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REVIEW ARTICLE

Assessing cancer pain—the first step toward improving patients' quality of life

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Abstract

Purpose Numerous studies on cancer patients have shown that cancer pain still remains underestimated, poorly assessed, and under-treated. Pain relief should be considered as early as possible within personalized care and as an integral part of quality healthcare in many countries. Nevertheless, personalized care is still insufficiently taken into consideration, partly due to improper or incomplete assessment of cancer pain. The objective of this article is to propose a practical approach to this complex assessment, as the first step to improving patients' quality of life.

Methods Critical reflection based on literature analysis and clinical practice.

Results Assessment of cancer pain means evaluating the pain intensity over time, the dimensions of pain (sensory-discriminative, cognitive, emotional, and behavioral), the pathophysiological nature of pain (neuropathic, nociceptive, and nociplastic), the etiology, and the patient's perception (diffuse, localized, global). Cancer patients may have simple or multiple forms of pain (mixed, overlapped, combined, and associated). Furthermore, with the use of new specific therapies, the symptomatology of pain is also changing, and certain cancers are becoming chronic. Thus, cancer pain is an archetype of multimorphic pain, and its dynamic assessments (regular and repeated) require a multimodal and targeted approach in order to offer personalized pain management. Multimodal pain treatment must be adapted to the elements that disrupt cancer pain, to the patient's cancer and to the specific treatments.

Conclusions The dynamic assessments of pain demand the simplest, and the most complete possible procedure, to avoid feasibility problems or self-/hetero-assessment excesses that might lead to less precise and less reliable results. Multimodal and interdisciplinary approaches are being developed, making it possible to optimize cancer pain management.

Keywords Pain measurement · Pain management · Personalized management · Multimorphic pain · Cancer pain · Patient-reported outcome measures

Introduction

In 1986, the IASP (International Association for the Study of Pain) defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. This definition reminds us that pain is a subjective symptom, and that "only those that suffer understand." The rules of good practices were established in 1987 by Ventafridda et al. [2] and are based on pain assessment, with a focus on the patient's past history and questionnaires. Nowadays, only about 50% of cancer patients worldwide receive pain relief, while 38% still experience moderate to severe pain [3], same results as a previous 40-year review of the literature [4]. The various studies carried out in cancer patients highlight that pain remains underestimated, poorly assessed and under-treated [5–12], while the negative

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influence of pain on the overall survival has nevertheless been observed in prostate cancer and possibly in several other types of cancer [13–16]. Hopefully, there are signs of awareness, such as WHO's planned recognition of chronic cancer pain in its ICD-11 classification, as a diagnostic entity of chronic primary pain caused by cancer itself and cancer treatments [17, 18].

In this context, this article in a series proposing a practical approach to personalized management of patients with cancer-related pain will present the *primum movens* in pain management: assessing the situation so as to offer patients the best-suited solutions. Pain assessment is a complex process, although its quality is a therapeutic prognosis factor [8].

Facing cancer patients with refractory cancer pain at their consultations, the authors have carried out a critical reflection based on literature analysis and their clinical practice. For each domain, the literature search was set up on recent reviews and on the latest publications on Medline.

Pain has many dimensions and often concerns several locations

Framework for pain assessment

Pain is not just about intensity; it has many dimensions and often concerns several locations. Pain leads to physical and psychological complications; it also decreases the patients' vitality and quality of life. It increases the suffering of families, friends, and caregivers, and also encourages certain relational traps [19, 20]. The people behavior during pain is not transcultural; the patient's beliefs and culture determine both the significance of the pain, and patient expectations or behavior.

Acute and chronic non-cancer pains have different characteristics [21–23]. There is a continuum between acute and chronic non-cancer pain, with brain reorganization in relation to various affective, psychological, and cognitive experiences (neuroplasticity) [24]. Assessing chronic pain must also be part of a more complex approach, addressing its four dimensions (Fig. 1): sensory-discriminative, cognitive, emotional, and behavioral. These dimensions must be considered at each assessment [25]. In addition, different types of chronic pain require specific management.

