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ORIGINAL ARTICLE

Oral mucositis-related neuropathic pain in head and neck cancer patients receiving radiotherapy or chemo-radiotherapy. A prospective study

Maria Kouri[1], Ourania Nicolatou-Galitis[1], Athina Vadalouca[2], Vassilis Kouloulias[3], Erofili Papadopoulou[1], Emmanouil Vardas[1], Euthimios Kyrodimos[4], Miltiadis Trichas[5], Anna Zygogianni[6], Zoi Liakouli[6], Evangelos Galitis[7], Ioanna Siafaka[8], Andromachi Kougioumtzopoulou[3], Amanda Psyrri[9]

[1]Clinic of Hospital Dentistry, National and Kapodistrian University of Athens, Dental School, Athens, Greece; [2]Pain Clinic, Athens Medical Center, Athens, Greece; [3]2nd Radiology Department, Radiotherapy Unit, National and Kapodistrian University of Athens, Medical School, Athens, Greece; [4]ENT Clinic, Hippokrateio Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece; [5]Radiotherapy Department, Iaso Hospital, Athens, Greece; [6]1st Radiology Department, Radiotherapy Unit, Aretaieio University Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece; [7]Department of Oral & Maxillofacial Surgery, National and Kapodistrian University of Athens, Dental School, Athens, Greece; [8]Department of Anesthesia Pain Therapy and Palliative Care, Aretaieio University Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece; [9]Oncology Department, Attikon University Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece.

Summary

Purpose: *Pain due to oral mucositis (OM) in head and neck cancer (HNC) patients receiving radiotherapy (RT) / chemo-radiotherapy (CRT) can be nociceptive and/or neuropathic. Neuropathic pain (NP) often remains underdiagnosed and untreated. The purpose of this study was to identify and quantify the presence of OM-induced NP in HNC patients under RT/CRT.*

Methods: *Pain was assessed using a 0-10 numeric scale (NRS). At an NRS≥5 score, patients completed the Douleur Neuropathique 4 questionnaire (DN4q), where a score ≥4/10 indicates the presence of NP. Oral mucositis and xerostomia were assessed using the European Organization for Research and Treatment of Cancer (EORTC) and the NRS scales accordingly. Pain medication was documented.*

Results: *Forty patients were recruited; twenty-six (mean age 63.54±13.96 years) completed a DN4 (mean pain NRS 7.46±1.42); five (5/26, 19.23%) had a DN4≥4. The most common NP descriptors were "burning" (34.62%), "electric shocks" (30.77%) and "pins-and-needles" (30.77%). A direct correlation was observed between DN4 and pain, mucositis, and xerostomia (p<0.02). Pain medication was administered to fifteen patients (15/26, 57.69%). Adjuvant medication was administered to one patient (1/5) with positive DN4 score.*

Conclusions: *Five (5/26, 19%) of the patients with NRS≥5 developed NP; adjuvant medication to address NP was prescribed to one patient. NP is likely underdiagnosed and undertreated in the HNC population undergoing RT/RCT.*

Key words: *head & neck cancer, neuropathic pain, oral mucositis, radiotherapy*

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Corresponding author: Maria Kouri, DDS, MSc, PhD(c), Clinic of Hospital Dentistry, Dental School, National and Kapodistrian University of Athens, Thivon 2, Athens, 11527, Greece.
Tel: +30 6944887347; Email: kourimari@yahoo.gr
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Introduction

Improvements in the treatment of head and neck cancer (HNC) have increased the survival rate of these patients but therapeutic interventions may create further challenges, because HNC therapy is not specific to cancer cells but also injures normal cells, tissues, and nerves. Painful oral mucositis (OM) is a side effect induced by radiotherapy (RT) and chemo-radiotherapy (CRT). Oral mucositis-induced pain (OMP) is one of the most devastating side effects of RT/CRT for HNC; it has been associated with patients' distress and suffering, frequent use of feeding tubes and opioid medication, hospitalizations and treatment breaks as well as increased medical costs [1,2]. During RT for HNC, patients receive approximately 60-70 Gy of radiation for a typical course of 6 to 7 weeks. OMP generally starts at week 3, peaks at week 5, and persists for 2-4 weeks after completion of RT [1,3]. The severity of OMP is usually related to the severity of OM due to mucosal atrophy and ulceration [2,4], although some studies found no such relation [5,6].

