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ANESTHESIOLOGY AND CRITICAL CARE (JP CATA, SECTION EDITOR)

Persistent and Chronic Perioperative Pain After Cancer Surgery

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Abstract

Purpose of Review Persistent and chronic pain after cancer surgery is a complex clinical problem. The etiology of pain in these cases is often multifactorial and, in addition to the surgery itself, can include or overlap with other painful syndromes such as direct effects of tumors, neuropathic pain, and pain syndromes secondary to chemotherapy and/or radiation.

Recent Findings There is a growing body of literature which suggests that treating pain in the acute and subacute periods can prevent chronic pain, an important step in reducing the morbidity of this clinical problem.

Summary This review describes the incidence of persistent pain after cancer surgery, its pathophysiology, and treatment considerations. Additional research on diagnostic criteria, pathophysiology, and novel medications, restorative therapies, and interventional treatments will be essential to continue to reduce the clinical burden of persistent and chronic perioperative pain after cancer surgery.

Keywords Chronic pain · Subacute pain · Cancer pain · Perioperative pain · Central sensitization · Edmonton staging system · Chronic cancer pain · National pain strategy · Interagency Pain Research Coordinating Committee

Introduction

The prevalence of cancer is rising, which suggests that the incidence of chronic cancer pain is rising as well, in line with an aging population [1]. The etiology of pain for these patients can include multiple causative factors (tumors, chemotherapy, radiation, surgery, psychological impacts of a cancer diagnosis, etc.). Pain related to surgical treatment for cancer is, in particular, a complex clinical and societal problem. In the setting of a recent cancer diagnosis and surgical treatment, persistent pain becomes more difficult to treat and thus warrants additional study and consideration. This review will describe the incidence of persistent pain after cancer surgery, its pathophysiology, and treatment considerations. Despite its complexity, there has been significant progress in the last several years in the description of this clinical problem. For example, the importance of the "subacute" period, between the initial surgery (acute pain) and a diagnosis of chronic pain, has become more apparent in the literature. Evidence on the treatment of subacute pain, however, remains limited. Further study of this and other knowledge gaps may provide a unique opportunity to prevent the transformation of acute and subacute pain into a chronic disease. These concepts and others will be further described in this review.

Incidence and Prevalence of Cancer Pain

The incidence of cancer is rapidly growing worldwide [2]. In 2020, there were an estimated 17 million new cases of cancer, with 66% of those patients expected to survive for 5 years [3]. Ten years after their initial diagnosis, 40% of diagnosed patients are expected to survive. This increase in the prominence of cases, in addition to the expected aging of

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the population, suggests that the clinical problem of pain in the cancer survivor is expected to become more burdensome.

The most common symptom of cancer at diagnosis is pain [4]. The prevalence of pain in patients with cancer increases during and after cancer treatment. This includes both patients with good and poor prognoses. For example, 30 to 40% of patients who completed a curative cancer treatment are estimated to have chronic pain [5, 6]. First-line treatment for many different types of cancer often includes surgery to remove the cancer and/or its metastases. Patients with breast or lung cancer have particular susceptibility to post-surgical cancer-related pain. In one study, for example, 63% of women reported persistent pain after a mastectomy at nine months postoperatively [7]. Similarly, 33% of patients who had a thoracotomy reported pain three years after the surgery in another study [8]. These figures can be compared to the incidence of pain after other surgeries with known post-operative pain syndromes. Post-thoracotomy pain syndrome, for example, has an incidence of around 50% [9].

Furthermore, patients with cancer pain may face unique barriers leading to under-treatment of their pain. This is supported by evidence that demonstrates differences in patterns of care for patients with cancer, in particular patients with poorer prognoses [10–12]. Given the high prevalence of cancer, the high prevalence of pain in cancer patients, and the barriers to care for cancer patients, it is imperative for clinicians to be well acquainted with how to approach this clinical problem.

Etiology

There are multiple potential causes of pain in patients with cancer. These can include the tumor itself, pain related directly to surgery, or nerve damage secondary to chemotherapy and/or radiation [13]. This list is not exhaustive. Furthermore, the clinical scenario can be made more complicated by multiple co-occurring etiologies. Post-chemotherapy peripheral neuropathy is a well-known side effect of multiple agents including vincristine, platinum, taxanes, thalidomide, and bortezomib. Radiation-induced damage to soft tissues and the nervous system may not present for many years after treatment, complicating the diagnosis. And post-surgical pain may be the poorest understood of the cancer-related pathologies. Correctly diagnosing the cause of cancer-related pain is important to achieve optimal symptomatic control. The importance of this diagnosis is emphasized by the addition of chronic cancer-related pain to the ICD-11, as recommended by a task force assembled by the International Association for the Study of Pain (IASP) [14].

