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Persistent Pain in Cancer Survivors: Pathogenesis and Treatment Options

Pain in cancer survivors is common and may arise from both the underlying malignant condition and the treatment undertaken by the patient. The predominant forms of pain observed in cancer survivors include persistent postsurgical pain (PPSP), chemotherapy-induced peripheral neuropathy (CIPN), and radiation-toxicity-associated pain. Additional, less common causes of persistent pain may be encountered, such as graft versus host disease-induced neuropathy and aromatase inhibitor-induced arthralgia [37].

There are currently 14.5 million cancer survivors (widely acknowledged as those living with and beyond a diagnosis of cancer) in the United States, and this number is projected to increase to 19 million by 2024. In the United Kingdom, the 1.8 million survivors are forecast to increase to 3 million by 2030 [34]. Early detection and improved treatments have seen significantly improved survival rates in many different types of cancer. The demographic of the survivors follows that of the cancer; 46% are older than 70, and only 5% are younger than 40. There have been recommendations about survivorship care plans, such as follow-up every 3 or 4 months for 3 years and then twice a year subsequently. This advice has tremendous implications for resource allocation. In other health care models it is not always evident that insurance providers will cover these expenses, despite the increasing awareness and realization that there is a survivor population with a significant symptom burden that compromises the patient's life and ability to contribute to society. In this article we will consider the more commonly encountered causes of persistent pain in cancer survivors, giving an overview of our current understanding of their pathophysiology, outlining their clinical features, and finally providing an overarching summary of the treatment options available.

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Persistent Postsurgical Pain

Surgery represents an important treatment for cancer as well as having a role in diagnosis and palliation. Chronic pain developing after surgery (persistent postsurgical pain [PPSP]) is an important condition [33] contributing to the symptom burden of cancer survivors and negatively affecting their quality of life.

Persistent postsurgical pain remains poorly defined, but it is broadly recognized as pain lasting more than 2–3 months after surgery. Recent published guidelines have attempted to reduce the diagnostic ambiguity associated with the condition (Table 1) [46].

The condition is common, with estimations of its prevalence ranging from 10% to 30% of all postsurgical patients. High-risk procedures include breast surgery, thoracotomy, cardiac surgery, limb amputation, and hernia repair [11] (Table 2). In the cancer survivor population, persistent pain may also be encountered following

- Improvements in oncological treatments combined with an aging population are leading to an increase in the number of cancer survivors.
- Pain is common in cancer survivors and may arise due to the underlying condition, its treatment, or both. Pain states unrelated to the cancer may also be encountered in this patient population.
- Management of pain in cancer survivors is complex, with a paucity of evidence to support specific interventions.
- Fear of recurrence may add to the challenge of successfully controlling pain in cancer survivors.

Table 1 Proposed diagnostic criteria for persistent postsurgical pain	
The pain develops after a surgical procedure or increases in intensity after a surgical procedure.	The pain should be of at least 3–6 months' duration and significantly affect quality of life
The pain is either a continuation of acute postsurgery pain or develops after an asymptomatic period.	The pain is either localized to the surgical field, projected to the innervation territory of a nerve situated in the surgical field, or referred to a dermatome (after surgery in deep somatic or visceral tissues).
Other causes of the pain should be excluded, such as infection or continuing malignancy in cancer surgery.	
Source: Adapted from [46].	

other interventional procedures such as biopsies and drain insertion.

Clinically, PPSP possesses many of the characteristics and features of neuropathic pain, including sensory changes associated with the surgical site such as cutaneous hyperesthesia, numbness or paresthesia, scar pain, or hypersensitivity and allodynia [20]. Some forms of PPSP are well represented in basic and clinical research, such as persistent post-breast surgery pain and phantom limb pain, but other areas that contribute a significant burden to this survivorship population, including PPSP following head and neck surgery and visceral PPSP, are woefully underrepresented in the literature.

