Management of Pain

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Overview

Most patients with advanced cancer, and up to 60% of patients with any stage of the disease, experience significant pain. The World Health Organization (WHO) estimates that 25% of all cancer patients die with unrelieved pain. Although pain can be relieved adequately in most cancer patients, it remains undertreated because of unfounded fears of opioid addiction, unavailability of analgesics from pharmacies, and cultural factors; however, it is the responsibility of healthcare professionals to address these barriers. Despite nearly 2 decades of awareness, medical oncologists continue to see poor pain management education during training, inadequate pain assessment, reluctance to prescribe opioids, and regulatory barriers. These trends are documented in every care setting, including designated cancer centers, where one-third of cancer patients continue to receive an inadequate dose of analgesics. Minority and elderly cancer patients continue to be more likely to have inadequate pain management, including administration of analgesics and palliative radiotherapy. The management of cancer-related pain is an ethical responsibility of healthcare professionals to relieve unnecessary suffering, as part of the duty to care.

Estimates of life expectancy—based on patient performance status, overall metastatic burden, central nervous system (CNS) metastases, and primary cancer site—do influence therapeutic recommendations, but these physician life-expectancy estimates are incorrect in approximately 80% of cases, with the length of survival overestimated in two-thirds of cases. The management of cancer- and treatment-related pain, however, is not restricted to cancer patients with a poor prognosis. The cause of cancer pain should be treated whenever possible. By doing so, rapid, lasting pain relief frequently can be achieved. Also, the need for pain medications may be diminished, thus reducing side effects and drug interactions.

Significant pain adversely impacts function and affects all domains of quality of life during cancer treatment and survivorship. Pain, which reduces the patient’s performance status, reduces potential tolerance of cancer therapy and may cause patients to discontinue their cancer treatments. Recent studies have demonstrated that improved pain management results in improved survival. On the basis of this, clinical trials should account for pain levels in reporting survival outcomes. The principles of cancer-related pain management are straightforward. Effective management of cancer-related pain can be accomplished by local healthcare providers, including oncologists and family physicians. More complex cancer pain syndromes may require the coordination of multidisciplinary professionals, including pain medicine specialists and palliative care and hospice care providers. Meticulous attention to management of controlled substances in the home is needed to prevent abuse and diversion. Patients, families, and professionals providing care share the responsibility for managing all medications, including controlled substances, in the home setting. Unneeded medications should be promptly disposed of according to direction. Home hospice agencies will destroy medications per protocol.

Pathophysiology

Pathophysiologic classification of pain forms the basis for therapeutic choices. Cancer-related pain may be broadly divided into two types: pain caused by ongoing tissue damage (nociceptive) or by nervous system dysfunction that is not associated with ongoing tissue damage (non-nociceptive or neuropathic). Often, cancer-related pain has both nociceptive and neuropathic components. Damage to the nervous system may result in pain and loss of sensation and function. Such pain is typically described as burning or lancinating. Patients may report bizarre complaints, such as painful
numbness, itching, or crawling sensations. The postamputation phenomenon of phantom pain (pain referred to the lost body part) and other neuropathic pains may be disabling. Underlying cancer pain, especially bone metastases, are complex mechanisms that include neuropathic, ischemic, and inflammatory contributors. Additionally, there are unique changes in cancer pain related to changes in peripheral signaling in the area of tumor growth, spinal cord sensitization, and central processing of pain impulses. The different balances between peripheral and central mechanisms are thought to explain the lack of correlation of the presence and intensity of pain with the size or number of metastases.

**Psychological Factors**

Psychological factors and comorbid psychiatric diagnoses, such as depression, may be associated with, and even result from, chronic unrelieved pain. Depressed mood and anxiety often are a consequence of the physiological impact of pain, including lack of sleep and declining function and nutrition. “Psychogenic pain” or somatoform pain disorder is extremely rare in cancer patients; psychogenic pain should be considered a diagnosis of exclusion. “Pseudo-addiction” is an iatrogenic physiological syndrome caused by the inadequate treatment of pain resulting in behaviors similar to those of opioid psychological dependence (addiction). Pseudo-addiction immediately resolves with adequate treatment of pain.

