Alleviating Cancer Pain

Pain, a common and distressing symptom of cancer, is not purely a physical experience. An individual's psychological, social, emotional, and spiritual suffering make up the ‘total pain’ experience. Spiritual distress, for instance, takes the form of existential questions, search for meaning and purpose, and anger at fate. A multidisciplinary team, addressing these bio-psychosocial concerns, is essential to effectively manage pain.

Epidemiology

An estimated 7 million people from around the world die from cancer each year. Pain can occur at any point during the course of the illness. Pain may be the first sign of malignancy. The prevalence of pain at the time of diagnosis is estimated to be approximately 50%, increasing to 75% at advanced stages. The prevalence of pain in cancer survivors is estimated to be 33%. The interventions used to diagnose cancer could be painful. Similarly, the treatment of cancer involving surgery, radiotherapy, chemotherapy, immunotherapy and hormonal therapy, could be associated with both acute and chronic pain (Table: 1). Finally, advancing disease invading the nerves, bone and viscus could lead to pain. The highest reported prevalence of pain is in tumours involving the head and neck, prostate, breast, genitourinary system and pancreas.

Pathophysiology

- Local and systemic inflammatory response, with production of pro-inflammatory cytokines, which facilitate pain transmission.

- Direct tumor-related pain: Cancer cells can cause invasion of viscera (visceral pain) or entrapment and injury of nerves (neuropathic pain). Tumors release proteolytic enzymes, endothelin, prostaglandins, and tumor necrosis factor alpha (TNF-α), causing peripheral and central sensitisation of the nervous system.

- Metastatic bone pain: Loss of mechanisms that regulate the balance between osteoclast and osteoblast activity may result in osteolysis, pathological fracture, and microfractures. Infiltration of peristomeum and sensory neurons that innervate the bone marrow can cause pain.

- Neuropathic pain: Chemotherapy disrupts tubulin function, with release of cytokines, resulting in degeneration of sensory neurons and sensitization of primary nociceptive afferents. Radiotherapy can cause tissue fibrosis with nerve compression and microvascular obstruction of the nerve.
Aetiology

Cancer pain patients commonly experience more than one kind of pain (Table: 2). The pain may be constant or intermittent, or acute pain superimposed on chronic background pain. Psychological factors such as depression, anxiety, and cognitive style may influence pain perception and contribute to the intensity of the pain.

Assessment

The general principles for an accurate, thorough, and systematic assessment of cancer pain include - using tools validated for the patient’s age and cognitive abilities; recording current and past medications, including efficacy and any adverse effect; assessing for functional impairment and the need for safety measures; incorporating a psychosocial evaluation into the assessment, including determination of the patient’s/family’s goals of care; using a pain diary to track the effectiveness of therapies and evaluate changes in pain; ordering a diagnostic evaluation (e.g., MRI, CT) when warranted, and only if it will contribute to the treatment plan; and evaluating for the presence of other symptoms such as fatigue, constipation and mood disturbances.

Essential components of the pain history include location(s), intensity, quality (nociceptive, neuropathic, visceral), temporal patterns, aggravating and alleviating factors, cultural factors, and medication history. Validated pain intensity scales include the Numeric Rating Scale, Verbal Descriptor Scale or Visual Analogue Scale. Several paediatric tools are available. We use Brief Pain Inventory, which is a multidimensional instrument. The symptom assessment tools commonly used are Edmonton Symptom Assessment Scale (ESAS), M.D. Anderson Symptom Inventory (MDASI), Memorial Symptom Assessment Scale (MSAS), and Rotterdam Symptom Checklist (RSC). Most patients referred for cancer-related symptom management have at least two anatomically distinct pain sites, and more than 40% have four or more sites.

