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TREATMENT AND TAXONOMY OF CANCER PAIN – IS THERE A NEED FOR A NEW APPROACH?

Ljiljana Vasic[1], Radisa Vojinovic[2]
[1] Department of Oncology, [2]Department of Radiology, Clinical Center Kragujevac, Kragujevac, Serbia

TERAPIJA I TAKSONOMIJA KANCERSKOG BOLA – DA LI JE POTREBAN NOV PRISTUP?

Ljiljana Vasić[1], Radiša Vojinović[2]
[1]Centar za onkologiju, [2]Centar za radiologiju, Klinički centar Kragujevac, Kragujevac, Srbija

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ABSTRACT

According to the International Association for the Study of Pain, pain is categorized according to: its location, involved organ or tissue system, temporal pattern, intesity and etiology. Cancer pain could not be classified according to etiology and pathophisiology only. A distinct taxonomy of cancer pain is therefore warranted, because a unique group of syndromes, therapies and other etiologies of pain occur in this setting. This paper reviewed a variety of current approaches for the classification of cancer pain. Currently, the World Health Organization (WHO) three-step analgesic ladder is the gold standard for therapy of cancer pain predominatly based on the etiology, pathophysiology and location of the symptoms. As the mechanisms of pain become more evident, especially at the cellular level, perhaps a true mechanistic taxonomy can be developed replacing the three-step ladder with a more complex approach.

Key words: pain, classification, carcinoma

SAŽETAK

Prema IASP (International Association for the Study of Pain), bol se klasifikuje prema: lokalizaciji, zahvaćenosti sistema organa ili tkiva, dužini trajanja, intezitetu i etiologiji. Korišćenjem ovog sistema, zasnovanog na etiologiji i patofiziologiji, razumevanje kancerskog bola nije potpuno. Precizna taksonomija kancerskog bola je neophodna jer ona obuhvata i posebnu grupu sindroma, terapija i drugih etioloških faktora. Ovaj rad prikazuje različite pristupe u klasifikaciji kancerskog bola. Postojeća trostepena analgetska lestvica, odredjena od Svetske zdravstvene organizacije (The World Health Organization - WHO) u čijoj osnovi dominiraju etiologija, patofiziologija i lokalizacija simptoma, je zlatni standard u terapiji kancerskog bola. Kako su mehanizmi bola postali jasniji, posebno na ćelijskom nivou, moguće je postaviti pravu taksonomiju mehanizma bola, menjajući i trostepenu lestvicu kompleksnijim pristupom u lečenju.

Ključne reči: bol, klasifikacija, karcinom

INTRODUCTION

Taxonomy, a compound word formed from the Greek taxis, meaning arrangement, and nomos, meaning law, is the science of systematic classification.

All current taxonomies of pain owe a debt to the International Association for the Study of Pain (IASP), which organized a task force on taxonomy to develop a classification for chronic pain (1). This scheme, most recently revised in 1994, categorized pain according to five axes:

1) location of the pain
2) involved organ or tissue system
3) temporal pattern of pain
4) pain intensity and time since onset of pain
5) etiology of pain.

However, the IASP classification does not formally distinguish cancer pain from nonmalignant causes of chronic pain, or do other diagnostic schema advanced by the U. S. Department of Health and Human Services or the World Health Organization (WHO), discused later. Grond and colleagues applied the IASP taxonomy of chronic pain to evaluate more than 2200 cancer patients with pain. (2). Substantial informatin regarding the etiology and pathophysiology of these patients' cancer pain could not be captured using the IASP system. A distinct taxonomy of cancer pain is therefore warranted, because a unique group of syndromes, therapies and other etiologies of pain occur in this setting (2–4). This paper reviewed, a variety of current approaches for the classification of cancer pain. The classificaton of cancer pain may have important diagnostic and therapeutic implications. (table 1)

Table 1. Various schemes for classifiying cancer pain.