Acute Pain After Cancer Surgery

Acute pain is an important risk factor for ongoing chronic post-surgical pain (Table 1) [15]. Thus, controlling acute pain is an important aspect of care in this population. Acute pain was defined in the 1970s by Merskey and again in the 1990s by Merskey and Bogduk as pain that has been present for less than three months. Surgery is a well-known cause of acute pain. Surgery causes a cascade of neural, hormonal, and chemical changes that result in hyperalgesia. A surgical stimulus will trigger nociceptive afferent signals along the spinothalamic tract to the cerebral cortex. Sodium channels that drive this peripheral nociception can demonstrate increased expression in injured or inflamed nervous tissue [16]. This may be one early step in the pathway towards chronic hyperalgesia, and is suggestive of how acute perioperative local anesthesia with sodium-channel blockers can prevent the development of chronic pain. This phenomenon is supported by evidence that peripheral A-delta and C fibers are sensitized after surgical incisions [17]. The mechanisms behind this sensitization are being studied with increasing urgency. For example, animal studies have demonstrated that local pH (pH ~ 6.8), oxygen tension, and lactic acid concentration (~ 6 mM) correlate well with pain behaviors one to two days after surgery [18–20]. The importance of acidity was also demonstrated in one study of cultured dorsal root ganglion cells, which demonstrated acid-sensitive ion channels that stimulate C fibers [21]. Continued research on mechanisms of acute pain may yield further treatment avenues for the prevention of chronic pain after cancer surgery.

Table 1 Risk factors for chronic post-surgical pain

Age	Increasing age reduces risk of chronic pain in breast surgery and hernia repair
Preoperative pain	Preoperative pain may sensitize the nervous system prior to surgery
Type of surgery	Amputations, thoracotomies, and other operations have clear links with chronic pain syndromes
Perioperative care	Preoperative anxiety has a consistent relationship with postoperative pain
Radiation/Chemotherapy	Both can cause chronic pain complicating and delaying proper diagnosis
Tumor recurrence	This can cause pain itself or complicate the picture by necessitating repeat surgery
Psychosocial factors	Anxiety, depression, catastrophizing, and educational level all influence outcomes after surgery
Genetics	Post-surgical pain may be linked with other diagnoses including fibromyalgia, migraine, irritable bowel syndrome, irritable bladder, and Raynaud's syndrome

Subacute Pain After Cancer Surgery

Recent data suggest that subacute pain, in addition to acute pain, may be an important risk factor for the development of chronic pain. Subacute pain is described in existing literature less frequently than acute or chronic pain. It was defined as early as 1997 by van Tulder et al. [22] as pain lasting between six weeks and three months. While the strict time-based definition is more pragmatic than physiologic, it may queue researchers to key underlying pathologic processes. For example, acute pain is typically due to a condition that is expected to resolve without intervention, whereas chronic pain may signify a condition that is unlikely to self-resolve. Subacute pain may be a harbinger of an underlying pathology that, if not promptly treated, may progress to a chronic pain syndrome. This issue has been examined in multiple studies. For example, in a 12-month prospective study, pain and functionality were assessed after musculoskeletal surgery comparing post-discharge pain levels (subacute pain) with pain levels at 12 months post-op. In this study of 87 patients, acute pain (10 days postoperatively) and subacute pain (6 weeks postoperatively) were both correlated with persistent pain at 12 months ($p = 0.01$ and 0.02, respectively) [23•]. In another randomized clinical trial in patients with back pain, intervention in the subacute period with biopsychosocial education, manual therapy, and exercise was more effective than advice to remain active [24]. These small studies suggest that subacute pain is an important factor in the development of chronic pain. However, larger studies need to be performed to better understand the progression of acute to subacute to chronic pain.

