

Pain Management in Cancer Patients

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ABSTRACT

Pain is always a subjective experience that is influenced by behavioral, biological, and social factors. Timely assessment and proper treatment can significantly reduce the consequences associated with inadequate pain relief. The pathophysiology of the pain that is suffered by cancer patients is overly complex and is thought to be due to various mechanisms involved. It is thought that many of them complain of severe neuropathic pains, which may be due to the ongoing compression, ischemia, and inflammation. In addition to the pain of their metastatic disease, they also suffer from treatment-related pains and procedural/surgical pains. This review article highlights the pathophysiology, and assessment and particularly focuses on the management of pain in cancer patients with different modalities using Oncological, Pharmacological, Non-pharmacological, and Interventional techniques.

Keywords: Cancer pain, pathophysiology, management.

INTRODUCTION

Pain continues to be a subjective experience influenced by behavioral, biological, and social factors. The revised IASP definition of pain says 'An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage' [1]. The quality of life of cancer patients is compromised mainly due to the burden of illness. Such patients are already at the edge of a psychosocial disability [2]. The acceptance and treatment of the pain they report is critically important to avoid the negative consequences associated with insufficient pain control [3].

On a global scale, the number of new cancer cases is increasing. The International Agency for Research on Cancer (IARC) has shown 0.18 million new cancer cases in PAKISTAN, of which breast cancer is the most prevalent followed by lip and mouth [4]. Several studies have identified inadequate and poorly managed pain management in cancer patients [5]. An investigation by Majeed *et al.* revealed that only 1/3 of cancer patients had adequate pain relief [6].

For the effective management of pain in cancer patients, the treating physician must have in-depth knowledge of the pathophysiology of pain and the type of pain that the patient suffers [7]. Rapid assessment and appropriate treatment can significantly reduce the impact of inappropriate pain management [8]. This review article sheds light on pathophysiology, and assessment and focuses in particular on pain management in cancer patients with different modalities.

CLASSIFICATION OF PAIN

The Institute of Health Care Improvement classified pain into four types; inflammatory, neuropathic, muscle, and mechanical/compressive (**Table 1**). Neuropathic pain, defined as the pathological change in the nervous system, can then further be categorized as central or peripheral [9].

PATHOPHYSIOLOGY OF CANCER PAIN

The pathophysiology of the pain that is suffered by cancer patients is complex and is thought to be due to various mechanisms involved. These mechanisms are similar to the physiology of non-cancer pain and can be due to ischemia, inflammation, and compression at various sites. It is thought that many of them complain of severe neuropathic pains, which may be due to the ongoing compression, ischemia, and inflammation. In addition to the pain of their metastatic disease, they also suffer from treatment-related pains and procedural/surgical pains [10].

The pathophysiology is complicated because of the interaction between the cancer cells and peripheral and central nervous system.

Table 1: Types of pain and their causes.

Type of pain	Causes
Inflammatory Pain	Infection Postoperative pain Tissue injury
Neuropathic Pain	Central Neuropathic pain: Myelopathies Post-stroke pain Parkinson's Disease Peripheral Neuropathic Pain: Complex regional pain syndromes Phantom limb pain Metabolic diseases
Muscle Pain	Myofascial pain syndrome
Mechanical/Compressive Pain	Low back pain Visceral pain Neck pain

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Table 2: Syndromes associated with cancer treatment.

Acute	Chronic
Chemotherapy-induced headaches	Hormonal therapy-related pain syndromes
Diffuse bone pain	Radiation therapy-related pain syndromes
Myalgia and arthralgia	Chemotherapy-related pain syndrome
Steroid-induced perineal burning	Surgery-related pain syndrome

Nociceptive Pain

Invasion of skin, connective tissues, bones, and joints by the tumor cells can give rise to somatic or visceral pain which can be superficial or deep. The reason for the symptoms mentioned could be attributed to various factors caused by tumor invasion or compression, which affect the blood supply to organs, cause distension and contraction of hollow organs, put pressure on solid organ capsules, compress or stretch ligaments, vessels, or mesentery, lead to the release of inflammatory mediators due to tumor infiltration, affect neural structures supplying the organs, and cause stretching of serosal or mucosal surfaces. All of these factors can contribute to the clinical manifestations experienced by the patient [11-13].

