

# Chronic Pain Management in Head and Neck Oncology



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## KEYWORDS

- Pain • Chronic pain • Head and neck cancer • Integrative medicine
- Pain management

## KEY POINTS

- Chronic pain is common in patients with head and neck cancer and is experienced during all phases of treatment, including survivorship. Patients with advanced cancers and with comorbid depression/anxiety are at increased risk of pain.
- Patients experience pain from a variety of causes, including tissue destruction, bone invasion, nerve compression, and alteration of central pain processing.
- Optimal pain control is achieved with a combination of nonopioid and opioid medications. World Health Organization guidelines support the use of nonsteroidal antiinflammatory drugs and oral opioids as the basis of maintenance pain control in chronic cancer pain.
- Adjuvant therapies, including antidepressants, anticonvulsants, interventional neurolysis, and acupuncture, may be offered to patients as part of a multimodal approach to pain control.

## INTRODUCTION

Pain is epidemic in the head and neck cancer population.<sup>1</sup> Patients with head and neck cancer experience pain from a variety of sources, related to both the cancer itself as well as interventions used to treat the cancer. Pain may last for years after completing initial therapy, becoming an on-going challenge well after a patient is declared cured. Chronic pain, which is traditionally recognized as pain that persists beyond normal healing time,<sup>2</sup> is a common and frustrating problem for patients and providers, because pain may persist despite a lack of obvious inciting factors. Providers working with patients with head and neck cancer should be able to:

1. Identify risk factors for chronic pain

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2. Seek out treatable causes of chronic pain
3. Provide thoughtful, multimodal therapy in the treatment of chronic pain

## EPIDEMIOLOGY

A large meta-analysis of 3300 patients with cancer reported high levels of pain during all phases of oncologic treatment: 59% in patients undergoing treatment, 33% in patients that had completed treatment, and 64% in patients with advanced or metastatic disease.<sup>3</sup> Of all types analyzed, patients with head and neck cancer reported the highest prevalence of pain at 70%. A prospective study of patients with head and neck cancer showed pain as a presenting symptom in 48%, with a quarter of all patients having chronic pain at 12 and 24 months after conclusion of therapy.<sup>4</sup> Chronic pain is frequently accompanied by physical impairments that affect the ability to treat pain, including dysphagia and trismus.<sup>5</sup>

## TYPES OF PAIN

Cancer pain may be classified according to its mechanism (**Table 1**), and may broadly be categorized as either (1) nociceptive pain or (2) neuropathic pain.<sup>6</sup>

Nociceptive pain is defined as pain that arises from activation of peripheral nociceptors (nerve endings) caused by damage to nonneural tissue. Nociceptive pain arises in patients with head and neck cancer from a variety of causes:

- Tumor destruction of local tissues, particularly bone
- Diagnostic interventions, including needle or surgical biopsy
- Surgical tissue injury
- Acute effects of radiotherapy and chemotherapy, including mucositis and dermatitis
- Osteoradionecrosis of mandible, maxilla, or skull base

Neuropathic pain is defined as pain caused by a lesion of the somatosensory nervous system. Neuropathic pain in patients with head and neck cancer may be caused by tumor compression or invasion of structures of either the peripheral or central nervous system. Traditionally, pain arising despite no evidence of tissue damage or evidence of a lesion of the somatosensory nervous system was deemed neuropathic pain; however, the term nociplastic pain was recently adopted to help more fully characterize the neurobiology of pain.<sup>6</sup> Nociplastic pain may arise from alterations to peripheral and central nervous pain processing after long-standing exposure to nociceptive or neuropathic pain.<sup>7-9</sup>

## RISK FACTORS

Discrete risk factors have been identified for increased pain in patients with head and neck cancer. Providers should be able to identify patients at risk for pain, particularly those with modifiable and treatable risk factors.

### *Tumor-Related Risk Factors*

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- Site: several studies describe an association with worse pain in oral cavity cancers compared with laryngeal or pharyngeal tumors.<sup>4,10</sup> This worse pain may be caused by the dense concentration of nerve endings in the oral cavity as well as the higher incidence of bone invasion in oral cancers.