Chronic Pain After Cancer Surgery

Chronic pain was defined by Merskey and Bogduk as pain present for more than three months. An important mechanism in the development of chronic pain is central sensitization: an abnormal state of responsiveness or increased gain of the nociceptive system [25•]. Nociceptive afferent signals drive the process of central sensitization. The dorsal horn of the spinal cord, particularly laminae I and II, receives nociceptive afferents from the peripheral nervous system. Central sensitization at this level, or spinal sensitization, is caused by increased nociceptive signaling from peripheral nerves. Nociceptive peripheral nerve signaling can pathologically increase after surgery. Surgery may also induce unique changes to the grey matter of the spinal cord, including wide dynamic range neurons. These gray matter cells are named after their typically broad receptive field, responding to stimuli from large areas of the body. Repeated stimulation of these neurons can broaden their receptive fields, decrease their threshold for activation, and ultimately promote nociceptive signaling to the cortex. This process, sometimes termed "wind-up," is multifactorial but N-methyl-D-aspartate (NMDA) receptor activation may be an important factor. However, studies of NMDA antagonism and post-surgical hyperalgesia have produced mixed results. A thorough review of pharmacological modulation of incision-induced pain is beyond the scope of this article; however, the interested reader is directed to any one of a number of thorough summaries of this body of work published in the last several years.

Surgery may also cause sensitization to occur in the brain. In animal studies, functional magnetic resonance spectroscopy has demonstrated unique signal changes after surgical incisions when compared to other mechanical stimulation. In animal models of pain, GABA levels within the thalamus have been shown to increase, suggesting a mechanism behind central sensitization in the brain [26]. In human studies, a lack of descending inhibition, neuroplasticity, and metabolic changes have all been shown to contribute to pain after surgery [27]. The hypothalamic–pituitary–adrenal system, and stress in general, have also been linked to central sensitization and the transformation of acute into chronic pain after cancer surgery [28]. The HPA axis and sympathetic system are less commonly targeted by therapeutic interventions; however, their involvement suggests that sympathetic blockade may be an important aspect of care for the patient progressing from acute to chronic pain.

Finally, epigenetic changes including DNA methylation, histone acetylation, and noncoding RNA have been implicated in the development of chronic pain after surgery [29]. DNA methylation and histone acetylation both increase mechanical as well as thermal hyper sensitivity in animal models. These changes occur in the peripheral and central nervous system. Opioids have been implicated in epigenetic regulation as well, and may contribute to the progression of acute to chronic pain after surgery.

Assessment of the Problem

Gaps in Knowledge

Universally accepted definitions/diagnoses for chronic pain after cancer surgery are lacking, creating logistical problems for researchers. However, some progress has been made in recent years. The Edmonton Staging System for Cancer Pain is a validated assessment and classification system for cancer-related pain [30]. But this does not adequately address the need for a widely recognized standardized taxonomy for the classification of cancer-related pain. The World Health Organization's International Classification of Disease (*ICD-10*) has one code for neoplasm-related pain (G89.3) but does not differentiate acute from chronic pain [31]. This limits the acquisition of accurate assessments of the scale of the

problem. Improving the characterization of the problem, through the use of accurate coding and gathering of epidemiological data, would allow for better recognition of the problem in the medical community and among lay people. An example of such a taxonomy has been proposed by the IASP and is in the WHO's proposed ICD-11 [32].

In the IASP classification, once a painful syndrome related to cancer has transitioned from the acute to the chronic phase, it can be further divided into chronic cancer pain and chronic post-cancer treatment pain. Chronic cancer pain is further categorized as either visceral, bone, or neuropathic pain. Chronic post-cancer treatment pain is further categorized as cancer medicine pain, radiotherapy pain, or surgery pain (this last division of chronic post-cancer surgery pain is coded in the International Classification of Disease 11 with all other postsurgical pain codes). This coding scheme highlights an important point: postsurgical pain syndromes, regardless of initial insult or injury, have similar evidence supporting their diagnostic criteria and treatments. For this reason, chronic post-cancer surgery pain is categorized alongside other chronic post-surgical pain syndromes. And while this is convenient logistically, it limits the generalizability of research on its mechanisms as both cancer and non-cancer etiologies are grouped together [31]. For example, pain after a biopsy, a chest tube insertion, or a breast tumor removal is given the same ICD code [31].

As described earlier in this review, definitions for pain related to cancer surgery exist for acute and chronic pain syndromes. For example, recent diagnostic criteria were published for acute pain following breast surgery in the *Journal of Pain*: the patient has undergone breast, lymph node, or breast-related reconstructive surgery; pain of some severity (> 0/10) is present; the pain is primarily in the area of the surgery; onset of pain is immediately following surgery and duration extends to the point of normal healing (two weeks to as long as three months) [33]. However, similar criteria are lacking for the subacute period between acute and chronic pain. While the importance of time-course for pain syndromes should not be over-emphasized, clear definitions for subacute pain can improve clinical research efforts, provide education and comfort to patients, and ultimately lead to better outcomes.

