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Cancer Pain

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Abstract

In 1986, the World Health Organization (WHO) has published a document entitled “A Declaration of the Rights of Patients with Chronic Cancer,” which says that according to the WHO, three-step analgesic ladder pain relief should be adequate for 70–90% of patients. However, despite increased attention on assessment and management, pain continues to be a prevalent symptom for patients with cancer. That is why refreshment of knowledge in cancer pain is necessary for every active practitioner. Broad overview of current understanding in cancer pain is presented in the chapter. Cancer pain syndromes are analyzed in between acute or chronic, and in among various causes occurred. Cancer pain assessment was presented with challenges meeting clinical practitioners. For cancer pain treatment, principles of multimodal approach are used. The pharmaceutical treatment presented in detail included rational use of opioids. Big attention is paid on palliative care of cancer pain patients and hospice-based palliative care model is presented too. New technologies of breakthrough cancer pain management are disclosed in detail including special questionnaire for patients. Cancer survivors’ pain treatment and general practitioner’s role among cancer pain problems are new topics presented in the chapter.

Keywords: cancer pain syndromes, assessment and treatment principles, multimodal approach, basic and breakthrough cancer pains, palliative care

1. Introduction

Cancer is diagnosed for more than 10 million people worldwide each year, and the illness of a malignant tumor is often associated with pain. The consequences of unrelieved cancer pain are devastating [1]. During the established diagnosis of cancer, the pain is present for 40% of tumor patients. The number increases up to 75–80% with the disease spread. About 4 million people in the world each day suffer from pain that comes due to oncological diseases, meaning that almost half of them do not receive proper treatment, and one-third live in severe or unbearable pain [2].

Despite increased attention on assessment and management, pain continues to be a prevalent symptom in patients with cancer. With reference to types of cancer, lower pain prevalence rates were demonstrated in prostate cancer compared to head and neck, lung, and breast cancer. Higher prevalence rates were seen in studies from Asia compared to Europe, in studies that used point or week prevalence rates compared to recall periods of a month or year [3].

Over the past few decades, we succeeded a better understanding of mechanisms underlying cancer pain, new developments achieved in pharmacologic cancer pain management, and increase in global opioid consumption becoming evident. Nevertheless, one-third of the patients worldwide still did not receive pain

medication proportional to their pain intensity levels [4]. Data from Asia and North America revealed comparable prevalence rates, which imply that opioid availability alone is not an explanation for the high prevalence rates [3]. Even after implementation into clinical practice of rapid release opioids (ROOs), which provide faster relief than immediate-release preparations of other opioids, the prevalence of breakthrough pain is still 59% [5]. All these mean the importance of skilled use of opioid analgesics in the relief of cancer pain but also acknowledge the lack of evidence to support clinical practice and guidelines, which in turn causes recommendations in practice guidelines to be based on expert consensus.

In 1986, the World Health Organization (WHO) has published a document entitled “A Declaration of the Rights of Patients with Chronic Cancer.” According to the WHO three-step analgesic ladder, in combination with appropriate dosage guidelines, pain relief should be adequate for 70–90% of patients. A systematic review on pain relief based on the WHO ladder, 20 years after its introduction, demonstrated adequate pain relief in 45–100% of patients [6, 7]. Among subjects of debates to improve the analgesic ladder the benefit of paracetamol (acetaminophen) with Step III opioids for which the evidence is “weak if any,” as well as the use of adjuvant analgesics for which outcomes are generally modest [8]. On the other hand, not only drugs are a guarantee of success in the cancer pain. It is widely accepted that a biopsychosocial approach in assessment and management is needed for treatment of pain in patients with cancer. Cicely Saunders elaborated on the concept of “total pain,” stating that pain is not purely a physical experience but involves various other components of human functioning including personality, mood, behavior, and social relations. A systematic review has identified an association between psychological distress, lack of social support, and cancer pain [9].

Different barriers have been acknowledged in relation to adequate pain management in patients with cancer. One of the most important reasons is lack of knowledge regarding the assessment and management of cancer pain. Health professionals are cautious when prescribing opioids because of fear of adverse effects, tolerance, and addiction. Otherwise, patients struggle with misconceptions about analgesic use, concerns about pain communication, and a belief that pain is inevitable and uncontrollable [10]. All reasons for the lack of adequate pain control are varied: (a) personal—fear of drug addiction, (b) legal issues by issuing a higher dose of these medicines, (c) material—with regard to the price and quantity of medicinal products, (d) organizational—regular supply and storage of medicines, (e) psychological—the conviction of the patient or his family members that narcotic analgesics can be used only in the last stages of the illness, (f) causes of medical staff in the absence of sufficient knowledge of analgesia and the principles for its administration, and (g) poor adherence to pain medication and poor pain relief, which appear to be more country-specific problems [11].

2. Cancer pain syndromes

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain is always subjective [the International Association for the Study of Pain (IASP)]. Cancer-induced pain may be acute or chronic. Cancer-induced pain may be nociceptive or neuropathic or psychogenic, but often it is mixed because there are several causes causing it to occur. The main (basic) is constant pain of controlled intensity. A breakthrough pain occurs when a basic pain is controlled. Breakthrough pain is a

temporary exacerbation with high intensity pain, which is felt in patients whose basic pain was adequately treated with opioids [12].

Cancer pain is not a single entity. It incorporates a range of etiological, pathophysiological, and anatomical subtypes, all requiring unique descriptive terminology, assessment techniques, and treatment modalities [13]. Among patients with cancer, there is substantial heterogeneity in how pain is experienced and in how it appears. In many cases, the constellation of symptoms and signs can suggest a specific cancer pain syndrome [14]. The identification of such a syndrome may help to elucidate the etiology of the pain, direct the diagnostic evaluation, clarify the prognosis for the pain or the disease itself, and guide therapeutic intervention.

2.1 Acute pain syndromes

Most acute cancer pain syndromes are primary as related to a diagnostic test or treatment. However, some are secondary as they are disease related, such as pain due to acute hemorrhage into a tumor, bone pain from a pathologic fracture, etc. Although some tumor-related pains have an acute onset (as after pathological fracture), most of these will persist unless effective treatment for the underlying lesion is provided. Generally, acute cancer pain syndromes are divided: (1) directly related to cancer, (2) cancer diagnostics related, and (3) associated with antineoplastic treatments.

A clinical picture of directly related to various cancer syndromes depends on cancer's etiology, location, surrounding tissues involved, growing speed, and other factors. Cancer-diagnostic-related syndromes also have miscellaneous presentation and can be presented as: (a) headache after lumbar puncture, (b) prostate pain after biopsy, (c) breast pain after mammography; (d) pain after any other intervention, and some others. Acute pain associated with antineoplastic treatments can be presented as: (a) pain related to chemotherapy and (b) pain after radiotherapy [15].

Related to chemotherapy pain has various causes depending on an agent used, a method of inclusion into organism, etc. Most typical are intravenous infusion pain (due to venous spasm, chemical phlebitis, vesicant extravasation, and anthracycline-associated flare), intraperitoneal chemotherapy pain (chemical serositis or infection), mucositis (due to cytotoxicity of cytarabine, doxorubicin, methotrexate, and others), painful peripheral neuropathy (toxicity associated with vinca alkaloids, cisplatin, oxaliplatin, and paclitaxel), headache (after intrathecal methotrexate), myalgias/arthralgias interferon induced, and others. Pain after radiotherapy can be incident pain precipitated by transport and positioning of the patient for radiotherapy, or it can be caused by acute radiation toxicity. Most typical are: oropharyngeal mucositis, early-onset brachial plexopathy, subacute radiation myelopathy, radiation enteritis and proctitis, and others. Some more acute cancer pain syndromes can be related to infection (herpes zoster) or venous thrombotic events.

2.2 Chronic pain syndromes

Chronic cancer pain syndromes usually are directly related to the neoplasm itself or to an antineoplastic therapy. The classification is presented in **Table 1** [16].

