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## Pain Control in Head and Neck Cancer

Ping-Yi Kuo and John E Williams  
*Royal Marsden Hospital Foundation NHS Trust  
United Kingdom*

### 1. Introduction

“An unpleasant sensory and emotional experience associated with actual or potential tissue damage” (Merskey & Bogduk, 1994), pain is one of the most common symptoms in cancer (Lorenz et al., 2006). Pain associated with head and neck cancer could result from the following causes (Williams & Broadley, 2009):

- Local or metastatic disease causing infiltration, pressure or ulceration
- Side effects from anti-cancer treatment: medication, chemotherapy, radiotherapy, surgery
- Incidental causes such as infection or coexisting morbidity

The assessment of pain should be thorough, the treatment prompt and carefully considered. The current international consensus is that “...the unreasonable failure to treat pain is poor medicine, unethical practice, and is an abrogation of a fundamental human right” (Brennan et al., 2007).

Undertreatment of pain may result in patients having increased morbidity (Carr et al., 1992; MacIntyre 2005), increased prevalence of depression and anxiety (Brennan et al., 2005; Gureje et al., 1998), poor sleep (Thorpe 1993; Cleeland et al., 1996), poor concentration and poor personal interactions (Ferrell, 1995). It also has massive socioeconomic costs including loss in productivity (Steward et al., 2003; van Leeuwen et al., 2006), work days (Brennan et al., 2005) and litigations (Blyth et al., 2003).

Management options should be kept as simple and easy to follow as possible to ensure compliance to treatment. Patients may prefer medication in liquid form as mouth opening may be difficult. However it has been noted that some oral elixirs may contain alcohol, which cause local irritation in a patient with oral mucositis, and tablets which are crushed may feel gritty and unpleasant (Weissman, 1989). Also in patients with dysphagia, the tablets may be difficult to swallow. Suffice to say that it is extremely important to keep re-assessing the patient to make sure that the treatment prescribed is not more unpleasant than the symptom itself! The clinician may need to be flexible and imaginative in finding ways for the patient to comply with treatment. Other routes of administration may need to be considered, including the use of suppositories, subcutaneous infusion pumps, nasogastric feeding tubes, percutaneous enteric gastric tubes and transdermal patches.

## 2. Prevalence of pain

Despite guidelines for treatment of cancer pain available from agencies such as the WHO (1996, 2008) and the Expert Working Group of the European Association for Palliative Care (2001), it has been shown in a recent meta-analysis involving 26 studies that nearly half of patients with cancer have pain that is undertreated (Deandrea et al., 2008). Another meta-analysis showed that cancer pain prevalence is around 53%, irrespective of staging - in particular for patients with head and neck cancer, the prevalence is the highest of all cancers at 70% (Van den Beuken-van Everdingen et al., 2007). In a pan-European survey screening over 5000 cancer patients, 56% had moderate-to-severe pain at least monthly (Breivik et al., 2009). Patients with brain cancer and squamous cell cancer of the head and neck were amongst those with the highest prevalence of pain - 90% and 86% respectively.

The prevalence of pain at diagnosis of head and neck cancers vary from 40% to 84% (Keefe et al., 1986; Chaplin, 1999; Epstein, 1993; Saxena et al., 1995). A higher incidence of pain was noted in more advanced disease i.e. stages III or IV (Keefe et al., 1986). A recent study showed that a third of patients who attend head and neck cancer outpatients had pain from any cause within the previous seven days, with over two-thirds of those having severe pain (Williams et al., 2010). No specific risk factors for pain were found in this population.

## 3. Aetiology of pain

The cornerstone of effective pain management is to determine the aetiology of the pain (Miaskowski et al., 2005). Pain can be due to the cancer itself, as a result of anti-cancer treatment such as surgery, radiotherapy or chemotherapy, or pain which is wholly unrelated to cancer - for example, incidental arthritic pain (Table 1). The type of pain suffered by patients could be nociceptive, neuropathic or mixed nociceptive and neuropathic.

Nociceptive pain often results from tissue damage - for example tumour pressure, the recurrence of tumour, bony infiltration, deafferentiation or neuroma formation secondary to nerve damage during neck dissection, mucositis, related or unrelated infection and inflammation (e.g. sinusitis), osteoradionecrosis, lesions in the cervical spine causing head and neck pain, to name but a few causes (Chua et al., 1999; Williams & Broadley 2009).

Some authors also distinguished myofascial pain from nociceptive *per se*. Talmi et al. (2000) in particular discussed a type of pain resulting from a musculoskeletal imbalance, and associated changes occurring in the shoulder as a result of surgical neck dissection and removal of neck muscles. They cited Fialka and Vinzenz (1988) who noted that 77% patients had shoulder dysfunction and strong to severe pain after radical neck dissection, and Krause (1992) who noted that 31% of patients develop shoulder-arm syndrome after radical neck dissection. Pain resulting from anti-cancer treatment is important as it may be long-lasting and may also adversely affect compliance to continued anti-cancer treatment.

