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REVIEW

The Missing Link: Integrating Interventional Pain Management in the Era of Multimodal Oncology

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ABSTRACT

Cancer-related pain (CrP) is one of the most frequent and debilitating issues that affect the quality of life of patients with cancer. Systemic analgesics, particularly opioids, have been the cornerstone of pain management. However, the following shortcomings of the mentioned therapies, such as side effects, tolerance, and inadequate relief in refractory cases, make implementing a more complete, multimodal treatment plan necessary. Interventional pain management (IPM) uses specific invasive procedures, with different degree of invasiveness, such as nerve blocks, neurolysis, neuromodulation, and intrathecal drug delivery systems to provide effective pain relief with reduced adverse effects compared with opioids. These approaches are frequently underutilized due to delayed referrals, insufficient awareness, and logistic inefficiencies, which delay access to pain management centers specializing in care for patients in pain. Recent technological advancements offer the potential to overcome these barriers, including artificial intelligence-driven decision support systems and automated referral pathways, enabling early intervention and individualized pain treatment plans. The future of CrP management

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should shift from the current reactive model to a proactive approach, enabling the earlier incorporation of interventional techniques into treatment plans. The integration of interdisciplinary collaboration and technological innovations will enhance cancer pain management and progress from current outdated approaches to provide more effective and timely pain relief for patients with chronic refractory cancer pain.

Keywords: Cancer pain; Epidural analgesia; Nerve block; Neurolysis; Spinal cord stimulation; Intrathecal injections; Palliative care; Radiofrequency ablation; Vertebroplasty

Key Summary Points

Cancer-Related Pain is a Major Burden: It affects up to 66.4% of patients, severely impacting daily function, mental health, and quality of life.

Multidisciplinary and Personalized Care is Essential: Effective pain management requires collaboration between oncologists, pain specialists, and palliative care teams.

Interventional Pain Management Should Be Used Early: It should not be a last resort; early integration can improve outcomes and reduce opioid-related side effects.

Interventional Techniques Provide Targeted Relief: Procedures such as neurolysis, spinal cord stimulation, intrathecal drug delivery, and vertebroplasty are minimally invasive techniques that can provide effective pain control with fewer systemic side effects, and should be integrated into a holistic, multidisciplinary framework.

The Future of Cancer Pain Management is Proactive: Shifting from reactive care to early interventions in proactive care, aided by artificial intelligence (AI) and predictive tools, will optimize pain control and patient well-being.

INTRODUCTION

Pain is not just a symptom of cancer. It is a disease within the disease.

According to the International Classification of Diseases 11th Revision (ICD-11) classification developed by the International Association for the Study of Pain (IASP) Task Force, chronic cancer-related pain (CrP) is chronic pain caused by the primary cancer itself or its metastases (chronic cancer pain) or its treatment (chronic post-cancer treatment pain). It is distinct from pain caused by comorbid disease [1].

CrP is a multidimensional phenomenon, involving sensory, cognitive, emotional, and behavioral components. It is not a static condition but a dynamic and evolving experience, which often persists or changes throughout the disease and its treatments [2] and remains one of the most debilitating aspects of the oncological experience. A meta-analysis reviewed 122 studies to assess cancer pain prevalence and severity, revealing that pain affects 55.0% of patients during therapy, 66.4% in advanced stages, and 39.3% post-treatment. Despite advances in pain management, 38% of patients still report moderate-to-severe pain [3].

CrP arises from multiple mechanisms, including nociceptive, nociplastic, neuropathic, and mixed pain, often with a strong inflammatory contribution [2]. Nociceptive pain results from the activation of nociceptors in response to actual or threatened tissue injury [4]; neuropathic pain arises from a lesion or disease affecting the somatosensory system [5]; and nociplastic pain [6], more recently defined, reflects altered nociceptive processing in the absence of clear structural damage. In the oncologic setting, these mechanisms frequently coexist, giving rise to mixed pain syndromes. Moreover, inflammatory mechanisms play a central role in the pathogenesis of CrP, regardless of its classification. Tumor cells, immune cells, and stromal components of the tumor microenvironment release a multitude of proinflammatory mediators: interleukins (IL-1β, IL-6), tumor necrosis factor-alpha (TNF-α), prostaglandins (particularly PGE2), bradykinin, and neurotrophic factors such as

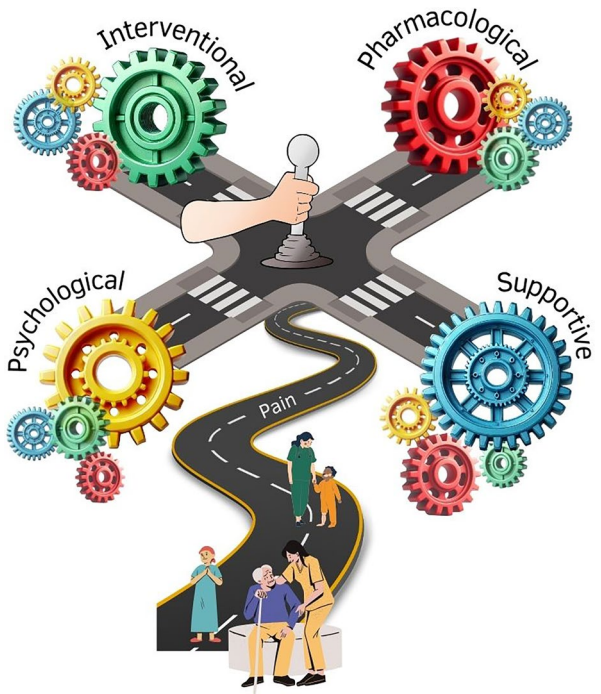

Fig. 1 Crossroad of cancer-related pain (CrP). Each patient with CrP reaches a crossroad where different therapeutic paths can be taken. The four gears represent the main approaches: interventional (green), pharmacological with NSAIDs, opioids, and adjuvants (red), supportive therapies such as nutrition and physiotherapy (blue), and psychological therapy (yellow). The central lever signifies key factors such as disease progression, treatment side effects, or end-of-life status, which can shift the chosen approach when operated by the clinician. The winding road reflects the patient's dynamic journey through these treatments, ensuring a personalized and adaptive pain management strategy

nerve growth factor (NGF), glial cell-derived neurotrophic factor (GDNF), and epidermal growth factor (EGF) [7]. These mediators act on specific receptors expressed on primary afferent neurons, such as TRPV1 [8], P2X3 [9], NK1 [10], and sodium channels Nav1.7 and Nav1.8 [11], inducing peripheral sensitization and enhancing nociceptive input to the spinal cord. The continuous activation of nociceptors and subsequent release of neurotransmitters such as substance P and glutamate at the spinal level contribute to central sensitization, further amplifying pain perception [12]. Additionally, tumor-associated inflammation promotes glial cell activation and the release of secondary mediators, reinforcing neuroinflammation and leading to persistent, often treatment-resistant pain [13]. This inflammatory framework frequently intersects with neuropathic and nociceptive elements, elucidating why mixed pain is the predominant manifestation in patients with cancer.

