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REVIEW ARTICLE

Strategies for interventional therapies in cancer-related pain—a crossroad in cancer pain management

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Abstract

Purpose Interventional therapies are important to consider when facing cancer pain refractory to conventional therapies. The objective of the current review is to introduce these effective strategies into dynamic interdisciplinary pain management, leading to an exhaustive approach to supportive oncology.

Methods Critical reflection based on literature analysis and clinical practice.

Results Interventional therapies act on the nervous system via neuromodulation or surgical approaches, or on primitive or metastatic lesions via interventional radiotherapy, percutaneous ablation, or surgery. Interventional therapies such as neuromodulations are constantly evolving with new technical works still in development. Nowadays, their usage is better defined, depending on clinical situations, and their impact on quality of life is proven. Nevertheless their availability and acceptability still need to be improved. To start with, a patient's interdisciplinary evaluation should cover a wide range of items such as patient's performance and psychological status, ethical considerations, and physiochemical and pharmacological properties of the cerebrospinal fluid for intrathecal neuromodulation. This will help to define the most appropriate strategy. In addition to determining the pros and cons of highly specialized interventional therapies, their relevance should be debated within interdisciplinary teams in order to select the best strategy for the right patient, at the right time.

Conclusions Ultimately, the use of the interventional therapies can be limited by the requirement of specific trained healthcare teams and technical support, or the lack of health policies. However, these interventional strategies need to be proposed as soon as possible to each patient requiring them, as they can greatly improve quality of life.

Keywords Pain management · Personalized management · Multimorphic pain · Cancer pain · Neuraxial analgesia · Nerve block

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Introduction

A literature review performed between 2005 and 2014 showed that half of the patients with cancer experienced pain. Among them, 38% rated their pain as moderate to severe, features of prevalence similar to those of a previous literature review over 40 years (up to 2007) [1, 2]. However, over the last 20 years, cancer survival rates have increased, and the disease is becoming a chronic condition with various degrees of improvement depending on type of cancer [3–5]. This situation and the emergence of new-targeted therapeutics impact pain management. Despite this, cancer pain still remains underestimated, poorly evaluated, and undertreated [6–14].

Depending on studies, a strict adherence to WHO's analgesic ladder leaves 20 to 40% of nociceptive cancer pain not adequately relieved [15, 16], corroborated by a study in a

German pain clinic strictly applying the WHO ladder [17]. Cancer-related pain refractory to conventional therapy remains frequent and more common in terminally ill patients than other cancer patients (respectively10–15% vs. 20%), even in pain clinics [18]. This may reflect the limits of the WHO ladder that focuses only on nociceptive pain while cancer patients are mainly confronted with several poly-mechanisms of pain including neuropathic mechanisms (e.g., mixed pains, such as compressive bone metastases and Pancoast syndrome pain, Table 1) [19, 20]. Furthermore, numerous classes of analgesics against neuropathic pain, even combined, have been developed. But their efficacy is still limited, as reported in various diseases [21].

Taking into account the paramount role of therapeutic strategies centered on the patient's diseases while facing cancer-related pain refractory to conventional treatments, the third step of the WHO ladder must be exceeded and new strategies must be applied. Rather than a step-wise approach, new interdisciplinary evaluations must lead to a multimodal response, including interventional radiology, neuromodulation, and surgery [22–26].

In this article, we present the interest of interventional therapies in refractory cancer pain management, in particular the positioning of intrathecal (IT) therapy and its limits. This specialized technique permits to perceive the whys and wherefores of the implementation of the interventional therapies, whereas neurolytic blocks for instance are of easier access even though the general procedures are similar (involvement of an interdisciplinary team, regular and dynamic assessments of pain, determination of the most appropriate available techniques for each patient, etc.).

Methodology

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 the latest publications on Medline.

Refractory pain in multimodal management

Managing pain starts by its assessment, and this cannot be restricted solely to questions of severity, because pain is not just about intensity. Pain leads to physical and psychological complications, and it also decreases patients' vitality and quality of life. Pain assessment is a complex process to cover all the interacting domains, and its quality is a therapeutic prognosis factor [8]. The evaluation of pain requires thus an interdisciplinary team to set up pain control as soon as diagnosis is made [22, 23, 27]. Furthermore, pain control has been associated with positive overall outcomes such as an increased survival in prostate cancer or a positive impact on certain solid tumors [16, 28].

