many randomized trials do not adequately inform practice have resulted in a distinction between explanatory trials and pragmatic trials (158), which best may be considered as the extremes of a continuum (157). Pragmatic trials aim to inform a clinical or policy decision by providing evidence for adoption of the intervention into real-world practice (158), and thus focus on maximizing external validity (157). Still, the results from randomized controlled trials may not be generalizable for clinical practice (157, 159). In palliative care, for ethical, economic, or practical reasons, clinical trials are not always appropriate (109). Additionally, in a single-center randomized controlled trial the risk of spillover effects from a complex intervention is present (160), possibly resulting in failure to detect an existing difference, or a type II error (161). A cluster-randomized study design may have solved this problem, but was beyond the scope of the current trial (162).

Studies with observational designs are often used to measure the effectiveness of an intervention in "real-world" scenarios (163). A Cochrane review reporting health care outcomes assessed with observational study designs compared with those assessed in randomized trials found little evidence for significant effect estimate differences (163). Nevertheless, due to limitations in study design, study III provided no certain inference on causality between the intervention and the effect (164). Lack of information on pre-study results and no comparison group contribute to this feature. The open-label, one-group study design opens for systematic errors, including bias and confounding, and the results obtained

might be influenced both by health care service-related factors and patient-related factors (137). Furthermore, the generalizability of the results may be limited by the single-center design in a specialized palliative care unit.

Health care improvement

Improvement science aims for advances in patient care (94). The planning, conduction, and reporting of study III was based on the Standards for QUality Improvement Reporting Excellence (SQUIRE) 2.0 publication guidelines (95). The application of a scientific methodology based on more robust study designs may increase validity and generalizability of health care improvement projects (94). The not-so-straightforward generalizability of findings in improvement projects is an inherent design weakness, related to lack of a structured explanation of mechanisms of change (93). In the planning of the study, effort was put into the task of carefully describing the context, interventions, and outcomes.

Interventions

The intervention included systematic and repeated use of PROMs and a mandatory use of physician-directed decision support, and the intervention was based on a care pathway structure.

Pain assessment by patient self-report is recommended (27), and PROMs represent all measures that can best, or only, be assessed by asking the patients themselves (58). In study III, the patients rated their worst and average pain intensity numerically (NRS 0-10). The assessment periods for worst and average pain intensity were the last 24 hours and the last 48 hours, respectively. In addition, the patients rated the degree of treatment satisfaction with both the ATC and the PRN pain medication numerically (NRS 0-10). Previous research has suggested that, in the measurement of transient cancer pain exacerbations, patients use NRS more appropriately than verbal rating scales (VRS) and that NRS should be preferred to VRS in this patient population (165). The questions on worst and average pain intensity were based on elements from the BPI, which is validated in Norwegian cancer pain patients (47). Comparison of different recall periods in cancer patients has shown a high correlation between a 24-hour and a 7-day recall period for cancer pain (151).

Paper II also demonstrated a high degree of agreement for pain intensity between the assessment periods “past 24 hours”, past 48 hours”, and “past week (118). Choice of recall periods for PROMs should depend on the specific purpose of the trial, the characteristics of the disease, and the treatment to be tested (151). For the purpose of the current study, short recall periods for pain intensity were preferred to capture the effect of the pain interventions applied during a relatively short hospital stay. Still, acknowledging the natural fluctuations in cancer pain intensity (166), average pain intensity was assessed for the past 48 hours. Treatment satisfaction, indicated by separate questions on effect and side effects of the pain medication, is assessed numerically (NRS 0-10) in the validated BTP assessment tool BAT as well (70). Also in paper I, the importance of patient-reported pain treatment satisfaction was recognized (116).

Classic clinical decision support ranges from alerts and reminders to feedback on quality indicators (106). Preserving the clinician’s autonomy, simplicity, and user-friendliness are considered important for the success of a decision support (105, 167). Furthermore, given the prevalence of cancer pain and the deemed potential for effective analgesic treatment in most cases (23, 27), we hypothesized that cancer pain management, provided rigorously according to established standards, would improve pain outcomes. The decision support in paper III was based on recommendations and guidelines for cancer pain treatment and included the patient perspective (58, 82, 84). As acknowledged in paper I, also considerations on pain mechanisms and the need for treatment of bone, neuropathic, or visceral pain were included (116). The decision support was formulated as ten questions, encouraging the clinicians to reflect on potential needs for changes in pain treatment. By nature, the decision support represented reminders on possible pain intervention revisions. With the intention to optimize user compliance, the decision support was presented as a single sheet paper form with three predefined response options.

A clinical care pathway is a method for the structured implementation of complex interventions in patient care (58). In paper III, cancer patients with pain intensity ≥ 5 (NRS 0-10) reported PROMs repeatedly and systematically. The clinicians were provided this

information, which had to be processed using a mandatory decision support. The pain management was then carried out within the existing framework of the multifaceted care process in a specialized palliative care unit. Thus, the intervention may be described as a care pathway for a sub-cohort of the admitted patients. A care pathway should ideally include explicit statements of the goals and key elements of care, the roles, and sequence of the activities of the multidisciplinary team, and the monitoring and evaluation of variances and outcomes (101). In fact, one might argue that the intervention, consisting of evidence-based practices grouped together to encourage delivery of evidence-based care, merely represented a bundle of care (103).

Measured effects, use of the intervention, and interpretations

A pain intensity difference of two points (NRS 0-10) was considered relevant for both primary outcomes (123, 124). Extensive work has been undertaken to identify meaningful cut points for pain intensity and relevant measures of changes in pain intensity (116, 121, 123, 124, 168-172). Pain intensity reductions can be assessed on numeric rating scales as a decrease in absolute score, a decrease to a predefined number, or as a proportion of decrease (169, 171). For raw numerical scores, a commonly cited clinically important difference in pain intensity is two points (NRS 0–10) (123). However, different viewpoints exist on relevant cutoffs for improvement and deterioration in symptom intensity, ranging from one point to more than two points (116, 172-174). The importance of strictly defining the magnitude of the pain intensity difference of interest was demonstrated in paper II (118). In paper III, the measured pain intensity differences were larger than those considered relevant for the primary outcomes.

Use of the intervention was part of the overall aim and secondary outcomes of paper III. We observed that the patients and the physicians filled in the PROMs and the decision support. We also observed that pain treatment was changed based on the PROMs for three quarters of the patients and that pain treatment was changed on the decision support for half of the patients. These observations ensure that the interventions were applied. However, despite the concordance between the response to decision support at admission and the

observed treatment changes during the hospital stay, no conclusions on causality can be drawn (175). The complexity of the palliative care given in a specialized hospital unit may influence both the intervention and the outcome and represent confounding factors (137).

The development in treatment changes based on the decision support and in LOS during the study period were both tested for statistical significance. There was no significant increase in use of decision support during the study period ($p = 0.17$). When testing for reduction in LOS during the study period, the 95 % CI did not include zero days, but ranged from 0.5 – 8.3 days ($p = 0.03$), indicating statistical significance (176). The CI can be thought of as the set of true but unknown differences that are statistically compatible with the observed difference (177). Wide CIs may indicate small sample sizes or large dispersion of values (176).

Sample sizing

Selecting an appropriate sample is a crucial step in study design, and a study with insufficient sample size may not have sufficient power to detect meaningful effects (178). The four principal components required to calculate a sample size are the alpha error, the minimal clinically relevant difference, the variability in the outcomes, and the power (179). With two primary endpoints, and based on the Bonferroni adjustment (180), an alpha error of 0.025 was chosen. A pain intensity difference of two points was considered relevant (123, 124), and SDs for worst and average pain intensity were estimated based on recent findings in cancer in-patients at the hospital where the study was performed (24). Repeated measures correlation is a statistical technique for determining the within-individual association for paired measures assessed on two or more occasions for multiple patients (181). When calculating power, repeated measures correlation was taken into consideration.

Missing data

Varying and high attrition rates are reported in supportive care and palliative oncology trials (125). Patients who died during the hospital stay resulted in missing data, and those not able to fill in the PROMs constituted patients in need of end-of-life care. Single imputations with last value carried forward were performed for the patients with missing

data (182). The mean average pain intensity and mean worst pain intensity at discharge for all included patients were computed for comparison with the complete cases. For all 52 included patients, the reductions in average and worst pain intensity during the hospital were 2.9 and 3.5 points (NRS 0-10), respectively.

5.2. Comparison with previous work

5.2.1. Pain flares outside the definition of BTP

BTP research has developed over the past three decades (45, 49, 128). The work by Davies et al. contributed largely to the operational criteria of BTP, by establishing an algorithm with the necessary preconditions for the diagnosis, including background pain, which must be controlled, and transient exacerbations of pain (49). Many authors have recognized the existence of significant transient cancer pain exacerbations outside the definition of BTP, including pain flares when the background pain is not controlled and pain flares without background pain (40, 50-52). Still, even among experts on BTP, there is dispersion in opinions on this subject (116). However, the experts agreed that pain flares on top of intense background pain and in the absence of background pain may be of clinical relevance. The expert opinions that pain flares may occur regardless of background pain intensity were supported by the findings in paper II, showing almost normally distributed background pain intensity in patients with self-reported pain flares (118). Furthermore, paper III demonstrated that worst pain intensity may affect the clinical decision making regarding ATC opioid pain medication (120). Similarities in pain descriptors, like localization and quality, for BTP and background pain are described in both older and more recent research (54, 183).

