Oral pain in the cancer patient

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Purpose of review
Oral pain is a common complaint in patients with cancer. This review aims to summarize the knowledge on the causes and approach to management of oral pain garnered over the past 2 years.

Recent findings
A systematic review and meta-analysis included in the review, assessed cannabinoid versus placebo and showed only a small effect on pain, physical function, and sleep quality. Another review showed that chemical neurolysis as an adjunctive therapy, is effective in patients with pain of shorter chronicity and refractory head and neck cancer-related pain.

Summary
Patients with cancer frequently experience oral pain because of a variety of factors. Factors inherent in the type and location of the malignancy, the modality of cancer treatment, and a holistic approach to management together contribute to their overall pain experience. Basic oral care should be implemented wherever possible, before, during, and after cancer treatment.

Keywords
cancer, causes, oral, pain, treatment

INTRODUCTION

Patients with cancer frequently experience orofacial and oropharyngeal pain that have underlying nociceptive, neuropathic, and psychosocial components. Oral pain may be because of the presence of primary tumors [head and neck cancers (HNCs)], metastasis from other body sites, and haematolymphoid cancers. At diagnosis, up to 85% of patients with HNCs report pain, which impairs eating, drinking, swallowing, and speaking [1]. Despite advances in treatment modalities for cancer, oral pain can occur because of surgery, chemotherapy, targeted therapy, and radiotherapy. Current protocols recommend use of opioid analgesics among other strategies for nociceptive pain relief [2].

PAIN BECAUSE OF TUMOUR

Carcinomas account for over 80% of orofacial malignant neoplasms [3] and up to 90% are squamous cell carcinomas [4]. Sixty percent of patients reported moderate-to-severe pain in a retrospective study involving 13 827 patients diagnosed with squamous cell carcinoma of the oral cavity, oropharynx, and larynx [5]. Trigeminal neuralgia-like pain has been previously described in a patient with nasopharyngeal carcinoma [6]. Temporomandibular joint pain with/without restriction in jaw movement in patients with nasopharyngeal carcinoma has also been reported [7] (Table 1).

Oral squamous cell carcinoma causes oral pain in affected patients because of the production of nociceptive mediators that sensitize primary afferent nociceptors in the cancer microenvironment [8]. A number of nociceptive mediators in oral cancer-related pain have been documented. These include endothelin-1 (ET-1), nerve growth factor, tumour necrosis factor alpha, protons, bradykinin, tryptase, trypsin, and prostaglandins [2]. In addition to nociceptive pain mechanisms, neuropathic pain descriptors are commonly reported by patients with HNC patients at diagnosis [9] and may be a direct consequence of a cancer-induced injury affecting the somatosensory system [10].

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KEY POINTS

- Oral pain in the cancer patient may occur because of the presence of orofacial tumours.
- Carcinomas occur more commonly compared to other tumor types.
- Several studies report underlying mechanisms and pain complaints in patients with orofacial malignancies.
- Cancer therapy may also lead to orofacial pain complication.
- With increase in the rate of cancer survival, there is the likelihood of chronic pain symptoms.

Sarcomas of the orofacial region are rare compared with other malignant orofacial tumours [11,12]. In a prior study, malignant fibrous histiocytoma, rhabdomyosarcoma, and osteosarcoma were the most frequently occurring sarcomas of the jaws [13]. Orofacial pain may be present in up to 70% of patients with jaw osteosarcoma [14]. Patients with rhabdomyosarcoma [15] and malignant fibrous histiocytoma [16] may also complain of pain in some cases.

Metastatic tumours constitute about 1% of malignancies of the oral cavity [17]. Although rare, they may be the first indicator of cancer at a distant site in 25% of cases. Primary tumours of the breast, prostate, lungs, liver, and kidneys may metastasize to the oral cavity. The mandibular molar region is the most affected intraoral site and may be accompanied by pain and paraesthesia. In the oral soft tissues, the gingiva is the most frequently affected site [18]. Cancers of the breasts and lungs may also metastasize to the temporomandibular joint (TMJ) causing TMJ pain [19].

