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REVIEW ARTICLE

Pain in head and neck cancer patients: the role of gender

Chiara Bianchini[1], Virginia Corazzi[1], Mariasole Malagò[1], Tiziana Bellini[2], Francesco Stomeo[1], Andrea Ciorba[1], Stefano Pelucchi[1]

[1]ENT & Audiology Department, University Hospital of Ferrara, Ferrara, Italy; [2]University Centre for Studies on Gender Medicine, University of Ferrara, Ferrara, Italy.

Summary

Purpose: *The purpose of this paper was to investigate the role of gender in the perception and tolerance of pain in head and neck cancer patients. Pain has a multifactorial etiology, characterized by personal experience and emotional impact, location, intensity and quality perception. Gender-related factors may have an impact on the development, perception and tolerance of pain. Gender medicine is an evolving transversal medical field, also focusing on algology and pain management.*

Methods: *Literature review. A systematic electronic search was undertaken using PubMed, Embase and Cinahl databases. A selection of available studies was then performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria (http://www.prisma-statement.org/).*

Results: *There were few studies in the literature examining the role of gender pain manifestation in head and neck cancer patients, including pain perception and tolerance after surgical treatment. However, available data show that (i) several factors can influence pain perception and tolerance among sexes, and that (ii) pain perception in head and neck cancer patients seems to be more prevalent in women, also in the postoperative stage.*

Conclusion: *Gender Medicine is an evolving field; in the future, additional investigations could help us in better understanding the origin, the features and the differences between pain perception and tolerance between sexes, therefore leading us to provide a more specific and tailored pain therapeutic plan, also for head and neck cancer patients.*

Key words: *pain, head and neck cancer, postoperative pain, surgery, gender, sex differences*

Introduction

Pain has been defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage", according to the International Association for the Study of Pain (IASP) [1]. Pain is not a simple symptom or subjective sensation; during the last decades, the definition of pain has become "multidimensional", as it is characterized by several features, such as location, intensity, frequency, quality perception and emotional impact [2,3]. When experiencing pain, the intensity of the sensation is the first clinical assessment, but emotional, psychological, cognitive and behavioral aspects are also involved in the subjective perception of pain [2-4].

In oncologic patients, pain represents one of the most feared and burdensome symptoms. The reported prevalence of pain in cancer patients is more than 50% [5,6] and up to 80-90% in patients affected by metastatic cancer, mostly due to chronic pain development [7]. Compared to other tumors, head and neck cancers are characterized by a significantly greater painful perception [8]; the estimated prevalence of pain in affected patients is about 70% [5,6] and pain is often reported to be inadequately treated [8].

Corresponding author: Andrea Ciorba, MD, PhD. ENT & Audiology Department, University Hospital of Ferrara, via Aldo Moro 8, Ferrara, Italy.
Tel: +39 0532 239746, Fax: +39 0532 237447, Email: andrea.ciorba@unife.it
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The purpose of this paper was to investigate, through a systematic literature review, the role of gender and sex in pain perception and tolerance of patients affected by head and neck cancer, including pain perception after surgical treatment.

Methods

The PubMed, Embase and Cinahl databases were searched going back for the last 10 years (from April 2009 up to March 2019). Full-text articles were obtained in cases where 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 in English; also, it was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (http://www.prisma-statement.org/). The medical subject heading (MeSH) terms used included: pain, postoperative pain, head and neck tumors, sex factors, sex distribution, and gender differences. The number of total papers identified from database search was 20 (Table 1); other papers were also identified from references in the published literature (n=54). Of this total (n=74) we selected 68 papers: inclusion criteria were: clinical series, review papers; exclusion criteria were: full text not available, manuscripts not in English, case reports. Then, after a critical discussion, the authors decided to include for evaluation just the clinical series with an adequate group of patients studied (n>20), and just the reviews published on relevant journals and owing a rigorous methods and rigorous reporting. After this further assessment, the total number of eligible papers became 61.