**Pain Syndromes**

Cancer pain syndromes vary by tumor type and are related to patterns of tumor growth and metastasis. Pain may also be related to antineoplastic therapy. Many patients have pain caused by other comorbid nonmalignant conditions, such as arthritis. Thorough evaluation is needed to distinguish cancer-related from non-cancer-related pains.

**Elements of Management**

*FIGURE 1: Algorithm for the integration of pharmacologic management approaches to cancer pain.*

First and foremost, elements of cancer pain management include adequate management of symptoms to relieve suffering while undertaking a diagnostic evaluation that determines the cause of the pain. Once the cause of the pain is determined, specific interventions are selected to target it to provide durable pain relief and prevent potential cancer-related morbidity, such as pathologic fracture and spinal cord compression. Interventions to relieve cancer pain should be chosen according to the (1) cause of the pain; (2) patient prognosis and performance status; (3) prior therapies; and, most important, (4) the preferences of the patient in the context of overall goals of care.

Ongoing care is needed to monitor the efficacy of the pain management plan relative to the evolution of other symptoms during treatment or to later disease progression. Recurrent pain or new sites of pain often are the first indications of cancer progression and should be promptly evaluated. The steps in medical decision making are to:

- Determine whether primary antineoplastic therapy (systemic therapy, radiotherapy, and surgery) is indicated
- Tailor pharmacologic analgesic therapy to individual needs (including analgesics, neural ablation and stimulation, and neuraxial infusion)
- Consider concurrent nonpharmacologic analgesic treatments, such as physical therapy
- Monitor response and modify treatment accordingly (*Figure 1*)

The patient is the focus of care, although family members and others often participate in treatment decisions and require emotional support.

**Medical Evaluation**
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TABLE 1: Features of the pain history—“PQRST”

FIGURE 2: Pain rating scale used to establish a baseline against which treatment results are judged; the numeric scale is also administered verbally.

Pain history
The medical evaluation should begin with a thorough history including the location, severity, and characteristics of the patient’s pain. Pain represents the most common presenting symptom in medicine and may reflect an acute condition, for example, appendicitis or a chronic condition such as bone metastases. The physiologic signs of acute pain—elevated blood pressure and pulse rate—are unreliable in subacute or chronic pain. The chronic pain of cancer usually is progressive over several months. The patient with cancer usually seeks medical attention when an acute exacerbation of pain occurs or when chronic pain significantly impacts function or quality of life, such as interfering with sleep. Restriction in function and fatigue, therefore, represent different physiologic signs of chronic pain. Most cancer patients report more than one site of pain. A detailed history of each type and site of pain should be elicited (Table 1).

Pain rating scales
Validated and reliable pain scales are a clinically useful part of the evaluation of response to analgesic therapy (Figure 2). There are standardized tools that can be used for patients who are unable to communicate, such as preverbal children and impaired adults. In noncommunicative agitated patients, it is acceptable to treat pain presumptively. Rating scales are supplemented with assessment of pain impact on domains of function and quality of life.

Physical examination
The assessment should evaluate the putative mechanisms that may underlie the pain. This includes careful neurologic testing, especially if neuropathic pain is suspected. A neuropathic process is likely when pain occurs in an area of reduced sensation or when the patient is experiencing allodynia (ie, when usually nonpainful stimuli are reported as painful) or hyperpathia (summation of painful stimuli).

Review of disease extent and current conditions
The extent of disease and current medical conditions must be understood. As with any sign or symptom of cancer, pain and neurologic debility must be carefully monitored.

Diagnostic tests
Diagnostics should be reviewed and supplemented as necessary. Any new site of pain or increase in pain severity should be diagnostically evaluated, because pain is often the most common sign of disease progression.

