Assessment of Hyposalivation and Xerostomia in Cancer Patients Undergoing Chemotherapy Treatment

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Avaliação da Hipossalivação e Xerostomia em Pacientes Oncológicos em Tratamento Quimioterápico

Evaluación de Hiposalivación y Xerostomía en Pacientes Oncológicos en Tratamiento de Quimioterapia

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ABSTRACT

Introduction: Oncology patients undergoing chemotherapy experience adverse effects. Hyposalivation and xerostomia in the oral cavity are reported as frequent findings resulting from this treatment. **Objective:** To investigate the occurrence of xerostomia and hyposalivation in oncology patients undergoing chemotherapy. **Method:** Quantitative cross-sectional study, with data collection carried out at "*Hospital São Vicente de Paula"* in João Pessoa, Paraíba, in the oncology sector, between August 2022 and March 2023. Patients underwent a clinical examination, followed by analysis of unstimulated salivary flow and completion of the Xerostomia Inventory instrument. Data were analyzed using descriptive and inferential statistics with the assistance of Jamovi software (version 1.8.4). **Results:** A total of 78 individuals joined the study, with a mean age of 53 years (± 12.5), predominantly females (n=63; 80.8%), and diagnosed with solid tumors (n=70; 89.7%). Hyposalivation was diagnosed in 59% of the patients (n=46), while xerostomia was reported by all individuals (n=78; 100%), categorized as mild (n=13; 16.7%) or moderate (n=65; 83.3%). There was a difference in salivary flow among patients with solid and hematological tumors, with individuals with solid tumors showing lower salivary flow (p = 0.0027, Mann-Whitney U test). Additionally, individuals with hyposalivation have an increased risk of developing moderate xerostomia (RR = 0.349; CI = 0.127 – 0.955; p = 0.006, Fisher's Exact Test). **Conclusion:** Individuals diagnosed with hyposalivation in this study have an increased risk of reporting the presence of xerostomia in moderate degrees during chemotherapy treatment.

Key words: Xerostomia/drug therapy; Saliva/drug effects; Antineoplastic agents/adverse effects.

RESUMO

Introdução: Pacientes oncológicos tratados com quimioterapia apresentam efeitos adversos. Na boca, a hipossalivação e a xerostomia são relatadas como achados frequentes oriundos desse tratamento. **Objetivo:** Investigar a ocorrência de xerostomia e hipossalivação em pacientes oncológicos em tratamento quimioterápico. **Método:** Estudo transversal quantitativo, com coleta de dados realizada no Hospital São Vicente de Paulo, em João Pessoa, Paraíba, no setor de oncologia, entre agosto de 2022 e março de 2023. Os pacientes foram submetidos a um exame clínico, seguido da análise do fluxo salivar não estimulado e do preenchimento do instrumento *Inventário de Xerostomia*. Os dados foram analisados por meio de estatística descritiva e inferencial com auxílio do *software* Jamovi (versão 1.8.4). **Resultados:** Participaram do estudo 78 indivíduos com média de idade de 53 anos (±12,5), predominantemente do sexo feminino (n=63; 80,8%) e com diagnóstico de tumores sólidos (n=70; 89,7%). A hipossalivação foi diagnosticada em 59% dos pacientes (n=46), enquanto a xerostomia foi relatada por todos os indivíduos (n=78; 100%), sendo categorizada como amena (n=13; 16,7%) ou moderada (n=65; 83,3%). Houve diferença entre o fluxo salivar de pacientes com tumores sólidos e hematológicos, sendo os indivíduos com tumores sólidos os que apresentaram menor fluxo salivar (p = 0,0027, teste U de Mann-Whitney). Além disso, pessoas com hipossalivação possuem um risco aumentado de desenvolver xerostomia moderada (RR = 0,349; IC = 0,127 – 0,955; p = 0,006, teste Exato de Fisher). **Conclusão:** Indivíduos diagnosticados com hipossalivação neste estudo possuem risco aumentado de relatar a presença da xerostomia em graus moderados durante o tratamento quimioterápico.

Palavras-chave: Xerostomia/tratamento farmacológico; Saliva/efeitos dos fármacos; Antineoplásicos/efeitos adversos.

