UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

LETÍCIA RODRIGUES DE OLIVEIRA

IMPACTO DO PERFIL SISTÊMICO DE PACIENTES COM CÂNCER DE BOCA E OROFARINGE SOBRE AS TOXICIDADES BUCAIS INDUZIDAS PELO TRATAMENTO ONCOLÓGICO

IMPACT OF THE SYSTEMIC DISEASE PROFILE OF ORAL AND OROPHARYNGEAL CANCER PATIENTS ON ORAL TOXICITIES INDUCED BY CANCER TREATMENT

Piracicaba
2021

LETÍCIA RODRIGUES DE OLIVEIRA

IMPACTO DO PERFIL SISTÊMICO DE PACIENTES COM CÂNCER DE BOCA E OROFARINGE SOBRE AS TOXICIDADES BUCAIS INDUZIDAS PELO TRATAMENTO ONCOLÓGICO

IMPACT OF THE SYSTEMIC DISEASE PROFILE OF ORAL AND OROPHARYNGEAL CANCER PATIENTS ON ORAL TOXICITIES INDUCED BY CANCER TREATMENT

Dissertação apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Mestra em Estomatopatologia, na Área de Estomatologia.

Dissertation presented to the Piracicaba Dental School of the University of Campinas in partial fulfillment of the requirements for the degree of Master in Stomatopathology, in Stomatology area.

Orientadora: Profa. Dra. Ana Carolina Prado Ribeiro e Silva

Co-orientadora: Profa. Dra. Thaís Bianca Brandão

ESTE EXEMPLAR CORRESPONDE A VERSÃO FINAL DA DISSERTAÇÃO DE MESTRADO DEFENDIDA PELA ALUNA LETÍCIA RODRIGUES DE OLIVEIRA E ORIENTADA PELA PROFA. DRA ANA CAROLINA PRADO RIBEIRO E SILVA.

Piracicaba
2021

Ficha catalográfica
Universidade Estadual de Campinas
Biblioteca da Faculdade de Odontologia de Piracicaba
Marilene Girello - CRB 8/6159

OL4i

Oliveira, Leticia Rodrigues de, 1993-
Impacto do perfil sistêmico de pacientes com câncer de boca e orofaringe sobre as toxicidades bucais induzidas pelo tratamento oncológico / Leticia Rodrigues de Oliveira. – Piracicaba, SP : [s.n.], 2021.

Orientador: Ana Carolina Prado Ribeiro e Silva.
Coorientador: Thaís Bianca Brandão.
Dissertação (mestrado) – Universidade Estadual de Campinas, Faculdade de Odontologia de Piracicaba.

1. Assistência odontológica. 2. Neoplasias bucais. 3. Neoplasias orofaríngeas. 4. Mucosite. 5. Custos. I. Ribeiro, Ana Carolina Prado, 1981-. II. Brandão, Thaís Bianca, 1982-. III. Universidade Estadual de Campinas. Faculdade de Odontologia de Piracicaba. IV. Título.

Informações para Biblioteca Digital

Título em outro idioma: Impact of the systemic disease profile of oral and oropharyngeal cancer patients on oral toxicities induced by cancer treatment
Palavras-chave em inglês:
Dental care
Mouth neoplasms
Oropharyngeal neoplasms
Mucositis
Costs
Área de concentração: Estomatologia
Titulação: Mestra em Estomatopatologia
Banca examinadora:
Ana Carolina Prado Ribeiro e Silva [Orientador]
Luiz Alcino Monteiro Gueiros
Gustavo Nader Marta
Data de defesa: 26-07-2021
Programa de Pós-Graduação: Estomatopatologia

Identificação e informações acadêmicas do(a) aluno(a)
- ORCID do autor: https://orcid.org/0000-0002-5775-6090
- Currículo Lattes do autor: http://lattes.cnpq.br/5600857641501545

DEDICATÓRIA

Dedico este trabalho aos meus pais Vera Lúcia e Luís Carlos por serem os meus maiores exemplos de vida, por terem se esforçado tanto para que eu pudesse realizar todos os meus sonhos e por sempre me apoiarem em todas as minhas escolhas.

Ao meu irmão Gustavo, por todo o amor, carinho, ajuda e por sempre se orgulhar de mim.

Sem vocês, nada disso seria possível. Sou eternamente grata.

AGRADECIMENTOS

À Universidade Estadual de Campinas (UNICAMP), na pessoa do Magnífico Reitor, Prof. Dr. Marcelo Knobel.

À Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas (FOP-UNICAMP), na pessoa de seu Diretor, Prof. Dr. Francisco Haiter Neto e seu Diretor Associado, Prof. Dr. Flavio Henrique Baggio Aguiar.

À Profa. Dra. Karina Gonzalez Silvério Ruiz, Coordenadora Geral da Pós-graduação da Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas (FOP-UNICAMP).

Ao Coordenador do Programa de Pós-graduação em Estomatopatologia da Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas (FOP-UNICAMP), Prof. Dr. Pablo Agustin Vargas pelo apoio e atenção durante o desenvolvimento de minha dissertação de mestrado.

Ao Prof. Dr. Márcio Ajudarte Lopes, pela atenção, por todas as oportunidades concedidas e por sempre estar disposto a ensinar.

Ao Prof. Dr. Alan Roger dos Santos Silva por todo o cuidado, atenção, oportunidades concedidas, ensinamentos e por ter permitido que eu fizesse parte do grupo de Revisão Sistemática.

À minha orientadora Profa. Dra. Ana Carolina Prado Ribeiro e Silva, por toda ajuda, empenho, dedicação e ensinamentos. Por sempre estar disponível e pronta para me orientar. Obrigada por ter me ensinado tanto, não apenas questões teóricas ou de manejo de pacientes, mas questões de vida também. Pode ter certeza que aprendi muita coisa com você.

À toda equipe do Serviço de Odontologia Oncológica do Instituto do Câncer do Estado de São Paulo (ICESP), na pessoa da coordenadora Dra. Thaís Bianca Brandão, pela agradável convivência durante todo o período em que desenvolvi meu projeto de pesquisa no hospital.

Aos meus amigos de pós-graduação Carolina, Elisa e Natália – obrigada pelas conversas, risadas e por toda ajuda neste período. Vocês fizeram tudo ficar mais leve.

Aos pacientes. Obrigada por terem aceitado participar desta pesquisa. Vocês me ensinaram muito todos os dias.

Aos meus pais e irmão. Todo o agradecimento do mundo não seria suficiente.

Aos meus avós. Agradeço por terem me educado e me ensinado tanta coisa.

Agradeço à Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Financiamento 001.

AGRADECIMENTOS ESPECIAIS

Agradeço imensamente minha mãe Vera e meu pai Luís por terem me ensinado que, com muita dedicação e esforço, somos capazes de conquistar tudo aquilo que almejamos. Lembro de um livro do Franjinha que meus pais me deram quando pequena. Contava o dia a dia de cientista dele. Não me recordo muito bem ao certo como, mas foi neste período e por conta deste livro que descobri que em algum momento da minha vida eu faria um mestrado. Na época não sabia ao menos o significado daquilo, mas havia tornado meu objetivo de vida. E toda essa trajetória até aqui, desde a escola, faculdade, residência, e a realização de um sonho de criança, o de fazer o mestrado, não teria sido possível sem o apoio deles que sempre fizeram o possível e impossível por mim.

Agradeço também ao meu irmão, que sempre me apoia em todas as minhas aventuras.

As minhas avós, Maria e Luiza, obrigada por terem me educado e me ensinado valores importantes que carregarei comigo pelo resto da vida.

RESUMO

Esta dissertação de mestrado contemplou dois estudos distintos envolvendo pacientes oncológicos. O primeiro estudo caracterizou o perfil pacientes diagnosticados com câncer de boca e orofaringe com necessidades odontológicas previamente ao tratamento oncológico, de acordo com suas comorbidades relatadas e exames laboratoriais solicitados. As comorbidades pré-existentes, medicações em uso, alterações laboratoriais e as toxicidades em região de cabeça e pescoço decorrentes do tratamento oncológico foram correlacionadas. Foram avaliados 110 pacientes dentados atendidos no Serviço de Odontologia Oncológica do ICESP durante o período de novembro de 2019 a dezembro de 2020. Os resultados mostraram que as principais comorbidades relatadas foram hipertensão arterial sistêmica, dislipidemia e diabetes, ao passo que os principais exames laboratoriais que se mostraram alterados foram proteína C reativa, hemoglobina, gama-glutamil transferase, 25-hidroxivitamina D, neutrófilos e glicose. As toxicidades em região de cabeça e pescoço durante o tratamento oncológico foram progressivas independente da modalidade de radioterapia. Houve uma correlação positiva entre o número de medicamentos em uso e mucosite oral (0,268) e uma correlação negativa entre o número de medicamentos em uso e os desfechos de disgeusia (- 0,257). Não houve correlação entre o número de comorbidades diagnosticadas e toxicidades. Exames de ureia e creatinina alterados, moradia e renda familiar podem ser considerados preditores clínicos de mucosite oral importantes; assim como o diagnóstico de sífilis e HIV podem predispor a candidíase oral. O presente estudo demostrou que embora os pacientes com câncer de boca e orofaringe apresentam comorbidades pré-existentes e um amplo espectro de alterações nos resultados dos exames laboratoriais, não houve impacto no tratamento odontológico. Não foram observadas complicações decorrentes do tratamento odontológico. Desta forma, entendemos que o cirurgião-dentista clínico geral é apto a realizar procedimentos em pacientes diagnosticados com câncer de boca e orofaringe previamente ao tratamento oncológico de forma segura. O segundo artigo apresentado nesta dissertação se trata de uma revisão sistemática que teve como objetivo avaliar os custos diretos associados ao tratamento da mucosite em diversas modalidades terapêuticas do câncer. Após uma busca nas bases de dados Scopus, MEDLINE / PubMed e Embase, um total de 37 estudos relevantes foram incluídos e analisados por meio de ferramentas recomendadas pelo guia PRISMA. A mucosite está associada ao aumento do uso de recursos, maior número de consultas, hospitalizações prolongadas e toxicidade econômica para os pacientes e serviços de saúde, atingindo valores que podem chegar a 299.214,14 dólares americanos.

Palavras-chaves: assistência odontológica, câncer de boca, câncer da orofaringe, radioterapia, mucosite, custos.

ABSTRACT

This master's dissertation included two distinct studies involving oncologic patients. The first study characterized through laboratory tests as systemic medical changes in patients diagnosed with oropharyngeal squamous cell carcinoma (OOPSCC) with dental needs prior to cancer treatment and how it correlated with pre-existing comorbidities, medication in use and treatment-related head and neck toxicities. A total of 110 OOPSCC patients that were also dentate and referred for dental treatment and evaluation at the Oncology Dentistry Service of ICESP from November 2019 and December 2020 were included in this study. The most common comorbidities reported were hypertension, followed by dyslipidemia and diabetes, while the six most abnormal test results were C-reactive protein, hemoglobin, gamma-glutamyl transferase, 25-Hydroxy Vitamin D, neutrophil, and glucose. Head and neck toxicities reported throughout cancer treatment were progressive regardless of the radiotherapy modality. There was a positive correlation between the number of medications in use and mucositis (0.268) and a negative correlation between the number of medications in use and dysgeusia outcomes (-0.257). There was no correlation between the number of diagnosed comorbidities and toxicities. The present study demonstrates that although patients with OOPSCC are diagnosed with previous comorbidities and a had several abnormal laboratory test results, no complications were reported following dental treatment. Thus, we understand that the general practitioner is able to safely perform dental procedures in OOPSCC patients prior to cancer treatment. Altered urea and creatinine levels, housing and family income may be important clinical predictors of oral mucositis; The diagnosis of syphilis and HIV can also be considered clinical predictors of oral candidiasis secondary to cancer treatment. The second study in this dissertation is a systematic review that aimed to evaluate and report the direct costs associated with the treatment of mucositis in different cancer therapeutic modalities. After a literature search that included the Scopus, MEDLINE / PubMed and Embase databases, a total of 37 relevant studies were included and evaluated according with the PRISMA guidelines Mucositis is associated with increased use of resources, extra consultations, hospitalizations and extended hospitalizations, and is an economic burden for patients and health services, reaching values that can go up to 299,214.14 American dollars.

Keywords: dental treatment, oral cancer, oropharyngeal cancer, radiotherapy, mucositis, costs.

