Oral cancer associated orofacial pain: An overview

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Abstract
Cancer pain is an ever-present public health concern. Most cancer patients will experience uncontrollable pain that creates a poor quality of life and limits normal function. Cancer-associated pain is associated with severe physical and psychological suffering. Unfortunately, pain associated with cancer or its treatment is frequently under-treated, probably due to several factors, including phobia of opioids, underreporting by patients, and under-diagnosis by health-care workers. The most common etiology of cancer pain is local tumor invasion (primary or metastatic) that involves inflammatory and neuropathic mechanisms.

Keywords
Opioids, orofacial pain, squamous cell carcinoma

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Introduction
Oral cancer is unique in that it causes intense pain at the primary site and significantly impairs speech, swallowing, and masticatory functions. Oral cancer patients experience pain early in the disease. In fact, orofacial pain is the initial symptom that leads to the diagnosis of oral squamous cell carcinoma (SCC) in patients. The overall 5-year survival rate for oral cancer patients is 60%. With the improved survival rate, there is an increase in the burden of pain that oral cancer patients must bear.

The character, severity, and unique features of oral cancer pain likely reflect the anatomy of the oral cavity, the continuous need for orofacial function, the biologic characteristics of oral SCC, and the interaction between the carcinoma and the peripheral nervous system. In a meta-analysis of 52 studies that calculated the prevalence of cancer pain, head and neck cancer (HNC) had the highest prevalence of pain, surpassing gynecological, gastrointestinal, lung, breast, and congenital cancer. The functional requirements and mechanical stimulation of oral structures during speech, mastication, and swallowing result in severe pain.

The pain is commonly associated with cancer, as it is the presenting symptom in 20-50% of all cancer patients and is significant in 75-90% of patients with advanced or terminal cancer. In HNC patients, pain has been associated with both disease and cancer treatment. Large surveys of HNC patients found that pain was frequently associated with the tumor (87-92.5%), whereas in 17-20.8%, the pain was secondary to therapy, and many patients reported pain from both disease and treatment. Following treatment of HNC, 78% of patients reported pain in the head, face, or mouth and 54% in the cervical region or shoulder. As many as 70% of patients may suffer pain from more than one site that involves inflammatory or neuropathic pain mechanisms.

Based on the current laboratory and clinical studies, there are 5 main causes that initiate or exacerbate oral cancer pain:

1. Mediators in the cancer microenvironment,
2. Lack of early palliative therapy,
3. Dense trigeminal innervation and continuous oral function,
4. Pain from cancer treatment, and
5. Opiate tolerance.

Pain in turn leads to other symptoms including anxiety, depression, and side effects of high-dose opiate use.

Pain due to Tumor

Pain due to primary head/neck tumor

The orofacial pain may be a presenting symptom of HNC and may motivate patients to seek care from an oral and maxillofacial surgeon. Primary SCCs of the oral mucosa are often associated with pain and other sensory disturbances when at an advanced stage of disease, as they may interfere with oral function and induce nerve damage/dysfunction.
Orofacial Pain in Systemic Cancer

Lymphomas and leukemias may also induce pain by infiltration of pain-sensitive structures such as periosteum and gingiva.\(^1\)

The orofacial pain secondary to non-metastatic malignancy at a distant site (referred pain). Rarely, the orofacial pain has also been reported in patients suffering from a distant non-metastasized cancer, most commonly from the lungs. In such circumstances, the facial pain is almost always unilateral, frequently described as severe and aching, and usually is continuous and progressive.\(^1\)

The mechanism by which a mass in the lung can refer pain to the face presumably involves either direct tumor invasion or compression of the vagus nerve by malignant lymph nodes. In addition, the orofacial pain may be caused by activation of nociceptive pathways in mediastinal or head and neck structures.\(^2\)

Acute Pain during Cancer Therapy

Surgical procedures

Acute pain is common secondary to surgical procedures for HNC. Surgery-related pain usually involves acute inflammatory responses related to the extent of the surgery and may be associated with a variable degree of concomitant nerve injury.\(^1\)

Acute Pain Secondary to Chemotherapy (CT)/Radiation Therapy (RT) (Mucositis)

