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ORIGINAL ARTICLE

Prevention and treatment of oral mucositis in patients with head and neck cancer treated with (chemo) radiation: report of an Italian survey

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Abstract
Purpose There is a limited number of therapies with a high level of recommendations for mucositis, while several strategies are currently employed with a limited evidence for efficacy. A national survey among Italian oncologists who treat head and neck cancer (HNC) was conducted in order to assess the most common preventive and therapeutic protocols (including nutritional support and pain control) for oral mucositis (OM) in patients undergoing chemoradiotherapy.
Methods From September to November 2012, a nationwide electronic survey with 21 focused items was proposed to chemotherapy and radiotherapy centers.
Results We collected 111 answers. Common Terminology Criteria for Adverse Events (CTCAE) scale is employed by 55 % of the physicians in assessing mucosal toxicity. The most relevant predictive factors for OM development are considered smoke, alcohol use, planned radiotherapy, and concurrent use of radiosensitizing chemotherapy. Prophylactic gastrostomy is adopted in <10 % of the patients. Preventive antibiotics or antimycotics are prescribed by 46 % of the responders (mainly local or systemic antimycotic drugs). Alkalinizing mouthwashes or coating agents are frequently adopted (70 % of the cases). Among therapeutic interventions, systemic fluconazole is administered by 80 % of the

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physicians. Pain is mainly treated by weak followed by strong opioids.

Conclusions A variety of preventive and therapeutic protocols for OM exists among the participating Italian centers, with some uniformity in respect to nutritional support, use of antimycotic and painkillers. There is an urgent need for well-conducted clinical trials aimed at assessing the best choices for OM prevention and treatment in HNC.

Keywords Oral mucositis · Standard of care · Prevention and treatment · Head and neck cancer

Introduction

Head and neck cancer (HNC) represents nearly 4–5 % of all cancers and is more common in men than in women and in those aged over 40 years [1]. The principal risk factors remain tobacco and alcohol use; but recently, the incidence of human papillomavirus (HPV) positive oropharyngeal carcinoma has been rapidly growing [2]. Oral mucositis (OM) in patients with HNC is one of the most common debilitating and troublesome side effects of chemoradiotherapy, with a strong negative impact on quality of remaining life. Virtually, all patients who are treated with radiotherapy for HNC, with or without chemotherapy, could develop OM; however, the incidence and the intensity of this disease vary according to the subsite of cancer, association with chemotherapy, radiotherapy fields, doses, and fractionation and other patient-related variables [3]. OM is associated with several signs and symptoms such as pain, dysphagia, infections, food intake impairment, and weight loss [4-7]; it may require feeding tube placement, hospitalization, and intensive supportive care and could represent an obstacle in treatment delivery [8-11].

Despite marked progresses and development of clinical guidelines on this topic, the current management of OM is still inadequate: there is a limited number of therapies which reach a high level of recommendations, as reported in recently adjourned Multinational Association of Supportive Care in Cancer (MASCC) guidelines [12], and particularly in HNC patients, no strategical interventions has consistently improved both incidence and treatment of this disease [13, 14].

On the other hand, in the clinical practice, there are several different approaches used both in prevention and in therapeutic settings. In fact, when evidence lacks due to the scarcity of clear-cut data, inadequate variable and non-evidence-based management enter clinical practice.

Because of this wide variation of practices, we proposed a national survey with the aim of updating the knowledge about susceptibility, clinical manifestation, diagnosis, and therapy of OM induced by radiation or chemoradiation treatments among Italian radiation oncologists and medical oncologists.

Materials and methods

From September 2012 to November 2012, a national survey was conducted among major Italian centers, within an e-mail sent to 200 radiation and medical oncologists. The survey had the support of the Medical and Radiation Oncologist Italian Associations (AIOM and AIRO). It consisted of 21 items designed to investigate the behaviors in OM diagnosis, prevention, and treatment in HNC patients undergoing chemoradiotherapy. (Supplementary Table).

