Provisional chapter

Cancer Pain — The Role of an Integrated, Comprehensive Rehabilitation Program in Its Management

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Additional information is available at the end of the chapter

1. Introduction

Pain is one of the most frequent and distressing symptoms occurring in cancer patients. Pain is present in 36–61% of cancer patients depending on the histopathological tumor type, on the stage of disease, and patient setting.[1, 3]

Sixty-four percent of patients with advanced cancer are believed to experience substantial pain as a consequence of the neoplastic condition.[4]

Unfortunately, cancer pain is often neglected and undertreated, resulting in a significantly unfavorable impact on the quality of life of the patients and their families. [5]

The National Cancer Institute estimates 1, 660, 290 new patients to be diagnosed with cancer, and about 580, 350 Americans were expected to die from cancer in any sites in 2013. [6]

Cancer pain management relies upon a comprehensive assessment characterized by pain symptoms in terms of phenomenology and pathogenesis, assessing the relation between pain and the causative disease, and clarifying the impact of pain and related co-morbidities on the patient's quality of life.

Despite recent improvements in the cancer management, obstacles to optimal cancer pain management still remain.

Additionally, the lack of psychological and psychiatric support services to support the treatment of cancer pain remains a serious issue.[7]

Hurdles to the treatment of cancer pain have been recognized, including a variety of educational, attitudinal and institutional obstacles. As regards the education in pain management,

there appears to be a deficiency in the training of physicians and nurses. Both physicians and nurses indicated that "inability to properly assess the pain" and "inadequate knowledge about pain management" ranked among the most relevant barriers preventing a multidisciplinary approach to pain treatment and adequate cancer pain management. [8]

Despite the increasing availability of pain medications, pain continues to be deemed as moderate-to-severe in more than 50% of cancer patients.

According to a recent population-based study, investigating cancer pain in eleven European countries and Israel, 56% of patients suffered from moderate to severe pain in the previous months, and 69% reported pain-related difficulties hindering everyday activities. [9]

A systematic review completed in 2007 showed that cancer pain is present in 64% of patients with metastatic, advanced disease, in 59% of subjects undergoing cancer-related therapies. Despite effective, curative treatment, a moderate-to-severe pain intensity being reported in more than one third of all cancer patients.

Pain is present in over 50% of cancer patients, reaching higher percentages in patients with cancer at specific sites, such as stomach, uterus, lung, prostate, cervico-facial district, biliary tract, breast, colon, brain, pancreas, cervix, and ovary. [10]

2. Cancer pain

The diagnosis of cancer is typically traumatic and full of uncertainties, due to its prognostic implications and the need for demanding treatment regimens. The word "cancer" still remains synonymous of "pain" and "death". Therefore, both mental and physical pain, in all the aspects and intensity of their clinical expression, characterize every stage of the disease. [11]

Cancer can cause pain at any time during its course, with frequency and intensity of pain tending to increase in the advanced stages. Indeed, roughly 75–95% of patients with metastatic cancer will experience significant amounts of cancer-induced pain.

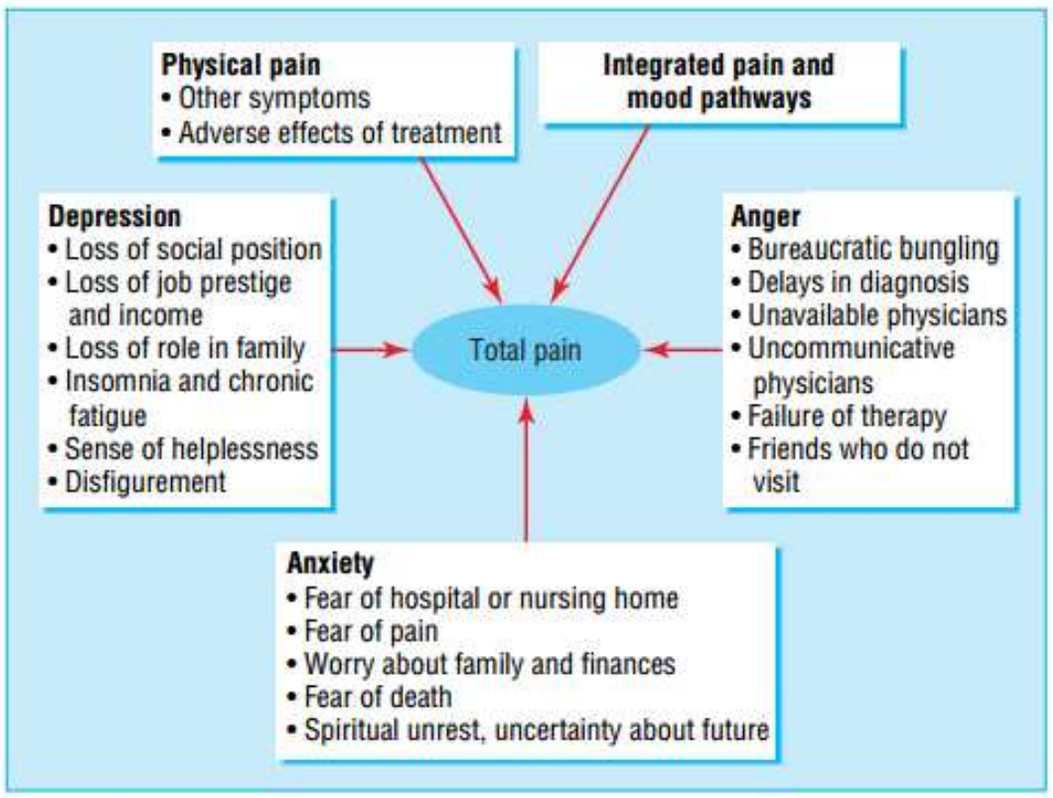
According to the International Association for the Study of Pain (IASP), pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” Pain occurring to cancer patients is defined as "total pain" (or "global suffering"), since people with cancer tend to manifest a wide array of functional needs (at a psychological, social, spiritual and existential level) that ought to be recognized and addressed in their complexity.

Relief of pain should, therefore, be seen as part of a comprehensive strategy of care addressing physical, psychological, social, and spiritual aspects of suffering. Physical aspects of pain cannot be treated separately from psychological aspects, whereas patients’ anxieties cannot be effectively addressed while patients are physically suffering.

Therefore, all various components of cancer pain should be addressed simultaneously.

Knowledge of the mechanisms of pain has improved considerably over the past few years. We now know that physical injuries, pain pathways, and the emotional processing of this infor-

mation are connected with each other within the nervous system. Anxiety, fear, and insomnia are re-elaborated at the level of the limbic system and the cortex. As a result, the brain responds sending signals back to the spinal cord and, thus, modifies the pain input at spinal levels. The spinal cord sends further impulses back to the brain, establishing in this way a reinforcing loop. [12]



Factors affecting patient's perceptions of pain (adapted from Twycross RG, Lack SA, *Therapeutics in terminal disease*, London: Pitman, 1984)

Figure 1. Factors affecting patient's perceptions of pain (adapted from Waycross RG, Lack SA, Therapeutics in terminal disease, London: Pitman, 1984) from : Principles of control of cancer pain BMJ 2006; 332

Pain is a subjective, heterogeneous experience, affected by patient's genetic background, anamnestic record, mood, expectations, and culture. Cancer pain can be classified according to a number of different features (i.e., etiology or physiopathology).

There is a wide array of potential causes resulting in pain in cancer patients. Indeed, the painful experience involves inflammatory, neuropathic, ischemic, and compression mechanisms occurring in multiple sites. [13]

This section highlights some of the most common causes of pain in cancer patients:

- diagnostic or therapeutic procedures (bone marrow aspiration or biopsy, lumbar puncture) that may result in acute somatic pain, and may require specific premedication protocols as well as analgesic treatments for several days following the mentioned procedures.
- acute postoperative pain or postsurgical syndromes (i.e., following tumor debulking or radical neck dissection) need to be treated with patient-controlled analgesics in selected patients. Such drugs may include cyclooxygenase-2 inhibitors, selective non-steroidal anti-inflammatory drugs (NSAIDs), calcium ligand-gated ion channel anticonvulsants, in addition to pre-procedural local anesthetic nerve blocks.
- direct tumor involvement may cause a painful experience which is often described as constant, aching, gnawing, and well localized (as a result of vascular obstruction or invasion, or mucous membranes ulceration).

Bone metastases are another common responsible of cancer-related physical impairment. Such causes of cancer pain may lead to nociceptive (somatic and visceral), neuropathic, or mixed pain; they may occur in combination with acute or active disease, subacute disease, or chronic disease undergoing palliative care-as well as disease in complete remission with residual effects.

Other sources of pain may include pathologic or osteoporotic stress fractures, and osteonecrosis (following steroids or Radiotherapy). Chemotherapy (CT) side effects may include mucositis, while Radiotherapy (RT) side effects may present as odontophagia, mucositis, or burns.

Lymphedema resulting from RT or surgical excision may result in painful swelling surrounding the affected region or the extremities, eventually leading to painful cellulitis or skin ulceration. A painful scar or keloid may occur following wound healing, carrying an increased risk of wound-site neoplasms.

