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This series aims to enhance the healthcare team's awareness of the importance of early detection by recognizing signs and symptoms of orofacial cancers and their management , and of prevention. It discusses treatment complications from surgery, radiotherapy (RT) and chemotherapy (CTX), summarizing the outcomes of a meeting on 'Oral Healthcare in People Living with Cancer' held in 2010, attended by 300 delegates from 33 countries – dentists, specialists, and Dental Care Professionals (DCPs), and the cancer support team. There is a considerable body of literature on oral cancer but very little is written on healthcare aspects of people living with cancer and a particular focus of this meeting was caring for survivors. The Faculty included European leaders in the field who have authored the series. The full peer-reviewed papers from the meeting are published in Oral Oncology 2010; ***46****; 485–570.*

Oral Cancer: Comprehending the Condition, Causes, Controversies, Control and Consequences

13. Pain

Pain is common in oral cancer and, though not always present, can be an early symptom at presentation, in patients on treatment, and post-treatment. However, little has been published on its management.

Pain is defined as 'an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage'. An individual's perception of pain is complex and involves not only pain (nociceptive) and non-nociceptive nerve impulses, but also psychological and emotional processes. It can also vary between cultures, and with tiredness and fatigue. The intensity of pain experienced is thus not always proportional to the type or extent of tissue damage.

Cancer pain

Cancer pain may arise from tumour invasion (especially where nerves are infiltrated), ulceration and infection, and the effects of diagnostic or therapeutic procedures (surgery, RT or CTX). Cancer pain can be controlled in approximately 90% of patients, but undertreatment is common, because of factors such as negative attitudes towards the use of narcotic drugs for pain relief, and clinicians' understanding of effective analgesia.

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Oral cancer pain

Oral cancer pain is particularly problematic because of the erosive nature of tumours, the rich innervation, and the inability to rest the area – with 'dynamic pain' provoked by movements such as chewing, swallowing and talking. These are prime concerns of many patients. Furthermore, neuropathic pain may be induced by mucositis following radiotherapy and chemotherapy.

Prevalence

Two of every three patients complain of pain or discomfort during the 6 months that precede diagnosis of oral cancer, and it is still reported by around 30% of treated patients. Pain is mainly seen in advanced cancer in the region of the tongue and tongue/floor of the mouth. Lesions on the anterior two-thirds of the tongue (oral tongue) typically produce pain, whereas base of tongue cancers more commonly give rise to dysphagia, and pain in the teeth, jaw or ear (otalgia).

Pathogenesis

Cancer pain may arise from stimulation of nerve endings in the oral mucosa; compression and invasion of sensory nerves such as the trigeminal; tissue ulceration and infection, leading to inflammation that potentiates pain; bone invasion with distension of the periosteum or secondary bacterial invasion with osteomyelitis; painful neuromas secondary to surgical resection; and, finally, mucositis, a common complication of RT and CTX.

It has been suggested that pain perception may be mediated by molecules such as calcitonin gene-related peptide, substance P, ATP receptor $P2X_3$, and capsaicin receptor TRPV1.

Pain control

Effective pain control requires a multimodal approach in which pharmacological management is based on the WHO (World Health Organization) analgesic ladder. There is no evidence for any efficacy of non-pharmacological methods such as acupuncture or transcutaneous nerve stimulation. Surgery, RT and CTX have been suggested, but their results have not been quantified.

Oral analgesia is the preferred route for pain control. Interventional approaches which may be required and can be effective include a peripheral nerve or ganglion blockade – which are considered the fourth step of the WHO analgesic ladder. For intractable pain, central neuraxial blockade may be needed, via the intraventricular or intrathecal administration of opioids .

The management of oral cancer pain, therefore, starts with a pharmacologic approach using analgesics and adjuvant drugs. If this is or becomes ineffective, alternative modalities include other routes of drug administration, nerve blocks, and ablative neurosurgery (Table 1).

The WHO simple and well -validated stepped regimen for the treatment of pain according to intensity (the WHO ladder) can be helpful. The essential concepts are: by the mouth, by the

Therapeutic approach	Technique
Pharmacological	Oral, rectal, transdermal, subcutaneous, or intravenous administration of NSAIDs, opioids and adjuvant drugs
Interventions	Peripheral nerve blocks - maxillary - mandibular - glossopharyngeal Ganglion blocks - sphenopalatine - trigeminal - stellate Central neuraxial techniques - intraventricular opiates - intrathecal pump

Table 1. Oral cancer pain management.

clock, by the ladder, for the individual, and with attention to detail. The steps are:

- To use acetaminophen(paracetamol), or non-steroidal anti-inflammatory drugs (NSAIDs) (eg aspirin, naproxen, diclofenac, or indometacin) for mild pain.
- An opioid (e.g. codeine or hydrocodone) should be added (not substituted) to the NSAID if pain persists or increases to moderate.
- Persistent pain, or severe pain at outset, should be treated by using opioids of increasing potency (mainly morphine, methadone, or fentanyl).
- When patients cannot take medications orally, the other less invasive routes (rectal or transdermal) should be tried.
- Parenteral routes, such as subcutaneous or intravenous, should only be used when simpler methods are unavailable or ineffective (Table 2).