Neuropathic Pain

Malignant invasion of the nervous system either sensory or peripheral can generate pain of this origin, and this usually presents as plexopathies. Radiation, chemotherapy, and surgery can all cause neuropathic pain as part of cancer treatment [11].

Cancer Pain Syndromes

Certain anticancer treatments are associated with pain syndromes, which can be acute in onset or chronic. Causes are listed in (Table 2) [11].

ASSESSMENT OF PAIN IN CANCER PATIENTS

The type of pain that the patient experiences is very important for providing adequate analgesia. The use of already validated classification systems helps clinicians to assess and classify pain syndromes and direct the tailored treatment modalities [14].

Van den *et al.* present in their study that 66% of the patients suffer cancer pain, however establishing the etiology is of prime importance [15]. The etiology is not always due to tumor burden. Pain due to treatment and other etiologies play a major role [16]. The patients can also have pain in more than one site due to various reasons such as primary tumor, bone metastasis, and compression effect [17].

There are several questionnaires such as LANSS, DN4, and pain DETECT which are used as screening tool for neuropathic cancer pain and has shown a correlation with clinical diagnosis [18]. A high level of pain due to the neuropathic component requires diagnostic evaluation since opioids alone are insufficient and must be combined with adjuvants like glucocorticoids, antidepressants, and anticonvulsants (Fig. 1) [19].

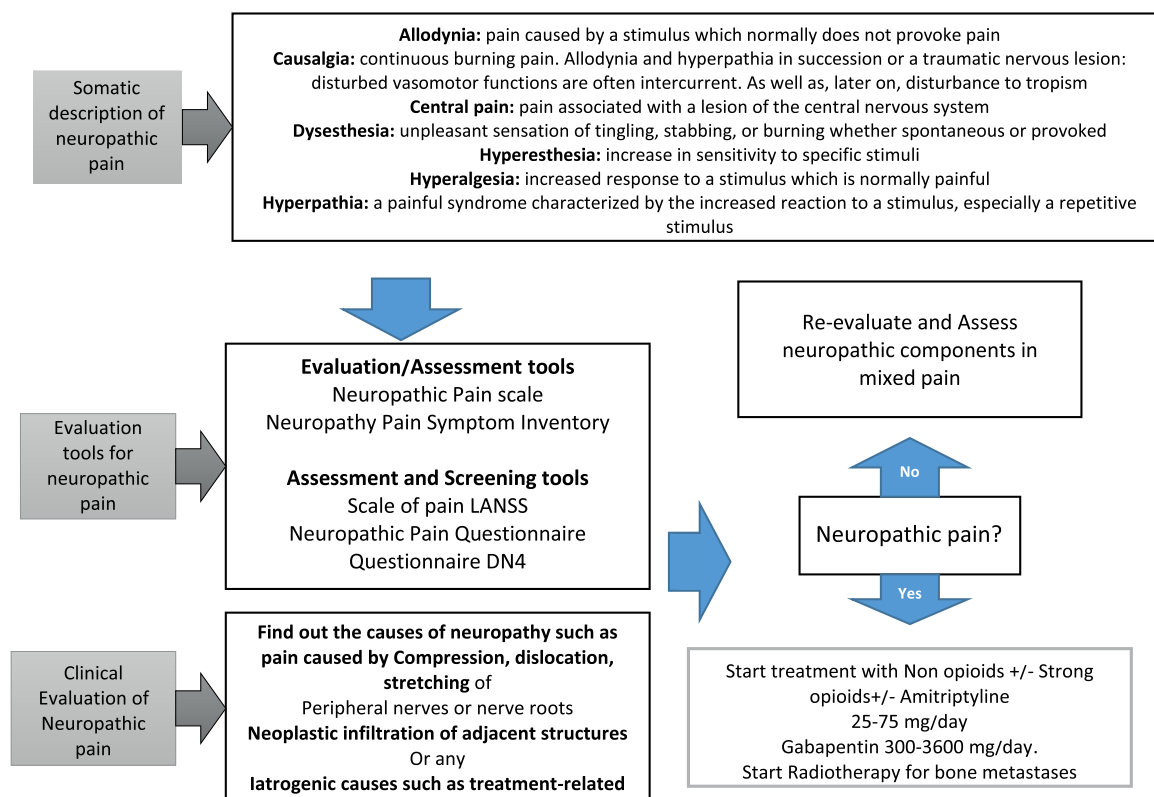
**Fig. (1):** Evaluation and management of neuropathic pain.

