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The point of pain in head and neck cancer

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ABSTRACT

Head and neck cancer (HNC) can have a devastating impact on patient's lives as both disease and treatment may affect the ability to speak, swallow and breathe. These conditions limit the oral intake of food and drugs, reduce social functioning and impact on patient's quality of life. Up to 80% of patients suffering from HNC have pain due to the spread of the primary tumor, because of consequences of surgery, or by developing oral mucositis, dysphagia or neuropathy as toxic side effects of radiotherapy, chemotherapy or both.

All healthcare professionals caring for HNC patients should assess palliative and supportive care needs in initial treatment planning and throughout the disease, with awareness when specialist palliative care expertise is needed. This paper focuses on assessment, characterizations and clinical management of pain in advanced HNC patients undergoing surgery, chemotherapy and radiotherapy, also underlining the importance of symptom assessment in HNC survivors and the need of clinical research in this field.

1. Introduction: the multidimensional importance of assessing pain in head and neck cancer

Head and neck cancers (HNCs) account for approximately 5% of all malignant tumors; they may have a devastating impact on patient's lives as both disease and treatment can affect the ability to speak, swallow and breathe. These conditions limit the oral intake of food and drugs, reduce social functioning and impact on patient's quality of life (QoL). Up to 80% of patients suffering from HNC have pain due to the spread of the primary tumor, because of consequences of surgery or by developing oral mucositis, dysphagia or neuropathy as toxic side effects of radiotherapy, chemotherapy or both (Dios and Lestón, 2010).

However, patient's experience of pain is modulated by intrinsic dimensions such as adaptive coping style, co-morbidities, psychological distress or depression (fear of permanent disfigurement, previous experiences of severe pain, etc.) (Epstein et al., 2007).

Clarifying the principal pain in this setting through detailed description of how patients report the history and presence of physical or psychological dysfunction may provide indications that can have implications for clinical practice and research (Reich et al., 2014).

All healthcare professionals caring for HNC patients should assess palliative and supportive care needs in initial treatment planning and throughout the illness, with awareness when specialist palliative care expertise is needed. This may involve a core multidisciplinary team at different levels of intervention: inpatient, outpatient, day care, home care and telephone advice. The management of pain is often a real challenge in HNC patients.

This paper focuses on assessment, characterizations and clinical management of pain in advanced HNC patients undergoing surgery, chemotherapy and radiotherapy.

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2. Material and methods

This is an overview of the evidence regarding the management of head and neck cancer pain. Due to the paucity of research in this area, the aim of this paper is to provide a focused examination of scientific literature about HNC pain evaluation, treatment and monitoring in several settings, from perioperative to radio- and/or chemo-induced settings among cancer survivors. To highlight each point in this review, we have carried out a literature search through PubMed, MEDLINE with cross-references in the last 20 years until 31 October 2018. Studies eligible for inclusion in this review were: case reports and retrospective or prospective studies addressing all the aspects of HNC pain management. Exclusion criteria were studies without any specific results, abstracts or poster presentations. This paper represents a simple literature review not necessarily focused on a single question and written by an expert group with a detailed and well-grounded knowledge of the issues.

3. Which instruments should be employed for evaluation and monitoring of pain in head and neck cancer patients?

In HNC, pain is often a tumor-revealing symptom. Therefore, pain in this area is both considered with great attention by the patient and the physician.

The assessment of pain during the clinical examination should be thorough, and the treatment should be prompt. A detailed history and careful examination are required in the HNC patient to determine the cause of pain, and the potential role of anti-cancer therapy in treating the cancer and thus decreasing or relieving the pain (Navez, 2007). The intensity and severity of cancer pain is a key domain in clinical evaluation, as it is often used to determine both the urgency of the pain state and also to monitor treatment response.

Adequate cancer pain assessment using valid and reliable tools is essential for proper cancer pain management (Burton et al., 2014). Several unidimensional, valid and reliable measures of pain intensity, which are highly inter-correlated, are used in clinical practice (Hjermstad et al., 2011; Cleeland et al., 2011).

The verbal rating scale (VRS) is a categorical scale with which patients select their pain intensity from a series of descriptors (Farrar et al., 2010). Although many of them exist, an example of a VRS would be a 4-point scale, which includes the following descriptors to select from: none, mild, moderate or severe. The numerical rating scale (NRS) consists of the numbers 0–10 to measure pain intensity, with 0 representing 'no pain' and 10 representing 'worst pain' over a defined time period (such as 24 h or past 1 week) (Oldenmenger et al., 2013). The patients rate their pain along this continuum. In this way, HNC patients can use all the various self-assessment scales: speech-related difficulties in no way impair thought and understanding. As of today, NRS and VRS represent the most common pain measurement tools among clinical trials and routine oncology practice.

However, additional functional problems including the ability to swallow, speak, hear and see, among others, also may need to be assessed and all will have an additional impact on QoL.