Treatment and drug history
Cancer treatment and prior analgesic interventions, along with their outcomes, should be known. Psychological dependency on any drug, including alcohol, must be identified. However, psychological dependency on any drug should not impede adequate pain management; when necessary, pain management specialists should be consulted to assist in such cases. Aberrant drug-taking may occur in cancer patients and should be addressed in an appropriate manner.
Psychosocial Assessment

To establish trust, the clinician should explore with the patient the significance of the pain complaint in terms of function and quality of life. The impact of pain and other symptoms on functional status must be understood in order to establish treatment goals.

Suffering may also be attributable to many factors besides physical complaints of pain. The clinician should ask about such socioeconomic and personal factors as financial worries, loss of independence, family problems, social isolation, and fear of death. Often, cancer patients meet diagnostic criteria for the psychiatric diagnosis of adjustment disorder with anxiety and/or depressed mood.

Subgrouping of Patients

To help define therapeutic goals, the patient’s performance status and prognosis may be considered. Pain in children is underreported and should be specifically elicited using age-appropriate assessment scales.

Pharmacologic Treatment

In the past, the WHO devised a three-step analgesic ladder outlining the use of nonopioid analgesics, opioid analgesics, and adjuvant medications for progressively severe pain. According to this schema, a nonopioid analgesic, with or without an adjuvant agent, should be tried first (step 1). If pain persists or increases on this regimen, the patient should be switched to an opioid plus a nonopioid agent, with or without an adjuvant medication (step 2). If pain continues or intensifies despite this change in therapy, a more potent dose of opioid analgesic should be prescribed, with or without a nonopioid and/or an adjuvant agent (step 3). This WHO three-step analgesic ladder has been especially useful in breaking barriers that impeded the control of cancer-related pain worldwide.

However, it is now accepted practice that the level of pain should determine what level of analgesic should be prescribed. It is now recognized that patients with severe cancer pain should initially receive opioid analgesics and not suffer through two inadequate analgesic courses before receiving relief with an appropriate type of administered analgesic. While concerns exist about opioid side effects, it is also important to recognize the significant potential side effects of nonsteroidal anti-inflammatory agents (NSAIDs).

TABLE 2: Nonopioid analgesics and NSAIDs useful for treating cancer pain
Nonopioid analgesics

Nonopioid analgesics, primarily NSAIDs, are associated with ceiling effects (maximum allowable dose), and exceeding the maximum dose ranges can result in severe organ toxicity. Potential side effects, such as hematologic, renal, and gastrointestinal reactions, may be of significant clinical concern in cancer patients (Table 2). Cyclooxygenase (COX)-2 inhibitors are many times more potent against COX-2 than COX-1. Clinicians are advised to monitor the emerging literature regarding the safety of these agents. These concerns extend to nonopioid analgesics that are compounded with opioid analgesics; when possible, it is advisable to prescribe opioids alone without NSAIDs.

Opioid analgesics

General guidelines for opioid therapy are outlined in Table 3.

**Dosage.** Opioid agonists do not exhibit ceiling effects. Dosing is guided by efficacy. Most opioid side effects can be anticipated and controlled. Unlike opioids alone, the nonopioid component limits the dosages of tablets that combine an NSAID or acetaminophen and an opioid (Table 4).

**Routes of administration.** The oral route should be used when possible, although some patients may express a preference for an alternative route. If the oral route is not feasible because of patient preference; physical difficulties, especially with swallowing; or side effects, then alternative routes (eg, transdermal, transmucosal, rectal, and spinal) are indicated. Such alternative routes of
administration of certain opioid agonists (see Table 5) may improve patients’ quality of life and may be particularly useful for treating certain types of cancer pain.

**Side effects.** Side effects of opioids can usually be anticipated and prevented. In particular, with regular opioid dosing, laxatives should be prescribed for constipation.

Physical dependence on and tolerance to some effects develop with long-term opioid use. Tolerance to respiratory depression, sedation, and nausea is likely. Nausea can occur when opioid-naive patients receive initial analgesic doses, and it should be controlled with antiemetic therapy. Tolerance to analgesia is not a major clinical problem and can usually be managed by changing the dose or substituting another analgesic agent.