This pain may be nociceptive, neuropathic, or a combination of both. Nociceptive pain arises from injury to non-neural tissues due to the activation of nociceptors, while neuropathic pain (NP) is caused by injury of the somatosensory nervous system. OM may develop following chemotherapy, RT/CRT, and/or hormonal therapy [7,8]. OMP is a well-recognized adverse event and may be caused by nociceptive or neuropathic mechanisms [9]; treatment induced polyneuropathy [10] and OM are associated with NP [1,9,11]. Nociceptive pain is commonly induced by the damaged tissues in the oral cavity. Persistent unrelieved nociceptive pain induced by OM ulcers along with therapy-related neuronal injury can result in NP; NP involves abnormal processing of noxious stimuli. In addition, chemical mediators such as tumour necrosis factor alpha (TNF-α), reactive oxygen/nitrogen species, bradykinin, substance P and others, are elevated in patients with OM; these substances may be involved in NP [9,12].

NP is described as sharp, shooting and/or burning sensations, sometimes described as "shocks" or "bee stings". NP may also include the paradoxical and unpleasant "pins and needles" sensation and can be associated with "numbness" or "tingling" of the affected area [13]. NP in HNC patients is underestimated, underdiagnosed and often untreated, negatively impacting the patient's quality of life during cancer therapy, resulting in a burden for patients and increasing healthcare expenses [14].

The Douleur Neuropathique 4 questionnaire (DN4q) has been validated [15] as an assessment tool for NP. It consists of 10 items, including 3 descriptors related to pain characteristics (burning, painful cold, and electric shock), 4 descriptors which might accompany pain (tingling, pins and needles, numbness, and itching), 2 descriptors assessed during clinical examination (tactile hypoesthesia and pinprick hypoesthesia) and 1 item regarding allodynia. Patients answer 4 multi-part questions and at 1 point per "yes" answer, the maximum score obtainable is 10. A score of ≥4 is considered indicative of NP. Mulvey et al [16] have reported that all items on the DN4 were associated with significantly increased odds between positive (≥ 4) and negative DN4 scores, when overall pain was assessed, but when treatment related pain was assessed only specific descriptors had a statistical significance.

Moreover, OM in HNC patients treated with RT/CRT is often complicated by candidiasis and herpetic infection, thus altering pain characteristics. The appearance of candidiasis during RT is about 38% [17,18]; candidiasis is often associated with a burning sensation of the mouth [17]. The prevalence of herpetic infection among HNC patients receiving CRT is 29% to 43% depending on the study [19,20]. Herpetic infection was observed to aggravate RT-induced ulcerative OM and exacerbate pain, as it is associated with painful ulcerations in the oral cavity [19].

Lack of lubrication of the oral mucosa due to xerostomia, increases the mucosal friction during oral functions, making it vulnerable to greater trauma and pain and predisposes to the development of candidiasis [13].

NP in cancer patients represents a therapeutic challenge, as these patients are already subject to polypharmacy [21]. It is important for treatment to recognize the overlap of NP with other pain mechanisms [22]. Nociceptive pain therapy does not necessarily address NP. Thus, the accurate diagnosis of NP from other pain pathologies is fundamental for the effective pain management.

To date, there is a paucity of published data on OMP [23]. Even less is available concerning OM-induced NP [9,24]. The objective of this study was to identify and quantify OM-induced NP in HNC patients receiving RT/CRT. Our hypothesis is that RT/CRT may result in OM and in some cases subsequent NP in HNC patients, and our investigation sought to better define, describe, and quantify the rate of OM-associated NP in this population.