When cancer pain is controlled, any symptom or change in cancer pain must be considered as a signal of disruption within pain management, patient's health, or general conditions (Fig. 1). Such event must thus trigger evaluations by the interdisciplinary team to guide the best therapeutic approach toward the symptom, its origin, or both. Conversely, patients enter a vicious circle after repeated inadequate management, and episodically controlled chronic cancer pain may become refractory to analgesics (Fig. 2).

When patients are facing refractory cancer pain, no approach should be neglected. The strategy must always lead to identify and, if possible, treat the cause of pain. If radiotherapy, hormonotherapy, and chemotherapy and surgery have shown their efficacy in pain relief for certain cancers [23, 29], these therapeutic approaches will not be developed in this article, even if they can be combined with certain interventional therapies acting directly on pain, described below. Ablative neurosurgical techniques

Table 1 Multiple forms of complex pain presented by cancer patients. Complex pains result from the combination of pains of different etiologies, locations, and physiopathologies

	Etiology of the different forms		Location of the different forms		Physiopathology of the different forms	
	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

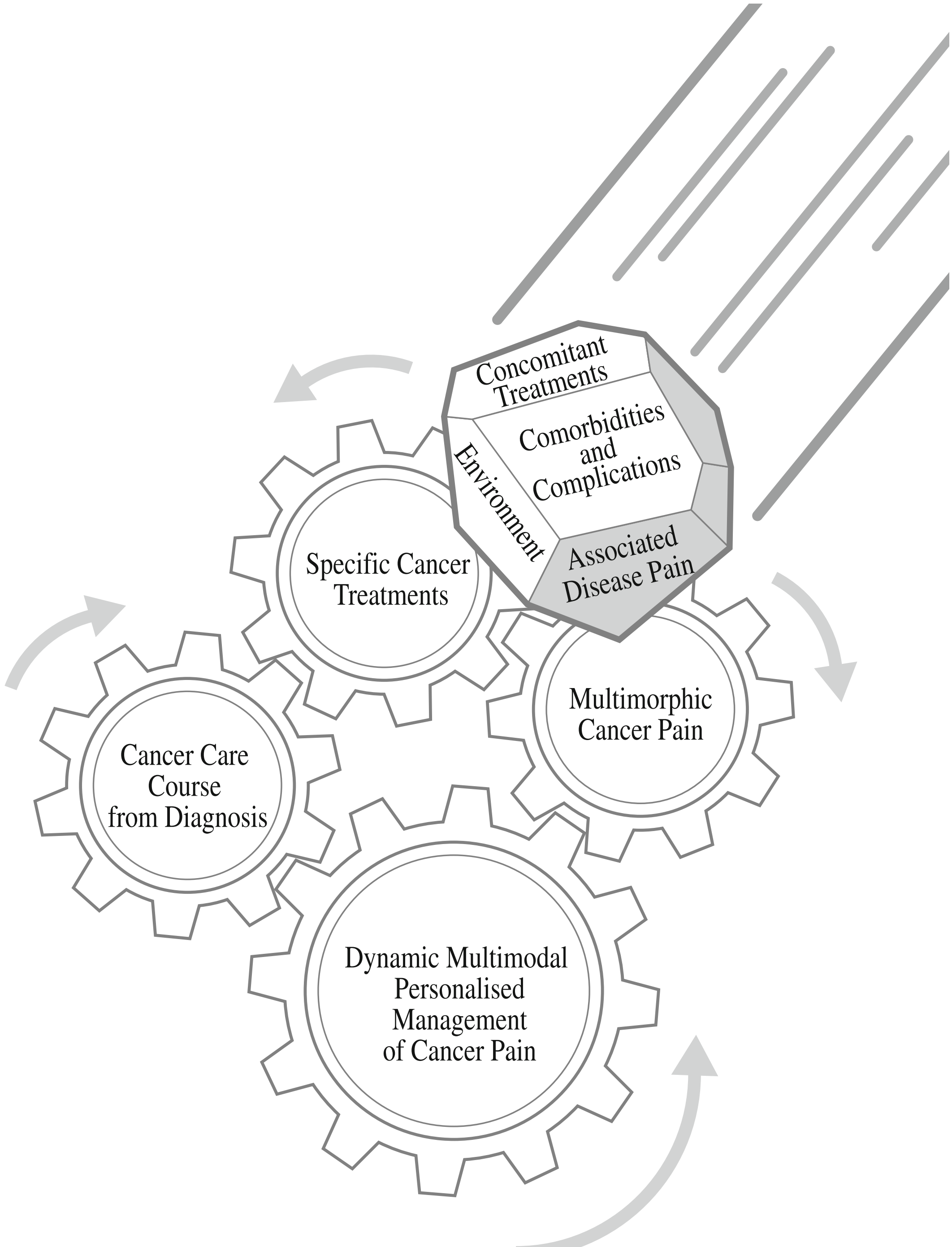

Fig. 1 Disruption key elements in the dynamic, multimodal, targeted, individualized management of multimorphic cancer pain

(including hypophysiolysis) are also relevant in some complex situations but they will not be developed in our review, mainly focused on interventional approaches specifically directed toward intractable pain.

When cancer pain has been treated properly, and pain control limits have been attained with conventional and complementary integrative therapies, cancer pain exacerbation is considered refractory. The therapeutic strategy for such uncontrolled pain must rely on the technical management of pain, known as the fourth step in the WHO ladder [30]. It should be noted that the stepwise progression of WHO's pain ladder may be circumvented in order to implement the optimal antalgic strategy, and within this vision, certain interventional strategies have to be considered even before the third step of the pain ladder, at the time of outset of neuropathic pain for instance [22, 26].

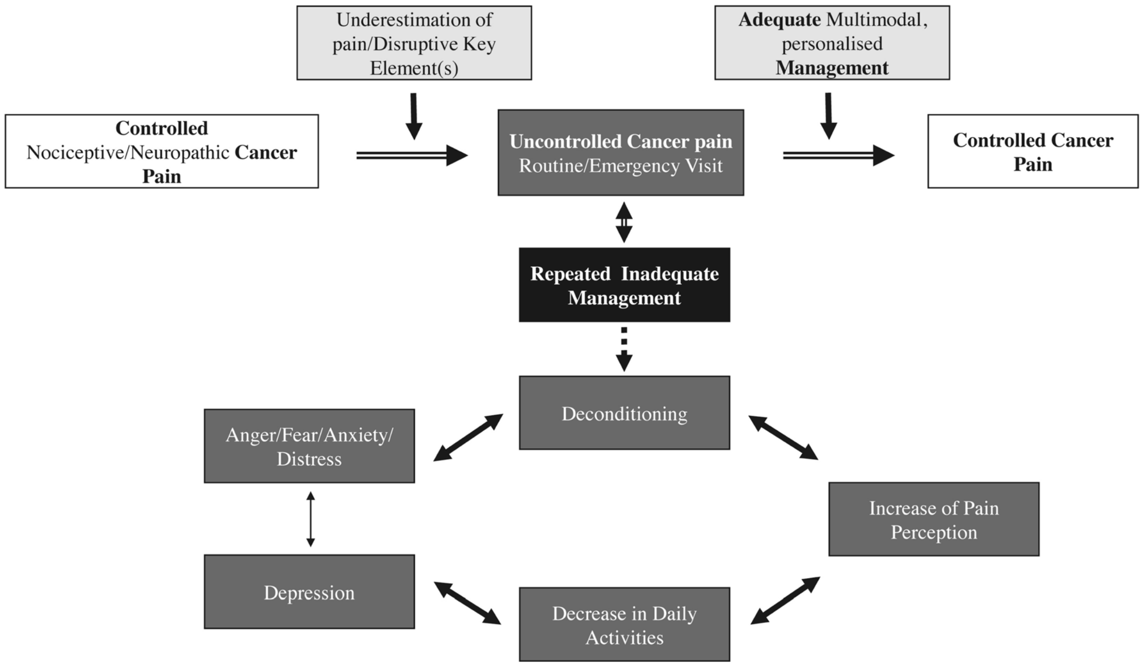

Fig. 2 The vicious circle of chronic cancer pain related to repeated inadequate management in patients with underestimated cancer pain or in the presence of disruption key element(s)

