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REVIEW

Pain following cancer treatment: Guidelines for the clinical classification of predominant neuropathic, nociceptive and central sensitization pain

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ABSTRACT

Background: In addition to fatigue, pain is the most frequent persistent symptom in cancer survivors. Clear guidelines for both the diagnosis and treatment of pain in cancer survivors are lacking. Classification of pain is important as it may facilitate more specific targeting of treatment. In this paper we present an overview of nociceptive, neuropathic and central sensitization pain following cancer treatment, as well as the rationale, criteria and process for stratifying pain classification.

Material and methods: Recently, a clinical method for classifying any pain as either predominant central sensitization pain, neuropathic or nociceptive pain was developed, based on a large body of research evidence and international expert opinion. We, a team of 15 authors from 13 different centers, four countries and two continents have applied this classification algorithm to the cancer survivor population.

Results: The classification of pain following cancer treatment entails two steps: (1) examining the presence of neuropathic pain; and (2) using an algorithm for differentiating predominant nociceptive and central sensitization pain. Step 1 builds on the established criteria for neuropathic pain diagnosis, while Step 2 applies a recently developed clinical method for classifying any pain as either predominant central sensitization pain, neuropathic or nociceptive pain to the cancer survivor population.

Conclusion: The classification criteria allow identifying central sensitization pain following cancer treatment. The recognition of central sensitization pain in practice is an important development in the integration of pain neuroscience into the clinic, and one that is relevant for people undergoing and following cancer treatment.

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Clear guidelines for both the diagnosis and treatment of pain in cancer survivors are lacking. This is problematic, given the fact that the health care systems not only aim to prevent cancer deaths, but also to optimize cancer survivors' quality of life. Without guidelines for the diagnosis or treatment of pain in cancer survivors clinicians are left wondering how to deal with pain in these patients, including providing appropriate treatment. A mechanism-based classification of pain in cancer survivors may be a critical step in informing clinical decision making. For effective pain management, correct identification of the dominant type of pain may be beneficial. Physiotherapy for cancer pain, patient-centered and founded on a mechanisms-based classification of pain, has previously been shown to yield positive findings in a prospective case series [1]. Such mechanism-based pain classification includes the differential classification of nociceptive, neuropathic and central sensitization pain [2,3].

Broadly, four classifications are widely considered in the pain literature: nociceptive (/inflammatory) pain, neuropathic pain, central sensitization pain and mixed pain [4–6]. Nociceptive pain is defined as pain attributable to the activation of the peripheral receptive terminals of primary afferent neurons in response to noxious chemical, mechanical or thermal stimuli [5], or as pain arising from actual or threat of damage to non-neural tissue and is due to the activation of nociceptors [7]. For clinical purposes, the term nociceptive pain can be used when pain is proportional to nociceptive input [6]. Neuropathic pain is defined as pain caused by a primary lesion or disease of the somatosensory nervous system [7]. Regarding neuroplastic pain, modern pain neuroscience

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has further advanced our understanding about pain, including the role of central sensitization in amplifying pain experiences [8]. Central sensitization implies increased neuronal response to stimuli in the central nervous system (i.e. central hyperexcitability) and reduced pain modulation [7–9]. Although the concept of central sensitization originates primarily from laboratory, the awareness is growing that it should be part of our clinical reasoning in daily practice [10–12].

Recently, a clinical method for classifying any pain as either predominant central sensitization pain, neuropathic or nociceptive pain was developed, based on a large body of research evidence and international expert opinion [6]. Here, we apply this classification algorithm to the cancer survivor population, and explain how clinicians can differentiate clinically between predominant nociceptive, neuropathic or central sensitization pain in people following cancer treatment. This is important for clinicians because neuropathic and mixed cancer pain (i.e. a mixture of nociceptive, neuropathic and/or central sensitization pain) are considered to be more difficult to treat than pure nociceptive pain [13,14], and the classification of the correct pain mechanism is relevant regarding choice of cancer pain treatment [13]. Indeed, in contrast to symptomatic and/or diagnosis-based treatments, mechanism-based treatments may have better outcomes [15]. Readers interested to learn more about our current understanding of nociceptive, neuropathic and central sensitization pain in cancer survivors can access Appendix 1 (available online at http://www.informahealthcare.com).

