Chronic Pain Management in Cancer Survivors

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Abstract
The problem of pain in cancer survivors is attracting increased attention. Although comprehensive information about the prevalence of persistent pain in the cancer survivor population is currently lacking, it is known to depend on the type of cancer, comorbid conditions, and the initial pain management. Epidemiologic studies generally categorize pain in patients with cancer as either pain directly caused by the neoplastic process or related phenomena, pain occurring as a complication of anticancer treatment, or pain unrelated to the neoplastic process, caused by debility or concurrent disorders. This article focuses on pain syndromes in cancer survivors and the safe use of opioid therapy in this population when its ongoing use is part of the pain management plan. The use of physical therapy, rehabilitation therapy, and cognitive behavioral therapy, which are all extremely important aspects of pain management in the cancer survivor, are briefly mentioned. (JNCCN 2010;8:1104–1110)

Unfortunately, some cancer survivors with chronic cancer-related pain meet significant barriers limiting their access to medications previously determined effective and well-tolerated. An unintended consequence is pain that had been well controlled during active cancer treatment becomes inadequately managed, resulting in unnecessary suffering. The American Academy of Hospice and Palliative Medicine (AAHPM) and the American Pain Society (APS) have provided guidelines to manage pain in cancer patients and survivors. Although the guidelines do reflect variations, the goal should be not to discontinue opioids, but to thoroughly assess the patient’s pain and arrive at an appropriate management plan. Long-term opioid use may be necessary to treat cancer-related or non–cancer-related pain in cancer survivors. If opioids are to be initiated or continued, then the approach is to optimize their risk–benefit ratio through monitoring clinical effectiveness, addressing side effects, and monitoring adherence.

Who is a “Cancer Survivor”? The NCI, in conjunction with the National Coalition for Cancer Survivorship, uses the term cancer survivor to include anyone who has been diagnosed with cancer, from diagnosis throughout life. A more clinically meaningful definition is provided by Macmillian Cancer Support, one of the largest British charities for patients with cancer, which defines a cancer survivor as someone who is “living with or beyond cancer,” namely someone who:

- Has completed initial cancer treatment and has no apparent evidence of active disease;
- Is living with progressive disease and may be receiving cancer treatment but is not in the terminal phases of illness; or
- Has had cancer in the past.

The term long-term survivor is commonly used in research literature. Most investigators use either 5-years after diagnosis or 2-years after completion of therapy as their marker.2

Approximately 11 million Americans are either currently undergoing treatment for cancer or have done so in the past. Long-term 10-year survival rates are approaching 59% in adults and 75% in children, making most cancer
patients candidates for becoming cancer survivors. This population is different from people without a history of cancer in terms of their medical and psychosocial needs, and general complexity. A treatment approach specifically tailored to this population is required.

Survivors of cancer have significantly poorer health outcomes across multiple burden-of-illness measures for years after diagnosis than do people without a history of cancer.\(^3,4\) Psychosocial complications and concerns in cancer survivors are also important and can affect the pain experience. Depression, for example, is up to 4 times more prevalent in cancer survivors than in the general population.\(^5\) Medicare beneficiaries with prostate, breast, lung, or colon cancers are at least twice as likely to use emergency departments and receive inpatient medical treatment if they have clinically significant depressive symptoms than if they do not.\(^6\) The psychiatric and social needs of cancer survivors and their caregivers have a direct effect on their pain experience and must be addressed long-term by clinicians monitoring these patients.

**Pain Syndromes in Cancer Survivors**

The problem of pain in cancer survivors is attracting increased attention.\(^7\) Epidemiologic studies generally categorize pain in patients with cancer as 1) directly caused by the neoplastic process or related phenomena (60\% of cases); 2) occurring as a complication of anticancer treatment (5\%); or 3) unrelated to the neoplastic process, caused by either debility (20\%) or concurrent disorders (15\%).\(^8\)

Posttreatment pain syndromes may result from surgery, radiation therapy (RT), or chemotherapy. The main postsurgical pain syndromes include those related to mastectomy, amputation, and thoracotomy, and neuropathic pain secondary to treatment-related pathology in cranial nerves. Chronic radiation-induced damage may surface decades later but is less common than postsurgical pain. Postchemotherapy painful neuropathy is well described, particularly with the use of vincristine, platinum, taxanes, thalidomide, and bortezomib.\(^9\) Occurring in up to one third of patients undergoing combination chemotherapy, painful neuropathy typically resolves within months after completion of therapy. Osteoporotic fractures and avascular necrosis secondary to high-dose corticosteroids may also be included under this category.