Reference	Pain due to cancer	Pain due to anti-cancer treatment	Pain associated with cancer disease	Non-cancer sources of pain
Grond et al., 1996	81%	31%	19%	7%
Williams et al., 2010	37%	42%	-	25%

Table 1. Presumed aetiology of pain in patients with head and neck cancer

Neuropathic pain is pain associated with injury or disease of the peripheral or central nervous systems, which may result in pathophysiological changes such as ectopic (spontaneous or evoked) discharge by nerves, microneuroanatomical changes, central sensitization, and many others beyond the scope of this review (Macintyre & Schug, 2007). Neuropathic pain for patients with head and neck cancer may involve all sensory nerves in the face, skull, neck and shoulders (Vecht et al., 1992). Some common symptoms of neuropathic pain experienced by the patients include spontaneous continuous burning (81%), shooting pain (69%) and allodynia (88%) – which describes abnormal pain elicited by light touch (Sist et al., 1999; Merskey & Bogduk, 1994). The percentage of patients with head and neck cancer in various studies who were assessed to have neuropathic pain is shown in Table 2.

Reference	Neuropathic (Mixed neuropathic /nociceptive)	Comments
Grond et al., 1993*	28%	From surgical treatment
Grond et al., 1996	47%	377 patients
Forbes, 1997	26%	
Vecht et al, 1992	23%	25 patients, from surgical treatment
Sist et al., 1999	100%	25 patients, post radical-neck dissection
Chua et al., 1999	7.5% (37.5%)	40 outpatients
Williams et al., 2010	10%	70 outpatients

Table 2. Numbers of patients with head and neck cancer and neuropathic or mixed neuropathic/nociceptive pain. \* Cited by Talmi et al., 2000

#### 4. Assessment of pain

Prior to commencing analgesic therapy, a detailed history and careful examination is required in the patient with head and neck cancer to determine the cause of the pain, and the potential role of anti-cancer therapy in treating the cancer and thus decreasing or relieving the pain. The relative impact of analgesic drugs and techniques should also be explored. Investigations such as radiological examinations may be required to accurately determine the cause of the pain.

The assessment of pain in any patient requires attention not only to the physical and physiological aspects, but also to psychological, including how the pain and disease may impact on their quality of life (Portenoy et al., 1999). The emotional and cognitive components of pain may be more significant in cancer compared with non-cancer pain (Huber et al., 2007). In patients with head and neck cancer additional functional problems including ability to swallow, speech, hearing, sight etc also may need to be assessed. All of which will have an additional impact on their quality of life. The expertise of specialties such as psychological medicine, psychiatry, neurology, allied health staff and others are required to provide a multi-disciplinary approach to pain. Palliative care medicine encompasses many of these facets of cancer management, and as such is an invaluable source of information and assistance.

Patients with cancer often have more than one distinct pain syndrome (Grond et al., 1996), or more than one location (Valeberg et al., 2008). In 377 patients with primary head and neck cancer, they described their regions of pain as in Table 3. Assessment and treatment of these patients must then be thorough so as to not miss symptoms and potential problems.

<b>Pain region</b>	
Head/face/mouth	78%
Cervical region	45%
Upper shoulder/limbs	9%
Thoracic	7%
Lower back, lumbar spine, sacrum, coccyx	7%
Pelvic region	1%

Table 3. Pain regions in patients with head and neck cancer (Grond et al., 1996)

### 5. Application of pain pharmacology and physiology in the clinical setting

Pain as a subject is still under research and much is yet not understood about the mechanisms of chronic pain. Treatment methods of pain, particularly those of chronic and neuropathic pain, are still being refined. Table 4 shows some aspects of pain pharmacology and physiology linked to clinical relevance.

<b>Pain Pharmacology and Physiology</b>	<b>Clinical Relevance</b>
<b>Peripheral nerve injury leads to ectopic discharge, microneuroanatomical and phenotypical changes*</b>	Chronic, neuropathic pain is not easily treatable by conventional analgesics
<b>Central sensitization as a result of neuroplasticity*</b>	Treat early before persistent changes to CNS synaptic processing take place due to neuronal damage
<b>Acute severe pain post-operatively is an important predictor of persistent pain*</b>	Acute post-operative pain need to be aggressively treated to prevent long term problems with persistent pain
<b>Evidence for pre-emptive analgesia is inconclusive*</b>	No good evidence in humans for analgesics given pre-painful stimulus versus post-stimulus
<b>Preventive analgesia to reduce chronic pain syndromes* †</b>	“Preventative analgesia” is a description of when the effects of the analgesics administered exceed the expected duration of effect of the analgesic strategy. There is some evidence in the effective use of ketamine and early use of calcitonin in preventive analgesia.
<b>NMDA receptor activation in central sensitization* ‡</b>	NMDA receptor antagonists, particularly ketamine, is of special interest, having been shown to have preventive analgesic effects in some circumstances
<b>Role of reorganisation in the somatosensory cortex*</b>	May contribute to neuropathic pain states such as phantom limb pain and complex regional pain syndrome (CRPS)
<b>Multimodal analgesia to combat central and peripheral plasticity†</b>	Use of more than one type of analgesic to treat pain
<b>Evidence for effectiveness of the multidisciplinary approach to pain treatment‡</b>	A holistic view of the patient situation should be employed, involving other practitioners in pain management

Table 4. Clinical relevance of pain pharmacology and physiology. (Brennan & Kehlet, 2005†; Macintyre & Schug, 2008\*; Williams & Broadley, 2009‡)

## **6. Acute pain**

Patients with head and neck cancer may suffer from acute cancer-related, or acute anti-cancer treatment related pain. Acute cancer-related pain may occur as a result of inflammatory and tumourigenic pain mechanisms such as local tumour pressure, or infiltration of tissues or bone, which may cause subsequent obstruction or compression of visceral structures or nerves and also paraneoplastic effects at distant sites (Portenoy & Lesage, 1999; Delaney et al., 2008). Anti-cancer treatments such as surgery, chemotherapy or radiotherapy can be a means of alleviating pain as the tumour is debulked, but they may also have side-effects causing acute pain after the treatment.