Methods

A single-center, prospective, cross-sectional study was carried out to assess the prevalence of OM-induced NP in HNC patients undergoing RT/CRT. The study was conducted from October 2014 to July 2017. Fifty-three consecutive patients were enrolled.

The research complied with the guidelines for human studies and was conducted ethically in accordance with the "World Medical Association Declaration of Helsinki". The study was approved by the Committee of Ethics for Research, of the School of Dentistry, National and Kapodistrian University of Athens, Greece, before the data collection. Patients signed a written informed consent form at the time of enrolment.

Patients were referred to the Clinic of Hospital Dentistry of the School of Dentistry, National and Kapodistrian University of Athens, Greece, from Cancer Centers, for oral oncology supportive care. All patients were introduced to standard oral mucosal and dental care; mouthwashes containing lidocaine and mucosal moisturizing and coating agents were also introduced. Patients were assessed for OM and were asked to score their "average within the day" pain and xerostomia, weekly during RT.

Medical data (regarding disease severity, treatment and pain medication) were collected on all included patients from their medical records.

Inclusion criteria

Adult HNC patients (≥18 years of age) who were scheduled to receive RT/CRT could enrol in the study.

Exclusion criteria

Patients reporting oral pain at the time of enrolment. Patients were excluded if they had known neurological disorders, could not communicate effectively in Greek, or were being fed via nasogastric tube or gastrostomy.

Measurements

Pain was evaluated using a 0-10 numeric rating scale (NRS) with scores <5 considered mild pain, 5-7 moderate, and scores ≥8 severe pain. The NRS is an established and validated instrument and has been extensively studied; it is considered a reliable measure for pain intensity. Acute pain can be adequately measured using uni-dimensional tools [25] while there is a significantly higher descriptive capability of the NRS compared to verbal rating scales in distinguishing between background and peak pain referred to the pain experienced in the previous 24 hours [26].

A presumptive diagnosis, upon clinical suspicion, was made for candidiasis and herpetic infection. Erythema located on the central dorsum of the tongue, or bilateral, the central area of the hard palate, symmetrical erythema of the buccal mucosa, angular cheilitis and non-painful easily removable whitish pseudomembranes were indicative of candidiasis [7]. Herpes labialis, ulcers coalescing on the hard palate and the dorsum of the tongue and early initiation or sudden development or worsening of ulcerative mucositis, were viewed as indicative of herpetic infection [7].

In patients without oral candidiasis and/or herpetic infection, who reported a NRS pain score ≥5, the Greek language-validated 10-item DN4 questionnaire [27] was administered only once. Patients with candidiasis and/or herpetic infection were treated with antifungal and/or antiviral medication for at least one week and then pain was assessed again; the DN4 questionnaire was administered, after treatment, when they reported an NRS pain score ≥5, only once.

The maximum possible score on the DN4 is 10 and a cut off score of ≥4 is considered indicative of NP. Using that cut off value, DN4 questionnaire showed a sensitivity of 93%, a specificity of 78%, a positive predictive value of 90% and a negative predictive value of 84% [27] in detecting the neuropathic element of pain. The total score was calculated as the sum of the 10 items and the cut-off value for the diagnosis of NP was a score of 4/10. The clinical descriptors were assessed on non-ulcered mucosal areas.

Xerostomia and OM were assessed weekly as well as at the time point the DN4 questionnaire was administered.

The NRS was also used for xerostomia assessment in the absence of a Greek language validated scale for xerostomia; NRS is widely used, valid and reliable [28-30]. Results were considered as 1-4 mild; 5-7 moderate; 8-10 severe.

OM was assessed using the European Organization for Research and Treatment of Cancer/ Radiation Therapy Oncology Group (EORTC/RTOG) 0-IV scale, as follows: Grade I (diffuse erythema, patient can eat solid food), Grade II (erythema and small foci of ulcers, patient can take soft diet), Grade III (painful ulcers extending on more than half of the oral mucosa, patient can take liquids only), Grade IV (painful ulcers covering almost all mucosal surfaces, alimentation is not possible) [31]. The results were considered as I mild; II moderate; and III-IV severe.