A controversial aspect related to iatrogenic pain is the phenomenon of hyperalgesia observed during chronic treatment with opioids; although the exact mechanism underlying this phenomenon is still unknown, it seems to be related to tolerance to opioid drugs administered chronically, repetitive stimulation of spinal NMDA receptors, dynorphin activity at the spinal level, specific abnormalities of central processes regulating the neural transmission to the nerve, and a possible action of cholecystokinin at the central nervous system level. [14]

3. Cancer pain: Pathogenetic classification

Onset and assistance of pain during the clinical course of cancer may stem from direct mass effect, relationship between tumor and host, iatrogenic damage; from a physiopathological standpoint, cancer pain may be classified as follows: [15]

- **Nociceptive pain** due to invasion/ulceration of surrounding tissues;
- **Inflammatory pain** through the classical cascade of acute inflammation;

- **Neuropathic pain** due to tumor infiltration / compression of nerves, plexuses, or nerve roots, remote effects of malignant disease on peripheral nerves or side effects of pharmacological treatments. [16]

Cancer pain shares the same neurophysiologic pathways as non-cancer pain. Such nociceptive mechanisms involve activation of sensory afferents by persistent noxious stimuli, signal transduction, transmission, modulation, and, finally, pain perception. [17]

4. Nociceptive pain

Nociceptive pain stems from an acute or persistent injury to somatic or visceral tissues. Somatic nociceptive pain is described by patients as "aching", "stabbing", or "throbbing", and arises from injury to bones, joints or muscles. Visceral nociceptive pain results from injury to viscera. It is poorly localized and is reported as "cramping" or "gnawing", especially when it involves a hollow viscus (e.g. bowel obstruction). Conversely, visceral nociceptive pain may be described as "aching", "stabbing", "sharp", and it is similar to somatic nociceptive pain, whenever it involves other visceral structures (e.g. organ capsules, myocardium). Visceral pain is often referred to somatic sites due to the convergence on somatic afferents within the dorsal root ganglia and dorsal horns. [18]

Stimuli from tissue injury activate primary afferent neurons called nociceptors, located in the skin, muscles, joints, and visceral organs. Nociceptors are high-threshold receptors, i.e. they are silent unless significantly stimulated. [19]

Most nociceptors are polymodal, responding to thermal, physical, and chemical stimuli. Neuron cell bodies are located within the superficial laminae of the dorsal root ganglia and trigeminal ganglia. Once depolarization occurs, transmission advances proximally via thin myelinated A-δ fibers (fast) or reduce unmyelinated C fibers (slow). Interneurons within laminae I and II of the dorsal horn amplify or neurotransmission. Afferent axons end in lamina I or II, and second-order afferent neurons cross the midline and ascend to the brainstem and thalamus through the anterolateral quadrant of the controlateral half of the spinal cord. Together with axons from second-order lamina I neurons, these fibers form the spino-thalamic tract, which is the major ascending pathway with regard to information about pain and temperature. Sensory fibers, associated with affective responses, also ascend in the contro-lateral dorsolateral spinal cord to the medial thalamus or brainstem and, then, to the cingulated cortex and limbic lobe. Downward modulation occurs through the periaqueductal gray (PAG) and rostral ventral medulla (RVM) with axons that run across the dorsal lateral funiculus. The axons just mentioned, modulate pain directly through connections to secondary afferent neurons in the dorsal horn or via connections with interneurons in laminae I and II.

The neurochemistry of these processes involves multiple neurotransmitters including endor-phins, prostaglandins, gamma-amino-butyric acid (GABA), cannabinoids, and many others molecules, that are all targets for analgesic medications.[20]

The spine is the most common target of bone metastases, with affected patients experiencing back pain. Direct extension of a vertebral tumor may lead to spinal cord or nerve roots damage,

thereby producing substantial neurological compromise. Back pain deriving from vertebral metastases is, therefore, a marker of an increased risk of epidural spinal cord or cauda equina compression.

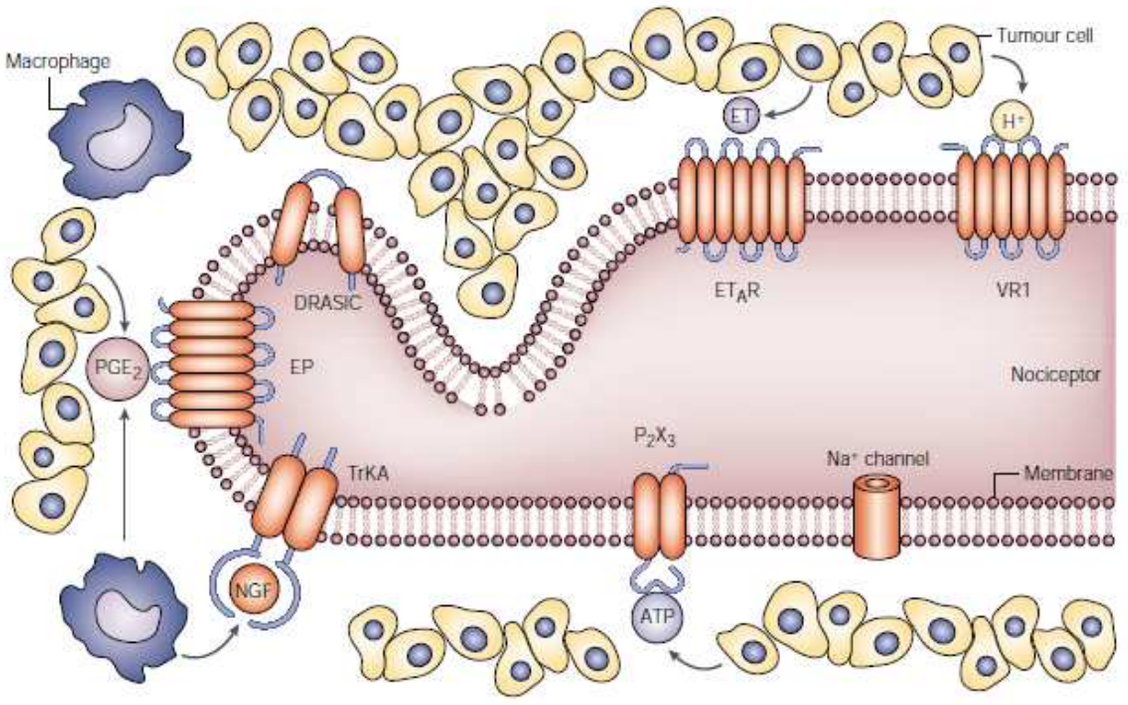


Figure 2. Detection by sensory neurons of noxious stimuli produced by tumours. Figure from Molecular mechanisms of cancer pain. Mantyh PW, Clohisy DR, Koltzenburg M, Steve P. Hunt. Nature reviews | Cancer Volume 2 | March 2002

5. Inflammatory pain

Any given neoplasm harbors several non-cancerous cell types, including immune-system cells such as macrophages, neutrophils, and T cells. These cells may secrete various sensitizing factors, or excite directly primary afferent neurons, such as prostaglandins [21, 22], tumor necrosis factor-α (TNF-α) [23, 24], endothelins [25], interleukin-1 and interleukin-6 [26, 28], epidermal growth factor [29], transforming growth factor-β [30], and platelet derived growth factor. [31, 33] Indeed, specific receptors for these factors are by expressed primary afferent neurons.

Intra- and extracellular pH of solid tumors is lower than that of the surrounding normal tissues. [34]

Local acidosis — secondary to the accumulation of acid metabolites — is a hallmark of tissue injury. [35]

The finding that sensory neurons can be directly excited by protons or acidic compounds has generated sizable interest among basic and clinical researchers. [36]

Studies have shown that several subsets of sensory neurons express different acid-sensing ion channels [37]. The two main classes of acid-sensing ion channels, expressed by nociceptors, are Vanilloid receptor subunit (VR1) [38, 40] and the acid-sensing ion channel-3 receptors (ASIC3). [41]

Both these types of channels are sensitized and excited by a decrease in pH. More specifically, VR1 is activated when the pH falls below the value of 6.0, whereas the pH-induced activation of ASIC3 seems to depend on the co-expression of other ASIC channels by the same nociceptor. [42]

There are several mechanisms by which tumors may induce a decrease in pH. As inflammatory cells invade the neoplastic tissue, they release protons generating local acidosis. The increased frequency of the apoptotic phenomenon within the neoplastic microenvironment contributes to acidosis, as apoptotic cells release intracellular ions in order to create a more acidic pH, thus activating the specific signaling by acid-sensing channels that are expressed by nociceptors. Tumor-induced release of protons and acidosis are thought to be particularly important in the generation of bone cancer pain. Both osteolytic (bone-destroying) and osteoblastic (bone-forming) metastases are characterized by osteoclast proliferation and hypertrophy [43, 45]

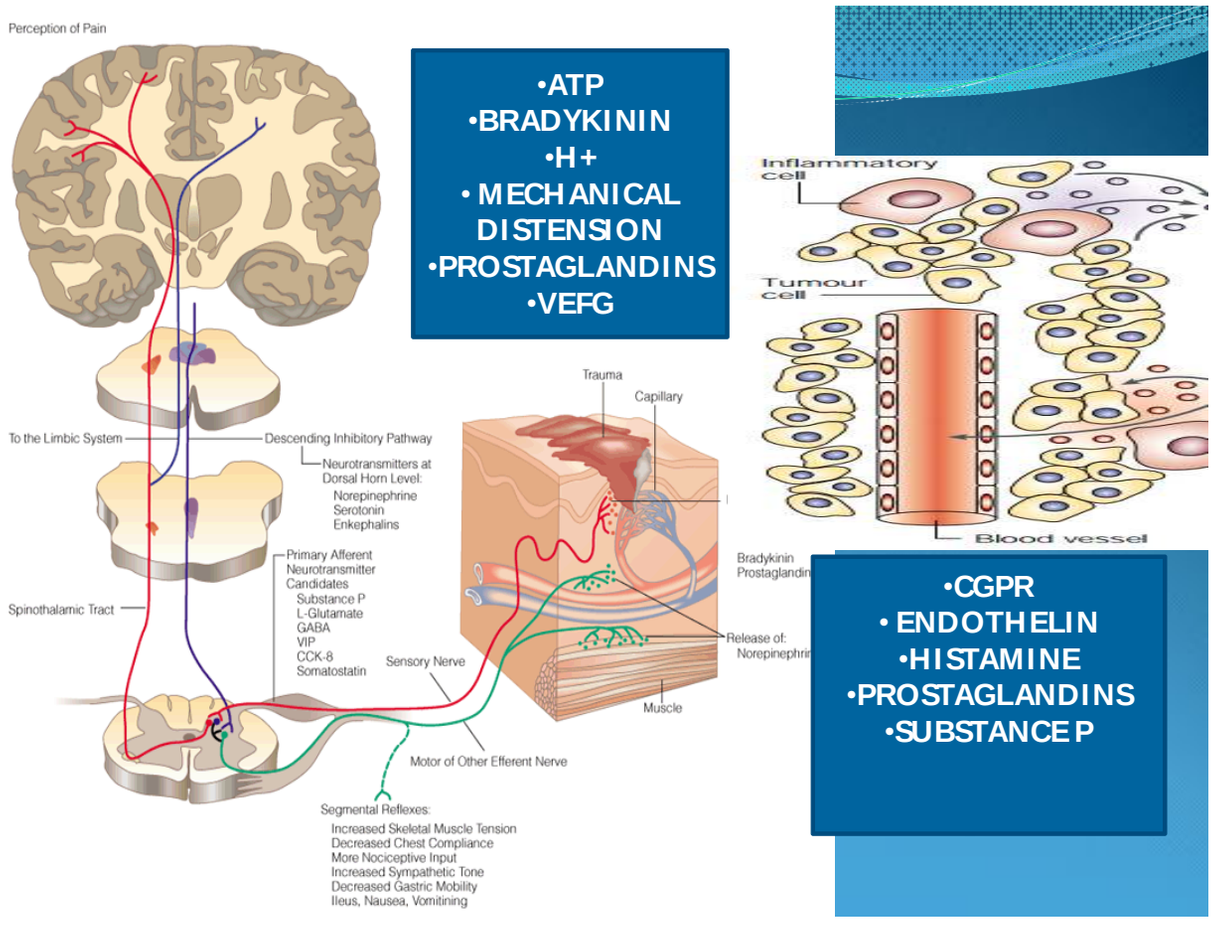


Figure 3. The tumor–nociceptor interface. Figure modified from: Farmaci e Dolore. Di Iorio P. In Saggini R, Buoso S, Pestelli G. (ed) Dolore e Riabilitazione. Minerva Medica 2014. p61