The complex and evolving nature of CrP reflects its capacity to change over time, shaped by tumor progression, treatment-related complications such as chemotherapy-induced neuropathy, emotional distress, and comorbidities [2]. This clinical reality leads to a fundamental concept: CrP often requires more than systemic pharmacological treatment alone. Yet, in many settings, interventional pain management (IPM) is still considered a last-resort option, offered only after conventional therapies have failed.

In contemporary cancer pain management, four therapeutic pillars must be synergistic rather than sequential: pharmacological, interventional, rehabilitative, and psychosocial [2]. Pharmacological agents, including opioids and adjuvants, remain essential tools, but side effects, tolerance, or inadequate control in complex pain syndromes often limit their efficacy. Rehabilitative strategies such as physical therapy, gait training, and occupational support aim to preserve function, counteract deconditioning, and improve autonomy. Psychosocial interventions, including psycho-oncology, cognitive behavioral therapy, and family counseling, address the emotional, cognitive, and existential dimensions of pain. These modalities do not represent alternatives to IPM, but coexisting strategies to be co-activated on the basis of individual needs and disease dynamics [2].

This conceptual shift is illustrated in Fig. 1, which proposes a non-hierarchical, unified model of cancer pain management. Throughout the course of illness, patients often find themselves at a therapeutic crossroad, where the optimal direction may vary depending on the clinical context and evolve over time. Within this framework, IPM should be considered early, when appropriate, and always as part of a broader, interdisciplinary plan (see Clinical Box 1 – Rosa).

The traditional foundation of CrP management has been systemic pharmacological therapy, particularly opioids [14]. While effective in many cases, conventional drugs have well-known limitations, including tolerance, dependency, and adverse effects that often burden both patients and caregivers [14]. Moreover, a significant proportion of patients continue to experience uncontrolled pain despite adequate pharmacologic regimens [15].

In this context, interventional strategies offer targeted, long-lasting solutions. Rather than being the endpoint of a stepwise ladder, they should be viewed as a core component of an integrated, dynamic approach. The concept of a "fourth step" to the World Health Organization (WHO) analgesic ladder, representing interventional therapies, was first proposed by Miguel in 2000 [16] and later revisited by Vargas-Schaffer in 2010 [17].

However, today we must go beyond that: we need not a stepwise ladder but a networked framework.

IPM includes a range of minimally invasive techniques to interrupt nociceptive pathways: nerve blocks, neurolytic procedures, spinal cord stimulation, and intrathecal drug delivery devices [18]. These methods circumvent systemic adverse effects and can dramatically improve function and quality of life, especially in patients with refractory pain.

Recent technological and methodological innovations have expanded the indications and accessibility of interventional strategies, opening new possibilities for personalized cancer pain management [19].

However, despite strong clinical rationale and growing evidence, interventional treatments remain underused and underrecognized. A 2007 postal survey of 107 UK pain clinics revealed that 75% of pain consultants did not include cancer pain in their job plan, and over half received five or fewer referrals annually. Collaborative consultations with palliative care teams were uncommon [20]. Unfortunately, a 2022 Delphi survey confirmed that this gap still exists, with many patients with cancer not being referred to pain units, and therefore not receiving timely, appropriate therapies [21].

This review focuses on the interventional pillar within this modern, integrated framework. We explore the rationale, evidence, and clinical application of IPM techniques (nerve blocks, neurolysis, spinal cord stimulation, and intrathecal drug delivery) not in isolation, but as part of an evolving paradigm in multidisciplinary, patient-centered cancer pain care.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

CLINICAL BOX 1 – ROSA, 50 YEARS OLD, PANCREATIC CANCER. FROM EXHAUSTION TO RELIEF: A MULTIMODAL TURNAROUND

Rosa, a 50-year-old woman with advanced pancreatic cancer, had discontinued chemotherapy due to uncontrolled abdominal pain despite escalating systemic opioids up to 300 mg/day morphine equivalent, adjuvants, and supportive care. She was referred to the pain unit, where an intrathecal catheter was implanted to deliver targeted analgesia.

She was started on a combination of 1 mcg/day ziconotide, 3 mg/day levobupivacaine, and 0.8 mg/day morphine. Within days, her pain significantly improved, allowing her to resume chemotherapy and regain daily function.

Over time, thanks to a reasonable control of the neoplastic disease and a supportive psychotherapeutic pathway, the intrathecal regimen was adjusted accordingly. Rosa's quality of life has markedly improved, and she has now been living well for over a year.

This case illustrates how early integration of interventional pain management can restore function, enable oncologic treatment,

and profoundly impact survival and quality of life

METHODS

This narrative review was conducted to evaluate the role of IPM techniques in cancer-related pain, within the broader context of multimodal oncology care. A comprehensive search of the PubMed, Embase, Cochrane Library and Google Scholar databases was performed for studies published from January 2000 to March 2025, using a combination of MeSH terms and free-text keywords.

The primary PubMed search string was: ("Cancer Pain"[MeSH Terms] OR "cancer pain"[Title/Abstract] OR "malignant pain"[Title/Abstract]) AND ("interventional pain management"[Title/Abstract] OR "nerve block"[Title/Abstract] OR "neurolysis"[Title/Abstract] OR "radiofrequency ablation"[Title/Abstract] OR "spinal cord stimulation"[Title/Abstract] OR "intrathecal drug delivery"[Title/Abstract] OR "cordotomy"[Title/Abstract] OR "neuromodulation"[Title/Abstract] OR "ganglion impar"[Title/Abstract] OR "superior hypogastric plexus"[Title/Abstract] OR "splanchnic nerve"[Title/Abstract] OR "vertebral augmentation"[Title/Abstract]).