Etiologic classification	Primarly caused by cancer Treatment of malignancy Debility Concurrent pathology
Pathophysiologic classification	Nociceptive (somatic, visceral) Neuropathic Mixed pathophysiology Psychogenic
Location of cancer pain syndromes	Head and neck pain Chest wall syndromes Vertebral and radicular pain Abdominal or pelvic pain Extremity pain
Temporal classification	Acute Breakthrough Chronic
Severity-based classification	Mild Moderate Severe

ETIOLOGICAL CLASSIFICATION OF CANCER PAIN

The four predominant etiologies of cancer pain are:

1) that directly produced by tumor
2) that due to the various modalities of cancer therapy
3) that related to chronic debility
4) that due to an unrelated, concurrent disease process (2, 5, 6).

It is important to clinically distinguish the different etiologies because of their distinct therapeutic and prognostic implications.

Most cancer–related pain is directly produced by malignancy itself (2, 5). The neoplasm may spread into surrounding tissue and exert pressure on nociceptors

Correspondence:
Ljiljana Vasić, MD, MSc
Bukureška 13, 34000 Kragujevac, Serbia
Tel. 381 64 159 33 29,
E-mail: ljiljana76@eunet.yu

in diverse organs, as well as nerves. Tumors involving luminal organs may cause pain by obstructing hollow viscera, while locally invasive and erosive cancers directly produce tissue destruction. Furthemore, recent studies have found evidence that pain-generating mediators are directly released from certain tumors or from surrounding tissue in response to tumor invasion or metastasis such as to the bone (7–12).

The various modalities of cancer therapy may cause pain. Cancer patients may experience acute discomfort following surgery or other invasive procedures. Also, there are numerous postsurgical chronic pain syndromes, including postmastectomy pain, phantom limb pain, postthoracotomy pain, and unintentional severing of perpheral nerves (13–16). The administration of chemotherapy itself may cause immediate acute pain or painful sequelae such as mucositis, arthralgias and headaches. Moreover, chemotherapeutic agents are associated with peripheral neuropathies (17–23). Radiation therapy may injure soft tissue or neuronal structures, resulting in mucositis, proctitis, enteritis, osteonecrosis and peripheral neuropathies (24–26).

Many cancer patients may be inactive or suffer debilities that are associated with painful conditions. For instance, patients who have received immunosuppressive therapy or have hematologic malignancies are at increased risk for developing postherpetic neuralgia (27–29). Also, many malignancies are associated with an increased incidence of thrombosis, wich may present as pain and swelling in the affected site (30).

Patients with cancer may experience discomfort as a direct consequence of a concurrent, benign disease process (e. g., degenerative join disease or diabetic neuropathy). Therefore, it is important to review patients past medical histories and to consider any coexisting nonmalignant condition as a potential source of symptoms.

PATHOPHYSIOLOGIC CLASSIFICATION OF CANCER PAIN

The three classic pathophysiologic types of cancer pain including nocioceptive, neuropathic and psychogenic pain (31–36). Nociceptive pain results from the stimulation of afferent nociceptive pathways in visceral or somatic tissue, including effects of inflammation. Neuropathic pain is caused by disfunction of, or lesions involving, the central or peripheral nervous system (1). Psychogenic pain is primarily due to psychological factors and is infrequently seen in cancer patients.

Somatic pain arises from soft tissue structures that are non-neurological and nonvisceral in origin, including bone, muscle, skin, and joints. The pain is usually well localized and the character of the discomfort is often described as a sharp, arching and throbbing. Somatic pain usually correlates well with the extent of tissue damage (37).

Visceral pain arises from the deep organs of the thorax, abdomen or pelvis. The underlying mechanisms are less understood than somatic pain. Visceral pain is typically a vague, dull discomfort (34). The pain is difficult to localize and is often referred to somatic structures. Malignancy may induce visceral pain by causing obstruction of hollow viscera, distension of the organ walls, or stretching of the capsule of solid organs such as the pancreas or liver, or by extension into mesentery. Peritoneal metastasis, usually arising from primary abdominal or pelvic tumors, is one of the more common causes of visceral pain. Other frequent visceral pain syndromes include hepatic distension, midline retroperitoneal syndrome, intestinal obstruction, urethral obstruction and perineal pain (38).

