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Nutritional, microbiological, and therapeutic factors related to mucositis in head and neck cancer patients: a cohort study

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Abstract

Purpose: **the objective was to demonstrate if treatment modality, nutritional status and oropharyngeal flora contribute to the development of mucositis in radiotherapy-treated head and neck cancer.**

Methods: **single-cohort study of patients with head and neck cancer (H&N) in which radiotherapy was indicated. Nutritional status was evaluated using SGA, BMI, and FFMI. A buccal smear was performed before radiotherapy for cultivation of bacteria and yeasts. Mucositis was evaluated using the WHO grades. Relative risk (RR) and its 95% CI were calculated.**

Results: **the study included 35 patients, 74.3% males, 63.8 (9.9) years of age, and 34.3% malnourished. The diagnoses included larynx (40.0%), oral (25.7%), and pharynx cancer (11.4%). Treatment comprised 66.0 Gy of radiation, chemotherapy (60.0%), and surgery (57.1%). Bacteria were found in 28.6%, including *Staphylococcus aureus* (8.6%) and *Escherichia coli* (8.6%). Yeasts (*Candida* spp.) were found in 35.3%. Mucositis was more frequent in patients with definitive radiotherapy [100% *vs.* 65%, p = 0.01; RR = 1.54 (CI95% 1.12 to 2.12)]. Neither SGA nor BMI or FFMI were related to the development or severity of mucositis. Positive cultures for bacteria before radiotherapy were related to severe mucositis [44.4% *vs.* 12%, p = 0.039; RR = 4.17 (CI95% 1.22 to 14.24)], but there was no relationship with the presence of yeasts. Previous surgery was not associated with the appearance of the studied strains of bacteria.**

Conclusion: **bacterial colonization of the oropharynx prior to radiotherapy may be a factor for severe mucositis in H&N patients.**

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Key words: *Radiotherapy. Head and neck cancer. Malnutrition. Mucositis. Bacteria. Yeast.*

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FACTORES NUTRICIONALES, MICROBIOLÓGICOS Y TERAPÉUTICOS RELACIONADOS CON EL DESARROLLO DE MUCOSITIS EN PACIENTES CON CÁNCER DE CABEZA Y CUELLO: UN ESTUDIO DE COHORTE

Resumen

Objetivo: **el objetivo fue demostrar si la modalidad de tratamiento, el estado nutricional y la flora orofaríngea contribuyen al desarrollo de mucositis en pacientes con cáncer de cabeza y cuello tratados con radioterapia.**

Métodos: **estudio de cohorte de pacientes con cáncer de cabeza y cuello (CyC) tratados con radioterapia. El estado nutricional se evaluó utilizando VGS, IMC e IMM. Se realizó un frotis bucal antes de la radioterapia para el cultivo de bacterias y levaduras. Se evaluó la mucositis usando los criterios de la OMS. Se calcularon el riesgo relativo (RR) y su IC del 95%.**

Resultados: **el estudio incluyó a 35 pacientes, 74,3% hombres, 63,8 (9,9) años de edad, y 34,3% desnutridos. Los tumores estaban localizados en laringe (40,0%), boca (25,7%) y faringe (11,4%). El tratamiento consistió en 66,0 Gy de radiación, quimioterapia (60,0%) y cirugía (57,1%). Se encontraron bacterias en 28,6%, incluyendo *Staphylococcus aureus* (8,6%) y *Escherichia coli* (8,6%). Se encontró *Candida* spp. en el 35,3%. La mucositis fue más frecuente en los pacientes con radioterapia radical [100% *vs.* 65%, p = 0,01; RR = 1,54 (IC95% 1,12 a 2,12)]. Ni VGS, IMC ni IMM se relacionaron con el desarrollo o la gravedad de la mucositis. Los cultivos positivos para bacterias antes de la radioterapia se relacionaron con mucositis severa [44,4% *vs.* 12%, p = 0,039; RR = 4,17 (IC95% 1,22 a 14,24)], pero no hubo ninguna relación con la presencia de levaduras. La cirugía no se asoció con la aparición de las cepas estudiadas de bacterias.**

Conclusión: **la colonización bacteriana de la orofaringe antes de la radioterapia puede ser un factor para la mucositis graves en pacientes con cáncer CyC.**