Furthermore, haematolymphoid malignancies, which include leukaemia, lymphomas, and plasma cell tumours are common neoplasms and they may be painful when they infiltrate bone, gingiva and when close to the teeth, may lead to gingival bleeding, swelling/mass, and mobile teeth. The osteolytic lesions present in multiple myeloma (a plasma cell tumour) can induce toothache and bone pain and can be misdiagnosed as dental pathosis [20]. The most frequent clinical symptoms of plasmacytoma of bone are pain in the jaws and teeth with paraesthesia/anaesthesia [21].

PAIN BECAUSE OF THERAPY

Cancer treatment may result in surgical pain, mucositis pain, neuropathy, fibrosis, osteonecrosis, limited oral function, and dysphagia [22]. Depending on clinical and histopathologic features, cancer therapy may include surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy as unimodal therapy or in various combinations. In many cases, HNC patients require multimodal treatment (Table 2).

With disease progression, oral cancer-related pain intensity may increase [23]. Complete surgical resection has been reported to cause a remarkable decrease in pain intensity but the need for multimodal treatment in many HNC patients often leads to chronic pain [23]. Post surgery, pain in cancer patients may last up to 2 months and improve with time [2]. Additionally, persistent postsurgical pain and postsurgical fibrosis may follow acute nociceptive orofacial pain related to surgical procedures [2].

Unremitting pain is often a complication of radiotherapy with or without chemotherapy in HNC patients requiring these modalities [23]. Pain in patients with squamous cell carcinoma may worsen during treatment, particularly in those receiving

Table 1. Causes of oral pain in cancer patients

Cause	Diagnosis
A. Tumour	
Head and neck carcinoma	Squamous cell carcinoma, nasopharyngeal carcinoma
Head and neck sarcoma	Osteosarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma
Haematolymphoid tumours	Leukaemia, lymphoma, plasma cell tumours
Metastasis to the head and neck	Primary tumours of the breast, prostate, lungs, liver, kidneys
B. Treatment-induced pain	
Surgery	Acute/surgical pain, postsurgical neuropathy
Chemotherapy	Mucositis, osteonecrosis, neuropathy
Radiotherapy	Mucositis, osteoradionecrosis, fibrosis, neuropathy
Targeted therapy	Mucositis, neuropathy

Table 2. Approach to oral pain management in cancer patients

Treatment phases	Approach
Precancer treatment	Thorough assessment and diagnosis Basic oral care[a] Use of analgesics (following the analgesic ladder) Use of adjunctive techniques[b] whenever indicated
Peri-cancer treatment	Basic oral care[a] Treat cause(s) whenever possible Use of conformal radiation, intensity-modulated radiation, proton beam therapy whenever indicated Use of analgesics – topical formulations for mucosal pain; add systemic if needed Use of adjunctive techniques[b] whenever indicated
Posttreatment/survivorship	Basic oral care[a] Use of analgesics (adjunctive analgesics often indicated for chronic pain) Use of adjunctive techniques[b] whenever indicated

[a]Basic oral care – use of bland rinses, brushing, flossing, denture care, follow-up care.
[b]Adjunctive techniques – physical therapy, PBM, acupuncture, biopsychosocial treatments.

chemoradiation therapy [5]. Osteoradionecrosis of the jaws (ORNJ), another postradiation complication may be associated with oral pain. However, it remains unclear whether concurrent chemotherapy amplifies the risk of ORNJ [24▪].

Oral mucositis is a frequent complication of chemotherapy protocols for hematologic malignancies. Variable incidence of grade III–IV mucositis have been reported for the different chemotherapy protocols. Protocols containing fluorouracil were documented to have an incidence of up to 66% [25] and up to 100% in those receiving chemoradiation therapy [26]. Chemoradiation therapy may result in increased frequency, severity, and duration of oral mucositis and associated pain [26,27].

Radiotherapy to the head and neck region, chemotherapy, and targeted therapy may cause oral mucositis in cancer patients. Pain associated with oral mucositis has both nociceptive and neuropathic components. Pro-inflammatory cytokines [e.g. tumour necrosis factor alpha (TNF-a), interleukin (IL) 2, IL-6] cause sensitization of nociceptors in affected sites [26].