SUMÁRIO

1 INTRODUÇÃO

De acordo com estimativas recentes do Global Cancer Statistics (GLOBOCAN), em 2020 cerca de 19,3 milhões de novos casos de câncer foram diagnosticados no mundo, incluindo 377.313 em cavidade oral e lábio e 98.412 em orofaringe, representando cerca de 2,5% de todos os casos de câncer.[1] No Brasil, a estimativa para 2020 foi de 15.190 novos casos, sendo 11.180 homens e 4.010 mulheres diagnosticadas.[2]

O uso prolongado de tabaco e álcool, principalmente quando associados, são os principais fatores de risco para o desenvolvimento de câncer de boca e orofaringe, mas a exposição a agentes infecciosos como o Papilomavírus Humano (HPV) também vem sendo relacionada ao desenvolvimento do câncer de orofaringe.[3,4] Na última década, houve um aumento na incidência do câncer de orofaringe associados a subtipos oncogênicos do HPV.[4,5] Pacientes diagnosticados com câncer de orofaringe, HPV positivo, geralmente se encontram na quarta década de vida, não fumantes e com histórico de exposição a múltiplos parceiros sexuais.[4,5]

O tratamento do câncer de boca e orofaringe depende de um modo geral do estadiamento clínico no momento do diagnóstico, da localização do tumor e das condições sistêmicas do paciente.[6] A cirurgia é uma das principais modalidades empregadas no tratamento do câncer de boca e orofaringe, tendo como intenção curativa a excisão cirúrgica com margens microscópicas livres da doença.[7]

A radioterapia (RDT) é a modalidade terapêutica empregada tanto para o tratamento de doenças localmente avançadas adjuvante à cirurgia ou concomitante com a quimioterapia (QT). [4] A dose de radiação empregada no tratamento varia de 60Gy a 70Gy.[4]

Embora sejam eficazes no tratamento do câncer, essas modalidades terapêuticas (cirurgia, RDT e QT) podem causar morbidades e efeitos adversos significativos tanto por danos diretos às estruturas em região de cabeça e pescoço quanto por danos indiretos da toxicidade sistêmica.[8] Os efeitos adversos possíveis em tratamento de câncer de boca e orofaringe incluem a mucosite, hipossalivação e xerostomia, disfagia, disgeusia, dor, infecções bacterianas, virais e fúngicas, cáries de radiação, trismo, osteorradionecrose, dentre outras.[9,13]

Neste contexto, o atendimento odontológico a pacientes diagnosticados com câncer de boca e orofaringe é extremamente importante e necessário, mas representa um desafio clínico ao cirurgião-dentista (CD); exige um plano de tratamento individualizado baseado principalmente no status clínico do paciente, histórico médico prévio com avaliação de comorbidades pré-existentes, diagnóstico e prognóstico oncológico, protocolo de tratamento

oncológico do paciente planejado pelas equipes médicas e, por fim, conhecimento das complicações e toxicidades orais associadas ao tratamento.[9,14,15]

A realização de um plano de tratamento odontológico no paciente com câncer de boca e orofaringe deve priorizar a remoção de focos orais (infecção de origem odontogênica ou periodontal) que possam vir a interromper ou interferir no tratamento oncológico.[4,5]

O CD na prática da odontologia contemporânea deve estar preparado para o manejo de pacientes com condições médicas complexas, devendo ter conhecimento para reduzir e evitar intercorrências, principalmente aquelas que poderiam ser previstas e prevenidas.[16]

Existem poucos estudos na literatura em que os pesquisadores solicitaram exames laboratoriais na triagem de pacientes que comparecem para atendimento no consultório odontológico. Em estudo realizado por Miller et al. (2014) que avaliou 171 pacientes que procuraram o serviço de odontologia de quatro hospitais distintos para procedimentos odontológicos de rotina, foi observado que apesar dos pacientes reportarem boa saúde geral, uma média de 2,42 exames laboratoriais se apresentaram alterados por paciente. Além disso, 83% dos pacientes avaliados desconheciam sua condição médica atual quando compareceram para o tratamento odontológico.[17]

A literatura científica pertinente endossa que cuidados bucais adequados prévios (adequação bucal) ao tratamento oncológico minimizam a gravidade e duração das toxicidades bucais. Adicionalmente, a adequação bucal, contribui significativamente para o sucesso do tratamento oncológico, evitando interrupções, melhorando a qualidade de vida dos pacientes e diminuindo os custos atrelados.[15]

A presente dissertação apresenta a caracterização, por meio de exames laboratoriais e anamnese detalhada, de 110 pacientes dentados diagnosticados com câncer de boca e orofaringe que foram atendidos no Serviço de Odontologia Oncológica do ICESP. Avaliamos as principais alterações sistêmicas encontradas previamente ao tratamento oncológico. Observamos também as toxicidades apresentadas e correlacionamos com os diagnósticos referidos, medicações em uso, e efeitos colaterais como mucosite, radiodermite, disfagia, disgeusia, xerostomia, trismo e candidose.

Além disso, por meio de uma revisão sistemática da literatura, foram avaliados os custos diretos associados ao manejo da mucosite em diversas modalidades terapêuticas do câncer, como: radioterapia, quimioradioterapia, radioterapia em associação com terapia alvo molecular, transplante de medula óssea, quimioterapia, terapia alvo molecular, terapia multimodal e terapia não especificada.

A mucosite é frequentemente associada com o aumento do uso de recursos financeiros devido à necessidade de consultas extras, visitas a serviços de emergência e internações prolongadas, culminando em um custo incremental substancial que apresenta impacto econômico adicional tanto para os planos de saúde, serviços públicos e para os próprios pacientes, atingindo valores que podem chegar a até 299.214,14 dólares americanos.

ARTIGO: SYSTEMIC DISEASE PROFILE OF PATIENTS WITH DENTAL NEEDS PRIOR TO ORAL AND OROPHARYNGEAL CANCER TREATMENT. A CROSS-SECTIONAL EXPLORATORY STUDY.

CÁPITULO 1 – Artigo será submetido para publicação no periódico Oral Oncology.

Authors: Leticia Rodrigues-Oliveira[1], DDS; César Rivera[2], DDS, MSc, PhD; Xaviera Alejandra López-Cortés[3], Engr, MSc, PhD; Milena Perez Mak[4], MD, PhD, Cesar Augusto Migliorati[5], DDS, MSc, PhD; Maria Cecília Querido de Oliveira[6], DDS, MSc; Natalia Rangel Palmier[6], DDS, MSc; Pablo Agustin Vargas[1] DDS, MSc, PhD; Thaís Bianca Brandão[6], DDS, MSc, PhD; Alan Roger Santos-Silva[1], DDS, MSc, PhD; Ana Carolina Prado-Ribeiro[1,6], DDS, MSc, PhD.

Affiliation:

(1) Oral Diagnosis Department, Piracicaba Dental School, University of Campinas (UNICAMP), Piracicaba, São Paulo, Brazil.

(2) Oral Medicine and Pathology Research Group, Faculty of Health Sciences, University of Talca (UTALCA), Talca, Maule Region, Chile.

(3) Department of Computer Sciences and Industries, Catholic University of the Maule, Talca, Chile.

(4) Medical Oncology, Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

(5) Department of Oral and Maxillofacial Diagnostic Sciences, University of Florida College of Dentistry, Gainesville, FL.

(6) Dental Oncology Service, Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Keywords: Medical History Taking, Medical Examination, Dental Care, Comorbidity, Oral Cancer, Oropharyngeal Cancer.

Corresponding Author:
Ana Carolina Prado-Ribeiro, DDS, MSc, PhD;
Dental Oncology Service, Instituto do Câncer do Estado de São Paulo (ICESP)
Address: Av. Dr. Arnaldo, 251 - Cerqueira César, São Paulo - SP, 01246-000, Brazil.
Postal code: 01246-000
e-mail: carol_pr@yahoo.com.br
Telephone: (+5519) 98831-0212

Conflict of interest statement: None to declare.

Acknowledgements: This work was supported in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

ABSTRACT

Objectives: Characterize oral and oropharyngeal squamous cell carcinoma (OOPSCC) patients with dental needs prior to cancer treatment including underlying medical conditions, and laboratory tests results. Comorbidities, sociodemographic data, medication in use, treatment-related head and neck toxicities and altered laboratory tests results were correlated. **Materials and methods:** A prospective cohort study that recruited patients diagnosed with OOPSCC, dentate, and that were referred to the Dental Oncology Service at the Instituto do Câncer do Estado de São Paulo, Brazil, for dental treatment between November 2019 and December 2020. **Results:** A total of 110 OOPSCC patients were included. The most common comorbidities reported were hypertension, dyslipidemia and diabetes, while the six most abnormal test results were C-reactive protein, hemoglobin, gamma-glutamyl transferase, 25-Hydroxy Vitamin D, neutrophil, and glucose. Head and neck toxicities reported throughout cancer treatment were progressive regardless of the radiotherapy modality. There was a positive correlation between the number of medications in use and oral mucositis (0.268) and a negative correlation between the number of medications in use and dysgeusia outcomes (-0.257). There was no correlation between the number of diagnosed comorbidities and toxicities. **Conclusions:** The results of this study suggested that although OOPSCC patients have a wide range of comorbidities and several abnormal laboratory results, dental treatment prior to cancer treatment can be safely performed. Additionally, laboratory findings including altered urea, and creatinine may be useful clinical predictors of oral mucositis. Syphilis and HIV may also be considered reliable clinical predictors of oral candidiasis secondary to OOPSCC treatment.

Keywords: Medical History Taking, Medical Examination, Dental Care, Comorbidity, Oral Cancer, Oropharyngeal Cancer.

INTRODUCTION

Dental treatment for patients diagnosed with oral cavity and oropharyngeal squamous cell carcinoma (OOPSCC) poses a challenge for dental surgeons as it requires an individualized treatment plan that is based on the patient's dental/medical history, cancer stage, oncologic treatment protocol and prognosis, and hematological, physical and nutritional status [1-3].

The dental care for OOPSCC cancer patients should be performed and completed prior to the onset of the oncologic treatment, especially for patients undergoing chemotherapy (CT) or radiotherapy (RT), and must prioritize the removal of oral foci of infection that may interrupt the cancer treatment and impair prognostic outcomes. Periodontal, restorative, endodontic and surgical procedures may be performed based on clinical and radiographic assessments [1-2, 4].

Literature supports that adequate oral care and a proper dental treatment before the oncologic treatment is associated with fewer oral and systemic infections, and it also minimizes the severity and duration of oral toxicities, such as oral mucositis, radiation caries and osteoradionecrosis, thus contributing significantly to the success of the cancer treatment, avoiding interruptions and improving the patients' quality of life [3-4].

There are several dental care protocols for patients diagnosed with OOPSCC prior to cancer treatment [1-3,5-8]; however, none of them take into consideration systemic changes and underlying medical conditions that could interfere with and change the dental management and be associated with treatment complications, including infection and bleeding. Therefore, this prospective cohort study aimed to characterize, through laboratory assessments, the possible systemic changes in OOPSCC patients with dental needs prior to cancer treatment. The comorbidities, sociodemographic data, medication in use, and laboratory changes were further correlated with the frequency and severity of the head and neck toxicities from the OOPSCC RT treatment.

METHODS

Patients

This was a prospective cohort study that recruited patients diagnosed with OOPSCC set to undergo oncologic treatment [i.e. surgery, RT, chemotherapy, or chemoradiotherapy (CRT)], over the age of 18, and that were referred to the Dental Oncology Service at the Instituto do Câncer do Estado de São Paulo (ICESP), São Paulo, Brazil for dental treatment between November 2019 and December 2020. This study's ethical approval was obtained from the National Human Research Ethics Committee (CAAE: 23671019.1.1001.5418) [**Anexo 1**]. All participants provided written informed consent. The study was conducted per the Declaration of Helsinki and performed following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [9].

Inclusion Criteria

Fully or partially dentate patients able to provide written informed consent were included in the study.

Exclusion criteria

Patients with recurrent OOPSCC that underwent a previous treatment; those who did not perform the blood tests prescribed; and cases in which patient's data were not fully available from the electronic medical record system.

All patients underwent dental procedures when indicated, including surgery, periodontal, endodontic and restorative treatment. During dental treatment conditioning protocols, patients were followed-up in order to evaluate possible treatment complications, such as infection and persistent bleeding, among others.

Sociodemographic and clinicopathological characteristics

Patients' characteristics including gender, race/ethnicity, age, habits (smoking, drinking and use of drugs), years of education, current marital status, housing status, average monthly income, medical history and medications in use were collected from standardized in-person interviews. Tumor location, cancer staging (TNM, 8th edition) [10,11], p16 status, proposed cancer treatment protocol, and the Eastern Cooperative Oncology Group (ECOG) [12] and Karnofsky performance status (KPS) [13] scores were extracted from the Institutional Electronic Medical Record System Tasy (Philips Clinical Informatics, Blumenau, Brazil).

The systemic diseases that could be associated with oral complications during or after the dental management were evaluated. At the screening appointment, it was measured height, weight, oxygen saturation levels, heart rate, blood pressure (BP) and temperature.