6. Neuropathic pain

Tumors are not densely innervated by sensory neurons. [46, 47] Rapid tumor growth, however, frequently entraps surrounding nerves, causing mechanical injury, compression, ischemia or direct proteolysis.

Proteolytic enzymes that are produced by the tumor cells may cause injury to the sensory and sympathetic fibers, causing neuropathic pain.

Although the mechanisms that generate and keep up neuropathic pain are still not well understood, several therapies have proved to be useful for the control of neuropathic pain in the general population. Recently, the first animal model of cancer pain was developed through the injection of mouse osteolytic sarcoma cells into the intramedullary space of the mouse femur. A crucial component of this model is that the tumor cells are confined to the marrow space of the injected femur, without invading adjacent soft tissues. Once injected, the cancer cells proliferate, and both basal and movement-evoked pain responses increase as the tumor develops. These seem to be produce the same responses of patients with primary or metastatic bone cancer. [48, 50]

Additionally, the therapies aimed at tumor-cell eradication (such as chemotherapeutic agents) may also cause significant nerve fibers damage and lead to ensuing pain.

Potential mechanisms by which chemotherapeutic agents (such as paclitaxel and vincristine) may cause peripheral neuropathy include their ability to disrupt tubulin function. Tubulin polymerization is necessary for axonal transport of trophic factors, and drugs that interfere with this process may cause degeneration of sensory neurons and release of pro-inflammatory cytokines that sensitize directly the primary afferent nociceptors. [51] Chemotherapy-induced polyneuropathy may early develop during the first cycle of treatment but, in most cases, it appears 3-4 months after the first treatment.

Neuropathic pain is associated with dysesthesia, hyperalgesia, hyperpathia, and allodynia; such sensory disturbances occur predominantly at peripheral level, distally and symmetrically, over the upper and lower limbs with a "gloves and socks" distribution; painful disturbances may spontaneously occur or be evoked by tactile or thermal stimuli, with a continuous or intermittent course. [52]

Initially, the symptoms can be insidious and attributable to other conditions, becoming painful in about 25% of patients. Patients with neuropathic pain may also show osteotendinous hyporeflexia, impairment of proprioception, muscle cramps and hypotrophy, reduced muscle tone with reduced muscular endurance, tremor, dystonia, and dyskinesia, resulting in impairment of sensory-motor coordination and sensory ataxia. [53]

The incidence and severity of neuropathic pain are highly dependent on the type of chemotherapy protocol (mono- or poly-therapy with cumulative doses over time), the association with radiotherapy (RT), the age of patient, and co-morbidities such as diabetes, alcoholism, paraneoplastic neuropathies and other diseases affecting the nervous system.

In hormone-producing cancers deriving from endocrine tissues, the use of agents inhibiting the production or the activity of relevant hormones is a common feature, with particular regard to estrogens, progestins, androgens, corticosteroids, and thyroid hormones.

About 40% of women treated with aromatase inhibitors (AI) present joint and muscular pain in a widespread, symmetrical distribution, often associated with morning stiffness that tends to fade with movement, as well as sleep disorders. The onset of pain, usually mild-to-moderate in intensity, typically occurs within the first few months after starting the therapy. Relevant risk factors include: age over 60 years, obesity, recent menopause, rheumatic diseases, previous chemotherapy and hormone replacement therapy, as well as use of anxiolytics and antidepressants. Such symptoms are, most likely, related to the modification of the pain threshold as a direct consequence of the reduction of circulating estrogens, which have a peripheral antinociceptive effect and play an important role in the modulation of central pain. [54]

RT regimens play a synergistic role with CT, surgery, immunotherapy and hormone therapy for the control of primary and secondary tumor lesions, being also potentially useful to reduce the size or vascularization and bleeding of the tumor as well as to relieve the pain. With regard to the use of RT in palliative care, edema and inflammation in the tissues treated with radiotherapy frequently cause recurring pain. Radiodermatitis, whose severity ranges from simple rash to tissue necrosis, may result in skin discoloration with frequent association with hyperpathia.

Lymphedema causes pain because of locoregional tension within soft tissues and joint traction. These painful symptoms may even appear after a considerable time interval, being intensified by the load and the mobilization but, in advanced cases, pain is present even at rest, resulting in hypomobility and reduction of muscle tone.

Post-radiation fibrosis is a serious dose-dependent complication of RT and may involve the lungs and the soft tissues; fibrosis of skin and subcutaneous tissues (mainly in the neck, face and breast) results in hypomobility, compensatory postural defects, muscle and joint contractures and pain.

Radiotherapy can also determine cervical and lumbar pain developing from a few months up to several years after the beginning of the therapy.

A brachial plexus neuropathy (plexopathy) can occur due to radiation treatment for breast cancer, head and neck or pulmonary apex, may represent a difficult differential diagnosis with the possibility of neoplastic infiltration of the plexus.

Post-radiation plexopathies preferentially affect the upper roots (C5-C6), while direct infiltration by neoplastic cells normally involves the lower trunks (C7-C8-T1). The clinical picture may be initially characterized by dull and deep pain referred to the shoulder, armpit and arm, usually of mild-to-moderate intensity, associated with tingling paresthesia in the distribution root C5-C6-C7, followed by motor impairment, heaviness, predominantly proximal weakness, and functional limitations, especially with regard to flexion and abduction. [56]

Coexistence of plexopathy following radiotherapy and postsurgical lymph edema may occur as well, triggering a vicious circle in which limb pain is increased by the weight of the lymphedematous limb determining motor and functional impairment.

The progression of the neurological deficit occurs through multiple steps, with the final result being the flaccid paralysis of the upper limb.

The lumbosacral plexopathy is a rare, adverse effect following irradiation for pelvic, abdominal, uro-gynecological, or bowel tumors. In 50-75% of lumbosacral plexopathy cases, the neuropathy starts at lower limbs level presenting as bilateral deficit affecting the distal surface sensitivity and, to a lesser degree, proprioceptive sensitivity; the motor deficit, mainly involving the districts innervated by the distal roots L5-S1 (55% of patients), presents as a bilateral, asymmetrical lower limbs deficit, resulting in impairment of dorsiflexion of the foot as well as gait and balance disorders. The coexisting pain radiating along the face of the posterolateral thigh and leg increases the risk of falls in association with sensorimotor deficits.

Among patients undergoing RT for prostate cancer, 20% of cases may develop a challenging neuropathy as earlier as after the first 12 months of RT, resulting in chronic pelvic pain often associated with dysuria, dyspareunia, rectal tenesmus, and abdominal pain.

Spine irradiation may cause vascular damage, demyelination, and focal necrosis of the white matter of the spinal cord, resulting in a post-RT myelopathy, which may be classified in acute, sub-acute, and chronic subtypes, depending on the time of onset after RT.

Cancer pain syndromes may be further classified as acute and chronic syndromes.

Acute pain syndromes have a sudden, well-defined onset, present with an identifiable cause (e.g. surgery). They are affected by sympathetic responses (fight or flight response), and are expected to improve with adequate care. The acute form most commonly occurs in head and neck cancers after treatment of the cervical-cephalic district, being characterized by a positive Lehermitte sign, stabbing pains in the neck exacerbated by flexion of the head, and radiation to the column and the limbs, with sensory, motor, and autonomic symptoms.

Chronic pain has a less distinct onset, shows a prolonged and fluctuating course, and is largely driven by central sensitization. [57]

In chronic pain, the algic symptom, referred to the dermatomes at or below the levels treated by RT, precedes the neurological signs and leads to increased difficulties in motor coordination and execution of daily activities. The chronic form may present as transverse myelitis, with tetraparesis or Brown-Sequard syndrome. [58]

A crucial question is whether the spinal cord and forebrain undergo significant neurochemical changes while chronic pain develops. Studies involving the mouse model of bone metastases pain, described above, revealed extensive neuro-chemical reorganization in the spinal cord segments that receive input from primary afferent neurons innervating the tumor-bearing bone.

Such changes include astrocytes hypertrophy, accompanied by decreased expression of glutamate re-uptake transporters. [59, 60]

This results in increased extracellular levels of the excitatory neurotransmitter glutamate and excitotoxicity within the central nervous system. The up-regulation of the proalgesic peptide dynorphin was also observed in the spinal cords of tumor-bearing animals.

Spinal-cord expression of dynorphin — a pro-nociceptive member of the opioid family [61, 62] - has been observed in animal models of neuropathic [63], inflammatory [64, 65], and sarcoma-induced bone cancer pain states. Cancer pain induces, therefore, a state of central sensitization, in which neurochemical changes in the spinal cord and forebrain promote an increased transmission of nociceptive information.