When pain is from neither the disease or its treatment, it most often arises from muscles and connective tissue.\(^10,11\) Although many cancer survivors present with painful comorbidities, such as degenerative disc disease or fibromyalgia, pain in cancer survivors usually refers to chronic pain caused by successful treatment or related debility.

**Prevalence of Pain in Survivors**

Comprehensive information about the prevalence of persistent pain in the cancer survivor population is currently lacking. To address this knowledge gap, research is being conducted to evaluate a random sample of cancer survivors who completed treatment 1 to 10 years previously and were treated at Memorial Sloan-Kettering Cancer Center. These patients are asked to complete a telephone-administered pain interview and assessment battery focusing on pain, quality of life, and psychological distress.\(^12\)

The prevalence of pain in cancer survivors depends on the type of cancer, comorbid conditions, and initial pain management. For example, pain was reported 3 months after thoracotomy in 80\% of cases in one series.\(^13\) Pain after amputation includes stump pain and phantom limb pain and is reported in up to 70\% patients.\(^14\) The prevalence of chronic pain in breast cancer survivors is currently estimated to be at least 50\%.\(^15\) Pain after treatment of head and neck cancer may also be as high as 50\%, with more than 50\% disabled by pain after 12 months. Predisposing factors for pain in cancer survivors include preexisting pain, intensity of postoperative pain, treatment modalities used, extent of treatment, and psychological status.

**Postmastectomy Pain**

Although it is sometimes assumed that modern and less-invasive surgical techniques should result in a decreased incidence of pain in this population, this is not always the case. For example, lumpectomy and axillary dissection may result in a higher incidence of pain than a modified radical mastectomy. The extent of the axillary dissection increases the incidence of pain, and the need for combined treatment modalities with RT or chemotherapy in breast-conserving surgery contributes to the pain. Breast reconstruction surgery can also cause chronic pain. In a large Danish study of women who underwent breast surgery, 47\% reported pain, of whom 52\% had moderate to severe pain.\(^15\) Factors associated with chronic pain...
included young age (18–39 years) and adjuvant RT, but not chemotherapy. Axillary lymph node dissection was associated with increased likelihood of pain compared with sentinel lymph node dissection. Pain complaints originating from other parts of the body were associated with an increased risk of pain in the surgical area.15

Postthoracotomy Pain
Postthoracotomy pain is primarily caused by damage to the intercostal nerve, but severe rib retraction may also disarticulate the costochondral and costovertebral junctions, resulting in somatic pain and tenderness. Ipsilateral arm disability is also common because the latissimus dorsi and serratus anterior muscles are frequently cut. Pain seems to be less common with video-assisted thoracic surgery than with an open thoracotomy. Pain is also less common with an anterolateral approach than with a posterolateral one. Chronic pain is present in more than 50% patients, with 60% still taking analgesics at 1 year.16,17

Postamputation Pain
Phantom limb pain is more common after leg amputation than arm. Older age, bilateral amputations, and a more proximal amputation site are other known risk factors. The time elapsed since amputation is shorter among those with phantom pain.

Pain Status After Therapy for Head and Neck Cancer
Because treatment for head and neck cancer is usually a combination of surgery, RT, and/or chemotherapy, the incidence of chronic pain approaches 40% at 1 year. The accessory nerve and nerves of the superficial cervical plexus are commonly injured, typically resulting in neuropathic pain syndromes. In one study of patients at 1 year after retroperitoneal lymph node dissection, 33% reported neck pain, 37% shoulder pain, 46% myofascial pain, and 65% loss of sensation.18

However, not all cancer surgeries are associated with chronic pain. In a Norwegian study of long-term gynecologic cancer survivors with a median complete recurrence-free period of 12 years (range, 7–18), the prevalence of pain was 26%.19 The results showed no difference in the prevalence of pain between women who survived gynecologic cancer and those with no history of gynecologic cancer. Women with musculoskeletal disorders or living in households with low income were more likely to experience pain, irrespective of whether they were gynecologic cancer survivors.19