All the referred patients had been administered irradiation with a prescribed dose between 30.6Gy to 70Gy (1.8Gy to 2.25Gy per fraction). All patients had undergone a CT-based treatment planning with immobilization device with either ECLIPSE VARIAN (Palo Alto, USA) or ONCENTRA ELEKTA (Stockholm, Sweden) system. The QUANTEC criteria [32] for normal tissue constrains were met as follows:

Parotid grand: mean dose<25Gy; Oesophagus: V45<33%; Mandible: V75<1cc;

Oral cavity: mean <50Gy; Spinal cord: <50Gy.

Patients were irradiated with either a Trilogy Varian or Oncorde Siemens, or Versa Elekta or Tomotherapy Linac.

Outcomes

Our main outcome measure was the presence of NP using the DN4 questionnaire. As secondary endpoints, there were evaluated the significance of the NP descriptors on the DN4q between positive and negative DN4q scores and the correlation between DN4q scores and intensity of pain, OM and xerostomia.

Table 1. Characteristics of patients who answered a DN4 questionnaire

Variable	*n (%)*	*Mean (SD)*	*Range*
Age (years)		63.54 (13.96)	37 – 88
Gender			
Male	20 (76.9)		
Female	6 (23.1)		
ECOG performance status			
0	12 (46.2)		
I	9 (34.6)		
II	5 (19.2)		
III	-		
IV	-		
Cancer stage			
I	-		
II	2 (7.7)		
III	7 (26.9)		
IV	9 (34.6)		
Recurrence	2 (7.7)		
Missing	6 (23.1)		
Cancer site			
Oral / Oropharyngeal	16 (61.5)		
Nasal / Nasopharyngeal	3 (11.5)		
Parotid	3 (11.5)		
Unknown Primary	2 (7.7)		
Laryngeal	1 (3.8)		
Other	1 (3.8)		
Type of treatment			
Radical RT	11 (42.3)		
Postoperative RT	15 (57.7)		
Concomitant chemotherapy	20 (76.9)		
Radiotherapy dose (Gy)			
Total dose		62.11 (9.243)	30.6 – 70
Daily dose		2.04 (0.104)	1.80 - 2.25
Weight loss (kg)		8.014 (4.231)	17 - 0
Oral hygiene level			
Poor	5 (19.2)		
Medium	10 (38.5)		
Good	7 (26.9)		
Edentulous	4 (15.4)		
Infections (before the DN4q completion)			
Candidiasis	3 (11.54)		
Herpes	2 (7.69)		
Radiotherapy interruption (≥3 days)	6 (23.1)		
Oral pain	1 (3.8)		
Unable to consume any food	1 (3.8)		
Other reasons	4 (15.4)		
Hospitalization	4 (15.4)		
Unable to consume any food / gastrostomy	2 (7.7) / 1 (3.8)		
Other health reasons	2 (7.7)		
Pain medication			
Opioids	8 (30.77)		
Nonsteroidal anti-inflammatory drugs	7 (26.92)		
Adjuvant (Pregabalin)	1 (3.85)		

Analytic plan

SPSS software (SPSS Inc., Chicago, IL, USA, version 21) was used for data analysis. Categorical data are presented as n (%) and the continuous data as mean and standard deviation (±SD). Spearman's rho test was used to derive the correlations observed between DN4q score, intensity of pain, oral mucositis and xerostomia. Fisher's exact test was used to evaluate the statistical significance of the NP descriptors between positive (≥4) and negative DN4q scores. Statistically significant p values were considered when p≤0.05. We enrolled 53 consecutive patients in order to adequately power the study.

Hypothesis

The hypothesis of our study was that in the population of patients with HNC who were undergoing RT/CRT and who were thus at risk for OM, a subset of this population would develop NP. We sought to quantify this subpopulation.