The introductory part of this survey asked for demographic information, to classify the responding centers into four classes on the basis of the number of HNC patients treated per year (first class: less than 50 patients; second class: between 51 and 100; third class: between 101 and 150; fourth class: more than 150). The type of scale used to assess OM and the percentage of patients developing it were evaluated.

The survey also investigated the importance of the different risk factors in OM development, related both to the patient (smoking, alcohol, comorbidities, weight loss, nutritional profile, genetic susceptibility, and performance status) and to the treatment (total dose on oral cavity and oropharynx, radiotherapy in postoperative setting, or association with radiosensitizing drugs).

The following questions were about baseline nutritional aspects such as the percentage of patients suggested to place gastrostomy and the main determinants driving this decision (planned radiation dose on some critical structures such as oral and oropharyngeal mucosa, concurrent chemotherapy, previous weight loss, lack of caregivers, patient preference, and nutritional profile). The same was assessed during treatment.

In the second section of the survey, the use of drugs to prevent and treat OM was analyzed. The normally suggested drugs (mouthwashes, topical and/or systemic agents) were investigated; moreover, it was assessed in which percentage of cases of cultural exams on oral cavity were requested to investigate supra-infections. All questions were made twice, both for the prevention and for the treatment settings.

The last section of the survey investigated the management of the OM in terms of pain duration and type of treatment used (non-steroidal anti-inflammatory drugs, paracetamol, weak [codeine, tramadol], strong [morphine, buprenorphine, fentanyl, oxycodone, hydromorphone], or rapid-onset opioids, topical anesthetics, steroids).

Comparison of proportions was performed by the chi-square test supplemented by tests with Yates' when the value contained in each cell was more than 5, and the total number of observations was more than 30; otherwise, Fisher's exact test was used. The variable considered for different analysis was the specialty of responders, in order to assess possible different clinical behaviors. A p value <0.05 was considered statistically significant.

Results

We collected 111 answers (51 % by medical oncologists and 49 % by radiation oncologists), with an overall response rate of 56 % and all the Italian regions were represented. All data thereof are presented as percentages of the total number of physicians who replied (n=111). The majority of the responders (46 %) treat 51–100 HNC patients per year; 33 % of them treat <50 patients, 12 % 101–150 patients, and the remaining 9 % of the responders have an expertise of >150 patients treated per year. Most of the centers employ intensity-modulated radiation therapy (IMRT) as a radiotherapeutic technique.

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v 4.0) scale is employed by 55 % of the physicians in assessing mucosal toxicity, while World Health Organization (WHO) and Radiation Therapy Oncology Group (RTOG) scales are used by 22 and 35 % of the responders, respectively (Fig. 1). Multiple choices were allowed for this response.

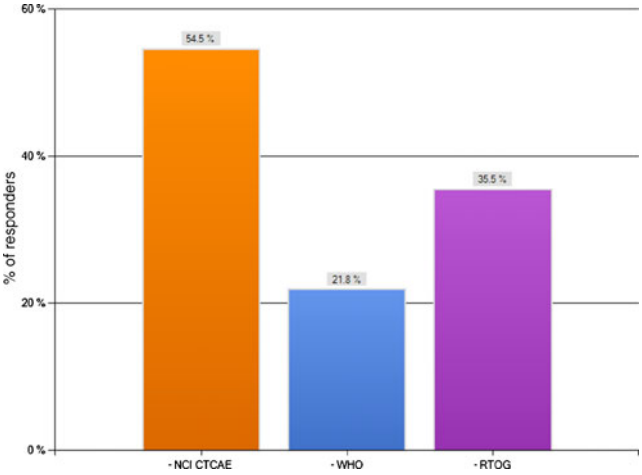

Fig. 1 Use of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v 4.0), World Health Organization (WHO), and Radiation Therapy Oncology Group (RTOG) scales assessing mucosal toxicity

Figure 2 shows the patient-related predictive risk factors (measured before treatment initiation) scored hierarchically by the responders as the most important for the development of OM. The following predictive risk factors were ranked among the first three in terms of importance: concurrent use of radiosensitizing chemotherapy (85 %), planned radiation dose on oral cavity and oropharyngeal mucosa (81 %), active exposure to oral stressors as smoking and alcohol (74 %), performance status (56 %), radiotherapy in postoperative setting and low nutritional profile and/or basal C-reactive protein concentration (23 %), metabolic comorbidities as diabetes (21 %), weight loss (20 %), and genetic susceptibility as polymorphism in detoxifying enzymes (17 %), even if not routinely performed and only for research purposes in selected centers.