Table 3: Management.

Management	
Oncological	Radiotherapy
	Bisphosphonates
	Surgery
	Hormone therapy
Pharmacological	Analgesic
	Non-analgesic
Non-pharmacological	Hypnosis
	Distraction
	Acupuncture
	Tele-medication
	Psychosocial
Interventional	Somatic nerve blocks
	Epidural Injections
	Radiofrequency Ablation and Cryoneurolysis
	Chemical Neurolysis
	Neuromodulation
	Vertebral augmentation
	Intrathecal drug delivery devices
	Sympathetic blocks

An important aspect of assessing cancer pain is to determine its temporal variation. Opioids are used to manage the background pain of cancer patients, but breakthrough pain (which is a temporary onset of increased pain intensity) can be experienced by patients as well. The treatment of such BTP involves rapid short-acting opioids with rescue doses [20].

The complexity of cancer pain has led to the development of cancer pain classification systems such as ICD 11 and the Edmonton Classification System for Cancer Pain (ECS-CP). As part of the clinical workup for cancer patients, standardized approaches have been implemented to assess pain in a standardized manner,

and consider not only the type, but also the duration, as well as modifiable factors such as psychological distress, addictive behavior, and cognitive function [21, 22].

MANAGEMENT

The management of pain focuses on different aspects of management. Well-supported data includes oncological, pharmacological, non-pharmacological, and interventional techniques (**Table 3**).

Oncological Management

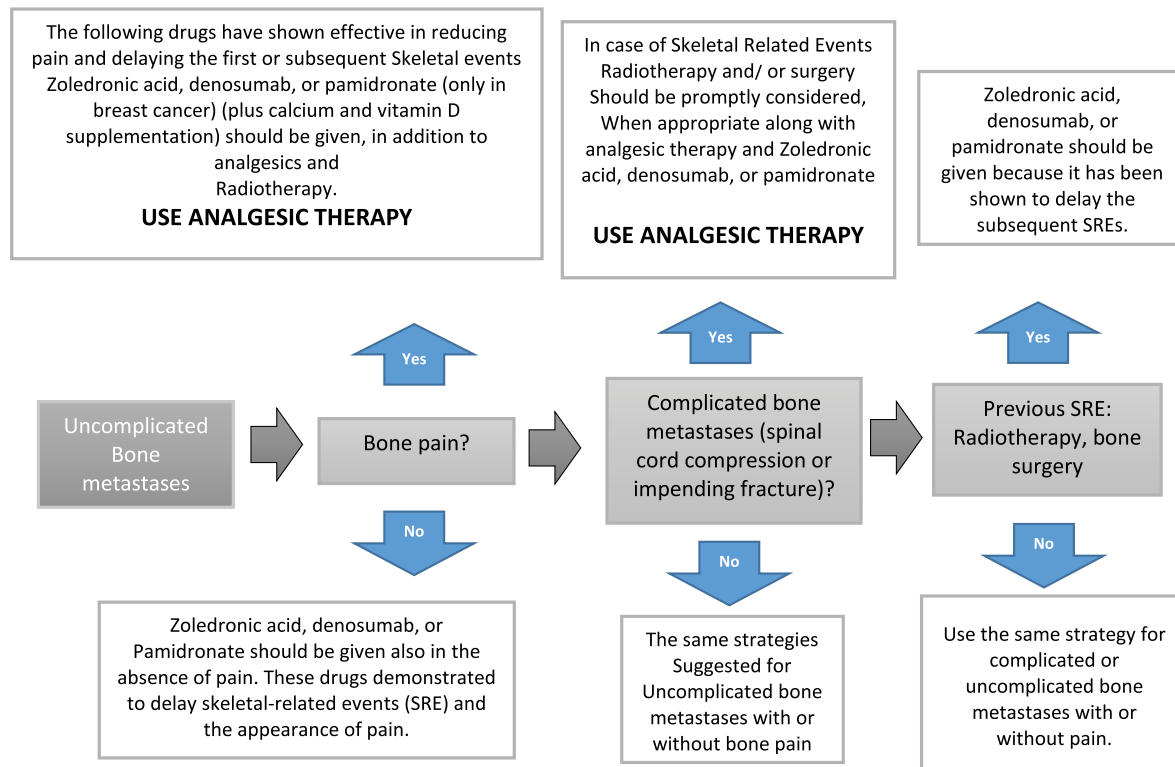
This encompasses four different modalities. The indications of these are listed below.