From the early stages, the cancer pain is characterized by a multimorphism, which can include the four dimensions described in chronic non-cancer pain [24], and specificities such as its multiple simultaneous forms in most patients [26, 27]. This multimorphism gives cancer pain its chronic nature, meaning that it can be classified according to its etiology, pathophysiology (neuropathic, nociceptive, and nociplastic), and temporality (continuous, intermittent, transient), as well as its multiple forms in location (diffuse, localized, overall) and in time.

Assessing cancer pain also means covering pain intensity over time, dimensions impacted by pain, pathophysiological nature of pain, etiology, and patient's location and temporal perception. This is not commonly performed, and too often patients in physical distress are not properly assessed because nowadays the main priority is the rapidity in pain relief. Consequently, this leads to a vicious circle (Fig. 2), as psychological distress may increase the perception of the burden of pain, while improper pain control may trigger psychological distress [19, 28].

Pain management starting from the cancer diagnosis

Pain must be managed as soon as the diagnosis of cancer is made [29], with a nociceptive pain relief strategy in conformity with the WHO scale or new alternative strategies [30]. Cancer pain is multimorphic and subject to different disruptive elements, which impact pain control (Fig. 3). The initial assessment must thus cover each aspect of pain's multimorphism to establish a treatment strategy, and regular re-assessments are required to address its evolving nature [30–33]. As mentioned above, communicating with cancer patients and their families must be the main focus [30], and this from the very first consultations [34]. Patients' very active role in the management of their pain provides healthcare personnel with all the needed information about their pain and its treatment [29, 30, 32, 35, 36]. Pain may be an indicator of cancer prognosis [16] and may precede the clinical and radiological signs in cases of cancer recurrence. Regular assessments can thus also serve as warnings.

The recent guidelines recommend a treatment strategy that depends on initial and regular assessments of pain, its treatments, and their side effects [29, 30, 32, 35, 36]. During the course of the disease, this dynamic evaluation is carried out using the same tools during follow-up of patients to assess their response to treatment, and to adapt it if necessary. Systematic screenings and assessments make it possible to prevent under-assessment of pain [36], which could lead to a loss of efficacy of the anti-cancer treatments, as has been shown in prostate cancer [37]. In particular, pain control was associated with increased survival in prostate cancer, which was not the case for quality of life. Finally, multidimensional and interdisciplinary management improves many patients' functional prognosis by more often making it possible to spare opioids [38].

Assessment of cancer pain in a few simple questions

Where does it hurt?

More than three-quarters of patients with persistent pain after breast cancer surgery experience pain in several areas [39]. Similarly, lung cancer patients with pain reported a mean of four pain sites per patient [40]. Fifty percent of these patients had at

