Chapter 8
The Impact of Pain

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Head and neck cancer is diagnosed in about 650,000 patients worldwide each year (about 6% of all cancer in the global population) [1]. A diagnosis of head and neck cancer can be physically and emotionally debilitating. The pathology and its treatment can affect the individual's vital and social function (e.g., breathing, eating and speech) with serious effects on psychological and psychosocial life. In fact, given the site of the appearance of the head and neck, the visibility of the disease, and treatment sequelae, head and neck cancer is one of the most psychologically traumatic cancers [2, 3] and one of the worst diseases in terms of physical dysfunction, related distress limit, or disrupt daily behaviors and social activities [4].

Patients adapt to their conditions differently: sometimes requiring little psychological support but other times developing depression and anxiety at varying degrees of severity and becoming socially isolated. The experience of psychological distress, particularly depression (including every step from subclinical depressive symptomatology until clinical depressive disorder), is quite common among cancer patients and may occur throughout the course of illness, often persisting months beyond the conclusion of treatment in cancer survivors [5, 6].

Nevertheless, depression in head and neck cancer patients has been estimated to be more prevalent than in other types of cancer [5], involving at every degree approximately 15–50% of head and neck cancer patients and affecting immunocompetence, treatment adherence, self-care behaviors, socialization, and quality of life [7–9]. Unfortunately, often, depression and other psychological distress go unreported in clinical trials [10].

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C. E. Fundakowski (ed.), *Head and Neck Cancer*,
https://doi.org/10.1007/978-3-030-27881-6_8

Pain in Patients with Head and Neck Cancer

Pain is one of the most debilitating symptoms of head and neck cancers, and it is present not only during or after treatment but also at the beginning, as one of the first symptoms of the disease presentation, and sometimes could be a signal of recurrence. In fact, at least half of head and neck cancer patients experience moderate to severe pain and almost all experience some degree of pain at presentation and/or during treatment and at the end [11].

Treatment for head and neck cancer is complex and, often, hard to deal with. Patients may undergo surgery, radiation therapy, chemotherapy, or combinations. These treatments are associated with a range of side effects including difficulties with essential functioning such as eating, swallowing, breathing, and speech as well as taste alterations (dysgeusia), hyposalivation (xerostomia), residual pain, and facial disfigurement [12, 13].

All these discomforts confer marked disability, so that almost half of the patients are unable to go back to work for a long time after treatment cessation [14, 15] and sometimes discontinued employment definitively [16, 17].

The evidences suggest that the use of concurrent chemoradiation improves survival rate and locoregional control but at the cost of increasing toxicities, in particular, the severity and the mean incidence of inflammation of oral mucosa (mucositis) and of pain as a result [18].

Nevertheless, the top patients' priority is being cured and living as long as possible with analgesia [19]. On the contrary, only a minority of the reports consider specifically pain due to the oncological management and pharmacological strategy to address it, and treatment outcome is the most reported endpoint in the available studies based on head and neck cancer patients.

Mucositis has a mean incidence of about 90% and may become severe and painful enough to prevent patients from speaking, eating, drinking, or swallowing, leading to poor quality of life and to a higher risk of psychological distress.

Multiple mechanisms are involved as the sequential interactions of all cell and tissue types, and various physiological elements (e.g., tissue factors and cytokines) of the oral mucosa.

It primarily affects the non-keratinized tissues, such as the soft palate, the pharynx, the floor of the mouth, and the lateral borders of the tongue.

Ulcerations and mucosal infections cause pain severe enough to reduce treatment compliance and its efficacy and, consequently, increase [18, 20] disease recurrence and mortality rate [21, 22].

The analgesic strategies employed for oral mucositis pain treatment vary from local to systemic therapies with different mechanisms of action such as opiates, anti-inflammatory drugs, and anticonvulsants employed to manage neuropathic pain [23–25].

There is insufficient evidence from randomized clinical trials to advice on an optimal intervention specifically for head and neck cancer pain. A few studies regard the management of pain on posttreatment adjustment and quality of life but none to

address this issue in head and neck cancer patients. MASCC/ISOO Guidelines recommend patient-controlled analgesia with morphine as the treatment of choice for oral mucositis pain [26]. However, despite individualized approaches, pain control is still often not satisfactory both for the patient and health provider in this care setting, in particular, during swallowing [24, 27].

This is the reason why, during chemoradiation, the consequences of suboptimal pain control could affect dysphagia, malnourishment, treatment acceptance, and compliance, ultimately influencing chemotherapy dose intensity or radiotherapy treatment (RT) continuity.