Bone metastases are the most common cause of chronic pain in cancer patients. Bone pain should be differentiated from non-neoplastic causes including osteoporotic fractures (such as associated with multiple myeloma), focal osteonecrosis (due to chemotherapy or corticosteroids, or radiotherapy), and osteomalacia. Vertebrae are the most common sites of bony metastases pain. Typical locations are atlantoaxial destruction and odontoid fracture, C7–T1 syndrome, and T12–L1 (thoracolumbar junction) syndrome. Epidural compression of the spinal cord or cauda equina is a common neurologic complication

Chronic cancer pain syndromes	Clinical presentation
Tumor-related somatic pain syndromes	Multifocal bone pain
	Soft tissue pain
Tumor-related visceral pain syndromes	
Tumor-related neuropathic pain	Leptomeningeal metastases
	Cranial neuralgias
	Radiculopathies
	Plexopathies
	Peripheral mononeuropathies
	Paraneoplastic syndromes
Headache	
Pain related to antineoplastic treatments	Chemotherapy-related neuropathy
	Bone complications and glucocorticoids
	Antiandrogens and gynecomastia
Postsurgical pain syndromes	Pain and phantom sensation after amputation
Postradiation pain syndromes	Plexopathies
	Myelopathy
	GI tract disorders
	Lymphedema
	Osteonecrosis

Table 1.
The classification of cancer chronic pain syndromes.

of cancer. Breast, lung, and prostate cancers each account for 20–25% of events [17]. And back pain is the initial symptom in almost all patients with epidural compression. The pelvis and hip are also common sites of metastatic involvement. Lesions may involve any of the three anatomic regions of the pelvis (ischiopubic, iliosacral, or periacetabular), the hip joint itself, or the proximal femur [18]. Leptomeningeal metastases, which are characterized by diffuse or multifocal involvement of the subarachnoid space by metastatic tumor, occur in 1–8% in patients with systemic cancer [19]. The most common presenting symptoms are headache, cranial nerve palsies, and radicular pain in the low back and buttocks. Gadolinium-enhanced MRI imaging of the neuroaxis is the investigation of choice when leptomeningeal metastases are suspected. Base of skull metastases can be presented with various syndromes: orbital syndrome, parasellar syndrome, middle cranial fossa syndrome, jugular foramen syndrome, trigeminal neuralgia, and others. Neuropathic pains can be presented as painful radiculopathy, postherpetic neuralgia, malignant brachial plexopathy (lymphoma, breast, lung cancers). Brachial plexopathy also is typical for radiation-induced syndromes. Radiation changes in the skin and lymphoedema are commonly associated. Malignant lumbosacral plexopathy is most frequently associated with colorectal, cervical, breast cancers, sarcoma, and lymphoma [20]. Paraneoplastic painful peripheral neuropathy can be related to injury to the dorsal root ganglion (also known as subacute sensory neuronopathy or ganglionopathy) or injury to peripheral nerves [21]. Subacute sensory neuronopathy is usually associated with small cell carcinoma of the lung. Even in the absence

of involvement of the chest wall or parietal pleura, lung tumors can produce a visceral pain syndrome, being unilateral or bilateral (less common).

Most treatment-related pains are caused by tissue-damaging procedures. Chronic-treatment-related pain syndromes are associated with either a persistent nociceptive complication of an invasive treatment (such as a postsurgical abscess), or more commonly, neural injury. Toxic peripheral neuropathy, avascular (aseptic) necrosis of femoral, or humeral head are among most common treatment-related chronic cancer pain syndromes. Breast surgery pain syndromes are very prevalent, too. Chronic neuropathic pain of variable severity is common for those patients, and severity of pain is correlated positively with the number of lymph nodes removed [22] both with tumor location (upper outer quadrant of the breast).

3. Cancer pain assessment

Despite significant medical, pharmacological, and technological advances in the area of cancer pain assessment and management, up to 90% of patients with advanced cancer experience pain [23], which means careful pain assessment is essential for successful pain management. Cancer pain assessment is a complex undertaking. The evaluation begins with a thorough history of both the pain and the underlying malignancy as well as its treatment. A localization and intensity of pain have to be analyzed in detail, constantly indicating it in the diary. After initial treatment, the effect of treatment pain intensity is to be re-evaluated. Because of the potential impact of pain on quality of life, it is also essential to determine the adverse effects of pain on physical and psychosocial well-being, as well as the spiritual impact of the pain. Also, it is important to remember that cancer pain may linger after the cancer is removed (as examples, postmastectomy, postamputation, or postthoracotomy syndrome), and this may have important psychological and spiritual impact. Other factors that may influence the pain experience should be overestimated and discussed with the patient and his family.

Current recommendations advise that pain severity should be assessed on an 11-point numerical rating scale (NRS) (0–10), with more comprehensive tools including the Brief Pain Inventory (BPI) and McGill Short Form Questionnaire reserved for occasions when more detailed assessment is required [24, 25]. Newer tools including the Alberta Breakthrough Pain Assessment Tool, specifically designed for breakthrough pain, also could be used in the clinical trial setting [26].

3.1 Pain measurement scales

Numerical rating scale (NRS)—the intensity of pain is measured by asking the patient to select a number from 0 to 10 that describes the intensity of his pain: “0” means “no pain” and “10” means “unbearable pain.” The numbers are arranged in one line. This method is easily understood by many patients, eliminates linguistic and cultural barriers between the investigator and patient, and is most often recommended for pain assessment. The lingual version of NRS can be easily adapted to ill patients who cannot write. In Verbal Rating Scale (VRS), patients are asked to choose the word best suited to describe their pain: no pain, mild pain, moderate pain, severe pain, and unbearable pain.

In Faces pain scale (FPS), five smileys are given, starting from a smiley face to the left (no pain) to a sad, and crying right (“unbearable pain”) (**Figure 1**). The patient points out the smile that most reflects the pain. The researcher compares the chosen smile with the expression of the patient’s face.

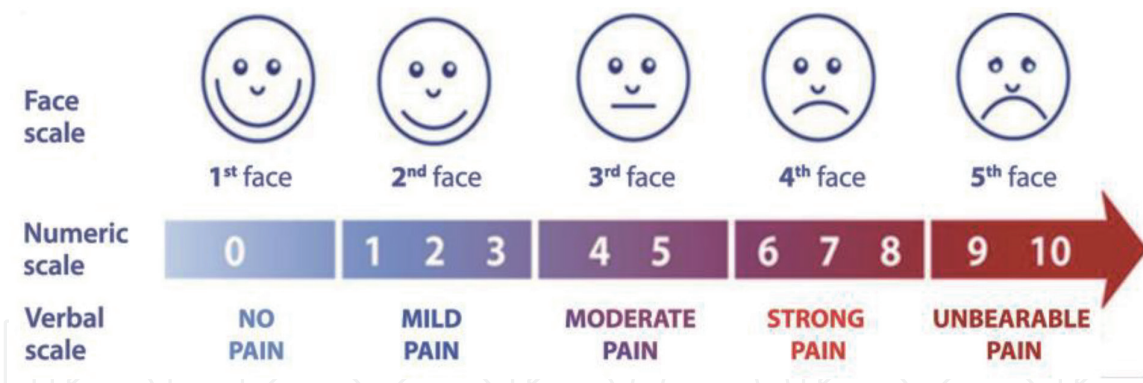


Figure 1. Lithuanian pain scales (Decree of the Lithuanian MOH V-608, 26-08-2004 [27], English version).

These three pain scales (NRS, VRS, and FPS) are useful clinical tools to assess pain intensity if they are integrated in **Table 1**, which allows a comparative assessment of the patient's pain intensity [27].

In Visual analogue scale (VAS), patients are asked to pinpoint their pain in the 10 cm section (in the straight line) as accurately as possible. The end of the left line indicates "no pain" and the right is "unbearable pain." The method is widely used in scientific research, but not all patient groups are easy to understand.

Inferred pathophysiology or types of cancer pain (nociceptive/neuropathic) are also core in diagnostics, that is why neurological somatosensory examination using specific sensory stimuli tools (von Frey filament, brush, pin prick, hot/cold water tubes, tuning fork) is essential.

In diagnosing a breakthrough in cancer pain, first is necessary to ask the patient to describe his/her baseline pain over 24 hours, including description of location, intensity, quality, and other features. If continuous pain has fluctuations and breakthrough pain suspected, it is necessary to ask the patient how many different types of breakthrough pains the patient experiences in a 24 hour period following pain variables: location, provocation, quality, etiology, etc. Finally, asking the patient about three most bothersome breakthrough pains allows us to determine what is a breakthrough pain really wearying the patient. Breakthrough pain intensity should be rated by NPS and filled in the pain diary. It also have to be investigated in detail including such characteristics as localization, number of episodes, possible irritant, beginning of pain outbreak, strength, quality, distribution, effectiveness of the medication used. It is also important to evaluate other symptoms of the patient's pain breakthrough: psychological stress, spiritual suffering, craving for chemicals and medications, and cognitive function.

To conclude the evaluation of cancer pain, it is necessary to agree with the patient what the aim of the intended treatment is, what is the analgesia (score from...to), and what pain intensity is tolerated.