It is difficult to define a threshold in their use, as this is not only driven by cancer stage, performance status score, or patient's age but also by the availability of the adequate technical team in patient's environment. Their use requires an interdisciplinary thought to propose a personalized strategy to such patients with refractory pain. Ethical considerations must be imperatively taken into account, and not only in palliative situations. This approach will result in proposing the best interventional therapy to the right patient, at the right time.

Neuromodulation

Neuromodulation aims to decrease pain by altering signal transmission within the nervous system with electrical or chemical means, using invasive or non-invasive interventional techniques [31, 32]. Neuromodulation techniques include spinal cord stimulation (SCS), neuraxial drug delivery systems [IT or epidural (EPI) or intracerebroventricular (ICV)], and peripheral nerve stimulation (PNS) or peripheral nerve field stimulation (PNFS), as well as techniques still in development such as deep brain stimulation, repetitive transcranial magnetic stimulation, transcranial direct current stimulation, or motor cortex stimulation [25].

SCS and dorsal root ganglion stimulation provide relief in particular for neuropathic pain [33–36], although little clinical research has been conducted in cancer pain [37]. Promising new developments for SCS involve high-frequency stimulation [38]. PNS and PNFS are used to treat neuropathic peripheral pain [39, 40].

In particular, since the early 1980s, when neuraxial analgesic therapy first showed its efficacy [41], IT and EPI have entered multimodal management of refractory pain unresponsive to oral or systemic opioids, intolerance to high-dose opioids, severe neuropathic pain due to nerve plexus invasion, widespread bone metastases, aggressive chemotherapy, visceral tumors and dysautonomia, or specific locations (pancreas, pelvis) [26, 42–44]. ICV infusions of opioids or ziconitide remain a safe and effective palliative therapy in patients with intractable pain [45, 46].

Of more frequent use, neuraxial infusions offer the opportunity for delivering an analgesic from the large panel of non-opioids (local anesthetics, ziconitide, etc.), as well as very low-dose opioids [47–49]. Patients may experience other drug-related side effects similar to systemic administration, but with a lower incidence [27, 50, 51]. Complications related to the device require a surgical intervention in 11% of cases [43, 52].

IT infusion reduced pain scores, relieved the toxicity of most analgesic therapies, and was associated with a possible 6-month survival increase in cancer patients [49, 50, 53]. In addition, using patient-controlled analgesia, (PCA) devices to control IT infusion minimized the resort to systemic opioids [28], with cost-effectiveness [54–57].

Since 2000, the Polyanalgesic Consensus Conference (PACC) panel has addressed research gaps and reviewed the existing data on neuraxial analgesic therapies [56, 58–60] and built algorithms to determine when to use them [60]. From our experience, EPI and IT delivery infusions present different patterns of pros and cons, which are presented in Table 2. These characteristics are evolving while neuromodulation is

Table 2 Comparison of epidural and intrathecal analgesia

Peridural analgesia	Intrathecal analgesia
Advantages	Advantages
Easy to implement	Large choice of treatments
Low cost	Internal pump
Dosing adaptability	Low dose and small volume
	Long lasting
Disadvantages	Large diffusion
Limited availability of treatments	Low infectious risk
Large volume	
Limited duration	Disadvantages
Local analgesia (mainly)	High cost
High infectious risk	Complex implementation

being more used. For two decades, EPI delivery was thus recommended for patients with a life expectancy of less than 3 months, and (implanted) IT for patients with longer life expectancy; however, this threshold is no longer debated as it was mostly supported by short-term cost considerations [51, 61–63]. EPI and IT procedures present few side effects with potentially high efficacy, leading to significant improvement in patients' quality of life [41, 51, 53, 57, 64–66]. The implanted IT delivery procedure allows patients to remain at home after implantation, and they can deliver analgesic bolus via a wireless remote control PCA [56]. However, these techniques require highly specialized teams and structures to guarantee the best security, not only in terms of technical considerations, but also in terms of follow-up and care course.