Filters applied: English language.

Articles were selected on the basis of their relevance to interventional management of cancer pain, including randomized controlled trials (RCTs), meta-analyses, systematic reviews, observational studies, and expert consensus statements.

Exclusion criteria included studies focusing exclusively on pharmacological or psychological treatments unless interventional methods were also discussed.

THE BURDEN OF CANCER-RELATED PAIN

Although CrP's prevalence and physiological processes are thoroughly established, its impact goes beyond simple numerical figures. CrP significantly impacts patients' everyday functioning, mental health, and social interactions, adversely affecting their quality of life throughout all stages of the disease. Pain frequently transforms into an all-encompassing feeling, undermining autonomy, restricting mobility, and disrupting fundamental functions such as eating, sleeping, or personal hygiene. The loss of independence fosters emotions of frustration, helplessness, and social isolation, intensifying psychological suffering, including anxiety and despair [22].

The phenomenon of symptom clusters, which has garnered heightened interest in oncology research, exacerbates this burden. Patients with cancer never experience pain in isolation; rather, CrP frequently occurs within interconnected symptom clusters that may encompass tiredness, sleep problems, emotional distress, nausea, cognitive impairment, and gastrointestinal dysfunction [23]. These symptom clusters not only exacerbate suffering, but also complicate treatment, as addressing a single symptom frequently does not mitigate the entire pain. A cluster of pain, exhaustion, and sleep disturbances is commonly reported in patients with cancer, with each symptom aggravating the others, resulting in a cycle of increased suffering and functional deterioration [24]. A gastrointestinal symptom cluster, including nausea, vomiting, and anorexia, is notably common in individuals receiving chemotherapy, frequently exacerbating the perceived load of cancer-related issues [24].

The burden of CrP greatly affects caregivers, who frequently experience emotional tiredness, burnout, and the intricate demands of delivering both physical and emotional assistance. Families observe their relatives in perpetual suffering, which can strain relationships and undermine overall familial well-being [25]. Furthermore, inadequately managed pain escalates healthcare consumption, resulting in recurrent hospitalizations, extended durations of stay, and significant resource expenditure, consequently inflicting a considerable financial strain on both families and healthcare systems [25].

Patients are frequently referred for sophisticated pain treatment just in the last phases of illness, when measures may provide minimal advantage. This highlights deficiencies in clinical practice and emphasizes the necessity for early, coordinated, and patient-centered strategies in pain treatment [26].

IPM techniques, which include intrathecal drug delivery systems (IDDS), nerve blocks, and neuromodulation to alleviate suffering in patients with cancer, have emerged as valuable strategies. IDDS have shown superior analgesia, while systemic opioid requirements are minimized, thereby decreasing linked side effects such as sedation, nausea, and cognitive impairment [27]. These techniques also improve pain control so that patients can maintain autonomy and daily functioning, thereby also reducing the emotional and physical burden on caregivers who often struggle with the constant demands of pain management [28]. Furthermore, IDDS may improve patients' survival [29].

Effectively addressing CrP necessitates a drastic change from reactive to proactive care, wherein prompt, multidisciplinary therapies are acknowledged as vital elements of an integrated approach in the management of CrP.

PRINCIPLES OF INTERVENTIONAL PAIN MANAGEMENT

IPM for CrP is an essential aspect of holistic pain treatment, designed to enhance quality of life, reduce opioid-associated adverse effects, and manage refractory pain syndromes. Contemporary best practices promote their early incorporation into a multimodal pain treatment strategy [30]. IPM should not be seen as a standalone approach, but rather as an asset to be combined harmonically with conventional pharmacological treatments, psychological assistance, and palliative measures to enhance patient outcomes across the illness continuum [30].

The backbone of IPM is the customization of therapy, informed by comprehensive pain evaluation, encompassing etiology (nociceptive, neuropathic, or mixed), anatomical site, illness progression, prognosis, and previous treatment outcomes. It is crucial to refer patients to professional pain care services because early intervention can stop the progression of pain, decrease opioid use, and enhance functional outcomes [31].

IPM encompasses a wide range of approaches. Some of the techniques included are neuraxial interventions, such as epidural and intrathecal drug delivery systems, nerve blocks, neurolytic procedures, such as chemical neurolysis and radiofrequency ablation, neuromodulation techniques, such as spinal cord stimulation, and structural interventions, such as vertebroplasty [30].

The first key point to consider when implementing IPM is the collaborative coordination and consensus between oncologists, palliative care specialists, pain management physicians, and radiologists to determine the best next step for CrP management to address all its aspects, including the physical, psychological, and social aspects.

Goals of IPM should include pain management to decrease the severity and discomfort of pain as well as functional improvement, as pain contributes to functional impairment, limitation on activity and movement, and dependency [30]. Interventional techniques aim to restore or maintain functional capacity, enabling patients to engage in meaningful activities, whether walking, self-care, or family participation. This ultimately leads to enhanced quality of life [32].

These goals are not static but should be considered dynamic and assessed regularly to align with the patient's evolving disease trajectory, treatment response, and personal priorities [2]. In palliative care, the focus may be on comfort care instead of long-term functional status, while keeping in mind that the patient's desires should be respected.

The ethical perspective should also not be forgotten, especially in patients with advanced cancer in which the tradeoff between the benefit and risk versus the quality of life may be complex [33, 34].

The principles of autonomy, beneficence, and non-maleficence should guide decision-making when potentially evaluating IPM:

Autonomy requires that patients be fully informed of interventional procedures' potential advantages and disadvantages to make decisions consistent with their values and goals. This requires open and sensitive communication of what the patients can expect to happen,

including the fact that in end-stage disease, there may be little or no improvement [35].

Beneficence and non-maleficence strike the need to provide interventions that offer meaningful pain relief while minimizing harm. This includes careful risk assessment to avoid unnecessary procedures that may not improve, or could even worsen, the patient's condition [36].