RESUMEN

Introducción: Los pacientes oncológicos tratados con quimioterapia presentan efectos adversos. En la boca, la hiposalivación y la xerostomía se informan como hallazgos frecuentes derivados de este tratamiento. **Objetivo:** Investigar la ocurrencia de xerostomía e hiposalivación en pacientes oncológicos bajo tratamiento quimioterápico. **Método:** Estudio transversal cuantitativo, con la recopilación de datos realizada en el Hospital São Vicente de Paulo, en João Pessoa, Paraíba, en el sector de oncología, entre agosto de 2022 y marzo de 2023. Los pacientes fueron sometidos a un examen clínico, seguido del análisis del flujo salival no estimulado y el llenado del instrumento *Xerostomia Inventory*. Los datos fueron analizados mediante estadística descriptiva e inferencial con la ayuda del software Jamovi (versión 1.8.4). **Resultados:** Participaron en el estudio 78 individuos con un promedio de edad de 53 años (±12,5), predominantemente de sexo femenino (n=63; 80,8%) y con diagnóstico de tumores sólidos (n=70; 89,7%). La hiposalivación fue diagnosticada en el 59% de los pacientes (n=46), mientras que la xerostomía fue informada por todos los individuos (n=78; 100%), categorizándose como leve (n=13; 16,7%) o moderada (n=65; 83,3%). Hubo diferencia entre el flujo salival de pacientes con tumores sólidos y hematológicos, siendo los individuos con tumores sólidos los que presentaron menor flujo salival (p = 0,0027, prueba U de Mann-Whitney). Además, las personas con hiposalivación tienen un riesgo aumentado de desarrollar xerostomía moderada (RR = 0,349; IC = 0,127 – 0,955; p = 0,006, prueba Exacta de Fisher). **Conclusión:** Las personas diagnosticadas con hiposalivación en este estudio tienen un mayor riesgo de informar la presencia de xerostomía en grados moderados durante el tratamiento de quimioterapia.

Palabras clave: Xerostomía/tratamiento farmacológico; Saliva/efectos de los fármacos; Antineoplásicos/efectos adversos.

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INTRODUCTION

Cancer is an abnormal growth of malignant cells leading to uncontrolled cellular division, making the cells susceptible to multiple divisions, aggressive and eventually forming tumors[1].

It is a public health problem worldwide with high rates of global morbimortality. According to Bray et al.[2], the global results for 2022 indicate the occurrence of approximately 20 million new cases, nearly 10 million of disease-related deaths and rising numbers. Demographic estimates point out that in 2050, the annual number of new cases will reach 35 million, a 77% rise compared to 2022. According to the National Cancer Institute (INCA), 704 thousand new cases were estimated for each year of the triennium 2023-2025[3].

Isolated or combined surgeries, radiotherapy and chemotherapy are the conventional cancer treatments, being chemotherapy the most common. Antineoplastic agents include drugs as cyclophosphamide, cisplatin and oxaliplatin as polyfunctional alkylating (blocking cellular reproduction); cytarabine, methotrexate, fluorouracil, fludarabine, gemcitabine, classified as antimetabolic interfering in the patient's regular metabolism and doxorubicin, dactinomycin, daunorubicin as tumoral antibiotics[4].

Chemotherapy agents cause adverse effects as their actions do not affect neoplastic cells only, but healthy tissues as well, especially those with high rate of cellular division[5]. According to Baig[6], chemotherapy has the following side effects: anemia, alopecia, infections, increased bleeding, petechia, oral mucositis, pH imbalance on buccal environment, hyposalivation and xerostomia.

Xerostomia, known as dry mouth, can or not be associated with hyposalivation, a reduction of saliva production. Typically, they are acute, but transitory effects of chemotherapy treatment, reversing after its end[7].

On its turn, hyposalivation is characterized by the reduction of salivary flow, can be identified clinically or through observation of signs on the oral mucosa, mainly caused by the use of medications[4].

Produced by salivary glands, saliva is a crucial biological fluid formed by water, electrolytes, proteins and carbohydrates chains, responsible for the maintenance of the buccal pH, playing a key role in the prevention of buccal problems[8,9]. In addition, it has properties as lubrication, facilitates taste, digestion and mastication, antimicrobial action and effective buffer against acid food, inhibiting demineralization of teeth and protecting from caries[10].

The volume of salivary production is approximately 1ml/min, reaching between 1,000 and 1,500 ml per day secreted regularly by the endocrine and autonomous nervous system[11].

Insufficient salivary function can cause negative impacts on inpatients, being susceptible to periodontal disease, caries, dental calculus and pain[9].