There were no statistically significant differences between the answers given by radiation oncologists and those given by medical oncologists, except for "postoperative setting" which was considered an important risk factor more frequently by medical oncologists (ratio=1,898, C.I. 95 % 1.16–3.11; p=0.013).

Three quarters of the responders report to rarely place a prophylactic gastrostomy (58 % in less than 10 % of the patients and 17 % in 10–20 % of the patients). The main reasons that guide gastrostomy placement before therapy are weight loss (84 % of the physicians), planned radiotherapy dose on oral and oropharyngeal mucosa (40 %), and therapeutic strategy employing concurrent use of radiosensitizing chemotherapy (36 %) (Fig. 3).

Naso-gastric feeding tube during treatment is placed in less than 10 % of the patients for half of responders (47 %), and in 10–20 % of the patients for one quarter of them.

Preventive therapy with antibiotics or antimycotics is used by 47 % of the treating physicians; among these, antimycotic drugs are the most prescribed agents (topical and systemic fluconazole by 72 and 84 %, respectively, topical nystatine by 47 %, and systemic itraconazole by 29 % of the responders). Antibiotics lozenges are suggested only to 10 % and systemic antibiotics to less than 18 % of the patients.

In order to prevent OM, alkalinizing mouthwashes or coating agents are the most frequently adopted measures (more than 70 % of the cases); chlorhexidine or benzidamine mouthwashes, topical steroids, and lactobacillus are adopted in 22–29 % of the cases. The low-level laser therapy is considered only by 3 % of the responders and palifermin in less than 1 % (Fig. 4).

With an overt diagnosis of OM, the majority of radiation and medical oncologists (64 %) rarely request cultural exams (in less than 10 % of the patients); nevertheless, in case of severity of signs and symptoms, therapeutic interventions with antibiotics or antimycotics are adopted however by almost all the treating physicians (87 %). The most prescribed solution is, once again, represented by the administration of antimycotic drugs (topical and systemic fluconazole by 72 and 80 %, respectively, topical nystatine by 48 %, and systemic itraconazole by 36 % of the responders). Antibiotics as penicillins, cephalosporins, or fluoroquinolones are administered by about 20 % of the responders each.

The most employed strategy to treat pain related to OM is composed of weak opioids followed by strong opioids (80 % of the responders); non-steroidal anti-inflammatory drugs (NSAIDs) are adopted by 45 % of the responders and steroids or paracetamol by 40 % and 34 %, respectively (Fig. 5).

Pain during swallowing is considered as a form of breakthrough pain by 69 % of the physicians. Short acting opioids are used in order to reduce pain induced by OM during eating and drinking in 77 % of the cases, while topical anesthetics in 37 % and NSAIDs and paracetamol in about 30 % of patients (Fig 6).