As cancer pain can be a complex construct, assessment of its many domains should be conducted by using multidimensional tools and is necessary to explore several other domains in addition to pain intensity in order to optimally capture the patient's cancer pain experience (Burton et al., 2014). Numerous available assessment tools for clinicians exist to better capture symptoms in a comprehensive fashion.

The Brief Pain Inventory (BPI) and its short form (BPI-SF) are scales aimed at assessing pain severity ('sensory' dimension) and pain impact on daily function ('reactive' dimension) (Cleeland and Ryan, 1994). The BPI-SF includes front and back body diagrams for the patient to mark the site of their pain, four items on pain severity (using the NRS from 0–10 for 'worst', 'least', 'average', and 'now' pain intensity), and seven items on pain interference with affect and activity (using the NRS from 0–10, with 0 designating 'no interference' and 10 designating 'complete interference', for general activity, work, mood, walking, enjoyment of life, relationships with others and sleep), as well as a question related to pain response to analgesics. A key difference between the long form and short form of the BPI is the recall period (the former uses 1-week recall, whereas the latter uses 24-h recall). The BPI-SF is more widely used in the clinical setting because of its relative brevity.

The McGill Pain Questionnaire (MPQ) (Melzack, 1975) and its short form (MPQ-SF) (Melzack, 1987) are widely recognized as useful multidimensional pain questionnaires in research and in the clinical setting, also for cancer-related pain (Ngamkham et al., 2012). The MPQ-SF is more appropriate for clinical use as it is less burdensome in the time-restricted clinic. The MPQ-SF consists of 15 descriptors. Eleven of these items are sensory descriptors – throbbing, shooting, stabbing, sharp, cramping, gnawing, hot burning, aching, heavy, tender and splitting. The remaining four are affective items – tiring–exhausting, sickening, fearful and punishing–cruel. Each item is rated using a 4-point VRS (none, mild, moderate and severe). In addition, a VAS for pain intensity and a VRS for Present Pain Intensity Index are included.

Because multiple symptoms coexist in the cancer patient population, it was considered necessary to assess these various symptoms together, rather than using separate tools for each symptom. The MD Anderson Symptom Inventory (MDASI) (Cleeland et al., 2000), developed on the basis of the BPI, is an instrument for measuring multiple cancer-related symptoms, including pain, designated as patient-reported outcomes (PROs). It consists in 13 core items that are considered to be experienced most frequently by the cancer patient, as follows: pain, fatigue, nausea, disturbed sleep, emotional distress, shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, memory difficulties and numbness/tingling.

In this way, the Edmonton Symptom Assessment System (ESAS) (Chang et al., 2000) and its most recent revision (ESAS-r) are instruments designed to assess nine symptoms commonly present in the advanced cancer patient, as pain, nausea, tiredness, depression, anxiety, drowsiness, appetite, well-being and shortness of breath, as well as the option for adding a tenth patient-specific symptom. Each symptom is rated using the NRS from 0–10, with 0 meaning 'not experienced' and 10 meaning that the symptom experience was quantified as worst possible. In all cases, global management requires a multidisciplinary team to draw up a consensual multimodal treatment program.

There is a lack of agreement on a standard assessment tool or a standard classification system for cancer pain, although research continues to be undertaken to develop such resources for clinical and research purposes.

However, self-reporting of adverse effects, which can be discordant with clinician reporting, has the potential to offer unique insight into the patient's perspective of treatment toxicity. Despite the increased time and effort, patients are often eager to share their experience, especially if they know it may positively affect future patients undergoing cancer treatment. In this way, to improve the assessment of symptomatic toxicity in cancer clinical trials and to complement clinician-based toxicity reporting using the Common Terminology Criteria for Adverse Events (CTCAE), the US National Cancer Institute has developed a new measurement system called the Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE) (Basch et al., 2014).

Designed to be used in conjunction with CTCAE, PRO-CTCAE symptom terms amenable to self-report were derived from CTCAE version 4.0. Each PRO-CTCAE symptom term is evaluated by ≥1 question that capture ratings of frequency, severity, interference, amount and presence or absence. Individual PRO-CTCAE items are scored using a 5-level verbal descriptor scale and are coded from 0 to 4. Validation studies performed across a diverse sample of patients receiving chemotherapy and/or radiation for a variety of malignancies support the content validity and favorable psychometric properties of PRO-CTCAE (National Cancer Institute, 2019).

Observational experience among patients who had undergone

radiotherapy for HNC reveled that pain was one of the most commonly reported symptom experiences endorsed by two-thirds of the participants (Sandler et al., 2018).

Pain items currently available in the PRO-CTCAE item library (version 1.0) include general pain, muscle pain, joint pain and abdominal pain, as well as other specific types of pain experiences, such as headache and neuropathy. However, there are still several aspects of HNC pain to be improved (pain in the mouth/throat, pain with swallowing, etc) which deserve to be studied.