Radiotherapy

One of the most common indications of radiotherapy is cancer pain and its exacerbation. It is given as a first-line indication for tumor mass reduction, capsular liver, and spleen pain, or epidural metastasis. Management of bone metastases is the second most common indication and palliation of localized symptoms of pain [23]. Pathological fractures of inoperable sites and neurological complications including cord compression and nerve pain using different doses of radiotherapy are indicated [24]. RCTs have shown 60-80% of pain relief following radiotherapy [25].

Bisphosphonates

Cancer-induced bone pain or metastatic bone pain, is managed with different modalities (**Fig. 2**). Using radiotherapy for localized pain, chemotherapy, or hormone therapy for scattered pain. A Cochrane review showed evidence for the use of bisphosphonates

**Fig. (2):** Pain treatment option due to bone metastases.

where there is limited or inadequate relief of pain using analgesics or other oncological therapies [26].

Surgery

Surgical pain management for cancer patients can be very important and crucial. Internal fixation for pathological fractures, shunts for obstructive hydrocephalus in patients with CNS tumors suffering from headaches, debulking, stent placement in patients with dysphagia in cases of esophageal carcinomas, and drain placement in case of ascites can be very beneficial in mitigating cancer-related pain [10].

Hormone Therapy

One of the palliative methods of alleviating pain in patients with metastatic disease is hormone therapy. A response rate of around 90 % is observed by anti-androgen therapy in prostate cancers. Anti-estrogens and progesterone in breast cancer can be very helpful [10].

Pharmacological Management

The unpleasant sensation of pain which is experienced by almost all the patients suffering from this disease is very difficult to deal with, and a multimodal system is required to address this issue. This pain is usually constant and a well-managed strategy for its relief. The goal is to provide comfort and functionality. Various pharmacological agents have been used to provide good pain relief in these patients, and are considered as the mainstay of the treatment [27]. After a comprehensive assessment of the patient, a non-opioid analgesic should be started for those suffering from mild pain, with special attention given to preventing peptic ulcers. For those who have moderate to severe pain, an opioid analgesic must be started with treatment of its side effects as well. If the patient complains of continuous pain despite starting opioid analgesics, the dose of the opioids must be increased. For breakthrough pain (BTP) rescue drugs should be started and the treatment specific to the type of BTP should be given [28]. Precise pharmacological management is summarized in Table (4).

Analgesic Pharmacological Agents

The common analgesic pharmacological agents used were described in the WHO Ladder of Pain Management for Cancer Patients.

WHO Ladder

The World Health Organization (WHO) in 1986, issued a stepladder approach for the management of cancer pain

Table 4: Pharmacological Management.