In addition to acute treatment-related pain during therapy, oral complications were assessed at 6 months postradiation therapy for HNC. Oral mucositis was observed in 8.1% of the cancer patients as well as ulcerations in 3.8%, with continuing oral pain [28]. In another study, 89 HNC patients receiving radiation therapy were followed up for 12 months postradiotherapy; 68% had symptoms of temporomandibular disorders (TMDs) before cancer treatment, 94% at 6 months, and 81% at 12 months following treatment and was associated with limited jaw opening, stiffness, fatigue, and pain [29]. Radiation-induced limitation in mouth opening and TMDs in HNC patients post radiotherapy have been documented [30].

Another phenomenon, breakthrough cancer pain, may occur during chemotherapy or radiotherapy, and this is frequently seen in HNC patients, in relation to oropharyngeal function, during eating and swallowing [27]. Breakthrough pain refers to an episode of severe pain that 'breaks through' a phase of constant pain being partly controlled by stable analgesics, such as an opioid regimen.

PAIN IN SURVIVORSHIP

Variability in the usage of the term 'cancer survivor' exists in the literature. A cancer survivor refers to an individual from the time of diagnosis of cancer until the end of life [31]. For majority of cancers, long-term survivorship is characterized as starting 5 years following diagnosis, hence suggesting cure of the index cancer [32].

Multiple factors were found to be responsible for pain among survivors of a variety of cancers. These factors were frequently related to treatment and occurring as part of individual syndromes [33]. These include postsurgical pain syndromes, radiation-induced pain, and chemotherapy-induced pain [22]. As treatment modalities and techniques improve, oral cancer patients are living longer. Thus, with improved rate of survival, issues related to chronic pain are also likely to be of increasing importance. Long-term HNC survivors (>3 years) experience more pain compared with other cancers [2].

In a previous study, it was reported that worse pain at 1 year after treatment was associated with pretreatment pain, less physical activity, use of a feeding tube at 1 year, xerostomia, depressive symptoms, taking more medication, poor sleep quality, and neck dissection [34]. In another study, 45.1% of

175 HNC survivors at a median of 6.6 years after diagnosis reported pain [35].

In long-term HNC survivors, inflammatory and neuropathic pain mechanisms contribute to persistent oral pain, and this typically depends on the location and extent of surgery, and the addition of chemoradiation therapy [2].

MANAGEMENT OF ORAL PAIN IN CANCER PATIENTS

Management of oral pain in cancer patients is challenging. A proper assessment at diagnosis and throughout survivorship and directing therapy to the cause(s) of pain is key to successful management. Basic oral care (use of bland rinses, brushing, flossing, denture care, follow-up care) is necessary before, during, and after cancer therapy to control plaque levels and decrease the likelihood of tissue irritation [1]. As prevention of pain is invaluable in pain management, recommendations to prevent long-term pain include advances in cancer care including intensity-modulated radiation, proton beam therapy prevention, and treatment of dental complications, and osteoradionecrosis, and after-treatment physical therapy for muscle pain [36]. In addition to nociceptive and neuropathic pain mechanisms, a patient's pain experience is modulated by underlying comorbidities, psychological distress, anxiety, and depression [1]. Hence, a comprehensive approach to management is needed.

To decrease nociceptive pain, opioid analgesics are included in current pharmacologic treatment recommendations [22,37]. In a review of SEER data 2008–2011, 976 Medicare patients with oral/oropharyngeal cancer were identified. 83.1% received opioid during treatment and 15.4% had ongoing opioid at 3 months, and 7% at 6 months [37]. In addition, intrathecal opioid delivery has been reported to provide effective pain relief for chronic intractable cancer pain. It is of particular benefit to patients on long-term toxic chemotherapy regimens by lowering the risk of adverse events [38]. In cancer patients, opioids are limited in efficacy for treatment of neuropathic pain but use of anticonvulsant medications, centrally acting antidepressants, and biopsychosocial treatments are often indicated [1].