3.2 Challenges in cancer pain assessment

There are a number of significant challenges associated with the precise assessment of a cancer patients' pain [28]. They include: (1) multiple cancer pain mechanisms, patients often have multiple coexisting pain disorders even in the one cancer as the example of breast cancer, pain can be caused by surgical outcome, tumor spread, chemotherapy and bony metastases to the spine, (2) lack of a universal cancer pain classification system, (3) lack of objective testing modalities, (4) time constraints of staff that failing in continuous reassessment of pain as this is a vital sign to be fully controlled, and (5) individual differences in cancer pain sensitivity.

The National Cancer Institute (NIH, USA) has funded a Patient Reported Outcome Measurement System (PROMIS). This aims to develop a widely available set of standardized instruments to measure subjective outcomes in illnesses, including cancer [29].

4. Cancer pain treatment principles

Adequate pain relief can be achieved in 70–90% of patients when well-accepted treatment guidelines for cancer pain are followed (World Health Organization [30]). Therefore, pain management techniques should be implemented as early as possible to prevent the development of persistent pain, which can lead to a significant reduction in quality of life. Unfortunately, the availability of effective therapy and updated guidelines from reliable leading societies has not eliminated the problem of undertreatment of cancer pain [3]. The causes of undertreatment are multifactorial and reflect the combined effects of clinician-, patient-, and system-related barriers as been provided in this chapter previously (p.2, Introduction).

Methods of pain control in cancer pain can be divided into: (a) pharmacological, (b) oncological, (c) surgical, (d) interventional, (e) psychological, (f) physiotherapy, and (g) complementary.

Medications are mainstream in the treatment of cancer pain and taken on a regular basis to provide pain relief. They are mostly given by oral administration as this increases ease of use and is usually the most cost-effective solution. Other forms of pain relief medication may be required in some cases, including rectal suppositories, transdermal patches, or injections.

The WHO analgesic ladder provides a structured starting point for the pharmacological treatment of the patient with cancer pain. It is not without controversy, however, some authors questioning the need to start all patients with severe pain on the bottom rung (i.e., managing with paracetamol alone rather than proceeding directly to stronger drugs). Some also have suggested that the second step (weak opioids) should be omitted in favor of low-dose strong opioids for the sake of both clinical effectiveness and simplicity [31]. For mild to moderate cancer pain, simple analgesic medications such as paracetamol or nonsteroidal anti-inflammatory medications (e.g., ibuprofen or aspirin) can usually provide effective pain relief. Nevertheless, opioid analgesics are mainstream in treating the cancer pain as in most cases it is severe or even unbearable [32]. Some important rules must be followed before starting with the prescription with opioids. Careful assessment of the pain and its effect on function, and of the possible risks associated with use of an opioid, are the first step. When opioids are considered, providers should assess every patient for risk factors for addiction. Providers should also employ strategies to reduce the risk of misuse for all patients who are taking opioids. These strategies may include urine testing, checking state prescription drug monitoring programs to evaluate a person's history of filling prescriptions for controlled substances, doing pill counts, and using patient-provider agreements or contracts.

Long-acting opioids may be administered orally or can be given in the form of a transdermal patch. Long-acting opioids are usually started at an initial low dose and titrated upward every 2–3 days for oral formulations and 5–6 days for patches. Short-acting opioid preparations may be used to treat breakthrough pain. One-sixth of the daily opioid requirement is commonly prescribed, and is often a useful starting point. Well-documented side-effects of opioid therapy include sedation, constipation, confusion, nausea and vomiting, pruritus, urinary retention, and occasionally, respiratory depression is necessary. Chronic administration

may lead to problems such as tolerance, physical dependence, and addiction. It must be noticed that by case, opioids may worsen pain—a phenomenon known as opioid-induced hyperalgesia. Management principles of side effects include: (a) opioid reduction or cessation, (b) opioid rotation, where one therapeutic opioid is substituted for an equivalent dose of another, (c) symptomatic treatment, and (d) administration of a specific antagonist.

Another group of pharmaceuticals used for the treatment of cancer pain is adjuvants (**Table 1**). Common adjuvants are antidepressants, anticonvulsants, bisphosphonates, and others [33]. An adjustment of adjuvants to the treatment plan of cancer pain is typical if the pain has a neuropathic element or is wholly neuropathic. In such cases, antidepressants and anticonvulsants may be more effective in providing balanced analgesia and better tolerance than the high doses of opioids. Bisphosphonates are helpful in reducing the severity of bone pain secondary to both osteoporotic vertebral collapse and metastatic deposit. They are incorporated into the structure of mineralized bone as pyrophosphate analogues, to be then taken up by active osteoclasts, which are then inhibited. High-dose steroids can be given to reduce inflammation and edema associated with tumor growth, and to partially mitigate local mass effect. Capsular distension of intra-abdominal visceral can be very painful, and steroids may be helpful in this situation. They are also used for the immediate management of metastatic spinal cord compression and in the palliation of intracerebral lesions.

Chemotherapy, radiotherapy, endocrinotherapy, and immunotherapy are oncological methods used for cancer pain relief. Chemosensitive tumors include small-cell lung carcinoma, myeloma, colorectal, and breast cancers. These drugs are designed to target rapidly dividing cells, but can lead to the well-known side-effects of hair loss, mucositis, and diarrhea. Also, many chemotherapeutic agents are neurotoxic and cause varying degrees of temporary and permanent nerve damage, resulting in peripheral neuropathy.

Radiotherapy is particularly useful in the treatment of bony metastases and nonoperable pathological fractures, but may be used in various other contexts where the tumor type is known to be radiosensitive. Several types of radiotherapy exist: (a) localized external beam radiotherapy, (b) wide-field external beam radiotherapy, (c) brachytherapy, and (d) radioisotope treatment. Certain types of tumor may be dependent on circulating hormones to affect growth, and therefore susceptible to manipulation of the endocrine system, for example, prostate cancer. The use of immunotherapy in cancer treatment has shown to improve survival even in some advanced cancers, such as breast tumor.

Surgery can be undertaken with curative or palliative intent. If a cancerous tumor is responsible for causing the pain, techniques to reduce the size or obstruction of the tumor offer the greatest benefit. This may involve surgical removal of the tumor or shrinking of the tumor with radiation therapy. Neurosurgery to cut or block the nerves involved in the pain pathways can also help to reduce severe neuropathic pain. Bone fixation may be necessary to palliate a pathological fracture or decompress the spinal cord.

The aim of interventional cancer pain management is to interrupt nociceptive transmission at one or more points between periphery and cortex to achieve adequate analgesia. This can be achieved via reversible, nondestructive techniques for diagnostic purposes and short-term analgesia, or offer a longer-lasting solution via the physical or chemical destruction of the nervous tissue.

The diagnosis of a life-threatening illness has a huge psychological impact on patients and their families. Grief reactions, anxiety, and depression are particularly problematic at nodal points in the cancer pathway: at diagnosis, starting treatment, recurrence, failure of treatment, and facing the prospect of dying. Such

psychological states exacerbate, and also are exacerbated by, uncontrolled pain, and addressing them is often of paramount importance in beginning to manage pain and improve the quality of life. Multidisciplinary input, with the use of evidence-based interventions such as cognitive behavioral therapy, distraction and relaxation techniques, graded exercise, and goal setting can be delivered with the involvement of psychologists, physiotherapists, and occupational therapists.

There are some complimentary medicinal techniques that can be used as additional complex in the treatment of cancer pain. These include: (a) acupuncture, which can help to relieve pain through the manipulation of pressure points in the body, (b) biofeedback is a technique that promotes awareness of bodily processes such as heart rate and blood pressure to influence the severity of the pain, (c) distraction techniques such as music therapy can be useful to shift attention away from the pain to a more pleasant stimulus, (d) hot or cold packs can be helpful to regulate pain and provide relief, (e) hypnosis can be used to manage pain by focusing the patient's consciousness to process pain information more effectively, and (f) relaxation exercises can be used to refocus the attention of the patient on a specific task, such as breathing, to lessen the pain.

In general, an effective strategy for cancer pain management is predicated on several broad principles [34]:

- A detailed assessment of the pain should be performed initially; careful reassessment is indicated whenever a change occurs. The initial assessment of the patient with cancer pain always includes a history and examination, and often requires imaging or laboratory tests. The approach may be conceptualized as collecting data are sufficient to characterize key elements of the pain (a specific pain syndrome, the inferred pathophysiology, the etiology of pain, etc.).
- The second principle recognizes that pain may be addressed by disease-modifying antineoplastic therapy and other interventions directed against the etiology of the pain. Treatments that address the underlying etiology of pain, such as radiation therapy, surgery, or in some cases, chemotherapy can be integrated into a broader plan of care for symptom control. Treatment of cancer-related pain usually requires close consultation with an oncology specialist, who can provide the necessary information about the availability of antineoplastic therapy.
- Whether or not primary disease-modifying therapy is possible, a large proportion of patients with pain due to active cancer require symptomatic treatment. Beginning in the early 1980s, a worldwide consensus has evolved that considers opioid-based pharmacotherapy as the mainstay approach for the symptomatic treatment of cancer patients with active disease and pain that is moderate to severe. This conclusion was originally codified in the World Health Organization's (WHO) "analgesic ladder" approach, which was originally published in the mid-1980s and has had a global influence on clinical practice and policies pertaining to medication availability.