Postradiation Pain Syndromes
The most well-studied postradiation syndrome is radiation-induced brachial plexopathy (RBP), although it is frequently painless. Typically occurring months to years after axillary or supraclavicular radiation, the incidence of severe RBP is less than 5% in women undergoing RT after mastectomy, but less-severe RBP may be present in another 10% of patients. Severe RBP is more common with higher doses of RT and after chemotherapy. An acute RBP may develop either during radiation or within weeks of treatment completion in patients undergoing external beam radiation when the treatment field includes the brachial plexus. This pain usually resolves spontaneously within weeks or months. Radiation-induced lumbar plexopathy is rare. Like RBP, sensory and motor symptoms commonly precede pain, although pain does not develop in half of the patients. Plexopathy follows radiation by an average of 5 years, but this ranges considerably. Symptoms are usually bilateral but asymmetric.

Debility-Related Pain in Cancer Survivors
Because inactivity and deconditioning predisposes to muscle pain, the debilitated cancer patient has good reason to experience muscle pain. The fatigued patient is at a higher risk for muscle injury. Muscle pains include trigger points and myofascial pain syndrome, tension, weakness, stiffness, cramps, and spasms.20

Standards for Cancer Pain Management, Including Nonpharmacologic
As cancer evolves into a chronic illness, the landscape of cancer pain for many patients has shifted into a chronic pain situation lasting months, years, or a lifetime.21

When ongoing pain management is required for a patient whose cancer is cured or in remission, and whose care has shifted from a tertiary cancer center back into the community, the community physician may be concerned if ongoing opioid therapy is expected. These concerns generally focus on the potential for harm associated with chronic opioid use, including psychological dependence (addiction), management of behavior classified as pseudo-addiction (drug-seeking and other behavior that is consistent with addiction but actually results from inadequate pain relief; once the pain is adequately treated, the person no longer exhibits these behav-
iors), tolerance necessitating escalating opioid doses to manage the pain, and opioid side effects that are difficult to manage.

The management of pain in patients with cancer is well studied, and various clinical guidelines, including those from the APS and NCCN, have been developed to help clinicians manage the pain. However, few data have been collected on the long-term use of opioids in cancer survivors.22,23 Unfortunately, some cancer survivors with chronic cancer-related pain encounter significant barriers that limit their access to the previously effective and well-tolerated medications. Patient, family, professional, and system-related barriers that may be seen during active treatment can become even more problematic during survivorship (Table 1).23–28 It is important that community physicians have access to state-of-the-science education on the management of cancer-related pain and chronic pain in cancer survivors. This includes knowledge of the appropriate use and titration of opioid drugs in response to pain, management of opioid-related side effects, and use of coanalgesics, such as antidepressants and anticonvulsants. Rapidly escalating pain in cancer survivors or a sudden onset of new opioid-related side effects usually indicates that something else is occurring in the patient medically. Ethical issues surrounding undertreatment of pain in cancer survivors also warrant attention.

In most cancer survivors who require opioid therapy to adequately manage pain, these drugs can be used responsibly and safely. Optimizing pain control and preserving or improving function is the goal. Any patient with a history of cancer who presents with acute or chronic pain requires a careful evaluation not only to establish a pain diagnosis clarifying the causes of the pain, but also to guide the treatment approach. The patient may have several sites and sources of pain, and each site requires a careful assessment. New pain or escalation of previously well-controlled pain should be promptly evaluated to rule out cancer recurrence or progression. The basic components of a pain history are 1) sites and quality of the pain, 2) exacerbating and relieving factors, 3) temporal pattern of the pain, 4) associated signs and symptoms, and 5) degree of interference with function. These should be placed within the context of the patient's cancer history and treatment.

If pain subsides or a patient prefers to stop taking opioids, a slow taper to prevent opioid withdrawal symptoms can be implemented. The lowest effective dose should be continued when appropriate. Usually, 25% of the daily opioid dose is sufficient to prevent withdrawal symptoms. In some patients it may take several months to taper and discontinue even small opioid doses, such as 5 mg of oxycodone taken twice daily. In rare instances, a clonidine patch and acetaminophen may be used to treat withdrawal symptoms. Both clonidine and acetaminophen are associated with a ceiling effect (increasing the dose will not increase the desired effect but will increase adverse side effects). As with any medications, side effects should be anticipated and managed as appropriate.