NIH Federal Pain Research Strategy

In response to the substantial disease burden of chronic pain and the opioid epidemic, the United States Department of Health and Human Services (DHHS) created an Interagency Pain Research Coordinating Committee (IPRCC) as an advisory committee to improve research efforts targeting the diagnosis and treatment of pain. The group created a National Pain Strategy, and its executive summary was released on May 30th, 2019. Highlights include an emphasis on safe opioid stewardship as well as clarifying disparities faced by special populations, including that cancer population [34].

The IPRCC also developed a Federal Pain Research Strategy to oversee a long-term strategic plan in the field of pain medicine. The agenda includes developing physiological, clinical, behavioral, psychological, and health services research as well as an emphasis on coordinating research proposals across all federal agencies. Key areas of focus include the prevention of acute to chronic pain, chronic pain management, and disparities in care in different populations (again, including the cancer population) [35•].

Treatments

Treatment options for chronic pain after cancer surgery include, but are not limited to, analgesic medicine, anticancer therapy (or change in existing treatment regimen), educational interventions including behavioral health approaches, interventional procedures, restorative therapies, and complimentary/integrative health approaches.

Medication

Medications that are commonly used for pain control include acetaminophen, non-steroidal anti-inflammatories, gabapentinoids, musculoskeletal agents, benzodiazepines, salicylates, anti-depressants, topical lidocaine, hypnotics, and opioids [36]. There is limited evidence for analgesic medications specific to patients transitioning from acute to chronic pain after cancer surgery. While the WHO pain medication ladder has been validated for the treatment of acute pain, its use in the treatment of chronic pain is not supported by evidence [37]. However, data on the mechanisms of peripheral and central sensitization suggest multiple therapeutic targets for preventing the transition from acute to chronic pain. Acute multimodal pain control is important and local anesthesia with sodium channel blockers may prevent the peripheral sensitization driven by these channels. Central sensitization may be prevented and treated by a combination of NMDA antagonists, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists, anti-inflammatory agents, and gabapentinoids [38]. Synergistic effects of these medications in animal models suggest that trials of combined drugs for treatment refractory chronic pain could be considered. Special considerations in surgical planning for cancer surgeries can also reduce the risk of acute pain developing into chronic pain. For example, minimally invasive surgeries confer better quality of life at 1-year follow-up, compared to open surgeries [39].

In the perioperative period, commonly used medications include opioids, gabapentinoids, magnesium, lidocaine, and

ketamine. Recent data have put the use of gabapentinoids into question. In 2020, Verret et al. found "no clinically significant effect" on the prevention of chronic pain after surgery with the use of perioperative gabapentinoids [40]. Results were similar for gabapentin as well as pregabalin. In fact, no effect was observed on pain intensity at 72 h after surgery, nor in the subacute period. In another 2020 review, Nguyen et al. highlight perioperative analgesics for sinus and skull-base surgeries: they found that opioid use in this time period poses a substantial abuse and dependence risk, whereas non-steroidal anti-inflammatories (NSAIDs), acetaminophen, and gabapentinoids may be reasonable alternatives (though these authors were likely unaware of Verret et al.'s findings) [41]. The use of perioperative gabapentinoids remains controversial; however, given the emphasis on clinical outcomes of Verret et al.'s analysis, and its concordance with prior studies, this class of medications should be used less frequently for perioperative analgesia. There may continue to be a role for this class of medications in select populations as an alternative to opioids.

Restorative Therapy

Restorative therapies can include therapeutic exercise, transcutaneous electric nerve stimulation, massage therapy, traction, topical cold/heat application, therapeutic ultrasound, and bracing. For the cancer pain population, preoperative therapeutic exercise, or "pre-habilitation," may improve long-term functional outcomes (Table 2) [42]. Post-operatively, the pain practitioner can circumvent common complications by encouraging early mobilization and physical therapy after cancer surgery. Prolonged bed rest increases the extent of muscle loss, pulmonary complications, insulin resistance, and the risk of venous thromboembolism [43].

Interventional Procedures

A wide variety of interventional procedures are available for patients with pain after cancer surgery. Reasonable interventions include the following: epidural steroid injections, facet joint nerve block injections, radiofrequency ablation, peripheral nerve injections, sympathetic nerve blocks, interventional neuromodulation, intrathecal medication pumps, vertebral augmentation, trigger point injections, and regenerative/adult autologous stem cell therapy (Table 3).