Pain in head and neck cancer patients

The etiology of oncologic pain has been reported to be multifactorial: edema, inflammation, ulceration, infection, local invasion caused by tumor enlargement may cause nociceptive, somatic or visceral pain, while tumor compression or direct infiltration of nervous fibers may be responsible for neuropathic pain [8,9]. Head and neck cancers have been also described as the most related to neuropathic pain, compared to other oncologic diseases [10]. The greater prevalence of pain in patients affected by head and neck tumors could be attributed also to psychological factors related to the modification of the vital functions supplied by these regions (such as chewing, swallowing, phonation, breathing) and also to the aesthetic alteration of the face in some cases [11].

Oncologic surgery may be itself the cause of a greater postoperative pain perception, potentially aggravating a pre-existing pain condition; the reported prevalence of postoperative pain is up to 80% in head and neck patients [12]. Surgical procedures may worsen the painful perception due to trauma of the nervous fibers [8,13]; furthermore, the major oncologic treatments on head and neck are usually disfiguring, and therefore, psychological, depressing, anxious and social factors may increase the subjective pain perception [14]. Literature data described an uncontrolled postoperative pain in about 48% of surgically treated patients affected by head and neck cancers [15]. Some authors suggest a high prevalence of opioid drug use in the long-term among head and neck cancer patients [16]; Pang et al [17,18] reported that those using opioid drugs preoperatively, will use more often a chronic opioid treatment after surgery. Also, an inadequate pain management has been correlated to poor wound healing and poor functional recovery in head and neck cancer patients after surgery [19].

The most frequent reported predictive factors influencing pain perception in head and neck cancer patients are: alcohol abuse, smoking, depression and neck surgery [20-23]. The increased prevalence of pain after neck surgery could be due to the interruption of nervous fibers and a consequent deafferentation, which may also induce hypersensitivity, dysesthesia and/or paraesthesia [24]. Furthermore, a more intense postoperative pain has been described in older subjects as well as in those with comorbidities [11], and could be worsen by movements related to speech, chewing or swallowing [11,20,25,26].

Table 1. Literature evaluation and selection, according to PRIMA criteria (http://www.prisma-statement.org/)

Total number of articles obtained by PubMed, Embase and Cinahl search	20
Other papers from references in the published literature	54
Total number of papers identified	74
Paper excluded[1]	6
Article assessed for eligibility	68
Paper excluded[2]	7
Total number of papers finally identified	61

[1]Inclusion criteria were: clinical series, review papers. Exclusion criteria were: not availability of a full text; manuscripts not in the English language; case reports.
[2]Inclusion criteria were: for clinical series, papers with an adequate group of patients studied (n>20); for reviews, papers published on relevant journals and papers showing a rigorous method and rigorous reporting.

Pain in Head and Neck cancer patients: the role of gender

Available data on the role of gender-related factors in pain perception and tolerance, in patients

affected by head and neck cancer are still limited (Table 1). However, there is a growing attention to quality of life and, in particular to pain perception in oncologic patients. Over the past years, several efforts have been made in order to evaluate, monitor and control pain, especially after cancer surgery, as an adequate postoperative pain treatment contributes to a significant reduction of perioperative morbidity, postoperative complications, days of hospitalization and costs and may accelerate patient's overall recovery after major surgery [27]. In addition, a better understanding of the multidimensional characteristics of pain, and of the possible role of sex and gender-related biological and psychological features, may help develop new strategies to improve pain management and control. Gender medicine is an evolving transversal medical field, focusing on the study of sex and gender-related differences existing in anatomy, physiology, biology, psychology and social, cultural, functional and behavioral aspects [28,29]. During the last decades, evidence showed that differences between men and women deeply influence the pathophysiologic mechanisms of several diseases and coping strategies of patients, also conditioning the efficacy of therapy [28,29]. Algology and pain management represents an interesting research field of gender medicine. Literature data have shown that several factors (such as hormonal, genetic, anatomical-physiological, social, cognitive, emotional) may be involved in the different pain perception and tolerance between men and women [30].