### **6.1 Acute post-surgical pain**

In the patient with head and neck cancer, surgical procedures such as radical neck dissection or other major head and neck surgery will cause acute post-surgical pain – this is not unexpected by most people. The treatment of this acute post-surgical pain commences peri-operatively by the anaesthetist administering analgesics or local anaesthetic techniques such as local infiltration to the wound or nerve blocks. Some patients may be given analgesics as a pre-medication pre-operatively. Treatment of post-surgical pain continues into the recovery area and onto the wards and eventually home ideally using multi-modal analgesia via all routes of administration, as will be discussed later in the chapter.

Acute post-surgical pain is usually easily amenable to treatment and as such should be promptly and adequately treated to prevent development of chronic post-surgical pain (CPSP). Patients reporting high levels of acute post-operative pain and at 4 days post-operation are at high risk of increased pain, poor global recovery with functional limitations and lower quality of life at 6 months post-operatively (Peters et al., 2007). This is concordant with review articles by Perkins & Kehlet (2000) and Kehlet et al. (2006) citing numerous studies to show that acute moderate to severe post-operative pain is a predictive factor for CPSP. Occasionally acute post-surgical pain is difficult to treat as nerve damage occurs peri-operatively from direct resection, bruising or stretching, particularly patients undergoing radical neck dissection (Talmi et al., 2000). Referred shoulder and arm pain may also occur (Chaplin, 1999; Talmi et al., 2000).

### **6.2 Acute pain following radiotherapy and chemotherapy**

Pain following radio- and chemo-therapy in patients with head and neck cancer normally manifests itself as oral mucositis. However, other problems such as radiation fibrosis syndrome, infection and chemotherapy-induced peripheral neuropathy can also cause acute or chronic pain.

#### **6.2.1 Oral mucositis**

Radiation-induced mucositis is common in head and neck cancer patients, with increasing frequency due to the use of more intensive altered radiation and concurrent chemotherapy regimes (Rosenthal & Trotti, 2009). The incidence however will significantly vary amongst different treatment regimens and modalities. Oral mucositis normally becomes symptomatic between the second and fourth week of treatment of radio- or chemotherapy. In many

patients, oral mucositis is associated with considerable pain, which may lead to dose reductions, delays and abandonment of further anti-cancer treatments, to increases in healthcare costs, and impairment in the patient's quality of life. Details of the pathophysiology of oral mucositis is beyond the scope of this chapter. As an outline, the available evidence supports the view that oral mucositis is a complex, interactive process involving all the tissues and cellular elements of the mucosa, with suggestions of genetic risks of developing mucositis (Sonis et al., 2004). Further detailed work is required to clarify the process.

Pain is only one symptom of oral mucositis. Dysphagia, another common complaint, leads to a dependency on feeding tubes and its associated complications or parenteral nutrition, dehydration, micronutrient deficiencies, weight loss, and aspiration (Rosenthal & Trotti, 2009, Sonis et al., 2004). Mucositis also leads to ulceration and subsequent infection, which are both additional causes of pain. In children with mucositis, it should be remembered that their smaller airways may prove problematic with airway compromise. Hospitalisation is sometimes necessary both for initial control of pain and treatment of the other complications already mentioned.

Treatment of oral mucositis was recently the subject of a Cochrane Collaboration Review (Clarkson et al., 2008). They concluded that the evidence for allopurinol mouthwash, granulocytemacrophage-colony stimulating factor, immunoglobulin and human placental extract to improve or eradicate mucositis is weak and unreliable and requires further research.

Symptomatic control of oral mucositis pain by using analgesics may be via many different routes. Many patients with head and neck cancer are still able to take oral analgesics, so the oral route should not be disregarded altogether. One must bear in mind however the other routes of administration, including the transdermal patch, intravenous, intramuscular or subcutaneous routes. Although there is no evidence that patient controlled analgesia (PCA) is more beneficial than a continuous infusion method for controlling pain, patients using PCA used less opiate per hour, and had shorter durations of pain (Clarkson et al., 2008), and thus may suffer less from the side-effects of opiate medication. Multi-modal analgesia should also be considered. In particular, there is evidence that concomitant administration of adjuncts such as gabapentin is useful in radiation-induced mucositis (Bar et al., 2010a, 2010b).

### **6.2.2 Other complications of radio- and chemotherapy**

Radio- and chemotherapy can also cause other pain syndromes in patients with head and neck cancer, such as radiation fibrosis syndrome, chemotherapy-induced peripheral neuropathy and infection.