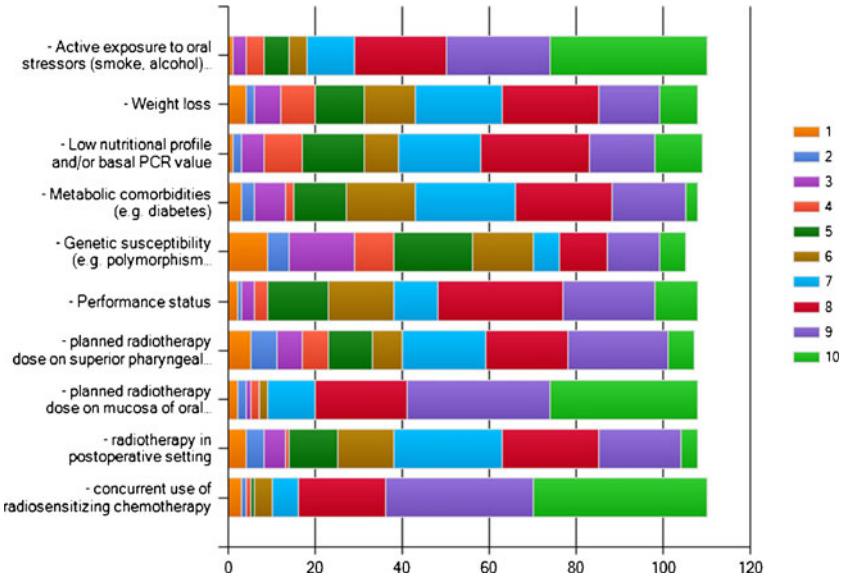

Fig. 2 The patient-related predictive risk factors (measured before treatment initiation) scored hierarchically by the responders as the most important in the development of OM

Discussion

This national survey showed different approaches used by Italian radiation and medical oncologists for the management of OM in HNC patients undergoing chemoradiotherapy.

Despite the high incidence of this adverse event, there is a lack of evidence-based and standardized protocols for its prevention and treatment. Often, also in MASCC and ASCO (American Society of Clinical Oncology) guidelines, as well as in NCCN (National Comprehensive Cancer Network) task force report [12, 15, 16], the recommendations on these topics appear inadequate and/or conflicting.

Moreover, a great variety of clinical reports has been employed to rate assessment and grade of OM. About grading, the most commonly utilized scales are those proposed by NCI/CTCAE v 4.0, RTOG and WHO [17-19]. Nevertheless, there is still a lack of a universally accepted scale, and this limits the possibility of a reliable comparison between complications reported in different studies [20].

Last, adverse events (including OM) assessed by physicians are less accurate than patient-reported outcome (PRO) instruments and, also for OM, some clinicians have proposed replacing physician scales with patient-assessed reporting [6, 21, 22]. However, in our survey, this anamnestic instrument was not routinely employed by the physicians. This fact could constitute a limit for a prompt recognition and treatment of this symptom; future observational or therapeutic trials should assess PRO scales.

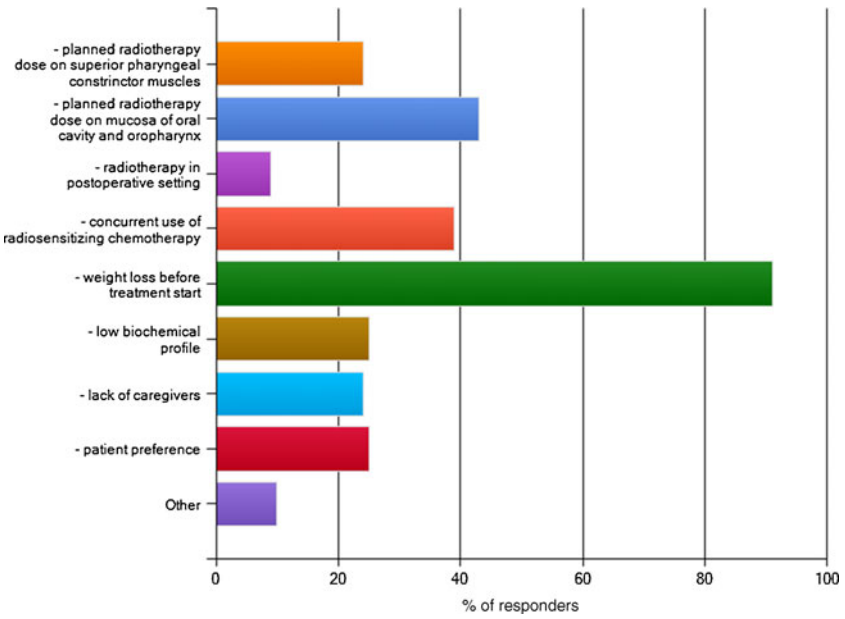

Fig. 3 The main determinants that guide decision on gastrostomy placement before theraphy