Here we explain how clinicians can differentiate clinically between predominant nociceptive, neuropathic or central sensitization pain in people following cancer treatment.

Step 1: Examining the presence of neuropathic pain

Guidelines for the classification of neuropathic pain are available [16,17] and can be employed as recommended by [18]. The criteria specify that a lesion or disease of the nervous system (either central or peripheral) is identifiable and that pain is limited to a 'neuroanatomically plausible' distribution and is supported by both the clinical examination findings and findings from imaging and laboratory testing. Critically, Mulvey et al. [18] outlined that identification of pain distribution would also include identification of the distribution of hyperalgesia; that a link between etiology and pain distribution is established, and that sensory testing is of importance for the diagnosis of neuropathic pain, although it should be combined with diagnostic procedures confirming or refuting the nervous system lesion or disease where possible [16,17]. Electroneuromyography is useful for identification of the level of plexus damage, and magnetic resonance imaging (MRI) and computed tomography (CT) are used to differentiate with cancer recurrence and for identification of compressive nerve fibrosis [19,20]. Imaging may also involve review of tumor position and reviewing surgical notes may reveal whether nerves were identified, preserved or damaged during surgery [18].

Screening for neuropathic allows possible, probable or definite neuropathic pain to be established as a predominant cause of the cancer survivor's pain. It is important to recognize the overlap of pain mechanisms with neuropathic pain frequently characterized or accompanied by sensitization; peripheral and central (segmentally-related) pain pathways can become hyperexcitable with neuropathic pain [21], thus cancer survivors can have both neuropathic and central sensitization pain. Therefore the presence of neuropathic pain does not exclude the co-existence of central sensitization pain and mixed pain types.

In cases without neuropathic pain or with a mixed type of pain, screening for nociceptive and central sensitization pain is the next step. The following section explains the use of a clinical algorithm to differentiate between nociceptive and central sensitization pain in this population.

Step 2: Differentiating between predominant nociceptive and central sensitization pain in cancer survivors

To differentiate predominant nociceptive and central sensitization pain in cancer survivors, clinicians are advised to use the algorithm (Figure 1), guiding clinicians through the screening of three major classification criteria, each of which is explained below.

Criterion 1: Pain experience in cancer survivors disproportionate to the nature and extent of injury or pathology [*6*]

Per definition, central sensitization is characterized by "an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity" [8] and "augmented responsiveness of central nervous system neurons to their normal or subthreshold afferent input" [7,9]. These overlapping definitions imply that central sensitization pain is disproportionate to the nature and extent of injury or pathology, making it a go- or no-go criterion for central sensitization pain in cancer survivors.

For screening this first criterion, it is necessary to assess the individual's amount of injury, pathology and objective dysfunctions capable of generating nociceptive input. This includes imaging techniques for identifying such nociceptive sources (e.g. x-rays, CT scan and NMRI), but frequently relies on interpretation of the clinical examination. Hence, knowledge of common sources of nociception in cancer survivors is required (Supplementary Table 1 in Appendix 1). Further, diagnostic procedures performed during routine follow-ups may cause temporary nociceptive input, i.e. during and following biopsy.

The next step involves considering whether the amount of injury, pathology and objective dysfunction capable of generating nociceptive input is sufficient to explain the cancer survivor's subjective pain experience. In many cancer survivors with pain, the clinical examination and/or imaging reveals some type of potential nociceptive source, which makes thorough clinical reasoning necessary for weighting the nociceptive input with the pain experienced. This includes taking into account all personal and environmental factors. Given the