Finally, we have to consider that the existence of many types of pain can be understood by the identification of four broad categories: nociception, perception of pain, suffering and pain behaviors (Loeser and Melzack, 1999). Just as cancer affects the physical health, it can bring up a wide range of feelings that patients are not used to dealing with. It can also make existing feelings seem more intense. They may change daily, hourly or even minute-by-minute. Loeser (2000) underlined that 'suffering can be the result of pain, or it can be engendered by many other states, such as fear, anxiety, depression, hunger, fatigue, or loss of loved objects. Suffering exists only in the mind and the events that lead to suffering will differ from one patient to another. There are no physical examination clues or laboratory tests or imaging studies that reveal its presence. We must ask the patient and listen to his or her narrative to find "suffering".

Moreover, neuropathic cancer pain (NP) is also common among patients with HNC. It may be a direct consequence of a cancer-induced injury to the somatosensory system or a complication due to cancer treatment such as nerve fibrosis after RT, chemotherapy-induced or postsurgical NP represents prominent examples. A probable or definite NP can be identified using the revised definition and grading system proposed by the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) (Treede et al., 2008).

We can therefore summarize the evaluation and monitoring of total cancer pain at three different levels:

1) At the first level, we can place the visual (VAS), the numerical (NRS) and the verbal scales (VRS) for a rapid assessment of pain, especially for pain intensity;
2) For a clearer assessment of pain, at the second level, we place the BPI and the MPQ questionnaires along with their short forms;
3) At the third level, for the assessment of cancer pain and multiple cancer-related symptoms, especially for the assessment of cluster symptoms, we recommend the MDASI or the ESAS questionnaires. Moreover, questionnaires exist to investigate specific domains or characteristics of pain.

To conclude, we are confident that in the near future PRO-CTCAE will soon enter into daily clinical practice, but for now their use remain exclusive for clinical trials.

4. Perioperative pain in head and neck cancer

The overall incidence of pain following treatment for HNC may be as high as 50%, with more than 50% of patients disabled 1 year after diagnosis. Moreover, the presence of disability is highly correlated to pain score (Chaplin and Morton, 1999; Vecht et al., 1992; Olsen and Creagan, 1991; Taylor et al., 2004).

Treatment for HNC patients often involves surgery as a first step in multimodal therapy. Surgical treatment typically causes severe side effects, such as facial deformity, speech and swallowing difficulties, and pain in the oral cavity, neck, face and shoulder (Burton et al., 2007). Perkins and Kehlet identified several risk factors that predispose surgical patients to persistent pain (Perkins and Kehlet, 2000). These factors are: pre-existing pain, repeat surgery, psychological vulnerability, additional complementary treatment, and depression and anxiety.

Perioperative pain is defined as the pain experienced by the patient during the period between the phase immediately before surgery and the 12-month post-operative recovery phase.

A literature review of perioperative pain in HNC patients reveals a critical issue: pain and treatment-related symptoms are not generally recorded as a single parameter but are, instead, recorded in a more complex evaluation of health-related QoL (HR-QoL). This means that incidence and severity of perioperative pain cannot always be extrapolated from the studies focused on general patient QoL.

In these patients, orofacial pain is usually due to nerve damage from neuromas or misalignment leading to functional disorders, particularly during chewing or swallowing. However, the majority of previous reports also show that patients who underwent neck dissections had increased levels of post-operative pain, weakness and overall loss of function (Shah et al., 2001; Van Wilgen et al., 2004).

Shoulder dysfunction is not uncommon after neck dissection in patients with nodal metastasis (Remmler et al., 1986) Approximately 35% of patients develop severe pain in the shoulder or neck, and this symptom is closely related to surgical treatment. There is debate in the literature regarding the morbidity associated with radical neck dissection versus more conservative surgical procedures, and functional or selective neck dissection. In addition, preservation of the accessory spinal nerve and innervations of trapezius muscle should prevent painful shoulder syndrome (Shah et al., 2001). However, some authors believe that there are no differences in pain or post-operative shoulder dysfunction between patients who have had radical neck dissection and those who have had modified neck surgery (Chaplin and Morton, 1999). Overall, the literature agrees that the best outcomes are reached if post-surgical physical therapy programs are systematically performed (Burton et al., 2007).

Published trials suggest that 80–100% of patients with advanced disease stages experience pain; the percentage of patients with severe pain is the tip of the iceberg and most of these patients only experience mild to moderate pain (Olsen and Creagan, 1991). Most of the studies published the highest pain prevalence at diagnosis and during the pre-treatment period (Chaplin and Morton, 1999; Remmler et al., 1986). When the treatment is effective at controlling the disease, both prevalence and severity of pain in the cervicofacial area are reduced. Persistent or increased pain after surgical treatment could be a symptom of persistence or recurrence of disease (Chaplin and Morton, 1999).

