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Erik Torbjørn Løhre, MD, Pål Klepstad, MD, PhD, Michael I. Bennett, MB, ChB, MD (Hons), FRCP, FFPMRCA, Cinzia Brunelli, ScD, Augusto Caraceni, MD, Robin L. Fainsinger, MD, Anne Kari Knudsen, MD, PhD, Sebastiano Mercadante, MD, Per Sjøgren, MD, Stein Kaasa, MD, PhD

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Brief Report **15-00706R1**

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

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European Palliative Care Research Centre (E.T.L., C.B., A.C., A.K.K., S.K.), Department of Cancer Research and Molecular Medicine, and Department of Circulation and Medical Imaging (P.K.), Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway; Department of Oncology (E.T.L., A.K.K.. S.K.) and Department of Anaesthesiology and Intensive Care Medicine (P.K.), St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway; Academic Unit of Palliative Care (M.I.B.), Leeds Institute of Health Sciences, School of Medicine, University of Leeds, Leeds, United Kingdom; Palliative Care, Pain Therapy and Rehabilitation Unit (C.B., A.C.), Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Division of Palliative Care Medicine (R.L.F.), Department of Oncology, University of Alberta, Edmonton, Alberta, Canada; Pain Relief and Supportive Care Unit (S.M.), La Maddalena Cancer Center, Palermo, Italy; and

Section of Palliative Medicine (P.S.), Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Address correspondence to:

Erik Torbjørn Løhre, MD

European Palliative Care Research Centre

Department of Cancer Research and Molecular Medicine

NTNU, Faculty of Medicine

Trondheim, N-7491, Norway

E-mail: erik.t.lohre@ntnu.no

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 sub classification 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 twenty 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 NRS score of ≥ 7 and an interquartile range of ≤ 3.

Results. Fifty-two authors had published three or more papers on BTCP over the past ten 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. Sub classification 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.

Key Words: Cancer pain, pain classification, pain assessment, breakthrough pain, episodic pain, Delphi study

Running Title: From “Breakthrough Pain” to “Episodic Pain”?

Accepted for publication: December 24, 2015.

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 sub classified in order 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 ten 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 co-authors on BTCP articles were contacted by email and invited to participate in a web survey. Two reminders were mailed to non-responders in both rounds, and the survey was closed one week after the final reminder.

The selection of issues to be addressed was initially based upon 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 paper further

discussed these issues and formulated twenty statements (Table 1) for the Delphi survey. This work was done on behalf of the European Association for Palliative Care Research Network (EAPC RN).

The study participants were asked to rate their agreement with the statements on an eleven 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 inter-quartile range (IQR) of more than three were reassessed, except for statements were 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 co-authors had published three or more papers on BTCP over the past ten 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 due to 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.

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 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 sub grouping 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 below a defined level, e.g. NRS (0-10) ≤ 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 sub group of the population with an average background pain of NRS (0-10) ≤ 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 (PROMs) 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 cut-off 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 cut-off 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 papers 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 EAPC (27). In a topical review preceding the latest update of the International Classification

of Diseases (ICD-11), cancer pain is described as continuous (background pain) or intermittent (episodic pain) (28), in line with the consensus reached in this study.

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 ICD-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 PROMs 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 even though authors of papers 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 sub classified according to pathophysiology. Patient

reported treatment satisfaction is important both when assessing background and episodic pain.

Disclosures and Acknowledgments

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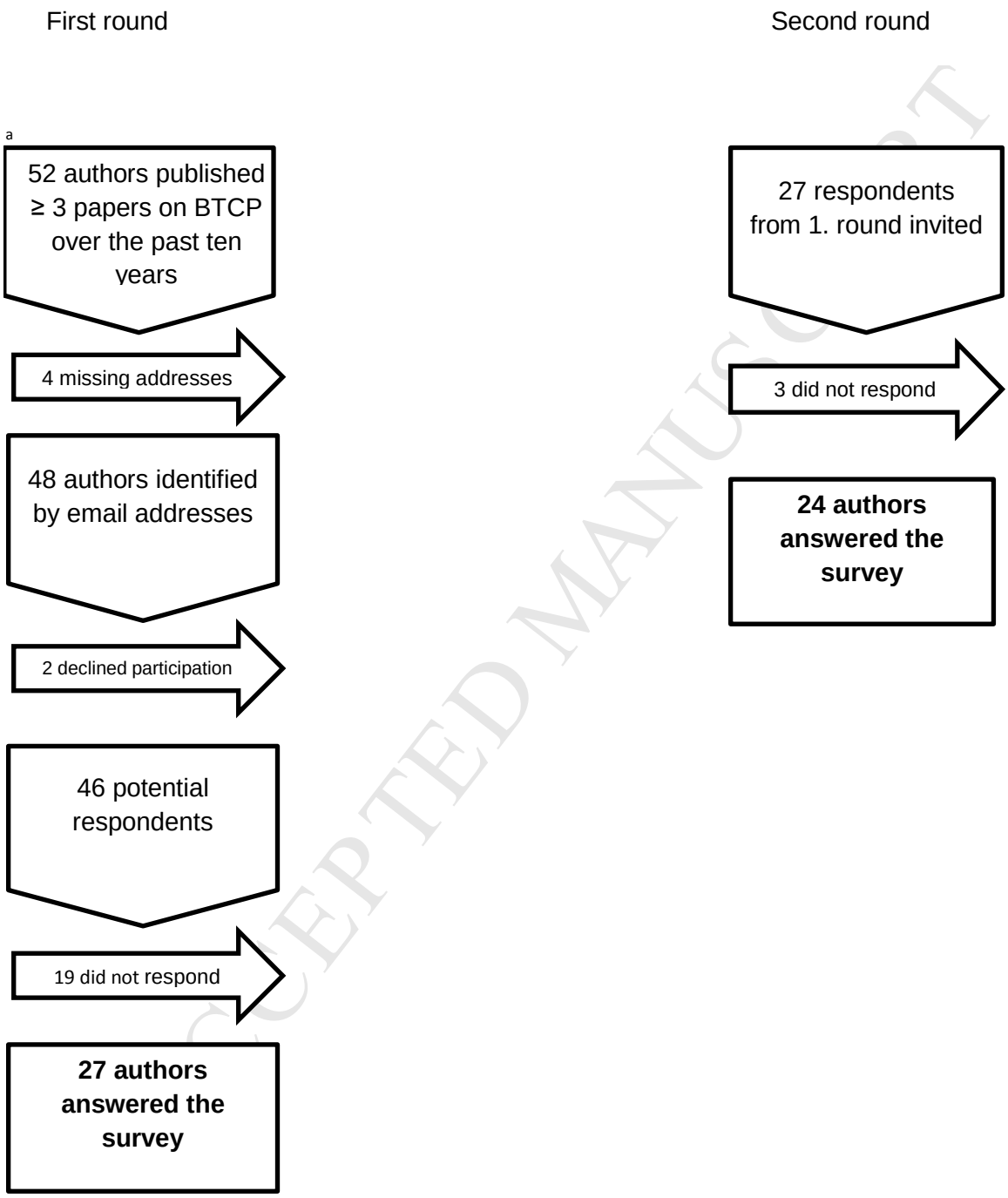
Table: Statements and Consensus Ratings