In fact, high incidence of painful swallowing due to mucositis is also associated with reduction of food and liquid intake, worsening of nutritional status, dehydration, renal insufficiency, need for enteral nutrition or intravenous hydration, reduced compliance with cancer treatment, increase of hospital admissions and unscheduled visits, and long-term dysphagia.

Consequently, acute pain mainly due to oral mucositis, to the neck skin inflammation (dermatitis) in the radiation field, and to radiation-induced fibrosis (e.g., costoclavicular or temporomandibular joint disorder, trismus, and neuropathic pain) dramatically impair quality of life and possibly reduce the chances of cure, hesitating in a lower dose intensity of systemic therapy or in radiation treatment breaks [28].

Thirty-nine studies carried out in head and neck cancer patients showed that pain is present in 50% of patients at the diagnosis, 81% during treatment, and 70% after the oncological treatment (Fig. 8.1). In 30% of the patients, the severity of pain during treatment was higher than during the pretreatment period.

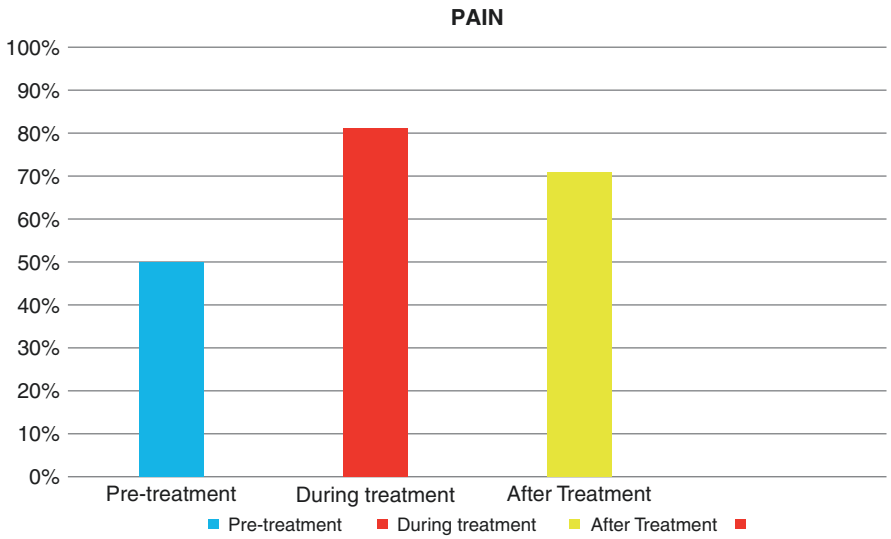

Fig. 8.1 Percentage of head and neck cancer patients who experienced pain divided in the two periods of treatments

Patients report that mucositis is the most debilitating side effect of their head and neck cancer therapy [29] and, especially, of combining radiation and chemotherapy. Severe acute effects on the mucosa can also result in consequential effects that can chronically impair organ function. Putative risk factors for mucosal sensitivity include aggressive chemoradiation regimens, xerostomia, and active cigarette smoking. Hot, spicy, and acidic food/liquids and dry air can enhance oral pain.

Moreover, mucosal pain may be caused or exacerbated by oral infections; hence, a careful oral exam to rule out infection and to treat it in an easier way is suggested. In fact, basic oral care reduces the frequency and severity of oral mucositis and its associated pain. Pain correlates also with radiation treatment fields, dose, and fractioning. Concomitant chemotherapy or cetuximab results in increased frequency, severity, and duration of mucositis pain.

When making treatment plans, patients' general conditions and their capability to tolerate severe oral pain and high doses of opioids need to be considered. In fact, patients' frailties, age, or severe comorbidities may lead to poor tolerance, considering that the highest peak of RT pain is during the fifth week, and it may not improve earlier than 2–4 weeks after RT, healing in about 2 months [30].

To understand the impact of RT regimens on overall patient well-being, in 2004, Rose-Ped A. et al. [31] interviewed 33 patients who had received RT for head and neck cancer in order to characterize the effects or consequences of RT from the patients' perspectives.

Patients had particularly troublesome or debilitating painful sore throat (20%), followed by mouth sores/pain (18%), and dry mouth (14%) (Fig. 8.2), which cause significant discomfort but most of all serious difficulty to eat, drink, or swallow.