Finally, patient selection criteria for IPM rely on both clinical and ethical considerations. Ideal candidates are those who:

- Have pain refractory to optimal medical management or experience intolerable side effects from systemic analgesics [37].
- Exhibit localized pain that correlates with a specific anatomical target for intervention (e.g., celiac plexus neurolysis for pancreatic cancer pain) [38].
- Possess a functional status sufficient to tolerate the procedure, with consideration of life expectancy to ensure that the benefits outweigh procedural risks [39].
- Demonstrate realistic expectations and understand that interventions aim to improve quality of life, not necessarily eliminate pain entirely [40].

Contraindications may include psychiatric disease that impairs procedural cooperation or post-intervention coping. Psychological suffering that arises as a direct consequence of uncontrolled pain should not exclude patients from IPM; in such cases, effective pain relief may itself contribute to emotional stabilization [41, 42].

KEY INTERVENTIONAL PROCEDURES FOR CANCER-RELATED PAIN

Interventional procedures may be grouped into the following subgroups:

(1) Peripheral nerve blocks, neurolysis, and percutaneous ablative techniques
(2) Implantable devices
(3) Interventional radiology procedures
(4) Surgical options

An overview is presented in Table 1.

Peripheral Nerve Blocks, Neurolysis, and Percutaneous Ablative Techniques

Peripheral nerve blocks are transitory and involve the use of local anesthetic solutions [43]; neurolysis involves the destruction of the afflicted tissues and nerve structures using destructive chemicals such as phenol or alcohol or with radiofrequency, the latter referred to as radiofrequency neurolysis (RFN) [61].

Peripheral nerve blocks may be used when the distribution of pain is limited to a single nerve or plexus. The origin of this pain may be linked to the cancer directly infiltrating the nerve, as well as previous radiation treatment and complications such as fractures and vessel obstruction [62].

Several studies have reported the use of peripheral nerve blocks to treat CrP. For instance, a trigeminal nerve block may be considered for head and neck malignancies [63], intercostal nerve blocks when the ribs are affected by metastases [64], femoral and sciatic nerve blocks for pain localized to the limbs [65], and serratus anterior blocks for pain post-mastectomy or thoracic surgery [66]. Intrapleural [67], distal lumbar plexus [68], paravertebral [69], brachial plexus [70], and suprascapular [71] blocks have also been reported.

Local anesthetics are typically used for nerve blocks, such as lidocaine, ropivacaine, bupivacaine, and levobupivacaine. Long-acting local anesthetics (duration of effect 4–18 h), such as the last three, are often used to achieve long-term treatment [72]. Continuous infusion with an indwelling catheter offers a longer duration of analgesia [73], even though a single injection of local anesthetic is adequate for short-duration analgesia, such as during an imaging test, surgery, or quick management of a pain crisis.

Klepstad reported in 2015 in a systematic review that most patients experience pain relief, and in some cases, the duration of this benefit lasted until the patients' death. However, these studies are mostly case reports and anecdotal data, which does not equal a lack of effectiveness [44].

Table 1 Summary of interventional and surgical techniques for cancer-related pain

Technique	Indications	Advantages	Limitations/considerations	Setting/use	Strength of evidence
Peripheral nerve blocks	Localized somatic or post-surgical pain	Immediate relief, minimally invasive	Low cost; low risk; limited duration; may require repeated administration	Outpatient; short-term use	Low [43, 44]
Plexus/neurolytic blocks	Visceral pain (e.g., pancreatic, pelvic); especially effective in upper abdominal cancers (e.g., celiac plexus neurolysis)	Long-lasting relief; opioid-sparing	Moderate cost; risk of transient hypotension or deafferentation pain; limited by life expectancy and anatomical considerations	Inpatient/outpatient; weeks–months	Moderate [30, 45, 46]
Percutaneous ablative techniques (RFA, MWA, LA, CA)	Painful bone or soft tissue metastases; tumor-related mass effect	Direct tumor destruction; reduces nociceptive input; minimally invasive; image-guided precision	Moderate cost; moderate risk due to proximity to vital structures; variable efficacy; requires specialized equipment and training	Interventional radiology; typically weeks-months	Low [47, 48], moderate for RFA in spinal metastases [30]
Spinal cord stimulation (SCS)	Selected neuropathic pain (e.g., CIPN, post-surgical)	Reversible neuromodulation; lower opioid use	High cost; moderate procedural risk (infection, lead migration); limited cancer-specific data. Trial required; MRI limitations	Patients with > 6–12 months prognosis; may be considered on a case-by-case basis	Low to moderate [30, 49]
Dorsal root ganglion stimulation	Focal neuropathic pain (e.g., CrPS-like)	Precise targeting; high efficacy for focal pain	High cost; moderate risk similar to SCS; limited availability and cancer-specific evidence	Similar to SCS	Low [50, 51]

Table 1 continued

Technique	Indications	Advantages	Limitations/considerations	Setting/use	Strength of evidence
Intrathecal drug delivery system (IDDS)	Refractory pain; opioid intolerance	Targeted analgesia; fewer systemic effects	High cost; moderate risk including infection and catheter issues; requires long-term prognosis for implantable systems. Requires implant; maintenance	Long-term (> 3 months prognosis):	Strong [27, 29]
Percutaneous intrathecal ports	Shorter prognosis; palliative setting	Intrathecal access without full implant	Moderate cost; low-to-moderate risk (infections); requires frequent access and maintenance;	Intermediate term (weeks–months)	Moderate [52, 53]
Cordotomy	Unilateral refractory pain below C4 (i.e., mesothelioma)	Effective for refractory unilateral pain	Moderate cost; high procedural risk including motor/sensory deficits; irreversible and specialized	Specialized centers; typically considered in patients with limited prognosis (e.g., < 6–9 months), after the failure of less invasive IPM options	Moderate [54, 55]
DREZotomy	Brachial plexus avulsion, pancoast tumor	Effective for focal neuropathic pain	Moderate-to-high cost; high risk due to invasive open procedure; requires rare expertise	Highly specialized centers	Moderate [30, 56]
Vertebroplasty/kyphoplasty	Painful vertebral metastatic fractures	Stabilizes spine; rapid axial pain relief	Moderate cost; low risk (risk of cement leakage); not indicated for neuropathic pain	Outpatient/inpatient; radiology suite	Strong [57, 58]