Pathophysiology

The underlying mechanisms that lead to the transition from acute postsurgical pain to PPSP have not been fully delineated but reflect the complex processes that occur when tissues are injured. Injury to sensory fibers that innervate the skin, accompanied by the shift to an inflammatory profile at the surgical site, results in localized neuronal peripheral sensitization, and the resulting afferent barrage of nociceptive signaling contributes to the development of central sensitization. Neuroinflammation plays an important role in the induction and maintenance of this central neuronal plasticity [26], with infiltration of immune cells and increased glial cell activity observed in the dorsal horn of the spinal cord following peripheral nerve and tissue injury. It has been suggested that remodeling of neuronal synaptic connections in the dorsal horn combined with pathological neuronal sprouting results in the formation of abnormal links between afferent fibers of differing modality (such as nociception and fine touch), the amplification of afferent signals, and reductions in descending inhibitory inputs [48]. Neuronal sprouting still remains a contentious issue with regard to its importance in human neuropathic pain states.

Risk Factors for the Development of PPSP

Despite being common following some procedures, the majority of patients who undergo surgery never develop PPSP, implying that predisposing factors exist. A number of risk factors related both to the patient and the surgery have been identified.

Surgical factors that may increase the risk of developing PPSP include extensive tissue damage, the use of surgical drains [40], division or prolonged retraction of nerves [29], and a duration of surgery greater than 3 hours. Acute pain over the first 3–4 postoperative days increases the risk of transition to a persistent pain state, with multiple studies demonstrating that severe acute pain accurately predicts the development of PPSP [40], as do the presence and intensity of preoperative pain [7].

Patient factors also contribute to the risk of developing PPSP. Age and sex are important, with younger females at higher risk of developing pain chronicity [31]. Psychological resilience is also key, with the degree of anxiety or depression or the propensity to catastrophize rendering patients more vulnerable to developing PPSP [4]. Genetic factors are also thought to play a role.

The ability to risk-stratify individual patients with regard to developing

Table 2 Variations in the incidence of persistent postsurgical pain (PPSP) depending on type of surgery		
Type of Surgery	Incidence of PPSP	Incidence of Severe PPSP
Breast surgery	>50%	10–15%
Thoracotomy	30–50%	3–16%
Limb amputation	30–85%	5–10%
Hernia repair	20–60%	10–25%
Cardiac surgery	30–55%	5–10%
Source: Adapted from [11].		

PPSP could enable the use of targeted preventative interventions to hinder its development, and work is ongoing in developing validated screening tools for specific surgical cohorts [43].

Chemotherapy-Induced Peripheral Neuropathy

Chemotherapeutic neurotoxicity represents a major cause of pain and symptom burden in cancer survivors. While it may affect any part of the nervous system, peripheral sensory neuropathy (CIPN) is most common, with a prevalence of 68% 1 month and 60% 3 months after chemotherapy [42]. The development of CIPN is influenced by a number of factors, including the presence of comorbidities (such as preexisting nerve damage), the choice of chemotherapeutic agent, and the cumulative dose [38]. Many antineoplastic agents are neurotoxic, and the effects of CIPN are often severe enough to make dose adjustment or cessation of treatment necessary, resulting in potentially suboptimal therapy.

Pathophysiology

The underlying pathophysiology of CIPN is complex and remains relatively poorly understood. CIPN is predominantly sensory in nature, with both large and small sensory fibers affected; motor nerve fiber involvement occurs less frequently and is often subclinical. Neurons rely upon anterograde and retrograde axonal transport systems to move substrates and metabolites, and disruption of this system renders neurons vulnerable to damage [35].

Chemotherapeutic neurotoxicity represents a major cause of pain and symptom burden in cancer survivors

Disruption of the microtubule scaffold that facilitates axonal transport reduces peripheral nutrient supply and leads to nerve dysfunction, and is caused by the taxanes and vinca alkaloids. CIPN manifests as neuronal "dieback" caused by the Wallerian degeneration of distal nerve segments, most susceptible according to their distance from the nerve cell body, explaining the "length-dependent" nature of the neuropathy. For Aδ and C fibers innervating the skin, dieback reduces the density of unmyelinated fibers, and remaining fibers have abnormal morphology and function.

These gross changes may just be the final common pathway and not necessarily contributory to mechanisms resulting in pain. Other theories to explain pain include mitotoxicity (disrupting neuronal energy supply: the "peripheral mitotoxicity theory"), the triggering of immunological mechanisms, and the sensitization of neurons through changes in ion channel function [16].

Structural and functional abnormalities in mitochondria are closely associated with painful neuropathies [18]. Mitotoxicity is observed in CIPN caused by platinum-based compounds, paclitaxel and bortezomib.