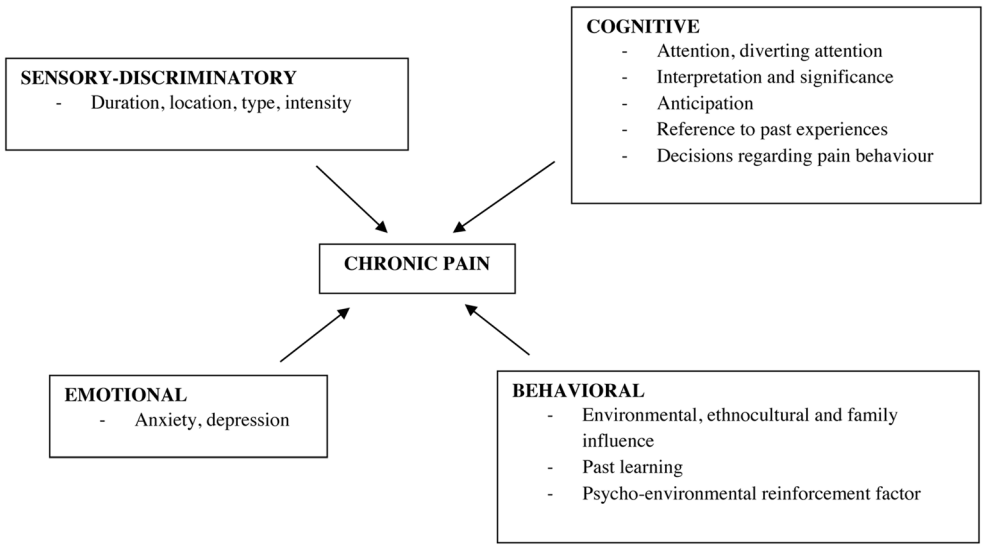

Fig. 1 Multidimensional model of chronic pain

least one neuropathic pain site, and 25% of the overall pain sites were neuropathic. Patients with neuropathic and nociceptive pain (40% of the patients) experienced more intense pain than patients with only nociceptive pain or neuropathic pain [40]. Cancer patients can thus be confronted with multiple simultaneous types of pain, which are mixed, overlapped, combined, or associated depending on their etiology, location, and type (Table 1). The suffering can evolve in various ways in relation to these significantly different characteristics.

When questioning the patient, it is necessary to identify the different types of pain and their irradiation in order to orient the etiological diagnosis and ultimately decrease the risk of treatment failure.

What is the temporality of the pain?

Patients with cancer pain describe various temporal pain patterns, and those with continuous patterns have been shown to report more frequently two or more pain locations, higher pain intensity, and worse pain quality according to verbal descriptions than patients without a continuous component [41]. Transient and intermittent pains must thus be treated rapidly so as not to

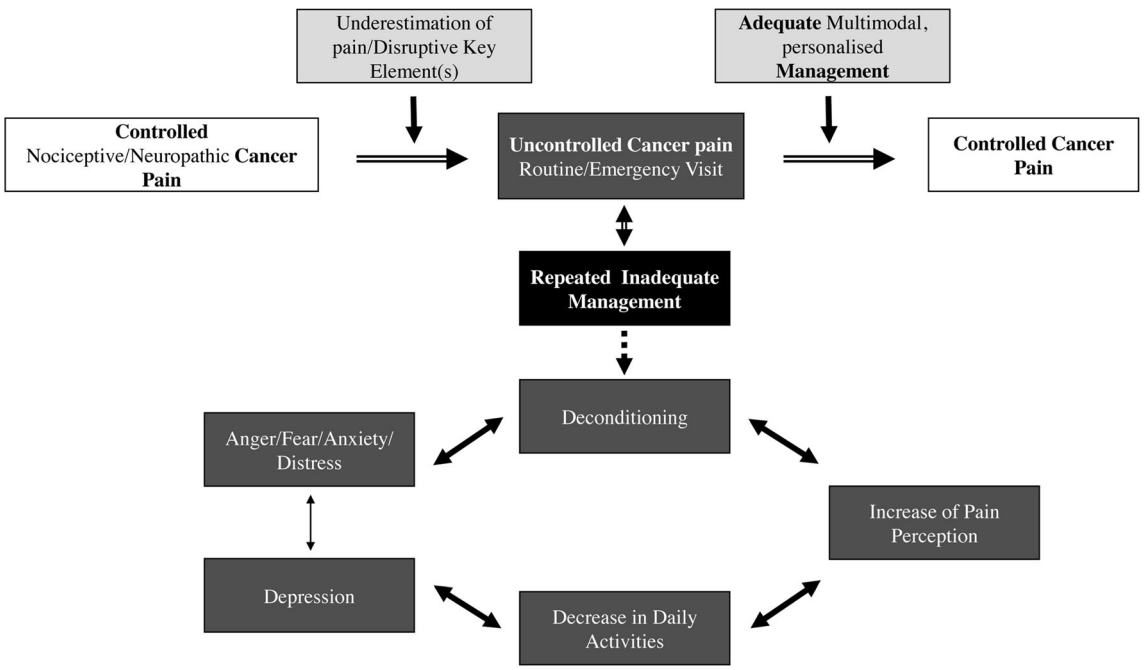

Fig. 2 The vicious circle of chronic cancer pain related to repeated inadequate management in patients with underestimated cancer pain or in the presence of disruptive key element(s)