According to a recent systematic review, pain in head and neck cancer seems to be more prevalent in women [31]. Since 1992, Berkley observed the existence of a clinical difference between men and women, as many more women were suffering from chronic pain than men; moreover, Berkley observed a gender difference in the response to the analgesic therapy [32]. Gender could play a key role as a determinant of pain perception and tolerance; efforts have been made to understand how gender may influence pain sensitivity and, in particular, to understand the influence of genetic background and hormonal variations. In clinical studies, a greater prevalence of benign chronic painful syndromes (non-oncologic) has been described in women compared to men [33,34]; in particular, in women has been highlighted: (i) a systemic prevalence of painful syndromes, with a more severe, more frequent and longer pain perception; (ii) a greater number of somatic painful points or areas; (iii) a greater use of pain-killer drugs; (iv) a different drug response and different side effects of drugs; and (v) a better description of painful sensation [35]. Also, several factors have been reported to be involved in the different manifestation and tolerance of pain in men and women: (1) influence of sexual hormones; (2) differences in plasmatic and/or tissue sex hormones levels inducing differences of neurotransmitters release; (3) differences in cognitive and emotional experiences and in coping strategies; (4) differences in social and occupational roles; and (5) different influence of biopsychosocial factors [4,34-37].

Primarily, gonadal hormones have been reported to influence pain perception. Epidemiologic studies revealed that healthy women complained for intensified painful symptomatology during premenstrual phase [38]. Gonadal hormones have been reported to influence the release/levels of neurotransmitters such as acetylcholine, involved in pain perception [39]. Estrogenic levels and their cyclic variations can influence the acetylcholine release in central nervous system, directly modifying the stratification processes of pain perception [40]. Furthermore, a persistent painful stimulation may activate both hypothalamic and hippocampal neurons, which are involved in choline-dependent functions (such as attentive, learning and memory functions) possibly modifying the vigilance and the emotional status. Therefore, it has been proposed that females' central nervous system may elaborate the same painful stimulus differently than men, and retain more information. Also, estrogens may also influence the transmission from periphery to superior centers of pain signals [40,41], and the lower pain sensitivity of men may be due to the analgesic effect of testosterone.

Chromosome Y is reported to be able to stimulate nervous system in order to develop a greater number of dopaminergic neurons, which play a central role both in the modulation of contentment, reward and motivation sensations, and in motor coordination and harmonization. These differences between men and women in dopaminergic system may determine a different attitude and pain tolerance [4].

Both, fear of pain and the phenomenon described as "catastrophism" (a cognitive and affective answer to pain), have been found to be significantly more common in women than in men. This fact could lead to a delay in applying the resolving reactions, determining a continuous exacerbation of pain or rather establishing a chronic pain [42,43]. A close connection between chronic pain and depression with a bidirectional interaction has been highlighted: chronic pain suffering determines depression, and depression itself contributes to the worsening of pain, amplifying physical sensation and reducing the perception threshold [44]. These facts could be due to a correlation between the me-

diators of mood and those of pain. The "cognitive-style" hypothesis [41] suggested that the activations of different neuronal systems in response to pain experiences of comparable intensity in men and women could be one of the main causes for the different affective experience of pain between genders. Also, Fillingim reported that pain threshold in healthy women could be related to the number of pain episodes experienced in the previous months [36]; moreover, in women suffering from chronic pain (such as temporomandibular pain, headache, fibromyalgia), a greater temporal summation induced by nociceptive stimuli has been found compared to control group, determining in those women posthumous pain sensations of greater amplitude [36,37].