Neuroimmune interactions occur when the neuronal soma and glial cells present in the dorsal root ganglia (outside the nerve/blood barrier) are exposed to high levels of antineoplastic agents. Macrophage activation and glial cell dysfunction can occur, leading to abnormal cellular signaling and changes in the expression of mediators that are associated with both cell death and pain. These mediators include nerve growth factor (NGF), tumor necrosis factor alpha (TNF-α), interleukins IL-1β, IL-6, and IL-8, and activation of pro-apoptotic genes.

The structural changes observed in axonopathic sensory neurons are amplified by alterations in the function, distribution, and quantity of ion channels. Reductions in neuronal energy levels due to mitochondrial dysfunction result in membrane depolarization and spontaneous neuronal discharge. Individual chemotherapeutic agents may directly affect specific ion channels. For example, paclitaxel sensitizes the transient receptor potential vanilloid 4 (TRPV4) receptor, resulting in enhanced nociception [1]. The presence of increased levels of reactive oxygen species (markers of cellular oxidative stress) and NGF in C fibers contributes to increased expression of TRPV1 thermoreceptors [41].

The underlying pathophysiology of CIPN is complex and remains relatively poorly understood

Chemotherapeutic agents interfere with neuronal functioning via a number of agent-specific mechanisms.

Clinical Features

As a predominantly sensory neuropathy, CIPN presents with signs and symptoms related to disrupted sensory function, including paresthesia; numbness; impaired vibration, temperature, and proprioceptive sensation; dysesthesia; and neuropathic pain [45]. Sensory symptoms are length dependent, starting in fingers or toes and then progressing proximally, leading to a characteristic symmetrical "glove and stocking" pattern [47]. Autonomic dysfunction commonly occurs in vincristine- and bortezomib-related CIPN [5].

Table 3
Key features of chemotherapy-induced peripheral neuropathy caused by a variety of chemotherapeutic agents

Chemotherapeutic Agent	Class of Agent	Features	Putative Mechanism	Onset (Coasting)	Duration
Cisplatin Carboplatin	Platinum	Pain, numbness, paresthesia, loss of distal reflexes	↑ TRPV1, TRPA, and TRPM8; activation of P38 MAPK and ERK1/2; NMDA-receptor effects; mitotoxicity	From 1 month, peak at 3 months (++)	80% recover with cessation of chemotherapy
Oxaliplatin	Platinum	Sensory neuropathy; 80% acute cold-induced paresthesia	↑ TRPV1, TRPA, and TRPM8; activation of P38 MAPK and ERK1/2; ↓ membrane K^+ channels, $TREK_1$ and TRAK; NMDA-receptor effects; mitotoxicity	Acute onset, 2-3 days	Median recovery in 3 months
Paclitaxel Docetaxel	Taxane	Sensory neuropathy; myopathy/muscle spasms; loss of proprioception	Microtubule disruption; neurotoxicity at dorsal root ganglia	Some onset after 1st dose, >50% after 2nd dose (+)	75% have some recovery at 6 months
Bortezomib	Proteasome inhibitor	Painful sensory neuropathy, autonomic neuropathy	Activation of mitochondrial caspases; demyelination	Dose related and cumulative; most after 2nd cycle (+)	60–70% resolve 3 months after cessation
Thalidomide	Immunomodulator	Sensory neuropathy, muscle cramps	Not elucidated	Related to daily dose, not cumulative dose	Poor recovery from neuropathy observed
Vincristine	Vinca alkaloid	Sensory neuropathy, lower > upper limbs, autonomic neuropathy, muscle cramps	Changes in mitochondrial and cellular Ca^{2+} flux; NMDA-receptor effects; microtubule disruption; activation of mitochondrial caspases	Within 3 months (+)	70% have full recovery at 2 years

Source: Adapted from [6].

The peak incidence of CIPN is influenced by both agent and dose, and the greater the cumulative dose, the greater the neurotoxicity. Cessation of antineoplastic treatment does not guarantee resolution of symptoms, and "coasting" is also observed, where symptoms of neuropathy progress or even first appear following termination of treatment [8]. Coasting is seen with most agents, including bortezomib. The key features of commonly encountered CIPN states are detailed in Table 3.