In a series of advanced carcinomas of the head and neck, oral analgesics achieved total pain relief on more than 35% of days and significant relief on more than 50%.

RT can relieve both pain

Intervention	Advantages	Disadvantages
Oral NSAIDs	■ Useful for mild to moderate pains ■ Widely available, some over the counter ■ May be combined with opioids ■ Can be administered by patient or carer	■ Ceiling effect to analgesia ■ Adverse effects, especially gastritis and renal toxicity ■ May increase risk of haemorrhage
Oral opioids	■ Effective for both localized and generalized pain ■ Ceiling effect to analgesia imposed only by adverse effects ■ Sedative and anxiolytic properties may be useful ■ Administered by patient or carer ■ Long acting, controlled-release forms available	■ Adverse effects may limit effectiveness ■ Prescription regulated ■ Stigma associated
Transdermal fentanyl	■ Long duration of action (48–72 hours) ■ Can be useful for patients who cannot tolerate morphine ■ Can be administered by patient or carer	■ Adverse effects may be more persistent ■ Difficult to rapidly modify dose ■ Relatively slow onset of action
Subcutaneous infusion	■ Can provide rapid pain relief ■ Morphine and derivates are the preferred drugs	■ Only a limited volume can be administered ■ Induration and irritation at infusion site ■ Requires trained staff
Intravenous infusion	■ Can provide rapid pain relief ■ Most opioids can be given this way ■ Not limited by infusate volume	■ Infection and obstruction of intravenous lines not uncommon ■ Requires trained staff
Epidural, intrathecal, and intraventricular	■ Indicated for pain that fails to respond to less invasive measures ■ Local anaesthetics may be added to spinal opioids	■ Infection at catheter site ■ Pruritus and urinary retention not uncommon ■ Special expertise and careful monitoring needed

Table 2. Analgesics for oral cancer pain relief.

caused by local spread of the primary disease and from metastases, but there is little or no significant pain relief in advanced oral cancer. In selected patients tumours debulking may reduce pain from obstruction or compression. Pain control is the operative indication in palliative surgery for nonresectable tumours.

Peripheral nerve blocks using local analgesics or neurolytic agents such as glycerol are an attractive option in selected patients (Table 1); use of an indwelling maxillary catheter has been reported. Ganglion blockade using diathermy coagulation or glycerol injection has also been used.

In patients in whom oral narcotic therapy has failed, daily preservative-free morphine administered as a bolus intraventricular injection via an implanted catheter connected to a subcutaneous reservoir may be effective. For intractable pain, opioids may be administered alone or in combination with local anaesthetics via an indwelling silastic catheter inserted into the epidural or intrathecal space (at the level of the C1 or C2 vertebra) and connected to an intrathecal pump (usually located on the abdominal wall).

In patients dying of incurable oral cancer, central and peripheral analgesics and neuroleptics are needed in 75% of cases. Analgesia should be individualized starting with low-dose oral morphine, and following a stepped regimen. Epidural morphine administered via a catheter inserted into the epidural space at the level of C7-T1 may reduce pain transmitted via the trigeminal or cervical nerves, with lower toxicity than oral morphine.

Trigeminal tractotomy (division of the descending trigeminal tract in the medulla), and nucleotomy (lesioning of the nucleus caudalis) have been used. Recently, CT-guided percutaneous trigeminal tractotomy-nucleotomy has been suggested to provide effective relief of intractable oral cancer pain.

Pain after oral cancer therapy

Surgery may leave patients with the need for continued pain management. Immediately post-operatively, the whole pain-control armamentarium may be required. Patients undergoing segmental mandibular resection usually report more pain than in those having rim resection. Pain scores after segmental mandibulectomy and reconstruction, using composite free tissue transfer, however, are relatively good, with little difference compared with rim resections. In patients in whom prosthetic rehabilitation is performed following partial jaw resection, those with maxillary resection show higher pain threshold values than patients with segmental mandibulectomy.

In patients undergoing such major surgical procedures, including myocutaneous flap reconstruction, both epidural and intravenous morphine appear to provide good pain relief. Post-operative pain usually decreases progressively over the first post-operative year; the best recovery values being found in patients diagnosed with early cancer.

Mucositis is the most debilitating and painful complication of cancer therapy. Mucositis-induced treatment interruptions and dose reductions have negative consequences on the outcome of treatment of cancer. In both CTX- and RT-associated mucositis, pain intensity is related to the extent of tissue damage and local inflammation. Management involves the aggressive use of analgesics, typically opioids. Patient-controlled analgesia is better than continuous infusion, since fewer opiates are used per hour, and pain duration is shorter.

Polyvinylpyrrolidone-sodium hyaluronate, by shielding the exposed nerve endings, reduces the pain. Soft laser therapy may also be effective.