

## REVIEW ARTICLE

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# Pain in head and neck cancer: prevalence and possible predictive factors

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### Summary

The purpose of this article was to review the main aspects of pain and its prevalence among head and neck cancer patients, as well as to identify the presence of possible pain predictive factors. For an integrated presentation of this topic a Pubmed database systematic search for relevant published studies was performed.

When considering the prevalence of pain in head and neck cancer patients the studies available in this field show great variations in relation to the number of patients included, surgical procedures performed, and established approaches to analgesia.

Despite the recognized association between cancer and pain, insufficient attention is paid in the head and neck pain problem, and to date, only few studies in the literature address the diagnosis of head and neck pain or its management. Further efforts are necessary in order to understand the real dimension of this problem in head and neck cancer patients, and therefore to recognize pain predictive factors and/or pain genetic factors aiming (i) to identify those subjects most at risk for pain, and (ii) to tailor, in a near future, 'targeted' analgesic interventions.

**Key words:** head and neck cancer, nociceptive and neuropathic pain, pain, pain predictive factors, prevalence

### Introduction

Head and neck cancer is the sixth most common cancer type worldwide. Unfortunately, despite significant advances in surgical and other treatments that improve the quality of life, survival has shown only moderate improvement during the last 20 years [1-3]. Moreover, as already described, head and neck cancer has a severe impact on patients' quality of life, and the significant morbidity following the different treatment modalities requires long term multidisciplinary care [3].

Pain is the most frequent symptom on presentation among head and neck cancer patients, and it is believed that this is mainly due to the rich nerve supply of these areas. The reported prevalence of pain at the time of diagnosis ranges from 40 to 84% [4-7]. Nonetheless, insufficient attention is being given to this problem, especially in the head and neck oncology.

For an integrated presentation of this topic Pubmed database was searched from December 2003 to December 2013; full text articles were registered and studied when the title, abstract or key words suggested that the study may be eligible for this review. The search was carried out independently, and restricted to papers written in English language. Other papers were also identified from the references in the published literature.

The medical subject heading (MeSH) used included: cancer, pain, nociceptive and neuropathic pain, head and neck cancer.

### Pain in head and neck cancer: a multidimensional problem

Over the past years, the definition of pain has become "multidimensional", as it is considered not only just as a sensation, but it has also been described by several characteristics such as quali-

ty, location, intensity, emotional impact, frequency. Cancer pain, in addition to the overwhelming physical weight of pain itself, is almost always accompanied by psychological, emotional, social problems and it is one of the most feared consequences of cancer.

Pain in head and neck cancer patients has been classified into acute and chronic, nociceptive and neuropathic [8].

Nociceptive pain is often the consequence of tissue damage, such as tissue infiltration by neoplastic cells in the nearby structures [9,10]. Neuropathic pain can be due to tumor' nerve compression or invasion. It has been described that this phenomenon may lead to uncontrolled neuronal discharge, or increased expression of sodium channels and voltage dependent calcium channels among involved neuronal pathways; neuropathies can therefore induce a remodeling process of the neuronal excitability [8,11]. In addition, the genesis of neuropathic pain can be due to the release of inflammatory mediators, such as TNF, reactive oxygen species, bradykinin, substance P and other cytokines (i.e. secondary to inflammatory processes linked to tumor, such as a mucositis) [12,13].

Other researchers have also shown that neuropathic pain can be due to changes in the nociceptive stimulus processing, at the spinal cord level [14].

Acute pain can result from the infiltrative processes of the tumor [10], or can be related to treatment effects, such as the type of surgical procedure and its duration or to the occurrence of operative complications [15].

The surgical procedure itself represents a major stress for the body as it activates an immune and endocrine response, which can lead to an increased demand of oxygen by tissues and immunosuppression. It has been described that nociception induces an hypothalamic autonomic response and neuroendocrine stimulation (stress reaction). Consequently, hyperventilation, increased sympathetic tone and catecholamines levels, enhance cardiac output, peripheral vascular resistance, blood pressure, cardiac workload, myocardial consumption of oxygen, levels of cortisol, ACTH and glucagon [15]. The neuroendocrine response also induces other metabolic responses, such as increasing glucose blood level, plasma cyclic AMP, free fatty acids, lactate and ketones. All these changes determine a catabolic state [15].