Diagnosis

Clinical examination in patients with early CIPN may prove unremarkable, as changes in peripheral sensory thresholds may be too subtle to be detected by tests of gross neurological function. More targeted examinations may isolate abnormalities in two-point discrimination (touch), vibration sensation, and proprioception in a symmetrical peripheral pattern [38]. Areflexia may occur, indicating the presence of more advanced CIPN [21], and postural hypotension may suggest autonomic nerve involvement. Validated, CIPN-specific questionnaires may also be used to aid the diagnostic process [27]. Quantitative sensory testing (QST) allows the identification of fiber type involved [19], while intra-epidermal nerve fiber loss can be quantified using skin biopsies to identify small-fiber neuropathy [30] although these tests are of questionable utility in a busy clinic.

Radiation-Toxicity Associated Pain

For over one hundred years, ionizing radiation has formed a mainstay of cancer treatment as a primary therapy or as an adjunct to surgery or chemotherapy. Approximately 50% of oncology patients receive a form of radiotherapy during their treatment. Side effects associated with radiotherapy can be classified as being acute or late, the latter occurring 90 days after treatment and potentially lasting many years.

Owing to its rapid cell turnover, the mucosa of the gut is particularly susceptible to radiation-induced damage, which can result in nausea, vomiting, and diarrhea. Development of late

bowel toxicity following radiotherapy of the pelvic, abdominal, and lumbar regions commonly results in chronic pain. In patients who receive radiotherapy for cancers of the pelvis, chronic abdominal pain is encountered in approximately 10–15% of cases, which often leads to marked reductions in the survivor's quality of life. Late radiation toxicity may also present as neural damage, the archetype being brachial plexus neuropathy (BPN), which occurs following radiotherapy of targets close to the plexus [9]. The majority of symptoms of BPN are experienced in the ipsilateral upper extremity and include motor weakness, paresthesia, edema, and commonly pain.

Radiation-induced neural injury occurs due to a progressive process of intra- and extraneuronal fibrogenesis driven by reactive oxygen species and pro-inflammatory mediators. This fibrogenesis results in demyelination, axonal injury, and nerve ischemia owing to microvascular interruptions [13]. Radiation-induced neuronal injury is characterized by both its clinical heterogeneity and its variable time of onset, which may occur a decade after the triggering radiotherapy [27]. The occurrence of BPN is influenced by dosimetry, where a greater dose leads to a faster onset time, and by the age of the patient (symptoms develop more quickly in younger patients). Additionally, there is considerable variation in the symptomatology of BPN, with some patients experiencing sensory disturbance with minimal pain and others developing severe neuropathic pain with few other sensory symptoms.

Treatment of Pain in Cancer Survivors

The treatment options for managing pain in cancer survivors are limited both by the paucity of efficacious analgesic agents and by the challenges posed by this unique patient population. When a management plan is formulated, consideration should ideally be made of the presenting pain phenotype, the underlying cancer diagnosis and oncological treatments, the presence of relevant comorbidities such as renal impairment, and the performance status of the patient. Non-pharmacological options may also be considered as part of the multifactorial approach to treatment that acknowledges and attempts to remedy the psychosocial aspects of chronic pain.

A common approach to manage cancer survivors can initially be taken. Firstly a comprehensive history and examination should be conducted, focusing on the points described above, including a consideration of the biopsychosocial aspects of the patient's pain state: how is it being caused, the ramifications of the pain on the patient's psychological well-being, and the impact on the patient's social interactions. A holistic multidisciplinary team approach should be adopted, and implementation of the management plan should involve the patient, oncologist, and primary care provider. Regular reassessment of the pain and other outcomes such as improvements in functional status and quality of life in general should occur, and practitioners should be consistently mindful of the risk of cancer recurrence.

A personalized, patient-based approach to pain management … is of paramount importance in pain of cancer survivors

A personalized, patient-based approach to pain management long predated the current vogue for "individualized medicine," but it is of paramount importance in pain of cancer survivors. Emerging data indicate that identification of underlying pain mechanisms may help with pharmacological management [14], although the value of this approach is currently questionable [24].

One important consideration for this population is that remission or cure from cancer moves them into a demographic indistinguishable from chronic pain sufferers in the non-cancer population. Thus, the use of opioids in these cancer survivors conceivably raises the same concerns and problems that perturb practitioners treating chronic nonmalignant pain.