As cancer-related pain is multimorphic [67], and in order to optimize patient responses or prevent the risk of subsequent insuperable events (such as complex pain, Table 1), the adequacy of the intervention must be assessed via comprehensive interdisciplinary evaluation. This should include medical and sociological professionals such as oncologists, neurologists, psychologists, or social workers. For example, the absence of a psychologist assessment may hinder the detection of patient's refusal of the implementation of a foreign device. To prevent the failure of the intervention, the interdisciplinary evaluation should consider different variables to support the IT strategy: patient diagnoses, and expected patient survival, previous exposure to opioids, location of pain (diffuse, localized, or global), type of pain (nociceptive, neuropathic, or complex), and nutritional or psychological status of the patient (Fig. 3) [60]. When these evaluations are conclusive, a

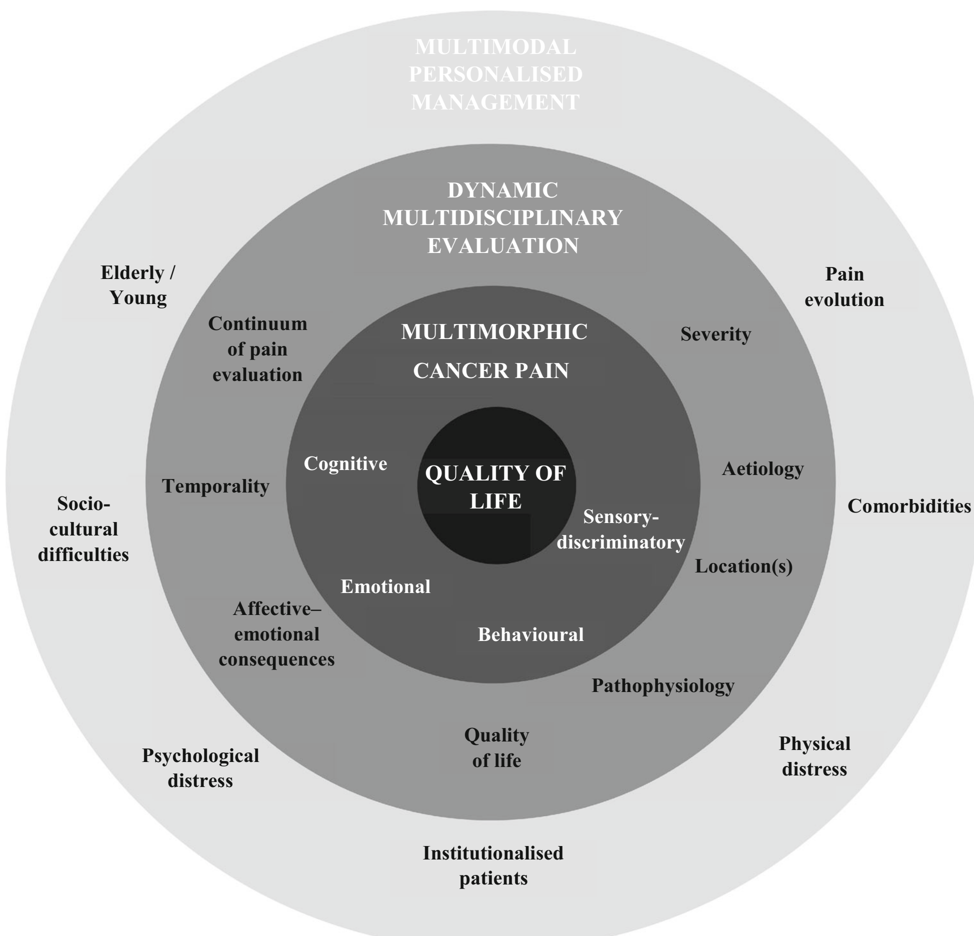

Fig. 3 Model of multimodal, targeted, personalized management of multimorphic cancer-related pain

specific set of appraisals of the intervention must be carried out to address the limits of drugs distribution in the CSF and spinal cord and the baricity of spinal anesthetic combination solutions, which modifies their diffusion [68].