Type	Mechanism	Examples	
Nociceptive	Somatic Visceral	Stimulation of pain receptors on sensory nerve endings	Mucosal tumors, bone invasion Lung metastasis
Neuropathic	Nerve compression	Stimulation of nervi nervorum	Mass effect on cranial nerves or spinal rootlets
	Peripheral nerve injury	Lowered firing threshold of sensory nerves	Cranial nerve invasion by tumor
	Central nerve injury	Alteration of pain processing	Intracranial invasion by skull base tumor
	Sympathetic injury	Dysfunction of autonomic nervous system	First-bite syndrome after parapharyngeal surgery

- Stage: pain tends to be worse in patients with advanced tumor sizes and T stages,<sup>11–13</sup> as well as for patients with TNM (tumor, node, metastasis) stage III and IV cancers.<sup>14,15</sup>

### **Treatment-Related Risk Factors**

In general, patients receiving multimodal oncologic therapy (surgery with adjuvant radiotherapy, chemoradiotherapy) tend toward worse pain outcomes than those who receive surgery or radiation alone.<sup>16–19</sup> Outcomes comparing radiation versus surgery are less clear. Patients with oropharyngeal cancer treated with nonsurgical therapy have worse pain than patients treated with primary surgical therapy,<sup>20</sup> whereas total laryngectomy patients seem to have worse pain than patients treated with a laryngeal preservation approach.<sup>13,21,22</sup>

### **Patient-Related Risk Factors**

Increased pain is associated with multiple sociodemographic factors. Younger patients tend to report worse pain than older patients.<sup>12,23,24</sup> Several studies have described an association between gender and pain, with women reporting worse pain scores than men,<sup>12,25</sup> although functional outcomes may be worse in male patients.<sup>15</sup> In addition, patients who are unemployed,<sup>26</sup> divorced,<sup>27</sup> and with low incomes<sup>28</sup> showed worse pain scores.

Psychological comorbidities are important risk factors for pain in patients with head and neck cancer. Both anxiety and depression are significantly associated with pain.<sup>27,29</sup> One study analyzed personality as a predictor of quality of life in patients with head and neck cancer.<sup>30</sup> Patients with head and neck cancer showing dispositional optimism as evaluated by the Life Orientation Test described less pain and better global quality of life compared with pessimists.

## **TREATMENT GUIDELINES**

The World Health Organization (WHO) published updated guidelines in January 2019 for the pharmacologic management of cancer pain in adults and adolescents.<sup>31</sup> The WHO identifies 7 guiding principles in the management of cancer pain. These principles provide a framework for providers in their approach to developing optimum pain treatment plans (Table 2).

<b>Table 2</b>	
<b>World Health Organization recommendations for analgesic dosing</b>	
7. Cancer pain management should be integrated as part of cancer care	
<b>Recommendation</b>	<b>Explanation</b>
By mouth	Oral administration is preferred whenever feasible because of high effectiveness and accessibility as well as low cost. Dysphagia and gastrostomy tube dependence may require use of alternate formulations
By the clock	Analgesics should be given at appropriate intervals, with fixed intervals for continuous pain relief. Dosage should be increased until the patient is comfortable, and the next dose is given before the previous dose's effect has worn off
For the individual	Individualized pain treatment is prescribed in the context of careful assessment of the patient, identification of the source of the pain (eg, nociceptive vs neuropathic), and to a degree that the patient finds acceptable to maintain a quality of life. The previous WHO guidelines included a pain management ladder, which escalated pharmacotherapy from nonopioid medications to weak opioids and then strong opioids. The current guidelines acknowledge individualized pain strategies rather than a generalized pain management plan
With attention to detail	Patients should be aware of adverse effects of treatments they are prescribed. The treatment plan should be written out in full for patients and their families, including medication names, reasons for use, dosage, and dosing intervals

1. The goal of optimal management of pain is to reduce pain to levels that allow an acceptable quality of life

Providers and patients should approach pain control with realistic expectations, because the complete elimination of pain in all patients is unfeasible. Therefore, the goal of pain management is to reduce pain to a degree that results in an acceptable quality of life for the patient.

2. Global assessment of the person should guide treatment, recognizing that individuals experience and express pain differently

Assessment and reassessment at regular intervals is encouraged to identify patients with pain, ensure treatment is appropriate and safe, and monitor side effects. The WHO provides multiple pain assessment tools to add in the evaluation of patients.

3. Safety of patients, carers, health care providers, communities, and societies must be assured

Providers are encouraged to practice opioid stewardship to ensure patient safety and minimize the effects of addiction and diversion on society. Attention should be paid to patients' psychological history, patterns of opioid consumption, and history of substance use and abuse.