5. WHO analgesic ladder in twenty-first century

In 1986, the World Health Organization (WHO) declared cancer pain management algorithm, so called three-step analgesic ladder (**Figure 2**) [35].

Cancer Pain Management- 3step WHO analgesic "ladder" (WHO)

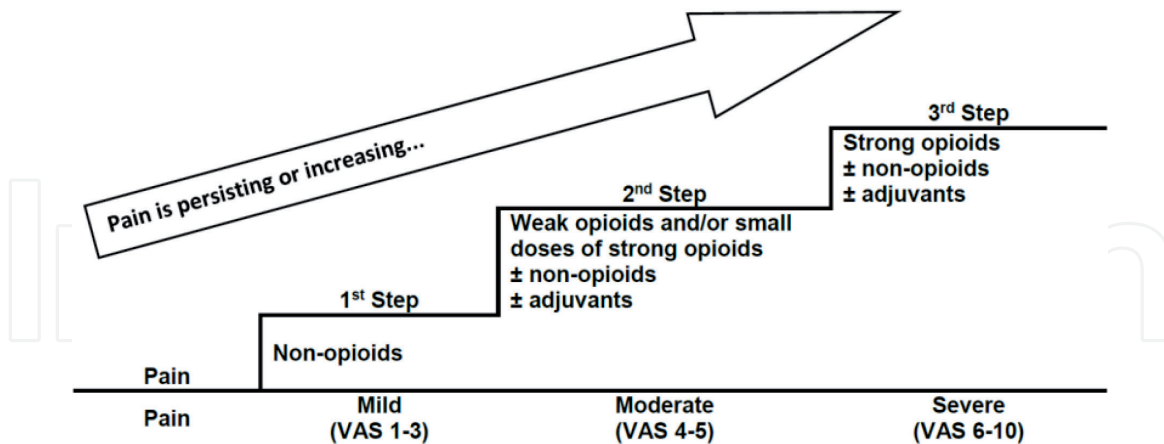


Figure 2. Cancer pain management—three step WHO analgesic "ladder" [35].

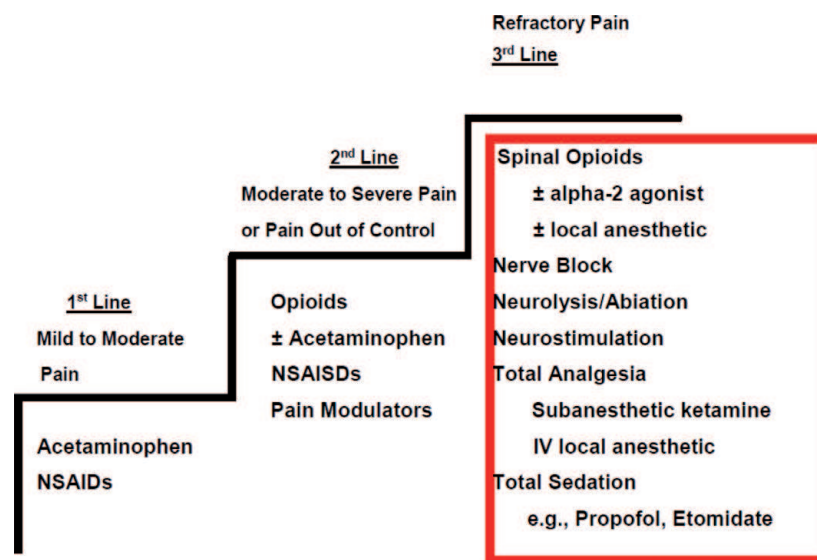


Figure 3. Modified WHO ladder approach for cancer pain (Fine P G, 2005).

I step: main medication— aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs) are used for the treatment of mild pain (score 1–3 in NAS). Nonopioids can be used as adjuvants in II and III steps analgesia.

II step: medication—weak opioids: codeine, dihydrocodeine, and tramadol are used for moderate intensity pain relief (4–6 by NAS). The upper tramadol daily (ceiling) dose is 400 mg. If oral or parental route of administration is not possible, for moderate pain treatment, one can use strong opioids in low doses, e.g., transdermal fentanyl patches.

III step: medication—strong opioids: morphine, fentanyl, methadone, and others are used for severe and intolerable cancer pain (NAS-7-10) relief [36].

Adjuvants may be administered in all steps together with main analgesics. They enhance pain relief and decrease or prevent opioids side effects. In 2000, algorithm was revised in decreasing limitations of opioid use, enabling to start treatment with

strong opioids if patient is suffering from severe cancer pain. Other modifications of WHO three-step analgesic ladder were later applied (2005), introducing spinal opioids for refractory pain (see **Figure 3**).

6. Pharmaceuticals

There are two groups of medication for cancer pain management: (1) analgesics: opioids and nonopioids and (2) adjuvants.

6.1 Analgesics

Opioid analgesics are: (a) weak: tramadol, codeine (and dihydrocodeine) and (b) strong: morphine, fentanyl, methadone, buprenorphine, pethidine [37]. The route of administration are as follows: (a) noninvasive (oral, rectal, transdermal, nasal, sublingual), (b) invasive-parenteral (intramuscular, intravenous, subcutaneous, etc.), including long acting devices such as “morphine pumps” with subcutaneous or epidural catheters and PCA-patient-controlled analgesia option, allowing patient to determine and regulate the needed day and night doses of opioids. The day dose is determined by giving short-acting (immediate release) opioids, such as morphine hydrochloride 1% or morphine sulfate, 1–2% solution injections or tablets (e.g., 10 mg every 4 hours), day dose correction is made after 24–48 hours. After the needed day dosage is achieved (after 3–4 days), we switch to long-acting (slow release) (12–24 hours) morphine medication—tablets, suspension, suppositories, or fentanyl patches (72 hours) [38]. If morphine was administered parenterally, the needed daily oral or rectal dose of morphine should be three times bigger than the injected one earlier. Short-acting (immediate release) opioids should be used for breakthrough pain relief.

The use of opioid analgesics may induce [39]:

- (a) tolerance—a state of adaptation in which exposure to a drug induces changes that result in diminution of one or more of the drugs’ effects over time, which is while using opioid, one has to increase its dose after some time due to the decrease in analgesic effect;
- (b) physiologic dependence—a state of adaptation that is manifested by a drug-class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. It can be avoided by gradual opioid dose reduction;
- (c) psychologic dependence (addiction)—a primary chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behavior that includes one or more of the following: impaired control over drug use, compulsive use, and continued use despite harm and craving (AAPM, APS, ASAM, 2001).

Adverse effects of opioids: constipation, nausea/vomiting, respiratory depression, urinary retention, pruritus, sedation, and more rarely, neurotoxic disorders—hallucinations, seizures, delirium, hyperalgesia. To evade or decrease these effects, one uses adjuvants (laxatives, antiemetics) or opioid rotation (changing one strong opioid to another and adapting the dosage).

Medication	Route of administration	Equivalent of 10 mg morphine dose
Codeine	Oral	100 mg
Tramadol	Oral/parenteral	50–100 mg/25–50 mg
Oxycodone	Oral/parenteral	5–7.5 mg/3.33–5 mg
Pethidine	Parenteral	25 mg
Methadone	Oral	5 mg*
Fentanyl	Patch	0.067 mg**
Morphine	Parenteral	3.33–5 mg

*Methadone/morphine, if morphine day dose: (a) >30 mg 1:4, (b) >100 mg 1:8, and (c) >300 mg 12:1.
 **Fentanyl/morphine, if morphine day dose: (a) 30 mg—12 mcg/hours, (b) 60 mg—25 mcg/hours, (c) 90 mg—37 mcg/hours, (d) 120 mg—50 mcg/hours, etc.

Table 2.
Opioid equianalgesic day doses.