Table 1 continued

Technique	Indications	Advantages	Limitations/considerations	Setting/use	Strength of evidence
Percutaneous transarterial embolization	Painful bone metastases refractory to RT	Reduces tumor vascularity and pain	Moderate-to-high cost; moderate risk including non-target embolization; emerging evidence; requires interventional radiology expertise	Interventional radiology; short recovery	Low [59, 60]

Techniques are listed with their primary indications, advantages, limitations, and typical clinical setting. *CIPN* chemotherapy-induced peripheral neuropathy, *SCS* spinal cord stimulation, *DRG* dorsal root ganglion, *IDDS* intrathecal drug delivery system, *RFA* radiofrequency ablation, *MWA* microwave ablation, *LA* laser ablation, *CA* cryoablation, *RT* radiotherapy, *CrPS* complex regional pain syndrome

Neurolytic procedures may target sympathetic pathways at various levels, which may ease visceral abdominal pain [74]. This method is especially advantageous for patients with advanced cancer, particularly those with a limited prognosis, as it offers prolonged comfort and may reduce opioid requirements [75]. While the 6-month threshold is often used as a clinical reference, prognostic estimation is inherently uncertain and should be individualized.

Although previous literature [45] has rated the quality of evidence for these procedures as low due to reliance on nonrandomized studies, more recent, specialty-specific guidance from the American Society of Pain and Neuroscience (ASPN) Best Practices assigns level I–III evidence and grade A–B recommendations to celiac, splanchnic, and superior hypogastric plexus neurolysis [30]. These updated classifications reflect consistent clinical efficacy and widespread expert support, especially for celiac plexus neurolysis (CPN) in upper abdominal malignancies.

CPN is frequently employed for pain related to pancreatic and upper abdominal tumors. In contrast, superior hypogastric plexus neurolysis (SHPN) addresses pelvic pain stemming from malignancies of the bladder, uterus, or rectum.

Greater and lesser splanchnic nerves from T5 to T12 send sympathetic fibers to the celiac plexus. These nerve fibers encircle the celiac trunk and extend inferiorly to the level of the superior and inferior mesenteric plexus. The celiac plexus innervates most abdominal viscera, including the stomach, liver, biliary system, pancreas, spleen, kidneys, adrenal glands, omentum, small bowel, colon, and splenic flexure [76]. CPN has been shown in a RCT on 61 patients with pancreatic cancer pain to provide complete pain relief in 48% of patients, while 52% required additional therapy for residual visceral pain [77]. Similar results can be seen in another study [78]. Overall, CPN lessens opioid-induced adverse effects, decreases opioid intake, and enhances analgesia [46]. Different techniques can be used to perform CPN, mostly percutaneous guided fluoroscopy, which was used in the first place, and later on an endoscopic ultrasound-guided approach. It was demonstrated that the latter was not inferior

to the former [79]. A computed tomography (CT)-guided anterior approach is also available, offering precise needle placement, superior anatomical visualization, and real-time monitoring of neurolytic spread [80]. It allows comfortable supine positioning and reduces the risk of neurological complications compared with posterior techniques. This makes it particularly suitable for patients with altered anatomy, coagulopathies, or obesity. However, it entails higher costs, greater radiation exposure, longer procedural times, and the need for access to a CT suite [80].

The most common adverse effects of CPN are transient diarrhea and hypotension [81], although some potentially rare serious adverse effects have been described, such as neurologic issues, pulmonary function impairment, peritonitis, and hematuria [82].

In selected patients, such as those with pancreatic body or tail tumors or in cases in which the celiac plexus is inaccessible due to tumor encasement or displacement of this plexus, neurolysis of the thoracic splanchnic nerves via a transdiscal approach offers a viable alternative [83]. This technique targets the greater and lesser splanchnic nerves before they converge into the celiac plexus and may effectively relieve upper abdominal cancer pain. A recent retrospective study demonstrated its feasibility and safety in patients with pancreatic cancer. Although generally well tolerated, splanchnic neurolysis may lead to complications such as transient hypotension, diarrhea, and back pain; in rare cases, pneumothorax or retroperitoneal hematoma may occur, particularly in patients with distorted retroperitoneal anatomy [83].

SHPN is a validated and increasingly used intervention for managing pelvic pain associated with malignancies of the uterus, bladder, rectum, and prostate. It can be performed under fluoroscopic, CT, or ultrasound guidance using chemical neurolysis (typically with alcohol or phenol). Studies have shown significant reductions in pain scores and opioid requirements with minimal complications. In a randomized controlled trial, Rocha et al. [84] reported substantial and sustained analgesia in patients with pelvic cancer. Combining SHPN with ganglion impar neurolysis may further enhance efficacy for perineal pain [85]. The anterior ultrasound-guided approach has been successfully applied in gynecologic cancers and offers an alternative in patients with anatomical challenges or coagulopathy [86–88].

Lumbar sympathetic block, occasionally combined with neurolysis or radiofrequency ablation (RFA) (typically fluoroscopy or CT-guided), is indicated for sympathetically mediated pain in the lower limbs, vascular insufficiency in select cases, and herpes zoster affecting the lower extremities. However, they are not typically appropriate for visceral abdominal or pelvic pain, which is better addressed by celiac, superior hypogastric, or ganglion impar blocks [89].

The stellate ganglion is a cluster of sympathetic nerves situated near the base of the neck, usually resulting from the merging of the inferior cervical and first thoracic ganglia. Located anterior to the transverse process of C7, adjacent to the first rib and subclavian artery, it is essential for modulating sympathetic nervous system function in the head, neck, upper chest, and arms. In upper limb pain, the stellate ganglion block (SGB) can alleviate neuropathic pain and enhance functionality by regulating sympathetic tone [90]. Furthermore, in patients with breast cancer, persistent discomfort in the chest, shoulder, and arm resulting from surgery, radiation, or tumor infiltration can be markedly mitigated with SGB, resulting in enhanced pain management and improved sleep quality [91]. Likewise, this method is also advantageous for alleviating facial pain linked to head and neck malignancies by mitigating autonomic dysfunction [92].