Therefore, the main reported clinical consequences caused by acute postoperative pain are [15,16]:

a) respiratory modifications such as alteration of the ventilation / perfusion ratio for a combi-

nation of factors that include the reflex muscle contraction (thoracic muscles and diaphragmatic excursions);

b) increased cardiac workload, increased blood pressure and oxygen consumption;

c) alterations of gastrointestinal and urinary function, such as paralytic ileus, nausea, vomiting;

d) change of muscular metabolism and function: the persistence of postoperative pain and the consequent movement restriction can cause muscle atrophy, with consequent modification of their metabolism and delayed restoration of resected muscle structures;

e) blood modifications: it is known that the platelet hyperactivity, due to the increased adrenergic status, in association to movement restriction due to pain, increases the risk of thrombosis;

f) psychological and emotional effects: a severe postoperative pain can cause emotional distress, fear and anxiety about a possible new operation [16].

Acute pain may also be the consequence of radiotherapy and chemotherapy. It is mainly caused by mucositis induced by these treatments, but it can also be secondary to radiation-induced fibrosis or peripheral neuropathy. Oral mucositis usually becomes symptomatic between the second and the fourth week of treatment after radiation or chemotherapy. In several patients it is associated to considerable pain, which can lead to decrease of doses, treatment postponement, or therapy plan modification. Pain is not the only symptom of oral mucositis, as dysphagia due to mucosal ulceration and subsequent infections can also often occur [17-19].

Since a 'not well-managed' acute postoperative pain can contribute to the development of chronic pain [17], it is necessary to offer to patients adequate and effective treatments.

Chronic cancer pain is considered to be the consequence of the tumor itself or be the result of the different therapeutic modalities [20]. It has been reported that persistent pain can lead to physical deterioration and emotional and behavioral changes, especially in head and neck patients, due to development of sleep disturbances, decreased appetite, decreased ability to concentrate and irritability [17,21,22].

### **Prevalence of pain in head and neck cancer: still an underestimated problem?**

Despite the recognized association between cancer and pain, still insufficient attention is be-

ing paid to this problem. In fact, up today, only 0.1% of the literature on cancer is addressed to diagnosis of pain or to its treatment [23]. Moreover, most of the papers available that are focused on cancer pain and its prevalence, report different and often inaccurate results. Available studies in this field aim to explore different features of pain, including also head and neck cancer patients.

Overall prevalence of pain in cancer patients is reported to be a very frequent symptom. Van den Beuken et al. after analyzing 52 articles in a meta-analysis, reported a prevalence of pain in cancer patients > 50%, with a highest prevalence in head and neck cancer patients (up to 70%). Pain is also reported to have even a higher prevalence (up to 64%) among cancer patients with advanced or metastatic disease, and during treatment (up to 59%) [24].

A European survey conducted in 2009 in 11 European countries and Israel included 5084 cancer patients and showed that 56% of them suffered from moderate to severe pain at least once a month, and that the prevalence of pain in head and neck cancer patients was 86 % at the time of first diagnosis [25]. According to Olsen and Creagan, patients with head and neck tumors and advanced disease had a pain prevalence that ranged between 80 and 100% [23].

Recent estimations on the prevalence of pain at the time of diagnosis indicate pain as symptom on presentation in head and neck cancer patients in 40-84% of the cases [4-7,26]. In addition, patients with advanced disease at diagnosis (i.e. stage III or IV), and in particular those having by oropharyngeal and oral cavity tumors, have been reported to show higher pain intensity (about 90% of the subjects experienced pain) [7,27].

Concerning the prevalence of postoperative acute pain after head and neck surgery, the studies available show a great heterogeneity in relation to the number of patients involved, surgical procedures performed, established approach to analgesia and methods adopted for pain evaluation [28-31]. However, in major surgical procedures, the prevalence of acute pain is estimated between 30 and 70% [28]. A Swedish study conducted on 191 patients showed that 76% of the patients experienced moderate to severe postoperative pain after major surgery [32], whereas a recent study with a larger sample (1736 patients), showed a postoperative prevalence of pain (Numerical Rating Scale/NRS > 4) of 28.5 % immediately after general anesthesia [33].

According to a recent paper by Sommer et al. the prevalence of acute postoperative pain in head

and neck surgery varies in relation to the type of operation and the anatomic site of the intervention: oral, pharyngeal and laryngeal procedures show a pain prevalence of 48%, endoscopic procedures (i.e. Functional Endoscopic Sinus Surgery/FESS) of 30 %, while ear procedures of less than 20% [34].