4. A pain management plan includes pharmacologic treatments and may include psychosocial and spiritual care

The experience of pain is molded by the patient's social, cultural, and spiritual background in addition to the tumor biology. Psychosocial care, including spiritual and culturally appropriate counseling, is an essential part of holistic pain management.

5. Analgesics, including opioids, must be accessible: both available and affordable

The WHO identifies regulatory, legal, and economic policies as barriers to adequate pain relief, citing poor access and availability in low-income and middle-income nations.

6. Administration of analgesic medicine should be by mouth, by the clock, for the individual, and with attention to detail

Pain management should be integrated into the treatment plan throughout the patient's oncologic care, from diagnosis through treatment and beyond.

The WHO approach to cancer pain management has been validated in several large studies,<sup>32,33</sup> with less than 15% of patients reporting inadequate cancer pain relief when treated using the WHO guidelines. However, nonpharmacologic approaches to pain are not incorporated into the WHO guidelines. These strategies have become important tools in the management of head and neck cancer pain, as discussed later.

## TREATMENT STRATEGIES

### *Initiation of Pain Relief*

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Treatment of pain in the head and neck is initiated after clinical assessment of the patient as well as evaluation of pain severity. Nonopioid analgesics, such as nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen, should be started in all patients if no contraindications are present. Nonopioid analgesics may be appropriate as monotherapy in mild pain, but should be combined with opioids for patients in moderate to severe pain in order to achieve rapid and effective pain control.

Previous WHO guidelines recommended initiation of a weak opioid (eg, codeine) before starting a strong opioid, such as morphine or oxycodone (**Table 3**). One randomized trial comparing codeine with morphine in moderate cancer pain reported significantly reduced pain in the morphine group, with similar adverse effect profile and tolerability.<sup>34</sup> Furthermore, genetic variations in codeine metabolism, present in about 10% of the North American population, may result in either ineffective pain control or rapid intoxication after drug administration.<sup>35,36</sup> As a result, the WHO makes no specific recommendations about initiation of a weak opioid rather than a strong opioid in patients with moderate or severe cancer pain.

Combination analgesic formulations are commonly prescribed in the United States, usually hydrocodone or oxycodone combined with acetaminophen. Although convenient, consideration should be made toward prescribing these medications independently, to allow titration of the opioid dose up to an effective level while limiting the hepatotoxic or nephrotoxic effects of high-dose acetaminophen or NSAIDs.

### *Maintenance of Pain Relief*

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Round-the-clock pain control is achieved with appropriating dosing of<sup>1</sup> maintenance pain medicines, usually acetaminophen/NSAIDs with or without opioids, and<sup>2</sup> through management of breakthrough pain with rapid-acting analgesics. See **Table 4** for typical starting doses.

1. Maintenance pain control: the choice of analgesic medications for maintenance pain control has been intensely studied. Overall, high-quality data show that a combination of strong opioid and an NSAID provides the most reliable maintenance pain relief.<sup>37–47</sup> No study has shown a difference based on choice of opioid with regard to speed of pain relief, durable pain reduction, functional outcomes, or adverse events. The choice of opioid should be tailored to the patient's response

<b>Medicine Group</b>	<b>Medicine Class</b>	<b>Example Medicine</b>
Nonopioids	Acetaminophen	Acetaminophen tablets, liquid, suppository
	NSAIDs	Ibuprofen tablets and liquids Naproxen tablets Ketorolac tablets and IV Celecoxib tablets
	Weak opioids	Codeine tablets and liquids Hydrocodone <sup>a</sup>
		Strong opioids
Adjuvants	Steroids	Dexamethasone, prednisone, methylprednisolone tablets
	Antidepressants	Amitriptyline tablets Venlafaxine tablets
	Anticonvulsants	Gabapentin tablets

*Abbreviation:* IV, intravenous.

<sup>a</sup> Hydrocodone is available in the United States only in combined formulations with acetaminophen or ibuprofen (see text).

*Adapted from* World Health Organization. Noncommunicable diseases and their risk factors. Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents 2019, Retrieved from <https://www.who.int/ncds/management/palliative-care/cancer-pain-guidelines/en/>.

to the analgesic, tolerability of side effects, and ability to adhere to the dosage schedule.

2. Breakthrough pain control: patients should have access to a rapid-acting opioid, such as immediate-release morphine or hydromorphone, in order to manage pain flares that occur in the setting of round-the-clock maintenance analgesia.