6.2 Opioid rotation

Opioid rotation is a change of one opioid drug to another due to acquired tolerance or unmanageable side effects. These are the rules of opioid rotation:

- additional clinical assessment of pain and its diagnostics;
- adaptation of the day dosage for the newly prescribed opioid (in 24 hours period);
- determine the equianalgesic dose of the new opioid (**Table 2**);
- decrease the determined dose of newly applied opioid by 25–50% to avoid cross-tolerance of both drugs and possible inadequacy of the dosage;
- if after applying new opioid, the pain relief is not enough and its dose is increased by 100–125%;
- titrate new drugs' dose for 24 hours until good pain control is achieved;
- evaluate side effects and drugs' effectivity; and
- pain re-assessment for every 2–3 days.

Opioid rotation is applied according to opioids equianalgesic doses table, thus changing the daily dose of the new drug [40].

In the event of opioid overdose antagonist, naloxone is applied.

The adequate pain control is achieved gradually, by dose titration and administration of various treatment options. Preliminary period of time to achieve:

- no awakening at night due to pain—2–3 days;
- no pain while not in movement (seated or lying in bed)—3–5 days;
- no pain while moving—3–7 days (not for patients with multiple vertebral and pelvic bone metastases—for them total pain control may not be achieved); and
- for patients experiencing anxiety and depression—3–4 weeks.

Nonopioids: aspirin, paracetamol, and nonsteroidal anti-inflammatory drugs (NSAIDs). They are effective in treating mild pain (score 1–3 by number analogue pain intensity scale (NAS)), due to bone metastases, soft tissue or muscular irritation, and damage. They are treating inflammation and decreasing fever and pain. NSAIDs are COX-1 and COX-2 also COX-3 inhibitors. They can be quite toxic to the GI tract (dyspepsia, erosions, ulcers, bleeding, constipation), slowing thrombocytes aggregation, impairing renal and liver function, enhancing hypervolemia, provoking rashes, headaches, dizziness, and allergic reactions. These drugs have their upper dose limit so-called “ceiling effect” when the analgesic effect cannot be increased but the adverse effects are progressing.

6.3 Adjuvant drugs

Glucocorticoids (dexamethasone, prednisolone, hydrocortisone)—indications: increased intracranial pressure, spinal cord compression, nerve compression or infiltration, bone metastases, extended liver capsule, soft tissue cancer infiltration (head and neck, abdominal, and pelvic tumors). Contraindications: no absolute contraindications, dose is limited by adverse effects, and being cautious with peptic ulcers, diabetes, cardiovascular dysfunction, and endemic situations. Adverse effects: Cushing syndrome, gastric ulcers, erosions, bleeding, increased appetite, weight, hyperglycemia, diabetes complications, muscle wasting, euphoria, dysphoria, emotional lability, depression, steroidal psychosis, edemas, hypertension, thrombosis, myopathies, decreased immunity to infections, potassium blood levels, liquid detention in the body, insomnia, skin purpura, etc.

Drugs for neuropathic pain: antidepressants, anticonvulsants, local anesthetics, and myorelaxants (baclofen).

Antidepressants—not always effective for neuropathic pain treatment and is better to prescribe tricyclic antidepressants (TCAs). Start with amitriptyline — 10–25 mg dose in the evening and then increase to 50–100 mg/day. If no effective pain relief is achieved, it is discontinued after 1 week of use. Adverse effects: somnolence and hypotension.

Anticonvulsants—for neuropathic pain—gabapentin, carbamazepine, and clonazepam. The starting dose is the same as treating epilepsy. Increase until pain relief is achieved, or unmanageable adverse effects (nausea, vomiting, somnolence, ataxia, dizziness, disorientation) occur.

Local anesthetics (lidocaine, mexiletine)—for neuropathic pain systemic treatment when other options are not working. Adverse effects: somnolence, nausea, tremor, dyspepsia (better use while eating).

NMDA receptors antagonists (ketamine)—for persistent neuropathic pain and other chronic pain when opioids are not tolerated. Routes of administration of ketamine: oral, intravenous, starting with 100 mg/day, and titration till 500 mg/day. Adverse effects: psychomimetic can be reversed by benzodiazepines and haloperidol.

According to medical literature, about 20% of women have neuropathic pain after mastectomy and about 1/3 of cancer patients suffer from neuropathic pain (or both—nociceptive and neuropathic—together).

Bisphosphonates (pamidronate, zoledronic acid)—decrease bone resorption, effective in treating cancer hypercalcemia, decrease bone pain and occurrence of pathologic bone fractures for the patients with bone metastases, inhibit activity of osteoclasts, and are useful with ineffective radiotherapy and analgesics.

Radionuclides—Strontium 89 systemic administration effectively relieves pain due to bone metastases, better works for osteoblastic metastases, and helps about

80% of patients. The response lasts from 3 to 6 months and is evident already after 2–3 weeks. Adverse effects: myelosuppression, monitored by blood tests. Trials with radioisotopes of samarium and rhenium were also performed.

Psychotropic drugs—neuroleptics. Common neuroleptics (e.g., haloperidol) have no analgesic effect but decrease anxiety, insomnia, treat nausea, and delirium. Levopromazine has analgesic effect: 20 mg dose is equivalent to 10 mg of morphine. Adverse effects: somnolence and hypotension. Benzodiazepines (diazepam, lorazepam, oxazepam) are useful for muscle spasms or acute bone-muscular pain. Adverse effects: hypotension, somnolence, and fatigue. Psychostimulants: metilphenidate has no analgesic effect and may be used to decrease severe opioid-induced somnolence. Adverse effects: dysphoria, tolerance, and dependence.

Myorelaxants—baklofen (act on spinal cord level, start with 5 mg/day dose, and increase till 100 mg/day, for severe hiccup (hiccough)). Adverse effects: fatigue and somnolence. It should be discontinued slowly due to possible withdrawal syndrome and convulsions. Dantrolene—primary effect on muscles. Start with 25 mg/day, and continue with maximal titration till 400 mg/day. Adverse effects: fatigue, somnolence, and hepatotoxicity.

7. Invasive cancer pain management

In most patients, cancer pain can be adequately controlled with pain medication; however, in 5–14% of oncological patients, invasive pain management is needed [41]. Invasive procedures are the part of the option available for cancer pain management. Anesthetic, neurosurgical, or other invasive procedures can be given. Interventional pain management can improve pain control and reduce the amount of systemically administered drugs and their side effects. Also, invasive procedures can be an option when it is not possible to administer oral or parenteral medications. Final decision maker is a physician (anesthetist, pain specialist, and neurosurgeon) who will perform the procedure. He is main person that will decide about indications and contraindications for intervention treatment and will explain and talk with the patient or his relatives about the possibility of intervention and of course risk factors and possible complications. Invasive cancer pain procedures can be divided in to nondestructive and destructive.

Nondestructive procedures are such that the pain signal is modulated or interrupted (blocked) by the administration of a pharmacological agent to a source of pain. The pharmacological preparation may be administered by a single shot dose or via a catheter for long-term administration of the medication. Usually, the catheter is placed neuroaxially (into the spinal canal) or near the peripheral nerves or plexuses. Peripheral nerve blocks/injections can be used, but they are effective for short term and are usually performed in patients with limited survival when the pain source is one or more nerves or when the pain is caused by pathological fractures or vascular occlusion. As a first-line treatment, these blockades are rarely used and, if applicable, it is necessary to combine with systemic analgesics.

Neuraxial invasive procedures can be: intrathecal or epidural. For example, an epidural medication injection (transforaminal or translaminar) or catheter/device placement is applied in most of the cases when the nerve structures are involved in pain cause.

In case of complicated cases and intolerable pain, opioid analgesics can also be delivered through neuraxial delivery systems. The use of neuraxial system for long term can range from simple percutaneous (tunneled) patient controlled to implantable complex programmable medication delivery systems. Implantable systems are expensive, but safe and their application is always justified, if patient need pain

control longer than 3 months and other medical treatments are not effective [42, 43]. These techniques may be on an oncological pain management plan, but they do not generally apply to everyday cases.

Destructive procedures can be applied in cases where pharmacological preparations cannot modulate the pain signal. For example, in case of small cell lung cancer and mesothelioma, chest pain is poorly localized, severe, and intolerable. This is because intercostal nerves and their branches can be infiltrated in cancer cells, during metastatic spread and making it difficult to manage the source of pain. Then, the cordotomy can be applied—a neurosurgical procedure in which the spinal cord-spinothalamic tract ablation is performed in the area opposite to the pain. After the ablation pain disappears, but along with the disappearing of pain on the part of the body below, the ablation area develops temperature and paresthesia [44]. Another destructive procedure is rhizotomy, segmental or multisegmental destruction of spinal cord nerve roots. It can be done in several ways: (a) surgically, (b) chemical neurolysis (phenol), and (c) radio-frequency ablation [45, 46].