Oral mucositis is a common acute complication of CT and/or RT and typically manifests as erythema and/or ulceration of the oral mucosa. Ulcerative mucositis occurs in approximately 40% of patients receiving standard CT and about 75% of patients who undergo hematopoietic stem cell transplants receiving high-dose CT.\(^1\) In about half of the patients with ulcerative mucositis, the lesions are severe and painful, and the breakdown of the epithelial barrier is a potential portal for systemic infection. Medical intervention is often required with severe ulcerative mucositis and may lead to modification or interruption of cytotoxic therapy, which may negatively affect treatment outcome and increase morbidity and mortality. Mucositis is self-limiting when uncomplicated by infection and typically heals within 2-4 weeks after cessation of cytotoxic CT. In RT, oral mucositis is the result of cumulative tissue dose and is almost universal in patients undergoing treatment involving the oropharynx. Mucositis pain is common (58-75%) and may be severe, interfering with daily activities and oral function that affect the patient’s quality of life. Pain often escalates at week 3, peaking at week 5, and persisting for weeks with gradual remission of signs and symptoms.\(^2\)

Chronic Pain Secondary to Cancer Treatment

Chronic changes involving oral mucosa are the result of hypovascular, hypocellular, and hypoxic changes that occur during cancer treatment, most commonly RT.\(^2\)

Slow-healing Mucosa

The chronic mucosal changes may lead to an atrophic, friable mucosal barrier, which may predispose oral tissues to ulceration following trauma or injury. Soft-tissue necrosis may then ensue due to reduced vascularity of the tissue and poor wound healing. Pain will generally become more prominent as soft-tissue necrosis progresses.\(^2\)

Neuropathic Pain

Neuropathic pain is defined by the International Association for the Study of Pain as pain initiated or caused by a primary
lesion or dysfunction in the nervous system. This dysfunction in the nervous system may be exacerbated by persistent, unrelied nociceptive (inflammatory) pain associated with the tumor or cancer treatments, such as surgical procedures and neurotoxicities due to CT and RT or combinations of these treatments. Neuropathic pain is an extremely debilitating form of pain that occurs when peripheral, autonomic, and/or central nerves are affected. In addition, changes occur in the immune system that modifies the normal function of nociceptors. These alterations in pain processing at the peripheral and central levels produce characteristic symptoms such as hyperalgesia, allodynia, and paresthesia. The International Association for the study of pain defines hyperalgesia as an increased response to a stimulus, which is normally painful; allodynia as pain due to a stimulus, which does not normally provoke pain; and paresthesia as an abnormal sensation, whether spontaneous or evoked.\(^2\)

### Neuropathic Pain Secondary to Surgical Procedures

Surgical procedures used in the treatment for HNC commonly result in acute orofacial pain and may lead to painful posttraumatic neuropathy. Resection of the mandible for tumor excision will inevitably lead to sensory impairment, with 50% experiencing regional hyperalgesia or allodynia. At 2-5 years post maxillectomy, approximately 90% of patients reported persistent pain. The severity of the neuropathic pain may be increased following RT. In addition to tissue injury at tumor resection, morbidity has been found to be increased by neck dissection.\(^2\)

### Treatment-related Toxicity (CT, RT)

Chemotherapeutic agents used in the treatment of HNC often initiate painful peripheral neuropathies that often affect the orofacial region.\(^3\) This debilitating adverse effect may result in the inability to provide the patient with the full chemotherapeutic regimen and limit ideal dosing, thereby greatly affecting survival rate. This side effect known as CT-induced peripheral neuropathy (CIPN) is commonly seen during CT cycles. Typically, the neuropathic pain resolves with or without symptomatic treatment. However, in some patients, this resolution does not occur and may evolve into a chronically painful condition. In these patients, the symptoms cause a notable decrease in functional capacity and overall quality of life. Prevalence during treatment is variable among agents, the intensity of treatment (dose intensity and cumulative dose), other ongoing therapies (such as surgery and RT), age of the patient, and the use of combinations of CT agents. Estimates of prevalence range from 4% to 76% during CT. Pre-existing nerve damage such as that caused by diabetes, alcoholism, inherited neuropathy, or paraneoplastic syndrome may increase the incidence and severity of CIPN. Commonly used neurotoxic agents such as the taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine, vinblastine), platinum-based compounds (cisplatin, oxaliplatin), thalidomide, and bortezomib appear to be the most responsible for precipitating CIPN. The majority of the CIPN demonstrate a mixed sensory (positive and negative symptoms) and motor (muscle weakness and atrophy) signs; however, autonomic dysfunction (hypotension, cardiac conduction irregularities, impotence, and bowel and bladder involvement) may also be present. Interestingly, both small-diameter sensory fibers, unmyelinated C fibers and thinly myelinated A-delta fibers and large myelinated A-beta fibers are affected by chemotherapeutic agents, with the large fibers being preferentially injured by CT agents such as vinca alkaloids, taxanes, and platinum-based compounds.\(^4\)

