*Episodic pain; Delphi Paper outline*

*Front page with title, authors, affiliations, corresponding author, key words, abstract*

From “breakthrough” to “episodic” cancer pain? An EAPC RN expert Delphi survey towards a common terminology and classification of transient cancer pain exacerbations

Introduction

Cancer 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 indicate specific treatment strategies and need to be classified accordingly. Intermittent spikes of higher pain intensity may occur, and breakthrough cancer pain (BTcP) is the most commonly applied term for the transient exacerbation of pain in cancer patients (1). The ability of the current BTcP nomenclature to capture significant pain variations and give clinical guidance on treatment strategies is questionable (2). The definitions used for BTcP vary, but all assume a stable or controlled background pain (1). However, also when the background pain is not controlled, cancer pain may fluctuate due to disease or treatment-related factors.

The prevalence of BTcP varies widely between studies. A recent systematic review found a pooled BTcP prevalence of 59.2%, with a range from 40% in outpatients to more than 80% in hospice patients (3). Factors other than differences in the actual patient symptom and disease burden might influence the reported prevalence of BTcP and contribute to the variety of reported prevalence. These factors include differences in definition and diagnostic criteria of transient cancer pain exacerbations (4, 5), and inclusion of patients with poorly controlled background pain (6) .

The concept of BTcP involves at least three different elements: The presence of a background pain, a description of the background pain, and short periods of higher intensity, or transient cancer pain exacerbations, called BTcP. Algorithms for diagnosing BTcP have been proposed (7, 8), and recently Webber et al. presented the development and initial validation of a new Breakthrough Pain Assessment Tool (BAT) for use in clinical settings (9). 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 intensity of a controlled background pain or on the needed increase in pain intensity for a transient cancer pain exacerbation to be considered clinically significant. Both the Edmonton classification system for cancer pain and the Alberta breakthrough pain assessment tool addresses the subject (10, 11), but there is still no agreement on classification of transient pain exacerbations according to pain etiology. Together these disagreements on definitions and diagnostic criteria may influence the use and interpretation of classification systems and lead to discrepancies between clinicians, researchers and centers.

Based on the unresolved issues identified in a systematic review on the topic (1), and with the overall aim of a higher degree of consensus on definitions and terminology of transient cancer pain exacerbations, 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 Delphi study distills the judgements of experts through an iterative group facilitation technique (12), and is applicable when the goal is improved understanding of problems and solutions (13). A two-round modified 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 (14, 15), and a predefined initial number of approximately 50 experts was chosen to ensure a final sample size large enough to provide trusty results (16) (*Figure 1*). The authors and co-authors on BTcP articles were contacted by email and invited to participate in the web survey, powered by SurveyMonkey and made accessible by a hyperlink in the invitation mail. Two reminders were mailed to non-responders in both rounds, and the survey was closed one week after the final reminder was posted.

The selection of relevant questions to be addressed in the Delphi process was initially based upon areas with low degree of consensus identified by Haugen et al. 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. A task force, consisting of the authors of this paper, further discussed these issues and formulated twenty statements (*Table*) 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 degree of 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 (12, 17), 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 in round two, except for statements were the participants universally did not agree with the statement (median NRS 0). In keeping with the Delphi technique rationale, 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 (15, 17), 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 (18).



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 (*Figure 1*). The contact details were not available 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 according to study protocol was reached for 11 statements in the first round (*Table*). In addition, there was a unison disagreement with two statements. After reassessment in the second round, consensus was reached for two more statements, altogether resulting in consensus in favor of the statement on 13 of 20 statements.

Regarding the statements on definitions of transient cancer pain exacerbations, consensus in the first round was reached 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 of 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 sub classification: “ *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 unison complete 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 further assessed.

The two statements on definitions and terminology that reached consensus after reassessment in the second round were (1. & 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 & NRS 7.0, IQR 3.0), and *“There are significant cancer pain exacerbations other than breakthrough pain* (NRS 9.0, IQR 5.0 & NRS 8.0, IQR 2.75)

For five statements consensus could not be reached, even after reassessment in the second round (1. & 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 & 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 & 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 & 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 & 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 & NRS 7.5, IQR 6.75).