Even though trialing is required by some European authorities and many insurers in the USA, the necessity and predictive value of trials is questioned as important factors cannot be appraised (e.g.: quality of life, risk of future opioid-induced hyperalgesia or disease progression, failure of neuraxial delivery, and survival) [53, 59, 60]. The appropriate initial opioid dose may be established on a patient's previous systemic opioid dose using Malhotra's equation [69].

Regular routine evaluations of IT delivery systems by pain specialists are required to screen for technical malfunctions and prevent potential related adverse events [47]. In addition, frequent multidisciplinary re-assessment will then determine the need for analgesic drug switch or discontinuation of neuraxial delivery [53].

It should be noted that, as with other analgesia, the availability of analgesics for IT and EPI varies depending on country. In 2018, few drugs had been approved for IT delivery analgesia: preservative-free morphine and ziconotide are currently approved in the USA, Europe, the Middle East, and Africa [56]. With a limited number of approved IT opioid agents, off-label drugs are often tried after failure of on-label trial. Furthermore, new drugs are investigated such as new conopeptides, inhibitors of transcription factor EGR1, and capsaicin analogues [44].

Analgesia by percutaneous neurolysis

Neurolytic blocks

Percutaneous neurolytic block is used in cases of neuropathic refractory cancer pain [70]. The gesture is getting increasingly precise with multimodal guidance requiring the combination of different image techniques in some cases [70, 71]. The IT injection of ethanol or phenol on to/within the dural sac damages the dorsal roots of the targeted nerve (neurolytic block) and permanently relieves the pain triggers by the nerve when successful [72]. In case of low emergence of the artery of Adamkiewicz, a vasospasm may be experienced. Instead of neurolytic blocks, temporary blocks can be carried out with injection of local analgesics.

In case of breast, upper limb, or posterior cervical spine cancers, a stellate ganglia block (SGB) may be performed [70, 73, 74]. After SGB, patients experienced a significant decrease in cancer-related pain in more than 50% of cases [70]. The adverse events of SGB reflected the technical success and were permanent in case of neurolysis; however, these events may also be present in case of tumor invasion in the sympathetic chain.

With abdominal and epigastric cancer pain caused by tumor extension reaching sympathetic chains via the coeliac trunk or the superior mesenteric artery, coeliac plexus neurolytic block (CPB) or splanchnic neurolytic block (SB) may be performed [75–80]. For more than two decades, several studies have demonstrated the efficacy of CPB on cancer pain [75]. Severe complications with CPB and SB are rare, and occasionally reported as case reports [75]. Vasodilation of the mesentery with increased upper abdomen temperature and intestinal motility are expected as signs of technical success.

Patients with pelvic cancer pain of visceral origin may undergo superior hypogastric plexus neurolytic block (SHB). However, only a few studies have been conducted, leading to weak recommendations [71, 75, 81]. Nevertheless, CPB, SHB, and lumbar sympathetic ganglion chain block in patients receiving low and high opioid doses have shown better efficacy on pain control, reduced opioid consumption, and improved quality of life, in comparison with analgesics alone [81].

For lower rectal and perianal burns, ganglion impar neurolytic block (GIB) is a treatment option, even though GIB, like SHB, has shown some efficacy on pain intensity [82, 83]. Nevertheless, only a few studies have been conducted, leading to weak recommendations [70, 71, 75, 81].

Usually, short-term relapse is due to tumor progression, and long-term relapse to nerve regeneration. However, a neurolytic block may be repeated.

Cryoanalgesia

Cryoanalgesia is a procedure that temporarily blocks nerve conduction along peripheral nerve pathways, by freezing the target nerve. The degree of freezing, induced nerve injury, and duration of anesthesia/analgesia depend on the cryoprobe diameter and positioning, the size of the resulting ice ball, the temperature of the immediately surrounding tissue, and the rate and duration of cold application [84]. The resulting analgesia can last from 2 weeks with minimal neuron damage, to several months after destruction of axon and myelin sheaths. This intervention allows nerves to regenerate by preventing post-procedural neuritis [85]. Longer duration analgesia can be reached by destroying the fibrous architecture, but it may lead to more severe pain than at the start [85]. Short-term cryoanalgesia is relatively safe, minimally invasive, and allows for repetition of neurolyses without permanent neurologic damage [86].