Several studies have assessed the longitudinal changes in pain and HR-QoL in patients treated for HNC (Burton et al., 2007; Remmler et al., 1986; De Graeff et al., 1999). A recently published systematic review showed that higher pre-treatment levels of physical functioning (including pain domain) and an increase in global QoL 6 months after treatment were associated with increased survival in patients with HNC (van Nieuwenhuizen et al., 2015). In general, pain score deterioration was observed during the first 3 months after surgical treatment, followed by a slow recovery (Remmler et al., 1986). Notably, problems with oral pain, neck pain, loss of sensation, reduced range of jaw motion and shoulder disorders were more persistent. However, inflammation, contracture of denervated muscles, contraction of wound tissue after tumor removal, neck dissection and partial or total organ loss following surgical excision may also result in pain (Tarsitano et al., 2012).

Patients who had curative surgery had increased HR-QoL scores and reduced pain between 6 and 12 months after treatment, indicating that pain had a positive trajectory at the end of the first year (De Graeff et al., 1999; van Nieuwenhuizen et al., 2015; Tarsitano et al., 2012). In a study assessing patients surgically treated for oral cancer, a longitudinal worsening pain score between 6 and 12 months after surgery correlated with the risk of relapse and poor long-term prognosis (Osthus et al., 2011a).

In conclusion, data in the literature provide information about pathogenesis and changes in pain in relation to surgical treatment.

Table 1
Summary of the key points for perioperative pain in HNC.

Summary: Perioperative pain in head and neck cancer patients is generally not recorded as a single parameter but is captured in a more complex evaluation of health-related quality of life (HR-QoL). Persistent or increased pain after surgical treatment could be a symptom of persistence or recurrence of disease. In general, pain score deterioration is observed during the first 3 months after surgical treatment, followed by a slow recovery.	
Risk factors	Pre-existing pain Neck dissection Repeat surgery Psychological vulnerability Additional complementary treatment Depression and anxiety
Recommendation for clinical practice	To reduce post-operative pain To propose physical rehabilitation for all patients undergoing neck dissection
Recommendation for future studies	To collect homogeneous data with regards to: • Instruments for detection of perioperative pain • Definition of type of pain and sites (specific and validated visual analogue score questionnaires for pain) • Pain in relation to type of surgery • Cancer anatomical sub-site (oral cavity, oro-pharynx, nasopharynx, larynx, hypopharynx).

However, no systematic therapies with conclusive results have been found to improve pain. Furthermore, additional studies should be conducted to assess perioperative pain in homogeneous patient cohorts. In particular, pain should be assessed with specific instruments, and the association between pain and type of surgery performed should be examined. Therapeutic improvement is needed to improve post-treatment patient recovery. Physical rehabilitation should also be systematically proposed for patients undergoing neck surgery. A summary of the key points of this chapter can be found in Table 1.

5. Breakthrough cancer pain during (chemotherapy) radiotherapy

Breakthrough cancer pain (BTCP) is defined as a transitory exacerbation of pain that occur on a background of stable pain otherwise adequately controlled by around-the-clock opioid therapy. BTCP may arise spontaneously in unpredictable way or it may be related to a specific predictable trigger as incident predictable pain.

Painful dysphagia can be categorized as incidental predictable BTCP, which arises in the act of swallowing. It occurs as response to a predictable stimulus in context of pharmacologically controlled or uncontrolled baseline pain. Odynophagia results in decreased oral intake and may lead to dehydration, reduction of caloric intake with associated weight loss and nutrient deficiencies. During chemo-radiation treatment of locally advanced HNC pain exacerbation due to swallowing can be defined as BTCP; one patient described this pain as “razor blades cutting up your insides” being so intense that many patients “avoid swallowing at all cost” (Wong et al., 2006a).

During radiotherapy for HNC at week 2, no difference was found between pain intensity scores with and without swallowing. From week 3 on, patients reported significantly higher pain intensity scores with swallowing compared to those without swallowing. These scores peaked at week 7 with moderate to severe pain with swallowing and mild to moderate when not. This pattern was more pronounced in male patients. The real incidence, intensity and duration of BTCP is not really known because data on adequate pain control by opioids are lacking; anyway, a successful treatment of BTCP is frequently not attained even if early intervention seems more effective than late intervention (Stenstrom Ling and Larsson, 2011; Takase et al., 2011). No difference in BTCP incidence according to different radiation and chemotherapeutic protocols is reported.

Of note, recent estimates suggest a prevalence of 25–50% of BTCP, in HNC patients treated with concurrent chemo-radiotherapy (Bossi et al., 2017)

Uncontrolled pain may lead to decreased overall swallowing attempts and this can lead to long-term dysphagia secondary to lymphedema, fibrosis, stricture and muscular atrophy. Thus, adequate pain control may play an important role in maintaining swallowing ability both in the short and long term. The data of duration and intensity about persistent BTCP after treatment completion are not clearly reported. However up to one-third of the patients continued to report problems with swallowing, which were present in similar magnitudes before cancer treatment (Epstein et al., 2007).

To our knowledge, comprehensive and detailed clinical guidelines concerning pharmacological treatment of BTCP including pain assessment, choice of drugs, administration routes, pharmaceuticals forms and evaluation of treatment effect are lacking.