5.2.2. Episodic pain as an umbrella term for all clinically relevant pain flares

Over the past two decades, several authors have addressed the need for improved cancer pain terminology (44, 53, 57). Almost twenty years ago, episodic pain was suggested as a broader term for transient exacerbations of cancer pain (53). The definition of BTP has narrowed over the years (44), which may result in the exclusion of clinically important

episodic pains (45). Based on the need for more international agreement on cancer pain terminology, the Delphi study was conducted. The most frequent authors on BTP literature acknowledged the need for an umbrella term, including all clinically relevant pain flares. The term episodic pain was found suitable as an overarching term for all significant cancer pain exacerbations. In the aftermath of the Delphi Survey, a topical review preceding the publication of ICD-11 described cancer pain in terms of a continuous background pain and an intermittent episodic pain (17). In the recently published review, describing the new classification of chronic cancer-related pain for ICD-11, the temporal characteristics of cancer pain is described similarly, as background pain and episodic pain (18).

5.2.3. Cancer pain classification based on pathophysiology and etiology

The importance of cancer pain classification based on pain etiology and pathophysiological pain mechanisms is emphasized in ICD-11(18). This seems intuitively logical, as the treatment approach may vary widely dependent on whether the pain is caused by the cancer or the cancer treatment, and dependent on whether the tumor expands into bone, intestines, or nerve tissue. The ECS-CP also points out the importance of pain classification based on pathological processes and pain mechanisms (39). Furthermore, pain mechanisms and pathophysiology is frequently described in studies concerning classification of pain in cancer patients (36). The expert Delphi panel agreed that knowledge on pathophysiological pain mechanisms may affect treatment choices. In paper III, the decision support on pathophysiological pain mechanisms yielded high concordance with specific treatment measures for neuropathic, visceral, and bone pain taken during the hospital stay.

5.2.4. Strict definitional criteria in BTP research

A systematic literature review including studies published from 1990 to 2012 reported BTP prevalences ranging from 40% to approximately 80% (153). The definitional criteria for BTP varied, and the prevalence rate was higher when cutoff for background pain intensity was moderate (57.2%) vs mild (49.7%) (153). Similarly, the BTP prevalence rate tended to decrease from the oldest to the most recent publications (153). Background pain of moderate intensity or less was a criterion in the first BTP definition (54). In more recent

literature, adequately controlled background pain is defined as “mild”, or specified as ≤ 4 on the 11-point numeric rating scale (NRS 0–10) (49, 55). The results from the systematic review are consistent with the findings in paper II, where we demonstrated a decreased BTP prevalence with lowered cutoff for background pain intensity. The distribution of background pain intensity in paper II was similar to previously published research, with a large proportion of the patients reporting uncontrolled background pain (51). It could be argued that the findings in paper II would be different if all patients had controlled background pain. However, a previous paper studying the prevalence of BTP in patients with different background pain before and after optimization of the analgesic regimen reported unchanged general prevalence of BTP, even though the number, intensity, and duration of BTP decreased (184).

5.2.5. Structured pain assessment reflecting available treatment options

The European Pain Federation recently published a position paper on standards for cancer-related pain management (60), based on GRADE recommendations for evidence (185). There are strong recommendations for pain assessment that includes the temporal variations of pain intensity, the pain mechanism, and pain etiology (60). After assessment, the patients should receive tailored multimodal treatment. Access to specialist services for patients responding insufficiently to standard care should be readily available and include options for palliative radiotherapy and intrathecal pain treatment (60). Also the ESMO clinical practice guidelines for management of cancer pain in adult patients emphasize the importance of repeatedly assessing pain based on intensity, temporal patterns, localization, pathophysiology, and etiology (84). Recommendations for the treatment of both background pain and episodes of severe pain that “breaks through” the persistent pain are provided (45, 84). The recommendations describe multimodal treatment of neuropathic, visceral, and bone pain (84). Multimodal cancer pain treatment includes the use opioids and adjuvant drugs administered by different routes, ranging from oral to intrathecal drug delivery, and the use of specific treatment approaches for neuropathic and visceral pain, and radiotherapy for painful bone metastases (84). Furthermore, a review on cancer pain assessment and classification published in 2019 also underlined the significance of pain

assessment resulting in a tailored treatment strategy (10). The described approaches will enable a structured pain assessment reflecting the available treatment options.

In paper I, a diagnostic workup guided by important symptom descriptors and PROMs followed by a symptom diagnosis with related pathophysiology and etiology was presented. The importance of acknowledging the occurence of episodic pain outside the definition of BTP was demonstrated in paper II. In paper III, large reductions in pain intensity was demonstrated when pain assessment reflecting the practical possibilities for treatment options was utilized systematically to provide cancer pain management according to existing guidelines.

5.2.6. The patient perspective

As part of interactive shared decision making, the patient's voice must be heard by their medical team during the diagnostic workup and treatment planning process (58). In cancer care, the patient perspective is recognized as valuable or even decisive regarding symptoms, function, and quality of life (58). The patient perspective has been recognized as important in pain assessment for decades, and already the BPI included elements of treatment satisfaction by questions on pain relief provided by the pain medication both in its long and short form (46). Also in BTP assessment the importance of the patient perspective is recognized, and treatment related factors in general, and pain relief provided by the BTP medication specifically, are often addressed (43, 68, 70). The ABPAT includes a specific question on satisfaction with the BTP medication, whereas the corresponding approach in the BAT is separate questions on effects and side effects from the BTP medication (70).

The patient perspective in assessment and reassessment of pain was further developed by the introduction of personalized pain goals (186). Even though a reduction in pain intensity of one point (NRS 0-10) on the ESAS is considered clinically important (172), for the individual patient this may not represent a meaningful reduction in pain intensity (65). A PSG represents the level of symptom intensity the patient would be comfortable with (65).

In paper I, The Delphi panel acknowledged the importance of treatment satisfaction as an important indicator of pain control. In paper III, the concept of treatment satisfaction was utilized both in the assessment of pain and in the physician-directed decision support. And both for ATC and PRN pain medication, there were concordance between low degree of treatment satisfaction at admission and pain management interventions during the hospital stay. Available information on the patient's personalized pain goal of course would have opened for further individual tailoring of the pain management.

5.2.7. Systematic utilization of available information in pain management

Only a year after the publication of the WHO guidelines for cancer pain relief (79), the systematic approach for cancer pain management advocated in the guidelines proved efficacious (80). In addition to being effective, the method was safe (81). Later research, using a randomized study design, showed that educational interventions with focus on a standardized approach for cancer pain management reduced pain intensity (187). These results were confirmed in a cluster randomized trial, where the intervention represented systematic assessment, treatment guidance, and reassessment to determine both treatment effects and side effects (107).

The aim of a clinical care pathway is to organize and standardize the care process in order to maximize patient outcomes, promote patient safety, and increase treatment satisfaction, in addition to improving organization efficiency (99, 101). Thus, important goals in a care pathway structure are similar with the desired outcomes in cancer pain management, and a care pathway represents a suitable method to implement systematic pain management (58).

Also bundles of care are systematic compound interventions intended to improve clinical outcomes, and the essential components are based on best evidence, local considerations, and open to change with time (102), much like the recommended management of cancer pain (60, 84, 188). A recent systematic review suggested that care bundles may reduce the risk of negative outcomes compared with usual care (104).

The wide specter of clinical decision support systems address the gap between optimal and actual practice, by supplying the clinician with reminders, information summaries, or

knowledge (105, 106). Thus, decision support may contribute to the systematic utilization of available knowledge, whether hampered by busy clinicians or lack of expertise.

On a more general level, improvement interventions and implementation research aim to achieve appropriate and not wasteful health care interventions by addressing the gap between available knowledge and real-world practice (91, 92, 96). Cancer pain guidelines, clinical care pathways, bundles of care, and decision support systems are all means to reach the goal of best clinical practice. In study III, elements from these different procedures were combined to ensure that acknowledged standards were applied systematically, through an intervention based on the systematic checklist approach used in aviation for decades (189). Even though the intervention was implemented according to the intentions and pain intensity was reduced as hypothesized, the level of generalizable or transferable knowledge, applicable in other setting, may be debated (94).

5.2.8. Evidence-based cancer pain management

Systematic cancer pain assessment with symptom self-reporting, studied with a randomized trial design, is associated both with clinical benefits and improved survival (59, 190). Cancer pain assessed by PROMs is a recommended standard and its use is supported in updated review articles and guidelines (10, 60, 84). Although the evidence-base for cancer pain treatment has expanded since the publication of the WHO guidelines for cancer pain relief (79), much of the conventionally accepted practice remains supported by clinical observations only (76). Still, there is high level evidence for opioids as a mainstay for treatment of cancer pain, but also for tailored multimodal treatment including radiotherapy, adjuvant drugs, and invasive pain management (60, 82, 84). The management of cancer pain in study III was based on available evidence and conventionally accepted practice.

5.2.9. Compliance with recommended standards

The stable high prevalence of cancer pain, the reported undertreatment, and the identified factors limiting improvement in cancer pain treatment illustrate the gap between available knowledge and real-world practice (23, 27, 86, 92). Suboptimal assessment and lack of knowledge are commonly described barriers for improved cancer pain management (86-

88). To collect best available information on patient symptomatology, systematic and repeated assessment of PROMs must be encouraged (58). Still, an easily available presentation of PROMs and evidence-based decision support for the physicians may not necessarily improve pain management (191). Previous research on decision support indicates no impact if the reminders are easy to ignore, that the clinicians ability to exercise their own judgment is important, and that simple interventions work best (105).