Neuropathic pain is caused by pathology affecting the nervous system, rather than activation of nociceptors by a noxious stimulus. The dysfunction may be centrally located (brain, spinal cord) or may involve peripheral components of the nervous system (spinal nerve roots, plexuses, peripheral nerves). Neuropathic pain is a heterogeneous entity that can be produced by multiple etiologies (39). In the setting of malignancy, neuropathic pain can be generated by nerve compression, deafferentation nerve injury and sympathetically induced pain (40). Stute and colleagues found nerve compression to be the most common cause of neuropathic pain in cancer patients (79%), followed by nerve injury (16%) and sympathetically mediated pain (5%) (41).

Neuropathic pain is clinically distinct from nociceptive pain (35). The character of neuropathic pain is often described as burning, electric, pricking or shooting. It may be associated with motor, sensory and autonomic deficits. Specific sensory abnormalities, including dysesthesia, hyperalgesia or allodynia may be present. Neuropathic pain is classically located in a dermatomal pattern or in the area innervated by the involved spinal root or nerve plexus. Neuropathic pain is believed to be relatively less responsive to opioids (42–45). Nonopioid adjuvant drugs, including antiepileptics, antidepressants and antiarrythmic agents, are important therapeutic options (46–48).

A significant percentage of cancer patients have more than one identifiable pathophysiologic class of cancer pain (49). One study reported that 31% of subjects had mixed nociceptive-neuropathic cancer pain (2). Moreover, Ashby and colleagues identified two or more pathophysiological classes of pain in 79% of patients presenting with advanced cancer (45).

Psychogenic pain can also be diagnosed after pathology in pain-generating tissues is excluded. Although psychological factors certainly can contribute to pain and suffering, a pure psychogenic etiology of pain is rare in cancer patients. A comprehensive clinical evaluation and workup of the cancer patient almost always results in indentification of tumor-related pathology (48, 49).

ANATOMIC CLASSIFICATION OF CANCER PAIN

Cancer pain may involve virtually any anatomic region of the body (49). Several authors have organized malignancy-related discomfort according to the localization of the involved structures or tissues (6). Cancer pain may originate from the head and neck regions, chest wall,

abdomen or pelvis, vertebral structures or the extremities. There is a lack of consensus regarding the utility of an anatomic based classification because it lacks specificity as to the mechanism of pain. Nonetheless, the site of origin of cancer pain clearly influences whether, and how, certain invasive therapies such as external radiation, neurolytic blocks, electrical stimulation or targeted drug delivery may be best applied.

TEMPORAL CLASSIFICATION OF CANCER PAIN

As mentioned earlier, a variety of circumstances can potentially cause acute pain in cancer patients, including diagnostic or therapeutic procedures and other modalities of cancer therapy (e. g., chemotherapy, radiation therapy) (49–51). Often, the presence of acute pain may signal a new metastasis or a serious cancer-related complication such as a pathologic fracture. Therefore, comprehensive evaluation to determine the source of acute pain is necessary in cancer patients (52). An important type of acute cancer pain is breakthrough pain, the flare-up of discomfort in patients whose baseline pain is well controlled on a by-the-clock analgesic regimen (53, 54). There is a high prevalence of breakthrough pain in cancer patients. Furthemore, poorly controlled breakthrough pain is associated with more severe discomfort and functional impairment (55). Pain is often termed „chronic“ if it has persisted for longer than three months. Typically, chronic cancer pain is directly due to the tumor. However, chronic post-therapy syndromes include phantom limb pain, chronic chemotherapy-associated neuropathies and radiation-induced proctitis or enteritis.

SEVERITY-BASED CLASSIFICATION OF CANCER PAIN

The severity of cancer pain may reflect the size of the tumor, its localization and extent of tissue destruction. The mechanism of pain is also an important determinant, as metastatic bone lesions and injury to nerves are notoriously more severe than pain arising from tumor growth within soft tissue. Absent compression of nerves or obstruction of lumens, for example, retroperitoneal masses may grow quite large before they become symptomatic.

Pain intensity is frequently used to guide analgesic therapy. Valid tools to quantifity pain intensity include the visual analog pain scale (VAS), numerical rating scale, verbal descriptors of pain severity (e. g., none, mild, moderate, severe), and the Faces Pain Scale (56). The severity of cancer pain is dynamic, often fluctuates as the disease progresses and as different therapies are administered. Therefore, it is necessary to reevaluate and determine the severity of the pain on a serial basis.