Nearly all patients (90%) reported experiencing dysgeusia, including complete loss of taste (54%), distorted taste (33%), or reduced taste (13%) and about 70% of

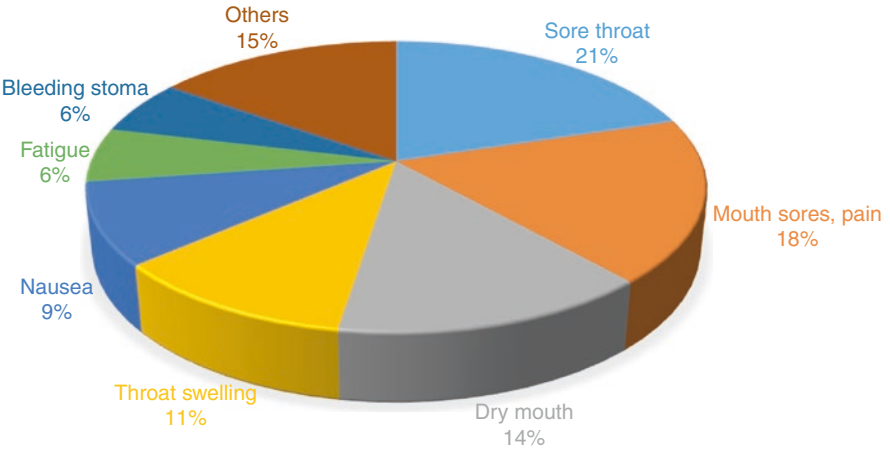

Fig. 8.2 Single most debilitating side effects

patients reported mouth sores, dry mouth, pain, and irritation too. Hundred percent of oral cavity cancer patients and 86% of pharyngeal cancer patients reported changes in their mouths.

Patients reported that oropharyngeal mucositis developed within approximately 2.5 weeks (range 1–8 weeks) after the start of RT with a healing time ranging from 2 to 24 weeks (mean 8.7 weeks) after completion of RT. Nearly all (92%) patients received supportive care with opioid analgesics, mouthwashes or rinses, and nutritional supplements.

Good oral hygiene and analgesics are the approaches most commonly used to prevent and treat the symptoms associated with oropharyngeal mucositis.

Although optimal management strategies for RT-induced mucositis and its associated complications have not been identified yet, standard oral care protocols are used to prevent or minimize mucositis [31].

Nevertheless, a large number (88%) could not eat or drink or did so with extreme difficulty and reported a significant weight loss (83%), (between 12 and 79 pounds, mean 29 pounds), leading to gastric tube implantation for 29% of patients. Oral pain worsened during the course of RT and persisted after the end of treatments, periods that patients described as the worst part of treatment experiences.

Another study published in 2001 explored the quality of life in 58 head and neck cancer patients during and after radiation treatment. They collected data of physical, emotional, functional, and social aspects at the first week of treatment, at the last week of treatment, and 1 month after treatment with two validated questionnaires: Functional Assessment of Cancer Therapy: Head and Neck (FACT-H&N), a subscale that assesses social and emotional well-being, and the Hospital Anxiety and Depression Scale (HADS).

Results indicated overall increased levels of physical and functional symptoms, head and neck specific concerns, and depression between the first and the last week. However, except for depression, there was some improvement between the last week of treatment and 1 month after although this improvement was not to the pretreatment level. FACT and HADS did not show significant changes across time, suggesting the need of interventions to assist patients when they have completed the radiation treatment course and the need of improvement assessment in some areas of emotional distress [32].

In 2010, Cheng et al. [33] analyzed the incidence of severe oral mucositis associated with cancer therapy, underlining patients' self-reported moderate and severe oral symptoms and quality of life modifications.

This study revealed that patients with severe oral mucositis also suffer from pain and chewing/swallowing difficulties reported as the worst oral functional problems, leading to decreased intake and nutritional deficiencies.

Nevertheless, surprisingly the severity of oral mucositis did not seem to be a significant predictor of oral dysfunction while throat pain was the strongest predictor of chewing, swallowing, and speaking difficulties, suggesting that individuals at increased risk of throat pain were exposed to oral functional impairment.

Pain in the oropharyngeal junction and throat is the most symptomatic and difficult problem to deal with. It may reflect activation of nociceptive receptors at the site of oral mucosal injury to compromise the muscular movement which makes chewing and swallowing difficult and unpleasant.