Examples of treatment-related pain that require chronic pain management include chronic postmastectomy pain syndrome, severe hip pain from arthritis.

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and avascular necrosis resulting from high-dose steroids given during bone marrow transplantation, or chronic pelvic pain after extensive radiation for uterine carcinoma. Opioids should not be automatically stopped in a cancer survivor who is compliant with the medications and has stable and well-controlled pain. Bothersome opioid-related side effects should be assessed and managed whenever possible. Difficult to control or neglected constipation is a major concern and may be the reason patients ask to have an opioid tapered or discontinued despite significant pain.

A multidisciplinary approach tailored to the individual patient needs using a combination of opioids, coanalgesics, physical therapy, psychosocial interventions, and complementary and alternative modalities is usually the most effective approach to managing pain in cancer survivors. Some patients need only one of these interventions, whereas others benefit from a combination. In some instances, invasive interventional procedures can be helpful.

The pharmacologic management of pain in cancer survivors usually consists of opioids in combination with coanalgesics, such as antidepressants and anticonvulsants, for controlling neuropathic pain, or with nonsteroidal anti-inflammatory drugs for controlling nociceptive pain.

For chronic pain, opioids should be prescribed on an-around-the-clock basis, and long-acting opioid preparations are preferred. Commonly used opioids include controlled-release morphine, controlled-release oxycodone, transdermal patches of fentanyl, and methadone. Rotation among different opioids requires consideration of their different relative potency ratios. In the case of methadone, rotation is complicated by the fact that the ratio is dose-related, as seen in Figure 1. Methadone is also known to have a long and unpredictable half-life. Careful titration with close monitoring of pain intensity and side effects, especially sedation, is required during the first 5 to 7 days of treatment. Because of these factors, methadone is usually considered a third-line opioid, and best used in experienced hands.

In most situations, immediate-release preparations should also be made available to patients for episodes of breakthrough pain. The dose for the breakthrough pain is proportional to the 24-hour around-the-clock dosage, is usually 10% to 20% of the patient’s 24-hour dose, and should be made available every 3 to 4 hours as needed. Long-acting opioids may be used without immediate-release opioid formulations when a patient has a strong history of substance abuse. Risk of relapse in this group of patients may be higher with the use of short-acting opioids. Whenever a patient is on chronic opioid therapy to manage pain, ongoing monitoring and follow-up is mandatory, including assessment of analgesic effectiveness, activities of daily living, and adverse drug effects such as constipation, nausea, or sedation, and screening for aberrant drug-taking behaviors. Almost all patients undergoing chronic opioid therapy require a consistent bowel regimen involving a combination of a large bowel stimulant, a stool softener, and other laxatives as needed, including osmotic agents.

**Individualizing Goals for Pain Management**

Although the pain management guidelines proposed by the AAHPM and APS contain variations, the common goal is not to deny cancer survivors opioids if their use is indicated.23-28

The cancer survivor with chronic pain who is no longer followed up at a tertiary cancer center and now presents to the primary care clinician for care needs the risk–benefit ratio of long-term opioid treatment assessed and documented. The goal is not to taper down opioids, but to optimize the risk–benefit ratio; in other words, to achieve analgesia or improve functional status with minimal side effects and without aberrant drug-taking behavior.

The treatment plan should include an open discussion about goals and expectations of chronic opioid treatment. Consent for initiating opioid therapy and a contract outlining the physician and patient responsi-
bilities may be introduced. A similar approach may be useful if established opioid therapy is to be continued.