For more than a decade, there has been a growing focus on checklists and bundles of care to promote quality in health care (189, 192-196). The implementation of the WHO Surgical Safety Checklist is associated with reduced rate of complications and especially when fully completed (194). However, the success of the checklist approach is dependent on the contemporary socio-adaptive changes to improve practice, which essentially means that its success is dependent on the concurrent and lasting positive changes in the teamwork, communication, and culture of the health care providers (193, 195).

The intervention in study III constituted evidence-based principles for pain assessment and treatment and was applied in a dedicated palliative care unit. The intent was to apply a simple, yet mandatory decision support, which systematically encouraged the physicians to reflect on the need for change in existing treatment and the need for additional available treatment options. The effect of the intervention in other settings and for health care providers less proficient in pain treatment is unknown, as is the long term effects of the study intervention.

6. Implications of the thesis

Focus was put on transient cancer pain exacerbations outside the definition of BTP. The umbrella term “episodic pain”, intended to comprise all clinically relevant pain flares and endorsed by experts on BTP, is suggested incorporated in the ICD-11 revision for cancer pain.

Episodic pain outside the definition of BTP is prevalent and hence must be accounted for in inclusion and exclusion criteria in research and addressed in clinical practice.

Pain assessment, reflecting available treatment options for worst and average pain originating from bone, nerve tissue or viscera, can result in large reductions in pain intensity, if that information is utilized systematically to provide pain treatment according to established guidelines and in accordance with the patient’s wish. These findings should be studied in other settings and with a controlled design.

7. Conclusions

The thesis addressed assessment, classification, and treatment of cancer pain, specified by the research questions, outcomes, objectives and aims repeated in italics below.

7.1. Research questions paper I

How should transient cancer pain exacerbations be defined?

The Delphi panel agreed that short-lived episodes of more severe cancer pain can occur without background pain, with uncontrolled background pain, and independently of opioid pain medication. Patient-reported treatment satisfaction is important when defining controlled background pain and significant transient cancer pain exacerbations. However, consensus was not reached for most statements specifying numerical pain intensity scores.

How should transient cancer pain exacerbations be termed?

There are transient cancer pain exacerbations other than BTP. The benefit of an overarching term comprising all transient pain exacerbations was acknowledged, and the suggestion that he term ‘‘episodic pain’’ could serve the purpose was endorsed.

How could transient cancer pain exacerbations be subclassified to guide treatment?

Consensus was reached for the importance of identifying the pathophysiological mechanisms of transient cancer pain exacerbations.

7.2. Research questions paper II

How is the assessed BTP prevalence affected by different definitions for cutoffs for controlled background pain intensity, assessment periods for background pain, and cutoffs for the difference between worst and average pain intensity past 24 hours?

BTP prevalence estimates were dependent on both the cutoff for controlled background pain and the population background pain intensity during the assessment period for background pain. The prevalence estimates were approximately doubled if assessed without including controlled background pain as a criterion. Different cutoff criteria for a necessary numeric difference between worst and average pain intensity had a substantial impact on the assessed BTP prevalence.

7.3. Aim and outcomes paper III

The overall aim of paper III was to investigate effects and use of an intervention based upon a care pathway structure, including systematic and repeated use of PROMs and a mandatory use of a physician-directed decision support, in cancer pain management in a specialized palliative care unit.

In a specialized palliative care unit, and studied in a single sample with an open-label design, standardized assessments and physician-directed decision support were used and pain intensity reductions were demonstrated.

The two primary outcomes were average and worst pain intensity reductions from admission to discharge.

There was a reduction in average pain intensity during the hospital stay of 3.4 points (CI 95% 2.7–4.1, p = 0.00). There was a reduction in worst pain intensity during the hospital stay of 4.1 points (CI 95% 3.4–4.8, p = 0.00).

The number of eligible patients included and reporting PROMs, if and how the physicians used and based their decision-making on the PROMs and decision support, and development in hospital length of stay during the study period, were secondary outcomes.

Only two eligible patients were not included. All 52 included patients reported PROMs at admission, and all 46 and all 41 available patients reported PROMs at day four and at discharge, respectively. Decision support forms were filled in by the physicians for all 52

and for all 46 available patients at admission and day four, respectively. For 80% (95% CI 69–90%) of the patients, the physicians reported pain intervention revisions at admission based on the PROMs. For 55% (95% CI 41–69%) of the patients, the physicians reported pain intervention revisions at admission based on decision support information. There was a significant reduction in hospital length of stay of 4.4 days (CI 95% 0.5–8.3 days, p = 0.03) from patients enrolled early to late in the study period.

7.4. The objectives of the thesis

To reach a higher degree of international expert consensus on definitions, terminology and subclassification of transient cancer pain exacerbations.

The Delphi survey provided consensus on several key statements. There were, however, diverging opinions on numerical descriptors of the definitions of controlled background pain intensity and clinically relevant pain flares.

To study the support for the expert opinions and BTP prevalence variability using data from a previous cross-sectional study.

Paper II verified that episodic pain outside the definition of BTP is prevalent. Moreover, the need for strict definitional criteria for controlled background pain intensity and clinically relevant pain flares in BTP research was demonstrated.

To examine the effect of implementing scientific evidence into practice by the means of a clinical care pathway, including the patient perspective and integrated decision support, for cancer pain management.

Study III showed that structured pain assessment, reflecting available treatment options for both background pain and episodic pain and including the patient perspective, can result in significantly reduced pain intensity, provided the information is utilized systematically in cancer pain management based on pathophysiological pain mechanisms and evidence-based principles.

7.5. The aims of the thesis

To improve cancer pain assessment and classification, suitable for both research and clinical practice.

Consensus was reached among experts on cancer pain for a common terminology for all relevant pain flares, an approach planned incorporated in the new ICD revision. The importance of recognizing pathophysiological pain mechanisms was acknowledged, is planned included in ICD-11, and showed relevance in a clinical study. Also the thesis displayed the importance of accurate definitional criteria in BTP research.

To improve cancer pain management by rigorous use of available knowledge.

In a health care improvement project, with potential for generalizability and further research, improved cancer pain treatment, with the rigorous use of assessment and classification reflecting relevant treatment options, was demonstrated.

8. Future perspectives

8.1. Simplifying pain assessment and classification without losing important information

Pain due to cancer is a complex symptom that affects the patient's physical functioning and activities, psychological and emotional status, and social life (36). In addition, comorbidity like impaired cognitive function and addiction are significant predictors of complexity of pain and must be accounted for (39). The emotional impact and the cognitive evaluation of pain has been an integral part of pain assessment for decades (67). The BPI measures distress and impairments caused by pain (46), as also evaluated in BTP assessment (70). In the classification of cancer pain, the ECS-CP includes the features psychological distress, addictive behavior, and cognitive function (197). Still, although being an established core clinical activity, systematic symptom assessment is rarely done or actively used in the decision-making process in oncological and palliative care practices (58). The completion of the ECS-CP has been limited due to its perceived complexity of decoding each feature (38). Hence, a significant simplification was suggested (38). One challenge in future cancer pain research is developing assessment and classification simple enough for practicality and complex enough for effect.

8.2. Methodological rigor in cancer pain research

Understanding study design is important not only for the researcher, but also for the individual practitioner (137). The demonstrated deficiencies in quantity, design, and scope of the palliative oncology literature may further complicate this task for the clinician (198). BTP prevalence estimates vary among different populations and settings, and a systematic review on prevalence of BTP reported a large variability in definitional criteria (153). Hence, the prevalence range in BTP literature may be related to both real differences and measurement differences (199). The degree to which the content of an instrument is an

adequate reflection of the construct to be measured, or the content validity, is often considered the most important measurement property of PROMs (200). All studies are subject to some degree of error, and systematic errors like bias on selection criteria and measurements must be considered (137). The application of clinical study findings in patient care depends on the concept of generalizability, and if a patient differs from the patients studied in a trial the applicability of the results is in question (137). Problems with the evaluation of external validity in trials have been acknowledged, and computer-aided assessment of the generalizability of trial results has been suggested to enable better interpretation of their results (201, 202). Therefore, when designing studies clear definitions of inclusion and exclusion criteria are paramount. Furthermore, international collaboration to improve the standardization in assessment and reporting of BTP should be prioritized (203). For the clinician, guidance on the applicability of trial results in real-world practice is of great importance.

8.3. Closing the gap between available knowledge and actual practice

The multidimensionality of the problem of inadequate cancer pain management must be addressed (86). Obstacles hindering improved cancer pain management related to both the patient and the physician must be overcome (86). On a system level, standardization and quality of care are essential factors for improvement (91, 189). Clinical care pathways ensure that care is organized with the right people, at the right place, and at the right time and represent a bridge between evidence-based guidelines and clinical expertise (58). Whilst care pathways represent structured multidisciplinary care plans for patients with a defined clinical problem (100), bundles of care address specific parts of the care process (104). Evidence-informed practice is a goal for both approaches. Also decision support systems address the gap between optimal and actual practice and may contribute to the systematic utilization of available knowledge (105). An increased focus on improvement science and implementation research may further contribute to secure positive changes and identifying effective ways of translating research findings into practice (92, 93).