Anthropometric, pulse oximetry, blood pressure and body temperature measurements

Height (cm) and weight (kg) were measured using a standardized scale with a stadiometer. Subjects were asked to stand straight and barefoot and to wear light clothes when being measured. Scale and stadiometer were calibrated before use. The body mass index (BMI) was calculated as body weight divided by height squared (kg/m^2) [14].

A pulse oximeter was used to measure the oxygen saturation levels and the heart rate [15]. Blood pressure (BP) was measured using an electronic BP monitor on the right upper arm and the participants were asked to rest in a sitting position for 5 minutes before the measurement [16,17]. The body temperature was measured with a digital thermometer in the axillary region [18].

Laboratory tests

Venous blood was collected using standard methods and sent to the hospital's laboratory for a complete blood count (CBC) and a standard blood chemistry panel **(supplementary material 1).**

- CBC with differential [erythrocytes, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, erythrocyte distribution width, erythrocyte distribution width (standard deviation), erythroblasts, platelets, mean platelet volume, leukocytes, neutrophils, eosinophil, basophil, lymphocytes, and monocytes];

- Basic electrolyte panel (sodium, potassium, chloride, iron, creatinine, urea, glucose, magnesium);

- Metabolic panel [(calcium, bilirubin (total, direct, and indirect)], alkaline phosphatase, AST (aspartate aminotransferase), ALT (alanine aminotransferase, gamma-glutamyl transferase];

- Lipid panel [(total cholesterol, high-density lipoprotein (HDL), triglycerides, low-density lipoprotein (LDL), non-high-density lipoprotein (non-HDL) cholesterol, VLDL (very-low-density lipoprotein)];

- Thyroid function (TSH, T3, T4, FT4);

- Glycated hemoglobin (Hemoglobin A1C);

- Coagulation assay [prothrombin time (PT), International Normalized Ratio (INR), activated partial thromboplastin time (aPTT)];

- Human immunodeficiency virus (HIV) testing;

- Hepatitis B and C;

- 25-Hydroxy Vitamin D;

- C-reactive protein (CRP);

- Syphilis.

Treatment-related head and neck toxicities

Systemic changes and abnormal laboratory results were assessed and correlated with the treatment toxicities. Included patients were clinically assessed by a calibrated dentist at days 5, 10, 15, 20, 25, 30, and 33/35 of radiation therapy and included oral mucositis, radiodermatitis, dysgeusia and dysphagia outcomes following the Common Terminology Criteria for Adverse Events (NCI, version 4.0, 2010) [19], graded 0-4. Additionally, *Candida albicans* infection, xerostomia, and trismus were qualitatively evaluated [20].

OHIP-14

The validated Brazilian Portuguese version of the Oral Health Impact Profile (OHIP-14) questionnaire was applied to every patient at the first appointment. It comprises 14 items that that include functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap. The responses were classified using a Likert scale with five options that ranges from “never” (0) to “very often” [21,22].

Statistics analysis

Clinicopathological, sociodemographic, anthropometric, pulse oximetry, blood pressure, and temperature measurements, and OHIP-14 data were summarized using mean values and standard deviations for continuous variables, frequencies, and percentages for categorical variables. For the laboratory results, the percentage of exams not altered, mean values and standard deviation were evaluated. Pearson correlation test was used to evaluate the association between medication in use and treatment-related toxicities. All toxicities were

associated with the laboratory findings and a p value < 0.05 was considered statistically significant.

The worst oral mucositis score (separated in group 1: mucositis grades 1 and 2 and group 2: grades 3 and 4) was correlated with the full set of data (including comorbidities, laboratory results and sociodemographic data). Continuous dataset (variables in its numerical forms), discrete dataset (coded data), and a full dataset including all data were used. A biomarker analysis was performed with the following classifications: accuracy, sensitivity, specificity, positive predict value (VPP), negative predict value (VPN), and area under the ROC curve (AUC). A heat map was presented in order to evaluate the clinical predictors of mucositis.

RESULTS

Sociodemographic and clinicopathological characteristics

A total of 484 head and neck cancer patients were referred to the Dental Oncology Service for dental treatment and evaluation. Of which, 110 (22.7%) were included in this study and 368 (76%) were excluded for the following reasons: edentulism, a head and neck cancer diagnosis other than OOPSCC, a second OOPSC cancer diagnosis or for not agreeing on participating. Six (1.3%) patients were further excluded for not doing the bloodwork prescribed.

Most patients were male (n = 85; 77.3%), and ages ranged from 23 to 83 (mean 57.32) years. Most participants identified their race/ethnicity as white (n = 48; 43.6%) or brown (n = 48; 43.6%) and reported a history of tobacco (n = 94; 85.4%) and alcohol consumption (n = 94; 85.4%). The majority of participants had an education level of 4 to 7 years (n = 42; 38.2%), were married/living with a partner (n = 46; 41.8%), owned a house (n = 72; 65.4%), and the most prevailing monthly income was of 1,045 Brazilian Real (BRL) [approximately 205 United Stated Dollars (USD) - 2021 values] (n = 38; 34.5%). Fifty-four percent of patients (n=50; 54.5%) were diagnosed with oropharyngeal squamous cell carcinoma, while 45.5% had an oral

squamous cell carcinoma diagnosis. Most patients had advanced stage III/IV (n = 85; 77.3%) disease. Summaries of the sociodemographic and clinicopathological characteristics are shown in **Table 1.**

ECOG and KFS performances

Most patients (n = 72; 65.5%) scored 1 for the ECOG performance status and 56 patients (50.9%) scored 90% for the KPS scale.

Referral patterns and oncologic treatment plans

Most patients were referred for dental treatment before the start of RT (n = 80; 72.8%), 24.5% (n = 27) before surgery, and 2.7% (n = 3) during CT. Curative treatment was the most common treatment modality (n=82; 75.5%) and the most performed treatment was CRT (n=25; 30.5%) **[Table 1].**

Self-reported medical conditions and medication in use

Forty (36.4%) patients did not report having any medical conditions other than cancer, 31 (44.3%) reported having one medical condition, and 39 (55.7%) patients had two or more underlying medical conditions other than OOPSCC.

The most common comorbidity reported was hypertension (n = 36, 51.4%), followed by dyslipidemia (n = 16, 22.8%) and diabetes (n = 11, 15.7%). Five (4.5%) patients reported HIV infection, 3 (2.7%) reported being diagnosed with syphilis (2.7%) and 2 (%) with hepatitis C virus (1.8%). Five (4.5%) patients reported a previous cancer diagnosis (1 renal cancer, 2 skin cancer, and 2 Kaposi's sarcoma). Full self-reported diagnoses can be seen in **Table 2**. Fifty-one (46.4%) patients reported a daily use of prescribed medication.

Anthropometric, pulse oximetry, blood pressure and body temperature measurements

The mean [standard deviation (SD)] body mass index was 23.86 (± 5.56), mean (SD) blood pressure was 125.65 (± 25.58) x 84.46 (± 14.72) mmHg. Only 14.5% of patients presented BP measurements within the normal range. None of the body temperature measurements were abnormal or indicated fever. Mean (SD) heart rate was 81.01 (± 17.48), and mean O_2 saturation was 95.90 (2.31).

Laboratory tests

The laboratory results are summarized in **Table 3.** The six most abnormal test results were C-reactive protein (CRP) (63.6%), hemoglobin (60%), gamma-glutamyl transferase (45.5%), 25-Hydroxy Vitamin D (47.3%); neutrophil (35.5%); and glucose (34.5%). Although 3 (2.7%) patients reported a syphilis diagnosis, through laboratory tests results, 9 (8.2%) additional syphilis diagnoses were confirmed, thus a total of 12 (10.9%) diagnosis of syphilis were observed in this study. Overall, 11 (10%) of the included patients reported a systemic infectious diseases at baseline.

OHIP-14

The mean OHIP-14 score from the study population was 19.5 and ranged from 0 to 49. The worst domain reported was physical pain (4.37 out of possible 8) which evaluated pain and difficulty on eating. **Table 4** shows the full analysis outcome.

Treatment-related head and neck toxicities

Sixty three (57.3%) patients underwent full curative treatment (i.e. RT or CRT followed by previous surgery or not). Toxicities were progressive over time and were independent on the chosen RT treatment modality, intensity-modulated radiation therapy (IMRT) or 3-dimensional

(3D). There was a positive correlation between the number of medications in use and oral mucositis (0.268), and a negative correlation between the number of medications in use and dysgeusia (- 0.257) outcomes. There were no correlations between the number of diagnosed comorbidities and toxicities. Full correlation values are shown in **Table 5.**

The association of altered laboratory exam results at days 5, 10, 15, 20, 25, 30 and 33/35 of treatment-related head and neck toxicities (mucositis, disgeusia, dysphagia, xerostomia, radiodermatitis, trismus, and candidiasis) can be seen in **Table 6**. For the oral mucositis domain, T4 had significative P values ($P < 0.05$) starting at D15; calcium levels were altered at D5, D10 and D30; urea levels were altered at D25, D30, D33/35; creatinine levels were altered at D15 and D30; alkaline phosphatase levels were altered at D20 and 25; a positive syphilis diagnosis was correlated with mucositis at D15 and D30. Candidiasis was associated with syphilis and HIV at D20. **Table 6** presents the full association between altered laboratory exams and treatment-related head and neck toxicities.

The most important predictors for oral mucositis were family income and housing, both outcomes are presented in navy blue in the heat map (Figure 1).

DISCUSSION

Every OOPSCC patient should receive comprehensive oral assessment, and dental treatment before any cancer treatment. It ought start right after the cancer diagnosis, and when a surgical procedure is indicated, ideally, it should be concluded 2 to 3 weeks prior the cancer treatment to allow time for bone and soft tissue healing [2-4, 23]. In the present study, the results suggested that although OOPSCC patients have comorbidities and also several abnormal laboratory tests results, the dental treatment in these cancer population can be safely performed. It was also observed that the OOPSCC diagnosis does not pose an additional challenge for the

dentist, as treatment complications such as unexpected bleeding, or infection were not identified in the population evaluated.

By definition, comorbidity refers to disease processes that coexist and are not related to the index disease being studied [26]. Literature highlights that the frequency of comorbidities in OOPSCC patients is high compared to the general population and it is mainly associated with chronic smoking, and alcohol exposure [25,27]. A review demonstrated that approximately 60% head and neck cancer patients have concurrent illness [26]. The current study, that originally assessed a Brazilian population with advanced OOPSCC, observed 85.4% of tobacco/alcohol consumption, and a comorbidity rate of 63.6% (44.3% of the patients reported having one, while 55.7% had two or more concurrent).

The most common comorbidity reported were hypertension (51.4%), followed by dyslipidemia (22.8%) and diabetes (15.7%), which was similar to a study population of 10,524 head and neck cancer patients (3049 diagnosed with oral and 2499 diagnosed with oropharyngeal cancer) and the comorbidities most frequently encountered were hypertension (59.6%), hyperlipidemia (31.4%), chronic obstructive pulmonary disease (COPD; 26.4%), and diabetes (21.1%) [28]. It is known that comorbidities can impact the diagnosis, prognosis, survival and treatment of patients with cancer [27,29]. The presence of comorbidities not only dictates the cancer treatment modality, but it also shapes the referred dental treatment.

The most frequent laboratory pathologies were elevated C-reactive protein (CRP) values, hemoglobin, gamma-glutamyl transferase, 25-Hydroxy Vitamin D, neutrophil and glucose. A retrospective study of 261 head and neck cancer patients that evaluated pretherapeutic laboratory values also demonstrated that elevated CRP values were the most frequent laboratory anomaly (60%), but they also observed impaired liver enzymes (30-50%), leukocytosis (20%) and anemia (10%) [30]. This study suggests that these changes do not

require dental treatment modifications and may not generate complications related to invasive dental procedures.

CRP is a nonspecific inflammation marker synthesized in response to acute inflammation or destruction of tissue cells. Over-expressed CRP levels are demonstrated to be prognostic markers in various tumors including lung, lymphoma, ovary, and more recently, head and neck cancers [31,32].

Altered liver function gamma-glutamyl transferase can be explained by the chronic alcohol abuse in this population [30]; 25-Hydroxy Vitamin D monitors vitamin D levels and deficiency is highly prevalent among adults and low counts have been associated hypertension, cancer, and diabetes mellitus [32,33]; neutrophils are the most abundant leukocytes in blood and are considered to be the first line of defense during inflammation and infections, high counts are associated with poor cancer prognosis including the head and neck cancer population and low counts are associated with infection [34,35]. The high incidence of altered blood glucose concentration is associated with the high number of diabetic patients in this targeted sample.