Early diagnosis and treatment of mucositis as well as an adequate and timely analgesic approach continues to be mandatory to the management of oncological treatments side effects, but even if most of the patients used analgesics and despite the wide use of opioids, pain control continued to be an unmet need. This confirms that oral mucositis need a multidisciplinary approach since it includes sensory and affective dimensions of pain experience [34] as well as a neuropathic component [35].

Moreover, the significant impairment of quality of life resulted from a complex interaction of the extent of oral mucosal injury, the patients' perceptions of pain, and the altered oral functional capacity as confirmed by the literature data in patients who are not being no longer able to eat and enjoy food [36–38].

Therefore, the prevention or reduction of intensity and duration of oral mucositis is important to permit the administration of the full dosage of cancer treatment and, thereby, potentiate the curative or control intent of treatment.

Mucositis-Induced Pain Management

Currently, mucositis-induced pain management includes the use of topical anesthetics and systemic analgesics even if systemic administration of opioids may be complicated by well-known side effects (e.g., nausea, vomiting, mental clouding, constipation, sedation, and tolerance) which could worsen quality of life.

In head and neck cancer patients, pain due to mucositis may also present as incidental breakthrough pain (BTP), a transitory exacerbation of pain that occurs against a background of stable pain otherwise adequately controlled by opioid therapy with a prevalence of 48% (average of 3.85 episodes per day) [39].

In about a half of head and neck cancer patients, pain is incident, a quarter is spontaneous or due to end of dose failure, while in 5% of the cases the nature of pain could be unknown or mixed (Fig. 8.3). Actually, the majority of pain episodes was associated with some precipitating factor [39].

In this setting, it may arise in response to a predictable stimulus or associated to a precipitating factor (48%) such as swallowing, or it may be related to a specific predictable trigger as incident predictable pain [39, 40] (IP-BTP).

Odynophagia (painful dysphagia or pain with swallowing) due to mucositis can be categorized as incidental and predictable and should be considered as breakthrough pain to be treated with appropriate breakthrough medication dosing.

Preventive administrations of breakthrough pain medication half hour before eating may improve swallow function. Transmucosal intranasal route administration of fentanyl in this setting was judged as the most effective way of administration of analgesics since oral transmucosal administration could be difficult

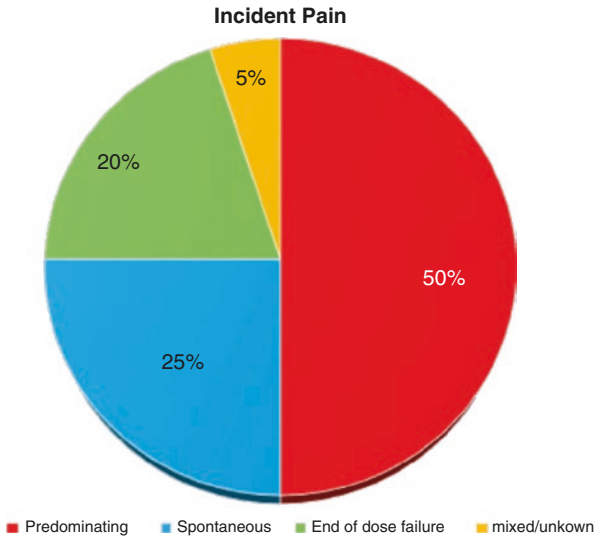

Fig. 8.3 Different types of incident pain

because of sticky saliva, xerostomia, or oral ulcerations, and irradiated mucosa may have a different absorption of BTP.

There is no standardized treatment protocol for treatment of pain due to mucositis in head and neck cancer with a lack of consensus about the class of drugs, kind of administration, pharmaceutical forms, and side effects of this therapy [24].

Bossi et al. published an experience concerning the feasibility and the activity of fentanyl pectin nasal spray (FPNS) against incidental feeding BTP due to chemoradiation-induced oral and oropharyngeal mucositis in HNC patients [33], showing good activity and acceptable safety of FPNS when administered during concurrent chemoradiation.

This clinical study evidenced the feasibility and the activity of FPNS against incidental feeding BTP due to chemoradiation-induced oral and oropharyngeal mucositis in head and neck cancer patients. The reduction of BTP allows the improvement of swallowing and, potentially, the reduction of a series of mucositis consequences included psychological ones.

Adequate pain control may substantially enhance swallow effort during and after the radiation, minimizing disuse atrophy and fibrosis and optimizing long-term swallow function [41].

Treatment of painful mucositis may benefit also from opioid-based systemic drugs. In fact, an adequate pain regimen should include a fixed and breakthrough medication with an appropriate dose and schedule.