Results

Fifty-three consecutive HNC patients scheduled to receive RT/CRT were enrolled in this study. Thirteen of the enrolled patients (13/53) did not attend follow up visits during RT; nine did not respond to contact calls, one was hospitalized due to general health reasons, and three did not attend follow up due to administrative reasons. Forty patients participated in this study; the mean age was 64.23±13.184 years and most of them were male (82.5%). Patients had an Eastern Cooperative Oncology Group (ECOG) performance status ≤2.

Five (12.5%) patients had clinical signs of candidiasis and six (15%) had signs of herpetic infection.

Six (6/40, 15%) patients developed pain only while swallowing (mean NRS 6±2), three developed mild pain (mean NRS 3.33±0.58) and five did not report pain (NRS=0) in the oral cavity during RT/CRT.

Twenty-six patients (65%) developed moderate or severe pain (NRS≥5) (mean NRS 7.46±1.42) during their treatment and completed a DN4 questionnaire; thirteen (13/26, 50%) developed moderate and another thirteen (13/26, 50%) severe pain (mean NRS 6.23±0.60 and 8.69±0.75, respectively).

Characteristics of the patients who completed a DN4 questionnaire (n=26)

As shown in Table 1, the twenty-six patients who completed the DN4 questionnaire had a mean age of 63.54±13.96 years. The primary tumour site was the oral cavity/oropharynx (n=16, 61.5%). Among our patients, twelve (46.2%) underwent a 3-dimensional conformal and fourteen (53.8%) underwent an IMRT radiation treatment.

Most of the patients had multimodal cancer therapy. Cancer therapy delivered was RT alone (n=3, 11.5%; one of them had induction chemotherapy), a combination of surgery and RT (n=3, 11.5%), CRT (n=8, 30.8%) and a combination of surgery and CRT (n=12, 46.2%).

Candidiasis and herpetic infection before completion of the DN4 questionnaire were found in 3 (11.54%) and 2 (7.69%) patients, respectively.

Table 2. Pain, oral mucositis and xerostomia in patients who answered a DN4 questionnaire

Variable	*N (%)*			*Mean (SD)*		
	Total (n=26)	*DN4q≥4 (n=5)*	*DN4q<4 (n=21)*	*Total (n=26)*	*DN4q≥4 (n=5)*	*DN4q<4 (n=21)*
Pain				7.46 (1.42)	8.40 (0.548)	7.24 (1.48)
No	-	-	-	1.96 (0.92)	3.00 (0.00)	1.71 (0.85)
Mild	-	-	-	6.50 (2.14)	8.40 (0.548)	6.05 (2.13)
Moderate	13(50)	-	13(61.9)			
Severe	13(50)	5(100)	8(38.1)			
Oral mucositis						
No	3(11.5)	-	3(14.3)			
Mild	2(7.7)	-	2(9.5)			
Moderate	14(53.8)	-	14(66.7)			
Severe	7(26.9)	5(100)	2(9.5)			
Xerostomia						
No	-	-	-			
Mild	4(15.4)	-	4(19.0)			
Moderate	10(38.5)	-	10(47.6)			
Severe	12(46.2)	5(100)	7(33.3)			

Table 3. Correlations between DN4q score, intensity of pain, oral mucositis and xerostomia in patients who answered a DN4 questionnaire

	DN4q	*Pain*	*Oral mucositis*	*Xerostomia*
DN4q		r=0.617 p=0.001	r=0.752 p<0.001	r=0.590 p=0.002
Pain	r=0.617 p=0.001		r=0.314 p=0.119	r=0.733 p<0.001
Oral mucositis	r=0.752 p<0.001	r=0.314 p=0.119		r=0.444 p=0.023
Xerostomia	r=0.590 p=0.002	r=0.733 p<0.001	r=0.444 p=0.023	

Correlations were derived using the Spearman's rho test.