With fibrosis from radiation pain may occur when the skin and underlying structures contract. An example is "dropped head syndrome", described by Rowin et al. in 2006 as one potential complication of radiation of the mantle field (neck, axillary and mediastinal lymph nodes). This is a late complication of radiotherapy, characterised by fibrosis and contractures of the anterior cervical muscles and atrophy of the posterior neck and shoulder girdle.

Chemotherapy-induced peripheral neuropathy (CIPN) is frequently a complication of common anti-cancer treatments, but is often under recognised and undertreated, with additional difficulties of it being difficult to diagnose, with no universally accepted assessment tools and a lack of interobserver agreement (Stephens et al., 1997 and Postma et al., 1998, as cited in Farquhar-Smith, 2011). As an example, docetaxel causes less CIPN than paclitaxel, carboplatin can also cause CIPN, but less than cisplatin (personal communication, Farquhar-Smith, 2011). Being neuropathic in nature, it is not easy to treat and is commonly a problem in the cancer survivor. There is conflicting, inconclusive evidence that anti-neuropathic agents such as gabapentin may be effective for CIPN (Farquhar-Smith, 2011, quoting Tsavaris et al., 2008; Rao et al., 2007). The heterogeneous nature of CIPN with different anticancer therapies, resulting in distinct neuropathies adds another layer of complexity to its management.

As with other complications of anti-cancer treatment, the discomfort of CIPN may impact on the willingness of patients to enter into future anti-cancer treatments. Additional clinician and patient education is required to highlight the potential problems with this syndrome and further research is necessary to improve current treatment options and potential preventative measures.

Infections, both local and systemic, may also play a role in exacerbating pain in the patient with head and neck cancer. This can occur at any stage of treatment and may often present as a worsening pain problem. Local infections are common with patients who have head and neck cancer. Cellulitis, localised tumour infections and orocutaneous fistulae contribute to more than 20% of febrile episodes in patients with head and neck cancer. Infections may or may not be accompanied by clinical signs such as local inflammation or systemic involvement with fever and leucocytosis (Bruera & MacDonald, 1986 and Hussain et al., 1991, as cited by Williams and Broadley, 2009), particularly due to their already immunosuppressed state from the disease itself or the treatment already undergone. Treatment of the pain will be symptomatic as well as treating the infection itself.

## 7. Chronic pain

The definition of chronic pain as according to the International Association for the Study of Pain (IASP) is “pain which has persisted beyond normal tissue healing time”, which, in the absence of other criteria, is taken to be 3 months (IASP, 1986). Chronic pain may be accompanied by severe psychological and social disturbances. Whilst acute pain management focuses on the cause of the pain, the aim of chronic pain treatment is about managing the effects of the pain, including the physical and psychological aspects, to maximise the function of the patient with chronic pain (Clinical Standards Advisory Group, 2000).

Chronic pain in cancer often occurs as a consequence of cancer treatment. With survival being the primary goal of cancer treatment, side-effects or risks to treatments such as pain are frequently being brushed aside as inconsequential (List et al., 2004), although it is essential to bear in mind - a survey of chronic pain patients in the UK revealed that the second most common aetiology of chronic pain was surgery (Crombie et al., 1998).

Figure 1 shows 3 different pain transmission states:



1. Normal physiological pain transmission – the pain stimulus causes action potentials to travel from the periphery to the brain, with no neuroplasticity (“wind-up” mechanism).
2. Nociceptive pain transmission, with both peripheral stimulation and some central sensitization. Pain may be persistent, but should resolve once the stimulus is removed/resolved.
3. Neuropathic pain transmission. Abnormal transmission of action potentials as a result of “wind-up”, causing altered sensations to both noxious and normally non-noxious stimuli, leading to symptoms such as allodynia and other descriptions of “nerve pain” such as “shooting”, “burning”, “pins and needles” etc.