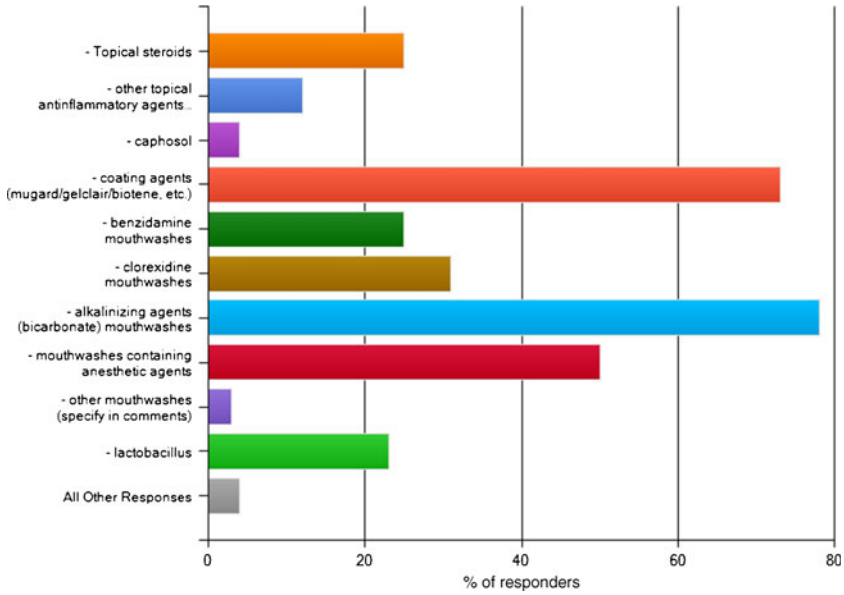

Fig. 4 Agents suggested to prevent/treat mucositis

OM often impairs the ability of the patient to maintain an adequate caloric and liquid intake, so giving the start to a complex cascade of complications which include dehydration, weight loss, fatigue, impaired quality of life, increased susceptibility to infection, reduced treatment compliance, with an increase of health resource utilization [3, 8, 23, 24]. There is no consensus on the optimal timing and method for enteral supplementation during concurrent chemoradiation. In particular, there is no definite evidence to recommend gastrostomy insertion as prophylactic strategy to prevent nutrition decline or to adopt a reactive strategy suggesting naso-gastric tube placement during treatment when a substantial nutritional decline is shown [25].

As evidenced in the survey, prophylactic gastrostomy is not routinely employed, with the majority of the physicians reporting to rarely suggest its insertion before starting treatment. However, reactive naso-gastric feeding tube is only slightly more often employed. When interpreting these results, it should be considered that the survey was applied to all-stage HNC cancer undergoing radiation at different doses and fields with/without concomitant chemotherapy.

The identification of the subset of patients who can mostly benefit from an intensive nutritional strategy and the adoption of a tailored intervention are of utmost importance. Several risk factors, related both to treatment (i.e., dose and field of radiation, concurrent chemotherapy) and to patient (i.e.,

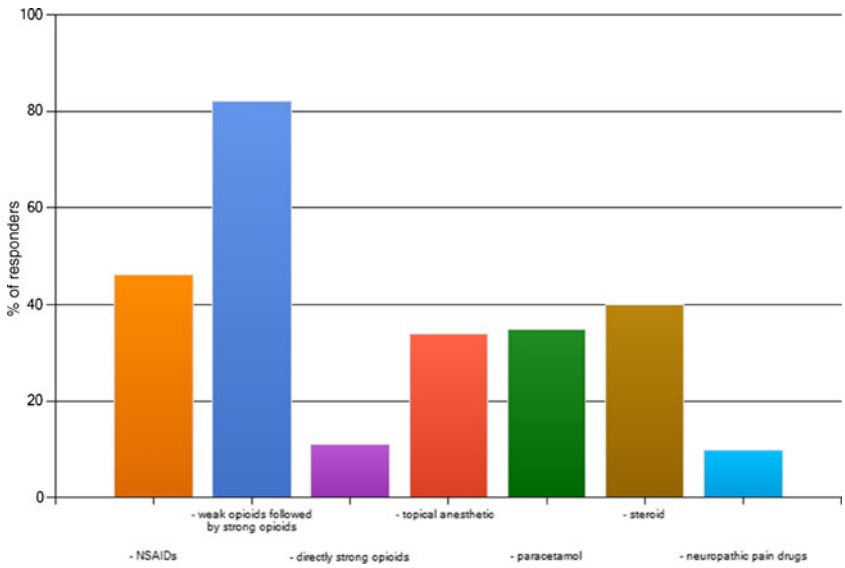

Fig. 5 Strategies to treat pain related to OM is composed of weak opioids followed by strong opioids