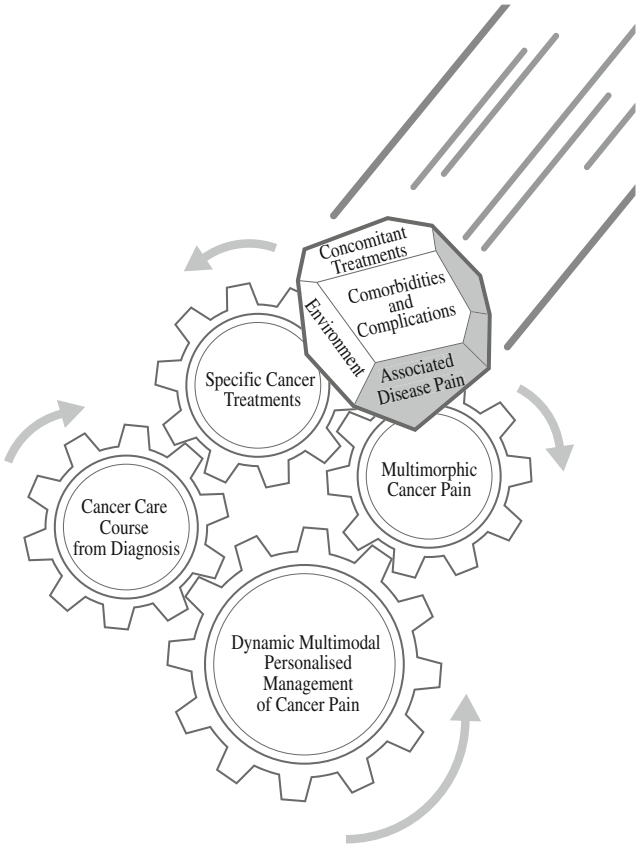

Fig. 3 Disruption key elements in the dynamic, multimodal, targeted, personalized management of the multimorphic cancer pain

complexify cancer pain with new impairments (such as activity avoidance) (Fig. 2). This stage is a risk factor that triggers re-assessment after 72 h.

The more the cancer pain remains uncontrolled, the more it becomes difficult to manage. Furthermore, changes in any dimension of cancer pain impact on quality of life (Fig. 1). For this reason, for patients with vertebral metastases, the cognitive and behavioral repercussions are not the same as if they had acute lower back pain for instance, even if the intensity of the pain is the same. Chronic pain that exists prior to cancer is a risk factor for intense pain, as pain fear avoidance behaviors may produce lower pain tolerance and promote pain disability [41]. In addition, Valeberge et al. suggest that outpatients with a combination of cancer and non-cancer pain may be at greater risk for under-treatment of pain [7].

The evolution of chronic cancer pain, during the remission phase of this potentially fatal illness, may compromise both physical and psychosocial rehabilitation. Preventing the acute and persistent pain associated with cancer and/or its treatments (20% to 45% of pain is associated with cancer treatments [6, 42]) is a key issue in dynamic multimodal pain management. The multimorphism of cancer pain thus justifies interdisciplinary management, which includes repeated pain consultations. *What is the pathophysiological nature of the pain?*

The pathophysiological nature has an influence on how unique pain is managed, as well as the multiple forms of pain presented by cancer patients, by participating in differentiating these pains of different etiologies (Table 1).

Nociceptive pain is secondary to tissue lesions, other than the nervous system, with mechanical, inflammatory, and visceral consequences. Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system [43]. Other type of pain that can occur in parallel to the cancer and its treatments can belong to the third mechanistic descriptor called nociplastic pain [17].