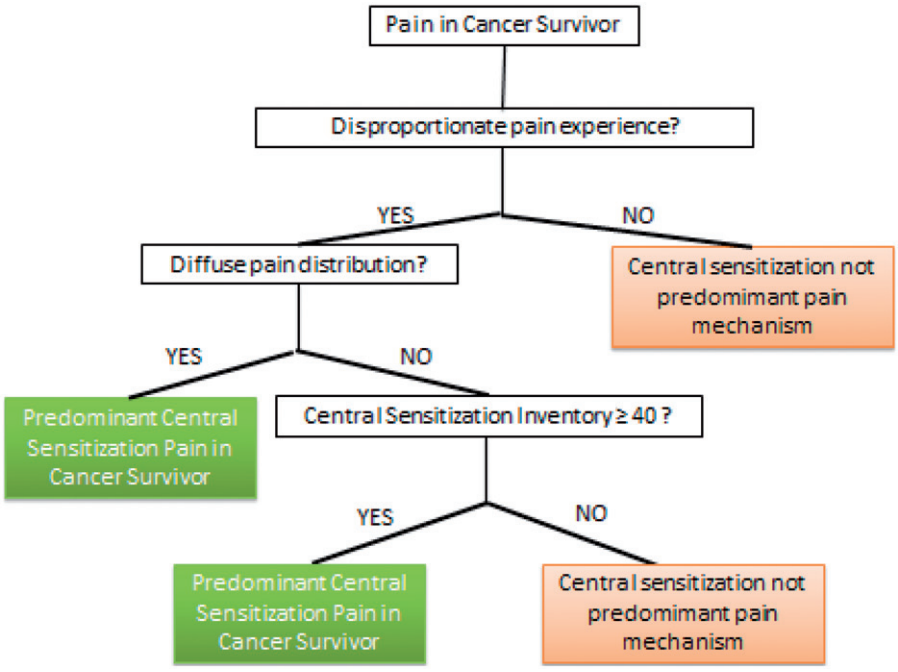

Figure 1. Algorithm for the differential diagnosis of predominant nociceptive versus central sensitization pain in cancer survivors (modified from [6]).

multidimensional nature of pain, a multidimensional assessment of pain is warranted. This can be done using the Short-Form McGill Pain Questionnaire-2, a measure found to have good clinimetric properties both in cancer and non-cancer patients [22].

Taken together, the weighting of the identified sources of nociception with the self-reported pain and disability can result in a number of outcomes:

1. The pain experienced by the individual is considered 'proportionate' as there is evidence of injury, pathology or objective dysfunctions justifying the self-reported pain. Nociceptive pain can be considered and central sensitization pain can be ruled out as the dominant source of symptoms.
2. The individual presents with insufficient evidence of injury, pathology or objective dysfunction capable of causing the self-reported pain. The individual likely fulfills this first out of three criteria for predominant central sensitization pain. At this point, the patient may have predominant central sensitization pain, but the clinician needs to proceed with screening of the remaining criteria (Figure 1) before making a decision.
3. There is evidence of injury, pathology or objective dysfunctions capable of causing pain, but not enough nociceptive input for explaining the pain experienced by the cancer survivor. This would also imply that the patient fulfills this first out of three criteria for predominant central sensitization pain. The individual may have predominant central sensitization pain, and the clinician must proceed with screening of the remaining criteria (Figure 1).

Criterion 2: Neuro-anatomically illogical pain pattern [6]

This criterion is related to the issue of a neuro-anatomically plausible pain pattern: a neuro-anatomically illogical pain pattern is present when the cancer survivor presents with a pain distribution that is not neuro-anatomically plausible for the presumed sources of nociception [6]. Neuro-anatomically plausible relates to allodynia and/or hyperalgesia outside the segmental area of primary nociception and has been used for establishing central sensitization in studies of various chronic pain disorders [23–27], including people following breast and colon cancer treatment [28–30].

For screening this criterion a thorough assessment and interpretation of the patient's self-reported pain distribution, in light of the identified possible sources of nociception, is required. Pain drawings [31,32] can be used to standardize and optimize the assessment of the individual's pain distribution in a reliable way. Examples of pain distribution patterns that fulfill this criterion are bilateral pain/mirror pain (i.e. a symmetrical pain pattern), pain varying in (anatomical) location, large pain areas with a non-segmental (i.e. neuro-anatomically illogical) distribution, widespread pain, and/or allodynia/hyperalgesia outside the segmental area of (presumed) primary nociception [6].