Sialometry is one of the diagnosis tests of hyposalivation which allows to identify the reduction of salivary flow, while xerostomia, a chronic and subjective condition is diagnosed by means of questionnaires applied directly to the patient[12].

Cancer treatment-related hyposalivation and xerostomia demand attention, emphasizing the importance of identification and observation of buccal manifestation in patients submitted to chemotherapy[4].

Due to the relevance of saliva and its impact on patients in chemotherapy treatment, it is essential to recognize buccal problems that can negatively influence the systemic condition, increasing the necessity of hospitalization. The objective is to analyze the occurrence of hyposalivation and xerostomia in patients submitted to chemotherapy and identify associated factors.

METHOD

Cross-sectional, observational, quantitative study carried out at the "*Hospital São Vicente de Paulo (HSVP)*" in João Pessoa, Paraíba, Brazil following the hypothetical-deductive method and statistic-comparative procedures. Direct observation technique was adopted through the application of an instrument to identify xerostomia and saliva collection to analyze the salivary flow.

Patients in chemotherapy treatment between August 2022 and March 2023 were enrolled in the study sample. The prevalence of xerostomia (n=30) and salivary flow for this population (0.33± 0.16) were utilized to determine the sample size as described in a previous study[13]. The final sample included 78 patients with significance of 0.05, confidence interval of 95% and Z score of 1.96.

The eligibility criteria of the study were: patients of both sexes, aged 18 years or older, diagnosed with cancer in chemotherapy treatment alone. The exclusion criteria were smokers, alcohol users, pregnant and breast-feeding women with history of radiotherapy and those with syndrome of Sjögren or other known xerostomia-induced systemic disease as rheumatoid arthritis, knotty polyarthritis, systemic sclerosis or erythematous lupus.

The study procedures complied with the ethical guidelines of the Declaration of Helsinki and Directives 466/2012[14] and 510/2016[15] of the National Health Council for researches with human beings. The Coordination of Studies and Researches of HSVP concurred with the study which was approved by the Institutional Review

Board of "*Centro Universitário Uniesp*" report number 5.620.924 (CAAE (submission for ethical review: 62879722.8.0000.5184). Data collection was initiated soon after the ethical approval.

Data collection occurred in the chemotherapy room of HSVP when the patients were approached and invited to join the study, but before, they were briefed about the objectives of the study and any doubt was clarified. Those who agreed to join, signed the Informed Consent Form (ICF).

After signing the ICF, saliva was collected utilizing the technique of sialometry with unstimulated salivary flow always at the same time, respecting the circadian cycle of salivary flow to keep the consistency of the results.

The patients were guided to remain seated comfortably with the head inclined forward at an angle of 90°, with the mouth shut, not speaking, moving the tongue or swallowing during one minute and depositing the saliva in a recipient, repeating this action each one minute for five minutes. The amount of saliva and foam in milliliters (ml) was evaluated and some drops of simethicone (three to five drops, depending on the foam volume) were added to a collection cup to precipitate the foam and convert in saliva. With a disposable hypodermal syringe, saliva was removed from the collection cup, the amount was divided by the time of collection, resulting in the salivary flow at rest in milliliter per minute (mL/min). The diagnosis of hyposalivation was concluded when unstimulated salivary flows rate reached ≤ 0.1 mL/min (value for the patient at rest)[13].

Later, the participants were submitted to a simple clinical evaluation of oral health with a mirror and exploration probe. Next, they responded to the original version of the Inventory of Xerostomia by Thonson et al.[16], validated to Portuguese by Mata et al.[17], with 11 objective questions to reflect the perception of xerostomia. The medical charts were the source of the primary tumor location, medication utilized and current chemotherapy cycles, in addition to sociodemographics.

The data collected were tabulated in Excel and analyzed by descriptive and inferential statistic with the software Jamovi[18] (version 1.8.4). Prior to the tests, normality tests were applied and the results determined parametric or non-parametric statistics. Level of significance of 5% with confidence interval of 95% and at least 80% of statistical power were considered.

RESULTS

The sample consisted in 78 patients with mean age of 53 years (± 12.5), predominantly females (n=63; 80.8%), all of them diagnosed with cancer and in chemotherapy treatment.

The majority had solid tumors (n=70; 89.7%) and only 10.3% (n=08) were hematologic neoplasms. Breast cancer was the most incident malignant tumor (n=46; 59.0%).