Nociceptive pain sites are the most frequent (75%), but all pain sites are classified as nociceptive for half of the patients and for 10% of patients all pain sites as neuropathic [40]. Neuropathic pain has been characterized in about 50% of cancer patients with single or multiple forms of pain [6, 40].

In the last decade, the characteristics of cancer pain have evolved: the symptomatology can be complex, as cancer can become chronic with the availability of new targeted cancer therapies. However, the percentage of cancer patients with pain has remained stable even though pain treatments have evolved too, with varied success rates in neuropathic pain [3, 44].

Table 1 The characteristics of the multiple forms of complex pain presented by cancer patients

	Etiology		Location		Pathophysiology	
	Identical	Different	Identical	Different	Neuropathology	Nociceptive
Mixed[a]	Yes	No	Yes	No	Yes	Yes
Overlapped[b]	No	Yes	Yes	No	Yes	Yes/no
Combined[c]	Yes	No	No	Yes	Yes	No
Associated[d]	No	Yes	No	Yes	Yes	Yes/no

[a] Example of mixed pain: bone metastases and Pancoast syndrome pain

[b] Example of overlapped pain: bone metastases and lumbago

[c] Example of combined pain: cancer and taxanes

[d] Example of associated pain: cancer and rheumatoid arthritis

What is the intensity of the pain?

Measuring pain intensity is crucial and must be carried out using self-assessment tools [45], mostly with numeric rating scales (NRS). However, this simple method takes a particular importance during the patients' follow-up when assessing the progression of their condition. This practical approach revealed that most of the patients are undertreated [8–10].

The definition of the controlled background pain has been evolving and differs between recommendations. The French consensus considers cancer pain to be controlled by means of a strong opioid-based treatment if it satisfies the following five criteria [31]: little or no pain intensity, non-insomnia-inducing, with less than four exacerbations of pain per day and treatment efficacy of more than 50%, minor or no treatment side effects, and daily activities still possible or limited little by the pain, even if they are limited by the cancer's progression. The definitions are less restrictive in some other countries' recommendations, e.g., in Great Britain and Ireland where controlled background pain is defined as pain rated "none" or "mild" with a duration of more than 12 h per day during the last week [46].

Patients can experience transitory, spontaneous exacerbations of cancer pain, also called breakthrough cancer pain (BTcP), but the definition is not consistent within the literature and guidelines, as no single definition has been widely accepted. The French consensus definition is a sudden transitory pain exacerbation of short duration, with moderate to severe intensity, occurring in a context of background pain controlled by means of a strong opioid therapy [31, 47]. This definition of BTcP, which is in harmony with other European definitions [46, 48], distinguishes BTcP from insufficient background pain relief (e.g., end of dose exacerbations of pain). As some definitions do not refer to the presence of controlled background pain [49], patients with pain relief dosage adjustment (exacerbations of pain during initiation/titration of opioid analgesics) may also be included in some BTcP studies. BTcP may be predictable in half of the cases (provoked by a voluntary act, e.g., bowel movements), spontaneous in others [50]. However, predictable BTcP must not be confused with exacerbation of pain related to the setting of care [32]. Finally, definitions are still debated [51, 52].

Estimates of the prevalence of BTcP thus vary considerably, between 35 and 95% depending on the studies, and this is mainly because of the definition retained for BTcP and the phase of the patient's illness [53, 54]. Nevertheless, the results of a French study and an European study (12 countries) indicate a frequency of more than 80% with a restrictive definition of BTcP [5, 50].

The climax of the BTcP is reached in less than 3 min and 90% of BTcP lasts less than 1 h (and 50% less than 30 min), with moderate to severe intensity [50, 53, 55, 56]. It has consequences that are physical (immobilization, insomnia), psychological (anxiety, depression), and social (inability to work and perform daily activities, social isolation, increased consumption of healthcare). As a result, BTcP alters patients' quality of life [57]. In particular, eight out of 10 patients cease their usual activities because of BTcP [58], and their hospitalization rates are higher than those of patients without BTcP (37% versus 23%) [57]. Sudden, unpredictable episodes of BTcP are a burden for these patients and their families; therefore, they can and must be better considered [49].