Recent studies have demonstrated that head and neck cancer patients develop neuropathic besides nociceptive pain during their radiotherapy course, suggesting the need to treat both types of pain [42]. Moreover, patients may also experience long-term spontaneous or evoked pain due to epithelial atrophy, neurologic sensitization, and/or neuropathy also due to a chronical recurrent/metastatic disease. Nevertheless, pain could be also expression of a disease recurrence or metastatization.

In fact, neuropathic pain could be also caused by tumor infiltration or due to paraneoplastic or treatment-induced polyneuropathy, and it may be adequately controlled by opioids added to adjuvant drugs [43] because neuropathic pain sometimes poorly responds to narcotics alone [44–47]. Even if high doses of gabapentin have been reported to reduce the need for high total dose of opioids, neuropathic pain control remains a critical item with very frequent failures.

Amitriptyline and gabapentin have been effectively used to treat multiple neuropathic pain syndromes, but only limited data are available in head and neck cancer patient's pain [47–53]. Opiates and gabapentin are believed to interact favorably through a simultaneous decrease in hyperexcitation and increased inhibition of nociception [54, 55]. This effect enhances morphine efficacy and relieves neuropathic pain [54, 56] with a beneficial effect on daily activity, mood, sleep, and quality of life [49, 56]. These data suggest the possibility of satisfactory results, avoiding opioids dose escalations, and reducing the risk of associated adverse side effects, but randomized clinical trials are needed to establish the role of this analgesic combination in this group of cancer patients.

In conclusion, there is a clear need for multidimensional and multidisciplinary pain management algorithms to reduce pain severity and to better manage these symptoms as well as the consequent discomfort (Fig. 8.4) involving palliativists, nurses, physiotherapists, logopedists, and psychologists into patients' care.

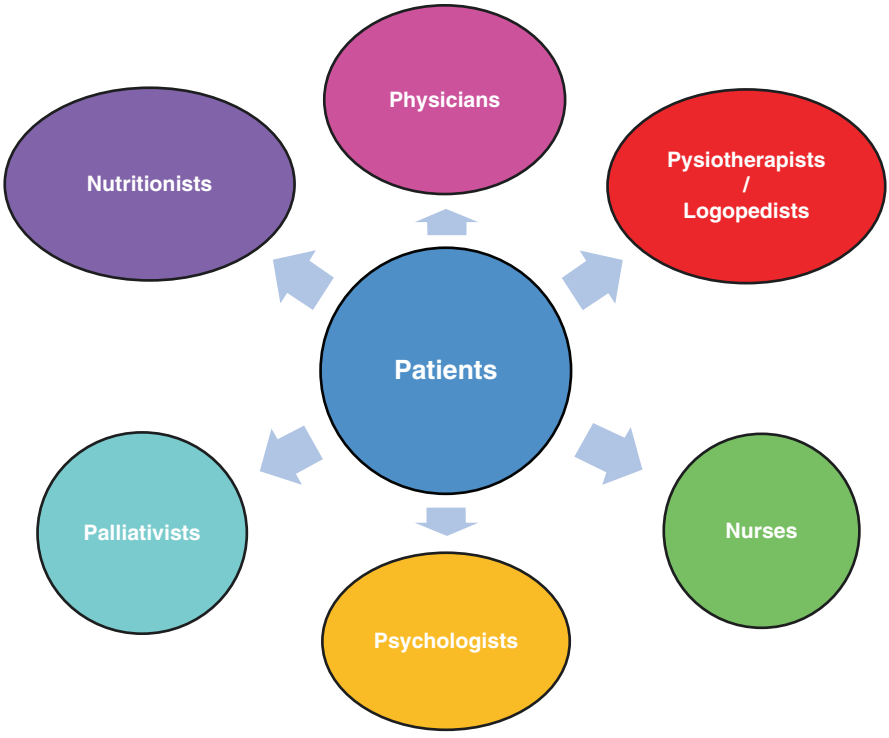

Fig. 8.4 The multidisciplinary approach to physical and psychological distress of head and neck cancer patients

For this reason, it could be necessary not only to standardize clinical management and treatment according to international guidelines but also to preview psychological support and initiatives to help patients to preserve their quality of life and psychological well-being.

Further research including larger studies with more comprehensive evaluations of pain, quality of life, and psychological distress in head and neck cancer patients is required as an important outcome measure in the evaluation of new preventive and curative interventions to alleviate suffering and to improve the quality of pain and nutritional management.

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