Pharmacological Management

A wide range of pain management therapies are available, and evidence shows that 85–90% of cancer pain can be controlled by using the guidelines of the World Health Organization.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are beneficial in pain due to bone cancer or metastasis because of their anti-inflammatory effect and because they may decrease tumor growth. They should be used with caution if there is a risk of gastrointestinal bleeding, decreased kidney function or heart failure. Elderly patients are particularly vulnerable to the adverse effects. Gastric protection should be considered. COX-2-selective NSAIDs are no more effective as analgesics compared with non-selective analgesics, and Paracetamol can be considered when NSAIDs are contraindicated.
**Opioids:** The preferred *route of administration* is by mouth. Transdermal fentanyl can be considered if pain is stable and the required opioid doses are moderate. Transdermal absorption of fentanyl is impaired in cachetic patients. Subcutaneous administration by continuous infusion can be considered if the patient cannot take medications by mouth. Spinal (epidural or subarachnoid) opioid administration can be considered when less invasive methods are not effective.

*Weak opioids* (e.g., codeine, tramadol) can be used in moderate pain. They have a maximum recommended dose after which the adverse effects increase more than the analgesic effect. *Strong opioids* (e.g., morphine) have a broader dose range. *Long-acting opioids* for stable or baseline pain and *fast- and short-acting opioids* for breakthrough or incident pain (via oral, transmucosal, or inhaled routes of administration) could be used, and are available in India.

Respiratory depression, nausea and vomiting (treated with haloperidol, metoclopramide or 5-HT3-antagonists), and constipation (treated with osmotic stool softeners, stimulant laxatives) are the common adverse effects. Opioid antagonists (e.g., methylnaltrexone) that do not penetrate the blood-brain-barrier are a new effective treatment for opioid-induced constipation. Sedation, dysphoria, hallucinations, and nightmares, as well as sweating and itching, are other opioid-related adverse effects.

*Addiction* is rarely a problem, but development of *physical dependence* is typical for opioids, which should never be abruptly discontinued, so as to avoid *withdrawal* symptoms. Similarly, development of *tolerance* is typical for opioids. Tolerance can be dealt with by increasing the dose; by changing the opioid (cross-tolerance is not complete); by changing the route (spinal administration); or by adding other drugs, such as ketamine or clonidine. Methadone can be particularly effective when tolerance has developed to other opioids, perhaps because of its non-opioid. Because of its difficult pharmacokinetics, methadone is not a first-line opioid.

**Adjuvants:** *Antidepressants* can be used to treat both depression and neuropathic pain. *Anticonvulsants* can be used to alleviate neuropathic pain. Gabapentin and pregabalin have been studied in cancer-related neuropathic pain (the drugs were effective) and in chemotherapy-induced neuropathic pain (the drugs had no effect), and they are currently being studied in bone cancer pain. Gabapentin and pregabalin have anxiolytic effects that may be useful in cancer pain. *Corticosteroids* reduce edema and inflammation and stabilize nerve membranes. They can be useful in pain due to edema (e.g., in the brain, spinal cord, or liver). They also alleviate nausea and increase mood and appetite. *Ketamine* has been used in subcutaneous or intravenous infusions to alleviate opioid-induced hyperalgesia and tolerance. It can be given by mouth, but its oral bioavailability is low and variable. *Bisphosphonates* are useful in relieving both the continuous and the incidental pain components in patients with bone cancer pain. *Anti-spasmodics* such as Oxybutynin reduce the pain of visceral spasm.

**Interventional Techniques**
Interventional techniques targeted to control pain may be appropriate adjuvants or alternatives to oral or systemic pharmacological treatment. These techniques may also be more appropriate in patients who are unable to tolerate side effects of systemic medications.

**Epidural** is the most common option for spinal or radicular pain caused by primary or metastatic lesions. It is performed at cervical, thoracic, lumbar, or caudal levels to provide highly selective pain relief. It could be done as a single injection of a steroid, sometimes with a local anaesthetic (e.g., lidocaine or bupivacaine) or as continuous infusions of an opioid with a temporary catheter. **Intrathecal** injections provide highly selective pain relief with minimal side effects, due to significantly reduced concentration and dosages. It involves implantation of intraspinal catheter and a subcutaneous pump, if the patient’s survival expectancy is more than 3 months. The agents, which could be administered in combination, include Morphine, Fentanyl, Bupivacaine, Clonidine, Baclofen, and Meperidine (pethidine).