Jaw dysfunction including limited movement and pain may accompany HNC therapy but has been the subject of limited study. Physical therapy, analgesics, muscle relaxants, oral appliances, and attention to psychosocial factors are addressed [39▪]. Trismus is an important concern in the management of TMDs in HNC patients because of post-surgical changes and postradiation effects. In a systematic review, trismus was found to be increased from 17.3% at baseline to 44.1% at 6 months and decreased to 32.1% at 12 months [40].

Transnasal fentanyl (a rapidly acting opioid) may be used for treatment of breakthrough pain in patients with HNC, especially because of increased likelihood of mucosal damage and associated difficulties with administration of transoral or transmucosal preparations. In addition to baseline systemic analgesics, topical oropharyngeal preparations may be applied [27].

Management of mucositis-related pain often requires use of multimodal approaches of care. A study reviewed use of oral rinses and systemic analgesics that includes opioids and introduced investigation of novel use of methylene blue oral rinse in management [41]. A systematic review of topical anaesthetics and analgesics for oral mucositis pain, provided a suggestion for use of morphine 0.2% solution. Other agents that have been discussed include topical coating agents, topical anaesthetics, and topical doxepin [42▪▪]. In a randomized trial of 275 patients who underwent head and neck radiotherapy, oral mucositis-related pain reduction was reported within the first 4 h after a single dose of doxepin rinse or diphenhydramine-lidocaine-antacid mouth wash versus placebo. Pain reduction was similar for both. However, more drowsiness was observed with doxepin [43]. In a systematic review, two studies out of nine were high-quality controlled trials and found pregabalin and doxepin rinse effective for neuropathic pain and pain associated with oral mucositis, respectively, in HNC patients [44▪▪]. Application of photobiomodulation (PBM) has been described for prevention of oral mucositis associated with radiotherapy to the head and neck and has been shown to provide pain reduction and reduced analgesic use during and following cancer therapy as seen in a meta-analysis including 14 studies [45].

On the efficacy of cannabinoids for cancer pain-related treatment, differing conclusions have been reported. In a prior meta-analysis, selected studies with a low risk of bias revealed that for adults with advanced cancer, cannabinoid–opioid combination provided no reduction in cancer pain compared with placebo [46]. On the contrary, relief of cancer pain has been reported with tetrahydrocannabinol (THC) and cannabidiol combination [47]. Furthermore, in a systematic review, which included 79 trials, with 6462 patients, reduction in pain with cannabinoids versus placebo (37 versus 31%; odds ratio 1.41) was described, pain reduction by VAS (−0.46), with common adverse events including dizziness, dry mouth, nausea, fatigue, memory, and confusion. Moderate-quality evidence was seen for chronic pain management [48]. In another systematic review involving 32

trials, 5174 adults, 29 assessed cannabinoid versus placebo showing a small effect on pain (on a 10cm VAS a 1cm reduction of pain), physical function and sleep quality [49▪▪]. Oral cancer pain studied in an animal model found a direct role of cannabinoid receptor agonists in reduction of mechanical allodynia and potential positive effects upon cancer cell viability, suggesting potential of antitumor effect [50].

Other documented pain reduction techniques have been assessed. A literature review on the efficacy of positioning stents during radiotherapy for HNC showed only weak effects on mucositis prevention. Further research is needed to confirm their efficacy [51▪]. Also, chemical neurolysis for intractable HNC pain was examined in 33 patients. Significant relief was reported at 1 month post neurolysis in approximately 75% of patients treated with less than 10% reporting adverse effects [52▪]. In another study, sphenopalatine nerve block with bupivacaine for pain in the maxillary division of the trigeminal nerve caused a decrease in HNC-related neuropathic pain scores by 38–80% [53]. A controlled study assessing transcutaneous electrical nerve stimulation (TENS) during the last 2 weeks of radiotherapy for HNC over the TMJ and upper neck documented a reduction in pain but no effect on functional measures was observed, suggesting potential nonpharmacologic pain effect [54].

CONCLUSION

Patients with cancer frequently experience oral pain because of a variety of factors. Factors inherent in the type and location of the malignancy, the modality of cancer treatment, and a holistic approach to management together contribute to their overall pain experience. Basic oral care should be implemented wherever possible, before, during, and after cancer treatment.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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