Discussion

The first step in improving a classification system is to reach consensus on its core elements. There exist controversy and disagreement regarding basic definitions of transient cancer pain exacerbations (1). This Delphi Survey provided relevant consensus on several key statements. That is, cancer pain exacerbations can occur both without background pain as well as when the background pain is not controlled, and regardless of opioid treatment present or not. Furthermore, patient reported treatment satisfaction is an important outcome measure when defining controlled background pain and significant transient cancer pain exacerbations. However, consensus was not reached for statements on specifics of pain intensity assessments; except that the experts after two rounds agreed that a pain intensity increase has to be more than two points for the transient cancer pain exacerbation to be significant. The experts also agreed in that there exist transient cancer pain exacerbations other than breakthrough pain, for the benefit of an overarching term that could comprise all such transient pain exacerbations, and that the term “episodic pain” could serve that purpose. Finally, consensus was also reached for the importance of identifying the different pathophysiological mechanisms of transient cancer pain exacerbations.

In some former definitions, regularly administered opioid medication was suggested as a prerequisite for BTcP (19). In more recent literature, that imperative has generally been abandoned (7, 8, 11, 20). This reflects the logical inconsistency in demanding the application of a specific therapy for a medical phenomenon to be present. The current definitions of BTcP require the presence of a background pain, and the background pain to have intensity below a defined level, e.g. NRS (0-10) ≤ 4 (8). An Italian cross-sectional multicenter prevalence study explored the effect of different levels of background pain on the prevalence of transient cancer pain exacerbations (episodic pain) (6). When comparing patients with any background pain intensity level to a sub group of the patient 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. Previously Portenoy et al. observed that patients with BTcP to had more intense background pain than patients without BTcP (21).

Patient reported outcome measures (PROMS) are important for assessments in oncology and palliative medicine. As a result of the identification of more than 40 different ways to measure pain intensity (22), a need for international consensus on symptom assessment applicable both for clinical and research purposes has been advocated (23). Outcome measures should capture clinically important data and be responsive to change over time (24). 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 has been suggested (25-28). For transient pain exacerbations contrasting views and approaches have been advocated illustrated by Mercadante et al. who found a meaningful cut-off point for requesting BTcP medication to be NRS 7.1 (27), and Hui et al. who identified a change in NRS (0-10) score of 1 to be a clinically important difference in symptom improvement or deterioration (29). The international Delphi panel reached agreement on the statements implying that the best way of describing a pain as controlled or in need for further treatment is the patient’s satisfaction with the ongoing medication or wish for further medication, respectively. However, there was a lack of consensus on all but one of the statements presenting specific cut-off points for controlled background pain, BTcP intensity, and meaningful changes in pain intensities. This illustrates that experts agree on that PROMS reflecting patients satisfaction and experiences are the important outcomes but generally disagree in how results should be categorized.

BTcP has been recognized as a spectrum of very different entities (7). Within the international expert panel there was consensus that there are intermittent pain flares other than BTcP, supporting the need for an overarching term for all such transient pain exacerbations, and endorsing the idea that the term “episodic pain” could serve this purpose. Episodic pain was already suggested as a clinical entity by an EAPC working group in 2002 (30). In a topical review preceding the latest update of the International Classification of Diseases (ICD-11) of the World Health Organization, improvements in classification of chronic pain are introduced (31). Cancer pain will be will be described as continuous (background pain) or intermittent (episodic pain) (31), in line with the consensus reached in this study.