Chemotherapy protocols varied according to the use of 36 drugs. The most frequent combination utilized was doxorubicin associated with cyclophosphamide (n=10; 12.8%), widely utilized for breast cancer.

The current analysis of salivary disorders revealed that most of the patients (n=46; 59%) who presented salivary flow below normal (≤0.1mL/min) were diagnosed with hyposalivation during chemotherapy treatment. In addition, all the patients (n=78; 100.0%) claimed they had some level of xerostomia post-chemotherapy: 83.3% (n=65), moderate and 16.7%, mild (n=13) (Table 1).

Salivary flow varied according to the type of patients' tumor, being found difference between the two groups (p = 0.027; Mann-Whitney U test). In patients with solid tumors, the mean of salivary flow was 0.542mL/min, but for patients with hematologic tumors, the mean of salivary flow was 1.16 mL/min, indicating that individuals with solid tumors were the most affected by hyposalivation during chemotherapy treatment (Graph 1).

Difference between the salivary flow of patients who reported mild or moderate xerostomia (p < 0.001; Mann-Whitney U test) was found. Individuals reporting moderate xerostomia presented lower salivary flow than patients reporting mild xerostomia (Graph 2).

It was possible to infer that the individuals diagnosed with hyposalivation in the present study have increased risk of reporting moderate xerostomia during chemotherapy treatment (RR = 0.349; CI = 0.127 – 0.955; p = 0.006) (Table 2).

DISCUSSION

The epidemiological characteristics found in the present study concur with the Brazilian scenario. According to Santos et al.[19], new cases of cancer occur more in females, being breast cancer the most incident, as concluded herein when sex and primary tumor location are analyzed.

As a consequence, the most common chemotherapy protocol for breast cancer treatment was the combination doxorubicin + cyclophosphamide, widely utilized for this type of cancer and followed by taxane[20], similar to what was found in the present study, but ranked second as the most frequent protocol utilized.

Chemotherapy medications can cause salivary changes. Primary studies listed in a systematic review[21] investigated the biochemical and histological effects of anti-tumor drugs in salivary glands. Anticancer treatments can induce cellular death through oxidative

Table 1. Descriptive data of oncologic inpatients (n=78). João Pessoa-PB, Brazil, 2023

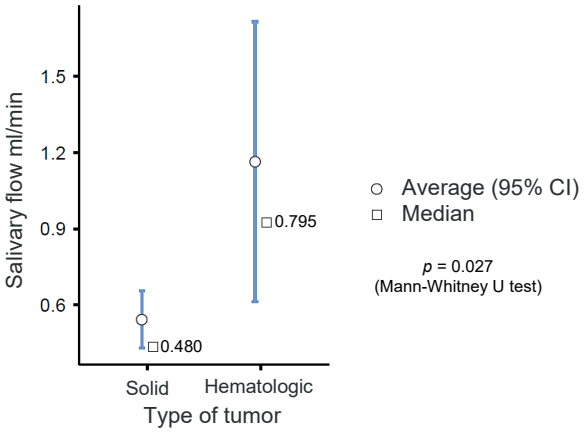
Characterization of the sample	
Age (years)	53 (±12.5)
Sex	Female – 63 (80.8%) Male – 15 (19.2%)
Type of tumor	Solid – 70 (89.7%) Hematologic – 08 (10.3%)
Primary location of the tumor	Breast – 46 (59.0%) Hodgkin Lymphoma – 05 (6.4%) Ovary – 03 (3.8%) Gastric – 02 (2.6%) Uterus – 02 (2.6%) Stomach – 02 (2.6%) Rectum – 02 (2.6%) Myeloma – 02 (2.6%) Intestine – 02 (2.6%) Maxillary sinus – 01 (1.3%) Mouth – 01 (1.3%) Sigmoid – 01 (1.3%) Leukemia – 01 (1.3%) Liver – 01 (1.3%) Lung – 01 (1.3%) Neuroendocrine carcinoma – 01 (1.3%) Pancreas – 01 (1.3%) Colon – 01 (1.3%) Endometrium – 01 (1.3%) Prostate – 01 (1.3%)
Chemotherapy Protocols	
Doxorubicin+cyclophosphamide	10 (12.8%)
Doxorubicin+cyclophosphamide+paclitaxel	06 (7.7%)
Trastuzumab	06 (7.7%)
Adriamycin+bleomycin+vinblastine+dacarbazine	04 (5.1%)
Paclitaxel	03 (3.8%)
Taxol	03 (3.8%)
Carboplatin +paclitaxel	02 (2.6%)
Docetaxel+herceptin+perjeta	02 (2.6%)
Cisplatin	02 (2.6%)
Paclitaxel+herceptin	02 (2.6%)
Cisplatin+irinotecan	02 (2.6%)
Gemcitabine	02 (2.6%)
Cisplatin+gencitabine	02 (2.6%)
Calcium folinate+fluorouracil	02 (2.6%)
Bortezomib+cyclophosphamide+dexamethasone	02 (2.6%)
Carboplatin+Taxol	02 (2.6%)
Docetaxel+cyclophosphamide	02 (2.6%)
Capecitabine+oxaliplatin	01 (1.3%)
Cisplatin+vinorelbine	01 (1.3%)
Gemcitabine+cisplatin+docetaxel	01 (1.3%)
Pregabalin+cyclophosphamide	01 (1.3%)
Avastin+gencitabine+carboplastin+diphenydramine+cortisone+allegra	01 (1.3%)
Brasart+paclitaxel	01 (1.3%)
Carboplatin+docetaxel+herceptin+perjeta	01 (1.3%)