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Papers I, II and III

Paper I

Brief Report

From "Breakthrough" to "Episodic" Cancer Pain? A European Association for Palliative Care Research Network Expert Delphi Survey Toward a Common Terminology and Classification of Transient Cancer Pain Exacerbations

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Abstract

Context. Cancer pain can appear with spikes of higher intensity. Breakthrough cancer pain (BTCP) is the most common term for the transient exacerbations of pain, but the ability of the nomenclature to capture relevant pain variations and give treatment guidance is questionable.

Objectives. To reach consensus on definitions, terminology, and subclassification of transient cancer pain exacerbations.

Methods. The most frequent authors on BTCP literature were identified using the same search strategy as in a systematic review and invited to participate in a two-round Delphi survey. Topics with a low degree of consensus on BTCP classification were refined into 20 statements. The participants rated their degree of agreement with the statements on a numeric rating scale (0–10). Consensus was defined as a median numeric rating scale score of ≥7 and an interquartile range of ≤3.

Results. Fifty-two authors had published three or more articles on BTCP over the past 10 years. Twenty-seven responded in the first round and 24 in the second round. Consensus was reached for 13 of 20 statements. Transient cancer pain exacerbations can occur without background pain, when background pain is uncontrolled, and regardless of opioid treatment. There exist cancer pain exacerbations other than BTCP, and the phenomenon could be named "episodic pain." Patient-reported treatment satisfaction is important with respect to assessment. Subclassification according to pain pathophysiology can provide treatment guidance.

Conclusion. Significant transient cancer pain exacerbations include more than just BTCP. Patient input and pain classification are important factors for tailoring treatment. J Pain Symptom Manage 2016;51:1013–1019.

Key Words

Cancer pain, pain classification, pain assessment, breakthrough pain, episodic pain, Delphi study

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Accepted for publication: December 24, 2015.

0885-3924/$ - see front matter
http://dx.doi.org/10.1016/j.jpainsymman.2015.12.329

Introduction

Cancer pain can be caused by the cancer itself or by cancer therapy. Tissue damage may occur in sites such as bone, viscera, and nerve structures and sometimes call for specific treatment strategies. Intermittent spikes of higher pain intensity may occur, most often named breakthrough cancer pain (BTCP).[1] The definitions used for BTCP assume a stable or controlled background pain.[1] However, also when the background pain is not controlled, cancer pain may fluctuate.

The prevalence of BTCP varies between studies.[2] Factors other than differences in symptom and disease burden might influence the reported prevalence. These factors include differences in definitions and diagnostic criteria,[3,4] and inclusion of patients with poorly controlled background pain.[5]

The concept of BTCP involves the presence of a controlled background pain and short periods of higher pain intensity, or transient cancer pain exacerbations. Algorithms for diagnosing BTCP have been proposed.[6–8] Still, there are unsolved issues both regarding definitions and terminology of transient cancer pain exacerbations. There is no agreement on how to classify transient cancer pain exacerbations appearing without background pain. Furthermore, there is no universal agreement on the upper limit of pain intensity of a controlled background pain or the magnitude of increase in pain intensity for a transient cancer pain exacerbation to be clinically significant. And although the issue has been addressed,[9,10] there is no agreement on classification of transient pain exacerbations according to pain pathophysiology or etiology. Discrepancies on definitions and diagnostic criteria may influence the use and interpretation of classification systems.

Based on the unresolved issues identified in a systematic review,[1] and with the overall aim of a higher degree of consensus on definitions and terminology, a Delphi survey was undertaken among international experts on BTCP. The study addresses the following research questions:

1. How should transient cancer pain exacerbations be defined?
2. How should transient cancer pain exacerbations be termed?
3. How could transient cancer pain exacerbations be subclassified to guide treatment?

Methods

A two-round international Delphi expert survey was performed from February to May 2015. The participants, identified by a literature search performed in PubMed using the same strategy as in a recent systematic review on BTCP,[1] were the most frequent authors on the subject over the past 10 years. Delphi surveys may have low response rates,[11,12] and a predefined initial number of approximately 50 experts was chosen to ensure a final sample size large enough for valid results[13] (Fig. 1). The authors and coauthors on BTCP articles were contacted by e-mail and invited to participate in a Web survey. Two reminders were mailed to nonresponders in both rounds, and the survey was closed one week after the final reminder.

The selection of issues to be addressed was initially based on areas with low degree of consensus identified in a systematic literature review on assessment and classification of BTCP.[1] These areas included the question of opioid medication as a prerequisite for the diagnosis of BTCP, the issue of controlled background pain and how to measure it, and the lack of a formal classification system. The authors of this article further discussed these issues and formulated 20 statements (Table 1) for the Delphi survey. This work was done on behalf of the European Association for Palliative Care Research Network.

The study participants were asked to rate their agreement with the statements on an 11-point numeric rating scale (NRS 0–10), with the anchors, "do not agree at all" and "completely agree," respectively. Based on previous research and in accordance with the study protocol,[14,15] the statements reaching a median score of less than seven (NRS 0–10) or an interquartile range (IQR) of more than three were reassessed, except for statements where the participants universally did not agree with the statement (median NRS 0). The median NRS rating and the IQR for each statement in the previous round were disclosed to the participants in the second round. According to a priori agreement and in line with recently published research,[12,15] consensus was defined as a median NRS (0–10) score of seven or more and an IQR of three or less. The results are reported as medians and IQRs of the agreement with the statements.[16]

Results

Fifty-two authors and coauthors had published three or more articles on BTCP over the past 10 years and were eligible for the study (Fig. 1). The contact details were unavailable for four authors; therefore, an invitation mail was sent to 48 potential participants. Two authors declined participation because of lack of clinical experience, leaving 46 potential respondents. After two reminders, 27 respondents provided complete answers to the first round. After two reminders, 24 respondents provided complete answers to the second round.

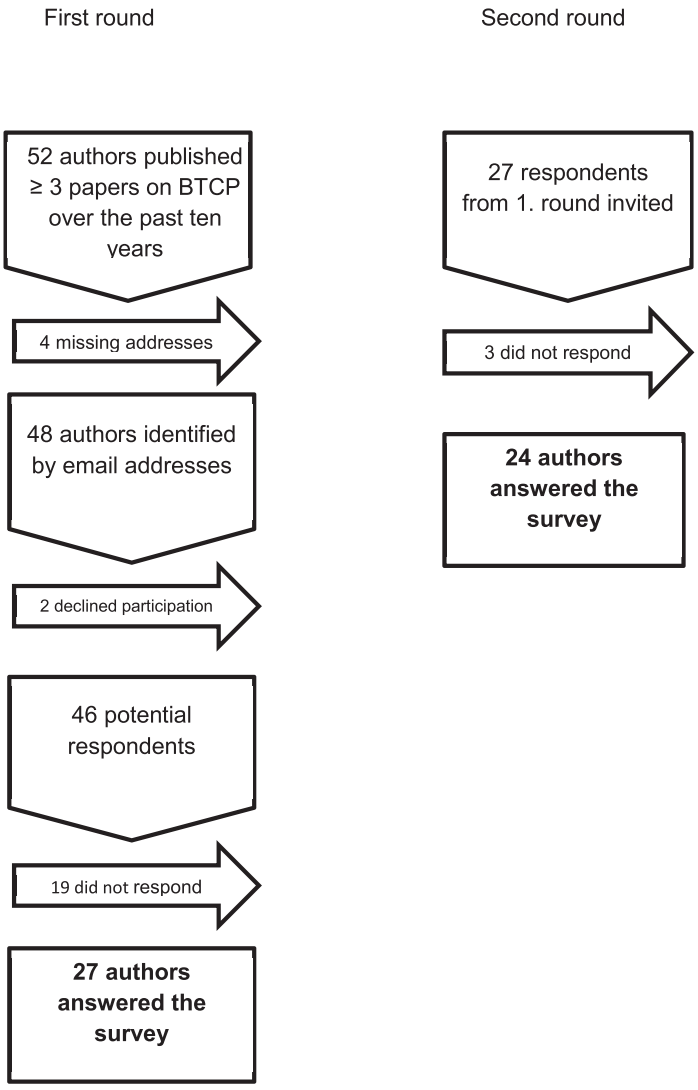

Fig. 1. Participant inclusion. BTCP = breakthrough cancer pain.

Consensus was reached for 11 statements in the first round (Table 1). In addition, there was a unison disagreement with two statements. After reassessment in the second round, consensus was reached for two more, resulting in consensus on 13 of 20 statements.

Regarding the statements on definitions, consensus was reached in the first round for: "Transient cancer pain exacerbation is possible without significant background pain" (NRS 9.0, IQR 3.0), "Significant transient cancer pain exacerbation is possible without background pain being controlled" (NRS 10.0, IQR 3.0), and "Significant transient cancer pain exacerbation can occur in patients currently not on opioids" (NRS 10.0, IQR 2.0). Consensus was also reached in the first round for the statements: "Background pain is best described as controlled when the patient is satisfied with the overall pain control the around the clock pain medication provides" (NRS 8.0, IQR 3.0), and "A significant transient cancer pain exacerbation can best be assessed by the patient's wish/need for rescue medication" (NRS 7.0, IQR 3.0).