Treatment of PPSP

PPSP presents a therapeutic challenge and has forged interest in the potential of preventive strategies and combination treatments. Preemptive and protective analgesia (using drugs such as gabapentinoids or antidepressants) has been investigated in the prevention of PPSP, and although it failed to demonstrate a conclusive benefit, it may reduce some neuropathic pain, albeit at the expense of increased adverse effects such as postoperative sedation [10,36]. Similarly, the use of local anesthetic infiltration and regional anesthesia, such as paravertebral blocks, may be of some merit. This possibility is highlighted by the few systematic reviews conducted in this area (most publications discuss evidence regarding risk factors or are narrative in structure) [3,25].

Additionally, the use of psychological interventions and pain education during the perioperative period may also be beneficial. In light of the scarcity of specific treatments for PPSP, the pragmatic approach (if neuropathic pain is confirmed) is to adopt existing guidelines for treatment of neuropathic pain, such as the NeuPSIG recommendations [17].

PPSP presents a therapeutic challenge and has forged interest in the potential of preventive strategies and combination treatments

Treatment of CIPN

CIPN has a limited evidence base for effective treatments either by topical or systemic routes of drug administration. In one randomized controlled trial (RCT), the only RCT to show efficacy for CIPN for any treatment, duloxetine reduced pain intensity in patients with CIPN, although there was a reduction of just over 1 on a 0–10 numerical rating pain scale [44]. Despite the paucity of evidence, guidelines recently published by the American Society of Clinical Oncology recommend, given the demonstrated efficacy of these drugs in other neuropathic pain states, that a trial of amitriptyline or gabapentin may be advocated for CIPN [22]. This guideline collates all the existing clinical experimental evidence and forms the basis of this section, since no formal meta-analyses have been published.

Topical preparations are also used clinically to treat CIPN, commonly off licence. Capsaicin 0.025% cream, capsaicin 8% patches, or 5% lidocaine patches have all been shown to be efficacious in a selection of other peripheral neuropathies [2], although as outlined above, there is minimal evidence for their use in CIPN. Another "topaceutical," menthol cream has demonstrated some efficacy in CIPN [15], and although RCT evidence is lacking and its optimal strength remains to be elucidated , the minimal adverse-effect profile makes it a popular therapeutic option with patients and practitioners alike. Nonpharmacological approaches are also advocated for treatment of other elements of CIPN, such as addressing psychological aspects and providing occupational therapy for adjustments and aids to assist with activities of daily living.

Treatment of Radiation-Induced Pain

Little work has been performed to establish optimal therapeutic approaches for radiation-induced nerve plexopathies, and again, the adoption of recommendations for the management of neuropathic pain at least provides a framework for treatment. Abdominal visceral pain associated with late radiation toxicity also presents a challenge to control as pain is often coupled with significant physiological and functional derangement, and analgesics (such as opioids) may worsen this dysfunction. Treatment is also hindered by a lack of understanding and recognition among health care professionals. Management should focus not just on the control of pain but on optimizing visceral functionality (which may in turn also improve pain), ideally in specialist centers. With such a paucity of evidence to guide management, a pragmatic and rational multidisciplinary approach that includes the use of "opioid-sparing" medications should be adopted [12]. It is clear that pain in cancer survivors represents a complex clinical landscape with restricted treatment options. In this situation the adoption of high-quality management approaches, delivered by pain specialists, is viewed

as being preferential by both oncology patients and clinicians alike [39].

Cancer Survivors: The Lost Legion

In 2005 the Institute of Medicine and National Research Council of the National Academies published a document [23] titled "From cancer patient to cancer survivor: lost in transition," which aimed to: "Raise awareness of the medical, functional, and psychosocial consequences of cancer and its treatment. Define quality health care for cancer survivors and identify strategies to achieve it. Improve the quality of life of cancer survivors through policies to ensure their access to psychosocial services, fair employment practices, and health insurance." A similar approach was commenced in the United Kingdom with the launch in 2007 of the National Cancer Survivorship Initiative. However, it is only relatively recently that guidance has been produced that expounds the evidence base and cost-effectiveness for action plans in the survivorship population [32]. Despite the admirable efforts of these learned institutions, a shortfall between guidance and implementation undoubtedly remains.

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