Classically, the main emphasis when examining the ascending conduction of pain has been placed on spino-thalamic tract neurons. This means that the general mood and attitude of the patient might also be a significant factor in determining the intensity and degree of pain.

Clinical studies, however, have resulted in the revision of such thesis, showing that attenuation of some forms of visceral cancer pain can be achieved by disruption of non-spinothalamic-tract axons. [66]

Chronic pain entails adverse effects on various organ systems, as seen with non oncological pain.

An inadequate treatment of pain has negative effects at the psychological, respiratory, cardiovascular, endocrine and metabolic, and gastrointestinal levels. The persistently active proalgesic stimulation affects both somatomotor neurons, generating reflex phenomena such as muscle spasm, and sympathetic neurons, with norepinephrine-mediated activation resulting in peripheral vasoconstriction, cardiac work increase, visceral hypotonia, and gastrointestinal and genito-urinary incontinence.

Indeed, the persistence of pain determines augmented sympathetic nerve activity, with increased release of catecholamines, antidiuretic hormone, (ADH), angiotensin II, aldosterone system, and related cytokines. The activation of the sympathetic-adrenal axis with release of corticotropin releasing hormone (CRH) and ADH activates a subset of processes that the body normally implements when facing emergency situations: in particular, activation of catabolic reactions (ie, those reducing the lean body mass) is accompanied by chronic fatigue and insomnia, as seen when dealing with stressing situations.

Mood disorders (anxiety, apathy, depression) associated with catabolic metabolism are accompanied by an imbalance in the levels of electrolytes, especially potassium. These changes affect the excitable tissues (muscles and nerves) as potassium is a regulator key of the electricity transmission; likewise, it may have effects on the nervous system and transmission of painful signals.

Gastrointestinal disorders (bloating, feelings of fullness, food intolerance, slow digestion) may also occur, as a consequence of the imbalance of electrolytes; indeed, peristalsis is implemented by muscles which, despite not being voluntarily controlled, have similar characteristics to the skeletal.

In addition, the state of catabolism induced by the action of stress factors affects blood regulation and storage of sugars, which are mostly accumulated in muscle tissue. Loss of muscular tissue leads, therefore, to a deregulation of glucose metabolism resulting in loss of appetite or excessive and unjustified sense of hunger (typically during the night). These two symptoms often alternate between each other.

Dysregulation of cortisol release results in peripheral vasoconstriction and limbs muscles catabolism. The inadequate cortisol regulation and the consequent loss of muscle mass can as well affect the amount of adipose tissue, leading to a relative increase of the latter. Chronic pain often predisposes to a complex series of physiological and psychosocial changes, which are an integral part of the chronic pain issue, being added to the existing burdens occurring to those who suffer. [67]

7. Chronic pain syndromes

Causes	Disorders
Nociceptive somatic pain due to bone metastases	Multifocal bone pain, vertebral pain syndrome in epidural spinal cord compression, pain syndrome related to pelvis and hip, base of skull
Nociceptive somatic pain due to soft tissue involvement	Headache and facial pain, ear and eye pain, pleural pain, muscle cramps
Nociceptive visceral pain due to malignancy	Hepatic distention syndrome, chronic bowel obstruction, midline retroperitoneal syndrome, malignant perineal pain, ureteric obstruction
Neuropathic pain due to malignancy	Radiculopathies, mononeuropathies, plexopathies, neuralgias, peripheral neuropathy
Antineoplastic therapies (i.e. chemotherapy, radiation therapy, hormonal treatments, surgery)	Peripheral neuropathy, chronic post-surgical pain (eg.mastectomy, thoracotomy, neck dissection, pelvic surgeries), phantom limb pain, chronic radiation myelopathy, chronic radiation plexopathy, chronic radiation proctitis and enteritis, lymphedema pain, osteoradionecrosis

Table 1. Chronic pain syndrome

8. Breakthrough pain

Breakthrough pain is a common problem in patients with cancer, being associated with significant morbidity. Currently, there is no universally accepted definition of ''breakthrough pain". Portenoy et al. have defined breakthrough pain as ''a transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline (background) pain" (Portenoy et al., 2004).

Breakthrough pain is usually classified into one of two categories:

1. Spontaneous pain (''idiopathic pain") – the episodes are not related to any identifiable precipitant factors.
2. Incident pain (''precipitated pain") – the episodes are related to an identifiable precipitant factor. Incident pain is usually sub-classified into one of three categories:

3. Volitional incident pain – pain is exacerbated by a voluntary act (e.g., walking).
4. Non-volitional incident pain – pain is exacerbated by an involuntary act (e.g., coughing).
5. Procedural pain – pain is related to a therapeutic intervention (e.g., wound dressing).

Breakthrough pain is associated with poor overall pain control (Bruera et al., 1995) as well as decreased patient satisfaction with overall pain management (Zeppetella et al., 2000). In addition, breakthrough pain may result in a number of physical (e.g., immobility), psychological (e.g., insomnia, anxiety, depression) and social (e.g., unemployment, social isolation) complications (Skinner et al., 2006). Indeed, the presence of breakthrough pain may have a significant impact on the quality of life (Skinner et al., 2006).[68]

9. Pain assessment

Clinical practice guidelines developed by the National Comprehensive Cancer Network (NCCN) [69] and American Pain Society (APS) emphasize the essential need of a comprehensive pain assessment. [70]

A careful evaluation of pain should include history, pain description (in particular, establishing whether it worsens during the sleep), precipitating and alleviating factors, functional impairment, psychological associated factors, psychosocial history as well as patient's beliefs, physical examination, and a general knowledge of the different features of cancer-induced and nonmalignant pain; such evaluation will allow a comprehensive assessment of pain. Conversely, an inadequate measurement and assessment of pain poses a significant obstacle to any effective pain management strategy.

Patient interview:

Onset of pain?
Frequency of pain?
Site of pain?
Radiation of pain?
Quality (character) of pain?
Intensity (severity) of pain?
Duration of pain?
Exacerbating factors?
Relieving factors?
Response to analgesics?
Response to other interventions?
Associated symptoms?
Interference with activities of daily living?

Figure 4. Pain assessment: Interview

An adequate pain assessment requires a thorough pain anamnesis as well as physical examination prior to any radiographic study or physiological testing. Failing to collect a comprehensive anamnesis and performing a correct physical examination will result in frequent

mistakes, as correspondence between pain severity, as reported by the patient, and presence of underlying pathology, as revealed by imaging studies, is often poor. Location, radiation, quality, intensity and temporal pattern of pain should be ascertained along with provocative and palliative factors associated with pain; afterwards, the physician should map the source of pain and investigate any clues to a possible cause; finally, the following pain features should be identified:

- Type of pain (nociceptive, neuropathic, psychogenic);
- Temporal characteristics (acute, chronic, intense episodic);
- Intensity (mild, moderate, severe).

Physical examination should be focused on the area of pain without overlooking areas of referred pain (such as the right shoulder in case of hepatic metastases).

Physical examination is followed by specific maneuvers in order to provoke or improve pain.

For instance, pain due to bone metastases may be provoked through local palpation and manipulation. Spinal cord compression resulting from epidural tumor extension represents a known challenge. Accordingly, a comprehensive neurologic examination, coupled with manual muscle testing, percussion of point of tenderness, evaluation of joint mobility, and inspection of muscle symmetry are crucial steps of any physical examination.

The assessment of psychiatric and psychosocial co-morbidities is crucial to address factors that may adversely affect pain perception and worsen patient's distress. Radiographic studies should be guided by the anamnesis and the physical examination, as well as stage of disease, patient performance status, therapeutic options, and care endpoints. When dealing with terminally ill patients, or when little would be gained by radiographic procedures, palliative measures should be implemented without putting the patient through painful, unnecessary testing. Whenever appropriate, pain treatment should be started as early as possible so that patients may be comfortable and able to complete the diagnostic procedure. Plain radiographs of painful areas may be of value.

Magnetic resonance imaging (MRI) of the spine and brain and computed tomography (CT) scanning of the chest and abdomen often provide the greatest amount of information. In case of pericardial effusions or biliary or urinary tract obstruction, ultrasonography may be easily accomplished with a portable device, thus avoiding radiation exposure. Electrophysiologic studies may be useful to distinguish mononeuropathies and entrapment neuropathies from plexopathies, as well as ulnar and peroneal entrapment syndromes from brachial and lumbar plexopathies, respectively. Conduction velocities, specific latencies, amplitudes, duration, and configurations of sensory and motor evoked potentials are the keys to identify and locate the neural pathology. Importantly, it should be remembered that results of electrophysiologic studies may be normal even with significantly damaged non-myelinated fibers.

The ability to measure pain implementing valid and standardized approaches has improved in the last years, increasing our ability to quantify the impact of adequate care in terms of outcomes. The use of standardized instruments (scales), both of a specific type (focused on the

pain) and of a generic type (quality measures of life), as well as the implementation of other measures aimed to capture the results in terms of consumption of resources and medical care, has made it possible, when required, to assess the overall impact of pain on the health and life of patient. Initial and ongoing assessment of pain includes the evaluation of pain intensity using a visual or numerical rating scale ranging from 0 (absence of pain) to 10 (presence of the worst imaginable pain). Other relevant factors in pain assessment include ascertaining the quality of pain, onset, and duration as well as any actions that may worsen or relive the pain. Careful patient interviews should also evaluate the extent of patient distress resulting from pain as well as various psychological or social factors.

The Pain Research Group of the WHO Collaborating Centre for Symptom Evaluation in Cancer Care has developed the Brief Pain Inventory (BPI), a pain assessment tool devised for cancer patients. The BPI measures both the intensity of pain (sensory dimension) and the interference of pain with the patient's daily activities (reactive dimension). It also queries the patient about pain relief, pain quality, and patient perception of the cause of pain.

The BPI is a powerful tool and, having demonstrated both reliability and validity across different cultures and populations, it has been adopted in many countries for clinical pain assessment, epidemiological studies, and in studies evaluating the effectiveness of pain treatment.