Table 4. Statistical significance of the neuropathic pain descriptors between positive (DN4≥4) and negative DN4q scores

NP descriptors	*Total (n=26)* *n(%)*	*Negative DN4q (n=21)* *n(%)*	*Positive DN4q (n=5)* *n(%)*	*p value*
Burning	9 (34.62)	6 (28.6)	3 (60.0)	0.302
Painful cold	-	-	-	-
Electric shocks	8 (30.77)	3 (14.3)	5 (100)	0.001
Tingling	5 (19.23)	2 (9.5)	3 (60.0)	0.034
Pins and needles	8 (30.77)	4 (19.0)	4 (80.0)	0.020
Numbness	5 (19.23)	1 (4.8)	4 (80.0)	0.002
Itching	4 (15.38)	2 (9.5)	2 (40.0)	0.155
Hypoesthesia to touch	1 (3.87)	-	1 (20.0)	0.192
Hypoesthesia to prick	-	-	-	-
Brushing	9 (34.62)	7 (33.3)	2 (40.0)	>0.999

Significance was evaluated using the Fisher's exact test.

Eight (8/26, 31%) patients with severe pain received opioid medication. Eleven (42.31%) patients with moderate or severe pain did not receive analgesic medication. One patient received adjuvant medication (pregabalin) for NP.

Seventeen patients (17/26, 65.38%) reported at least one NP descriptor. Five patients (19.23%) had a positive score for NP, that is, a DN4 questionnaire score ≥4. The most common NP descriptor was "burning" (34.62%) followed by "electric shocks" (30.77%) and "pins and needles" (30.77%). None of the patients reported "painful cold" or "pricking hypoesthesia".

All five patients (100%) with a positive DN4 questionnaire score reported severe pain and xerostomia (NRS≥8) and developed severe (grade III) OM; in patients with a negative DN4 questionnaire, 38.1% reported severe pain, 33.5% reported severe xerostomia and 9.5% reported severe OM. None of the patients developed OM grade IV (Table 2).

A direct correlation was observed between total DN4 questionnaire score and intensity of pain (Spearman's r=0.617, p=0.001), xerostomia (r=0.590, p=0.002) and OM (r= 0.752, p<0.001). A statistically significant correlation was observed between the intensity of pain and xerostomia (p<0.001), and, OM and xerostomia (p=0.023) but not between pain and OM (Table 3).

Each pain descriptor assessed was experienced more often in patients with a positive DN4 score, but statistically significant (p<0.05) differences were found for the NP descriptors "electric shocks," "tingling," "pins and needles," and "numbness" (Table 4).

Discussion

Patients with HNC undergoing RT report pain related to radiation induced toxicity even in the IMRT era, independently to xerostomia [33]. Patients were enrolled to this study before the initiation of RT/CRT and were excluded if they reported any pain in the oral cavity at the time of enrolment. Pain developed during the RT/CRT in 87.5% of the 40 participants, a finding that aligns with other studies [3]. Severe pain developed in 32.5% of the patients. Other investigators reported similar findings, with about 40% of patients developing severe pain [7].

According to the literature about 10% of HNC patients with pain did not receive any analgesic therapy [1]. We observed that 42.31% of the patients who had moderate or severe pain did not re-

ceive any analgesic medication, moreover four out of five patients with a positive DN4q score did not receive adjuvant medication for NP. In our study opioid analgesia was prescribed for 31% of the patients with severe pain due to RT/CRT while other investigators [34] reported prescription of opioid analgesia only for 8% of the patients with severe pain due to chemotherapy-induced mucositis. This suggests an important unmet need for better pain management in HNC patients receiving RT/CRT. Treatment strategies for nociceptive pain and NP vary, so identification of the neuropathic component, even as part of mixed pain, is crucial.

Patients were evaluated using the DN4q when they reported moderate or severe pain (NRS≥5) accordingly to the Validation of the Greek Version of the DN4 Diagnostic Questionnaire for NP where there was a ≥5 scoring of pain in the inclusion criteria [27].