### **Adjunctive Medications**

A variety of nonanalgesic medications have been used as adjuvant treatment in head and neck cancer pain. Their uses and limitations are reviewed here.

1. Steroids: steroids are occasionally prescribed to treat bone pain or neuropathic pain related to nerve compression. However, steroid use should be limited to as short a duration as possible because of toxicities including hyperglycemia, mood changes and delirium, and gastrointestinal bleeding.
2. Antidepressants: tricyclic antidepressants (TCAs, eg, amitriptyline) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs, eg, venlafaxine) have shown good clinical efficacy in treating neuropathic pain.<sup>48,49</sup> In addition, TCAs and SNRIs are useful in the treatment of depression, which is epidemic in the head and neck cancer population.<sup>50</sup>
3. Anticonvulsants: gabapentin has shown good efficacy in patients with head and neck cancer as an adjuvant analgesic treating neuropathic pain both in the perioperative period<sup>51</sup> as well as during radiation therapy.<sup>52</sup> However, industry-sponsored trials of gabapentin have shown discrepancies in reporting of methods, analyses, and outcomes.<sup>53,54</sup> This has called into question the drug's efficacy despite widespread use in the treatment of neuropathic pain.

Medicine	Typical Starting Dosage	Notes
Acetaminophen	500–1000 mg orally every 6 h	Maximum dose 4 g daily
Ibuprofen	400–800 mg orally every 8 h	Take with food to reduce gastric side effects. Avoid in patients with bleeding risk Maximum dose 2400 mg
Morphine	5 mg orally every 4 h	No maximum dose
Fentanyl	25- $\mu$ g transdermal patch every 72 h	No maximum dose
Amitriptyline	10–25 mg orally at bedtime	Anticholinergic side effects Maximum dose 100 mg daily

Adapted from World Health Organization. Noncommunicable diseases and their risk factors. Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents 2019, Retrieved from <https://www.who.int/ncds/management/palliative-care/cancer-pain-guidelines/en/>.

## NONPHARMACOLOGIC INTERVENTIONS IN HEAD AND NECK CANCER PAIN

### *Interventional Techniques*

When patients have persistent pain despite the appropriate use of multimodal systemic analgesics, interventional pain therapies may be considered. Neurolysis, deliberate injury of a nerve in order to interrupt transmission of pain signals, is an effective tool in the treatment of chronic head and neck pain. Local anesthetic blocks of sensory nerves may be used to select patients who would respond to more definitive neurolysis. If the patient's pain is alleviated by a local block, neurolysis should be considered and the patient offered referral to an interventional pain specialist. Examples of nerves amenable to neurolysis in the head and neck include the trigeminal ganglion and its branches, sphenopalatine ganglion, occipital nerve, superior laryngeal nerve, and glossopharyngeal nerve.

### *Integrative Therapies*

Integrative medicine, also known as complementary and alternative medicine, is commonly used by patients with head and neck cancer, with at least a third to half reporting its use.<sup>55–57</sup> Integrative medicine includes natural products such as herbs, vitamins, and probiotics; mind-body techniques such as yoga, tai chi, and meditation; chiropractic manipulation; homeopathy; and acupuncture. Although the data for integrative medicine in the prevention or treatment of cancer are poor, there is extensive evidence supporting integrative medicine for symptom management.<sup>58</sup>

Acupuncture has perhaps the most robust body of literature supporting its use in head and neck oncology. Patients with chronic pain after neck dissection showed significant reductions in pain and dysfunction compared with patients randomized to usual care with analgesics and physical therapy.<sup>59</sup> Auricular acupuncture reduced pain intensity scores compared with placebo in patients with pain that was inadequately controlled with oral analgesics.<sup>60</sup> In addition, multiple trials have shown reduction of xerostomia in patients with head and neck cancer treated with acupuncture.<sup>59,61,62</sup>

## SUMMARY

Pain is epidemic in patients with head and neck cancer. Providers involved in the care of patients with head and neck cancer should be able to describe the common pain

syndromes experienced by these patients, identify patients at risk of pain, and provide multimodal treatment of chronic pain. Treatment of chronic pain encompasses analgesic medications; adjuvant pharmacotherapy, including antidepressants and anti-convulsants; interventional techniques; as well as integrative medicine.

## DISCLOSURE

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