Table 2 Potential components of pre-habilitation for cancer surgery

Nutritional evaluation and supplementation
Psychological counseling
Medical optimization
Structured exercise program (both aerobic and strengthening activity)

Education

Education and counseling are essential for patients preparing for surgery, particularly education on post-operative expectations [44]. This can take the form of education directly from the surgical team, behavioral therapy, cognitive behavioral therapy, acceptance and commitment therapy, mindfulness-based stress reduction, emotional awareness and expression therapy, and self-regulatory or psychophysiological approaches, among others. Finally, complementary and integrative approaches may have particular benefit in cancer patients. These include acupuncture, massage and manipulative therapies, yoga, and tai chi [45].

One approach that may synthesize patient education with appropriate medical, restorative, and interventional approaches to postsurgical pain was described by Katz et al. in 2015 [46]. This group outlined a transitional pain service which implemented a multidisciplinary program to treat and prevent chronic postsurgical pain. Patient assessments took place preoperatively, postoperatively in the hospital, and postoperatively in an outpatient setting for 6 months following surgery. High-risk patients for chronic postsurgical pain were identified early in their care and the group's aims included preventing the transition from acute to subacute and chronic pain.

Future Directions and Research Priorities

Assessment of the scale of the problem of pain secondary to cancer surgery should remain a priority, as efforts to study relevant diagnoses and treatments depend on accurate epidemiological data. Special efforts should be made to categorize distinct diagnoses related to pain after cancer surgery. This might involve more research into effective clinical workup and diagnostic tools. As diagnoses and their criteria become more clearly defined, detailed investigations into the pathophysiology of each diagnosis should shed light on the most effective treatments. Studies that emphasize patient-centered outcomes such as quality-of-life and functional scores should be emphasized. A team-based approach to comprehensive pain care going forward will likely include minimizing acute and subacute pain, management of co-occurring psychological factors, making accurate diagnoses, and utilizing multimodal pain management.

Conclusion

Persistent pain after cancer surgery is a complex clinical problem. The aging population and the increasing prevalence of cancer diagnoses suggest that the prevalence of persistent pain after cancer surgery will also continue to

Table 3 Interventional procedures for pain after cancer surgery

Procedure	Description	Indications	Reference
Epidural steroid injection	Injection of corticosteroid into the epidural space	Radiculopathy, spinal malignancy-related pain secondary to tumor, fracture, instability, inflammation, or nerve root/spinal cord compression	Oh et al. 2020[1]
Nerve block	Injection of anesthetic over sensory afferent fibers/ganglia	Pain localized to a particular body region or dermatome	Amr and Makhtarita 2014[2]
Radiofrequency ablation	Thermal destruction or modulation of sensory afferent fibers/ganglia	Pain localized to a particular body region or dermatome	Amr et al. 2018[3]
Cryoneuroablation	Application of cool temperatures to achieve destruction or conduction block of a sensory afferent fiber/ganglia	Pain localized to a particular body region or dermatome	Trescot 2003[4]
Interventional neuromodulation	Delivery of electric fields between metal electrodes and nerves, most commonly in the epidural space which modulates pain signaling in the spinal cord	Neuropathic pain	Hagedorn 2020[5]
Intrathecal medication	Drug delivery directly to the spinal cord	Chronic intractable malignant pain	Stearns et al. 2020[6]
Vertebral augmentation	Percutaneous, image-guided augmentation for vertebral compression fractures	Cancer-related vertebral compression fractures	Health Quality Ontario 2016[7]
Trigger point injection	Injection of local anesthetic into hyperirritable nodules located within a taut band of skeletal muscle	Pain caused by myofascial trigger points	Hasuo et al. 2017[8]

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grow. The etiology of pain in these cases can include surgical pain as well as direct effect of tumors, neuropathic pain most commonly in the peripheral nervous system, and treatment-related pain syndromes secondary to chemotherapy and/or radiation. The importance of treating pain in the acute and subacute periods and the prevention of chronic pain syndromes is becoming increasingly evident. Novel patterns of care which include coordinated inpatient and outpatient multimodal treatments may serve as an effective tool in reducing the burden of this clinical problem. Additional research on diagnostic criteria, pathophysiology, novel medications, restorative therapies, and interventional treatments will also be essential to continue to reduce worldwide morbidity due to persistent and chronic perioperative pain after cancer surgery.

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Declarations

Conflict of Interest The authors declare no competing interests.

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