Pharmacological Management	
Analgesic pharmacological agents	WHO ladder Non-opioid analgesic Opioid analgesic Adjuvants
Non-analgesic pharmacological agents	Relaxants Anticholinergic medications Calcium channel blockers Steroids

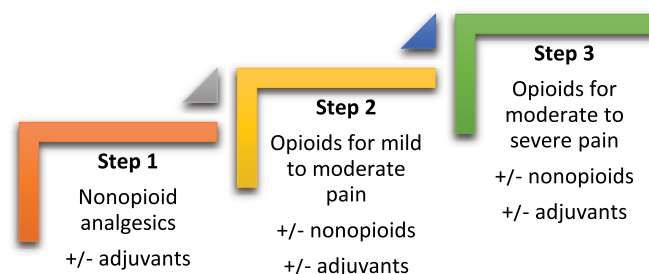


Fig. (3): WHO stepladder.

in patients. The ladder included 3 steps (**Fig. 3**). Step 1 is to provide the patient with a non-opioid analgesic which may be an NSAID, or acetylsalicylic acid to prevent the formation of prostanoids from arachidonic acid, the production of which is controlled by two separate cyclooxygenase systems (COX-1 and COX-2). The non-opioids are used with or without adjuvants. Step 2 is to provide the patient with an opioid analgesic with or without non-opioid analgesic and with or without adjuvants. The provision of strong opioids for severe pain with or without non-opioid analgesics and adjuvants comprises the third step of the ladder. The three steps lead to freedom from pain. WHO recommends the provision of analgesics by the clock approach that is every 3-6 hours, rather than on demand of the patient [10, 28]. Fallon *et al.* found that the two-ladder approach can be used as an alternative to the traditional 3 stepladder approach provided by the World Health Organization [29]. It remains a foundational treatment for chronic pain [30].

Non-Opioid Analgesics

Three widely used non-opioid analgesics aspirin, acetaminophen, and NSAIDs, are very effective in treating chronic pain and mitigating excessive use of opioids [31].

Non-steroidal anti-inflammatory drugs inhibit cyclooxygenase enzyme in turn leading to inhibition of prostaglandin synthesis. They are used for mild to moderate pain and for periodic flairs-ups, rather than for chronic use. Long-term use can lead to cardiovascular and renal complications. Moreover, it can cause gastritis and often GI bleeding and should be used with caution in patients with coagulopathies [9].

Acetaminophen, a selective COX-2 inhibitor, should be prescribed to patients with mild to moderate cancer pain. It has a potential for hepatotoxicity. Kylie *et al.* found that in hospitalized cancer patients acetaminophen provided no additional benefit to strong opioids [32].

Opioid Analgesics

Morphine along with other strong opioids is considered as gold standard in the treatment of cancer pains. It is available in oral, rectal, and parenteral routes. Its metabolites accumulate in renal diseases [28, 33].

Methadone is a long-acting opioid and is associated with arrhythmias. Metabolism is by the liver [33].

Fentanyl can be administered via rectal, intravenous, spinal, and subcutaneous routes, and is very effective in cases of acute pain [33].

Cannabis

Its use is cited most commonly for chronic pain. It is recommended to be used as an adjuvant in the treatment of refractory pain. However, it is associated with side effects such as hallucinations, hyperemesis, and addiction [34].

Adjuvants

Antidepressants including SSRIs, MAOIs, TCAs, and atypical antidepressants have been shown to have analgesic as well as anti-inflammatory effects in cancer patients [35].

Anticonvulsants like gabapentin, a third-generation anticonvulsant tend to alleviate neuropathic pain in combination with opioids [36].

NMDA receptor antagonists decrease the production of inflammatory mediators and block the uptake of serotonin, dopamine, and noradrenaline. In sub-anesthetic doses, it reverses pain crises and opioid-induced neurotoxicity. Thus, it's a very helpful adjunct to opioids for cancer pain management [37].

Beyond their anesthetic effects, local anesthetics also have effects as anticancer medications. The common use in pain relief is usually by local infiltration, peripheral nerve blocks, epidural block, spinal anesthesia, and intravenous administration [38].

Non-Analgesic Pharmacological Agents

Relaxants like baclofen and diazepam, anticholinergic medication, and calcium channel blockers can be used to treat and relieve spasms associated with cancer syndromes. Moreover, pain due to the involvement of the nervous system in cancer patients can be alleviated by the use of steroid medications [10, 39].

Non-Pharmacological Management

In recent years, non-pharmacological interventions have become increasingly common for the treatment of cancer pain, after modifications to pharmacological management. Several methods have been developed, but research is still lacking [40]. In this section, we will try to discuss some of these modalities.