Most current definitions of addiction imply a behavioral syndrome. An important distinction is that addiction does not require physical dependence or tolerance. Tracked over several decades, aberrant drug-taking rarely occurs in patients without a history of substance abuse. Consistent with current guidelines, compliance should always be monitored when opioid analgesics are prescribed.

**Precautions during long-term therapy.** During long-term opioid therapy, certain precautions should be observed:

- Meperidine is **contraindicated** in the treatment of cancer pain, because normeperidine, a toxic metabolite of meperidine, accumulates and can cause significant side effects, such as seizures.
- Propoxyphene is also **contraindicated** because of accumulation of norpropoxyphene (and this drug has come off of the market in the United States).
- Placebo use is **contraindicated** because the patient’s report of pain should be accepted as would be any other medical symptom.
- Physical withdrawal symptoms can be avoided by tapering doses.
- A change in mental status **should not** be attributed to opioid therapy until medical and neurologic factors have been fully evaluated. Especially important is to exclude potential disease progression, including brain metastases.
- The mixed agonist-antagonist and partial opioid agonist drugs are **not** recommended for cancer pain (see Table 5).
- Methadone has unique pharmacokinetics. **Inexperienced practitioners should consult a pain medicine expert before prescribing methadone.** See clinical guidelines and US Food and Drug Administration warnings.

**Adjuvant medications.** Neuropathic pain may be less responsive to standard analgesics alone. Adjuvants, such as antidepressants, anticonvulsants, benzodiazepines, local anesthetics, neuroleptics, psychostimulants, antihistamines, corticosteroids, levodopa, calcitonin, and bisphosphonates, improve the effectiveness of standard analgesics and are useful for particular indications (Table 6). These agents may be administered via oral and other routes. Administration of topical local anesthetics, NSAIDs and other preparations, and anesthetic and neurosurgical procedures (Table 7, Table 8) should also be considered. Referral to a pain specialist should be considered for refractory neuropathic pain.

**Bone Metastases: The Paradigm for Oncologic Treatment of Pain**

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**TABLE 6: Adjuvant drug therapy for cancer pain**

**TABLE 7: Anesthetic/neurosurgical approaches for controlling cancer pain**
Surgery for bone metastasis

Surgical intervention is warranted for bone metastases to stabilize a pathologic fracture or preempt an impending fracture. The objectives of surgery are to palliate pain, improve patient mobility and function, and control the disease in the bone to prevent further morbidity when nonsurgical therapies fail. In general, surgery involves excision of all gross tumor followed by stabilization of the bone before or after fracture by means of an internal fixation or prosthetic device. Restoring the anatomic integrity of the spinal cord by relieving bony compression (eg, due to vertebral collapse) is an absolute indication for surgery, with rare exception based on prognosis.

### TABLE 8: Neurolytic procedures that may be considered early in certain pain situations

**Indications.** Clinical parameters, such as the patient’s general medical condition, performance status, nature of the primary tumor, effectiveness of other therapies, extent of extraskeletal disease, and degree of osseous involvement, as well as the patient’s life expectancy, must be considered before surgery.

- **Fracture and long bone pain**—In general, the presence of a pathologic fracture, an impending fracture, or a painful lesion in a long bone despite radiotherapy should be considered to be indications for surgery. A pathologic fracture can also result from structural insufficiency and can develop in the absence of a viable tumor following treatment with irradiation and/or systemic therapy. Current guidelines derived from retrospective clinical studies include lytic lesions larger than 2.5 cm in diameter, cortical destruction of more than 50%, and pain despite local irradiation. In the proximal femur, an avulsion fracture of the lesser trochanter places the hip at high risk for fracture.