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Palabras clave: *Radioterapia. Cáncer de cabeza y cuello. Radioterapia. Mucositis. Desnutrición. Bacteria. Levadura.*

Introduction:

Radiation-induced tissue damage is a complex process in which oxidative stress, inflammation, cellular apoptosis and genetic changes are involved. The acute toxicity caused by radiotherapy (RT) may be observed during exposure, last over 1-2 months, and is caused by the loss of functional, replicating cells[1]. Factors such as radiation dose, its mode of administration, the sensitivity of organs to radiation, the volume of irradiated tissue, other treatments (e.g. chemotherapy), and certain patient characteristics (e.g. age), could influence the development of toxicity during RT.

Oral mucositis may develop in patients treated for head and neck squamous-cell cancer. This side effect is observed in more than 80% of RT-treated patients and can last for more than 5 weeks[2]. Acute radiation-induced oropharyngeal mucositis is related to the need for analgesics, generates episodes of hospitalization, deteriorates patients' quality of life, and increases resource consumption by two or threefold, depending on its severity[3]. Breaks in treatment due to mucosal toxicity lead to incomplete radiation doses, the proliferation of residual malignant cells and poor local tumor control, and may adversely affect mortality[4].

Classically, the pathogenesis of mucositis includes 4 phases: inflammation, reduced epithelium turnover, ulceration, and healing[5]. During these phases patients are at risk of malnutrition as their energy expenditure increases and 50% of them develop dysphagia, factors that promote an energy deficit and significant weight loss [6,7,8,9]. Bacterial overgrowth over ulcerative lesions has been suggested as a pathogenic factor, as microflora of the oral cavity can produce substances which contribute to inflammation and cause sepsis by breaking the epithelial barrier[10]. Different treatments, which act via different mechanisms, have been evaluated for the prevention of radiotherapy-induced mucosal toxicity, including cytoprotectors (aminofostine), topical anti-inflammatories (benzydamine), glutamine, and others (honey, ice chips, n-3 fatty acids)[11,12,13,14]. Nevertheless, none of them has been proved to be clearly useful. The aim of this study was to identify which therapeutic, nutritional and microbiological factors influence the development and severity of oral mucositis in head and neck cancer patients undergoing radiotherapy. The hypothesis was that the oral microflora before RT influences both the development and severity of oropharyngeal mucositis.

Patients and methods:

A single-cohort study was designed to demonstrate if oropharyngeal flora, nutritional status, and treatment modality contribute to the development of mucositis in RT-treated head and neck cancer. The study was evaluated by the local Research Ethics Committee, which confirmed that the study conformed to the ethical and legal standards required for biomedical research according to the Declaration of Helsinki.

Patients >18 years for whom RT was planned because of head and neck cancer, regardless of other cancer treatments (surgery, chemotherapy), were considered suitable for the study. Recruitment was made in a consecutive manner among patients referred to the Clinical Nutrition and Dietetics Unit for nutritional support during cancer therapy. Inclusion criteria included: diagnosis of head and neck cancer and indication of RT, independent of other treatment modalities (chemotherapy, surgery). Exclusion criteria comprised age < 18 years, impossibility of obtaining buccal smear, current antibiotic therapy, RT in progress at the moment of recruitment, and inability to understand the provided information.

Patients were assessed at three different moments during the study: before RT (recruitment), in the midst of the RT period, and after finishing RT. They were asked about the appearance of symptoms and the oropharynx was thoroughly explored. Mucositis was classified according to the World Health Organization (WHO) criteria: grade 0 (no symptoms or signs), grade 1 (soreness, erythema), grade 2 (erythema, ulcers, patient can swallow solid food), grade 3 (ulcers with extensive erythema, patient cannot swallow food), and grade 4 (mucositis to the extent that alimentation is not possible). Severe mucositis included cases of grades 3-4. A buccal smear was obtained before the beginning of radiotherapy. Culture (bacteria and yeasts) and identification of different isolates were recovered from clinical samples using phenotypic methods. The organisms were recovered from blood, chocolate, mannitol, MacConkey and Saboureaud-chloranphenicol agar plates (bioMérieux, France) after 24-72 h of aerobic incubation at 35-37ºC. For identification were used panels MicroScan TM (Siemens Healthcare Diagnostic, USA) and API ID 32C TM (bioMérieux, France).