What are the consequences of pain?

Assessing each aspect of the multidimensional nature of pain is essential for establishing a treatment strategy. The consequences of pain on the anxious/depressive aspect (mood, taking into account, for example, the impact of remnant pain or new morbidities associated with targeted therapies), on behavior, daily activity, autonomy, sleep, and relationships with others must be assessed [26, 27, 32]. By modifying the emotional component, drug treatments, accompaniment, therapeutic relationships, or psychotherapy can impact how the pain is experienced [28, 59]. Similarly, it is essential to understand the cause of pain in the vision of the patients [34, 60]. For example, in a metastatic context, the pain associated with treatments or other non-neoplastic causes may be interpreted by patients as a sign of the unavoidable aggravation of the illness. Intense pain may also be perceived as having serious causes, even if it is for example harmless muscular pain. Identifying these cognitive distortions is a means of proposing adapted explanations to change the patient's behavior and encourage the success of the different therapeutic approaches.

Thus, pain is multimorphic, and its dynamic evaluation must cover all its dimensions and characteristics. A multimodal, targeted therapeutic approach is therefore required to offer personalized pain management to all patients, as presented in Fig. 4. Establishing the most relevant healthcare strategy supposes comprising pain management to overall health management, and ascertaining interdisciplinary approach with the involvement of the healthcare staff representatives from the appropriate domains for each cancer patient.

What tools can be used to assess pain?

Patients' experience of their disease must be noted, as well as the meaning that they attribute to their pain, the means of announcing the diagnosis and/or prognosis, and identifying any possible relational traps. Past history will also make it possible to assess the patients' somatic or psychiatric past, as well as that of their families, the support provided by family and friends, the presence of kinesiophobia (i.e., inappropriate behavior for avoiding activities considered as capable of provoking or exacerbating the pain), and living conditions.

As recommended in the guidelines [30–32, 35, 36, 61], using patient self-assessment tools is also mandatory. These