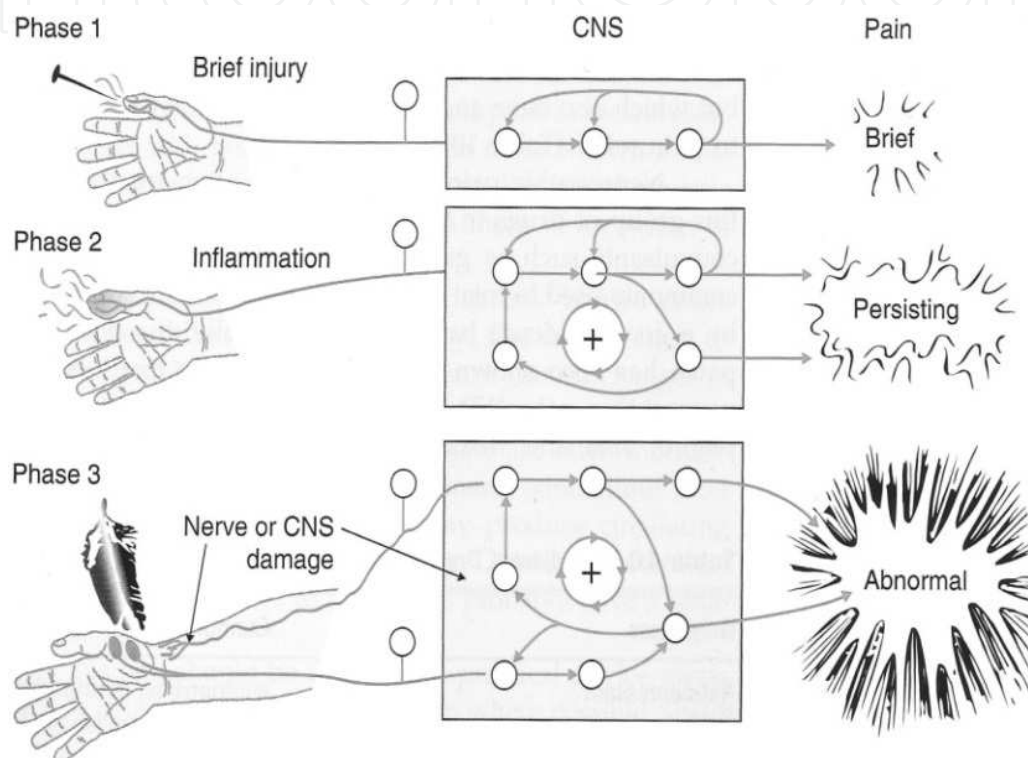


Fig. 1. Three pain transmission states: Phase 1 - normal physiological pain transmission; Phase 2 - nociceptive pain transmission, with peripheral stimulation and central sensitization; Phase 3 - neuropathic pain transmission. Reproduced with permission, Williams & Broadley, 2009.

## 8. Treatment of pain

The mainstay of the management of pain in the patient with head and neck cancer is to target the source of the pain. According to the WHO (2008), up to 90% of cancer pain can be effectively managed. Pain can often be controlled with anti-cancer treatments such as radiotherapy, chemotherapy and surgery. Analgesic drugs and techniques are used concurrently to alleviate pain.

### 8.1 Drug therapy

The WHO guidelines for the treatment of cancer pain advocate a stepwise increase in drug dosages and drug type. The recommendation is summed up as in Table 6.

Head and Neck Tumour/Treatment	Neuropathic Pain Syndrome
Intraorbital	Sharp, lancinating pains in the distribution of the ophthalmic nerve
Maxillary antrum	Sharp, lancinating pains in the maxillary nerve distribution
Infratemporal fossa	Mandibular nerve distribution neuralgia, trismus, temporal pain
Nasopharynx, oropharynx, tonsillar region, oral cancers	Glossopharyngeal and vagal nerve distribution neuralgia and palsies, occipital pain radiating to vertex, referred pain causing otalgia, tinnitus, dental pain
Postherpetic neuralgia	Commonly affects trigeminal nerve with stabbing pains and hyperaesthesia
Post-radical neck dissection	Diffuse burning sensation neck and shoulders, sensation deficits, allodynia, shooting pain, severe shoulder pain and dysfunction, superficial cervical plexus neuralgia
Chemotherapy	Chemotherapy-induced neuropathic pain, causing distal "stocking and glove distributions", usually symmetrical, predominantly sensory symptoms

Table 5. Neuropathic pain syndromes in head and neck cancer, adapted with permission from Willams & Broadley, 2009 (Talmi et al., 1997; Chua et al., 1999; Sist et al., 1999; Farquhar-Smith 2011)

WHO recommendation	Comments
By mouth	Use the oral route unless contra-indicated. In the patient with head and neck cancer, drugs can still be taken enterally by nasogastric or gastrostomy tubes or rectal administration. Patients unable to use the enteral route could try different preparations such as subcutaneous, intravenously or transdermal patches.
By the clock	Regular administration to be given before the previous dose wears off. Breakthrough analgesia is not a substitute but is given in addition to regular.
By the ladder	Follow the WHO 3-step ladder
For the individual	There are no standard doses – the correct dose is one that relieves pain. Titrate dose and add adjuvant therapy as necessary.
Attention to detail	Individualised details such as timing, side effects, response, follow-up, weaning etc. Regular reviews to ensure a personalised treatment plan.

Table 6. WHO guidelines for the treatment of cancer pain. (WHO, 1996)

The WHO 3-step ladder was developed for the treatment of cancer pain (WHO, 1996). It encourages the clinician to assess the severity of pain, administer the appropriate medication, and then re-assess. The patient may then be moved up or down the ladder depending on the clinical assessment of his/her pain. An additional step 4 is now often

advocated for some patients (Figure 2). Patients often are prescribed analgesia from more than one step, as part of the concept of “multi-modal analgesia”. Drugs from Step 1 in particular have been shown to work synergistically with opioids and can often be opioid-sparing, which helps to decrease the side-effect profile of the opioids used (Macintyre & Schug, 2007).