RT plays an important role in the management of HNC. The early or acute effects depend on the radiated fields and include skin/mucosal reactions, nausea, diarrhea, and neutropenia and are usually self-limiting. Late effects, including connective tissue fibrosis, neural damage resulting in neuropathic pain, and secondary malignancies, can occur long after completion of RT. It has been shown that there is an elevated morbidity to neural tissues with high-dose regimens.\(^4\)

### Post Radiation Osteonecrosis (PRON)

PRON is another well-recognized complication of head and neck RT that may be associated with pain. Loss of bone vitality occurs secondary to injury to osteocytes, osteoblasts, and osteoclasts as well as relative hypoxia owing to reduction in vascular supply. These changes can lead to a reduced capacity of soft tissue and bone to recover from injury, predisposing to soft-tissue necrosis and osteonecrosis.\(^5\)

Patients who develop PRON should be comprehensively managed to include removal of bony sequestra and topical antibiotics (i.e., tetracycline) or antiseptics (i.e., chlorhexidine) that may contribute to wound resolution. Analgesics for pain control are often effective. In cases associated with pain and progression, hyperbaric oxygen therapy is recommended for management of PRON. Hyperbaric oxygen therapy increases oxygenation of irradiated tissue, promoting angiogenesis, and enhancing osteoblast repopulation and fibroblast function. Hyperbaric oxygen therapy is usually prescribed as 20-30 dives at 100% oxygen and 2.8 atmospheres of pressure. If surgery is needed, 10 dives of postsurgical hyperbaric oxygen therapy are recommended.\(^5\)

### Table 1: Effect of cancer pain on quality of life

<table>
<thead>
<tr>
<th>Physical</th>
<th>Decreased functional capability, diminished strength, endurance, nausea, poor appetite, poor or interrupted sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological</td>
<td>Diminished leisure, increased anxiety, fear, depression, personal distress, difficulty concentrating, loss of control</td>
</tr>
<tr>
<td>Social</td>
<td>Diminished social relationships, decreased sexual function, affection, altered appearance, increased caregiver burden</td>
</tr>
<tr>
<td>Spiritual</td>
<td>Increased suffering, altered meaning, reevaluation of religious beliefs, etc.</td>
</tr>
</tbody>
</table>

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Cancer pain effects patient’s life in quite a different manner which may completely disorganize patient’s life [Table 1].

One routine clinical approach to pain assessment and management is summarized by the mnemonic “ABCDE”:[3]
A - Ask about pain regularly. Assess pain systematically
B - Believe the patient and family in their reports of pain and what relieves it
C - Choose pain control options appropriate for the patient, family, and setting
D - Deliver interventions in a timely, logical, and coordinated fashion
E - Empower patients and their families. Enable them to choose the modality.

Elements of cancer pain assessment are summarized as follows:[3]

<table>
<thead>
<tr>
<th>Factor</th>
<th>Question</th>
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<tbody>
<tr>
<td>Intensity</td>
<td>How severe is your pain?</td>
</tr>
<tr>
<td>Character</td>
<td>How would you describe your pain?</td>
</tr>
<tr>
<td>Location</td>
<td>Where is your pain?</td>
</tr>
<tr>
<td>Radiation</td>
<td>Does your pain go anywhere else?</td>
</tr>
<tr>
<td>Timing</td>
<td>When does your pain occur?</td>
</tr>
<tr>
<td>Correlated factors</td>
<td>What makes your pain better or worse?</td>
</tr>
<tr>
<td>Implications of pain</td>
<td>How does this pain affect your daily living?</td>
</tr>
<tr>
<td>Meaning of the pain</td>
<td>What does the pain mean to you?</td>
</tr>
</tbody>
</table>

The Initial Evaluation of Pain Must Include[3]

- A detailed history including an assessment of the pain intensity and character
- Physical examination, emphasizing the neurological examination
- Psychosocial assessment
- Appropriate diagnostic and investigative workup to find out the cause of the pain.

A psychosocial assessment should emphasize the effect of pain on patients and their families, as well as patients’ preferences among pain management methods.

Conclusions

Oral cancer pain is unique due to its function-related pain at the primary site. The most common etiology of cancer pain is local tumor invasion (primary or metastatic) involving inflammatory and neuropathic mechanisms. Since pain is frequently multifactorial, addressing each of the dimensions of the patient’s pain can improve pain control. Attention should be paid to the patient’s overall medical as well as oral status. Understanding the molecular and neurophysiological mechanism of pain will be a boon to treat orofacial pain in cancer patients.

References