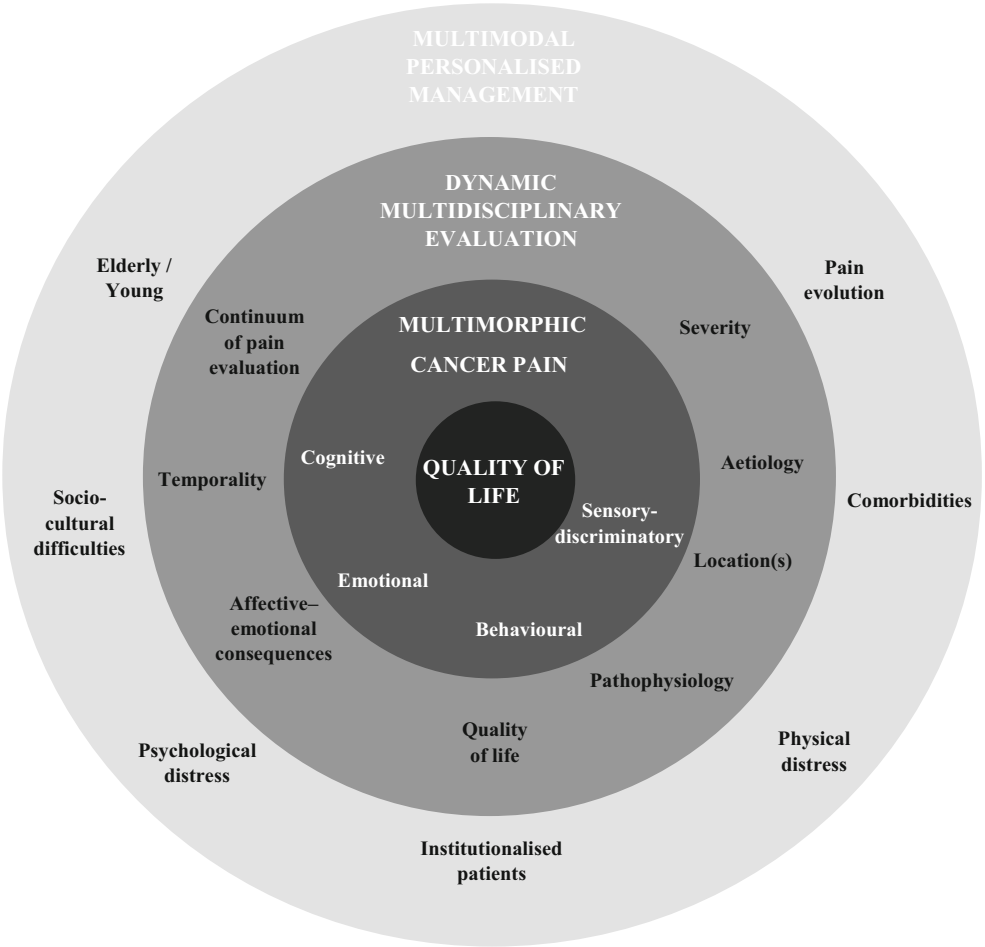

Fig. 4 Model of the multimodal, targeted, personalized management of the multimorphic cancer-related pain

assessments must be included in a genuine therapeutic relationship, and the assessor (registered nurse, doctor, caregivers) must be the same throughout the patient's follow-up, unless patient conditions justify a change. The same is true for questionnaires and scales. Patient self-assessments are thus based on questions and global self-rating scales [NRS (0 to 100%, the preferred test in routine practice), visual analogue scale (VAS), or word-graphic rating scale (WRS)] or descriptive scales within specific questionnaires if needed [61]. As previously mentioned, covering the multimorphism of pain, the patient-reported outcome (PRO) measurements focus on the pain itself [25, 36, 62, 63], but also on mood [64], and quality of life [65, 66]. If self-rating does not seem reliable, or in cases of patients incapable of understanding simple instructions or with psychomotor atonia, adapted hetero-assessment scales for acute pain [67], chronic pain [68], and pain associated with treatments [69] can be used.

Neuropathic pain assessment requires specific tools, and systematic screening must also be carried out by trained healthcare professionals [30, 70–72].

However, as the assessments must be repeated, the simplest possible procedure must be used to avoid feasibility problems or self-/hetero-assessment excesses that can lead to less precise and less reliable results.

Is the pain relieved?

Following the implementation of the personalized treatment, the obtained level of relief must be assessed using a NRS specific to pain relief or the seven-point patient global impression of change (PGIC [73]).

During each of these interviews with patients and their relatives, it is necessary to ensure that all the information has been exchanged and understood by the different parties [32]. Family, friends, and caregivers must be asked to identify any changes in the patients' behavior [74]. For instance, received information may make it possible to orient toward certain therapeutic measures (e.g., adapting showers, chairs, bedding).

As far as possible, what is the diagnosis of the pain?

Pain management must start as soon as the diagnosis is established [29, 32, 35]. According to the guidelines, a

wide range of possible treatments can associate the painkillers taken systemically (enteral, parenteral, and/or local) with non-invasive approaches (psychological interventions and rehabilitation) allowing to reach a satisfactory level of pain control in most patients [30, 32, 36].

Thus, obtaining a reliable diagnosis from the initial evaluations must provide patients with optimal comfort through a treatment strategy that takes into account the multimorphic nature of pain. These evaluations must be complete in order to avoid all the traps associated with pain, such as referred pain or differential diagnosis.

Similarly, regular monitoring and repeated evaluations of the patient will detect pain progression according to WHO scale [75, 76]. This early diagnosis of worsening may allow the use of the invasive therapies (nerve blocks, stimulation of the spinal column, interventional radiology, and surgery) as soon as necessary.