Nutritional status was evaluated at each of the 3 visits using the Subjective Global Assessment (SGA) and anthropometry. This included the measurement of height and body weight, body mass index (BMI), dynamometry (Smedlay's Dynamo Meter©), and the determination of fat-free mass (FFM) and fat mass (FM) by bioelectrical impedance (Tanita Body Composition Analyzer TBF-300©). The Fat-Free Mass Index (FFMI) was calculated by dividing an individual's fat-free mass by the square of their height (kg/m^2). BMI was considered low when <20 kg/m^2, and sarcopenia was diagnosed if FFMI was <18.2 kg/m^2 for men and <15 kg/m^2 for women[15].

The normality of quantitative variables was assessed using the Kolmogorov-Smirnov test. Those variables with a normal distribution were summarized as the mean and standard deviation (SD) and compared using the paired Student's *t*-test. Quantitative variables without a normal distribution were summarized

by the median (Md) and interquartile range (IQR) and compared using Mann-Whitney's U-test. Categorical variables were summarized as percentages and compared using the χ^2 test. Relative risk (RR) and its confidence interval of 95% were also calculated (CI 95%).

Results:

A sample of 35 patients was recruited for the study, and their characteristics are summarized in table I. Regarding nutritional status, 34.3% (12/35) were malnourished according to SGA, 10 with severe malnutrition (SGA-C) and 2 with moderate malnourishment (SGA-B). Eighty percent (28/35) of patients developed oropharyngeal mucositis: 17.9% (5/27) grade 1, 53.5% (15/27) grade 2, and 28.6% (8/27) grade 3; none presented grade 4 mucositis. There were no differences in this toxicity according to sex (females 100.0% vs. males 73.1%, p = 0.082), cancer site (pharynx 100.0% vs. oral 88.9% vs. larynx 78.6% vs. others 62.5%, p = 0.393), tumour stage (stage II 100.0% vs. stage III 87.5% vs. stage IV 73.9%, p = 0.541), nor there were differences in age between those who developed mucositis and those without it [62.8 (9.8) yr vs. 67.8 (10.6) yr, p = 0.250).

Table I.
Patient characteristics

Sex (male/females)	26/9
Age (yr)	63.8 (9.9)
Diagnosis	
Larynx cancer	40.0% (14/35)
Oral cavity cancer	25.7% (9/35)
Pharynx cancer	11.4% (4/35)
Others	22.9% (8/35)
Tumor stage	
I	0% (0/35)
II	6.1% (2/35)
III	24.2% (8/35)
IV	69.7% (25/35)
Treatment	
Radiation dose (Gy)*	66.0 (0.0)
Chemotherapy	60.0% (21/35)
Previous surgery	57.1% (20/35)
Anthropometry	
Usual weight (kg)	72.6 (12.7)
Current weight (kg)	67.0 (12.7)
Weight loss (%)	6.9 (1.6)
Height (cm)	163.2 (6.1)
BMI (kg/m2)	25.1 (3.9)
FFMI (kg/m2)	28.2 (1.6)
Grip strength (kg)	30.2 (9.4)

Gy: Grays; yr: Years; BMI: Body mass index: FFMI: Fat-free mass index.
* Median and interquartile range.

Bacterial colonization was found in 28.6% (10/27) of patients, and the isolated strains included *Staphylococcus aureus* (3/10), *Escherichia coli* (3/10), *Pseudomonas aeruginosa* (2/10), *Serratia spp*. (2/10), *Enterobacter cloacae* (2/10), *Citrobacter freundii* (2/10), *Klebsiella oxytoca* (1/10), and *Agrobacterium radiobacter* (1/10). In 4 cases more than 1 bacterial stain was isolated. Yeasts were cultivated in 35.3% (12/35) of patients: 11 samples corresponded to *Candida albicans*, and 1 sample to *Candida tropicalis*.