For statements on terminology, consensus was reached in the first round for the statements: "An overarching concept for all significant transient

Table 1
Statements and Consensus Ratings

	1. Round		2. Round	
Consensus Reached in Favor of the Statement	NRS	IQR	NRS	IQR
Definitions				
Significant transient cancer pain exacerbation can occur in patients currently not on opioids	10.0	2.0		
Significant cancer pain exacerbation is possible without the background pain being controlled	10.0	3.0		
Transient cancer pain exacerbation is possible without significant background pain	9.0	3.0		
Background pain is best described as controlled when the patient is satisfied with the overall pain control the around the clock medication provides	8.0	3.0		
A significant transient cancer pain exacerbation can best be assessed by the patient's wish/need for rescue medication	7.0	3.0		
The increase in pain intensity on an NRS scale (0−10) has to be more than two points for the transient cancer pain exacerbation to be significant	7.0	5.0	7.0	3.0
Terminology				
An overarching concept for all significant transient cancer pain exacerbations will contribute to standardization in assessment and classification	7.0	3.0		
The term episodic pain could serve as an overarching concept for all significant transient cancer pain exacerbations	7.0	3.0		
There are significant cancer pain exacerbations other than breakthrough pain	9.0	5.0	8.0	2.75
Subclassification				
Identification of transient cancer pain exacerbations due to bone metastases can affect treatment choices	9.0	2.0		
Identification of transient cancer pain exacerbations due to neuropathic pain can affect treatment choices	9.0	2.0		
Identification of transient cancer pain exacerbations due to visceral pain can affect treatment choices	9.0	3.0		
A subgrouping of transient cancer pain exacerbations will provide better opportunities for a more precise diagnosis and better tailored treatment	8.0	3.0		
No consensus in favor of the statement				
Background pain is best described as controlled when the background pain intensity is 3 or less on an NRS scale (0−10)	7.0	5.0	7.5	6.75
Background pain is best described as controlled when the background pain intensity is 4 or less on an NRS scale (0−10)	7.0	6.0	6.0	3.0
A significant transient cancer pain exacerbation can best be assessed by an increase in NRS score to a certain predefined number	5.0	6.0	5.0	3.0
A significant transient cancer pain exacerbation can best be assessed by a percentage increase in NRS score	5.0	6.0	5.0	5.0
An increase in pain intensity of two point on an NRS scale (0−10) is a significant transient cancer pain exacerbation	4.0	4.0	5.0	3.75
An increase in pain intensity of one point on an NRS scale (0−10) is a significant transient cancer pain exacerbation[a]	0.0	2.0		
Background pain is best described as controlled when the background pain intensity is 6 or less on an NRS scale (0−10)[a]	0.0	2.0		

NRS = numeric rating scale; IQR = interquartile range.
[a]Statement not reassessed in the second round.

cancer pain exacerbations will contribute to standardization in assessment and classification" (NRS 7.0, IQR 3.0), and "The term episodic pain could serve as an overarching concept for all significant transient cancer pain exacerbations" (NRS 7.0, IQR 3.0).

Finally, consensus was reached in the first round for all the statements on subclassification: "A subgrouping of transient cancer pain exacerbations will provide better opportunities for a more precise diagnosis and better tailored treatment" (NRS 8.0, IQR 3.0), "Identification of transient cancer pain exacerbations due to bone metastases can affect treatment choices" (NRS 9.0, IQR 2.0), "Identification of transient cancer pain exacerbations due to neuropathic pain can affect treatment choices" (NRS 9.0, IQR 2.0), and "Identification of transient cancer pain exacerbations due to visceral pain can affect treatment choices" (NRS 9.0, IQR 3.0).

There was a unanimous disagreement with two of the statements: "An increase in pain intensity of one point on an NRS scale (0−10) is a significant transient cancer pain exacerbation" (NRS 0.0, IQR 2.0), and "Background pain is best described as controlled

when the pain intensity is 6 or less on an NRS scale (0–10)" (NRS 0.0, IQR 2.0). Those statements were not reassessed.

Two statements on definitions and terminology reached consensus after reassessment in the second round (1. and 2. round, respectively): "The increase in pain intensity on an NRS scale (0–10) has to be more than two points for the transient cancer pain exacerbation to be significant" (NRS 7.0, IQR 5.0 and NRS 7.0, IQR 3.0), and "There are significant cancer pain exacerbations other than breakthrough pain" (NRS 9.0, IQR 5.0 and NRS 8.0, IQR 2.75).

For five statements, consensus could not be reached (1. and 2. round, respectively): "An increase in pain intensity of two points on an NRS scale (0–10) is a significant transient cancer pain exacerbation" (NRS 4.0, IQR 4.0 and NRS 5.0, IQR 3.75), "A significant transient cancer pain exacerbation can best be assessed by a percentage increase in NRS score" (NRS 5.0, IQR 6.0 and NRS 5.0, IQR 5.0), "A significant transient cancer pain exacerbation can best be assessed by an increase in NRS score to a certain predefined number" (NRS 5.0, IQR 6.0 and NRS 5.0, IQR 3.0), "Background pain is best described as controlled when the background pain intensity is 4 or less on an NRS scale (0–10)" (NRS 7.0, IQR 6.0 and NRS 6.0, IQR 3.0), and "Background pain is best described as controlled when the background pain intensity is 3 or less on an NRS scale (0–10)," (NRS 7.0, IQR 5.0 and NRS 7.5, IQR 6.75).

Discussion

Controversy and disagreement regarding basic definitions of transient cancer pain exacerbations persist.[1] This Delphi survey provided consensus on several key statements. That is, short-lived episodes of more severe cancer pain can occur both without background pain as well as when the background pain is not controlled, regardless of opioid treatment. Furthermore, patient-reported treatment satisfaction is important when defining controlled background pain and significant transient cancer pain exacerbations. However, consensus was not reached for most statements specifying numerical pain intensity scores. The existence of transient cancer pain exacerbations other than BTCP was recognized. The benefit of an overarching term comprising all such transient pain exacerbations was acknowledged, and the suggestion that the term "episodic pain" could serve the purpose was endorsed. Finally, consensus was reached for the importance of identifying pathophysiological mechanisms of transient cancer pain exacerbations.

In some former definitions, regularly administered opioid medication was suggested as a prerequisite for BTCP.[17] In more recent literature, this requirement has generally been abandoned.[6,7,10,18] The current definitions of BTCP require the presence of a background pain, and that the background pain has an intensity less than a defined level, for example, NRS (0–10) $\leq$ 4.[7] A multicenter prevalence study explored the effect of different levels of background pain on the prevalence of transient cancer pain exacerbations (episodic pain).[5] When comparing patients with any background pain intensity to a subgroup of the population with an average background pain of NRS (0–10) $\leq$ 6, a higher prevalence of episodic pain was found when including patients regardless of background pain intensity level. This result supports our consensus finding that transient cancer pain exacerbation, or episodic pain, is possible irrespective of background pain intensity.

Patient-reported outcome measures are essential assessments in oncology and palliative medicine and should capture clinically important data and be responsive to change over time.[19] Extensive work has been undertaken to identify meaningful cutoff points for pain intensity measurements, including pain exacerbation and pain relief, and different cut points and methods to measure changes in pain intensity have been suggested.[20–25] The lack of consensus on the statements presenting specific cutoff points for BTCP intensity and meaningful changes in pain intensities must be interpreted in the light of the ongoing research. Also the definition of a controlled background pain is currently being discussed,[26] and the absence of consensus must be viewed against this background. Several articles have applied the criterion not more than "mild" intensity for a controlled background pain.[6,8,18] In even more recent research, controlled background pain is defined as NRS (0–10) $\leq$ 4,[7] based on previous findings.[24]

The international Delphi panel reached agreement on the statements implying that the best description of pain as controlled or in need for further treatment is the patient's satisfaction with the ongoing medication or wish for further medication, respectively.

BTCP has been recognized as a spectrum of very different entities.[6] Within the international expert panel, there was consensus that there are intermittent pain flares other than BTCP and support for the idea of "episodic pain" as an overarching term for all such transient pain exacerbations. Episodic pain was previously suggested as a clinical entity by European Association for Palliative Care.[27] In a topical review preceding the latest update of the International Classification of Diseases–11, cancer pain is described as continuous (background pain) or intermittent (episodic pain),[28] in line with the consensus reached in this study.

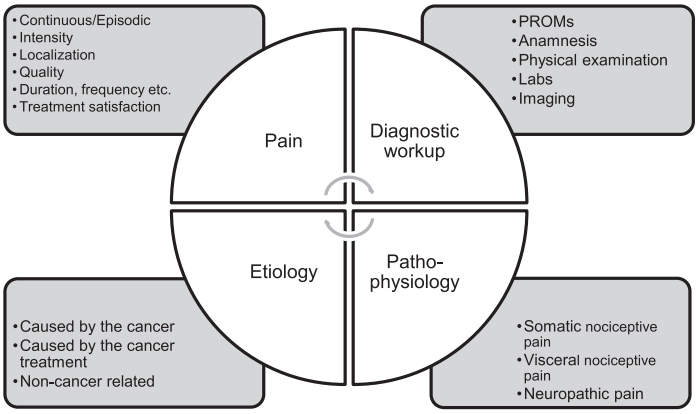

Fig. 2. Cancer pain (multiple parenting); diagnostic workup. PROMs = patient-reported outcome measures.

Different pain etiologies and pathophysiological mechanisms may call for different treatment modalities, as affirmed in this study. Although underused, single-fraction radiotherapy is efficacious in palliating uncomplicated bone metastases.[29] Neuropathic pain, associated with an unpredictable response to conventional analgesic treatment, can potentially be relieved by addition of specific adjuvant drugs.[15] Furthermore, episodic pain with visceral etiology is an important finding in patients with abdominal cancer.[30] Also in the topical review preceding the latest International Classification of Diseases–11 update,[28] the importance of pain etiology, pathophysiology, and body site is emphasized. Moreover, the principle of multiple parenting is introduced, allowing the same diagnosis to be subsumed under more than one category. In clinical practice, the diagnostic process can be guided by important symptom descriptors and patient-reported outcome measures followed by a symptom diagnosis with related pathophysiology and etiology (Fig. 2).