**Nerve Blocks** target regional symptoms in the distribution of single or multiple peripheral nerves, to provide short-term, and potentially long-term benefits, but not permanent relief. Trigger point injection for myofascial pain, local anaesthetic injection administered in sympathetic ganglia for CRPS, stellate ganglion block for head and neck pain, and lumbar sympathetic chain block for nociceptive or neuropathic cancer pain affecting the lower extremity, are some examples. **Neurolytic Procedures** are useful in neuropathic or visceral pain in the distribution of specific peripheral or autonomic nerves. Hyperbaric phenol saddle block for midline perineal pain in patients with rectal and pelvic malignancies, coeliac plexus block for visceral pain of gastrointestinal origin, particularly pancreatic cancer, intrapleural phenol block for visceral pain associated with esophageal cancer, superior hypogastric plexus block for tumor extension into the pelvis, and ganglion impar block for visceral pain of the perineum, are commonly performed.

**Percutaneous vertebroplasty and kyphoplasty** are two closely related interventional techniques used to treat painful vertebral compression fractures due to malignancy or osteoporosis. Vertebroplasty is the injection of a vertebral body with bone cement. Kyphoplasty adds the placement of balloons into the vertebral body with an inflation/deflation sequence to create a cavity and perhaps restore height prior to the cement injection. These procedures are most often performed in a percutaneous fashion on an outpatient basis. The ideal candidate has severe axial (non-radiating) pain due to fractured vertebrae. The procedure produces prompt, significant pain relief in 80–90% of cases, with a low complication rate. The risks include spinal cord compression, nerve root compression, venous embolism, and pulmonary embolism (including cardiovascular collapse). **Spinal Cord Stimulation** is useful in chronic regional pain syndrome, postherpetic neuralgia, chemotherapy-induced peripheral neuropathy, and postradiation nerve injury. **Peripheral Nerve Stimulation** has the same indications as above, but its utility is limited to neuropathic pain involving specific non-dermatomal peripheral nerves. They are very rarely used in managing cancer pain in India. Neurological procedures such as **percutaneous cordotomy** are increasingly done by pain specialists.

**Radiotherapy**
Radiotherapy is the single most effective oncological treatment of cancer pain. In the treatment of bone metastases, the pain-relieving efficacy of both external radiotherapy and systemic radionuclide therapy is well documented. Radiotherapy is also effective in treating pain caused by soft-tissue tumors. The mechanism behind the pain-relieving effect of radiotherapy is incompletely understood. There is no direct correlation between the effectiveness of radiotherapy and the radiosensitivity of the tumor or the dose administered. Tumor shrinkage and inhibition of the release of chemical pain mediators seem to be the main mechanisms by which radiotherapy acts. The rapid onset of pain relief—within days—is attributed to the decrease of various chemical pain mediators, whereas tumor shrinkage and recalcification of osteolytic bone lesions contribute to the long-lasting effect. Systemic Radionuclide Therapy with strontium-89 and samarium-153 alleviates pain caused by bone metastases. The effect is best documented in prostate cancer, where bone lesions are predominantly osteosclerotic. The average onset of pain relief is somewhat slower, taking 2 to 4 weeks. Transient hematologic toxicity should be taken into consideration.