Literature supports that general dentists may have limited experience in care of the oncology patient, and that dental professionals with experience in oncology may be required to identify and manage oral conditions and diseases in OOPSCC patients [23]. While the beforementioned may be true for patients already undergoing or that have already finished cancer treatment, dental treatment prior cancer treatment might be performed by general dentists. This professional scenario may be reinforced by the results of the current study, in which although comorbidities and laboratory changes were observed, they did not generate treatment complications that contraindicated dental treatment.

Several dental practitioners are afraid of performing dental procedures in patients diagnosed with OOPSCC before oncologic treatment, as they believe that the cancer diagnosis alone may compromise the proper dental treatment and may bring inherited treatment

complications. The current study suggests that the OOPSCC diagnosis does not bring any further complication and, instead, what is imperative to dental treatment is the underlying medical condition that may be diagnosed with specific protocols.

Head and neck cancer treatment-toxicities are frequent and may cause treatment breaks, may impair prognosis and affects the quality of life of patients [3-4]. According to our knowledge, this study is the first study to correlate laboratory changes and toxicities from the curative treatment (RT or CRT) and therefore, some correlations are not supported by the literature. However, some findings may be considered predictive of oral toxicities during the oncological treatment. This study demonstrated that urea levels were altered at D25, D30, D33/35 and creatinine at D15 and D30 of RT treatment which may be indicative of renal dysfunction, and an impairment of drug metabolism in patients undergoing CRT which could imply in a more severe mucositis [36]. Candidiasis was associated with syphilis and HIV diagnosis at D20 of the RT treatment, which can be explained by the immunosuppression these patients already have because of their diagnosis and the immunosuppression from the cancer treatment [37].

Additionally, it was found that both family income and housing were the most important predictors factors for mucositis. The beforementioned predictors may be explained in the sociodemographic context of OOPSCC patients in Brazil – a low income and low education level context can possibly impair the follow-up of recommendations regarding, for instance, drug administration for pain, oral hygiene after meals, diet (low acid foods, room temperature), which could worsen oral mucositis grades [38].

Due to the short follow-up time after diagnosis and treatment, it was not possible to carry out a direct correlation between abnormal laboratory test values and the OOPSCC prognosis and cancer treatment outcomes. The heterogenic population included, the different

treatment modalities underwent by patients in our population and some of the correlations observed are also limitations in this study.

CONCLUSIONS

The results of this study suggested that although OOPSCC patients have a wide range of comorbidities and several abnormal laboratory results, dental treatment prior to cancer treatment can be safely performed. Laboratory findings may be useful clinical predictors of oral mucositis, including altered urea, creatinine, and CRT levels. Systemic infectious diseases, such as syphilis and HIV, may also be considered reliable clinical predictors of oral candidiasis secondary to OOPSCC treatment.

REFERENCES

1. Epstein JB, Güneri P, Barasch A. Appropriate and necessary oral care for people with cancer: guidance to obtain the right oral and dental care at the right time. Support Care Cancer. 2014; 22(7): 1981-1988. doi:10.1007/s00520-014-2228-x

2. Levi LE, Lalla RV. Dental Treatment Planning for the Patient with Oral Cancer. Dent Clin North Am. 2018;62(1):121-130. doi:10.1016/j.cden.2017.08.009

3. Carvalho CG, Medeiros-Filho JB, Ferreira MC. Guide for health professionals addressing oral care for individuals in oncological treatment based on scientific evidence. Support Care Cancer. 2018;26(8):2651-2661. doi:10.1007/s00520-018-4111-7

4. Samim F, Epstein JB, Zumsteg ZS, Ho AS, Barasch A. Oral and dental health in head and neck cancer survivors. Cancers Head Neck [Internet]. 2016;1(1):1–7. Available from: http://dx.doi.org/10.1186/s41199-016-0015-8

5. Hong CHL, Hu S, Haverman T, et al. A systematic review of dental disease management in cancer patients. Support Care Cancer. 2018; 26(1): 155-174. doi:10.1007/s00520-017-3829-y

6.Brennan MT, Woo SB, Lockhart PB. Dental treatment planning and management in the patient who has cancer. Dent Clin North Am. 2008;52(1):19-vii. doi:10.1016/j.cden.2007.10.003

7. Jham BC, Reis PM, Miranda EL, et al. Oral health status of 207 head and neck cancer patients before, during and after radiotherapy. Clin Oral Investig. 2008;12(1):19-24. doi:10.1007/s00784-007-0149-5

8.Tsuji K, Shibuya Y, Akashi M, et al. Prospective study of dental intervention for hematopoietic malignancy. J Dent Res. 2015;94(2):289-296. doi:10.1177/0022034514561768

9. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-349. doi:10.1016/j.jclinepi.2007.11.008

10. Brierley J, Gospodarowicz M, Wittekind C. UICC TNM classification of malignant tumours. Eighth ed. Chichester: Wiley; 2017.

11. Amin M, Edge S, Greene F, et al. AJCC cancer staging manual. Eighth ed. New York: Springer; 2017.

12. Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. Journal of Chronic Diseases; 1960:11:7-33.

13. Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.

14. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a World Health Organization Consultation. Geneva: World Health Organization, 2000. p. 256. WHO Obesity Technical Report Series, n. 284.

15. Chan ED, Chan MM, Chan MM. Pulse oximetry: understanding its basic principles facilitates appreciation of its limitations. Respir Med. 2013;107(6):789-99.

16. Oliveira GMM, Mendes M, Malachias MVB, Morais J, Moreira Filho O, Coelho O, et al. Diretrizes de 2017 para manejo da hipertensão arterial em cuidados primários nos países de língua portuguesa. Revista Portuguesa de Cardiologia. 2017;36(11):789-798.

17. Malachias MVB, Souza WKSB, Plavnik FL, Rodrigues CIS, Brandão AA, Neves MFT. 7ª Diretriz brasileira de hipertensão arterial. Arq Bras Cardiol. 2016;107(3):1-103.

18. Wunderlich CR. [Das Verhalten der Eigenwaerme in Krankheiten.] Leipzig: Verlag Von Otto Wigand; 1868.

19. Common Terminology Criteria for Adverse Events (NCI, version 4.0, 2010). Assessed June 22nd. https://www.eortc.be/services/doc/ctc/ctcae_4.03_2010-06-14_quickreference_5x7.pdf

20. Sroussi HY, Epstein JB, Bensadoun RJ, et al. Common oral complications of head and neck cancer radiation therapy: mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis. Cancer Med. 2017; 6 (12): 2918-31.

21. Slade GD. Derivation and validation of a short-form oral health impact profile. Community Dent Oral Epidemiol. 1997;25(4):284-290. doi:10.1111/j.1600-0528.1997.tb00941.x

22. Oliveira BH, Nadanovsky P. Psychometric properties of the Brazilian version of the Oral Health Impact Profile-short form. Community Dent Oral Epidemiol. 2005;33(4):307-314. doi:10.1111/j.1600-0528.2005.00225.x

23. Jawad H, Hodson NA, Nixon PJ. A review of dental treatment of head and neck cancer patients, before, during and after radiotherapy: part 1. Br Dent J. 2015;218(2):65-68. doi:10.1038/sj.bdj.2015.28

24. Paleri V, Wight RG, Silver CE, et al. Comorbidity in head and neck cancer: a critical appraisal and recommendations for practice. Oral Oncol. 2010;46(10):712-719. doi:10.1016/j.oraloncology.2010.07.008

25. de Cássia Braga Ribeiro K, Kowalski LP, Latorre Mdo R. Perioperative complications, comorbidities, and survival in oral or oropharyngeal cancer. Arch Otolaryngol Head Neck Surg. 2003;129(2):219-228. doi:10.1001/archotol.129.2.219

26. Paleri V, Wight RG, Silver CE, et al. Comorbidity in head and neck cancer: a critical appraisal and recommendations for practice. Oral Oncol. 2010;46(10):712-719. doi:10.1016/j.oraloncology.2010.07.008

27. Habbous S, Harland LT, La Delfa A, et al. Comorbidity and prognosis in head and neck cancers: Differences by subsite, stage, and human papillomavirus status. Head Neck. 2014;36(6):802-810. doi:10.1002/hed.23360

28. Eytan DF, Blackford AL, Eisele DW, Fakhry C. Prevalence of Comorbidities among Older Head and Neck Cancer Survivors in the United States. Otolaryngol Head Neck Surg. 2019;160(1):85-92. doi:10.1177/0194599818796163

29. Schimansky S, Lang S, Beynon R, et al. Association between comorbidity and survival in head and neck cancer: Results from Head and Neck 5000. Head Neck. 2019;41(4):1053-1062. doi:10.1002/hed.25543

30. Peter F, Wittekindt C, Finkensieper M, Kiehntopf M, Guntinas-Lichius O. Prognostic impact of pretherapeutic laboratory values in head and neck cancer patients. J Cancer Res Clin Oncol. 2013;139(1):171-178. doi:10.1007/s00432-012-1320-1

31. Knittelfelder O, Delago D, Jakse G, et al. The Pre-Treatment C-Reactive Protein Represents a Prognostic Factor in Patients with Oral and Oropharyngeal Cancer Treated with Radiotherapy. Cancers (Basel). 2020;12(3):626. Published 2020 Mar 8. doi:10.3390/cancers12030626

32. Chen Y, Cong R, Ji C, Ruan W. The prognostic role of C-reactive protein in patients with head and neck squamous cell carcinoma: A meta-analysis. Cancer Med. 2020;9(24):9541-9553. doi:10.1002/cam4.3520

33. Marchiori DM. The prevalence of hypovitaminosis among us adults: data from the nhanes iii. 2015;15. Available from: http://dx.doi.org/10.1016/j.jmpt.2016.02.001

34. Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med. 2008;168(15):1629-1637. doi:10.1001/archinte.168.15.162914. Uribe-Querol E, Rosales C. Neutrophils in cancer: Two sides of the same coin. J Immunol Res. 2015;2015.

35. Ocana A, Nieto-Jiménez C, Pandiella A, Templeton AJ. Neutrophils in cancer: prognostic role and therapeutic strategies. Mol Cancer. 2017;16(1):137. Published 2017 Aug 15. doi:10.1186/s12943-017-0707-7

36. Mizuno H, Miyai H, Yokoi A, et al. Relationship Between Renal Dysfunction and Oral Mucositis in Patients Undergoing Concurrent Chemoradiotherapy for Pharyngeal Cancer: A Retrospective Cohort Study. *In Vivo*. 2019;33(1):183-189. doi:10.21873/invivo.11457

37. Deng Z, Kiyuna A, Hasegawa M, Nakasone I, Hosokawa A, Suzuki M. Oral candidiasis in patients receiving radiation therapy for head and neck cancer. Otolaryngol Head Neck Surg. 2010;143(2):242-247. doi:10.1016/j.otohns.2010.02.003

38. Rodrigues-Oliveira L, Kauark-Fontes E, Alves CGB, Tonaki JO, Gueiros LA, Moutinho K, Marta GN, Barros LRC, Santos-Silva AR, Brandão TB, Prado-Ribeiro AC. COVID-19 impact on anxiety and depression in head and neck cancer patients: A cross-sectional study. Oral Dis. 2021 Apr 14. doi: 10.1111/odi.13876. Epub ahead of print.

Table 1. Sociodemographic, clinicopathological, oncologic treatment and referral to dental treatment characteristics of the included patients (n = 110).

Variable	Value
Number of patients	110
Age, mean ± SD [range],y	57.32 ± 9.74 [87 – 23]
Sex, no. (%)	
Female	26 (23.6)
Male	84 (76.4)
Race/ethnicity, no. (%)	
White	48 (43.6)
Black	13 (11.8)
Yellow	1 (0.9)
Brown	48 (43.6)
Cancer diagnosis, no. (%)	
Oral cavity	50 (45.5)
Oropharynx	60 (54.5)
Stage, no. (%)	
In situ	1 (0.9)
I	10 (9.1)
II	11 (10)
III	22 (20)
IVa/b/c	63 (57.3)
Not informed	3 (2.7)
P16, no. (%)	
Negative	27 (24.5)
Positive	18 (16.4)
Not informed	65 (59.1)
Smoker (current or past), no. (%)	94 (85.4)
Drink alcohol (current or past), no. (%)	94 (85.4)
Drug user (current or past) no. (%)	3 (2.7)
Education	
No education or less than 1 year	6 (5.5)
1 to 3 years	4 (3.6)
4 to 7 years	42 (38.2)
8 to 10 years	13 (11.8)
11 to 14 years	25 (22.7)
15 or more years	20 (18.2)
Marriage	
Single	28 (25.5)
Married/ partnered	46 (41.8)
Separated/ divorced	22 (20)
Widowed	14 (12.7)
Housing	

Own	72 (65.4)
Rent	26 (23.6)
Borrowed	12 (11)
Average monthly income*	
< 1 minimum wage	32 (29.1)
1 minimum wage	38 (34.5)
2 to 4 minimum wage	33(30)
5 or + minimum wage	7 (6.4)
Average family monthly income*	
< 1 minimum wage	13 (11.8)
1 minimum wage	30 (27.3)
2 to 4 minimum wage	55 (50)
5 or + minimum wage	12 (10.9)
Oncologic treatment	
Curative	82 (75.5)
S	18 (22)
S + induction CT + CRT	1 (1.2)
S + CRT	18 (22)
Induction CT + CRT	3 (3.6)
RT	17 (20.7)
CRT	25 (30.5)
Palliative	28 (25.5)
Referral	
Before radiotherapy	80 (72.8)
During chemotherapy	3 (2.7)
Before surgery	27 (24.5)

Abbreviations: no., total number of patients; %, percentage; SD, standard deviation; S, surgery; CT, chemotherapy; CRT, chemoradiotherapy; RT, radiotherapy.
*National minimum wage equals to 1045 BRL/Month in Brazil (approximately 205 USD - 2021 values)

Table 2. List of the comorbidities reported by the included patients (n = 110).