In this regard, transmucosal intranasal route of administration of analgesic drugs represents a potentially suitable and practical treatment in patients with predictable pain; moreover, intranasal administration appears to have a particularly interesting pharmacokinetic profile. Data about the role of rapid onset opioids in swallowing pain are diffusely lacking.

QoL, sleeping disturbance, psychological distress, functional sequelae or economic impacts (nutritional support, healthcare provider visits, hospitalizations, work absences, loss of active employment) of uncontrolled BTCP are completely absent in the literature. In Table 2 key points for BTCP are summarized with recommendations for clinical practice and future studies.

6. Correlation between pain and compliance to oncologic treatment (dose and time) and other clinical issues

Even if pain is a well-known symptom related to radio(chemo) therapy in patients with HNC, its negative impact on the overall well-being, daily functioning, treatment compliance, nutrition, weight loss, lack of compliance to radiotherapy and QoL is almost always attributed to the onset of mucositis and confused with the global and unspecific term of “painful mucositis” (Russo et al., 2008). Weissman et al. conducted one of the first studies to characterize the temporal development and intensity of pain associated with radiotherapy-induced mucositis (Weissman et al., 1989). The escalation of pain intensity and pain interference scores showed a clinical and time course comparable to those of oral mucositis (Chaplin and Morton, 1999; Epstein et al., 2001; Trotti et al., 2003; Wong et al., 2006b; Huang et al., 2003). The maximum oral

Table 2
Summary of the key points for break through cancer pain in HNC.

Summary: Break through cancer pain in not well studied for head and neck cancer undergoing radiotherapy. Guidelines with appropriate choice of drugs, administration routes are lacking. Potential consequences result from uncontrolled pain in the short term e.g. decreased oral intake with dehydration, reduction of caloric intake and weight loss and in the long term e.g. dysphagia secondary to lymphedema, fibrosis, stricture and muscular atrophy.	
Risk factors	Age Comorbidities Cognitive impairment Radiotherapy dose Concomitant treatment Tumor site (oral cavity and oropharynx) Radiotherapy technique (3D conformal vs intensity-modulated radiotherapy)
Recommendation for clinical practice	Education of patients and care-givers Preventive and immediate pain treatment Use of feeding tube whenever indicated
Recommendation for future studies	To collect incidence and data related to consequences of breakthrough cancer pain To study different drugs in breakthrough cancer pain approach

pain score is frequently temporally correlated with the maximum grade of mucositis (Elting et al., 2007). In 20 patients with HNC, Epstein et al. recorded pain in 75% at 1-month post-treatment. Similarly, the most severe oral pain was recorded at the end of radiotherapy, which correlated with the severity of mucositis (Epstein et al., 2001).

In a systematic literature review of 33 randomized clinical trials of mucositis in HNC patients, only three studies reported oral pain separately (Trotti et al., 2003). In these studies, oral pain occurred in 69% of patients, while the incidence of grade 3–4 mucositis was 23%.

Consistent with previous reports, Elting described that virtually all patients (96%) with grade 3–4 mouth and throat soreness used analgesics during radiotherapy at weeks 5–6 (Epstein et al., 2001).

6.1. Hospitalization

Mucositis pain is frequently the major cause of decreased oral intake and dehydration. Generally, HNC patients were hospitalized for these specific pain-related sequelae, so the data about the rate of hospitalization specifically due to pain were scarce. Sutherland and Browman, in a meta-analysis, showed that approximately 15% of the HNC patients were hospitalized for inadequate pain control due to severe mucositis (Sutherland and Browman, 2001). In a prospective study on 49 HNC patients, Wong et al. showed that 28% of them required unscheduled hospitalizations, and 20% of the patients required emergency department visits for treatment-related problems, most of them for pain management (Wong et al., 2006b). Murphy et al. reported a total of 37% of patients that were hospitalized at least once during their study (Murphy et al., 2009). The primary reasons for hospitalization were categorized as mucositis or decreased oral intake. Furthermore, they reported that patients required a mean of 0.5 and 0.4 additional visits to the radiation oncologist and nurse, respectively, during the 6-week study, for management of pain or other complications of treatment. In another study including 33 HNC patients, 27% were hospitalized due to treatment complications, such as dehydration, inability to eat or drink, mouth pain, extreme weakness, and fatigue. Painful sore throat was mentioned most frequently (20%), followed by mouth sores and pain (18%), and dry mouth (14%) (Chaplin and Morton, 1999).

6.2. Swallowing and nutritional support

Mouth and throat pain may result in marked swallowing function loss that may result in unintentional weight loss because of decreased oral intake of food and medications. Murphy et al. showed that increasing pain was associated with severe limitations of drinking and eating and patients who are unable to swallow sufficient calories to maintain adequate caloric intake require a feeding tube with a significant association between the severity of mouth and throat soreness and the use of non-prophylactic feeding tubes (Murphy et al., 2009). Pain interfered with chewing, swallowing, drinking and talking in 40 patients with nasopharyngeal carcinoma (Huang et al., 2003). In a randomized trial of an oral antimicrobial versus placebo in 138 HNC patients, more than 75% of patients had pain in the mouth and soreness or burning in the mouth and 66% had difficulty chewing and difficulty swallowing (Duncan et al., 2005).