to be continued

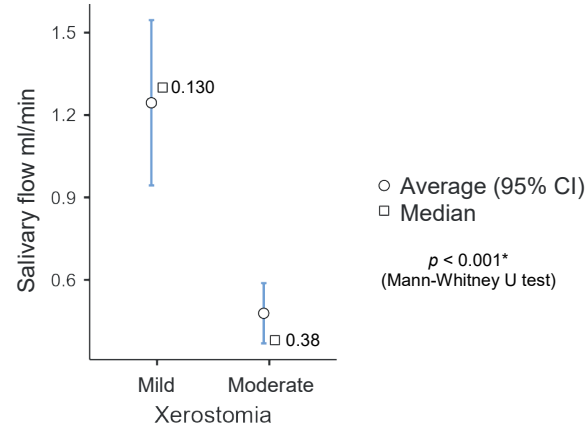
Table1. continuation

Fluorouracil+methotrexate+cyclophosphamide	01 (1.3%)
Rituximab+fludarabin+cyclophosphamide	01 (1.3%)
Gencitabine+vinorelbine+ifosfamide	01 (1.3%)
Avastin+irinotecan+fluorouracil	01 (1.3%)
Paclitaxel+trastuzumab	01 (1.3%)
Paclitaxel+trastuzumab	01 (1.3%)
Salivary changes	
Xerostomia	Mild – 13 (16.7%) Moderate – 65 (83.3%)
Hyposalivation	Present – 46 (59.0%) Absent – 32 (41.0%)

Note: Numerical variables: mean (standard deviation); median (percentile 25; percentile 75); nominal variables: n (%)



Graph 1. Difference of salivary flow of patients with solid and hematologic tumors (n=78). João Pessoa-PB, Brazil, 2023



Graph 2. Difference of salivary flow according to the inventory of xerostomia (n=78). João Pessoa-PB, Brazil, 2023

stress, triggering the formation of reactive oxygen species and resulting in apoptosis of cells producing saliva. For instance, cyclophosphamide, an immunosuppressor utilized for cancer treatment, affects salivary glands, causing xerostomia because of the reduction of saliva with persistent effects and 5-fluorouracil, for solid tumors, also induces the atrophy of salivary glands and xerostomia, associated with oxidative stress[21].

Therefore, it is suggested that hyposalivation in most of the patients investigated and xerostomia, reported by all the patients submitted to chemotherapy in the present study are explained by drug-related biochemical events resulting in death of glandular and myoepithelial cells and those of the ductal system, implying in reduced daily production of saliva and unpleasant symptom of dry mouth.

This symptom becomes more prevalent as the treatment advances according to Acharya et al.[22] which followed the evolution of salivary damages in women with breast cancer in chemotherapy treatment during 16 months. A significant decline of the mean flow of their salivary glands and increase of the viscosity of the saliva in the course of the treatment have been noticed; the patients reported xerostomia concomitant with the reduction of the salivary flow, which corroborates the findings herein where patients with hyposalivation presented increased risk of developing moderate levels of xerostomia (RR = 0.349; CI = 0.127 – 0.955; p = 0.006).