Only approximately 50% of the eligible authors responded in both rounds. Although expected,[11,12] this is a clear limitation of the study. And although authors of articles on BTCP will have special insights in this field of research, a risk of including participants with limited clinical experience was present. Additionally, no input was obtained from the patients.

In conclusion, transient pain exacerbations can occur independently of background pain level, ongoing pain medication, and include more than BTCP only. The phenomenon could be named "episodic pain" and subclassified according to pathophysiology. Patient-reported treatment satisfaction is important both when assessing background and episodic pain.

Disclosures and Acknowledgments

This study was supported by the Norwegian Cancer Society. There are no conflicts of interest.

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Paper II

Pain Ther (2018) 7:193–203
https://doi.org/10.1007/s40122-018-0107-8

ORIGINAL RESEARCH

Pain Intensity Factors Changing Breakthrough Pain Prevalence in Patients with Advanced Cancer: A Secondary Analysis of a Cross-Sectional Observational International Study

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Received: August 22, 2018 / Published online: November 10, 2018

ABSTRACT

Introduction: Different definitions of breakthrough pain (BTP) influence the observed BTP prevalence. This study examined BTP prevalence variability due to use of different cutoffs for controlled background pain, different assessment periods for background pain, and difference between worst and average pain intensity (PI).

Methods: Cancer patients from the EPCRC-CSA study who reported flare-ups of pain past 24 h were potential BTP cases. BTP prevalence was calculated for different cutoffs for background PI on numeric rating scales (NRS 0–10) for the past week, past 48 and past 24 h period. Furthermore, BTP cases were categorized based on the difference between maximum and average PI past 24 h (range, 0 to > 2 points, NRS 0–10).

Results: Of 696 respondents, 302 patients (43.4%) reported pain flares the past 24 h. The BTP prevalence when using a defined background PI ≤ 4 for the past week was 19.8%. This number varied for different defined cutoffs for background PI. Actual background PI and BTP prevalence also varied between the assessment periods "past week", "past 48 h", and "past 24 h" (PI 4.0, 3.6, and 3.4; BTP prevalence 19.8, 22.7, and 24.9% for background PI ≤ 4). For patients with background PI ≤ 4 past week, 105 had a difference between maximum and average PI

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≥ one point and 48 had a difference > two points.
Conclusions: The reported BTP prevalence is dependent on the cutoff for background PI in the BTP definition, population background PI during the assessment period, and defined cutoff for the difference between worst and average PI.
Funding: NTNU, Norwegian University of Science and Technology.

Keywords: Background pain; Breakthrough pain; Cancer pain; Pain classification

INTRODUCTION

The prevalence range in breakthrough pain (BTP) literature is wide [1]. Variability in diagnostic criteria and inclusion of patients with poorly controlled background pain may contribute to this feature [1]. The definition of BTP includes an adequately controlled and stable background pain [2, 3]. In addition, the patient must have transient exacerbations of pain, which are pain flares well distinguished from the background pain [2–5]. Despite international agreement on these basic characteristics, controversies about the definition of BTP continue in clinical as well as in research settings [6]. Differences in definitional criteria complicate both the clinical diagnosis and the comparison of epidemiological data between studies [6]. Within the scope of defining BTP according to characteristics that are universally understood and measurable [6], the current study explores consequences of definitional variability.

Background pain of moderate intensity or less was a criterion in the pioneer definition [5]. In more recent literature, adequately controlled background pain is defined as "mild", or specified as ≤ 4 on the 11-point numeric rating scale (NRS 0–10) [2, 4]. Furthermore, BTP prevalence has been reported for patients with background PI ≤ 6 (NRS 0–10) [7]. Pain flares are also described in cancer patients with uncontrolled background pain [7, 8]. It has been argued that narrow criteria for background pain intensity (PI) may result in the exclusion of clinically important pain flares [6]. How the prevalence of BTP varies with the defined cutoff for background PI has not been studied in detail.

The assessment period for background pain was originally defined as the past 24 h [5]. In a follow-up paper, the assessment period for background pain was changed to the previous week [9], an approach adopted in current BTP literature [2–4, 10]. The different recall periods for background pain have been compared [11, 12], showing a high correlation between PI for a 24-h and 7-day recall period [13]. The potential consequences for the BTP prevalence caused by different assessment periods for background pain have not been reported.

The magnitude of the pain flare was originally defined as a transitory increase in pain to greater than moderate intensity, which occurred on a background pain of moderate intensity or less [5]. Since then, extensive work has been undertaken to identify meaningful cutoffs for PI and relevant measures of changes in PI [14–19]. Different interpretations exist for the necessary size of a transient pain exacerbation in cancer patients in order to classify it as a significant pain flare [3, 16, 20, 21]. In a recently published study by Mercadante et al. [3], a difference of one point or more (NRS 0–10) between breakthrough PI and background PI was accepted as a significant transient increase in PI. Mercadante et al. also suggested a PI ≥ 7 (NRS 0–10) as a meaningful cutoff for BTP medication, aiming for a PI ≤ 4 (NRS 0–10) after treatment [16]. In a Delphi study including expert opinions from researchers within the field of BTP, the panel agreed with the statement that the increase in PI has to be more than two points on an NRS scale (0–10) for a transient cancer pain exacerbation to be clinically significant [20].

The EPCRC-CSA study included cancer patients whose pain was evaluated by several self-reported assessment methods [22], providing an opportunity to address the research question: How is the assessed BTP prevalence affected by different definitions for cutoffs for controlled background PI, assessment periods for background pain, and cutoffs for the difference between worst and average PI past 24 h?

METHODS

Study Design and Patient Population

The EPCRC-CSA (Trial registration: ClinicalTrials.gov identifier, NCT00972634) is a cross-sectional observational international study conducted in 17 centers within eight countries in 2008 and 2009 [22]. Adult patients with incurable cancer and able to complete a computer-based symptom assessment were eligible. Patients who rated their worst PI $\geq$ 1 (NRS 0–10) for the previous 24 h, were subject to further pain assessment and included in the present study, which is a secondary analysis of a study originally designed to assess the feasibility of computer-based symptom assessment [22].

Measurement Tools and Data Collection

The measurements used in the secondary analysis included: (I) A simplified item from the Alberta Breakthrough Pain Assessment Tool (ABPAT) [23], where all patients with worst PI $\geq$ 1 (NRS 0–10) for the past 24 h were introduced to the concept of BTP as characterized in the ABPAT instructions [23]. They were then presented with the question: "Have you had flare-ups of BTP in the last 24 h?" (Yes/No). (II) Elements from the Brief Pain Inventory (BPI), which is a widely used assessment tool for pain where each PI scale ranges from 0 (no pain) to 10 (pain as bad as you can imagine) [24]. BPI questions on worst PI past 24 h and past week were supplemented with questions on worst PI past 48 h, and average PI specified for the time periods "past 24 h", "past 48 h", and "past week". All data were collected electronically and obtained the same day.

Terminology and Statistical Analysis

Average pain was used as a measurement for background pain and, unless stated otherwise, with the assessment period "past week" [2]. Patients answering "yes" to the ABPAT-based BTP screening question were classified as "ABPAT+". The ABPAT-positive patients were grouped according to background PI past week, and the cumulative percentages of ABPAT-positive patients within each potential level of maximal background PI were computed. Subsequently, the procedure was repeated for the assessment periods for background pain "past 48 h" and past "24 h". Kappa statistic was used to compare agreement beyond chance between the cumulative percentages of ABPAT-positive patients with background pain $\leq$ 4 (NRS 0–10) for the three different assessment periods for background pain. Kappa values 0.61–0.80 indicate substantial agreement, and kappa values 0.81–1.0 indicate almost perfect agreement [25]. Finally, the ABPAT-positive patients grouped according to background PI past week were further categorized based on the difference between reported worst and average PI past 24 h. The chosen categories were: A difference of at least one point, a difference of at least two points, and a difference of more than two points (NRS 0–10) between worst and average PI past 24 h. Hypothetical BTP prevalences were calculated from percentages of ABPAT-positive patients satisfying specified criteria for background PI and difference between worst and average PI past 24 h.

Compliance with Ethics Statement

This article is based on a previously conducted study. All procedures performed in the primary study were in accordance with the ethics committees at the respective study sites and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the primary study.

RESULTS

Participant Characteristics

Among 1017 patients included in the EPCRC-CSA study, 715 persons reported worst PI $\geq$ 1 (NRS 0–10) past 24 h. Patient-reported BTP registrations according to the ABPAT-based screening question, and average PI registrations

for the three assessment periods "past week", "past 48 h", and "past 24 h" were available for 696 patients. Essential patient characteristics for the 696 patients included in the present analysis are displayed in Table 1.

Prevalence of self-reported flare-ups of pain in the past 24 h related to the level of background PI, the assessment period for background pain, and the difference between worst and average PI

Three hundred and two out of 696 patients (43.4%) who answered the APBAT-based screening question reported flare-ups of BTP for the past 24 h and were classified as "ABPAT +". The distributions of background PI for ABPAT-positive patients are displayed in Fig. 1 for the three assessment periods "past week", "past 48 h", and "past 24 h". The mean (median) average PI scores for the assessment periods "past week", "past 48 h", and "past 24 h" were 4.0 (4.0), 3.6 (3.0), and 3.4 (3.0) (NRS 0–10), respectively. Figure 1 illustrates that a large proportion of the ABPAT-positive patients had uncontrolled background pain.