1. Hypnosis: It is considered one the safest techniques when performed by an expert therapist. Its integration into the treatment regimen can provide the patient with pain relief and satisfaction [41].
2. Distraction: It has been found as a very promising psychological modality in treating pediatric oncological population [42].
3. Acupuncture: It is based on Chinese traditional medical methods, and is found to be effective along

with drug therapy in making the quality of life better without many side effects [43].

4. Tele-medication: It can be an aid in addressing the pain problems of these patients. It is a method of providing a service through telemedicine, which can help schedule follow-ups and possible readmissions to the hospital [44].
5. Psychosocial interventions: Music, writing, cognitive behavioral therapy, meaning enhancement, and others prove to be effective means of pain management in these patients [45].
6. Massage Therapy: Current literature supports the use of massage therapy which has shown improvement in cancer pain, physical well-being of patients, reduced anxiety and depression with better effects on fatigue [46].

Interventional Management

Somatic Nerve Blocks

Targeting peripheral nerve for blocks using different agents is recommended when advanced cancers causing pain are not controlled using pharmacologic agents. These peripheral nerve blocks are most commonly done for head and neck cancers, and lung and breast cancers. The site of the tumour determines the type of nerve to be blocked. Studies have shown that trigeminal and facial nerves are the most commonly affected. They are blocked alone or in combination with sphenopalatine block for tumour invasion. The trigeminal nerve is blocked for Cerebropontine angle tumor, glossopharyngeal nerve is blocked for alleviating pain in oropharyngeal cancer. For the metastatic disease of the ribs and chest wall, Intercostal neurolysis is indicated [47, 48].

Epidural Injections

Epidural injections for intractable cancer pain are an acceptable method and are very much practiced throughout the world. Single opioids can be used in epidural injections by using morphine, fentanyl, and butorphanol with morphine having long lasting duration of action [49]. Epidural injections with local anesthetic have superior analgesic effects than single steroid injections [50]. Epidural injections have excellent pain relief in thoracic and abdominal cancers [50].

Radiofrequency Ablation and Cryoneurolysis

Other less invasive neuro-destructive techniques *i.e.*, ablation (RFA) and cryoneurolysis, that has been used safely for cancer pain control. In this technique, the block can be done at various levels including nerve roots, ganglia, or the nerve itself. It is effective for the treatment of multiple pain syndromes, trigeminal neuralgia, and chronic segmental thoracic pain. RFA also spares the use of opioid requirements [51]. Cryoneurolysis, in which extremes of temperature are applied to a nerve to temporarily disrupt the neuronal pain pathways is also used in the event of failure of conservative treatment

in chronic pain conditions [52]. Compared to other modalities, RFA provides effective and long-term pain relief [53].

Chemical Neurolysis

Chemical neurolysis is common in cancer pain management. Target sites for chemical neurolysis may include Intrathecal injections, superior hypogastric plexus, celiac plexus, lumbar sympathetic chain, ganglion impar, and peripheral nerves, and can be used for muscle spasm. Common agents used for chemical neurolysis include ethanol 50–100% and phenol 5–10% [54]. In certain cancers pain may become refractory to increasing doses of opioids, chemical neurolysis is the best option at this stage [55].

Neuromodulation

Neuromodulation is a recent emerging technique in which the central, peripheral, or autonomic nervous system is stimulated, inhibited, or modified either chemically or electrically. Various types have been defined such as Peripheral neuromodulation which involves the electrostimulation of peripheral nerves for chronic pain [56, 57]. Its use is limited due to multiple factors such as lack of specific healthcare providers and technical support. Its availability and acceptability in patients still need to be discussed [58].

Other invasive types include Intrathecal pumps and spinal cord stimulation which also have a good effect on the quality of life of patients, particularly for those who have locally advanced disease and life expectancy is decreased [59].