According to the recently proposed classification method [6], if neuropathic pain is screened for, and criteria 1 and 2 are both met (i.e. the pain experience is disproportionate to the nature and extent of injury or pathology and has a neuro-anatomically illogical pain pattern), the classification of predominant central sensitization pain can be established. In the case where neuropathic pain is excluded, and only the first (disproportionate pain) but not the second criterion is met, further screening of criterion 3 is required (Figure 1).

Criterion 3: Hypersensitivity of senses unrelated to the musculoskeletal system [6]

Predominant central sensitization pain in cancer survivors may reflect increased responsiveness to a variety of

stimuli [33,34]. Given the overall hyper-responsiveness of central nervous system neurons, central sensitization may explain the altered sensitivity to many environmental (bright light, cold/heat, sound/noise, weather, stress, food [35]) or even chemical stimuli (odors, pesticides, medication). For assessing sensory hypersensitivity in cancer survivors, clinicians can use quantitative sensory testing (QST). The required equipment is available in many specialized pain centers. Many QST protocols are available [36–39], however they require further study, but its wider use may be hampered by its costs, complexity and time-consuming nature.

Other less expensive and less time-consuming options are available for routine clinical practice. Recent studies demonstrate that pain ratings on application of ice correlate well with quantitative measures of cold pain thresholds and may be a valuable clinical tool [40,41]. A second option is the Central Sensitization Inventory (CSI) [42], which assesses symptoms common to central sensitization [43]. Several studies support the clinimetric properties of the CSI [42,43]. The cutoff of 40 on the CSI allows correct identification of over 82% of central sensitization pain patients, but the chances of false-positives are relatively high, which supports our approach of combining this measure with a more comprehensive examination for identification of predominant central sensitization pain in cancer survivors. We are unaware of published work using the CSI in cancer survivors having pain.

Discussion

Clinical classification of pain in cancer survivors is of importance as it has clear therapeutic implications in terms of pharmacological and non-pharmacological management [19,20,44]. For example, pain education is an effective but underused strategy for treating cancer pain [45]. When providing pain education to cancer survivors, it is cardinal to understand (and explain) the predominant pain mechanism.

The present mechanism-based clinical classification guideline of pain in cancer survivors builds on the previously established clinical algorithm that was based on expert opinion and a comprehensive review of the scientific literature [6], and was adopted to the field of cancer survivors using the relevant scientific literature, clinical experience of the authors and expert opinion. Still, extensive validation of the clinical classification guideline of pain in cancer survivors beyond the primary publication is required. Such a validation process may include, but should not be limited to: systematic literature reviews, meta-analysis, repeatable input from patients and clinical experts and empirical data collections [13]. The latter may include interobserver reliability testing, cross-sectional as well as longitudinal studies comparing the outcome of the clinical algorithm with psychophysiological pain testing (e.g. the temporal summation of pain and conditioned pain modulation paradigms) as well as functional brain imaging findings. Such a validation process should preferentially be performed within an international collaboration consisting of clinical experts and clinical researchers [13], to optimize external validity and wide acceptance of the study findings.

In the meantime, the present work provides clinicians with a guide for classification of post-cancer pain as predominant neuropathic, nociceptive or central sensitization pain. The outcome can be either a dominant pain type or a mixed type of pain. Without claiming to be comprehensive, it also integrates our current scientific understanding of pain in cancer survivors into the clinical reasoning process. The stepwise approach to the classification of pain provides clinicians with a framework to apply knowledge on pain neuroscience in general, and pain in cancer survivors in particular, into clinical practice. The possibility of having a predominant central sensitization pain type in cancer survivors is underscored, and the paper provides the first clinical guide for recognition of central sensitization pain among cancer survivors.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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