The ganglion impar, also known as the ganglion of Walther, is a distinct sympathetic ganglion situated anterior to the sacrococcygeal junction. It functions as an essential pathway for nociceptive and autonomic fibers originating from perineal structures, such as the anus, distal rectum, urethra, scrotum, vulva, and vagina. A ganglion impar block or neurolysis efficiently alleviates persistent perineal pain [93].

Saddle block is another kind of neuraxial anesthesia that targets the sacral roots. It is injected intrathecally into the lower lumbar interlaminar area from between the fifth lumbar and sacral vertebrae while the patient is in the sitting position, frequently in combination with phenol-in-glycerol to cause neurolysis in perineal pain

associated with malignancy. This method minimizes systemic opioid consumption while delivering long-lasting analgesia, making it especially helpful for treating severe pelvic-sacral tumor pain [94]. Nonetheless, mindful patient placement throughout the process is essential to limiting the neurolytic agent's dissemination and avoiding unintended motor or autonomic dysfunction. However, it should be noted that bladder and rectal impairment may still occur [95].

Cordotomy is an ablative procedure that targets the spinal cord, precisely the contralateral spinothalamic tract, to the side of the body where pain is perceived [54]. It may be effective for unilateral pain below C4 [55]. For instance, it has been used for treating malignant mesothelioma-related chest wall pain [96]. Still, it also works well for brachial plexus involvement [97] and lower limb/pelvic pain brought on by tumor infiltration of the lumbosacral plexus and ilium [98]. This procedure is typically reserved for patients with a limited prognosis after the failure of other IPM techniques, as deafferentation pain can develop within months, sometimes as early as 3 months, as reported in some cases [99], potentially leading to new or more challenging pain syndromes [54].

Cordotomy can be performed percutaneously or surgically with an open approach, the latter classifying, therefore, as a surgical procedure.

Percutaneous cordotomy is performed with RFN on a supine awake patient targeting the spinothalamic tract at C1–C2, and it is usually done under fluoroscopic-CT or, even more lately, endoscopically guided. Some patients can even completely dismiss opioid therapy with a percentage of complete pain relief that can achieve 64% for the time being after the procedure [100]. A few complications may rarely occur, and they include dysesthesia, urine retention, ataxia, paresis, sympathetic dysfunction (including hypotension, Horner syndrome, and bladder dysfunction), decreased or lost sexual sensitivity, acquired central hypoventilation syndrome, and spontaneous new pain. Most of these adverse effects may develop due to the RFN accidentally firing onto reticulospinal tracts [101].

Alongside chemical neurolysis and RFN, several image-guided percutaneous ablative methods, including RFA with a target temperature of 60–80° [102], microwave ablation (MWA) [103], laser ablation (LA) [104], and cryoablation (CA) [105], are progressively employed in the therapy of CrP. These treatments eradicate tumor tissue by thermal or cryothermal mechanisms, diminishing tumor mass, periosteal irritation, and inflammatory mediators. RFA [102] and MWA are very efficacious for alleviating pain from bone metastases [47], sometimes utilized with cementoplasty to prevent fractures. CA facilitates real-time observation of the ice ball for improved accuracy, while LA permits precise treatment of diminutive or difficult-to-reach lesions. These techniques are particularly warranted when traditional neurolytic or systemic methods prove unsuccessful or are contraindicated [48].

Additional clinical research is necessary to develop standardized protocols and enhance patient outcomes, as the existing information predominantly derives from case series and retrospective investigations.

Implantable Devices

Implantable devices include pumps, i.e., IDDS that usually deliver the drug intrathecally, defining intrathecal analgesia and devices for neuromodulation that typically target the spinal cord (spinal cord stimulators, SCS), the dorsal root ganglia (DRG), or sometimes peripheral nerves.

Intrathecal analgesia entails the direct infusion of analgesic drugs into the cerebrospinal fluid in the proximity of the involved spinal levels that concern pain localization [30]. The catheter tip should be close to the dermatomal level of pain, considering that mostly all drugs except for ziconotide (a calcium channel blocker extracted from the pacific marine cone snail [106]) will stack at the tip of the catheter and migrate at most one or two levels above and below the tip [107].

IDDS are increasingly employed for the therapy of CrP owing to their safety, efficacy, and cost-effectiveness in patients with a prognosis exceeding 6 months in the case of fully implantable pumps. However, this threshold varies between healthcare systems, and prognosis estimation remains challenging.

These pumps are limited by a maximum capacity of 40 ml and an infusion rate of 1 ml/h [108]. Patient-controlled analgesia (PTA) is also available for intrathecal administration as a dedicated feature of these devices [53].

When intrathecal analgesia is needed, but life expectancy does not justify an implantable pump, a percutaneous port that delivers the drug intrathecally may be implanted [52, 109]. The drug may be delivered through a connected elastomeric pump [110].

Currently, the U.S. Food and Drugs Administration (FDA) has approved three medications for intrathecal administration: baclofen, ziconotide, and morphine. The Polyanalgesic Consensus Conference does, however, support the intrathecal injection of various opioid drugs, including hydromorphone, fentanyl, and sufentanil, as well as the nonopioids bupivacaine and clonidine, either alone or in combination [106, 111].

Several studies have confirmed that intrathecal administration improves pain control and reduces side effects [112–116]. Notably, intrathecal administration necessitates markedly smaller doses than epidural infusions (tenfold lower), thus diminishing systemic toxicity and side effects, including drowsiness and respiratory depression [112].

Nonetheless, vigilant oversight is essential to avert problems such as catheter migration, granuloma development, and infection [30]. Although rare, displacement and migration may still occur despite fixation techniques, requiring catheter repositioning or replacement [117].