Overall, most symptoms occur between the third and final week of radiotherapy and continue for 1 month following the completion of therapy. In a qualitative study of the side effects of radiotherapy, patients provided vivid descriptions of these symptoms; sore throat and mucositis were the most frequent, preventing swallowing and proper nutrition. These symptoms lead the patient to significant weight loss and often they need to use prophylactic or reactive feeding tube (Murphy et al., 2009; Duncan et al., 2005; Elting et al., 2008; Wells, 1998).

In the study by Murphy et al., feeding tubes were placed a total of 41-times in 38 (51%) patients at any time during the study. Many feeding tubes were placed prophylactically at baseline, while three patients underwent parenteral nutrition (Murphy et al., 2009). In the study by Elting et al., only 12% of the patients scoring 0–2 at mouth and throat soreness scale compared with 40% of the patients scoring 3–4, required non-prophylactic insertion of feeding tubes during radiotherapy (Elting et al., 2007).

6.3. Quality of life

Oral pain is the most frequently reported patient-related complaint affecting QoL during HNC therapy (Epstein et al., 2007, 2001; Epstein and Schubert, 2003). It was shown that patients who reported more pain and used analgesic opioids also had worse Oral Mucositis Weekly Questionnaire-Head and Neck (OMWQ-HN) scores.

A statistically significant correlation was found between pain and the level of psychological distress at 3, 12 and 24 months in 93 HNC patients (Chaplin and Morton, 1999). Moreover, QoL, as assessed by the life satisfaction score, was adversely and significantly affected by pain at 12 months and at 2 years. In a sample of 102 HNC patients' survivors, improvement over time was observed for global QoL, fatigue and pain, assessed by EORTC QLQ-C30 and the EORTC QLQ-H&N35 subscales (Verdonck-de Leeuw et al., 2014). These results show the strong link between pain and global QoL in this setting of patients. In a recent review on the QoL in patients suffering from HNC, the HRQoL decreased after treatment, but recovered to basal levels within 12 months; sub-analysis was not performed with regard to the specific role of pain in lower QoL, but it should be noted that more than 10 questions planned in questionnaires of QoL (EORTC, FACT and others) have focused on the evaluation of pain during and after radio-chemotherapy (Klein et al., 2014).

6.4. Fatigue

Fatigue during radiotherapy for HNC affects all patients and reaches maximum score at the week 6 of radiotherapy, slowly decreasing thereafter. Jereczek-Fossa et al. recorded a statistically significant association between post- radiotherapy fatigue and age, induction and/or concomitant chemotherapy, radiotherapy-related toxicity (mucositis, dysphagia, weight loss), and need of steroids during radiotherapy in 117 HNC patients (Jereczek-Fossa et al., 2007). In the Murphy study, fatigue scores paralleled the QoL scores. All QoL scores continued to decline until week 6, coinciding with the peak of mouth and throat soreness (Sutherland and Browman, 2001).

6.5. Radiotherapy delays

The association between oral mucositis, pain and patient's compliance is well documented in many studies, while the correlation between pain and compliance to radiation treatment and/or chemotherapy has been less frequently investigated.

Mucositis and the associated pain are one of the most important factors that can lead to unplanned treatment interruptions and/or dose reductions of chemotherapy (Russo et al., 2008; Weissman et al., 1989; Epstein et al., 2001; Trotti et al., 2003). Sometimes, patients with severe mucositis need changes in the intensity of treatment, to prevent further deterioration of general conditions.

Factors associated with discontinuity or early termination of treatments are of paramount importance because of the correlation with increased risk of local recurrence and lower survival (Rosenthal, 2007; Fesinmeyer et al., 2009). Loco regional treatment-related toxicities, particularly ulcerative mucositis and the consequences of ulcerative mucositis like aspiration, inanition, and severe pain lead to unplanned radio-chemotherapy breaks, with impairment of local control and survival. A summary of the key points of the influence of pain on compliance and the mentioned clinical issues is described in Table 3.

Table 3
Summary of the key points for pain and compliance to treatment and other clinical issues.