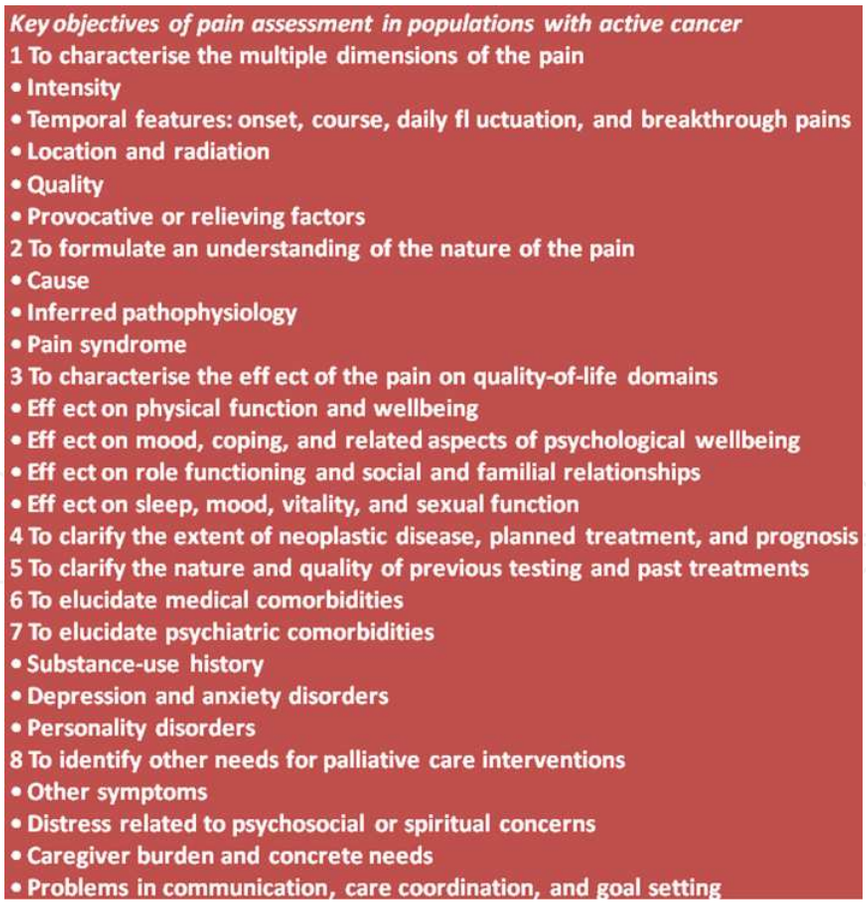


Figure 5. Pain assessment: Objective

With regard to specific assessment tools, the main validated scales used in oncology are the followings:

- Short-Form McGill Pain Questionnaire 8 (SF) ;
- Brief Pain Inventory (BPI);
- European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ C309);
- Karnofsky performance status.

10. The management of cancer pain

An adequate control of pain is reached through three basic strategies: modifying the source of the pain, altering the central perception of pain, and blocking the transmission of the pain to the central nervous system. [71]

The optimal use of these strategies in the control of cancer pain requires a thorough assessment of patient's pain, cancer features, concurrent medical problems, and psychosocial status. [72, 73]

An individualized plan of care must be established, implemented, reassessed, and then modified on a regular basis in order to maximize both the quality and duration of life. The pain affecting the vast majority of patients with cancer may be relieved through direct and indirect modifications of the source of pain combined with pharmacologic and non pharmacologic actions aimed at modifying the patients' perception of pain. [74]

The Three-Step Analgesic Ladder of the World Health Organization uses these three categories of pain to guide analgesic-drug therapy. [75]

Patients receiving no analgesic therapy who have mild-to-moderate pain should be treated with nonopioid analgesic drugs (step 1). If a patient has mild-to-moderate pain despite taking a nonopioid analgesic, the dose of the nonopioid analgesic should be maximized and a step 2 opioid analgesic should be added (step 2).

Patients who have moderate- to-severe pain despite being treated with step 2 opioids require an increase in the dose of the opioid or, if that is not feasible, a change to a step 3 opioid. This method has been estimated to effectively relieve pain in 80 to 90 percent of patients.[76, 77]

Many experts recommend a step 2 opioid as initial therapy for patients with moderate pain [78, 80], further suggesting that therapy with a step 3 opioid may be immediately started when pain is severe. Patients who have mild-to-moderate pain while taking a step 3 opioid should have the dose of that opioid increased until an effective level is reached. (Fig 5)

Non-opioid, step 1 analgesic drugs include acetaminophen, aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs). These drugs are of limited value to patients with pain from advanced cancer because of their relatively low maximal efficacy. [81]

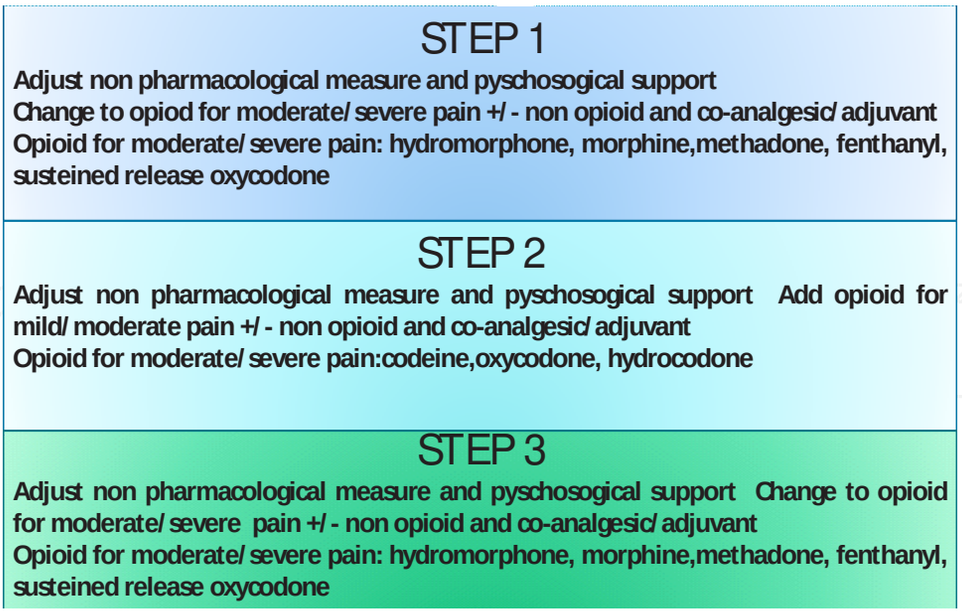


Figure 6. The Three-Step Analgesic Ladder of the World Health Organization uses these three categories of pain to guide analgesic-drug therapy.

The step 2 opioids used to treat moderate pain include codeine, dihydrocodeine, hydrocodone, oxycodone, and propoxyphene. Use of step 2 opioids is limited by dose-limiting side effects or because they are prepared in fixed combinations with non-opioid analgesics.

Step 3 opioids commonly prescribed for the relief of moderate-to-severe cancer pain include morphine, oxycodone, hydromorphone, and fentanyl.

These opioids should be used one at a time to take advantage of possible idiosyncratic differences in patients' responses.

Morphine is the step 3 opioid most commonly used to control severe pain, because of its wide availability, varied formulations, as well as well-characterized pharmacologic properties. [82]

In some patients, switching from one opioid to another can eliminate an unmanageable, idiosyncratic side effect of the initial drug. [83] In patients whose pain is well controlled, the initial dose of the new opioid should be 25 to 50 percent less than the estimated equivalent dose to allow incomplete cross tolerance. [84]

Over the years the above treatment strategy has been undergoing a number of critical changes, as it has been realized that the scale of treatment (i.e. step 1 vs step 2 vs step 3) should not be necessarily gradual, but it should rather comply with the stadium and the clinical phase of pain experienced by each patient.

Accordingly, if pain is already reported as severe from the beginning, then it should be treated with step 3 medications and adequate dosage without the need to follow the steps of sequential scale.

Analgesic drugs, indeed, remain the keys of cancer pain managment. The choice of drug should be based on the severity of the pain, rather than on the stage of disease. Drugs should be given

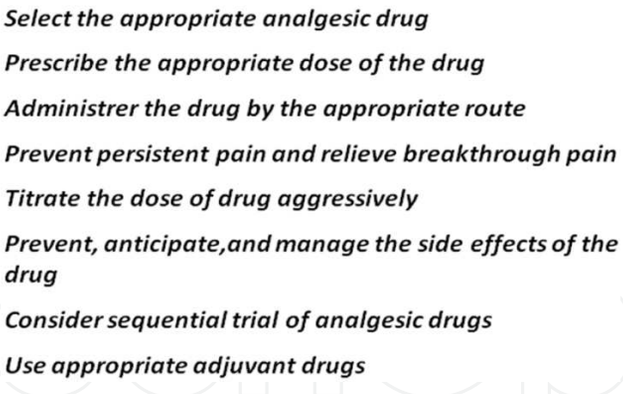


Figure 7. Pain assessment: Interview

in standard doses at regular intervals. When a non-opioid drug is to be used with an opioid for moderate pain, patients often prefer to receive fixed combinations of the two analgesic agents. Care must then be taken in order to assess the dose of each drug contained in such formulations; indeed, some combinations of codeine or dihydrocodeine with aspirin or paracetamol (including co-codamol and co-dydramol) contain subtherapeutic doses of the opioid. Likewise, the decision to use an opioid for severe pain should be based on severity of pain rather than on prognosis.

It is also important to emphasize that, at every step, adjuvants drugs may be added to the protocol treatment. Adjuvant drug therapy enhances the analgesic efficacy of opioids, treats concurrent symptoms that may exacerbate pain, and/or results in an independent analgesic effect for specific types of pain. [85]

Early use of adjuvant drugs is warranted in order to optimize patients' comfort and function by preventing or reducing the toxic effects of opioids. Cancer-pain syndromes most amenable to adjuvant therapy are those caused by bone metastases, nerve compression, nerve damage, and visceral distention.

The most commonly used drugs in adjuvant therapy for the treatment of cancer pain are NSAIDs, corticosteroids, tricyclic antidepressant drugs, and anticonvulsant drugs.[86]

Additionally, treatment of pain strategies should allow for two further variables: 1) the possibility to adopt an opioid rotation strategy, and 2) the choice of the correct drug administration route: non invasive or invasive.