Different pain etiologies may call for different treatment modalities. For instance, single fraction radiotherapy is efficacious in palliating uncomplicated bone metastases, but is still underused (32). In addition, neuropathic pain is associated with an unpredictable response to conventional analgesic treatment, and can potentially be relieved by addition of specific adjuvant drugs (17). Furthermore, episodic pain is an important finding in patients with abdominal cancer, and a recent study reported a prevalence of BTcP of 91% in a cohort with almost 50% pure visceral pain etiology (33). Both in malignant and non-malignant pain, breakthrough pain most often represents a flare at a site of chronic pain and is due to the same pain mechanism (21, 34). Still, different therapeutic approaches may be necessary, both for optimizing the background pain and the transient pain exacerbations. This opinion is endorsed by the consensus achieved in our survey, indicating a benefit of sub grouping and classification of transient cancer pain exacerbations based on pain etiology and pathophysiology. Also in the topical review preceding the latest ICD-11 update (31), the importance of pain etiology, pathophysiology, and body site is emphasized. Moreover, the ICD-11 introduces the principle of multiple parenting, allowing the same diagnosis to be subsumed under more than one category. Cancer pain can be caused by the cancer itself or by cancer treatment, classified as musculoskeletal, neuropathic or visceral, and described as continuous pain and episodic pain. 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 (*Figure 2*).



We recognize that this study has some strengths and some limitations. The selection of participants was based upon a systematic search of BTcP literature. This ensures that participants were selected without personal or other bias from the Delphi study group, but also excluded potential experts who had not participated in publications. Also, although 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. The selection of statements was based upon a previous systematic review. Still, there is a risk that items important for episodic pain classification are not included in the statements. It should be recognized that this Delphi process was performed by researchers only, no input was obtained from the patients.

In conclusion; transient pain exacerbations can occur independent of background pain level and ongoing pain medication and include more than BTcP. The phenomenon could be named “episodic pain”, and can be sub classified according to pathophysiology. Patient reported pain treatment satisfaction is an important outcome measure when assessing both background pain and episodic pain.

References

1. Haugen DF, Hjermstad MJ, Hagen N, Caraceni A, Kaasa S. Assessment and classification of cancer breakthrough pain: a systematic literature review. Pain. 2010;149(3):476-82.

2. Bennett MI. Cancer pain terminology: time to develop a taxonomy that promotes good clinical practice and allows research to progress. Pain. 2010;149(3):426-7.

3. Deandrea S, Corli O, Consonni D, Villani W, Greco MT, Apolone G. Prevalence of breakthrough cancer pain: a systematic review and a pooled analysis of published literature. J Pain Symptom Manage. 2014;47(1):57-76.

4. Fainsinger RL, Nekolaichuk C, Lawlor P, Hagen N, Bercovitch M, Fisch M, et al. An international multicentre validation study of a pain classification system for cancer patients. Eur J Cancer. 2010;46(16):2896-904.

5. Knudsen AK, Brunelli C, Klepstad P, Aass N, Apolone G, Corli O, et al. Which domains should be included in a cancer pain classification system? Analyses of longitudinal data. Pain. 2012;153(3):696-703.

6. Caraceni A, Bertetto O, Labianca R, Maltoni M, Mercadante S, Varrassi G, et al. Episodic (breakthrough) pain prevalence in a population of cancer pain patients. Comparison of clinical diagnoses with the QUDEI--Italian questionnaire for intense episodic pain. J Pain Symptom Manage. 2012;43(5):833-41.

7. Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. Eur J Pain. 2009;13(4):331-8.

8. Mercadante S, Lazzari M, Reale C, Cuomo A, Fusco F, Marchetti P, et al. Italian Oncological Pain Survey (IOPS): a multicentre Italian study of breakthrough pain performed in different settings. Clin J Pain. 2015;31(3):214-21.

9. Webber K, Davies AN, Zeppetella G, Cowie MR. Development and validation of the breakthrough pain assessment tool (BAT) in cancer patients. J Pain Symptom Manage. 2014;48(4):619-31.

10. Fainsinger R, Nekolaichuk C, Lawlor P, Neumann CM. Edmonton Classification System for Cancer Pain, Administration Manual. 2012.

11. Hagen NA, Stiles C, Nekolaichuk C, Biondo P, Carlson LE, Fisher K, et al. The Alberta Breakthrough Pain Assessment Tool for cancer patients: a validation study using a delphi process and patient think-aloud interviews. J Pain Symptom Manage. 2008;35(2):136-52.

12. Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol. 2014;67(4):401-9.

13. Hsu CC SB. The Delphi Technique: Making Sense of Consensus. Practical Assessment, Research & Evaluation. 2007;12(10):1-8.