EVALUATION OF CANCER PAIN

It is essential to perform a comprenhensive evaluation of pain in the cancer patient. Assessment of the cancer pain may alert physicians about malignancy-related complications (e. g., spinal cord compression, fractures), disease progression or new metastatic lesions. Furthemore, an understanding of the pathophysiology of cancer pain may have therapeutic implications and may influence the selection of pharmaceutical or nonpharmaceutical treatments such as biphoshponates or external radiotherapy, respectively.

In addition to a detailed medical hystory, a specific pain history is paramount to accurate evaluation of the cancer pain patient. Information regarding the pain, including localization, character, severity, onset, duration, temporal pattern, relieving and exarcerbating factors, associated symptoms, previous analgesic therapy and specific cancer treatments should be obtained. The patient's psychological state, including the presence of depression or anxiety, should be assessed. The most important parts of the physical examination are assessment of neurological and musculosceletal systems. Laboratory studies may be of value in certain cases. Serum tumor markers, including carcinoembryonic antigen (CEA), prostate specific antigen (PSA) may confirm the diagnosis of a specific type of malignancy, particularly in the setting of an unknown primary tumor or may confirm the suspicion of recurrent cancer.

Imaging studies play a significant role in the evaluation of malignancy-related pain. Computed tomography (CT) is especally useful for evaluating oncologic processes involving the mediastinum or abdominal organs (57–59). Moreover, CT may be used to guide diagnostic or therapeutic interventional procedures such as percutaneous stent placement or neurolytic blocks. MRI (magnetic resonance image) is technique of choice for imaging brain or spinal cord (60). Also, MRI is a sensitive modality for evaluating head and neck tumors, breast masses or malignancy involving the musculosceletal tissue (52, 61–64). The positron emission tomography (PET) scan is a functional imaging technique that plays an increasingly significant role in the workup of cancer (53). The PET scan can be used to detect diverse malignancies, including lung cancer, metastasis to lymph nodes and head and neck tumors (53, 54, 61).

The nuclear bone scan identifies abnormal foci of bone formation that may be malignant in origin. Other relevant nuclear medicine studies include lymphoscintigraphy, nuclear thyroid scans and radiolabeled antibody imaging (65, 66).

Invasive diagnostic testing may be indicated if clinical examination and imaging are unable to yield definitive results. Common diagnostic interventions include percutaneos needle biopsy, bronchoscopy, mediastinoscopy, colonoscopy, upper gastrointestinal endoscopy, laparoscopic intervention or even surgical laparatomy

THE WHO CANCER PAIN LADDER: APPLICATION OF A SEVERITY-BASED PAIN CLASSIFICATION

The WHO developed a simple, three-step, analgesic ladder for treatment of cancer pain that relies on widely available, inexpensive analgesic agents (67–72). The method was originally introduced in 1986 and advocates an approach based on pain intensity to manage cancer-related discomfort. The first step of the algorithm

manages mild pain with nonopioid analgesics, including nonstereoidal anti-inflammatory drugs (NSAIDs) or acetaminophen. The second step for persistant discomfort or mild to moderate levels of pain advises adding a "weak" opioid such as codeine to the nonopioid analgesic regimen. The third step recommends combination of a „strong" opioid (e. g., morphine, hydromorphone) and nonopioid agents for moderate to severe pain. Moreover, adjuvant drugs, including antidepressants, corticosteroids, or anticonvulsants are recommended when appropriate at many steps of the ladder (73).

A MECHANISM-BASED TREATMENT STRATEGY FOR MANAGEMENT OF CANCER PAIN

Ashby and colleagues described a mechanism-based treatment algorithm for cancer pain (45). The pathophysiology of each patient's cancer pain was classified as superficial somatic, deep somatic, visceral, pure neuropathic or mixed neuropathic/nociceptive. The dominant mechanism of pain, rather than intensity was used to determine the sequence of analgesic therapy. They conclude that while the concept of matching agent to mechanism is an attractive one, the heterogeneity of mechanisms in actual practice, and the only partial effeciveness of currently available agents, dictates that multiple agents should be applied simultaneously.