Summary: Few data are available on the detrimental impact of pain regarding the overall well-being, daily functioning, treatment compliance, nutrition, weight loss and quality of life. Moreover, no data linking a standardized management of pain during radiotherapy with a better compliance to oncological treatments are also available. The impact of the oral pain on the global quality of life is important although never addressed as primary outcome in most of the studies. A tool sensitive for this outcome should be developed and integrated in the future studies.	
Risk factors	Pre-existing disease or condition (diabetes, drug addiction, alcohol addiction, elderly person, depression, psychiatric disease) No multidisciplinary management of mucositis during treatment
Recommendation for clinical practice	Multidisciplinary management of mucositis during treatment Weekly assessment of oral pain during treatment using standard tools, such as the visual analog scale, Numeric Rating Scale and the McGill Pain Questionnaire Standardize the therapy of oral pain based on recommendations and/or guidelines
Recommendation for future studies	Assessment of oral pain using validated scales Verify the impact of the assessment and management of oral pain on quality-of-life dysphagia, weight loss, interruptions in treatment, opioid use, hospitalization, feeding tube use and the cost associated with complication treatments.

7. Pain in head and neck cancer survivors

Over the last decades, chronic pain as a consequence of cancer treatments has gained attention in the scientific literature because of the growing numbers of cancer survivors (Moye et al., 2014). Currently, in the USA, over 50% of the patients treated for cancer will become long-term survivors (> 5 years since diagnosis) and the attention to the health status of such population has gained of public interest (Funk et al., 2012; Rogers et al., 2006). Moreover, as more patients with head and neck cancer are living years after diagnosis secondary to the HPV epidemics and improved therapies, concerns for pain in survivors are expected to rise.

Quality of life and chronic treatment-related side effects in survivors of HNC are particularly significant. In a matched-pair study, Lopez et al. found that long-term survivors treated for oral cancer differed significantly from age and gender-matched sample of Spanish normative population for pain and social functioning domains (Herce Lopez et al., 2009).

Despite significant clinical relevance, chronic pain seems to be under-considered and under-treated in long-term survivors. Literature review of chronic pain in HNC survivors presents some critical issues:

1) Generally, persistent pain has not been recorded as a single parameter, but it is enclosed as a part of a more complex evaluation of QoL or HRQoL. Moreover, published studies used different QoL scales. As a result, incidence and severity of chronic pain cannot always be extrapolated.
2) Chronic pain could be localized in different sites of the body depending on treatment modality. Specifically, pain can be a consequence of surgical procedures (e.g., shoulder pain), radiotherapy treatments (e.g., pain localized in oral cavity, jaw and throat) or chemotherapy (painful peripheral neuropathy is well described with the use of vincristine, platinum, taxanes and other agents) (Rogers et al., 2006). A lot of studies have included patients undergoing different treatment modalities, and pain was collected only in its grade of intensity with no details of its location on the body.
3) Patients' perception of chronic pain could be influenced by psychological distress (depression, anxiety) and this aspect has not been always analyzed.
4) The time when chronic pain was assessed could be quite diversified (ranging from 3 months to > 5 years after treatment) in the published studies. Most of the analyses, in fact, focused their attention in pain during treatment (acute pain) or pain present during the short-term period after treatment (from 3 months to 3 years). It is well known that all the parameters of HRQoL undergo a significant decline during and immediately after treatments, with a gradual improvement starting around 6 months after treatment when the acute side effects start to diminish (Wells, 1998; Fesinmeyer et al., 2009). Because of this time-dependent variability of pain parameters, comparison between results of different studies could be difficult.

Because of all the above-mentioned criticisms, assessing the real incidence and severity of chronic pain in long-term HNC survivors is challenging. For this reason, literature data provides a wide range in incidence of chronic pain from 8% to 60% (Burton et al., 2007; Funk et al., 2012; Rogers et al., 2006; Logan et al., 2008; Van den Beuken-van Everdingen et al., 2007; Abendstein et al., 2005; Terrel et al., 1998; Cramer et al., 2018).

Chronic pain in long term head and neck cancer survivors can be generally classified as: postsurgical pain syndromes (such as loss of sensation and function), radiation-induced pain (mainly neural damage and osteoradionecrosis) and chemotherapy-induced pain (mainly due to peripheral neuropathy) (Cramer et al., 2018)

Different risk factors have also been analyzed:

1) Age: The scarce and heterogeneous literature data on correlation between age and chronic pain in HNC survivors are conflicting, as most studies demonstrated no differences while other found that old adults report less pain than the younger ones. It has been hypothesized that chronic pain may be considered by another chronic illness in older patients who are already suffering from limitation due to age and non-cancer-related comorbidites. Moreover, younger patients were found to have a higher incidence of depression (Moye et al., 2014).
2) Comorbidities, in particular for older patients, seem to be a parameter predicting chronic pain (Verdonck-de Leeuw et al., 2014; Moye et al., 2014).
3) Psychological issues: depression was found to be a significant independent predictor of function-related pain. In patients with more physical complaints (social eating, swallowing and pain) a lower level of QoL and a higher level of psychological distress was found (McNeely et al., 2012). According to Zwahlen et al., besides patient conditions, the high prevalence of anxiety disorders in wives should be also considered (Zwahlen et al., 2008).
4) Treatment modality (surgery vs radiotherapy): Boscolo Rizzo et al. found that patients treated with chemo-radiotherapy resulted to suffer from less pain as compared with patients treated with surgery for oropharyngeal cancer, even though different scales gave non-homogeneous results (McNeely et al., 2012). In another study, when radiotherapy was used as adjuvant treatment after surgery, incidence of chronic pain seemed to be higher as compared with the other groups of patients in which radiotherapy was not used (Logan et al., 2008). Shoulder dysfunction is a well-recognized complication in patients treated with surgery with an incidence ranging from 20 to 60%. The improvements in muscular strength of the scapular muscles complex have resulted to alleviate chronic pain (McNeely et al., 2012).
5) Radiation technique: intensity-modulated radiation therapy seems to reduce not only long-term xerostomia but also oral discomfort (in terms of pain in oral cavity and jaw) (Graff et al., 2007; Chen et al., 2014).
6) Tumor subsite: Patients treated for oral and oropharyngeal cancer