Diagnosis	Value n (%)
Hypertension	36 (51.4)
Dyslipidemia	16 (22.9)
Diabetes	11 (15.7)
Gastritis	9 (12.9)
HIV	5 (7.1)
Previous cancer	5 (7.1)
Acute myocardial infarction	5 (7.1)
Tuberculosis (treated)	5 (7.1)
Obesity	5 (7.1)
Asthma	3 (4.3)
Gout	3 (4.3)
Hypothyroidism	3 (4.3)
Impaired vision	3 (4.3)
Syphilis	3 (4.3)
Anxiety	2 (2.9)
Arrhythmia	2 (2.9)
Stroke	2 (2.9)
Bronchitis	2 (2.9)
Hepatic steatosis	2 (2.9)
Congestive heart failure	2 (2.9)
Prediabetes	2 (2.9)
Osteoporosis	2 (2.9)
Hepatitis C	2 (2.9)
Leg paresthesia	2 (2.9)
Arthritis	1 (1.4)
Chron disease	1 (1.4)
Coronary artery disease	1 (1.4)
Depression	1 (1.4)
Dyspepsia	1 (1.4)
Pulmonary emphysema	1 (1.4)
Migraine	1 (1.4)
Esophagitis	1 (1.4)
Glaucoma	1 (1.4)
Hemiparesis left	1 (1.4)
Hepatitis B	1 (1.4)

Spinal disc herniation	1 (1.4)
Parkinson investigation	1 (1.4)
Labyrinthitis	1 (1.4)
Osteoarthritis	1 (1.4)
Osteopenia	1 (1.4)
Hearing loss	1 (1.4)
Mitral valve prolapse	1 (1.4)
Gastroesophageal reflux	1 (1.4)
Poliomyelitis sequelae (leg)	1 (1.4)

Abbreviations: no., total number of patients; %, percentage.

Table 3. The laboratory results, percentage not altered, range, mean and standard deviation.

Laboratory tests	% not altered	Mean	STDEV
Complete blood count (CBC)			
Erythrocytes ($x10^6/mm^3$)	47 (42.7)	4.26	0.73
Hemoglobin (g/dL)	44 (40)	12.60	1.91
Hematocrit (%)	45 (40.9)	37.66	5.51
MCV (fL)	90 (81.8)	88.64	6.07
MCH (pg)	97 (88.2)	29.66	2.34
MCHC (g/dL)	101 (91.8)	33.45	1.06
RDW-CV (%)	95 (86.4)	13.33	1.25
RDW-SD (fL)	70 (63.6)	43.00	4.65
Erythroblasts (%)	109 (99.1)	0.1	0.07
Platelets ($x10^3/mm^3$)	85 (77.3)	325.57	115.38
MPV (fL)	80 (72.7)	10.20	1.10
Leukocytes ($10^3/mm^3$)	83 (75.5)	9.09	4.10
Neutrophils ($10^3/mm^3$)	71 (64.5)	6.66	6.64
Eosinophil ($10^3/mm^3$)	71 (64.5)	0.26	0.28
Basophil ($10^3/mm^3$)	83 (75.5)	0.05	0.05
Lymphocytes ($10^3/mm^3$)	73 (66.4)	1.93	0.72
Monocytes ($10^3/mm^3$)	75 (68.2)	0.73	0.30
Basic electrolyte panel			
Sodium (mEq/L)	98 (89.1)	138.66	3.30
Potassium (mEq/L)	93 (84.5)	4.53	0.45
Magnesium (mg/dL)	1.58 – 2.55		
Chloride (mEq/L)	106 (96.4)	2.01	0.22
Iron (ug/dL)	72 (65.5)	76.43	34.15
Creatinine (mg/dL)	83 (75.5)	0.87	0.24
Glucose (mg/dL)	72 (65.5)	96.94	21.41
Urea (mg/dL)	99 (90)	34.72	15.69
Metabolic panel			
Calcium (mg/dL)	89 (80.9)	9.94	1.05
Bilirubin total (mg/dL)	99 (90)		
Bilirubin direct (mg/dL)	103 (93.6)		
Bilirubin indirect (mg/dL)	85 (77.3)		
Alkaline phosphatase (U/L)	98 (89.1)	85.68	31.73
Aspartate aminotransferase (U/L)	104 (94.5)	19.53	7.67
Gamma-glutamyl transferase (U/L)	60 (54.5)	83.99	91.09
Alanine aminotransferase (U/L)	96 (87.3)	21.28	14.07
Lipid panel			
Total cholesterol (mg/dL)	71 (64.5)	183.05	42.06

High-density lipoprotein (HDL) (mg/dL)	71 (64.5)	45.81	12.18
Low-density lipoprotein (LDL) (mg/dL)	98 (89.1)	114.15	35.89
Non-high-density lipoprotein (non-HDL) cholesterol (mg/dL)	84 (76.4)	138.39	40.82
VLDL (very-low-density lipoprotein) (mg/dL)	93 (84.5)	24.81	10.76
Triglycerides (mg/dL)	79 (71.8)	136.63	80.30
Thyroid function			
Thyroid stimulating hormone (TSH) (ul/mL)	95 (86.4)	2.56	2.19
Total triiodothyronine (T3) (ng/dL)	98 (89.1)		
Thyroxine (T4) (ug/dL)	108 (98.2)	8.66	1.77
Free thyroxine (free T4) (ng/dL)	0.51 – 1.80	1.27	0.22
Glycated hemoglobin (Hemoglobin A1C) (%)	96 (87.3)	5.35	0.80
Coagulation assay			
Prothrombin time (PT) (s)	108 (98.2)	14.43	1.20
International Normalized Ratio (INR) (s)	82 (74.5)	1.07	0.13
Activated partial thromboplastin time (aPTT) (s)	98 (89.1)	29.83	3.19
25-Hydroxy Vitamin D (ng/mL)	58 (52.7)	26.86	14.41
HBsAg (Hepatitis B surface antigen)	110 (100)		
Anti-HBs (Hepatitis B surface antibody	92 (83.6)		
Anti-HBc (Hepatitis B core antibody)	101 (91.8)		
Hepatitis C	107 (97.3)		
HIV	105 (95.5)		
Syphilis	98 (89.1)		
C-reactive protein (CRP) (mg/L)	40 (36.4)		

Abbreviations: STDEV: standard deviation; %: percentage.

Table 4. OHIP-14 questionnaire, mean score and standard deviation per answer, and mean total, range and standard deviation.

OHIP-14 Domain	**Item**	**Mean (STDEV)**
Domain 1: Functional	1. Had trouble pronouncing any words?	1.41 (1,71)
	2. Felt sense of taste has worsened?	0.85 (1.49)
Domain 2: Physical pain	3. Had painful aching?	2.16 (1.69)
	4. Found it uncomfortable to eat any foods?	2.21 (1.86)
Domain 3: Psychological discomfort	5. Been self-conscious	2.29 (1.63)
	6. Felt tense	1.31 (1.56)
Domain 4: Physical disability	7. Felt diet has been unsatisfactory	2.31 (1.85)
	8. Had to interrupt meals	1.03 (1.43)
Domain 5: Psychological disability	9. Found it difficult to relax	1.36 (1.66)
	10. Been a bit embarrassed	0.57 (1.11)
Domain 6: Social disability	11. Been a bit irritable	0.59 (1.03)
	12. Had difficulty doing usual jobs	1.27 (1.64)
Domain 7: Handicap	13. Felt life less satisfying	1.62 (1.64)
	14. Been totally unable to function	0.52 (1.16)
	TOTAL (sum)	19.5 (12.5)
	Range	0 - 49

Abbreviations: OHIP-14 - The Oral Health Impact Profile.

Table 5. Correlation analysis between the number of medications in use and the number of medications in use with treatment related-toxicities.

	Pearson Correlation Coefficient	
	Number of medications	**Number of diagnosis**
Treatment-related toxicity		
Mucositis	0.268*	0.101
Xerostomia	- 0.043	0.233
Dysphagia	- 0.183	- 0.033
Disgeusia	- 0.257*	- 0.056
Trismus	0.031	0.082
Radiodermatitis	0.113	- 0.017
Candidiasis	0.119	0.076

* statistically significant association

Table 6: Treatment side effects and association with abnormal laboratory results.

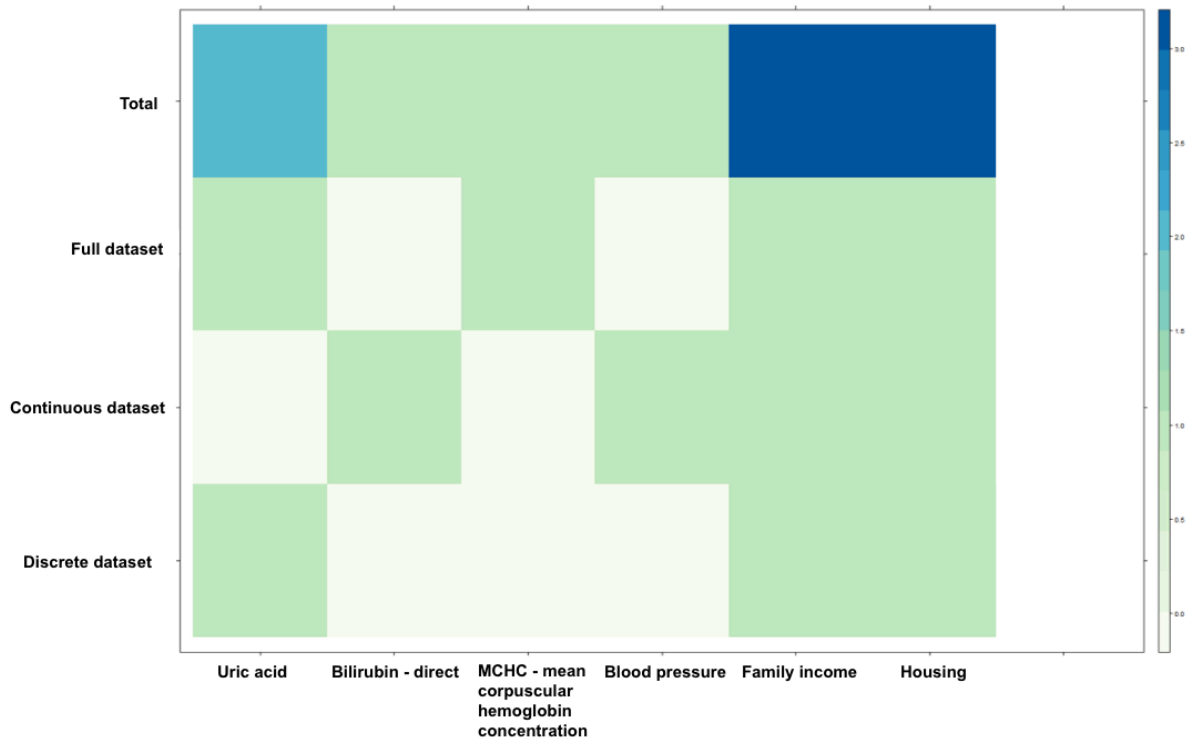
	Laboratory exam			
Treatment side effects	**MUCOSITIS**	**DISGEUSIA**	**DISPHAGIA**	**XEROSTOMIA**
- D5	FT4 (p = 0) Calcium (p = 0.002)	Erythroblasts (p= 0.007) Hepatitis C (p= 0.007) Aspartate aminotransferase (p= 0.013) Alanine aminotransferase (p=0.001) 25-Hydroxy Vitamin D (p= 0.055)	Sodium (p= 0.019) Basophil (p= 0.058) Hematocrit (p= 0.012) Erythrocytes (p= 0.002) Anti-HBc Hep B (p= 0.008) Cholesterol (p= 0.05) Calcium (p= 0.026)	Sodium (p= 0.019) Potassium (p= 0.003) Monocyte (p= 0.042) VLDL (p= 0.033) Cholesterol (p= 0.023)
- D10	Leukocytes (p=0.057) Hematocrit (p=0.0058) Iron (p=0.011) Calcium (p=0.023)	Syphilis (p= 0.012)	Sodium (p= 0.044) MCH (p= 0.043) Hematocrit (p= 0.006) Erythrocyte (p= 0.001) Anti HBc Hep B (p= 0.019) Gamma-glutamyl transferase (p= 0.027)	FT4 (p= 0.054) Syphilis (p= 0.02)
- D15	aPTT (p=0.019) FT4 (p=0.035) T4 (p=0.001) T3 (p=0.001) Syphilis (p=0.038) Creatinine (p=0)	Bilirubin (p= 0.01)	FT4 (p= 0) T4 (p= 0.041) Eosinophil (p= 0.003) Hematocrit (p= 0.004) Erythrocytes (p= 0.003) Glucose (p= 0.045) Calcium (p= 0.011) Alkaline phosphatase (p= 0.028)	FT4 (p= 0.04) Lymphocyte (p= 0) VLDL (p= 0.041) Cholesterol (p= Uric acid (p= 0.034)
- D20	FT4 (p=0) T4 (p=0.045) Basophil (p= 0) Eosinophil (p = 0.046) non-HDL (p= 0.057) Cholesterol (p=0.031) Glucose (p= 0) Alkaline phosphatase (p = 0.002)	TSH (p= 0.030) Basophil (p= 0.029) Hematocrit (p= 0.006) Erythroblasts (p=0.005)	Potassium (p= 0) MCHC (p= 0.001) Hematocrit (p= 0.023) Erythrocyte (p= 0.018) Aspartate aminotransferase (p= 0)	Hepatitis (p= 0.029) HIV (p= 0)
- D25	Urea (p=0.008) FT4 (p= 0) T4 (p= 0.004) Monocytes (p= 0.036) Basophil (p = 0.004) Glucose (p= 0.001) Alkaline phosphatase (p = 0.002)	Hematocrit (p= 0.017) Erythrocytes (p= 0.020)	Neutrophil (p= 0.049) Hematocrit (p= 0.001) Erythrocyte (p= 0.002)	
- D30	Urea (p= 0.001) FT4 (p = 0) T4 (p= 0) Syphilis (p= 0.018) Glycated hemoglobin (p= 0.030) Creatinine (p= 0.007) Chloride (p= 0.039) Calcium (p= 0.044) Bilirubin (p= 0.035)	Basophil (p= 0.008) Eosinophil (p= 0.019) Leukocyte (p= 0.048) Hematocrit (p= 0.025) Erythrocytes (p= 0.046)	Prothrombin time (p= 0.028) T4 (p= 0.028) Magnesium (p= 0) Neutrophil (p= 0.018) MCHC (p= 0.034) Hematocrit (p= 0.007) Erythrocyte (p= 0.023) Anti-HBc Hep B (p= 0.023)	Sodium (p= 0.025)