In our study, neuropathic descriptors were reported by 65.38% of the 26 patients who completed the DN4 questionnaire; similar findings were reported by other investigators [9]. Statistically significant differences regarding the descriptors used for NP, between positive and negative DN4 scores, were found for the "electric shocks," "tingling," "pins and needles," and "numbness." Potter et al. [24] using a different questionnaire while assessing overall HNC-related pain, also found statistically significant differences for the "electric shocks" descriptor but not for "pins and needles"; as in our study, there was no significant difference for the "burning" descriptor. This may indicate that clinicians may suspect the presence of NP, in HNC patients receiving RT/CRT, when patients report certain pain characteristics, such as "electric shocks."

In this study, a strong correlation between DN4 questionnaire scores and the intensity of OM ($p<0.001$) was established. A statistically significant correlation was observed between DN4 questionnaire scores and the intensity of pain ($p=0.001$) similarly to Sykioti et al [27]. All the patients who had a positive DN4 questionnaire developed severe pain and OM. This may correlate with the pathways related to the development of NP due to the extended exposure to the noxious stimuli (severe OM), where cytokines are released from microglia causing central sensitization due to severe pain [35].

The severity of OMP may be thought to be related to the severity of OM [4]. However, in our study there was no correlation found between total OM and total pain scores; similar findings have been reported from other studies [5,6]. This could be related to the different pain tolerance levels among patients as they have different pain thresholds under similar stimuli.

Six out of the forty patients (15%) had pain only while swallowing (odynophagia); other investigators reported almost the same percentage of intermittent pain, even though they did not specify whether this was occurred during swallowing or during other oral functions [9]. One study reported a statistically significant difference in pain levels with and without swallowing, but investigators did not report the percentage of patients, if any, who had pain only when swallowing [3]. Odynophagia should be considered as a form of breakthrough pain and treated accordingly [1].

In our study, five patients (5/40, 12.5%) had clinical signs of oral candidiasis. Four of them developed moderate to severe mucositis. Lalla et al. reported a 37.4% prevalence of oral candidiasis during RT for HNC [17], which is considerably higher than the findings in our study. This could be related to the fact that part of the standard care for our patients is to keep the oral mucosa moisturized using chamomile rinses; chamomile shows fungicidal activity against Candida albicans [36]. It might also be related to the more precise targeting of radiation as newer RT modalities, such as intensity modulated radiation therapy (IMRT), are increasingly used. The prevalence of herpetic infection is reported in the range of 23.3% to 42.8% of the HNC patients receiving CRT [19,20]. In our study, 6 patients (6/40, 15%) had clinical signs of herpes infection; all of them developed moderate to severe pain and OM. Studies report that after the administration of antifungal and antiviral medication, there was significant reduction of severe OM, pain, and xerostomia by the time RT concluded, compared to during RT/CRT [7,18,19]. Differential diagnosis of OM, candidiasis, and herpetic infection is important, as candidiasis and herpetic infection can exacerbate pain.

In this study, we were able to describe candidiasis and herpetic infection and treat them before completing the DN4 questionnaire. The presence of oral candidiasis could bias the results, because patients with candidiasis may report "burning pain" in the oral cavity [17]. Herpetic infection could also bias the results, as herpetic infection was observed to aggravate painful ulcerative OM, producing moderate or severe pain which is not related to OM [19]. Candidiasis and herpetic infection, before the completion of the DN4 questionnaire, were reported by three (3/26, 11.54%) and two (2/26, 7.69%) patients, respectively. Due to the small number of patients, we could not correlate candidiasis or herpetic infection to NP.

A limitation of this study is the small number of patients enrolled. Only a limited number of items related to NP perception could be statisti-

cally analysed. Additionally, the sample size could be too small for the generalizability of the findings. The clinical assessment of fungal and herpetic infections and the absence of cytologic smears for infection evaluation can also be considered as a limitation.

Further studies are needed, and more patients should be assessed in order to investigate the correlations between OM-induced NP and other parameters (e.g., oral hygiene, fungal and herpetic infections, treatment modalities, weight loss etc.). To our knowledge, this is the first attempt to quantify OM-induced NP during RT/CRT in HNC patients.

The prompt diagnosis and treatment of OM-associated NP is an important and largely unmet medical need in the HNC patient population.

Conflict of interests

The authors declare no conflict of interests.

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