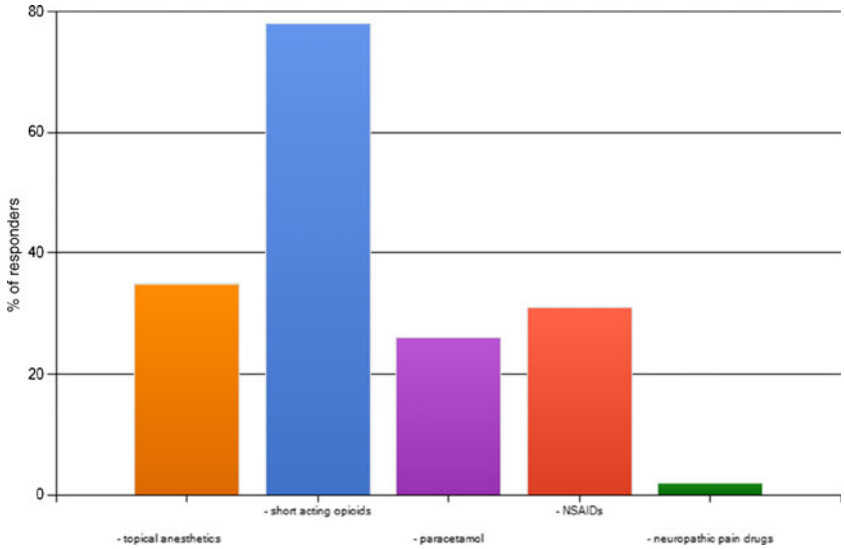

Fig. 6 Drugs used to treat pain induced by mucositis during eating and drinking

comorbidities, weight loss, and low nutritional profile, genetic susceptibility), could guide in this selection.

Eighty-one percent of the responders judged the quantity of radiated oral and oropharyngeal mucosa an important predictive risk factor for OM. Recently, Sanguineti and colleagues showed that the absolute amount of oral and oropharyngeal mucosa that received 9.5–10.1 Gy per week not only is an independent predictor of the development of confluent OM during treatment but also involves the need for dependence on a feeding tube during and after therapy [26, 27].

Concurrent chemotherapy increases the risk to develop grade 3 OM by about four times more than radiation therapy alone, and it is equivalent to an extra ≈6.2 Gy to 21 cm^3 of oral and oropharyngeal mucosa over a radical course of radiotherapy [26]. Therefore, trying to limit the dose on the oral and oropharyngeal mucosa at radiotherapy planning would be another strategy to prevent OM during radiotherapy or chemoradiotherapy.

The preventive administration of antimicrobials is adopted by almost half of the responders, mainly consisting in antimycotic therapy. In previous trials, the use of antibacterial and antiviral agents (both at topical and systemic levels) as preemptive therapy failed to show any benefit in reducing OM incidence and severity during radiation therapy for HNC, so no evidence exists in favor of this behavior. In fact, according to the five-step Sonis' model of OM pathogenesis, only at a late stage (fourth phase, during ulceration) there is a mucosal entry point for bacteria, virus, and fungi [28], with a possible occurrence of a systemic infection. More controversial is the use of antimycotic prevention. In a recent evaluation, about 60 % of the patients treated with chemoradiotherapy for HNC develop oropharyngeal candidosis [29]. An Italian randomized trial showed a benefit with systemic fluconazole in comparison to placebo in preventing and delaying oropharyngeal candidosis; however, no difference in OM severity was detected between the two groups [30]. Therefore, the role of oropharyngeal candidosis prevention in HNC is still a matter of debate, with concerns also regarding possible emergence of fluconazole-resistant fungal species [31]. With an overt diagnosis of OM, the survey showed a widespread use of antimicrobial therapy, with both topical/systemic antimycotic and systemic antibiotics (penicillins, cephalosporins, and fluoroquinolones).