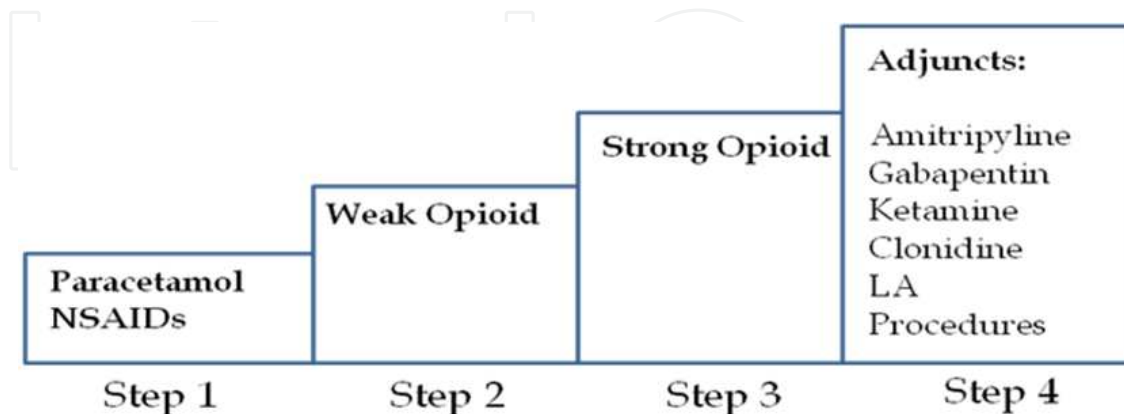


Fig. 2. The WHO 3-step ladder, with step 4 modification

### 8.1.1 WHO Step 1 – Non-opioid drugs

Step 1 drugs on the WHO ladder consist of paracetamol (acetaminophen) and non-steroidal anti-inflammatory (NSAIDs) drugs only. Paracetamol is used widely for mild-to-moderate pain with a well-established safety profile. Its mechanism of action is surprisingly not well defined, for such a prevalent drug, but it is thought that paracetamol acts as a centrally-acting cyclooxygenase enzyme inhibitor, with suggested modulations of the serotonergic system and interference with peripheral delivery of  $\beta$ -endorphins (Remy et al., 2006). Paracetamol is known to act synergistically with NSAIDs and is opiate-sparing. Intravenous paracetamol is particularly useful for those patients who are unable to use the oral route due to clinical or symptomatic reasons.

The class of NSAIDs include both non-selective cyclooxygenase enzyme inhibitors (COX-I and II), such as aspirin, ibuprofen, naproxen, diclofenac, and also selective cyclooxygenase II (COX-II) inhibitors such as celecoxib and paracoxib. Cyclooxygenase produces prostaglandins, which is one contributor to the peripheral inflammatory response, as well as playing a part in thrombosis, body salt and water homeostasis, blood pressure, and gastric protection (Gislason, 2009, citing Grosser et al., 2006). There are many well known potential complications with NSAIDs, including renal impairment, gastrointestinal (GI) irritation, leading to ulceration and haemorrhage, haematologic (anti-platelet effects) and aspirin-exacerbated respiratory disease (Risser et al., 2009). The COX-II selective NSAIDs are shown to have a lower incidence of problems with GI irritation compared to non-selective NSAIDs, however risk varies depending on the individual NSAID. An additional GI risk is a long plasma half-life and also the slow-release formulation (Massó González et al., 2010). The cardiovascular system is also affected, increasing the risk of fluid retention, oedema and destabilise existing heart failure. COX-II selective NSAIDs are particularly known to have effects on the cardiovascular system, but the rates of these events in general are so low, that

probably the estimates are imprecise and it is difficult to design a trial which would investigate this ethically and be financially viable (Trelle et al, 2011).

### 8.1.2 WHO Step 2 – Weak opioid drugs

In the UK the weak opioid drugs currently available are codeine, dihydrocodeine and tramadol. Weak opioids are used for mild-to-moderate pain, often in combination with Step 1 analgesics.

CYP2D6, an isoenzyme of the cytochrome P450 family, is important for the metabolism of codeine and tramadol. There are many variants of the CYP2D6 enzyme, which impact upon the metabolism of weak opioids (Leppert, 2011). This polymorphism results in some people being “poor metabolisers”, whereas some people are “extensive metabolisers”. The effects can be unpredictable. One metabolite of codeine is morphine, but the analgesic effect of codeine is approximately 1/10<sup>th</sup> of morphine analgesia. Tramadol is centrally-acting, on opioid receptors, but also on other mechanisms such as noradrenaline and serotonergic reuptake mechanisms (Macintyre & Schug, 2007). Both mechanisms are implicated in neuropathic pain pathways. The metabolism of dihydrocodeine is not affected by CYP2D6 (Leppert, 2011).

Some clinicians prefer to go directly from Step 1 to Step 3, to avoid the potential for uncertainty with CYP2D6 polymorphism. Instead, strong opioids are titrated carefully to the patients’ needs.

### 8.1.3 WHO Step 3 – Strong opioid drugs

Strong opioid drugs include morphine, diamorphine, oxycodone, fentanyl, which are mu-opioid receptor agonists, and also partial agonists such as buprenorphine. These Step 3 analgesic drugs are used for moderate-to-severe pain.

The most commonly used drug is morphine, of which there are several preparations. For patients with head and neck cancer who find tablets difficult to swallow, there are elixirs which can be taken orally or passed down a feeding tube. Both immediate release preparations and sustained-release preparations are available in elixir form.

Other forms of strong opioid drugs include the transdermal patch for fentanyl or buprenorphine. Buccal preparations of fentanyl are also available – as a lozenge or lollipop to be sucked, or a tablet which slowly dissolves. The type of preparation most suitable for the patient depends on their particular circumstances – for example, a head a neck cancer patient who has painful oral mucositis, with a persistently dry mouth may find it uncomfortable to use lozenges or buccal tablets, and may prefer transdermal patches, or intravenous or subcutaneous patient controlled analgesic devices (PCAs).