Conclusions and perspectives

Pain relief should be considered as early as possible in the management of cancer, and since the 1990s, pain has become a key issue in the global management of chronic pathologies such as cancer. This realization has had an influence right up to the very highest levels of health organizations and has made it possible to introduce pain into the quality processes of the management of patients in health establishments in many countries [77–80]. Personalized care has become an integral part of healthcare quality in many countries [77, 78, 80]; nevertheless, personalized medicine has not yet been sufficiently taken into consideration in Europe [81].

Pain in oncology is a factor for increased morbidity and suffering for patients, for their family and friends. In such difficult situations, the quality of the human relationship, overall appreciation of the individual's suffering and that of his or her entourage are a priority. Concepts and treatments evolve, and using them today requires all doctors to be familiar with cancer pain and its complex management, and consequently for them to attend the appropriate training courses. PRO measurements have demonstrated their benefit in patient satisfaction with care and in their communication with caregivers in oncology; use of PROs and feedback on cancer pain result in promising, modest, but significant, reductions in cancer pain intensity [36, 60].

Managing pain starts with its assessment, and this cannot be restricted solely to questions of severity. Understanding of the different aspects of a patient's pain must lead to a personalized treatment adapted to the pain's evolution over time, the patient's cancer, and its treatments. The patient's overall health status (e.g., cachexia, cognitive disorders, comorbidities, type of cancer…) is essential too, both in terms of assessment of the pain and choice of pain relief strategy. These criteria must thus be systematically addressed in studies on pain relief treatments to ultimately find adapted therapeutic responses for each patient. As a result, the evaluation of pain is dynamic and multidisciplinary. Furthermore, pain control has been shown to be associated with increased survival in prostate cancer and a potential independent positive prognosis factor in patients with certain solid tumors [16, 37]. The use of new cancer therapies is gradually modifying the characteristics of cancer pain, and thus the therapeutic approach for a growing number of patients. In such a context, multimorphic cancer pain evaluation must be part of personalized overall management of cancer patients subject to several potentially disruptive elements (Fig. 3), whatever the organization of cancer pain management is [82–84].

The development of this multimodal personalized management with targeted pharmacologic strategies with or without interventions, and complementary therapies, supported by dynamic interdisciplinary evaluations covering the various domains of multimorphic cancer pain, is one future avenue for research on cancer patient management. Furthermore, these multimodal and interdisciplinary approaches make it possible to spare opioids, and to provide the best care, for the right patient, at the right time.

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Compliance with ethical standards

Conflict of interest Christian Minello reports non-financial support from Kyowa Kirin, during the conduct of the submitted work; personal fees and non-financial support from Takeda; and non-financial support from Kyowa Kirin, Mundi Pharma, Mylan Pharma and Grunenthal, outside the submitted work. Brigitte George reports non-financial support from Kyowa Kirin, during the conduct of the submitted work; personal fees and non-financial support from Mundipharma; non-financial support from Grunenthal and Kyowa Kirin, outside the submitted work; and participation to a clinical study without honoraria from Bouchara. Gilles Allano reports non-financial support from Kyowa Kirin, during the conduct of the submitted work; personal fees and non-financial support from Grunenthal, Mundipharma and Medtronic; and non-financial support from Kyowa Kirin, outside the submitted work. Caroline Maindet reports non-financial support from Kyowa Kirin, during the conduct of the submitted work; personal fees and non-financial support from Mundipharma; and non-financial support from Kyowa Kirin, Grunenthal, Hospira, Takeda, and Janssen Cilag, outside the submitted work. Alexis Burnod reports non-financial support from Kyowa Kirin, during the conduct of the submitted work; non-financial support from Kyowa Kirin, outside the submitted work. Antoine Lemaire reports non-financial support from Kyowa Kirin France, during the conduct of the submitted work; personal fees and non-financial support from Kyowa Kirin International, Mundi Pharma, Grunenthal and Takeda; personal fees from Mylan; and non-financial support from Kyowa Kirin France, Archimèdes Pharma, Teva, Prostrakan, outside the submitted work.

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