One of the factors explaining saliva thickening during chemotherapy treatment is the contribution of the

Table 2. Descriptive data of test t for samples of salivary flow. João Pessoa-PB, Brazil, 2023

Hyposalivation					
Xerostomia	Yes	No	***p***	**RR**	**CI 95%**
Mild	03	10	0.006*	0.349	0.127 – 0.955
Moderate	43	22			

Captions: *< 0.05; RR = relative risk; CI = confidence interval (upper limit – lower limit).

products of major and minor salivary glands on saliva secretion. Physiologically, 96% of the salivary content is produced by major glands and only 4% by minor glands at rest. The production of the major glands increases to nearly 99% when stimulated[23]. In this setting, the biggest production occurs on submandibular (70%) and parotid glands (25%), which contain a significant amount of serous cells and secrete more fluid saliva, rich in proteins and water[24]. As a large portion of the stimulation is targeted to them, possibly the cellular damage is more severe with reduction of salivary fluidity.

It is evident, therefore, that medications against uncontrolled growth of neoplastic cells increase the production of reactive oxygen species and consequently, tissue damage to salivary glands[21], reducing salivary products, occurrence of xerostomia and clinical diagnosis of hyposalivation.

Silva et al.[25] evaluated the relation between xerostomia and quality of life associated with oral health in patients with head cancer. The results indicated high prevalence in women (85%), aged 51-70 years (40%), commonly diagnosed with head and neck cancer; all of them (100%) developed post-treatment xerostomia, demonstrating that antineoplastic therapies cause irreversible damages to salivary glands, increasing the prevalence of xerostomia and negatively impacting the oral health-related quality of life.

A systematic literature review summarized this type of negative impact on individuals submitted to antineoplastic treatment, it showed that, regardless of the treatment (chemotherapy and/or radiotherapy), the oral health of cancer patients is damaged in many ways, including salivary functions, impairing them to perform physiological stomatognathic functions[26].

The predisposition to microbial diseases as caries, stomatitis, candidiasis and angular cheilitis caused by the accumulation of biofilm on the tooth surface and mucosa are among the negative impacts and damages reported in the literature. Dental erosion due to change of salivary pH, buccal burning, dysgeusia and dysphagia that can lead to nutritional damages have been reported as well in addition to other negative impacts as sleep and speech disorders, social isolation and depression[24].

The results revealed differences among unstimulated salivary flow of patients with solid and hematologic tumors. In addition, the literature barely explains salivary dysfunctions caused by different chemotherapy protocols[27]. The disparity among patients with solid and hematological tumors may have influenced this result as the present study concluded.

Hematological tumors are more incident in children and adolescents while solid tumors affect adults mostly due to exposure to risk factors[2,3]. This difference may have been found because the present investigation did not include this population, since changes in salivary flow of individuals submitted to chemotherapy, regardless of the medication utilized are common, based in the review of the summary of primary studies[21].

Another factor influencing this result would be the low number of hematological tumors compared to solid tumors in the population living in the State of Paraíba[3], consistent with these findings because the sample was classified according to the type of tumor. It is believed that this difference is related to the sample disparity among the groups investigated.

Some limitations were noticed while the present study was being conducted as lack of data of daily water intake and performance issues of the stomatognathic activities caused by low salivary flow and feeling of dry mouth in addition to not having a control group formed by healthy patients. Based on these observations, new studies should be conducted addressing these variables; additionally, due to the wide diversity of tumors and therapeutic regimens found in the sample investigated, it was not possible to determine which drugs have more influence as risk factors for the development of these salivary conditions.

Besides contributing as primary source for other studies, and highlighting the importance of dental surveillance in reducing chemotherapy related adverse effects, the present results revealed the necessity of investigating new hypotheses on the theme, preferably by the same group who conducted the research.

It appears to be clear the relevance of the dental-surgeon in the multidisciplinary team of cancer hospitals; it is recommended the implementation of specific protocol to treat xerostomia and hyposalivation in this population during chemotherapy treatment for best control of changes arising from reduction and thickening of the salivary flow.

CONCLUSION

Cancer patients in chemotherapy treatment present hyposalivation and xerostomia, the most affected are individuals with solid tumors due to the low salivary flow when compared with individuals with hematologic tumors. In addition, individuals diagnosed with hyposalivation in the present study are more propense to report the occurrence of moderate xerostomia in the course of the chemotherapy treatment.

CONTRIBUTIONS

All the authors contributed to the study design, acquisition, analysis and interpretation of the data, wording and critical review. They approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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