Some patients become resistant or tolerant to strong opioids, particularly if they have required Step 3 medication for a prolonged period of time. In this case it may be necessary to change to a different drug. Any other strong opioid may be chosen - methadone is good option which is often forgotten. It is particularly convenient as a once daily administration due to its long half life.

The potential adverse effects of opioid medication, both weak and strong, must not be overlooked. The most common problems are constipation, nausea and vomiting, and sedation. For constipation, the patient should be advised to keep well hydrated, mobilise, and if prescribed opioid for more than a few days, all patients should also be prescribed laxatives – a stool softener and a bowel stimulant. Dose reduction of the opioid does not help with constipation. Newer agents such as the combined oxycodone/naloxone, and opioid antagonists such as methylnaltrexone have been shown to be effective in this regard (Clemens et al., 2011; Candy et al., 2011). Nausea and vomiting is perhaps the most unpleasant side-effect for the patient. Numerous classes of anti-emetics are available, and as with analgesic drugs, a combination of anti-emetics acting at a combination of sites may be a more effective method than single treatment (Macintyre & Schug, 2007). Mild sedation and cognitive impairment are common side effects of opioid therapy, however tolerance develops quickly. Sedation can be a warning sign of excessive opioid therapy, and will almost always precede respiratory depression. A decrease in respiratory rate is actually a late and unreliable sign of opioid-induced respiratory depression. Both sedation score and respiratory rate should be monitored, particularly when starting patients on new medications, in the acute setting.

#### **8.1.4 WHO additional Step 4 – Adjuvant drugs and interventions**

Step 4 is a modification commonly proposed to the original 3-step WHO analgesic ladder (Vargas-Shaffer, 2010). Consisting of both drug and interventional therapy, step 4 adjuncts may be added at any point, with any combination of other steps. The adjuvant drugs proposed are those that are now commonly used for chronic or neuropathic pain, including anti-depressants (amitriptylline, nortriptylline), anti-convulsants (gabapentin, pregabalin), NMDA-receptor antagonists (ketamine), steroids, capsaicin and so forth. Local anaesthetics are also included in this group – either as part of an intervention such as local anaesthetic infiltration/nerve blocks, or as a transdermal patch (lidocaine patch). As we have already seen, patients with head and neck cancer will often have neuropathic pain, and chronic pain. The addition of a step 4 adjunct may help in the treatment of their pain, and may also decrease the amount of opioids necessary to help control pain.

#### **8.2 Interventional therapy**

In the patient with head and neck cancer, interventional therapy for pain caused by cancer or cancer treatment is now not longer at the forefront of pain management. It was not possible to use single nerve blocks to relieve pain, as sensory innervations in the head and neck region typically arises from multiple cranial or cervical nerves. Numerous other methods have been tried with reasonable success. Examples include cervical plexus block (Dwyer 1972), lumbar CSF morphine injections (Sullivan 1987), long-term intraventricular infusion of morphine (Dennis & DeWitty, 1990) and intrathecal administration of analgesics (Crul et al., 1994). However, these interventions described are not without potentially very serious complications. The modern analgesics and their methods of delivery are now so well established such that these interventions are largely no longer performed.

### 8.3 Characteristics of studies investigating pain in patients with head and neck cancer

Study (Number of patients)	Cancer type	Duration of follow-up	Prevalence of head and neck pain
Bjordal (N = 126) 1992	Head and neck cancer	None	18% ("quite a bit" or "very much" pain)
Chaplin and Morton (N = 93) 1998	Newly diagnosed, curable head and neck cancer	2 years	48% at diagnosis (8% severe) 25% at 12 months (3% severe) 26% at 24 months (4% severe)
Forbes (N = 38) 1997	End-stage head and neck cancer	None	79% (26% neuropathic)
Keefe (N = 30) 1986	Head and neck cancer (100% squamous cell carcinoma)	3-6 weeks after initial evaluation 2-3 months after initial evaluation	40% at initial evaluation 50% at final evaluation
Olson (N = 51) 1978	Head and neck cancer, undergone surgical treatment previously	Unknown	32-39% mild to moderate (8% moderate) No patients reported severe pain
Robertson and Hornibrook (N = 522)	Head and neck cancer (~90% squamous cell carcinoma)		8% to 66%, depending on cancer type
Saxena 1995 (N = 117)	Head and neck cancer (90% clinical stage III or IV)		84% (55% moderate to severe, 50% of whom had unrelieved pain)
Talmi (N = 62) 1997	Terminal head and neck cancer (87% squamous cell carcinoma)	None	77%
Epstein (N = 34) 1993	Head and neck cancer pre-/post-radiotherapy (91% squamous cell carcinoma)	6-12 months	82% at diagnosis 100% at midpoint of treatment 46% 6-12 months after treatment
Weissman (N = 14) 1989	Newly diagnosed head and neck cancer patients undergoing radiotherapy	Unknown	29% before treatment 100% during treatment (moderate to severe pain on 37% of treatment days)

Talmi (N = 88) 2000	Head and neck cancer	1-8 months (prospective)	85% after neck dissection; 3% after 2 months
		>2 years (retrospective)	0%
		6-24 months (retrospective)	15%
Terrel (N = 175) 1999	Head and neck cancer	None	Unknown
Chua (N = 40) 1999	Head and neck cancer (83% squamous cell carcinoma; 60% T3 or T4)		100% at presentation (severe in 52%)
Grond (N = 167) 1993	Head and neck cancer	Unknown	100% at referral

## 9. Holistic care

Aside from direct treatment of the cancer itself by surgery, radiotherapy or chemotherapy, one must remember that treatment of the patient with head and neck cancer should always be undertaken in a holistic manner. As cancer treatments are improving, so too are the rates of cure and length of remission. 'Cancer survivorship' issues such as quality of life, good pain and symptom control are important aspects of holistic care that should be prioritised (World Health Organisation [WHO], 1996) - the patient may be debilitated for a long time with pain.