Concerning the prevalence of chronic pain in patients with solid tumors, it has been reported to range between 20 and 50%; in patients with advanced stage disease the estimated pain prevalence is 70-90 % [26]. Chaplin and Morton showed that in head and neck tumors at least 25% of the patients experience pain at 12 months after surgery, and 26% at 24 months [5].

Finally the effectiveness of cancer pain therapy in the postoperative period has also been investigated. In general, pain control in head and neck cancer patients is reported to be inadequate and not effective. Orgill et al. reported that the effectiveness of pain therapy after laryngectomy is adequate and effective only in 35% of the patients [35]. Deandrea et al. in their recent meta-analysis assessed the pain intensity reported by cancer patients and the analgesic treatment prescribed and concluded that in 43% of the cases pain was not adequately treated [36].

## **Pain predictive factors and genetics in head and neck cancer patients: towards a tailored analgesic therapy**

### *Predictive factors*

There are only few reports that have identified possible factors associated to head and neck cancer pain.

Age, physical and mental health, poor sleep quality and insomnia have been correlated to pain severity, as older female patients and greater psychological distress have been described to create a greater pain sensation [37-39]. Also functional impairment after surgical resection or radiotherapy (i.e. oral cancer) has been linked to greater emotional distress and also to pain [37,38].

Diet has been found to be related with pain in head and neck cancer patients. In particular, the potential importance of nutritional factors in the management of head and neck cancer patients is debated; even though experimental data are lacking, trials with immunonutrients such as glutamine, arginine, branched chain amino acids, n-3 polyunsaturated fatty acids and nucleotides indicate several beneficial clinical effects, particularly in operated patients, and also in the pain of head

and neck cancer patients [40].

On the other hand, increased physical activity, as well as fruit and vegetable intake have been linked to improved quality of life, and therefore to a higher pain tolerance in these patients [41].

Other specific identified predictive factors of pain are dry mouth, caries, and eating/speech difficulties, especially in those affected by oral cancer that have received radiotherapy [40].

Anxiety and depression have been correlated to pain, while no significant association has been found with the marital status, education level and employment status [42].

Also, pain itself has been identified as a negative prognostic factor, since spontaneous pain before treatment may be associated with poor prognosis in patients with oral squamous cell carcinoma [41].

Educational interventions, aiming to increase the patients' knowledge and attitude regarding pain, have been reported to affect pain treatment [43]. In particular, the quality of analgesic treatment in cancer patients with chronic pain could be enhanced by educating patients about pain and improving active participation in their own analgesic treatment [43].

#### *Pain genetics*

Research in the genetics of pain and analgesia has accelerated in recent years. Some considerations come from animals, as genetic correlation studies using artificially selected inbred strains and inbred strains have revealed similar genetic background of different analgesic drugs against the same pain symptom (i.e. chemical, thermal, mechanical), as well as a relationship between pain sensitivity and analgesic response [44].

Other findings from animal pain genetics studies suggest that there are interactions between genotype differences, pain sensitivity and

environmental factors [44].

Also, very rare genetic disorders of pain, in which pain sensitivity is markedly absent (congenital insensitivity to pain syndromes) have been described in humans. In these cases, gene mutations are responsible to encode erroneously proteins of different functional classes, such as ion channels, enzymes, transcription factors, therefore impairing the correct function of the analgesic response pathways.

It is likely that geneticists could soon explain satisfactory trait variances in clinical pain states or analgesic response; such studies could also help clinicians elaborate individualized pain therapy plans (i.e. gene-based pain management has already been proposed as an interventional procedure to set a new class of medicines for alleviating pain symptoms) [43,45].

## **Conclusions**

From the data available it is clear that pain is a significant problem in patients with head and neck cancer, since a significant proportion suffers from pain before, during and after completion of treatment(s). Pain should be properly addressed, otherwise the quality of life would be significantly deteriorated.

Moreover, when planning surgical and non-surgical treatment for head and neck cancer patients, it would be necessary not only to organize effective analgesic treatments, but also to identify those subjects most at risk for pain in order to tailor 'targeted' assessment and analgesic interventions.

Even if different aspects of pain have been addressed in head and neck cancer patients, still the available data are not conclusive and further studies are necessary in order to understand the dimension of this problem and thus to improve the quality of life of patients.

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