Defining a cutoff for background PI $\leq$ 3 (NRS 0–10) in ABPAT-positive patients resulted in a BTP prevalence of 14.9%. The corresponding number for a defined cutoff for background PI $\leq$ 4 was 19.8% (Table 2). Table 2 shows the cumulative percentage of ABPAT-positive patients in relation to each score for background pain, resulting in increased BTP prevalence when including patients with higher background PI.

The cumulative percentages of ABPAT-positive patients related to background PI scores are displayed in Fig. 2 for the different assessment periods for background pain "past week", "past 48 h, and "past 24 h". As indicated in the figure, differences between the assessments periods result in variable percentages of patients meeting the requirements for having BTP. For instance, compared to a 19.8% BTP prevalence using background PI $\leq$ 4 (NRS 0–10) assessed for the past week, the corresponding percentages were 22.7 using background PI the past 48 h (93% agreement, kappa 0.80), and 24.9 using background PI the past 24 h (92% agreement, kappa 0.76).

As illustrated in Fig. 3, among ABPAT-positive patients, the difference between worst and average PI past 24 h ranged from zero to more than two points (NRS 0–10). Defining a minimum difference between worst and average PI past 24 h of one point and background PI $\leq$ 4 (past week), resulted in a BTP prevalence of 15.1%. Using the same definition for background PI, but with a minimum difference of two points between worst and average PI, resulted in a BTP prevalence of 9.5%. Figure 3 illustrates a BTP prevalence variability related to difference between worst and average PI past 24 h ranging from 6.9% (48 out of 696 patients) to 19.8% (138 out of 696 patients), using the same definition for background pain (PI $\leq$ 4 past week). In addition, Fig. 3 illustrates that 60

Table 1 Patient characteristics (n = 696)

		%
Age (years), mean (range)	62 (20–90)	
Sex		
Female		49
Male		51
Inpatients		58
Outpatients		42
Karnofsky status, mean (range)	69 (20–80)	
Metastatic cancer		86
Locally advanced cancer		14
On current chemotherapy		42
On current radiotherapy		24
On current pain medication		79
Worst pain intensity past week (NRS 0–10), mean (SD)	5.4 (2.8)	
Average pain intensity past week (NRS 0–10), mean (SD)	4.0 (2.3)	
Cancer as patient-perceived reason for pain		73
Cancer treatment as patient-perceived reason for pain		26

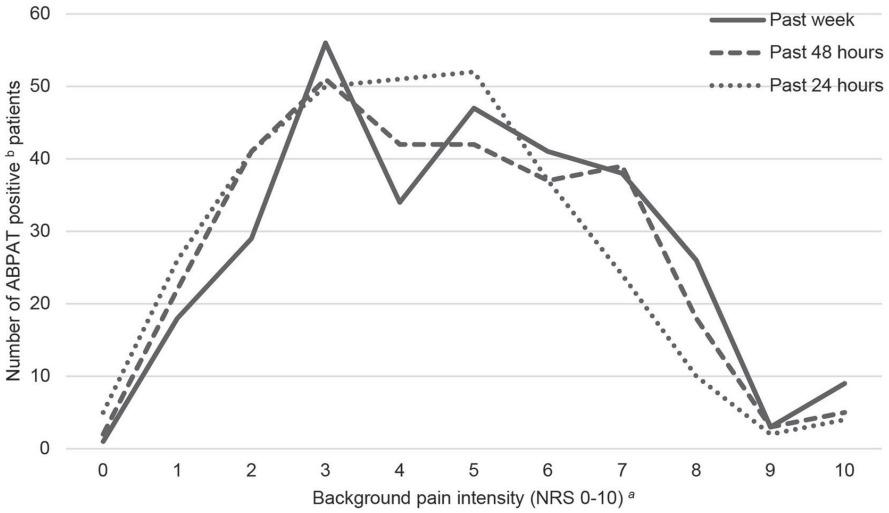

Fig. 1 Distribution of background pain intensity[a] in ABPAT-positive[b] patients. [a]Background pain intensity assessed for the three time periods "past week", "past 48 h", and "past 24 h". [b]Patients answering "yes" to the Alberta Breakthrough Pain Assessment Tool (ABPAT)-based breakthrough pain screening question were classified as ABPAT-positive

Table 2 ABPAT-positive prevalence variability related to cutoff for background pain intensity, percentages (*n*)

	Level of background pain intensity[b] (NRS 0–10)										
	0	**≤ 1**	**≤ 2**	**≤ 3**	**≤ 4**	**≤ 5**	**≤ 6**	**≤ 7**	**≤ 8**	**≤ 9**	**≤ 10[c]**
ABPAT+[a]	0.1	2.7	6.9	14.9	19.8	26.6	32.5	37.9	41.7	42.1	43.4
(*n* = 302)	(1)	(19)	(48)	(104)	(138)	(185)	(226)	(264)	(290)	(293)	(302)

[a] ABPAT +/positive: patients answering "yes" to the Alberta Breakthrough Pain Assessment Tool (ABPAT) based breakthrough pain screening question were classified as ABPAT-positive

[b] Background pain intensity: all calculations include the cumulative percentages of patients with the respective background pain intensity or less

[c] (Level of background pain intensity) ≤ 10 = all ABPAT-positive patients, irrespective of background pain intensity

of the ABPAT-positive patients reported no difference between worst and average PI past 24 h.

DISCUSSION

BTP prevalence estimates, defined as proportions of ABPAT-positive patients, were dependent on both the cutoff for controlled background pain and the population background PI during the assessment period for background pain. The prevalence estimates were approximately doubled if assessed without including controlled background pain as a criterion. Different cutoff criteria for a necessary numeric difference between worst and average PI also had a substantial impact on the assessed BTP prevalence.

Appraisal of Methods

Uncontrolled background pain should be treated before assessing BTP [2]. For the purpose of

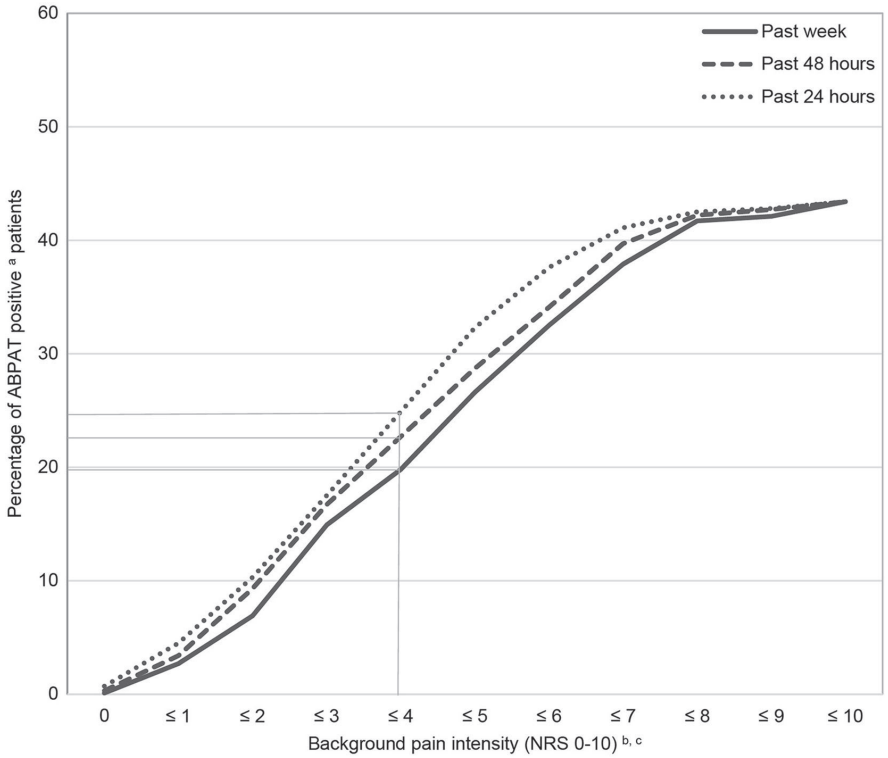

Fig. 2 ABPAT-positive[a] prevalence variability[b] related to different assessment periods for background pain intensity[c]. [a]Patients answering "yes" to the Alberta Breakthrough Pain Assessment Tool (ABPAT)-based breakthrough pain screening question were classified as ABPAT-positive. [b]ABPAT-positive prevalence variability related to different assessment periods for background pain indicated for a cutoff for background pain intensity ≤ 4 (NRS 0–10). [c]Background pain intensity assessed for the three time periods "past week", "past 48 h", and "past 24 h". Mean pain intensity for the three assessment periods were 4.0, 3.6, and 3.4 (NRS 0–10), respectively. All calculations include the cumulative percentages of patients with the respective background pain intensity or less

this analysis, the diagnosis of BTP was based on a screening question of pain flares, and afterwards the prevalence was calculated according to reported background PI. Without the intention of presenting precise prevalence estimates, but merely to demonstrate the effect of background PI when assessing BTP, this procedure was found acceptable.