Electrical neuromodulation has become a promising method for addressing refractory cancer pain, especially in patients experiencing neuropathic pain [118] or chemotherapy-induced peripheral neuropathy (CIPN) [119]. This approach operates by administering electrical impulses to regulate pain signal transmission in the neural system, thereby diminishing pain perception without the adverse effects of systemic analgesics [118]. SCS entails the implantation of electrodes in the epidural space to regulate pain circuits at the spinal level, offering substantial relief for patients experiencing localized or diffuse pain unresponsive to standard treatments [49]. DRG stimulation (Fig. 2) is especially advantageous for focal and segmental pain [120], including post-mastectomy pain [50] or neuropathic pain due to tumor infiltration or CIPN [51], as it directly activates pseudounipolar neurons at the DRG. Peripheral nerve stimulation (PNS), involving the placement of electrodes adjacent to peripheral nerves, is efficacious for alleviating pain in localized regions impacted by cancer or surgical procedures, including brachial plexus or intercostal neuralgia [121].

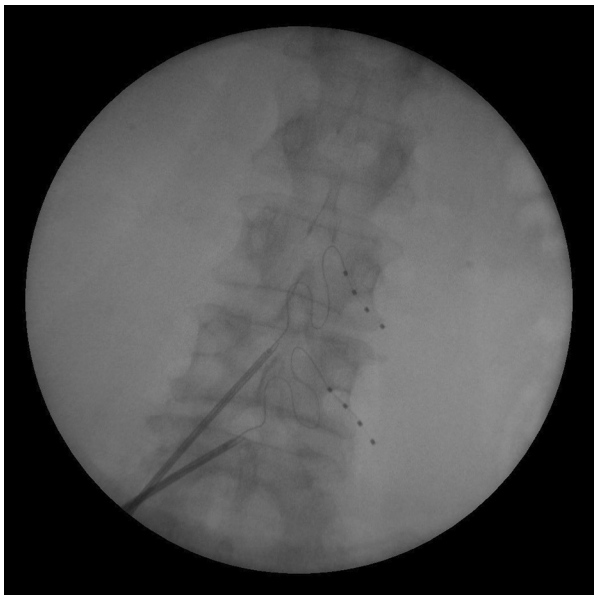

Fig. 2 Fluoroscopic image showing dorsal root ganglion (DRG) stimulation with two electrode leads positioned at the L3 and L4 ganglia. The patient, a cancer survivor, presented with chronic cancer-related pain (CrP) and right-sided gonalgia due to complex regional pain syndrome (CrPS). DRG stimulation was selected over conventional spinal cord stimulation (SCS) due to its ability to provide highly focal, segmental pain control, which is particularly advantageous in localized, mixed neuropathic pain syndromes

Advancements in device technology, such as magnetic resonance imaging (MRI)-compatible stimulators [122], could push neuromodulation toward being a valid asset for multimodal cancer pain management, but data from the

literature remain scarce. Notwithstanding favorable clinical results, the financial implications of neuromodulation, stemming from the expenses associated with devices, implantation procedures, and ongoing maintenance, remain a significant obstacle to its widespread adoption in standard cancer pain therapy.

Interventional Radiology Procedures

Percutaneous transarterial embolization is a developing interventional technique that is particularly useful for painful bone metastases that other treatment modalities, such as radiotherapy, have not controlled. Employing embolic chemicals to block the arterial blood flow to tumors selectively lowers tumor vascularity and pain. According to recent research, it may help relieve pain in metastatic spinal lesions and other skeletal tumors [123]. Such an approach is usually performed with the help of imaging techniques such as fluoroscopy or CT to ensure that the embolic materials are delivered to the desired location with minimal risk to the surrounding tissues [60]. A recent systematic review concluded that percutaneous transarterial embolization plus radiotherapy may be more beneficial than radiotherapy alone for pain relief and tumor containment. However, the author suggested that there is a need for more data to support this trend [59].

Vertebroplasty is a percutaneous, image-guided procedure typically performed by interventional radiologists or pain medicine physicians to treat painful vertebral compression fractures due to cancer. It is minimally invasive and often performed in a procedural or hybrid operating environment. It is frequently employed to address cancer-induced vertebral compression fractures resulting from spinal metastases or multiple myeloma [57].

This technique enhances structural stability, alleviates fracture-associated discomfort, and augments movement by injecting artificial bone cement into the inter-trabecular marrow space of a damaged vertebra [124]. Local anesthesia is generally acceptable. Due to its efficacy in mitigating axial spinal pain, it may be regarded as a supplementary surgical alternative, mainly when the pain arises from mechanical instability rather than neuropathic causes [58]. Kyphoplasty is similar to vertebroplasty, where a preliminary procedure (an operator percutaneously inserts, inflates, and deflates a balloon) is conducted before cement injection to facilitate the restoration of vertebral body height [125].

Surgical Options

These procedures encompass minimally invasive techniques as well as open approaches.

When there is axial pain below the diaphragm, a bilateral cordotomy procedure is required with an appropriate open neurosurgical approach, with the second lesion being made at C6 to spare diaphragmatic function [126].

The dorsal root entry zone (DREZ) lesioning technique specifically targets overactive dorsal horn neurons in the spinal cord implicated in neuropathic pain. This method relies on the accurate application of radiofrequency or laser ablation to pain-inducing neurons in the dorsal root entry zone, rendering it especially efficacious for brachial [56] plexus avulsion pain, and therefore, for CrP pain arising from tumor-infiltrating the brachial plexus, such as a pancoast tumor [127]. It requires an open approach, as laminectomy or laminotomy is performed to expose the appropriate levels.

This technique is unsuitable for patients with burning or limb pain associated with shoulder or pelvic pain [128].

In cases of spinal cord compression from metastases, decompressive laminectomy may be a therapeutic option for pain control and the prevention of paralysis [129]. This approach is typically considered when radiotherapy is not an appropriate option [130]. Additionally, pathological fractures of long bones may require surgical intervention, ranging from simple curettage to prosthetic reconstruction [131, 132].

CHALLENGES AND FUTURE PERSPECTIVES

The future of CrP management lies not in choosing the "best" drug or the best technique, but in integrating all available strategies in a timely, patient-specific, and interdisciplinary way. The traditional hierarchical vision, where pharmacological treatments come first and interventional techniques are reserved for failure, must evolve into a dynamic, nonlinear model that allows each therapeutic pillar to be activated when clinically appropriate, regardless of sequence.