There were no differences in bacterial colonization according to sex (females 11.1% vs. males 34.6%, p = 0.179), cancer site (pharynx 28.6% vs. oral 44.4% vs. larynx 25.0% vs. others 12.5%, p = 0.542), tumour stage (stage II 50.0% vs. stage III 25.0% vs. stage IV 30.4%, p = 0.789), previous surgery (operated 25.0% vs. not operated 33.3%, p = 0.589), or nutritional status (malnourished 33.3% vs. well-nourished 26.1%, p = 0.652). Age was similar among patients with and without bacterial colonization [65.9 (9.0) yr vs. 63.0 (10.4) yr, p = 0.446). Regarding yeast colonization, there were no differences in sex (females 44.4% vs. males 32.0%, p = 0.503), cancer site (pharynx 23.1% vs. oral 33.3% vs. larynx 50.0% vs. others 50.0%, p = 0.572), tumour stage (stage II 0.0% vs. stage III 14.3% vs. stage IV 39.1%, p = 0.285), previous surgery (operated 40.0% vs. not operated 28.6%, p = 0.493), nutritional status (malnourished 16.7% vs. well-nourished 45.5%, p = 0.093), and age [colonized 65.6 (10.6) yr vs. not colonized 62.3 (9.6) yr, p = 0.359).

Treatment factors related to mucositis.

Patients with mucositis received the same dose of radiation as patients without it [Md = 66.0 (IQR = 10.0) Gy vs. Md = 66.0 (IQR = 6.0) Gy, p = 0.856]. Mucositis was equally frequent among patients who received chemotherapy and among those without it (81.0% vs. 78.6%, p = 0.863), so chemo-radiotherapy was not associated with an increased risk of either mucositis [RR = 1.16 (CI 95% 0.22 to 6.21)] or severe mucositis [RR = 0.53 (CI 95% 0.25 to 1.14)]. Mucositis was more frequent with radical than with adjuvant RT (100.0% vs. 65.0%, p = 0.01), and there was a significant increase in the risk [RR = 1.54 (CI 95% 1.12 to 2.12)]. Patients in whom radical RT was indicated received a significantly greater dose of radiation [70.0 (6.0) Gy vs. 66.0 (6) Gy, p = 0.025] and chemotherapy was more frequently indicated (80.0% vs. 45.0%, p = 0.036).

Nutritional factors related to mucositis.

Patients who developed oropharingeal mucositis had similar anthropometric parameters as those without mucositis before initiating RT (table 2). There were no differences in the presence of mucositis re-

Table II.
Basal anthropometry according to radiation-induced mucositis.

	Mucositis	No mucositis	p
Previous weight loss (%)	6.7 (9.9)	7.8 (8.3)	0.786
BMI (kg/m2)	25.2 (4.2)	24.6 (3.1)	0.721
FFMI (kg/m2)	18.2 (1.7)	18.4 (1.6)	0.811
Grip strength (kg)	30.2 (9.8)	30.2 (8.5)	0.988

BMI: Body mass index: FFMI: Fat-free mass index.

garding nutritional status according to SGA [malnourished 75.0% vs. well-nourished 82.6%, p = 0.593; RR = 0.63 (CI 95% 0.12 to 3.44)], BMI [low BMI 75.0% vs. normal BMI 80.0%, p = 0.816; RR = 0.75 (CI 95% 0.07 to 8.55)], or sarcopenia [low FFMI 70.0% vs. normal FFMI 81.8%, p = 0.454; RR = 0.79 (CI 95% 0.40 to 1.58)]. None of these factors were related to severe mucositis.

Microbiological colonization and mucositis.

Neither bacterial [positive 90.0% vs. negative 76.0%, p = 0.350; RR = 1.26 (CI 95% 0.85 to 1.88)] nor yeast [positive 75.0% vs. negative 81.8%, p = 0.638; RR = 0.86 (CI 95% 0.43 to 1.72)] colonization were associated with mucositis. Nevertheless, bacterial [positive 50.0% vs. negative 12.0%, p = 0.016; RR = 4.17 (CI 95% 1.22 to 14.24)] but not yeast colonization prior to RT [positive 16.7% vs. negative 27.3%, p = 0.486; RR = 0.61 (CI 95% 0.15 to 2.57)] was related to severe mucositis.

Discussion:

The identification of risk factors for mucositis, especially for the more severe grades of this toxicity, can facilitate the detection of higher risk patients and provide a specific care plan for them during RT. According to the presented results, radical RT is associated with the development of mucositis, and bacterial colonization prior to treatment with severe mucositis. Radical RT required the administration of a greater dose of radiation and chemotherapy was more often administered, so mucosal damage was expected.