Chemical neurolysis is widely used in the treatment of intractable cancer-related pain, especially in abdominal and pelvic cancer-related pain. These procedures can provide prolonged pain relief (3–6 month) and decrease the need of opioids.

High evidence is for coeliac plexus neurolysis in pancreatic cancer-related pain [47].

Neurolytic agents that often used for chemical neurolysis are alcohol, phenol, and glycerol.

All procedures can be done under ultrasound, X-ray, or CT scan. After the procedure, patient may experience significant pain relief and opioid withdrawal symptoms [48].

8. Nonpharmacological cancer pain treatment

Palliative radiotherapy is effective for the treatment of cancer pain caused by bone and brain metastases, metastatic skin ulcerations, and infiltrative growth of tumor in soft tissues. The summary dose of palliative radiotherapy is smaller than the dose for radical radiotherapy; maximal effect is achieved giving minimal number of radiation fractions (1–5) [49].

Transcutaneous electroneurostimulation (TENS)-nerve stimulation via electrodes put on skin, thus, inhibits pain signal in spinal cord. Optimal dose varies for different patients. TENS is used for the treatment of mild and moderate cancer pain but is not effective for visceral pain. TENS is contraindicated for the patients with pacemaker (ECS). Pain relief effect is quick but usually not long-lasting (only for 15–20% of patients).

Psychotherapy-introducing patients psychological support groups, delivering enough information; relaxation therapies, meditation; cognitive therapy, auto-training, hypnosis, short psychotherapy seances with psychotherapist. Drug is administered if there is a need to correct renal, liver failure, and antidepressants for depression [50].

Acupuncture, physical therapy, mild massage can also be applied.

9. Cancer pain and palliative care

Palliative care includes palliative cancer treatment options, such as palliative radio therapy, palliative surgery, palliative chemotherapy, also pain relief and control of other symptoms caused by advanced cancer [51].

Palliative surgical procedures—palliative operations such as tumor mass reduction, stomas: colostomy, tracheostomy, gastrostomy, nephrostomy, etc., and drainage of pleural effusion and ascites.

Palliative chemotherapy is effective while treating pain, caused by chemotherapy-susceptible tumor and metastases. The main goal is to minimize its side-effects. Monotherapy of drug combination in reduced doses can be applied [52].

Most common symptoms control [53].

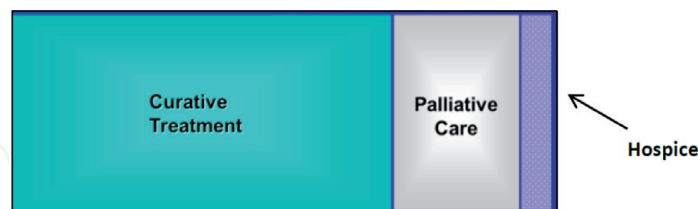
Anorexia is a loss of appetite, usually with decreased food intake. *Cachexia*-lack of nutrition and wasting. Causes maybe disease-related (bowel obstruction, etc.), psychological or treatment-related (intoxication due to chemotherapy, radiation esophagitis, etc.). Treatment-dietary consultation, parental/enteral nutrition, medications (e.g., megestrol acetate suspension), odor control, and counseling.

Constipation is a common symptom in palliative care. The key should be prevention. Causes can be diseases related to GI obstruction, neurologic (spinal cord compression), hypercalcemia, inactivity; or treatment related-opioids, other medication. Treatment-laxatives, other medication, increasing fluid intake, and dietary consultation.

Nausea and vomiting—common in advanced disease. Assessment of etiology is important, maybe acute, anticipatory (e.g. before chemotherapy) and delayed. Causes can be physiological (GI pathology, metabolic dysfunction, brain metastases, also-treatment related (opioids), psychological. Treatment—both pharmacological (anti-cholinergics, antihistamines, steroids, prokinetic agents, etc.) and non-drug treatment (small/slow feeding, dietary consultation, relaxation/distraction techniques).

Lymphedema—chronic, progressive swelling due to failure of lymph drainage. Patients limbs and whole body can be affected. Treatment—skin care, compression, limb elevation, education, etc. For those patients trophic ulcers and bedsores occur more often.

Current Practice of Hospice and Palliative Care



Palliative care

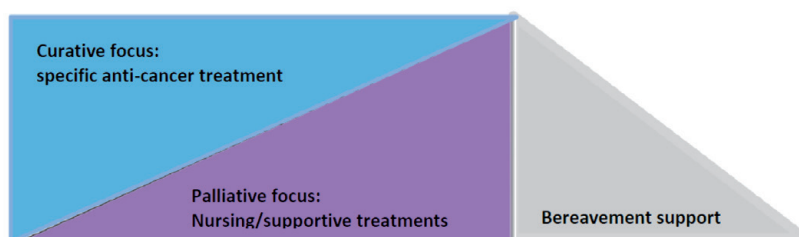


Figure 4. Palliative care models (WHO directives, 2002) (adapted by Skorupskiene (2018)).

Advanced cancer patients at the end of life also often exhibit *delirium* (acute change in cognition/awareness) with *agitation and confusion* (disorientation, inappropriate behavior, hallucinations). The causes vary, most common—medications, infection, bladder distention, hypoxemia. As treatment option medication re-evaluation, hydration, oxygen therapy, reorientation, psychotropic drugs should be considered.

Aging population and increasing number of long time cancer survivors, some of them finally ending as advanced cancer patients, now especially increase the need of *hospice and palliative care* [54]. It should be patient-oriented, and not related to artificial prolongation of life and failure to acknowledge the limits of medicine with inappropriate use of aggressive curative treatment. Palliative care should help with all patients' problems (physical, psychological, social, spiritual), include interdisciplinary team approach (doctors, nurses, social workers, psychologists, other specialists and volunteers) and is oriented to achieve better quality of life for the patient and his/her family members. Palliative care should start for the cancer patients still receiving specific anti-cancer therapies, not waiting until all treatment options are exhausted (**Figure 4**).

General principles of palliative care:

1. patient and family as unit of care;
2. attention to physical, psychological, social, and spiritual needs;
3. interdisciplinary team approach;
4. education and support of patient and family;
5. extends across illnesses and settings; and
6. bereavement support [55].

The main idea of palliative care—no matter how much the disease is advanced, and what complex treatment has been applied, one always can do something more to improve the quality of life, still left for the patient.

10. Cancer basic pain relief

Planning pain relief for cancer pain patients one should take into the consideration possible mechanisms and types of pain (nociceptive, neuropathic, mixed), patients' wishes, former treatment. If psychological distress is present, talking about pain assessment is needed, if there is suffering, help from the clergymen may be useful. If the signs of drug addiction appear, drug release should be more controlled, physical aspects of pain relief introduced. With cognitive disorders depression and anxiety should be treated, also opioid rotation should be available.

Basic pain	Breakthrough pain
Start—slow, gradual increase in intensity	Start—acute, not predictable
Duration—no less 12 hours/day	Duration—from several seconds to 30 minutes
Type—dull, pressing, gnawing...	Type—acute, shooting, irradiating
Treatment—long acting, slow release opioids, fixed scheme	Treatment—short acting, immediate release opioids, on demand basis

Cancer pain treatment algorithm [2]:

1. assessment of pain reason, type, and intensity;
2. pharmacological pain treatment: basic pain relief, breakthrough pain relief, and adjuvants;
3. nonpharmacological treatment of pain;
4. evaluation of results and correction of treatment plan; and
5. providing constant pain relief and palliative care.

10.1 Basic cancer pain drug treatment principles

After the cause and type of cancer pain is determined, the constant analgesia is started by the easiest route, the patient-oral or transdermal, individualizing the dose, and also providing drugs for relief from other symptoms. The drug is selected taking into consideration the type and intensity of pain, WHO “analgesic ladder,” also drug combinations, but combined medications should not be used and no placebo drugs as well [56].

To prevent pain becoming chronic, cancer pain relief should be started as soon as pain appears, as it helps to reduce drugs doses, adverse effects, and achieve better drug tolerance. It also reduces the cost of pain treatment, enhances the trust between patient and doctor, and patient is socially active for a longer time. The pain relief effect should be quick, so we can start with stronger medications and later pass on the weaker ones. Different medication is used for different types of pain: (a) nociceptive pain, due to soft tissue, bone damage, and visceral pain are treated by combinations of nonopioids and opioids and (b) neuropathic pain, due to nerve compression—by opioids, glucocorticoids, when nerve is damaged—by antidepressants, anticonvulsants, and NMDA receptor antagonists [57].

11. Cancer breakthrough pain management

Breakthrough cancer pain (BTCP) is a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain [58]. The frequency is less than four times/day, if it takes more than four times/day, we need to think about lack in background cancer pain control.