- D33/35	Urea (p= 0) FT4 (p= 0.02) T4 (p= 0.009) Hematocrit (p= 0.059)	RDW-SD (p= 0.027) Hematocrit (p= 0.016) Creatinine (p= 0.052)	T4 (p= 0.053) Magnesium (p= 0.001)	T4 (p= 0.059) Sodium (p= 0.008) Glycated hemoglobin (p= 0.054)

	Laboratory exam		
Treatment side effects	**RADIODERMATITIS**	**TRISMUS**	**CANDIDIASIS**
- D5	Prothrombin time (p= 0.024) Erythroblasts (p= 0.001) 25-Hydroxy Vitamin D (p= 0.002)	aPTT (p= 0) RDW-SD (p= 0.003) MCV (p= 0.001) HIV (p= 0.044) Anti-Hep B (p= 0.027)	MCHC (p= 0.009) Triglycerides (p= 0.047) Aspartate aminotransferase (p= 0.002)
- D10	MCH (p= 0.014) Erythrocyte (p= 0.021) Calcium (p= 0.049)	aPTT (p= 0) RDW-SD (p= 0.001) Anti-Hep B (p= 0.026)	Potassium (p= 0.015) Alanine aminotransferase (p= 0.035) Potassium (p= 0)
- D15	MCH (p= 0.014)	aPTT (p= 0) RDW-SD (p= 0.004) MCV (p= 0.001) Anti-HBc Hep B (p= 0.026)	Potassium (p= 0.05) Eosinophil (p= 0.032) Triglycerides (p= 0.035) Calcium (p= 0.039)
- D20	INR (p= 0.006) Sodium (p= 0) MCH (p= 0.013) MCV (p= 0) Chloride (p= 0.017) Uric acid (p= 0)	RDW-SD (p= 0.004) MCV (p= 0.001) Anti-HBc hep B (p= 0.026) aPTT (p= 0)	aPTT (p= 0.025) TSH (p= 0.015) Syphilis (p= 0.038) Eosinophil (p= 0.016) HIV (p= 0.018) Calcium (p= 0.011)
- D25	INR (p= 0.017) Lymphocyte (p= 0.004) Non-HDL (p= 0.02) Cholesterol (p= 0.009) Chloride (p= 0)	aPTT (p= 0) RDW-SD (p= 0.002) MCV (p=0.001) Hematocrit (p= 0.012) Erythrocyte (p= 0.012) Anti-HBc hep B (p= 0.023) Alkaline phosphatase (p= 0.042)	FT4 (p= 0.02) Eosinophil (p= 0.03) Glucose (p= 0.04) Alanine aminotransferase (p= 0.019)
- D30	INR (p= 0.034) Potassium (p= 0) Lymphocyte (p= 0.013) Chloride (p= 0) Bilirubin (p= 0.053) Aspartate aminotransferase (p= 0.019)	aPTT (p= 0) RDW-SD (p= 0.002) VCM (p= 0.001) Hematocrit (p= 0.031) Erythrocytes (p= 0.033) Anti-HpC Hep B (p= 0.022)	Potassium (p= 0.024) Eosinophil (p= 0.039) Iron (p= 0.059) Calcium (p= 0.037)
- D33/35	FT4 (p= 0.005) Potassium (p= 0) Aspartate aminotransferase (p= 0.01) Alkaline phosphatase (p= 0.056)	aPTT (p= 0) RDW-SD (p= 0.031) MCV (p= 0.007) Hematocrit (p= 0.008) Erythrocyte (p= 0.011) HDL cholesterol (p= 0.044) Iron (p= 0.050) Bilirubin (p= 0.026) Alkaline phosphatase (p= 0.039)	INR (p= 0.003) CRP (p= 0.026) Monocytes (p= 0.062) LDL (p= 0.041) Cholesterol (p= 0.038) Glucose (p= 0.005)

Abbreviations: aPTT: Activated partial thromboplastin time; CRP - C-reactive protein; D: days; free T4 - Free thyroxine; HDL: High-density lipoprotein; Hep B – hepatitis B; HIV - human immunodeficiency virus; INR - International Normalized Ratio; LDL - Low-density lipoprotein; MCH - mean corpuscular haemoglobin; MCV - mean corpuscular volume; MCHC - mean corpuscular hemoglobin concentration; RDW-SD - Erythrocyte Distribution Width (standard deviation); TSH - Thyroid stimulating hormone; T3 - Total triiodothyronine; T4 - Thyroxine; VLDL - very-low-density lipoprotein.

Figure 1. Heat map of oral mucositis predictors.



Legend: The picture above shows the predictors of oral mucositis according to our total, full, continuous, and discrete dataset. All data included in this study were evaluated for the predictors. Family income and housing are the most important predictors.

Supplementary material 1. Laboratory tests and the reference values.

Laboratory tests	Reference values
Complete blood count (CBC)	
Erythrocytes (x10^6/mm^3)	M: 4.5 - 6.5 / F: 3.9 – 5.6
Hemoglobin (g/dL)	M: 13.5 - 17.5 / F: 11.5 – 15.5
Hematocrit (%)	M: 40 – 52 / F: 36 – 48
MCV (fL)	80 – 95
MCH (pg)	27 – 34
MCHC (g/dL)	30 – 35
RDW-CV (%)	M: 11.6 - 14.4 / F: 11.7 – 14.4
RDW-SD (fL)	M: 35.1- 43.9 / F: 36.4 – 46.3
Erythroblasts (%)	0
Platelets (x10^3/mm^3)	150 – 400
MPV (fL)	9.4 - 12.4
Leukocytes (10^3/mm^3)	4 – 11
Neutrophils (10^3/mm^3)	2.5 – 7.5
Eosinophil (10^3/mm^3)	0.04 – 0.44
Basophil (10^3/mm^3)	0.00 – 0.1
Lymphocytes (10^3/mm^3)	1.5 – 3.5
Monocytes (10^3/mm^3)	0.2 – 0.8
Basic electrolyte panel	
Sodium (mEq/L)	135 – 145
Potassium (mEq/L)	3.5 – 5
Magnesium (mg/dL)	1.58 – 2.55
Chloride (mEq/L)	98 – 107
Iron (ug/dL)	M: 65 – 175 / F: 50 – 170
Creatinine (mg/dL)	M: 0.7 –1.2 / F: 0.5 – 0.9
Glucose (mg/dL)	70 – 99
Urea (mg/dL)	10 - 50
Metabolic panel	
Calcium (mg/dL)	12 - 60 years : 8.40 - 10.20 / 61 - 90 years: 8.60 - 10.20
Bilirubin total (mg/dL)	0.2 - 1.0
Bilirubin direct (mg/dL)	< 0.3
Bilirubin indirect (mg/dL)	0.10 - 0.60
Alkaline phosphatase (U/L)	M: 40 - 129 / F: 35 - 104
Aspartate aminotransferase (U/L)	M: < 37 / F: < 31
Gamma-glutamyl transferase (U/L)	M: 8 - 61 / F: 5 - 36
Alanine aminotransferase (U/L)	M: < 41 / F: < 31
Lipid panel	

Total cholesterol (mg/dL)	< 190
High-density lipoprotein (HDL) (mg/dL)	> 40
Low-density lipoprotein (LDL) (mg/dL)	Optimal: < 100, Near/ above optimal: 100 - 129, Borderline High: 130 - 159, High 160 – 189, and Very high >/ 190
Non-high-density lipoprotein (non-HDL) cholesterol (mg/dL)	Optimal: < 130, Acceptable: 130 – 159; High: 160 – 189, Very high: >/ 190
VLDL (very-low-density lipoprotein) (mg/dL)	< 35
Triglycerides (mg/dL)	< 150
Thyroid function	
Thyroid stimulating hormone (TSH) (ul/mL)	0.27 – 4.20
Total triiodothyronine (T3) (ng/dL)	80 – 200
Thyroxine (T4) (ug/dL)	5.1 - 14.1
Free thyroxine (free T4) (ng/dL)	0.93 - 1.7
Glycated hemoglobin (Hemoglobin A1C) (%)	4.1 – 6
Coagulation assay	
Prothrombin time (PT) (s)	10.3 - 16.6
International Normalized Ratio (INR) (s)	0.95 - 1.20
Activated partial thromboplastin time (aPTT) (s)	25.4 - 36.9
25-Hydroxy Vitamin D (ng/mL)	< 60 years old: >20 / > 60 years old: 30 - 60
HBsAg (Hepatitis B surface antigen)	reactive or not reactive
Anti-HBs (Hepatitis B surface antibody	reactive or not reactive
Anti-HBc (Hepatitis B core antibody)	reactive or not reactive
Hepatitis C	reactive or not reactive
HIV	reactive or not reactive
Syphilis	reactive or not reactive
C-reactive protein (CRP) (mg/L)	<5.0 mg/L

Abbreviations: MCV - mean corpuscular volume; MCH - mean corpuscular haemoglobin; MCHC - mean corpuscular hemoglobin concentration; RDW - Erythrocyte Distribution Width; RDW-SD - Erythrocyte Distribution Width (standard deviation); MPV - mean platelet volume (MPV).

ARTIGO: DIRECT COSTS ASSOCIATED WITH THE MANAGEMENT OF MUCOSITIS: A SYSTEMATIC REVIEW.

CÁPITULO 2 – Artigo publicado no periódico Oral Oncology **(Anexo 1)**

Rodrigues-Oliveira L, Kowalski LP, Santos M, Marta GN, Bensadoun RJ, Martins MD, Lopes MA, Castro G Jr, William WN Jr, Chaves ALF, Migliorati CA, Salloum RG, Rodrigues-Fernandes CI, Kauark-Fontes E, Brandão TB, Santos-Silva AR, Prado-Ribeiro AC. Direct costs associated with the management of mucositis: A systematic review. Oral Oncol. 2021 Apr 29;118:105296. doi: 10.1016/j.oraloncology.2021.105296. Epub ahead of print.