Pain closely parallels the severity of OM and can dramatically affect quality of life, being one of the most distressing symptom during chemoradiation for HNC [32].

The analgesic strategies employed vary from local treatments (topical steroids or anesthetic rinses, mainly with solutions containing lidocaine) to the administration of systemic drugs according to the WHO analgesic ladder for cancer pain relief [33]. It is interesting to underline that about 40 % of the responders treat OM-induced pain with NSAIDs, while the long-term use of these molecules could not be advisable due to adverse effect such as the well-known damage to the gastric mucosa. However, this behavior could reflect the fact that, despite individualized approaches, pain control is still often unsatisfactory in this setting [34].

There is insufficient evidence from randomized clinical trials to advise an optimal intervention specifically for HNC pain [35]. A significant difference in pain levels with and without swallowing has been identified in a prospective, longitudinal trial for HNC, underlining also the need for a careful pain assessment and for employment of more potent analgesics [36]. Pain during swallowing has been recognized as a kind of breakthrough pain (BTP) by 65 % of the survey responders. BTP in this setting is related to a specific trigger (eating, drinking) and it could be so defined as incident predictable BTP [37]. Another report showed a high incidence (48 %) of BTP in HNC patients,

with half of the cases linked to an incidental precipitant factor, such as coughing or eating [38].

The functional impact of pain during swallowing is highly clinically significant. In fact, it results in decreased or altered oral intake which may lead to dehydration, reduction of caloric intake with associated weight loss, nutrient deficiencies, and long-term dysphagia due to the lack of pharyngeal muscles use. In the survey, the most employed drugs to treat this symptom were short-onset opioids, followed by topical anesthetics and NSAIDs again. Considering the impact of pain during swallowing and the lack of recognized treatment deriving from clinical trials, BTP during swallowing should be considered as an unmet need in HNC patients treated with chemoradiation.

The results of this survey highlight the need of establishing a national consensus in order to reduce the variability of OM management and to disseminate clear and straightforward tools. Moreover, written protocols, available for both physicians and nurses, are to be encouraged.

When analyzing the answers of medical oncologists and radiation oncologists in this survey as a whole, a substantial agreement about the choices and behaviors may be identified. This may reflect the widespread adoption of the model of multidisciplinary tumor boards in the management of HNC and suggests that a formative action should be directed not to the single specialties but to the centers. An improved survival is observed in patients treated within a multidisciplinary team both for access to integrated treatment and for supportive care received, so possibly improving patient's compliance and treatment dose intensity [39].

In addition, educational initiatives should be prompted by the two societies with the aim of reducing the application of non-evidence-based practices. The survey is limited by the relatively small number of respondents and by the bias of volunteer responding, but it could be reasonably considered to be representative of clinical behaviors in Italian centers.

Conclusion

This survey showed some uniformity in OM diagnosis, prevention, and treatment among Italian medical and radiation oncologists dealing with HNC patients, particularly regarding nutritional aspects, use of antimycotic drugs, and painkiller employment. However, dissimilarity exists for what concerns scale of toxicity adopted, selection and type of antimicrobial prevention and the agents chosen for treatment.

This survey can be the basis of discussion for a subsequent consensus conference on supportive care in HNC that will be promoted by Italian associations, in order to give directions where there is absence of high-quality evidence, through the use of the modified Delphi consensus methodology [40].

Prospective, well-conducted clinical trials are urgently needed in order to expand our knowledge in the field of prevention and treatment of OM induced by chemoradiation in HNC patients.

Conflict of interest The authors have no conflicts of interest directly relevant to this article. The authors had full control of primary data; these are available upon request for review. We thank Luca Giacomelli, Ph.D, for the useful discussion.

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