Leading doctor in BTCP management should perform regular assessments and repeatedly investigate pain management after 1–4 weeks dependably on patient’s complexity.

It is important to understand that the BTCP management is different compared with background cancer pain, which is managed according to the ladder and “by the clock,” while for BTCP, “rescue medication” should be given as needed. Main feature is that the breakthrough cancer pain should be started when background cancer pain is well controlled (**Figure 5**) [59]. This type of pain can take about from 30 minutes but not more than 60 minutes. The highest intensity of the pain can be reached at tenth minute, and it can take 1–4 episodes/day [60]. For that reason, for BTCP should be given very strong, short-acting opioids.

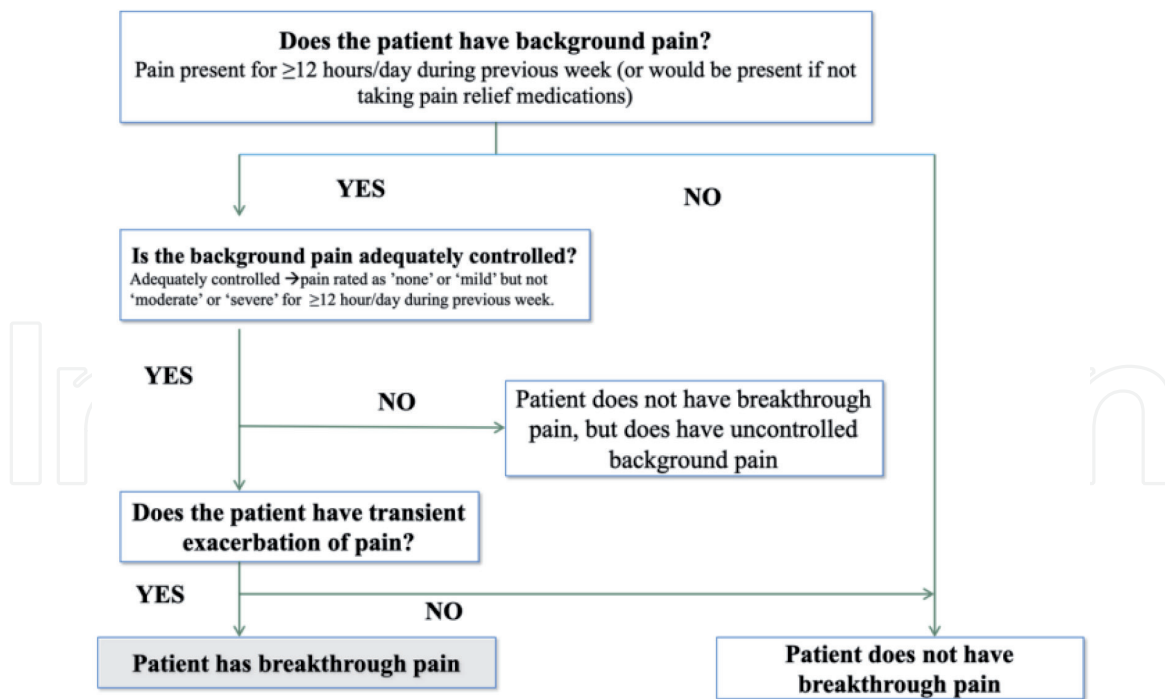


Figure 5. Association of Palliative Medicine of Great Britain and Ireland (APM) algorithm for assessing breakthrough cancer pain.

It is better to use the same chemical opioid structure, which is chosen to manage background cancer pain.

When fentanyl plasters/patches is used, the short-acting medication (buccal or sublingual tablet) for BTCP control can be prescribed. The dose should be titrated up to effective one, because of the lipophilic structure and the absorption, which is through the mucous of the mouth and gastrointestinal tract. There is a variety of short-acting fentanyl forms (**Table 3**). For example, BTCP management can be started with 200 µg of oral transmucosal fentanyl citrate tablet or 100 µg buccal-soluble film [61].

If for BTP management, immediate-release morphine is chosen, usually one BTP episode is needed, part of 1/6 injecting medication of all morphine day dose. Their pharmacokinetic characteristics have limitations, with a relatively slow onset of action (30–45 minutes) and duration of action of up to 4–6 hours [62].

BTCP management consists of other approaches as setting of pain management goals, education of the patient, and depending on the cause of breakthrough pain, occupational therapist, physiotherapist can be involved. Other acute causes as

Formulation	Description
Nasal spray	Phosphate-buffered solution Fentanyl pectin intranasal spray
Sublingual	Sublingual fentanyl orally disintegrating tablet Sublingual fentanyl tablet
Oromucosal	Oral transmucosal fentanyl citrate
Buccal tablet	Effervescent formulation
Buccal soluble film	Fentanyl buccal soluble film

Table 3. Fentanyl short acting formulations.

bone fractures, bowel perforation, etc. should be excluded, and if the BTCP can be predicted, pain medication should be given before the coming pain event.

The evaluation of the effectiveness of the pharmacological treatment of BTCP has a four-factor rule [63]:

1. pain relief;
2. day activity;
3. adverse effect of medications; and
4. possible inappropriate use of opioids.

Possible inappropriate use of opioids is very important factor in pain management, and it should be carefully investigated. It manifests as addiction or pseudoadiction for strong opioids and can be associated with mental disease. Clinically, it can be seen as seeking for opioids and/or problematic opioid use. In order to correct the possible misconduct in the use of opioids, it is important that these requirements are met before they are given:

1. to distinguish between people with risk factors (drug users, alcohol dependent, gambling, having mental problems); and
2. modifying the use of drugs for the prevention of BTCP (by giving a slightly higher dose of slow-release opioid to relieve background pain, try to use nonopioids for BTCP reduction, and family support-controlled home care, etc.) [64].

12. Cancer pain treatment for children and elderly patients

While treating cancer pain in children and elder patients, one should take into consideration the differences in metabolism, concurrent diseases. Children receive different adapted opioid doses, and opioid rotation is also different (e.g., better pain relief with methadone and not morphine).

Elderly patients more easily overdose opioids; one cannot double their opioid dose quickly for them. Also, one should be aware of elder persons' liver and renal function; if there is some failure, the correction is essential before prescribing opioid medication. There are usually a lot of tablets and other oral drugs prescribed for the concurrent diseases, so there is necessary to determine daily opioid dosage very carefully.

13. Cancer survivors pain treatment

Chronic pain can be a serious, negative consequence of surviving cancer. As a result of remarkable advances in cancer diagnosis and therapy, today there are a record 14 million cancer survivors in the United States. However, an estimated 40% of survivors continue to experience persistent pain as a result of treatment, which can be detrimental to their quality of life [3]. Two-thirds of these individuals are surviving more than 5 years after diagnosis, supporting the need to study pain in this growing population [65]. National Cancer Institute's Office of Cancer Survivorship characterizes the survivor as a person with a history of cancer who is beyond the acute diagnosis and treatment phase. Risk factors for chronic pain in survivors include the

type and invasiveness of the tumor, the treatment regimen used, the time since the cancer treatment has started, and the efficacy of initial pain therapy. Continuous pain is associated with impaired quality of life in this population [66]. As the population of cancer survivors expands, all clinicians, including oncologists, advanced practice providers, and primary care physicians who interact with these individuals, will require the knowledge and skills to implement best practices in the management of chronic pain. When analgesic drugs are used, the imperative to prescribe safely must expand beyond immediate adverse effects, such as the resulting respiratory depression or constipation associated with opioids, to incorporate awareness and mitigation of the long-term consequences of these and other analgesic agents.

Clinical practice guidelines are issued recently, and they deal comprehensively with the pain people experience after cancer treatment, and are unique in its focus on chronic pain among cancer survivors. Key guideline recommendations include: (1) clinicians should screen for pain at each encounter with a patient. Recurrent disease, second malignancy, or late onset treatment effects should be evaluated, treated, and monitored; (2) clinicians may prescribe nonpharmacologic interventions such as physical medicine and rehabilitation, integrative therapies (e.g., acupuncture and massage), interventional therapies, and psychological approaches (e.g., guided imagery, hypnosis, and meditation); (3) systemic nonopioid analgesics (NSAIDs, acetaminophen) and adjuvant analgesics (selected antidepressants and anticonvulsants), may be prescribed to relieve chronic pain and/or improve physical function; (4) clinicians may prescribe a trial of opioids in carefully selected cancer patients who do not respond to more conservative pain management and who continue to experience pain-related distress or impairment of physical function [67]. The management of cancer survivors suffering chronic pain requires greater consideration of a multimodality plan of care that balances pharmacologic and nonpharmacologic techniques and may necessitate the involvement of an interdisciplinary team; the goals of treatment in these populations may focus on improving function and limiting the long-term adverse effects of pain and of its treatment, as much or more as they do on improving comfort [68].