This study highlights the role of basal microflora in the severity of mucositis. Some factors, like oral hygiene, dental care, dental appliances, the existence of previous oral lesions, xerostomia, and neutropenia may influence the duration and severity of mucositis[16,17,18]. Neutropenia changes oral microflora, promoting significant growth of gram-negative enteric bacilli, *Neisseria* spp., and *Veillonella* spp.[19]. Xerostomia is a common side effect of RT that has been related to significant changes in oral microflora, which can be observed months after the completion of treatment[20,21]. In these studies *Staphylococcus aureus* was rarely isolated, but it was the most frequently cultured in the present study. Although there were no anaerobes in the studied samples, other studies have found them in more than 40% of patients before RT[22]. This wide variability in microbiota could be explained by factors like hygienic habits, dietary patterns, or the consumption of tobacco, but, according to the aforementioned results, it does not seem related to sex, age, tumour stage, cancer site, or previous surgery.

The results obtained in different trials support the role of microflora in the pathogenesis of mucositis. Intensive oral hygiene has been related to a lower incidence of mucositis in parallel with a significant reduction in the cultivation of opportunistic pathogens[23]. Antibiotic lozenges during RT have been associated with reductions in colonization by pathogens like *Candida* spp. and aerobic gram negatives, reductions in mucositis severity and duration, fewer patients needing tube feeding and lower weight loss. Although the incidence of mucositis was similar between groups, these nutritional outcomes can be considered surrogate markers of less severe mucositis[24,25,26]. These lozenges contained a mixture of polymyxin E sulphate, tobramycin and amphotericin B. The efficacy of oral mouthwashes in preventing mucositis has also been evaluated in a systematic review that grouped together 7 trials in which chlorhexidine, chamomile or iodine solution were tested. The meta-analysis of 5 trials showed that chlorhexidine was not associated with a reduction in mucositis, in spite of its broad-spectrum antibacterial activity. A small study found that patients using iodine solution had less severe mucositis and its duration was shorter, and yet another study did not find advantages with the use of chamomile[27].

Malnutrition is common in oncology patients and negatively influences survival. Body composition, especially sarcopenia, can also influence outcomes. Thus, sarcopenia has been related to shorter survival and chemotherapy-induced toxicity, and sarcopenic obesity is probably the worst scenario for cancer patients[28,29]. The greater incidence of toxicity in patients with less muscle mass may be related to chemotherapy dosage, due to the poor relationship between body surface area and fat-free mass, and distribution, due

to the differences in water content of muscle and fat. In patients with radiotherapy-treated head and neck cancer, severe weight loss before treatment predicts a shorter survival, independent of other factors[30]. Furthermore, weight loss during RT is related to a deterioration of quality of life[31]. Nutritional status has been related to the risk of severe mucositis as well. A study including 21 head and neck cancer patients undergoing RT found that grade 3 mucositis was more frequent among patients with baseline BMI <25 kg/m^2 and mid-arm circumference <30 cm[32]. These results were not confirmed in the current study, in spite of analyzing more patients and assessing nutritional status in a comprehensive way, including validated tools like SGA, body composition and functional status. None of these parameters were associated with either the development of mucositis or its severity.

Several limitations should be discussed. First, a relatively small number of patients were recruited. The small sample size impeded studying the relationships among specific strains and mucositis. Second, there is no standardized method for assessing oropharingeal microflora, and in the current study probably only the most evident potentially pathogenic microorganisms were cultured but normal flora was not assessed. Third, although bioimpedance is a widely used method for body composition analysis, there are more accurate methods like CT or DEXA, and there is a lack of population-specific cut off values for muscle mass or FFMI. Finally, factors that can influence microbiota like oral hygiene or the use of mouthwashes for mucositis were not registered.

Conclusions:

Head and neck patients undergoing radical radiotherapy are at high risk of mucositis, in relationship with the higher dose of radiotherapy and more frequent use of chemotherapy. The oropharingeal isolation of bacterial pathogens may favour the development of severe mucositis. In view of these results, a buccal smear before radiotherapy can help to detect high-risk patients, and selective oral decontamination may be a therapeutic option in order to avoid radiotherapy-induced toxicity.

Competing interest:

The authors have no conflicts of interest to declare.

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