Table 4
Key points for pain in HNC survivors.

Summary: Chronic pain in head and neck cancer survivors is a complex parameter due to the heterogeneous data of time, instruments of detection, patient population and cancer treatments. Moreover, it requires to be evaluated in a wider psychosocial context. Its incidence ranges from 8 to 60%.

Risk factors	Age
	Comorbidities
	Depression-anxiety
	Treatment strategy (surgery vs radiotherapy)
	Tumor site (oral cavity and oropharynx)
	Radiotherapy technique (3D conformal vs intensity-modulated radiotherapy)
Recommendation for clinical practice	To prevent chronic pain
	To investigate its incidence and severity in long-term survivors.
Recommendation for future studies	To collect data on pain both as absolute values, health-related quality of life parameters and psychosocial patients' characteristics
	To focus pain analysis on a homogeneous population
	To collect data related to long-term survivor patients ($\geq$ 5 years from diagnosis)

reported more oral pain but less speech problems than patients treated for hypo-pharyngeal or laryngeal cancer (Verdonck-de Leeuw et al., 2014).

In order to prevent and to reduce incidence and severity of pain in long term survivors, different guidelines have been published (Blanchard et al., 2014; Paice et al., 2016) Recommendation from these guidelines highlights the importance of providing a combination of pain medications, physical therapy, exercise, psychosocial intervention, and alternative therapies. A multidisciplinary pain clinic for patients with complex pain issues requiring long-term opioid should also be considered in selected cases.

Chronic pain also demonstrated to be a predictive parameter of QoL and clinical outcome. Funk et al. found that 1-year pain was among the strongest independent predictors of 5-year HRQOL outcomes (Burton et al., 2007; Funk et al., 2012). The 1-year pain was also associated with cancer prognosis as patients who became long-term survivors had less pain than the ones who died. Moreover, time course of pain was found to be different between the long-term survivors and the non-survivors. The former group experienced a linear improvement after treatments and no change or deterioration was observed in the latter (Logan et al., 2008).

Literature data did not provide definitive results for treatment of chronic pain. In surgically treated patients, chronic pain is mainly due to the neck dissection procedure and is therefore localized to the neck and shoulder. Different therapies (acupuncture and rehabilitation) have been used to improve this symptom but without conclusive results (Osthus et al., 2011b).

In conclusion, chronic pain in HNC survivors is a complex parameter to be extrapolated from literature data because of the heterogeneous data in terms of time, instruments of detection, patient population and cancer treatments. Moreover, it requires to be evaluated in a wider psychosocial context. A summary of the key points can be found in Table 4.

8. The unmet need in clinical research for pain in head and neck cancer

HNC is unique due to localization, patient's risk factors and comorbidities, disease epidemiology and treatment opportunities. A holistic approach incorporating all co-variables such as different treatment modalities, acute and long-term toxicity, psychological distress during and after treatment, nutrition status, organ functionality and preservation should be undertaken to define best supportive measures also for pain management.

Disease specific assessment tools, not only for pain but also for pain-related symptoms should be developed and validated on HNC patients. Some work has been done, but clinical research should not only consider all different time-points of the disease (diagnosis, treatment, post-treatment and rehabilitation), but should address the integration of these phases and relation between them. A focus should be on preventive interventions and early treatment of pain. Since QoL is the 'Holy Grail' in palliative treatment, integration of all these aspects is mandatory.

Even if all these aspects are addressed, several limits still remain. There is not a single 'pain' in cancer treatment neither for HNC patients, but different types of pain that should be assessed in a distinguished way, contemporarily studied and integrated in a specific clinical situation such as post-operative, chemo-radiation, survivorship setting, among others.

A multi-dimensional approach to pain treatment considers also alternative and complementary treatment modalities. Every caregiver should be aware of the specific properties of pain in these patients by education and training.

Future clinical trials have to address specifically these issues considering the impact of pain and pain distress on QoL.

Declarations of conflict of interest

Paolo Bossi: Roche, Merck, Kyowa Kirin, Astrazeneca, MSD, Angelini and Sanofi.

Raffaele Giusti: Kyowa Kirin, Angelini, Bristol-Myers Squibb, Boehringer Ingelheim.

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