Patients as unique individuals will vary not only in their reports of pain intensity and pain relief, but in their functional status related to opioid use. For example, a 43-year-old man with a history of recurrent lymphoma and recently diagnosed leukemia presents to the clinic complaining of severe back pain and requests a prescription for Percocet. Radiologic studies confirm severe lumbar stenosis as the likely source of his pain. After reviewing his medical records, the physician notes that the patient has run out of Percocet and OxyContin on several occasions over the past 4 years. The reason was identified as unilateral and the increases in his opioid dosage determined to be unsanctioned despite clear instructions not to do so. It was also revealed that the patient had obtained opioid prescriptions from multiple prescribers. The patient had mild renal insufficiency and was unable to receive non-steroid anti-inflammatory medications. Despite the patient’s painful condition, the decision was made not to prescribe further opioids. His aberrant drug behavior was deemed to be more detrimental to his health and functional status than the pain itself. The patient was referred for physical therapy and to a neurosurgeon to be evaluated for decompression surgery to alleviate the pain. A different patient with a similar chronic pain syndrome but no evidence of aberrant drug behavior would probably have been managed with a combination of low-dose opioid therapy and physical therapy.

In another case, a 50-year-old breast cancer survivor with severe chronic peripheral neuropathy severe enough to interfere with her ability to work was prescribed oral methadone, 20 mg, every 8 hours, for pain. This regimen has been continued for several years with what the patient describes as incomplete but “acceptable and sufficient” analgesia. Side effects were limited to mild fatigue. In this case, the patient’s functional status and pain control improved, and this improvement was maintained with a stable opioid dose. She is seen every 3 months for reevaluation and an opioid prescription refill.

**Issues of Addiction/Diversion**

Of the approximately 11 million cancer survivors living in the United States today, up to 30% have chronic pain. This statistic creates a large public health concern about adequate analgesia and prevention of opioid diversion and abuse in cancer survivors. In this population, with the higher comorbidities, mortality, and psychosocial sequela associated with cancer treatment, adequate treatment of pain and risk assessment of patients undergoing chronic opioid therapy is paramount. Survivor populations at especially high-risk for the undertreatment of pain include children, minorities, and persons who are elderly, have developmental disabilities, or have serious chronic diseases. Patients at risk for the undertreatment of pain are those who are active drug abusers or have a history of drug abuse, however distant. Patients who are actively abusing drugs or have a recent history of drug abuse benefit from the expertise of pain and addiction specialists working together; care of these patients can be complex and time-consuming.

Some physicians are reluctant to prescribe opioids to patients with chronic pain because of the concerns about legal or regulatory scrutiny, licensure issues, and fear of iatrogenic addiction and drug overdose. Most prescription drug overdose, however, occurs outside of the patient–physician relationship. A recent study showed that 66% of overdoses occurred in persons who had never received a prescription for an opioid, and another 21% occurred in those who had received opioid prescriptions from multiple prescribers (≥ 5 physicians).

With appropriate patient selection, screening, and monitoring, chronic opioid use can be safe for most cancer survivors and result in good pain relief, with maintenance or improvement of functional status. Patients who are identified as high risk for opioid abuse require adjustment of the clinic routine to provide closer monitoring, especially in cases of active or past history of substance abuse, psychiatric illness, or serious drug aberrant behavior. Risk factors for opioid abuse include personal history of substance abuse, family history of substance abuse, age (young), history of preadolescent sexual abuse, mental disease, psychological stress, polysubstance abuse, poor social support, cigarette dependency, and history of repeated drug/alcohol rehabilitation.

Adherence monitoring includes measures taken by health care providers to ensure adherence to opioid therapy, and to recognize and prevent aberrant behavior, abuse, and addiction. Clinical literature suggests a 50% or more reduction in opioid abuse occurs in the presence of opioid adherence and monitoring programs.
In these high-risk situations, clinicians may consider a consultation with a mental health professional or an addiction specialist.32

Conclusions
Cancer survivors with residual pain continue to need safe and effective analgesia. Chronic pain management in this group requires clinical skills and knowledge regarding the principles of opioid and adjuvant analgesics prescribing, and the assessment and management of risks associated with opioid abuse and addiction. The goal should not be to arbitrarily taper down opioids, but to optimize the risk–benefit ratio; in other words, to achieve analgesia or improve functional status with minimal side effects and without aberrant drug-taking behavior. Some patients may want to discontinue their opioids, and this can be done safely through a monitored taper. The use of physical therapy, rehabilitation therapy, and cognitive–behavioral therapy are all extremely important aspects of pain management in the cancer survivor.

References