Thermal neurotomy

Continuous radiofrequency (RF) has been used to provoke neurolysis by protein thermocoagulation and to control pain by blocking nociceptive input [87]. Alternatively, pulsed radiofrequency (PRF) reduces pain with little tissue damage

[88], as it elicits changes in axon ultrastructure, inhibiting evoked synaptic activity [89–91]. Therefore, PRF may be preferable to chemical or radiofrequency neurotomy when such approaches are required [89, 92].

Analgesia by percutaneous cordotomy

The ablation of upper spinal cord pain pathways may be used to provoke lesions to the spinothalamic tract on the contralateral side and to relieve unilateral pain, such as severe mesothelioma or breast carcinoma pain [93–97]. While the initial success on pain relief was reported in over 90% of the patients, long-term relief is at about 40 to 50% [93–97]; cordotomy is thus a salvage treatment for patients whose survival is limited by refractory nociceptive or neuropathic pain.

Analgesia by percutaneous ablation of metastatic lesions and tumors

Percutaneous ablation of metastatic lesions, either with radiofrequencies or cryotherapy, is indicated in patients with refractory metastatic disease [98, 99].

Percutaneous radiofrequency interventions are safe and provide significant relief for painful metastatic bone lesions [100, 101].

Percutaneous cryotherapy can be used with extreme cold (around − 75 °C) to destroy tumors. It is less painful and presents better intrinsic analgesic properties than thermoablation with superior monitoring capability on multimodal imaging [102]. It is also possible to treat larger tumors and preserve tissue's collagenous architecture [103], but with a longer procedure. Cryoablation has few interventional consequences and minor complications such as peritumoral inflammation, with low incidence on other oncologic therapies; nevertheless, there is a need of large studies to confirm the outcomes in the different uses of cryoablation [103].

Analgesia by other percutaneous interventions

Metastatic invasions into the spine (e.g., 22% of breast cancer patients) and secondary spine tumors (thoracic location, 70%; lumbar, 20%; cervical, 10%) are frequent evolutions in cancer [104, 105], and are detrimental to quality of life. The sharp, stabbing pain triggered by vertebral instability or spinal cord compression classically requires open surgery [106]. However, percutaneous interventions are now considered the first approach by surgeons, as patients have a lower risk of complications than with open surgery [107].

For such patients, the main percutaneous interventions are vertebroplasty or kyphoplasty [108]. Both cementoplasties relieve pain in patients with malignant bone tumors, and neither seems preferable [109]. Percutaneous vertebroplasty is the strengthening of the bone using percutaneous injection of a cement, polymethylmethacrylate, into the damaged vertebra [99]. From a recent review of ten case control studies, percutaneous vertebroplasty of spinal tumor resulted in a drastic pain reduction (2.83-fold on visual analogic scale), associated with a 16.3-fold increase of Karnofsky performance scores [110]. The technical approach of kyphoplasty is different with the percutaneous insertion and inflation of a balloon inside the bone to create a cavity to be filled by the cement to minimize leakage and kyphotic deformity [111, 112]. Recent studies have shown the efficacy and safety of kyphoplasty for treating vertebral fractures in cancer patients [111, 112].

Recently, percutaneous image-guided screw-mediated osteosynthesis has been used with good short-term results to fix impending fractures and non-displaced/mildly displaced pathological/insufficient fractures of the femoral neck in non-surgical cancer patients [113]. The feasibility of the technique has been demonstrated with a 91% success rate, as well as its safety as no intervention-related complications were experienced.

Discussion

In recent decades, several integration models for supportive care have been proposed as early as cancer diagnosis [114]. These models of supportive oncology have shown a positive impact on patients' quality of life, symptom management, and optimization of patients' care pathways [115–117]. Today, implementing multimodal, personalized management of cancer pain has definitively opened up access to interventional therapies adapted to patients' conditions, and with a positive risk/benefit ratio, in particular, in patients with refractory cancer pain (Fig. 3) [22, 26]. In a context of increased survival in most cancers, management of cancer-related pain has shifted toward chronic management, with an increase in refractory pain [118].