14. Keeney S, Hasson F, McKenna H. Consulting the oracle: ten lessons from using the Delphi technique in nursing research. J Adv Nurs. 2006;53(2):205-12.

15. Searle RD, Howell SJ, Bennett MI. Diagnosing postoperative neuropathic pain: a Delphi survey. Br J Anaesth. 2012;109(2):240-4.

16. Biondo PD, Nekolaichuk CL, Stiles C, Fainsinger R, Hagen NA. Applying the Delphi process to palliative care tool development: lessons learned. Support Care Cancer. 2008;16(8):935-42.

17. Brunelli C, Bennett MI, Kaasa S, Fainsinger R, Sjogren P, Mercadante S, et al. Classification of neuropathic pain in cancer patients: A Delphi expert survey report and EAPC/IASP proposal of an algorithm for diagnostic criteria. Pain. 2014;155(12):2707-13.

18. Jones J, Hunter D. Consensus methods for medical and health services research. BMJ. 1995;311(7001):376-80.

19. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. Pain. 1990;41(3):273-81.

20. Davies A, Buchanan A, Zeppetella G, Porta-Sales J, Likar R, Weismayr W, et al. Breakthrough Cancer Pain: An Observational Study of 1000 European Oncology Patients. J Pain Symptom Manage. 2013.

21. Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. Pain. 1999;81(1-2):129-34.

22. Jensen MP. The validity and reliability of pain measures in adults with cancer. J Pain. 2003;4(1):2-21.

23. Kaasa S, Loge JH, Fayers P, Caraceni A, Strasser F, Hjermstad MJ, et al. Symptom assessment in palliative care: a need for international collaboration. J Clin Oncol. 2008;26(23):3867-73.

24. Evans CJ, Benalia H, Preston NJ, Grande G, Gysels M, Short V, et al. The selection and use of outcome measures in palliative and end-of-life care research: the MORECare International Consensus Workshop. J Pain Symptom Manage. 2013;46(6):925-37.

25. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. Pain. 2000;88(3):287-94.

26. Farrar JT, Polomano RC, Berlin JA, Strom BL. A comparison of change in the 0-10 numeric rating scale to a pain relief scale and global medication performance scale in a short-term clinical trial of breakthrough pain intensity. Anesthesiology. 2010;112(6):1464-72.

27. Mercadante S, Adile C, Torta R, Varetto A, Fulfaro F, Giarratano A, et al. Meaningful cut-off pain intensity for breakthrough pain changes in advanced cancer patients. Curr Med Res Opin. 2013;29(1):93-7.

28. Oldenmenger WH, de Raaf PJ, de Klerk C, van der Rijt CC. Cut points on 0-10 numeric rating scales for symptoms included in the Edmonton Symptom Assessment Scale in cancer patients: a systematic review. J Pain Symptom Manage. 2013;45(6):1083-93.

29. Hui D, Shamieh O, Paiva CE, Perez-Cruz PE, Kwon JH, Muckaden MA, et al. Minimal clinically important differences in the Edmonton Symptom Assessment Scale in cancer patients: A prospective, multicenter study. Cancer. 2015.

30. Mercadante S, Radbruch L, Caraceni A, Cherny N, Kaasa S, Nauck F, et al. Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care. Cancer. 2002;94(3):832-9.

31. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. Pain. 2015;156(6):1003-7.

32. Chow E, Zeng L, Salvo N, Dennis K, Tsao M, Lutz S. Update on the systematic review of palliative radiotherapy trials for bone metastases. Clin Oncol (R Coll Radiol). 2012;24(2):112-24.

33. Mercadante S, Adile C, Giarratano A, Casuccio A. Breakthrough pain in patients with abdominal cancer pain. Clin J Pain. 2014;30(6):510-4.

34. Hojsted J, Nielsen PR, Eriksen J, Hansen OB, Sjogren P. Breakthrough pain in opioid-treated chronic non-malignant pain patients referred to a multidisciplinary pain centre: a preliminary study. Acta Anaesthesiol Scand. 2006;50(10):1290-6.