Holistic care in patients with head and neck cancer involves not only being concerned about the practical aspect of physical problems, but also the less 'medical' problems of psychological distress and social aspect of cancer as a disease, in particular the aesthetic appearance of head and neck cancer or anticancer treatment causing disfigurement. The functional aspect of having cancer in this region also requires particular care - speech and swallow may well be affected, as well as the possibility of requiring medical adjuncts such as the tracheostomy. This in turn will clearly have an effect on the psychosocial state of the patient with head and neck cancer. These symptoms may or may not be directly mentioned by the patient, and it may take a clinician who pays attention to detail to elicit this information. By identifying and resolving issues quickly, holistic needs assessment and care allows the opportunity for clinicians to make a huge difference to the overall experience of cancer, and the potential to improve outcome. Patients are also allowed to be fully engaged in their own care, thus feel empowered to support self-management of their condition (National Cancer Action Team, 2010).

Symptomatic control is relevant during all stages of the cancer, be it at diagnosis, during treatment for cure or palliation, after anti-cancer treatment, at palliation, or even once 'cured'. Commonly pain with head and neck cancer will occur as a result of anti-cancer treatment, as well as due to disease progression. Sometimes the most effective method of

symptom management or palliation may be further anticancer treatment. The potential adverse effects must then be weighed up when considering the expected benefit to undergoing therapy for pain. The patient and family members should be well informed before making a joint decision with the clinician to undergo any further treatment.

Treatment of pain in the patient with head and neck cancer may well be adequately managed by an experienced clinician. However many studies quoted by Brennan et al (2007) showed that many clinicians are not comfortable in prescribing opioids, having a lack of knowledge of pharmacology of the relevant drugs and experience of pain management. The Pain Management or Palliative Care Teams are experts in the hospital in this regard and timely advice should be sought when problems arise to prevent complications developing further down the line. Quite as importantly, bearing in mind the subjective nature of the pain as a whole, the clinician needs to believe in patients in their descriptions of their pain, and take action to help alleviate the pain.

## 10. Conclusion

Patients with head and neck cancer will often suffer from pain, resulting from the cancer itself, anti-cancer treatment, or wholly unrelated causes. A high percentage of patients will suffer from neuropathic pain, or mixed nociceptive and neuropathic pain, which may be difficult to treat. Many patients with head and neck cancer will also have pain in more than one location. When treating these patients, it is vital to carefully assess and determine the aetiology of their pain in order to effectively treat their symptoms. Early treatment is advised to help avoid progression into chronic pain and will further complicate treatment strategies. A multi-modal, multidisciplinary approach to pain management encapsulates the concept of holistic care and may make a huge difference to the experience of cancer for the patient. We should aim to empower our patients and encourage them to take ownership of their pain issues. By doing so, we will be positively contributing to the quality of the patient journey with cancer.

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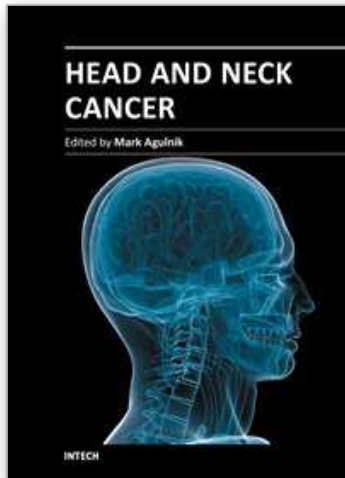
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## **Head and Neck Cancer**

Edited by Dr. Mark Agulnik

ISBN 978-953-51-0236-6

Hard cover, 440 pages

**Publisher** InTech

**Published online** 14, March, 2012

**Published in print edition** March, 2012

Head and Neck Cancer provides an interesting and comprehensive overview of all aspects of head and neck cancer including overviews of the disease, basic science aspects pertaining to the disease, diagnosis, treatment and outcomes for patients with this disease. The chapters written by world renowned experts cover the entire discipline of head and neck oncology and include discussions of regional disparity is, advances in basic science understanding, advances in her radiotherapy, chemotherapy and targeted agents as well as a focus on reconstruction, prostheses, and aspects of quality of life and health outcomes. The book is designed to be both practical and comprehensive for every physician treating his complex disease.

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Ping-Yi Kuo and John E Williams (2012). Pain Control in Head and Neck Cancer, Head and Neck Cancer, Dr. Mark Agulnik (Ed.), ISBN: 978-953-51-0236-6, InTech, Available from:  
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Phone: +86-21-62489820  
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