The importance of taking care of the cancer patient rehabilitation has been sanctioned also in the Italian Health Plan Oncology 2010-12, with the model "Simultaneous Care" expressing that "Rehabilitation in oncology should start from diagnosis and continue throughout life".

It is, therefore, necessary that the cancer patient is taken care of by a specialist who, through the formulation of Individual Rehabilitation Project, is specifically involved in the prevention, care and clinical monitoring of the pain and disease. [87]

The Cancer Rehabilitation Treatment has the following goals:

- Preventive – to improve function and reduce morbidity and disability;

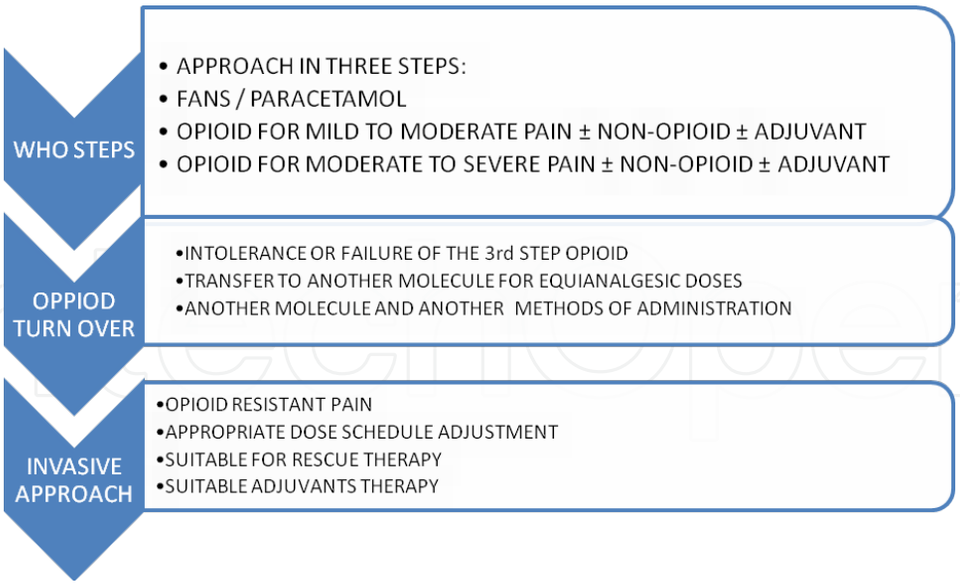


Figure 8. Pharmacologic pain management

- Restorative – for patients with the potential to be completely cured from cancer, to appropriately control, circumvent, or eliminate any residual disabilities;
- Supportive – for patients who are supposed to survive with cancer for a significant time with relative control of disease or remission, to lessen disability, handicap, emotional stress, or discomfort through rehabilitative care;
- Palliative – for patients whose disease is advanced and relentlessly progressive, but whose disability, discomfort, and stress can be mitigated by rehabilitation.

Physiatrists should tailor an individual rehabilitation project depending on the type of tumor, symptoms and signs, presence of complications, stage and evolution, needs and expectations of the patient and his family. [88, 89]

11. Rehabilitation approach to pain

A complex and global rehabilitation program in cancer pain is composed of the following components:

1. Recovery of residual capacity:
    - Educational interventions regarding lifestyle and behavior;
    - Nutritional support;
    - Multimodal Physical Activity;
    - Myofascial manual therapy (relaxation, lymphatic drainage, therapy of the scars);
    - Physical energies;

2. Sensory-motor and functional recovery capacity:
   - Analysis of posture and movement with tridimensional optoelectronics systems, implemented in collaboration with bio-engineers;
   - Therapy in microgravitary environments and Sensorimotor training with swinging platforms in the tridimensional space with the aim of learning again the balance, and postural control through vertebral reeducation and visual feedback;
   - Prescription of prostheses, orthoses;
   - Counseling activities for health and nursing;
3. Quality of life improvement: inclusive approach with home therapy and occupational therapy.

11.1. Recovery of residual capacity

The maintenance of an adequate nutritional status is important because it reduces the risk of recurrence and complications related to cancer therapy by contributing to the general well-being of the patient. Accordingly, nutritional support is an essential part of the treatment of cancer patients.

The need for informed lifestyle choices by cancer survivors becomes particularly important particularly important upon completion of of therapy when trategie self-care improve their long-term results.

Despite being highly variable depending on the type of cancer and stage at diagnosis, cancer may cause several metabolic and physiological alterations affecting the body requirements of macro- and micronutrients.[90]

The American Cancer Society (ACS) convened a group of experts in nutrition, physical activity, and cancer to evaluate and summarize the available scientific evidence and best clinical practices related to nutrition and physical activity after the diagnosis of cancer. Accordingly, it has been highlighted that patients undergoing cancer treatment often experience significant nausea and vomiting, leading to further weight loss. [91]

Because of such clinical evidence, cancer has been considered as a disease associated with weight loss, rather than obesity.

Nonetheless, with growing numbers of overweight or obese patients beginning the cancer treatment protocols, additional weight gain has also been noted as a possible complication of treatment. [92, 94]

Nutritional assessment for survivors should, therefore, begin immediately after diagnosis and should take into consideration treatment goals (curative, control, or palliation), while focusing on both the current nutritional status and the expected nutrition-related symptoms. [95]

During active cancer treatment, the overall goals of nutritional care for survivors should be to prevent or resolve nutrient deficiencies, achieve or maintain a healthy weight, preserve lean body mass, minimize nutrition-related side effects, and maximize the quality of life.

Malnourished patients are less able to tolerate surgical therapy, chemotherapy, radiation therapy, and drug therapy, undergoing pain and related complications such as prolonged bed rest and lymphedema more frequently than subjects in a better nutrition state. For all these reasons, cachexia may threaten the patient's life even more than the local effects of the tumor itself. Cancer cachexia presents clinically with anorexia, altered taste perception, and subsequent weight loss, loss of muscle mass and general malnutrition causing a significant reduction in physical, immune, and mental functions. As a consequence, the body cannot implement adequate defensive strategies.

The causes of anorectic-cachexia syndrome have not been fully clarified yet. The intermediate products of tumor metabolism and the immune response to the tumor itself may be a direct cause of anorexia or early satiety, or produce these same symptoms in a indirect way by an effect on hypothalamic functions.

Macrophage activation products Interleukin-1 and Tumor Necrosis Factor (TNF) thus increasing the release of triglycerides from the adipose tissue and amino acids from the muscular tissue. These cytokines may be important factors in the development of cancer cachexia, but the precise mechanism by which this occurs is not clear. These cancer-dependent metabolites may also be responsible for the anomalies in the sensation of taste and smell that have been observed in cancer patients.

Patients may notice increased or decreased perception of sweet taste. The threshold for salty and sour tastes is often increased, while the one for the bitter taste is usually decreased. A lower threshold for the bitter taste (specific testing substances that can be used include urea) is often responsible for the aversion to meat that is frequently present in these patients. [96]

The psychological stress associated with neoplastic disease may contribute to anorexia. Even in the absence of frank depression, the presence of pain, decreased sense of well-being, depressed mood and anxiety about the treatment regimen or the prognosis, tend to cause a state of emotional stress that antagonizes the sense of gratification from food. Patients complaining of nausea or other disorders, for example as a result of radiation therapy or chemotherapy, may develop food distaste. These aversions tend to persist even after therapy has been completed. Nutritional deficiencies or excesses may occur in patients who decide to avoid certain foods because of misplaced beliefs that they may contribute to the genesis of cancer, or in case of excessive consumption based on the false expectation of beneficial effects.

Although the reduction in nutritional intake seems the main cause of nutritional decay, it cannot entirely explain the progressive loss of weight that often occurs despite an apparently adequate nutritional intake.

Other mechanisms have been suggested, such as the followings: an abnormal adaptation to fasting, with an increase rather than a decrease in catabolism; the cancer invasion of the host tissue during the process of tumoral growth; the alteration of intermediary metabolism.

In general, the tumor is usually considered too small to have a significant effect of metabolic absorption so as to produce the decay of the host; nonetheless, the presence of a tumor may also induce alterations in the metabolism of carbohydrates, fats and proteins increasing, as a consequence, the energy demands.

Depending on the clinical setting, an adequate caloric intake should be 1.2-1.5 times the resting energy consumption (30-35 kcal / kg / day). Lower values should be considered at risk of malnutrition. A caloric intake below 50% of the needs for a period of at least a week poses the need for an artificial nutritional intervention.

Leucine, isoleucine and valine are part of the family of neutral amino acids, and their oral supplementation, at a dosage of about 10-20 g / day, has proved to be effective in improving anorexia (through their ability to reduce the entry of tryptophan in the brain, and therefore the synthesis of serotonin) and, at the same time, promote muscle protein synthesis, at the expense of degradation processes.

The omega-3 fatty acids, in particular eicosapentaenoic acid (EPA), having an anti-inflammatory effect and inhibiting the synthesis of several pro-inflammatory cytokines, have been showed to have, at a dosage of at least 2 g / day, an efficacy equal to that of megestrol acetate in improving the appetite of cancer patients. Such lipid substrates are also able to mitigate the ubiquitin-dependent protein degradation mechanism in a direct way or through an indirect modulation of the action of pro-inflammatory cytokines. Studies dating back to a few years ago seemed to demonstrate that the administration of specific nutritive supplements enriched in proteins and EPA could result in a significant increase of body weight, lean body mass, functional activity and quality of life in patients with pancreas cancer, provided that the daily intake of EPA was not inferior to 2g. A recent meta-analysis conducted on five controlled clinical trials showed that there are insufficient data confirming that supplementation with EPA as a single oral agent is advantageous compared to placebo for therapeutical purposes. However, recent experiences seem to show a significant advantage of EPA supplementation after esophageal surgery.

It seems more appropriate to administer these supplements with a preventive goal, rather than therapeutic, as part of a process of metabolic-nutritional follow-up, supervised by specialists in the field of nutrition.

Carnitine plays a decisive role in the metabolism of long-chain free fatty acids, thus affecting lipid metabolism and energy reserves within the cells. Carnitine is a necessary cofactor for the transport of long-chain fatty acids within the mitochondrial matrix, where they are subjected to oxidation for the production of cellular energy.