Psychosocial Interventions

From a psychological perspective, cancer pain is challenging for several reasons. First, for many cancer patients and survivors, the occurrence of pain may raise concerns about disease progression. Second, although cancer pain is often believed to be related to biological reasons, it often persists long after patients are believed to be cured of their cancer. Finally, because cancer pain is usually treated medically, patients and health care professionals often underestimate the impact of cancer pain on psychological distress. Health professionals working with cancer patients need to be alert to signs of psychological distress in patients experiencing pain. There are several reasons why psychological interventions may represent a valuable addition to cancer pain management. First, evidence indicates a strong link between cancer pain and psychological factors such as mood, distress, depression, and anxiety. Second, cancer patients' sense of confidence or self-efficacy about their own abilities to control pain has been related to decreased pain and greater psychological well-being. Finally, cancer patients who cope with pain by catastrophizing (i.e., ruminating about pain and feeling helpless) are much more likely to experience higher levels of pain and psychological distress.

Cognitive-behavioural therapy is currently the most widely used psychological treatment for persistent pain. It involves several steps. The first step is pain education. The second step is training in one or more coping skills for managing pain (e.g., relaxation or problem solving). The third step in training is home practice with learned skills. The final step in training involves helping patients develop a program for maintaining their skills after training is completed and for overcoming setbacks and relapses in their coping efforts. A recent review of the literature found that comprehensive cognitive-behavioural therapy significantly reduced pain in 46% of the studies reviewed.

Special considerations
**Final Days of Life:** If verbally report of pain is not possible, behavioural cues such as facial grimacing, guarding, or vocalizing should be evaluated. Administration of opioids may be complicated by the inability to swallow, and alternate routes of administration should be considered. Doses may need to be decreased, as organ system failure leads to reduced excretion of the drug and or its metabolites. Education of family members regarding signs of impending death will assist in reducing their anxiety. Honouring the patient’s culture and respecting cultural preferences and rituals is important. Similarly, the developmental stage of any children involved should be considered when communicating about death.

**Children:** Pain in children with cancer is usually well controlled using the World Health Organization’s guidelines. Non-pharmacological strategies may be beneficial in isolation or in tandem with pharmacological agents. They include physical techniques (e.g., massage, acupuncture, or transcutaneous electrical nerve stimulation [TENS]), behavioural techniques (e.g., relaxation or music therapy), and cognitive techniques (e.g., imagery, hypnosis, or music therapy). Nonsteroidal anti-inflammatory drugs impair platelet function and are often contraindicated in children who are at risk of thrombocytopenia and bleeding.

**Older People:** Cancer is predominantly a disease of aging. Predictors of cancer pain in older people include female gender, advanced disease, comorbidities, lower social support, depressed mood, and lower physical functioning. Cancer Pain has a detrimental impact on the quality of life of older patients, and older cancer patients are at risk for inadequate pain treatment. Treatment planning should be responsive to the risks associated with advancing age, comorbid medical conditions and the risk of polypharmacy. Observational scales may be used with patients unable to verbally self-report their pain. Pethidine (meperidine) and NSAIDs should be avoided because of a high risk of adverse effects. They may require lower doses of opioids to achieve adequate analgesia, and may have greater adverse effects and toxicity.

**Conclusion**

Cancer pain is a complex, multifaceted problem. Sometimes the pain and suffering from cancer and its therapy feels like a descent into hell. In India, the diagnosis of cancer is often viewed as a ‘death sentence’ because management options are severely limited by the time the patients reach hospital. Pain can be a volatile and fickle force and, when provoked, might unleash a torrent that overwhelms the initial provocation. Barriers that interfere with adequate cancer pain management could be related to health care professionals (poor assessment, inadequate knowledge and anxiety about controlled substances); to patients (not reporting pain, poor compliance, fear of addiction, adverse effects and thinking of pain as inevitable part of cancer); and to the health care system (restrictive regulation, low priority to cancer pain, cost, access to care and reimbursement policies).

Fortunately, the future of cancer pain management is encouraging, and novel agents in the research pipeline promise to revolutionize management. To meet the daunting challenges posed by cancer pain, clinicians must be prepared to bridge the gap between current knowledge and application. Ultimately, closing this gap will go a
long way to restoring a greater sense of control over disease and promoting optimism among patients with cancer in pain.