Authors: Leticia Rodrigues-Oliveira [a], DDS; Luiz Paulo Kowalski [b,c], MD, MSc, PhD; Marcos Santos[d], MD, PhD; Gustavo Nader Marta [e,f], MD, MSc, PhD; René-Jean Bensadoun[g], MD; Manoela D Martins [a,h] DDs, MSc, PhD; Marcio Ajudarte Lopes [a], DDs, MSc, PhD; Gilberto de Castro Jr [i], MD, MSc, PhD; William Nassib William Jr.[j], MD, PhD; Aline Lauda Freitas Chaves [k], MD, MSc; Cesar Augusto Migliorati [l], DDS, MSc, PhD; Ramzi G. Salloum [m], BSc, MBA, MA, PhD; Carla Isabelly Rodrigues-Fernandes [a], DDS, MSc; Elisa Kauark Fontes [a], DDS; Thaís Bianca Brandão [n], DDS, MSc, PhD; Alan Roger Santos-Silva[a], DDS, MSc, PhD; Ana Carolina Prado-Ribeiro[a,n], DDS, MSc, PhD.

Affiliation: [a] Oral Diagnosis Department, Piracicaba Dental School, University of Campinas (UNICAMP), Av. Limeira, 901, Bairro Areião, 13414-903, Piracicaba, São Paulo, Brazil; [b] Head and Neck Surgery Department, University of Sao Paulo Medical School, Av. Dr. Arnaldo, 455, Cerqueira César, 01246-903, São Paulo, São Paulo, Brazil; [c] Department of Head and Neck Surgery and Otorhinolaryngology, A C Camargo Cancer Center, Rua Tamandaré, 753, Liberdade, 01525-001, São Paulo, São Paulo, Brazil; [d] ISPOR – International Society for Pharmacoeconomics and Outcomes Research, Brazil Chapter; [e] Division of Radiation Oncology, São Paulo State Cancer Institute (ICESP-FMUSP), Av. Dr. Arnaldo, 251, Cerqueira César, 01246-000, São Paulo, São Paulo, Brazil; [f] Department of Radiation Oncology, Hospital Sírio-Libanês, Rua Dona Adma Jafet, 115, Bela Vista, 01308-050, São Paulo, São Paulo, Brazil; [g] Centre de Haute Energie (CHE), 10, Boulevard Pasteur, 06000 Nice, Nice, France; [h] Department of Oral Pathology, School of Dentistry, Federal University of Rio Grande do Sul, Rua Ramiro Barcelos, 2492, Santa Cecilia, 90035-003, Porto Alegre, Rio Grande do Sul, Brazil;

[i] Department of Medical Oncology, São Paulo State Cancer Institute (ICESP-FMUSP), Av. Dr. Arnaldo, 251, Cerqueira César, 01246-000, São Paulo, São Paulo, Brazil; [j] Centro Oncológico BP, Beneficência Portuguesa de São Paulo, Rua Maestro Cardim, 769, Bela Vista, 01323-001, São Paulo, São Paulo, Brazil; [k] DOM Oncology Group, Av. Antônio Olímpio de Morais, 1990, Santa Clara, 35500-071, Divinópolis, Minas Gerais, Brazil; [l] College of Dentistry, University of Florida, 1395 Center Dr, Gainesville, Florida, 32610, USA; [m] College of Medicine, University of Florida, 600 SW Archer Rd, Gainesville, Florida, 32610, USA; [n] Dental Oncology Service, São Paulo State Cancer Institute (ICESP-FMUSP), Av. Dr. Arnaldo, 251, Cerqueira César, 01246-000, São Paulo, São Paulo, Brazil.

Electronic address: Leticia Rodrigues-Oliveira (leticia.lro@gmail.com); Luiz Paulo Kowalski (lp_kowalski@uol.com.br); Marcos Santos (marcosrxt@gmail.com); Gustavo Nader Marta (gustavo.marta@hc.fm.usp.br); René-Jean Bensadoun (renejean.bensadoun@che-nice.com); Manoela D Martins (manomartins@gmail.com); Marcio Ajudarte Lopes (marcioajudartelopes@gmail.com); Gilberto de Castro Jr (gilberto.castro@usp.br); William Nassib William Jr. (williamwilliamjr@gmail.com); Aline Lauda Freitas Chaves (alinelauda@hotmail.com); Cesar Augusto Migliorati (cmigliorati@dental.ufl.edu)[;] Ramzi G. Salloum (rsalloum@ufl.edu); Carla Isabelly Rodrigues-Fernandes (carla.rodrigues212@gmail.com); Elisa Kauark Fontes (elisakauark@gmail.com); Thaís Bianca Brandão (thais.brandao@hc.fm.usp.br); Alan Roger Santos-Silva (alanroger@fop.unicamp.br); Ana Carolina Prado-Ribeiro (carol_pr@yahoo.com.br).

Corresponding author:

Alan Roger Santos-Silva

Oral Diagnosis Department, Piracicaba Dental School, University of Campinas (UNICAMP).

Address: Av. Limeira, 901, Bairro Areião, Piracicaba - SP, Brasil. Postal code: 13414-903

E-mail: alanroger@fop.unicamp.br

Telephone: +55 19 21065320

Abstract

Mucositis is one of the more frequent and costly adverse events following cancer treatment. To evaluate and report the direct economic outcomes associated with the management of mucositis across several cancer treatments we conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Scopus, MEDLINE/PubMed, and Embase were searched electronically and a total of 37 relevant studies were included. The costs attributable to mucositis in the hematopoietic stem cell transplantation setting ranged from 1124,47 US dollars (USD) to 299 214,14 USD per patient. The radiotherapy/ chemoradiotherapy/radiotherapy plus molecular targeted therapy accounted for mucositis costs that ranged from 51,23 USD to 33 560,58 USD per patient. Costs for mucositis in the chemotherapy setting ranged from 4,18 USD to 31 963,64 USD per patient. When the cancer treatment was not specified, costs of mucositis ranged from 565,85 USD to as high as 20 279, 12 USD per patient. Mucositis costs from multimodal therapy ranged from 12,42 USD to 5670,46 USD per patient. The molecular targeted therapy setting included only one study and depending on the healthcare providers' perspective of each country evaluated, mucositis' costs ranged from 45,78 USD to 3484,91 USD per patient. Mucositis is associated with increased resource use, consultations, hospitalizations and extended hospitalizations, leading to a substantial incremental cost that exacerbates the economic burden on the patient, health plan and health system across several cancer treatments and diagnosis. More studies with a prospective evaluation of the economic costs associated with mucositis management are needed.

Keywords: Mucositis, Health Expenditures, Health Care Costs, Hospital Charges, Hospital Costs, Systematic Review, Radiotherapy, Chemotherapy, Hematopoietic Stem Cell Transplantation, Molecular targeted therapy.

Introduction

Economic evaluation is of growing importance in oncology, as total medical spending on cancer care has been increasing at an unsustainable rate [1,2]. One of the more frequent and serious treatment-induced toxicities is alimentary mucositis following conventional chemotherapy, high-dose chemotherapy as conditioning for hematopoietic stem cell transplantation (HSCT), head and neck radiotherapy and molecular targeted therapies. Its incidence highly varies depending mainly on the treatment regimen; 20-40% of patients receiving conventional chemotherapy, 60-90% of patients receiving high-dose chemotherapy as conditioning for HSCT, and nearly all patients receiving head and neck radiotherapy [3-6].

Alimentary mucositis can manifest as erythema, atrophy, erosions, and ulcers in the entire oral cavity and in the gastrointestinal tract [7]. It is frequently accompanied by severe pain requiring opioids analgesics, decreased oral intake and weight loss resulting in a need for parenteral and enteral nutrition, affecting the patients' quality of life (QoL). Dose reductions, interruptions and discontinuations of the treatment are often associated with mucositis thus impacting on the success of the tumor control and survivorship. Not only do mucositis affect the QoL of patients, but it also results in extra consultations, emergency room visits and hospitalizations and poses an additional economic burden to healthcare payers, policymakers and patients [3,8-12].

We conducted this systematic literature review to evaluate the direct economic outcomes of mucositis, such as the incremental healthcare costs associated with its management across all modalities of cancer treatment.

Materials and methods

A systematic literature review search was conducted to identify articles that provided data on costs associated with alimentary mucositis in cancer patients following antineoplastic therapies- radiotherapy, chemoradiotherapy, chemotherapy, HSCT and molecular targeted therapies.

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13], and the protocol was registered in the International Prospective Register of Systematic Review (PROSPERO) database [14] (CRD42020173708).

Search strategy

Without restricting publication year (last search was on October 31st, 2020), we screened Medline/PubMed, EMBASE, and SCOPUS databases. The search strategies employed are outlined in **Appendix 1**. To supplement the primary search strategy, references listed in the bibliographies of included articles were also added if they had not been previously identified.

Inclusion criteria

With the exception of review studies, all study types that mentioned the costs associated with mucositis were included. Abstracts, case reports, animal and in vitro studies, letters to editors, study protocols, and unpublished data were not included. The reference manager software Rayyan QCRI [15] was used for managing the study selection phase. After duplicates were excluded, a screening of titles and abstracts were independently performed by two authors (LRO, CIRF). Pre-selected studies were assessed for eligibility and reviewed in totality (LRO, CIRF) to select the included studies. When discrepant ratings occurred between the reviewers, a final decision was made by a third reviewer (ARSS).

Data extraction

Study characteristics

Study characteristics extracted from included studies were: first author, year of publication, country of study, cancer type, cancer treatment, condition evaluated [oral mucositis (OM)/mucositis/stomatitis, other], grading system, study type, resource utilization, sample size, cost perspective, year/currency/cost type, and costs reported/estimates in 2020 US dollars (USD).

The costs reported were converted to 2021 USD (to compare data from several articles written at different times) by applying the gross domestic product deflator index (GDP values) and purchasing power parities conversion rates (PPP values) using the Campbell and Cochrane Economics Methods Group-the Evidence for Policy and Practice Information (CCEMG–EPPI)-Centre Cost Converter software (V1.6) [16,17], which automatically adjusts estimates for costs and price year. In situations where a reference year was not provided, we used the last year in which patients were included or, when this was unknown, the costs were calculated one year before the publication year.

Risk of bias (RoB) assessment

The RoB of selected studies was evaluated using "The Cochrane Collaboration's tool for assessing risk of bias" [18] for randomized studies and "The Risk Of Bias in non-randomized studies-of interventions (ROBINS-I)" [19] for non-randomized studies. The overall RoB of each study was categorized as a low, moderate, serious or critical for non-randomized studies and as low, unclear or high for randomized studies. Both reviewers (LRO, CIRF) answered each of the items included and then assigned an overall RoB for each study. A third reviewer resolved disagreements.

To critically appraise the quality of the economic evaluation, the Consensus on Health Economic Criteria (CHEC) list for each publication was used [20]. The CHEC-list consists of 19 yes-or-no questions, one for each category. Higher scores of 'yes' denote a better methodological quality of the economic study.

Data analysis

Due to the methodological heterogeneity of included economic evaluations, a meta-analysis was not feasible [21]. Therefore, this systematic review presented a detailed qualitative synthesis of the results from the included studies.

Results

Literature search results and study selection

This systematic review included 37 relevant studies that evaluated the cost of mucositis. Figure 1 depicts the results of the literature search and screening.

Characteristics of the included studies

Table 1 summarizes the characteristics of the included studies. A number of cancer sites were represented in these studies, including head and neck cancer (HNC), non-small cell lung cancer (NSCLC), breast/ovarian/colon/renal cancer, and hematologic/lymphatic malignancies. All major forms of cancer therapy were included in this systematic review: radiotherapy with or without concomitant chemotherapy, HSCT, chemotherapy, and molecular targeted therapy.

The majority of the studies (n=26) did not report the scoring system used to report mucositis. The remaining 11 mainly graded mucositis according to the National Cancer Institute (NCI) [22] or the World Health Organization (WHO) [23] scales. Twelve studies reported only one aggregate mucositis-associated cost combining all grades, while 14 studies considered costs of grade 3-4 events only. The remaining included articles differed its reporting of costs.

Most of the included articles evaluated costs retrospectively (n=33) using data from clinical trials/previous studies (n=15), chart review/databases (n=17) and an incidence-based model of resource based on a physician survey (n=1). Only four (n=4) studies evaluated costs prospectively.

The resource utilization methodology for deriving costs was different across studies and included a panel of experts to estimate resource use (n=11), chart review (n=20), data from previous studies (n=5) and data from public health sources (n=1). Additionally, the perspective of the cost analysis varied and included: payer (n=9), provider (n=12), societal (n=12), both payer/provider (n=3), and societal/payer (n=1) perspectives.