Despite the demonstrated reliability and validity of recalled pain measures as used in the present study, these registrations are still prone to recall bias and/or actual variations in PI [12, 13]. With 58% being in-patients and 42% of the patients still on chemotherapy, the observed lower background PI for the past 1 and 2 days compared to past week might represent a treatment effect increasing the proportion of patients with controlled background pain. For matters of stringency, the assessment periods for background pain and BTP should ideally be concurrent.

To get a precise measurement of the magnitude of a transient exacerbation of pain, as a minimum, PI before and during the painful

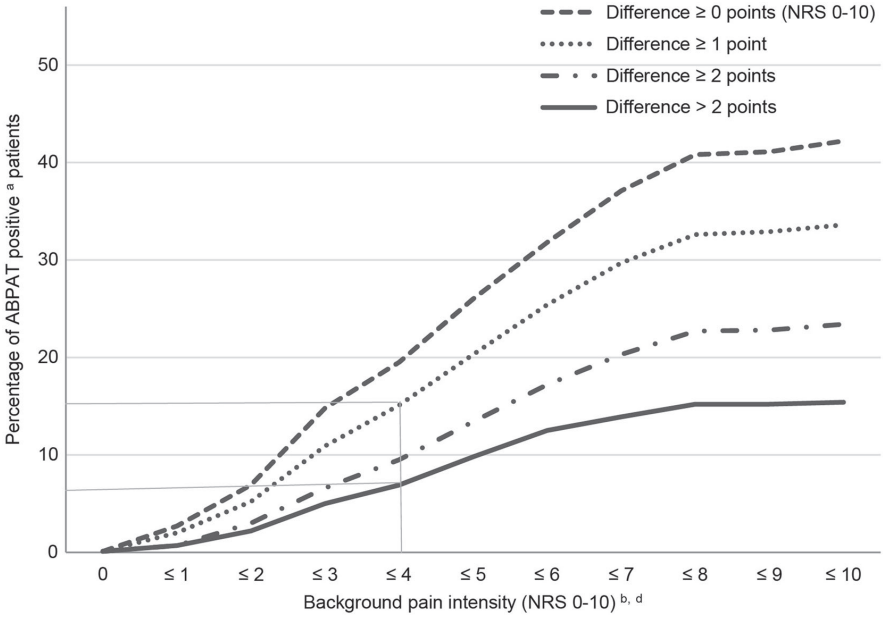

Fig. 3 ABPAT-positive[a] prevalence variability[b] related to difference between worst and average pain intensity[c]. [a]Patients answering "yes" to the Alberta Breakthrough Pain Assessment Tool (ABPAT) based breakthrough pain screening question were classified as ABPAT-positive. [b]ABPAT-positive prevalence variability related to difference between worst and average pain intensity past 24 h, indicated for a difference of at least one point and a difference of more than two points, and a cutoff for background pain intensity ≤ 4 (NRS 0–10). [c]Difference between worst and average pain intensity for the past 24 h, displayed for the differences: ≥ 0 points, ≥ 1 point, ≥ 2 points, and > 2 points (NRS 0–10). [d]Background pain intensity assessed for time period "past week". All calculations include the cumulative percentages of patients with the respective background pain intensity or less

episode is needed. Without this information at hand, worst and average PI recollected from the same period as the pain flare occurred may provide proxy knowledge on the size of PI fluctuations. Still, background PI before an episode of BTP may not be equivalent to average pain, and peak PI during the flare-up of pain may be different from patient-reported worst pain.

The screening question for BTP used in the primary study assessed the past 24 h [22]. Patients with BTP, but not experiencing any pain flares within this period were not included. Nor did the study specifically examine whether the pain flares were cancer related. However, the majority of the patients believed the cancer caused their pain (Table 1). Finally, average PI was used as a measure for background pain. The approach may open for interpretations, but the method has been used in both older and more recent studies [7, 9].

Comparison with Previous Work

Besides prevalence variations related to disease stage and symptom burden, the identification of BTP depends on the characteristics used to define BTP [1, 6]. The primary publication from the EPCRC-CSA study indicated that more than 40% of the patients had BTP last 24 h [22]. In a follow-up paper on the same study population, which demonstrated a nation-based range in prevalence from 14 to 75%, the authors emphasized the point that research on BTP has

been challenged by a lack of consensus on standard language and taxonomy [26]. A commentary on the follow-up paper implied that many of the patients with a pain flare might have uncontrolled background pain, a claim confirmed in the present analysis [27].

Patients with BTP are reported to have more intense background pain [9]. This seems reasonable considering that the transient exacerbations of pain increase the average pain, reflecting all variations in PI [1]. In line with this, previous studies have shown higher prevalence of transient exacerbations of pain when including patients regardless of background PI compared to a subgroup of the patient population with an average background PI of ≤ 6 or ≤ 4 (NRS 0–10), respectively [7, 28]. The present study supported these findings, and explored the implications of different intensity levels for background pain. Usually, no more than mild background PI is accepted as a prerequisite for diagnosing BTP [2]. Different cutoffs are applied for distinguishing mild from moderate pain, and a systematic review on symptoms included in the Edmonton Symptom Assessment Scale found NRS scores 1–4 best reflecting mild pain [17, 18, 29, 30]. As shown in Table 2, by raising the accepted level of maximum background PI by one point from 3 to 4 (NRS 0–10), the calculated BTP prevalence will increase from 15% to almost 20%.

Choice of recall periods for patient-reported outcomes should depend on the specific purpose of the trial, the characteristics of the disease, and the treatment to be tested [13]. Recalled average pain from the past 48 h has been shown to be a reliable and valid measure of actual pain in cancer patients [12]. The present study demonstrated a high degree of agreement beyond chance for prevalence estimates when changing the assessment period for background pain from "past week" to "past "48 h", supporting that possibility when appropriate due to trial purposes. In addition, there was substantial agreement between the prevalence estimates for BTP when changing the assessment period for background pain from "past week" to "past 24 h". However, despite this agreement, Fig. 2 illustrates a change in BTP prevalence from 19.8 to 24.9% for different assessment periods for background pain (background PI ≤ 4), reliant on the distribution (Fig. 1) and central tendency measure (average PI) of the background pain [31].

A transient pain exacerbation can be assessed as an increase in absolute score, an increase to a predefined score, or as a proportion of increase on a numeric rating scale, with different degree of support in favor of the various views [14, 20]. For raw numerical scores, a commonly cited clinically important difference in PI is two points (NRS 0–10) [14]. A large study exploring the responsiveness of the Edmonton Symptom Assessment Scale in cancer patients concluded that the optimal cutoff for improvement and deterioration was one point or more (NRS 0–10) for each of the ten symptoms, pain included [19]. The discussion in the aftermath of the study pointed out that although being a useful measure for power calculations and response determinations in trials, for the individual patient additional measures like personalized symptom goals may be useful [32–34]. The present study indicated that to predefine the necessary size of a transient pain exacerbation might add stringency to a study design. Interestingly, approximately 20% of the patients who reported pain flares the past 24 h also reported no difference between worst and average PI for the same period. Lack of clarity and misunderstandings may represent challenges when interpreting patient-reported questionnaires, and can result in information bias and systematic errors in study results [23, 35].

The present study supports previous findings and underlines that valid comparisons of prevalence and treatment effects are dependent on standardized and universally agreed upon criteria for BTP [6, 7, 28].

Limitations

The current study is based on a 10-year-old data set. Pain prevalence and pain control may have changed during the following years [36]. However, a recent study found no improvement in cancer pain management in a 5-year perspective from 2008 [37]. Furthermore, the study

population is patients with advanced cancer, limiting the generalizability of the conclusions.

CONCLUSIONS

The study underlined that BTP prevalence assessment needs to be standardized [6]. To reduce inter-study variability, both the numerically defined cutoff for controlled background PI and the actual background PI in the population should be reported. The necessary increase in PI for a transient pain exacerbation to be considered significant also should be stated, as this may have a substantial impact on the prevalence. However, the present study did not aim to identify the optimal definition of BTP, but simply addressed that variable use of BTP definitions will result in variable prevalence estimates. Lack of definition consensus makes it difficult to know to what extent differences between studies are due to the use of different BTP definitions or reflect actual differences in clinical pain experienced by the patients. Further international collaboration to improve standardization in assessment and reporting of BTP should be prioritized.

The present study also demonstrated that pain flares outside the definition of BTP is frequent, and hence must be accounted for in inclusion and exclusion criteria in research and addressed in clinical practice [20]. Finally, the study demonstrated that PI assessments that reflect the most recent changes in pain medication are applicable.

Due to the methodology of this study, which is based on a 10-year-old dataset, the findings should be studied prospectively and with a controlled design investigating a broader spectrum of pain characteristics and patient populations. Whether broad or narrow diagnostic criteria for BTP influence the number of treatment interventions, patients' pain reports and treatment satisfaction should also be addressed.

ACKNOWLEDGEMENTS

We thank the participants of the primary study.

Funding. The study is sponsored by NTNU, Norwegian University of Science and Technology. Article processing charges are covered by a publication fund organized by the sponsor. All authors had full access to all of the data in the study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Erik T. Løhre, Marianne J. Hjermstad, Cinzia Brunelli, Anne K. Knudsen and Pål Klepstad have nothing to disclose. Stein Kaasa is one of the shareholders in Eir Solutions A/S. He declares no income, dividend or financial benefits from the work presented here.

Compliance with Ethics Guidelines. This article is based on a previously conducted study. All procedures performed in the primary study were in accordance with the ethics committees at the respective study sites and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the primary study.

Data Availability. The dataset generated and analyzed during the current study is available from the corresponding author on reasonable request.

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Paper III