- **Clinical criteria for surgery**—All surgical interventions should be performed with the intent to provide benefit that will outlast the patient’s anticipated survival. All patients should be medically fit for anesthesia and the planned surgical procedure. The surgical goals should be achievable with reasonable certainty, and the potential benefits should outweigh the operative risks. The surgical goal of a stable, painless extremity allows optimal patient function and mobility.

- **Lesion site**—Major long bones (femur, tibia, and humerus), the vertebrae, and periacetabular regions demand specific attention. Osseous destruction sufficient to compromise the mechanical integrity of these bones should be addressed surgically. Lesions in the weight-bearing bones of the lower extremity (femur and tibia) are particularly vulnerable to fracture. Lesions in the humerus should be treated surgically when the upper extremities serve a weight-bearing function (eg, assisted ambulation using a walker, crutches, or cane). Early surgical intervention, aggressive rehabilitation, and vigilant postoperative surveillance may optimize patient outcome. Surgical techniques are designed to correct anatomical disruption. Vertebral augmentation techniques, vertebroplasty and kyphoplasty, are minimally invasive techniques of percutaneous injection of bone cement (methyl methacrylate) directly into vertebral bodies. With a low complication rate, these procedures are being used more commonly in conjunction with other treatments and even as a first-line approach for management of painful malignant spine fractures. It has been reported that there is a correlation between symptom duration and restoration of vertebral body height after kyphoplasty.

### Radiation Therapy

Cancer pain can often be relieved by radiation therapy delivered by localized external-beam irradiation, including stereotactic body radiation, or systemic treatment with radioactive isotopes (eg, strontium-89 chloride [Metastron], samarium-153 lexidronam [Quadramet], and alpharadin). Single-fraction external beam radiation is equivalent to more protracted and costly courses of multiple-fraction palliative radiation. Influences on practice patterns with regard to utilization of single-fraction radiation are related to primary tumor type, worse prognosis, greater physician experience, site of metastases, and location of training. Reirradiation, in about 20% of patients, for inadequate or recurrent bone metastases pain results in relief in almost 60% of patients. Other examples of cancer pain due to primary or metastatic cancer that are amenable to irradiation...
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include headache from CNS involvement, pain due to localized neural involvement (eg, brachial plexus or sciatic nerve), visceral pain (eg, adrenal or pelvic masses), and pain due to obstruction (eg, urethral, esophageal). Nearly 20% of patients with bone metastases referred for radiation therapy have neuropathic symptoms resulting in a more severe pain presentation.

Systemic radiotherapy

Like bone scans, systemic radiotherapy localizes in all of the bone metastases, while delivering minimal radiation to uninvolved normal bone; no radiation is delivered to adjacent soft tissues. On this basis, systemic radiotherapy is highly indicated in patients with diffuse metastases localized to bone without a soft tissue component. Systemic radiotherapy is contraindicated in bone metastases with soft tissue extension, because no treatment will be administered to the soft tissue component by the systemic radiotherapy. Given the localization of radiation to the bone, the only known toxicity is mild myelosuppression. The risk of myelosuppression depends on the extent of prior therapies, such as chemotherapy, that have previously compromised the bone marrow elements.

Strontium-89. Strontium-89 is a systemic radionuclide that has clinical efficacy in the palliation of pain from bone metastases, and its levels in bone are regulated much like regulation of calcium levels. The greatest level of experience published in the medical literature is with strontium-89 in prostate cancer.

Samarium-153. Samarium-153 is a β-emitting radioisotope that is bound to a phosphonate that preferentially localizes in active bone, specifically in sites of metastatic disease. Samarium-153 is associated with a lower incidence and severity of hematologic toxicity than strontium-89.

Alphanradin (radium-223 chloride). Alphanradin is an alpha-pharmaceutical with a shorter half-life of 11.4 days, which allows repeated dosing to achieve response.

Systemic therapy

Systemic therapy is the most common cancer treatment for bone metastases. The type of systemic therapy depends on the tumor type, prior systemic therapies, hematologic status, and performance status.