A mechanism-based algorithm is based on the premise that the various pathophysiologic types of pain may have different sensitivities to distinct classes of analgesics. Nociceptive pain typically responds to opioids; however, there is lack of consensus regarding the effectiveness of opioids for treatment of neuropathic pain (53). Some authors believe that neuropathic pain is intrinsically unresponsive to opioids (55). However, other trials suggest opioid responsiveness is a continuum and that neuropathic pain is only somewhat less sensitive to opioids than nociceptive pain (53–55).

Although it is logical that a taxonomy-driven, mechanism-based analgesic approach may one day be most effective, current evidence does not unequivocally support a mechanism-based treatment (36). In fact, no difference in pain reliefe has been found in cancer patients with neuropathic, nociceptive or mixed neuropathic-nociceptive cancer pain treated according to WHO guidelines (52, 71, 73).

Nevertheless, a mechanicistic approach to cancer pain taxonomy and analgesic therapy remains a promising concept, even thought it is at present confounded by several factors. As described above, the pathogenesis of malignancy-associated pain is often heterogeneous and a significant percentage of cancer patients have pain that is produced by multiple mechanisms (2, 49, 54). Also, many analgesic agents are nonselective and act on a variety of targets to alleviate different types of pain (74, 75).

THE FUTURE OF TAXONOMY

In the past several years, tremendous progress has been made in understanding the underlying mechanisms of cancer pain (12, 76, 77). Recently, several of the specific mediators of cancer pain have been identified. It has been discovered that certain tumors release factors that sensitize or stimulate primary afferent neurons. Many tumors express high levels of COX-2 (cyclooxygenase) and secrete prostaglandins (78, 79). Therefore, drugs, including NSAIDs, that inhibit the COX enzymes provide particularly effective analgesia for certain types of cancer pain. Selective inhibitors of COX-2 may have benefit not only for analgesia but also for inhibition of angiogenesis. Unfortunately, the results of one recent trial of the long-term administration of a COX-2 inhibitor prophylactically in patients with familial polyposis extended prior suspicions of increased cardio- and cerebrovascular risk in patients treated with this class of agents, leading to the withdrawal of rofecoxib from marketplace.

Certain metastatic tumors, including prostatic cancer, secrete the peptide endothelin (11, 78–80). There is increasing evidence that endothelin-1 is a significant mediator of pain in both animals and humans (11). Malignant cells have been shown to secrete several other pain-producing mediators, including nerve growth factors, interleukins and cytokines (10, 12).

Furthermore, malignancy-induced acidosis may exarcerbate cancer pain (12, 81). Two classes of PH sensitive ion channels are expressed on subsets of afferent nerve terminals, the vanilloid receptor TRPV1 (81, 82) and the acid-sensing ion channel 3 (ASIC-3) (81). It has been postulated that tumor-induced acidosis and release of protons may activate the TRPV1 and ASIC-3 channels, exarcebating pain (12). Therefore, antagonists of the TRPV1 and ASIC-3 channels may potentially provide analgesia in certain types of cancer pain (82).

As our understanding of the specific cellular mechanisms of cancer pain increases, more effective therapy can be developed that targets the precise mediators of pain, both according to the nature of the specific tumor and individual suffering from pain. An important step is to replace the broard, clinically based profiles that now form the basis for current taxonomic classification-akin to profiling of criminal suspects-with precise molecular characterization of the mediators involved in a specific individual's tumor, along with the neurochemical signatures produced in the peripheral and central nervous systems in response to distinct forms of nociceptive input (60–63, 83–89).

A well-defined, valid, and widely accepted taxonomy of cancer pain would likewise be of great importance in preclinical and clinical research and clinical practice. Current classification systems of cancer pain are predominatly based on the etiology, pathophysiology and location of the symptoms. As the mechanisms of nociception and pain become more evident, especially at the cellular level, perhaps a true mechanistic taxonomy can be developed.

Currently, the WHO three-step analgesic ladder is the gold standard for therapy of cancer pain. However, a treatment approach that determines the sequence of analgesic therapy based primarly on an individualized

therapy of the cancer pain, rather than epidemiologically based approach dictated solely by intensity of pain, is inevitable. Replacing the three-step ladder with a more complex approach is linked to the scientific progress of 21st century.

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