Consensus reached in favor of the statement	1.round		2.round	
	NRS[a]	IQR[b]	NRS[a]	IQR[b]
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
Sub classification				
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 sub grouping of transient cancer pain exacerbations will provide better opportunities for a more precise diagnosis and better tailored	8.0	3.0		

treatment				
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 a 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 [c]	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) [d]	0.0	2.0		

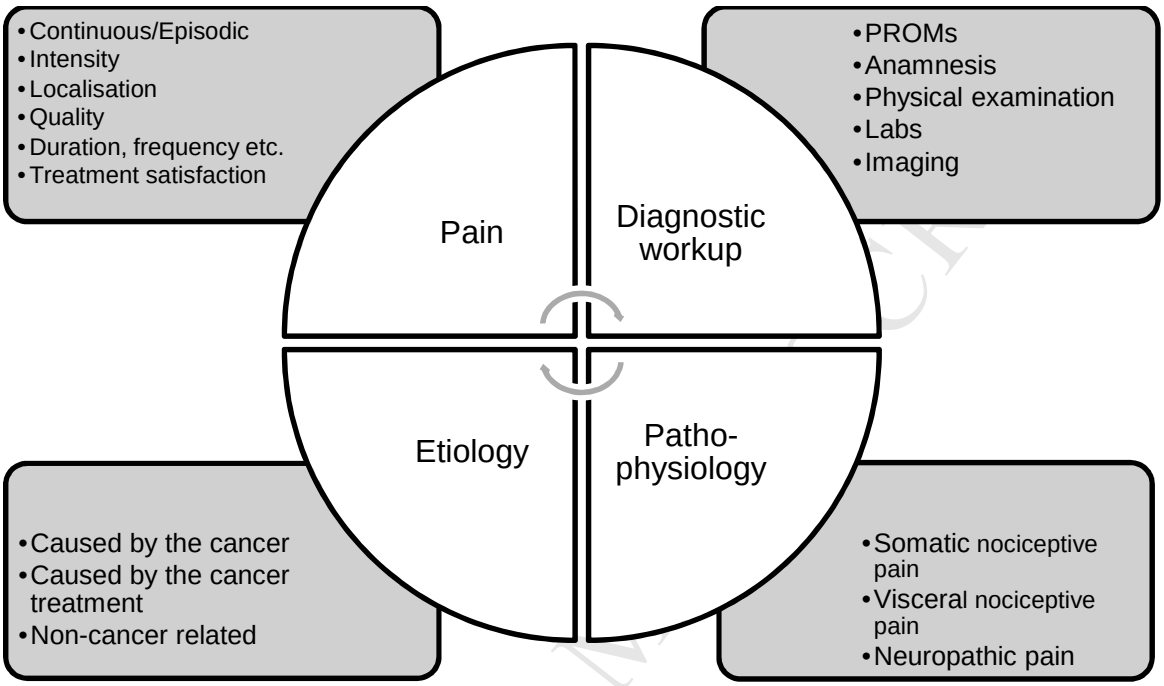
[a] NRS: Numeric Rating Scale (0-10), median
[b] IQR: Inter-Quartile Range
[cd] Statement not reassessed in the second round

Figure 1: Participant inclusion



[a] BTCP: Breakthrough Cancer Pain

Figure 2: Cancer pain (multiple parenting); Diagnostic workup



[a]

[a] PROMs: Patient Reported Outcome Measures