Physical treatments

Cancer patients may benefit from formal physical therapy and rehabilitation. Physical modalities, such as massage, hydrotherapy, transcutaneous electrical nerve stimulation, electroacupuncture, and trigger-point manipulation, are indicated for musculoskeletal pain. Also, any of these techniques may enhance exercise tolerance in a patient undergoing rehabilitation. Electrical stimulation may also be applied to the peripheral nerves, spinal cord, and deep brain structures to relieve pain.

Management of Psychological, Sociocultural, and Spiritual Factors

A multimodal approach to pain management recognizes the complexity of the human being, especially one with a terminal illness. Psychological, sociocultural, and spiritual factors significantly affect the patient’s quality of life. Patient-centered education, plus ongoing communication with health professionals that empowers patients to self-manage and coordinate care, represents the most effective strategy to overcome barriers at the levels of the patient, provider, and healthcare system. Empathic care helps relieve existential suffering integrated throughout the course of illness.

Psychiatric diagnoses

Psychiatric conditions, such as anxiety and depression, and psychological factors must be thoroughly addressed, as revealed by emerging evidence from the disciplines of psycho-oncology and psychoneuroimmunology. Techniques such as guided imagery, hypnosis, relaxation, and biofeedback also assist in pain and symptom management. There is growing evidence that mind-body approaches alleviate nonphysical as well as physical symptoms.

Sociocultural influences

Sociocultural factors may affect the patient’s experience and expression of pain. However, it is important to recognize that rating of pain severity on validated pain scales is not affected by sociocultural factors. Unrelieved pain, in addition to its negative physiologic effects, may represent the presence and progression of cancer, resulting in fear, anger, disappointment, and other negative emotions. Fear of unrelenting and unbearable suffering as cancer progresses becomes a particularly important emotion when pain is not adequately relieved. By relieving pain, healthcare providers reassure patients that they will not suffer throughout their course of cancer.
Existential distress

Achieving relief of psychic suffering allows the patient and family to realize improved quality of life and find peace in the face of failing health and imminent death. Prayer, meditation, counseling, clergy visits, and support groups may all be beneficial. Palliative care of the family includes bereavement counseling in anticipation of the loss of a loved one, and after the patient’s death. It is important for providers to have general cultural competencies when addressing end-of-life concerns.

Ongoing Care

The goals of pain management must be frequently reviewed and integrated into the overall management plan. Communication between the professional staff, patient, and family is essential. A sensitive, frank discussion with the patient regarding his or her wishes should guide medical decision making during all phases of the illness. The healthcare team should express commitment to the patient and family during the course of care and through to end of life if necessary (ie, the concept of nonabandonment). Evidence-based standards for cancer pain management exist. Providers should routinely screen for pain and describe its intensity and location, as well as pain-related functional impairment. Patients and caregivers should receive education about the treatment of pain. The treatment of pain should include breakthrough opioids when long-acting formulations are prescribed, bowel regimens, and continuity of opioid doses across healthcare settings. Pain, like other medical conditions, requires follow-up with the patient to insure its adequate management. For metastatic bone pain, single-fraction radiation should be offered, unless there is a contraindication. When compression of the spinal cord is suspected, administration of corticosteroids, diagnostic evaluation, and definitive treatment (radiotherapy or surgical decompression) should be performed within 24 hours.

Pain in Cancer Survivors

Pain continues to be a common problem in the first few years after cancer treatment, particularly in breast cancer survivors. All cancer treatment modalities have the potential to cause pain. Approximately 5% to 10% of survivors will have chronic severe pain that interferes with functioning. Multidisciplinary programs should be available for survivors with complex pain issues, and for the more than 40% of cancer survivors who now live longer than 10 years. As with chronic nonmalignant pain, these multimodal interventions should also include nonpharmacologic therapies to restore function and provide comfort. As with cancer-related pain, however, opioid analgesics are appropriate to treat some survivors with moderate to severe pain, while considering the individual benefits and risks. New or worsening pain must be evaluated to determine if the etiology is related to recurrent disease or a second malignancy.

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