A clinical study has shown that administration of 6 g/day of L-carnitine for the duration of 30 days was able to significantly improve the symptom "fatigue", appetite and lean body mass of patients. Therefore, the administration of L-carnitine should be recommended in cachectic patients at a dose of 4-6 g/day orally for a period of time of 3/4 months, being usually well tolerated by the patient. Occasional side effects of L-carnitine include epigastralgia and, more rarely, diarrhea. [97, 100]

After cancer treatment, weight gain or loss should be managed with a combination of diet changes, physical activity, and behavioral strategies. For patients who need to gain weight, this means increasing energy intake to exceed energy expenditure, while for patients who need to lose weight, caloric intake should be reduced while increasing energy expenditure via increased physical activity to exceed energy intake. Reducing the energy density of the diet by

recommending low-energy foods (eg, water- and fiber-rich vegetables and fruits) and limiting the intake of foods and beverages rich in fat and added sugars promotes healthy weight control. Likewise, limiting portion sizes of energy-dense foods is an important accompanying strategy. [101]

Two large randomized controlled trials have tested whether a reduction in fat intake following the diagnosis of early stage breast cancer may affect cancer outcomes. The WINS study tested a low-fat diet (aiming for less than 15% of total caloric intake from fat) in 2437 postmenopausal women with early stage breast cancer and found an effect on relapse-free survival that was of borderline statistical significance.[102]

On average, patients in the intervention group decreased their fat intake to 20% of total caloric intake during the first year of the study, and the intervention resulted in a 24% reduction in new breast cancer events, with subset analyses suggesting that this effect was greater among women with ER-negative disease.

As previously described, women assigned to the low-fat diet (intervention group) lost an average of 6 pounds over the course of the study, thus posing the dilemma as to whether the reduction in breast cancer events was due to dietary fat restriction or lower body weight.

The Women's Healthy Eating and Living (WHEL) Study tested the effect of a diet low in fat (aiming for 20% of total caloric intake) and very high in vegetables, fruits, and fiber on cancer outcomes in 3088 pre- and postmenopausal breast cancer survivors who were followed for an average of 7.3 years. After 4 years, women in the intervention group reported a reduction in fat intake (from 31.3% at enrollment to 26.9% of total caloric intake), but recurrence-free survival did not differ between the two groups. [103] Notably, women in the WHEL Study intervention group did not exhibit weight loss, in contrast to the low-fat diet intervention group in WINS. The WHEL Study recorded an improved prognosis in women without hot flashes at time of study enrollment, who were therefore likely to have higher circulating estrogen concentrations, suggesting that there may be a survival benefit in this subgroup. [104]

The maintenance of an adequate body weight is possible in our experience using a special composed Mediterranean food which is precooked and conveniently formulated (Eatarte & Corpo53 Italy) allowing a reduction of body mass index, a reduction in chronic inflammation indices, a decreased risk of lymph edema and a decreased risk of pathological fractures (being thus ultimately associated with an improvement in pain and quality of life).

The general benefits of multimodal physical activity in cancer treatment are numerous and include: improved cardiac output, increased ventilation, improved flexibility and range of motion; increased muscular strength and endurance; decreased resting heart rate; improved stroke volume, vasodilatation, perfusion; improved metabolism; improved blood count parameters; improved psychological attitude and ability to face the cancer disease. The cancer-specific benefits are related to cancer treatment toxicities, with particular regard to muscular degeneration, including 1) fatigue and weakness, 2) neurotoxicity, 3) cardiotoxicity, 4) pulmonary toxicity. [105]

The main goal of exercise is to address inactivity/immobility (specific or general) and fear of movement. The detrimental effects of immobilization are well documented and include muscle

wasting/weakness, joint stiffness, reduced motor control, mood changes, decreased self-efficacy, reduced coping capacity and cardiovascular unconditioning. The multimodal exercise program must be tailored to the individual needs of the patient and should start cautiously, building up gradually and being within the patient's tolerance levels.

A recent meta-analysis of 78 exercise intervention trials showed that exercise interventions resulted in clinically meaningful improvements in quality of life that persisted after the completion of the intervention. [106] In another meta-analysis of 44 studies that included over 3000 participants with varying cancer types, cancer survivors randomized to an exercise intervention had significantly reduced cancer related fatigue levels, with evidence of a linear relationship with the intensity of resistance exercise. [107]

Historically, there were concerns that cancer patients with upper extremity lymphedema should not engage in upper extremity resistance training or vigorous aerobic physical activity. There are now multiple trials that have demonstrated that such physical activity is not only safe, but actually reduces the incidence and severity of lymph edema.

There is substantial research on physical activity in breast cancer survivors and multiple systematic reviews focused on its role in these patient subset. [108, 109]

In a meta-analysis of 717 breast cancer survivors participating in 14 randomized controlled trials, physical activity led to statistically significant improvements in quality of life, physical functioning, and peak oxygen consumption, as well as reduction in symptoms of fatigue and pain. [110, 111]

Multimodal physical activity entails instructing patients in strengthening, stretching, and aerobic conditioning. The physical therapists should play a role in providing education on proper body mechanics, lifting techniques, proper posture, benefits of aerobic exercise and discussions of pain behaviors. Importantly, physical measures should be implemented as early as possible to minimize the generalized unconditioning and myofascial pain associated with reduced activity as well as intervals of immobility associated with cancer and its therapy. [112]

The benefits of exercise and increased physical activity among people diagnosed with cancer are numerous, including improved function, quality of life, strength, and endurance, and reduced depression, nausea, and pain. [113] Beaton et al, [114] in their systematic review found strong, high-quality evidence in favor of exercise interventions (aerobic exercises and strength training given alone or as part of a multimodal physical therapy program) in patients with metastatic cancer for improving physical and quality of life measures. McNeely et al, [115] found that a progressive resisted exercise training (PRET) program significantly reduced shoulder pain and disability and improved upper extremity muscular strength and endurance in postsurgical head and neck cancer survivors who had shoulder dysfunction due to spinal accessory nerve damage.

Keays et al [116] found improvements in shoulder range of motion and function in women with breast cancer undergoing radiation therapy, by virtue of a Pilates exercise program involving whole body movements with breath control. Similar improvements in pain and mobility were observed following physiotherapy intervention (exercises, soft tissue massage to surgical scar) in breast cancer patients who underwent axillary dissection. [117]

Graded and regular physical activity as a component of a multimodal physical activity program for the treatment of cancer pain [118] exerts a direct influence on the peripheral musculoskeletal system via the exercising muscles. Importantly, for these programs to be effective, physical activity should be always accompanied by behavioral training and adequate patient education.

Recovery of joint mobility and flexibility and treatment of soft tissue should be achieved through a strategy taking in to account age, sex and underlying disease as well as the intensity of the pain threshold. Additional treatment goals should include increased muscle tone of the healthy fibers as well as re-balancing muscle synergies and reprogramming both static and dynamic posture. Flexibility, one of the physiological parameters involved in almost all forms of human movement, is another trainable fitness parameter in addition to aerobic capacity, strength, and neuromuscular endurance.

Flexibility has been defined as mobility compliance or, alternatively, as the reciprocal counterpart of stiffness. Most of the authors define flexibility as range of motion either at or about a joint. Another definition classifies flexibility as the ability of a joint to move throughout its potential range of motion. Those definitions confuse the property of flexibility with the range of motion, despite the fact that these two terms are not synonymous; range of motion is one of the several variables determining flexibility, so that flexibility cannot be defined based only on range of motion.

We define flexibility like the disposition of body tissues to allow, without injury, excursions at a joint or set of joints. This property is measured through, but is not equivalent to, range of motion. Both joint tissues and the surrounding soft tissues contribute to flexibility, although only the latter should be targeted by specific treatment in order to augment flexibility.

The best method to properly stretch soft tissues involves a series of less than maximal isometric contractions of the agonist muscles in a pre-lengthened state (to set up the stretch), followed by concentric contractions of the antagonist muscle group (to lengthen the agonist) in conjunction with light pressure whenever needed and using an instrumentation like sensitized postural bench system (TecnoBody, Italy). This approach aims to alleviate muscle tension, facilitate healing via increased blood flow, and decrease muscle pain by reducing vasoconstriction. This stretching protocol should be delivered on a daily basis using a specific personalized postural bench like Fleximat postural bench (Posturale.org Italy).

Myofascial therapy improves local circulation and gently stimulates the free nerve endings, also helping draining local tissue edema and inducing local and general relaxation. One of the well-established scientific forms of massage is the manual lymphatic drainage therapy [119] and the complete decongestive therapy (i.e. combination of manual lymphatic drainage, compression garments, adequate skin care, and range of motion exercises). Massage therapy was shown to be very effective to relieve symptoms of cancer-induced pain in numerous studies. Soft tissue mobilization is widely practiced in the management of pain and includes techniques such as scar mobilization/massage, myofascial techniques and connective tissue massage. [120, 121]

Reeves [122] emphasized the relevance of changes in patient positioning, relaxation techniques against insomnia, and energy conservation techniques for chronic fatigue in patients with cancer pain.

Therapeutic modalities such as electrical stimulation (including transcutaneous electrical neurostimulation), heat, or cryotherapy, can be useful adjuncts to standard analgesic therapy in patients with cancer-treatment-related lymphedema and pain. The treatment of lymphedema by use of wraps, pressure stockings, or pneumatic pump devices with Slim Project Physio (General Project Italy) or vibrational technology with EndoSpheres (Fenix group Italy) may both improve function and relieve pain and heaviness. [123]

Physical therapy treatment techniques have also been reported to be effective in cancer-related fatigue by Watson and Mock, in prostate cancer and breast cancer-related lymphedema, cancer therapy-related hyperthermia, and colorectal cancer. [124]

Mufazalov and Gazizov [125] showed that laser therapy enhanced therapeutic efficacy of pain-relieving drug regimens in patients with cancer pain. Cancer treatments like radiation therapy can induce mucositis in patients with oral or head and neck cancer and can cause oral pain due to impaired wound healing. Bensadoun [126] commented on the importance of low-level laser therapy on wound healing and its role in mucositis treatments. Maiya et al, [127] subsequently showed that helium–neon laser therapy was effective to reduce pain and improve healing of radiation-induced mucositis after 6 weeks of therapy in head and neck cancer patients.