Vertebral Augmentation

Metastatic bone pain is the most common complication of end-stage cancer. Patients with spinal metastasis require palliative care in which percutaneous vertebral augmentation has an extraordinary role in managing cancer pain [60]. Spine metastasis has multiple complications which include sensory, motor deficits, and spinal cord compressions which compromise a patient's physical and mental health, kyphoplasty and vertebroplasty are the most common forms of vertebral augmentation. Researchers have found that there is a significant improvement in quality of life and disability after vertebral augmentation [61].

Intrathecal Drug Delivery Devices

Intrathecal drug delivery devices are also a method of pain relief in cancer as well as non-cancer pain management. The implanted intrathecal morphine pump is useful for patients who are already on oral or systematic opioids and pain is still the basic concern in such patients, but these patients with morphine implants come across opioid-induced complications with higher intrathecal morphine use such as urinary retention, nausea and vomiting [62]. Dexamethasone can be used in addition to opioids and local anesthetic in these pumps to reduce the refractory pain and depression in cancer patients,

this improves the pain scale of patients and reduces the side effects of high doses of opioids [63].

Sympathetic Blocks

Cervicothoracic (Stellate Ganglion Block)

The stellate ganglion block is the sympathetic block of the cervicothoracic ganglion for pain relief of the face, neck, arm, and chest. Head and neck cancer pain is difficult to treat with oral or IV analgesics from different categories. Patients experience shooting pricking type of pain and high grading on different pain scores, stellate ganglion improves pain in such patients [64]. Stellate ganglion block is not only effective in cancer pain but also helps in complex regional pain syndromes, vascular headaches, cardiac arrhythmias, and post-herpetic neuralgias [65]. It has also been observed that it is very effective in post-mastectomy pain syndrome patients, which has been observed in more than 40% of the patients. Multiple adjuncts can be used along with local anesthetics to increase the duration of pain relief in such patients [66]. Ultrasound and fluoroscopic guided blocks are safe methods for stellate ganglion but it has been observed that more accurate and effective drug delivery has been observed in ultrasound-guided blocks [67].

Thoracic Sympathetic Blocks

Indications for thoracic sympathetic blocks are the same as those of stellate ganglion blocks, they cover the pain related to the upper limb, chest wall, and sympathetically mediated pain which can be due to complex regional pain syndrome or cancer-mediated pain [68]. The thoracic sympathetic block is also effective in post-mastectomy pain syndromes as compared to the stellate ganglion block (SGB) because SGB interrupts the sympathetic supply to the upper extremity [69].

Splanchnic and Celiac Plexus Block

These blocks are indicated in abdominal cancers which include the esophagus, stomach, small and large intestine, liver, gall bladder, kidney, and adrenals. Pain experienced in abdominal cancers or metastases can be very severe and intolerable with the conventional analgesic therapies in such patients splanchnic and celiac plexus block are the best option. Pain relief through celiac plexus block is sometimes difficult and ineffective due to the tumor invasion itself or lymphadenopathy, in such cases, splanchnic nerve block can give better results and analgesia [70]. It has been observed that splanchnic block is very effective in unresectable pancreatic (stage 4) patients, in such opioids side effects are intolerable at such stage and they benefit from these blocks [71].

Lumbar Sympathetic Block

Lumbar sympathetic block has been utilized for tumour-related lumbosacral neuropathy, post-radiation plexopathy, and tumor related bladder spasm. The role of such a block is limited in literature for pain related to malignancies but improvement has been observed in a

few patients with bladder spasms. It has been indicated in patients who have a shorter life expectancy and any contraindication for intrathecal drug delivery devices these sympathetic blocks are useful, they will decrease the abdomen pelvic, and cancer-related leg and back pain [72].

CONCLUSION

Cancer pain is a complex process that first involves focusing on pathophysiology, assessing the type of pain, and a stepwise approach to its management. Various options are available owing to the nature of the pain that a patient suffers. As the incidence of cancer pain is quite high, the treating physician must be competent enough to diagnose early and manage or refer properly. The palliative care physician should have thorough knowledge and skills about treatment options from non-pharmacological to pharmacological and interventional procedures. Early and appropriate application of treatment modality is necessary to avoid unwanted effects of chronic cancer pain.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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