In experimental studies, available data suggests that there could be (i) a greater nociceptive sensibility in women than in men in response to mechanical or electrical stimuli, with a lower threshold of pain tolerance; (ii) a greater insular and prefrontal cortex or limbic system activation in women in condition of experimental acute pain compared to the activation of cognitive regions observed in men. These aspects could influence the different central integration of nociceptive stimuli and endogenous systems of pain modulation between genders. Indeed, Zubieta et al [44] demonstrated a greater release of endogenous opioids and increased activation of regions involved in the suppression of the sensorial and affective aspects of pain in men compared to women. Pain perception is therefore modulated by several endogenous systems and, in particular, by opioid system which acts differently in men than in women. The opioid system is involved in stress responses, in pain suppression and in efficacy of opioid drugs [44,45]. The existence of several and complicated gender differences in pain perception systems could be also related to the different therapeutic answers to drugs between sexes. It is likely that estrogens, menopause or pregnancy, but also morphological and functional differences between genders, could influence the pharmacokinetics and pharmacodynamics, and the efficacy and tolerability of drugs [46,47]. Several studies also described a greater incidence of side effects, after drugs use, in female patients, up to two times more than in men; this could be due not just to the class of medicine, type of side effect, age and physiologic state of patients, but also to the fact that women are generally exposed to drug dosages established on experimental results obtained on male subjects [34,48].

To date, not all the factors involved in the perception of pain are completely clear [49]. Liang and co-workers reported a greater intensity of pain in oncologic male patients and a consequent greater tendency to use opioid analgesics more frequently than women, even if they did not find any difference in opioid prescription between male and female patients [50]. Other studies described a greater risk of developing pain in women, since inappropriate drugs were more prescribed to women than to men [50,51].

Gender and postoperative pain perception

Despite the existence of worldwide approved guidelines for the management of postoperative pain [52], the reported percentage of patients experiencing a not controlled postsurgery pain is more than 50% [53-55] and the onset of a persistent postoperative pain is estimated to be in up to 40% of cases [56,57]. Women are reported to experience a more intense postoperative pain with a higher risk to develop a chronic postsurgical pain [12], while men are reported to use higher doses of opioid analgesics compared to women [58]. Women usually experience a more intense acute postsurgery pain than men [33], even if there are data describing no differences in the prescription of treatment and pain modulation in cancer patients [59]. Logan and Rose assessed a role of gender in postoperative pain modulation, since females were found to show higher preoperative anticipatory distress and to complain more of postsurgical pain compared to males [60].

In a recent review [61], gender did not show a significant factor influencing postoperative pain occurrence after oral surgery, even if a higher predisposition to the onset of chronic neuropathic pain has been observed in women. Even if there are some reports assessing no gender differences in pain intensity scores, the authors described a greater risk for insufficient analgesics prescriptions and a consequent inadequate pain management in cancer women compared to male patients [7]. In 2002, Katz et al [14] reported that women affected by head and neck cancer and undergoing disfiguring surgical oncological procedures, and with poor social support, presented a greater risk for psychosocial dysfunctions, due to visible facial deformities and distressing aspects related to interpersonal relationships and communication. It is likely that, these disorders could be probably related to a greater postoperative pain perception [14].

To date, the available data on the role of gender differences in postoperative pain after surgery, in those affected by head and neck cancer, are still limited.

Conclusions

Pain in head and neck cancer seems to be more prevalent in women, also in the postoperative stage, even if further confirmations are necessary in order to clarify the role of gender in the manifestation of pain and its perception.

In the future, additional investigations could help to better understand the origin, the features and the differences between pain perception and tolerance between sexes, therefore leading us to provide a more specific and tailored pain therapeutic plan, also for head and neck cancer patients. In this way, such an approach for the assessment and management of pain in cancer patients may involve a multidisciplinary team [62], therefore assessing physiological and psychological features of pain perception, including gender differences (a 'gender-targeted analgesic approach').

Conflict of interests

The authors declare no conflict of interests.

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