Improvement of the uninjured muscle tone and strength may be possible using a focused vibratory acoustic Cancer Treatment - a conventional and innovative approach using stimulation at high intensity with Vissone (Vissman Italy) - followed by anaerobic work with TRX system.

Vibrations are able to induce muscular changes aimed to the recovery of muscle tone through a frequency of 300 Hz, as well as to stimulate the upper motors centers in order to obtain a control of muscle recruitment work.

It has been noted that, using this treatment protocol, it is possible to: 1) activate the aerobic metabolism; 2) determine an analgesic effect; 3) increase local circulation and bone density; 4) finally increase the contractile capacity and elasticity of the treated muscle.

According to the existing literature, mechanic or acoustic vibratory waves at a frequency of 120Hz are a valid therapeutic tool for the treatment of musculoskeletal pain. The focused vibratory acoustic therapy with quadrangle wave shows a muscle relaxing effect, leading to a rapid interruption of the vicious circuit pain-injury-pain as well as a having a high draining, anti-fatigue and stress relieving effect. [128]

Human studies regarding ultra low frequencies and intensity magnetic fields effects have been carried out in several clinical settings over the last 20 years.

They have proven effective for treating bone and joint diseases, neuropathies, spinal cord injury, diabetic neuropathy, immune disorders and cardio myopathy. [129, 134]

Moreover, in addition to the above data, new possible fields of application have been advanced by studies showing possible effect in several specific neurological diseases. Sandik, for example, has published a number of case reports of diseases such as Parkinson's [135]

Alzheimer's disease [136] and Multiple Sclerosis [137], in which a beneficial effect of the fields ELF on cognitive deficits accompanying these morbid conditions has been documented. Another study [138] reported interesting effects on fatigue and quality of life of 117 patients with Multiple Sclerosis. An additional area of research in which there are promising studies is that of analgesia. [139]

The term bio-resonance points to the form of resonance which is established at the level of cell membranes using electromagnetic fields at a very low intensity and at a specific frequency (cyclotron) which is thought to be able to influence and stimulate the metabolism of human cells by adjusting the ordered traffic of selected ions between the internal and external environments of the cell and by stimulating the activity of those ion-dependent enzymes allowing the occurrence of several biological reactions. The above technology generates electromagnetic waves of low intensity and frequency, (Seqex Q.L.. S.i.s.t.e.m.i. Italy) allowing a particular ion current that optimizes the intrinsic ability of maintaining the potential difference between the intra and extracellular environments and which is thought to be indispensable for the proper functioning of metabolism and cellular homeostasis. [140]

One of the most promising fields of application for such technology is undoubtedly the oncological sector; accordingly, it has been observed that a correct use of ELF fields may lead to a reduction of tumor growth and vascularization as well as of the metastatic spread. [141, 142]

The accumulation of lactic acid in cancer tissues is a well-known source of pain. Studying the metabolism of cancer at the cellular level, Otto Warburg demonstrated in 1930 that tumor cells prefer a particular form of metabolism known as anaerobic (non-oxygen-dependent) glycolysis. Indeed, tumor cells are metabolically active and release several waste products. [143]

The ability to modulate the channels of the membrane by the above-mentioned magnetic fields allows the hypothesis that cancer pain, secondary to oxidative stress, may be controlled through the arousal of appropriate currents of cations and anions.

In particular, it is of particular interest the possibility to modulate the water channels, whose opening would allow the efflux of intracellular water. Inflammatory processes in the cells of the muscle or dermis leads to significant water retention (as shown by visible swelling). This water absorption and swelling, which is thought to be linked to associated painful symptoms, may persist over time (as occurs, for example, after the welding of bone fractures). Accordingly, the induction of the opening of membrane channels allowing the leakage of intracellular water might enable rapid resolution of swelling and pain due to excess intracellular water. [144]

11.2. Sensory-motor and functional recovery capacity

The second phase begins with the clinical physiatrist reassessment, aided by specific diagnostic tests and apposite rating scales, analysis of movement and posture through optoelectronic systems in collaboration with bioengineers, gait analysis with pod barometrical examination, body composition assessment through bio-impedenziometry, and evaluation of cardiac and hematological parameters.

To implement an adequate sensory-motor and functional recovery program the patient needs to reach an acceptable walking ability. The ability to walk is the key to any human movement, despite the fact the human movements are not limited to bipedal locomotion; bipedal locomotion is a fundamental part of daily life and is a prominent target of public health physical activity guidelines.

The human gait is a complex combination of concerted movements; objective monitoring of walking evolution, using pedometer and accelerometer technologies, offers an opportunity to formulate guidelines and recommendations for cancer patients.

Available studies in literature have used a variety of objective parameters based on instruments that have been previously validated.

In order to get a better walking performance, two integrate procedures may be implemented:

1. normalization of the foot-ground reaction forces using customized viscoelastic orthotics to control vertical and shear forces on the foot during the stance phase with no need for the obligatory use of athletic shoes;

2. use of the microgravitary system S.P.A.D (Corpo53, Italy) that determine the sensory-motor and functional recovery of the posture during the walking activity in combination to the development of proprioceptive information trasmitted from the periphery to the cortical central system.

After a period of unconditioning typical of the acute phase of cancer, it is necessary to learn again the correct body schema and achieve the complete recovery of postural control through spinal rehabilitation with floating platforms in tridimensional space and visual feedback. It is important to attempt correction of such postural abnormalities early in the rehabilitation process in order to prevent further dysfunctional patterns of movement. [145]

For example, breast cancer patients may develop chronic post-surgical pain following breast cancer treatment (Macrae, 2001) and, thus, adopt specific protective postures resulting in muscle spasm and muscle imbalances (Cheville & Tchou, 2007). Growing evidence is being produced in support for the use of Progressive Resistive Exercise training in head and neck cancer patients, in order to manage shoulder dysfunction and pain secondary to spinal accessory nerve damage. The importance of correcting posture and scapular stability prior to resistance exercise has been documented by McNeely et al (2004).

The system I-Moove is equipped with a balancing platform with helical movement which allow the continuous realignment of the subsystems of the body in order to maintain an optimal posture as well as the use of a traction force. It also provides a real-time visual feedback that allows physicians to monitor the correction. [146]

11.3. Quality of life improvement

The inclusive approach entails therapeutic techniques implemented by physical therapists to improve the quality of life, including: EMG Biofeedback, home therapy-related imagery with Riablo-System (coRehab Italy), music therapy, play therapy, virtual reality- and exercise. The

environment was shown to influence perceived well-being with outdoor exercises being perceived as energizing and indoor exercises being perceived as relaxing; furthermore, Qigong exercises has been shown to have positive effects on mood and anxiety. [147]

Attention-diversion approaches involve redirecting attention to competing external or internal stimuli, with related strategies including relaxation training, diaphragmatic breathing, guided imagery, self-hypnosis, mindfulness meditation and distracting thoughts and activities (Hanson, 1990). Engaging in meaningful and stimulating activities, for example talking to friends, listening to music and going outdoors, may reduce awareness of pain. Using methods deriving from cognitive therapy, patients are taught how to identify and change unhelpful or negative thoughts (cognitive restructuring) that contribute to psychological distress, while facilitating coping thoughts that reduce distress and enhance other coping efforts. Occupational therapists can help patient to maintain or resume their previous social role despite cancer-related pain. Occupational or Physiotherapists' role in this context encompasses active listening, education, prevention, problem solving, and provision of experiential learning.

A controversial aspect is the role of rehabilitation in patients with pain from bone metastases.

Patients with skeletal metastases may have a relatively long clinical course. Coleman and Rubens determined that the median duration of survival for 498 patients with metastatic breast cancer with first relapse in bone was 20 months.

In 253 of these patients, where disease spread was confined to the bone, the median duration of survival was even longer (24 months).

Rehabilitative intervention to optimize the functional capacity of patients with smoldering bone metastases is often needed. Such intervention is frequently aimed at preventing patients from becoming bed-bound and helping them to maintain as much autonomy as possible.

Treatment sessions commonly focus on training the patient to use residual function or to develop compensatory techniques, training in the use of assistive equipment, and educating both patient and family to help them adjust to an altered way of life. [148]

12. Conclusion

The management of cancer pain with a planning of a complex rehabilitation program, in the context of a comprehensive treatment, encompasses nutritional support, multimodal training, correction of lifestyle, as well as use of advanced physical energies. Therefore, for the purposes of the optimal management of cancer pain, it is essential to identify the pathogenetic features and the clinical characteristics of pain, in order to tailor the different treatment modalities in rehabilitation. Terminal patients should have access to rehabilitation services and be encouraged to remain functional and independent.

Clinical experience suggests that the application of the fundamental principles of rehabilitation medicine is likely to improve the care of patients with cancer.

A specialist in the identification, evaluation, and rehabilitation of neuromuscular, musculoskeletal, and functional disorders associated with cancer and its treatment should aim to the restoration and maintenance of function and quality of life.

Too often physicians tend to limit the treatment of pain in cancer patients to a pharmacological approach, tailored according to the severity of the symptoms as per the guidelines of the OMS.

A global and complex rehabilitation program may decrease the need for pharmacological medications and the occurrence of related side effects.

While oncologists are responsible for prolonging survival and nurses and counselors for optimizing comfort, the physical therapists play a major role in optimizing functions in patients suffering from cancer pain.

Physiatrist and physical therapists should thus be part of the team taking care of the integrated cancer management in primary, secondary and tertiary care, with a particular role being played with regard to cancer pain.

Molecular mechanisms in pain perception will direct mechanism-based drug therapy prescription in palliative care, whereas understanding of pain pathogenesis will direct physical therapy treatment, allowing proper decision-making and efficient treatment delivery in patients with cancer pain.

Despite being unquestionable that the primary goal in cancer patients management should be to prolong the overall survival, treatment of cancer pain is important in order to preserve daily functions and quality of life.

The development of an evidence-based body of knowledge will ensure that patients receive appropriate rehabilitation interventions in cancer pain.

Future research should, thus, focus on a better understanding of the role of rehabilitation and on defining appropriate interventions for this patient population.

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