To achieve this, we propose reframing the outdated concept of the pain ladder into a functional "crossroad" model, where interventional, pharmacological, rehabilitative, and psychosocial paths can be accessed on the basis of individual needs, goals, and clinical evolution (Fig. 1). This conceptual framework emphasizes not only integration, but also clinical flexibility and anticipatory planning.

However, realizing this model in practice requires addressing major barriers [133]: delayed referral to pain specialists, poor interprofessional communication, lack of awareness or training in IPM, and systemic inertia within healthcare structures. With the advancement of knowledge of pain mechanisms and technological advancement, a more detailed approach to patient assessment and choice may be established. A recent systematic review highlighted that machine learning and artificial intelligence are advancing to predict pain-related outcomes and support decision-making in CrP progress [134]. For instance, one study explored the use of machine-learning algorithms to predict neuropathic pain following breast cancer surgery [135]. In contrast, another one applied a deep learning model to predict the time of CrP exacerbation onset [136], which can be very useful in interventional pain management as a preventive strategy.

Moreover, an integrative approach is crucial in CrP management because pain control cannot be achieved by direct analgesic interventions only. Some treatments, for example, radiotherapy [137] and chemotherapy, which are mainly directed toward tumor control, also have a marked effect of pain relief through decreasing tumor mass and thus relieving pressure on the nerve or tissue. This shows the importance of collaborating with the oncologist, pain specialist, palliative care teams, and interventionalists in developing a holistic and patient-specific plan that addresses the disease progression and pain.

Nutritional strategies, already a core part of supportive care, may also influence CrP by modulating systemic inflammation and neuroimmune signaling via the gut microbiota (GM). Recent guidance suggests that cancer patients should consume 25–30 g of fiber daily, which supports eubiotic microbial composition and may attenuate inflammatory tone [138]. More broadly, GM modulation is emerging as a promising future avenue to influence multiple pain pathways, including nociceptive, inflammatory, and neuropathic processes [139–142]. This is particularly relevant in oncology, where analgesic drugs themselves (especially opioids and nonsteroidal antiinflammatory drugs (NSAIDs)) can significantly alter GM composition, potentially reinforcing a cycle of dysbiosis and pain sensitization [143].

Despite promising results, several interventional techniques still lack high-quality evidence in oncologic populations. For instance, DRG and transarterial embolization are supported primarily by small case series or extrapolated data from non-cancer settings [50, 60, 120]. Comparative studies, such as neurolysis versus radiofrequency ablation or DRG stimulation versus SCS, are largely absent. Prospective, multicenter trials and real-world registries are urgently needed to evaluate long-term outcomes, define patient selection criteria, and clarify cost-effectiveness in cancer pain populations. Addressing these evidence gaps is essential to expanding the role of interventional therapies in guideline-based cancer pain management.

Ultimately, the real challenge is cultural: shifting the mindset from "treating pain" to "treating the patient with pain" through an early, multidisciplinary, and personalized strategy.

To aid clinicians in identifying appropriate candidates for IPM, we propose a practical checklist (Box 2) on the basis of clinical

and ethical selection criteria. Early IPM referral allows for individualized planning, reduces opioid-related toxicity, and enhances patient-centered outcomes.

BOX 2 REFERRAL TO A SPECIALIZED PAIN MANAGEMENT TEAM SHOULD BE CONSIDERED WHEN ONE OR MORE OF THE FOLLOWING CRITERIA ARE MET:

1. Moderate-to-severe pain persists (≥ 5/10 on the Numeric Rating Scale [NRS]) despite optimized systemic pharmacologic treatment, including opioids and adjuvants.
2. The patient experiences adverse effects from analgesics (e.g., sedation, nausea, cognitive dysfunction) that limit dose escalation or impair quality of life.
3. Pain significantly interferes with activities of daily living and quality of life.
4. Neuropathic or mixed pain is present and has proven refractory to appropriate pharmacologic management.
5. Rapid pain control is required, such as in cases of functional decline, uncontrolled symptoms, or limited prognosis.
6. Cancer survivors with persistent or recurrent pain.
7. The patient has a history of substance use disorder, and IPM may offer an opioid-sparing strategy that enables safer pain control when integrated into a structured multidisciplinary care plan.
8. Patients with significant comorbidities or organ failure (e.g., hepatic, renal, cardiac) where high-dose systemic analgesics are contraindicated or poorly tolerated.
9. The patient expresses a desire to reduce systemic medications or pursue targeted procedural options aligned with their values and goals

LIMITATIONS

This narrative review is limited by the heterogeneity of the included literature, which encompasses randomized trials, observational studies, expert opinions, and case series of varying methodological quality. While we aimed to provide a comprehensive overview, the lack of standardized outcome measures and variability in procedural techniques limit the strength of generalizable recommendations. Evidence for some interventions, such as DRG stimulation, transarterial embolization, or saddle block neurolysis, remains sparse or based on retrospective data. Potential publication bias cannot be excluded, especially regarding positive results in smaller studies. Furthermore, differences in access, training, and reimbursement policies may affect the clinical applicability of interventional pain management strategies across different healthcare settings. These limitations underscore the urgent need for multicenter, prospective studies, and clear clinical guidelines.

CONCLUSIONS

CrP is a considerable burden that causes a great deal of suffering to patients and is often still present after the use of conventional pharmacological treatments. Although systemic drugs, especially opioids, have been considered the most important type of treatment for CrP, the role of interventional procedures as a part of the treatment plan is becoming more and more critical. CrP as a population problem may become an immediate issue because the life expectancy of oncologic patients is increasing because of new treatments [144]. However, this may mean a longer time during which patients are exposed to CrP. Despite these therapies' effectiveness, many are not used adequately due to delayed consultant appointments, lack of knowledge, and system-related barriers in healthcare institutions. Some new technologies, such as data-driven clinical decision support systems and automation, may help to change the current situation and make pain management more

preventive and individualized. The domain of CrP treatment is set for a transformation, one in which human knowledge, augmented by artificial assistance, nurtures a patient-centered strategy that ensures no person endures unnecessary suffering. However, this is not always possible at present, thus cooperation and improvement are needed. We strongly encourage medical professionals, researchers, educators, and policymakers to enhance the research, education, and provision of interventional pain management strategies for patients. Further research is necessary to improve the current methods and create new perspectives to manage CrP.

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Declarations

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