As therapeutic treatment options and outcomes improve, patients with cancer are living longer. Chronic pain can develop from a variety of sources: peripheral neuropathy, muscle or bone pain, surgery, radiation, and other conditions. Comorbidity with other conditions or syndromes can make assessing chronic pain more difficult. Different chronic pain syndromes may be present for cancer survivors. Chronic inflammatory polyneuropathy is one of many well-recognized pain disorders, together with other treatment-related pain syndromes, such as postsurgical and postradiation pain. Hormonal therapies, such as aromatase inhibitors, can produce arthralgias. As the use of hematopoietic stem-cell transplantation expands, graft-versus-host disease (GVHD) is seen with greater frequency, leading to pain syndromes that can affect almost any organ system. In addition, immunosuppressive agents used to treat GVHD can lead to painful complications (e.g., corticosteroids and avascular necrosis). The recent validation of a tool specific to musculoskeletal symptoms in hematopoietic stem cell transplantation will allow better characterization of this painful phenomenon [69–71]. The important consideration when designing an usage of analgesics is the potential for harm, and drug-drug interactions with cancer therapies, or other treatments should be considered. Cytochrome P450 CYP 3A and CYP2D6 inhibitors can increase concentrations of opioids, such as codeine, oxycodone, hydrocodone, fentanyl, tramadol, and methadone, metabolized by this system [72, 73]. Methadone and buprenorphine can prolong the QT interval, an effect that can be potentiated by many chemotherapeutic agents, notably doxorubicin [74]. If pain is severe and disabling, and long-term opioid therapy is being considered, the potential for

opioid-related harm over time must also be evaluated. Persistent adverse effects such as constipation are well recognized, and risk of sleep-disordered breathing suggests that these conditions must be considered when opioid therapy is initiated and later during the course of treatment. The potential for neurotoxicities, such as persistent mental clouding, increased risk of falls in the elderly, and other phenomena may occur. Opioid-induced hyperalgesia is well described in preclinical models but has uncertain clinical importance; the potential is considered when a patient reports escalating pain in tandem with opioid dose escalation in the absence of identifiable worsening of a pain cause. Opioid-related harm may also result from misuse or abuse, the development of opioid addiction, or the occurrence of drug diversion within the community. The problem of prescription drug abuse is serious, leading to an increase in opioid-related deaths [75]. The treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions, referred to as multiple chronic conditions, is challenging. Insomnia and psychological distress are common conditions in patients with chronic pain, present in 17–90% of adult sufferers, respectively. The most common psychiatric disorders comorbid with chronic pain include depression, anxiety, personality disorders, and PTSD [76]. Evidence also suggests that patients with comorbid conditions are less likely to improve with standard chronic pain treatment [77].

Because cancer posttreatment pain is so complicated; good communication between patients and their medical providers is essential. Cancer survivors may have varying capacities to deal with a great source of information that can sometimes be overwhelming. Some patients may even be reluctant to discuss their pain, seeing it as a sign of weakness or fearing a recurrence; some may see it as an expected and untreatable complication of their cancer treatment. That is why a pain assessment is recommended at every visit. In teasing out how they are coping, clinicians need to ask patients how chronic pain is affecting them and suggest how they can work together to better manage their symptoms and improve their quality of life. The question arises regarding who should provide pain management for the cancer survivor: the oncologist and his or her team, the patient's primary care provider, a multidisciplinary pain service, or any other professional? Oncology teams providing ongoing care for cancer survivors may be the optimal group to address pain, because they routinely manage a complex regimen of cancer therapies and related symptoms.

Comprehensive assessment, including the impact of pain on function and quality of life, is warranted for all survivors. Long-term assessment is also needed after clinical trials to better recognize novel or previously unrecognized painful consequences of treatment, including those syndromes that may occur after treatment is completed. Carefully designed, extended studies of pharmacologic and nonpharmacologic interventions to relieve pain and improve function are indicated in this population. An especially relevant and urgent need is research identifying those cancer survivors who respond optimally to opioid therapy and those at greatest risk of adverse effects.

14. General practitioner's role

Cancer care generally requires the technical knowledge and skills of specialty physicians such as medical oncologists, surgeons, and radiation oncologists. General practitioners (GP) may play an essential role because they are often the initial point of contact for patients in obtaining screening or evaluating symptoms, and they may make referrals, coordinate care, and manage symptoms or comorbid

conditions. One of the main role for GP also is counseling cancer patients about treatment options and monitoring treatment progress and side effects [78].

The roles of GP's for patients with cancer such as managing comorbid conditions, chronic pain, or depression, and referring patients to hospice were tested in the study and showed that 22% of GPs reported no direct involvement in cancer care roles, while 19% reported heavy involvement, and rural practice location was not associated with greater GP involvement in cancer care [79]. There is a gradual move toward shared care models with GPs playing a central role alongside other healthcare providers. In this context, it will be important to understand the factors influencing the involvement of GPs in cancer care and how to maximize their involvement throughout the spectrum of cancer care [80]. The studies also confirm that the great majority of GPs are familiar with the modern management of pain control problems commonly encountered in practice, but are less aware of the drug options available for less common situations, particularly the use of syringe drivers [81]. Fortunately, there is no evidence of a reluctance to start strong opioids for severe pain, as identified in previous works [82]. However, it is of concern that only minority of GPs still are suggesting immediate-release opioids for breakthrough pain, and laxatives or antiemetics when starting strong opioids, which is a recommended practice in community palliative care [83].

Most common mistakes in the treatment of cancer pain are as following:

- monotherapy (NSAIDs or opioid analgesics only);
- a prescription of slow release (SR)-form opioids for intake regime “as needed”;
- improper treatment of side effects caused by medicines;
- medicine for breakthrough pain is added in the situation where basic pain is not controlled sufficiently;
- pain breakthrough is not treated at all;
- adjuvants (antidepressants, anticonvulsants) and related medicine are not used; and
- with the prescription of opioids, behavioral aspects of patients are not evaluated.

A general practitioner, who has diagnosed pain in a cancer patient, starts treatment with analgesics. A ladder analgesia scheme is used. Opioids may even be prescribed for moderate pain, and if the pain is severe and unbearable, the opioid analgesic is the main remedy for pain relief. A sufficient daily dose for baseline (basic) analgesia should be achieved by increasing the dose (titration) of the product [84]. When titrating the product, the following rules should be used: (a) pain is controlled and there are no side effects—treatment to continue the current dose, (b) pain is controlled, but there are side effects—reduce the dose of the product, (c) pain is uncontrolled and there are no side effects—increase the dose of the preparation, and (d) pain is uncontrolled, in case of side effects, change the medicine [85].

It goes without saying that controlling such a complex syndrome as cancer pain can lead to other problems that require the help and advice of the pain physician. Therefore, GP should refer the cancer patient to a pain clinic for a clear indication of the following cases (indications):

- when initiating opioid analgesics, basic pain control is not achieved and there is an unadjusted side effect of the drug;
- failure to achieve control over cancer breakthrough pain in cases where basic pain is well controlled;
- the control of basic pain by an opioid analgesic becomes ineffective, a tolerance to the preparation is suspected, and it needs to be changed to another opioid analgesic (opioid rotation);
- pain must be controlled by combining the pharmaceutical treatment and invasive procedures (patient controlled analgesia, pain relief block);
- inappropriate behavior with opioid analgesics is identified or developing of psychological dependence on them is suspected;
- repeated multidisciplinary pain assessment and specialized control (specialists' meeting) is necessary; and
- if a cancer patient is given a palliative care nursing home or nursing home and cannot physically access the pain clinic, according to the above indications, the pain clinic staff can consult on arrival at the place of destination.

15. Conclusion

Following the International Association for the Study of Pain cancer pain is “unpleasant sensory and emotional experience associate with actual or potential tissue damage resulting either from the treatment of cancer or the cancer itself.” Due to the complexity of symptoms and multimodality of treatments, cancer pain is built in the most sophisticated field of medicine, where each patient’s stage of disease and diagnosis will require an individualized pain treatment plan to optimize the quality of life. Such tasks can only be carried out using multidisciplinary approach. That is why basic knowledge about cancer pain is essential for every healthcare professional. We believe that the text you have just read will help you to be an active practitioner giving the patients the cancer pain relief.

Acknowledgements

The authors acknowledge Lithuanian Pain Society for text support.

Notes

Materials from “Cancer induced pain,”(Lithuanian Pain Society’s guidelines) 2nd ed., 2018, are used in the text.

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