In order to respond to the different needs of patients, clinicians must stop working in silos and switch to dynamic interdisciplinary management [114]. Supportive care interdisciplinary teams have the knowledge to cover patients' cancers, multimorphic cancer pain, and other concomitant pathology managements with a general overview [119, 120], and to properly implement alternative interventional therapies when 3-step WHO ladder treatment benefits, combine with neuropathic treatments, are limited [22–26]. Multimorphic cancer pain requires dynamic evaluations to include all its dimensions and different pathophysiological, temporal, and environmental characteristics; therefore, when a disruptive event occurs, a multimodal, targeted therapeutic approach is thus needed (Fig. 1). At every moment of a patient's life, supportive oncology makes it possible to adapt pain treatment to global patient management, which may lead to earlier use of adequate interventional therapies not only in palliative situations [30].

As for opioid analgesia, which requires specific knowledge for use under optimal safety and efficacy conditions [120], gaining the best possible understanding of such interventional techniques, especially in the best indication for the right patient at the right time, and the balance between their benefit and limits, requires specific training for their implementation. In the case of IT therapy, for instance, follow-up may be carried out in institutions geographically closer to patients' living places, if local teams are trained to fill the pumps, with availability of adequate infuscate (trained pharmacists) and awarded clinical-specific follow-up. Such procedures need to be implemented to offer patients IT interventions when needed. Thus, in addition, knowledge of the pros and cons of the different interventional therapies, and which ones are available for each patient with a minimum of access constraints, must be debated within the interdisciplinary management teams.

Otherwise, interventional therapies require highly specialized teams with appropriate technical support and subsequently specific organizations. For instance, IT patients need specific management regarding their past history, concomitant medications, and IT infusate. Vigilant and frequent early monitoring must thus be set-up for the delivery system [121]. Studies on IT infusions have highlighted a risk of overdosing or sub-dosing IT mixtures, because admixture requires accurate dose prescription and precise, aseptic mixture preparations [121, 122]. In routine practice, the infusate is prepared by either the implantation-specialized clinical team and/or the pharmacist depending on local regulation; this last option is often preferable [49]. Later, similar issues arise when refilling the pump. IT drugs are usually stable, except for low-concentration ziconotide which presents a linear admixture degradation, requiring specific preparation conditions to compile with the delay between two refills [123]. To offer preparation security and access to IT delivery system refills close to patients' homes, locally delivered centralized refill preparation may be an option [49]. Costs are also to be considered before choosing to perform an IT therapy, even though IT is cost-effective in the long-term [43, 57].

Furthermore, the need of frequent and regular pain evaluations, or training the health care team, can be an obstacle to a wider use of these alternative techniques.

Choosing interventional therapy is synergic with the cancer treatment; it is thus based on the combination of both to get the optimal outcome for cancer and pain. The negative influence of pain on overall survival has been reported in prostate cancer and possibly in several other types of cancer [124–128]; nevertheless, using these interventional therapies is often postponed for extreme palliative situations, while earlier implementation would have mitigated patients' cancer pain earlier, with potential benefits for patients' life expectancy.

Conclusions and perspectives

Increased cancer patient survival rates have turned the management of cancer-related pain toward long-term management. First, chronic cancer pain management needs to be established on dynamic interdisciplinary evaluation for an adequate conventional and complementary therapy guided toward the characteristics of cancer-related pain. When patients become refractory to treatments, there is a need for interventional therapies, and a panel of interventions is now available to provide the appropriate answer. However, these alternative procedures require specific training, skilled health care teams, technical support, and an appropriate organization. The current pain relief strategies are also based on such interventional procedures, which should be proposed as soon as needed when they are available to patients, and not only in palliative situations.

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Compliance with ethical standards

Conflict of interest 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. 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; participation to a clinical study without honoraria from Bouchara. 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. 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. 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. 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, and Prostrakan, outside the submitted work.

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