Risk of bias and quality of the included studies

Cochrane's RoB measures and CHEC-list measures for each study are summarized in **Figure 2**.

Of the 37 studies, six were classified as low RoB, three as high RoB and the remaining articles had a moderate RoB. The quality of studies was generally good as all of them fulfilled more than 50% of the CHEC-list items evaluated.

Costs evaluation – mucositis

Different treatments modalities were examined in the included studies and, therefore, cost findings were organized according to the following treatment categories: 1) radiotherapy/chemoradiotherapy/radiotherapy plus molecular targeted therapy; 2) HSCT; 3) chemotherapy; 4) molecular targeted therapy, 5) multimodal therapy and 6) treatment not specified (**Table 2** and **Table 3**).

1) Radiotherapy/chemoradiotherapy/radiotherapy plus molecular targeted therapy

A total of seven articles examined either radiotherapy alone, chemoradiotherapy, or radiotherapy plus molecular targeted therapy [3,9,11,24-27]. Costs attributable to mucositis varied across studies, depending on the activities observed in each cost-analysis and the average hospitalization rates/stay period, ranging from 51,23 USD [26] to 33 560,58 USD [24].

Peterman et al. [9] evaluated HNC patients with radiotherapy- or chemotherapy-induced mucositis using low and high estimates of charges, and on average, mucositis was associated with 4799,27 ± 1599,76 USD. Murphy et al. [11] estimated the additional charges of mucositis at 3452,32 per patient and Elting et al. [3] observed an incremental cost of 7770,68 USD in patients that underwent radiotherapy and 7859,08 USD for chemoradiotherapy patients.

Nonzee et al. [24], evaluated HNC and NSCLC patients after chemoradiotherapy and reported incremental costs of 23 093,32 USD for HNC patients and 33 560,58 for NSCLC patients. Mean duration of hospitalization attributed to mucositis was higher than previous studies and influenced the higher incremental cost reported.

Antunes et al. [25] and Lopes Martins et al. [26] evaluated grades 3-4 mucositis costs for HNC patients undergoing chemoradiotherapy or radiotherapy alone in Brazil and reported mean incremental costs of 288,99 USD and 51,23 USD respectively. Lopes Martins et al. [26] observed higher costs for emergency department visits of 196,40 USD and 268,86 USD for hospitalization.

Brown et al. [27] based their cost-evaluation on a randomized trial that evaluated locally advanced HNC patients undergoing radiotherapy alone or in combination with weekly cetuximab. Costs for mucositis were reported in five European countries: Belgium - grades 2/3/4: 6987,79 USD, France - grades 2/3: 2716,62 USD and 4: 5006,26 USD, Italy – grades: 2/3/4: 6214,38 USD, Switzerland - grade 3: 4485,01 USD and 4: 35 877,41 USD and UK - grade 2: 4192,51, and 3/4: 6998,86 USD. For Switzerland, the higher cost of grade 4 mucositis was due to higher average inpatient length of stay of 28 days.

2) Hematopoietic Stem Cell Transplantation (HSCT)

Five articles evaluated the costs associated with mucositis following HSCT [5,6,28-30]. Reporting of costs ranged from 1124,47 USD for autologous patients when accounting only for drug treatment and nutrition costs [6] to costs exceeding 299 214,14 USD for allogeneic transplant recipients when including hospitalizations charges [5].

Sonis et al. [29] reported that outcomes associated with the presence of ulceration increase the total costs to 64 100,50 USD (autologous and allogeneic HSCT patients) and that one-point increase in the Oral Mucositis Assessment Scale (OMAS) is followed by an additional hospital charge of 38 093,83 USD. Vera-Llonch et al. [5], also reported that the higher the scores of mucositis, higher the costs associated in allogeneic patients and that while grade 0 is associated with 286 584,05 USD in charges, grade 5 is responsible for 585 798,19 USD, representing incremental charges of about 299 214,14 USD. In this study, cases ranged from grade 0 (i.e., no sites with erythema or ulceration/pseudomembrane) to grade 5 (four or more sites with ulceration/pseudomembrane).

Jones et al. [30] observed that the incremental costs associated with mucositis in autologous HSCT patients ranged from 21 271,67 USD to 70 905,56 USD. Similarly, Cho et al. [28] found

the additional mean hospital costs (unadjusted) of mucositis to be of 25 146,06 USD for autologous and 56 704,82 USD for allogeneic HSCT patients.

Berger et al. [6] reported the incremental costs of mucositis following autologous and allogeneic HSCT accounting only for drug treatment and nutrition costs. Mucositis in autologous HSCT was associated with incremental costs of 1124,47 USD [31,39 USD nutrition, 19,11 USD analgesia, anti-infectives (6,82 USD in prophylaxis, 4,09 USD in antivirals, and 114,63 USD in antibiotics) and 949,80 USD in antifungals] in comparison with patients that did not develop mucositis. HSCT patients had an incremental cost of 10,92 USD for analgesia.

3) Chemotherapy

Sixteen studies evaluated the costs of mucositis in patients undergoing chemotherapy alone. The selected studies included a wide range of cancer diagnosis and chemotherapeutical agents [4,31-45]. Associated costs or incremental costs related to mucositis differed significantly and ranged from 4,18 USD [39] to costs exceeding 31 963,64 USD when evaluating inpatient costs for grades 3-4 mucositis [36]. Costs were lower in the ambulatory setting (284,98 USD [31] and 174 USD [34]) when compared to the hospital setting ([3980,81 USD [45], grade 1-2: 3936,11 USD and grade 3-4: 8038,33 USD [4] and 31 963,64 USD [36]). The two studies from China reported the lowest incremental costs for mucositis, 4,18 USD [39] and 5,65 USD (supportive care symptoms/hydration) [38]. Fragoulakis et al. assumed that the costs for one week of supportive therapy for stomatitis grades 4 and 5 to be of 24,64 USD [32]. Ojeda et al. [42] and Capri and Cattaneo [44] reported similar costs for mucositis (grades 1 through 4) among ovarian cancer patients treated with pegylated liposomal doxorubicin hydrochloride versus topotecan. Incremental costs by grade were: grade 1: 0 USD, grade 2: 233,38 USD, grade 3 1581,59 USD and grade 4: 2904,76 USD while the later reported grade 1: 26,01 USD, grade 2: 52,02 USD, grade 3: 1687,06 USD and grade 4: 2904,76 USD. This was the only study to report individual costs for each grade of mucositis associated with chemotherapy alone, finding that higher grades of mucositis were associated with higher costs. Three of the chemotherapy studies only associated costs with grades 3-4 events: 3371,28 USD [37], 805,76 USD [43], 825,78 USD [40]. Rashid et al. [36] evaluated the costs of grade 3-4 single episodes in the outpatient (5863,24 USD), hospital setting (31 963,64 USD) and multiple episodes (82 504,19 USD for emergency room and hospital expenditures).

In contrast, one study reported that mucositis alone in the hospital setting was not associated with incremental costs compared to no adverse events; and that mucositis is not usually the only

diagnosis leading to hospitalization, and instead, a condition named MUPLUS that includes inpatient clusters anemia(A), neutropenia(N), thrombocytopenia(T), mucositis(M) and dehydration(D) is associated with additional 642,13 USD [34].

4) Molecular Targeted therapy

Only one study, Mickisch et al. [46], evaluated the cost of adverse events for molecular targeted therapy. The study included stomatitis grades 2 and 3-4 in patients diagnosed with metastatic renal carcinoma treated with either bevacizumab+interferon-alpha-2a (IFN) or sunitinib. Average costs were estimated at 104,39 USD in Germany, 187,90 USD in the UK and 3484,91 USD in France for grade 2 and 45,78 USD in France, 730,95 in the UK and 2591,99 in Germany for grades 3-4.

5) Multimodal therapy

Five studies examined more than one therapy (most commonly, chemotherapy versus molecular targeted therapy). Three of these studies focused on NSCLC patients [47-49], one on colorectal cancer patients [50] and one on sarcoma patients [51]. Costs associated with mucositis varied significantly and ranged from 12,42 USD (mouthwashes) [48] to 5670,46 USD [51].

Four of the studies evaluated costs in grades 3-4 mucositis [47-50], and only one reported aggregate costs comprising all grades [51]. For NSCLC patients treated with erlotinib versus docetaxel/pemetrexed, erlotinib or pemetrexed in which adverse events data were retrieved from a phase III trial then costs were estimated from a panel of experts, grade 3-4 stomatitis/mucositis was responsible for incremental 169,60 USD in Brazil, 495,57 USD in Germany, 636,15 USD in France, 72,52 USD in Italy and 173,28 USD in Spain [47,49]. An additional study reported incremental costs of 12,42 USD (mouthwashes) for mucositis in Germany [48]. Incremental costs of grades 3-4 stomatitis in colorectal cancer patients treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab, and epithelial growth factor receptor inhibitors (EGFRI) were estimated at 1110,67 USD [50]. Soft tissue sarcoma patients treated with olaratumab+doxorubicin versus doxorubicin alone had an additional cost of 5670,46 USD associated with mucositis [51].

6) Not specified treatment

We have also included three studies that evaluated costs associated with mucositis in cancer patients but did not specify the cancer treatment [52-54]. Bermejo de Las Heras et al. [54] evaluated the cost of adverse events in metastatic breast cancer patients and estimated an additional 1620,47 USD associated with mucositis. Zhang et al. [54] estimated inpatient and outpatient costs of mucositis in patients diagnosed with acute lymphocytic leukemia using insurance claims data (9233,69 USD and 565,85 USD, respectively). Wong et al. [52], evaluated the incremental costs per treatment episode of stomatitis/mucositis of any severity (1893,73 USD), severe (20 279,12 USD) and the incremental cost by cancer type: breast (1073,67 USD), lung (3673,50 USD), lymphatic/hematopoietic tissue (7474,37 USD) and digestive organs/peritoneum (2738,37 USD).

Discussion

Total medical spending on cancer care has been increasing at an unsustainable rate, and there is a fundamental value problem as to how to optimize treatment outcomes at the lowest possible cost [1,2]. Nevertheless, what is not measured or evaluated cannot be managed or improved [55]. In this context, as mucositis treatment is challenging, and costs can lead to a financial burden to hospitals, health insurance, governments, and the patients themselves [3,5,6,23,38], we sought to synthesize alimentary mucositis cost findings into a systematic review. To the best of our knowledge, this is the first systematic review to address the direct incremental healthcare costs associated with mucositis in all cancer treatments in which mucositis may be involved. Even though we included a wide range of cancer subtypes and treatments in evaluating the costs associated with mucositis, only 37 articles were selected.

Considering the severe outcomes associated with mucositis, resource utilization increased significantly among affected patients, leading to significant incremental costs. Mucositis following radiotherapy/chemoradiotherapy/radiotherapy plus molecular targeted therapy, HSCT, chemotherapy, molecular targeted therapy, multimodal therapy and treatment not specified warrants a substantial need for resource utilization, resulting in increased costs that ranged from 4,18 USD [39] to 299 214,14 USD [5]. Although costs varied across the studies depending on cancer treatment modality, resource utilization, hospitalization rates, additional hospital stay reported, and country evaluated, there is overwhelming evidence that the economic burden of mucositis is high [3,11].

HSCT is steadily rising in the treatment of cancer, and it requires highly specialized, resource-intensive care, and therefore is a costly treatment [56]. Accordingly, mucositis also

appears to be a significant cost driver in HSCT, where it was associated with an increase in the length of hospital stay. Mucositis costs in this setting were higher than any other setting evaluated. The highest recorded grade of mucositis was a significant predictor of febrile days, days of total parenteral nutrition, days of injectable narcotic therapy, resulting in an increased length of hospital stay and exacerbated total inpatient charges [5].

It is important to note that the costs of mucositis vary substantially worldwide and therefore, mucositis management costs should be assessed on an individual country basis, and the findings cannot be extrapolated to other countries [31,42,46,49].

In a particular study that evaluated costs associated with adverse events, the driver of total costs was hospitalizations, accounting for 94.3% of all costs [44]. Similar findings were also valid for mucositis, and hospitalization often to manage mucositis accounts for the majority of treatment costs [9,5,24,26,36,53].

One study reported that mucositis alone in the hospital setting was not associated with incremental costs when compared to no adverse events costs; they mention that mucositis is not usually the only diagnosis that leads to hospitalization, and instead, clusters of MUPLUS are what predispose costs [34]. It is noteworthy to report that patients with mucositis often present with other complications (i.e., gastrointestinal bleeding, volume depletion, cardiac failure, renal failure) that also could result in more extended hospital stays and higher costs of care [5].

On average, costs were greater for patients experiencing more severe mucositis. In one study, stomatitis and mucositis of any severity were associated with incremental 1893,73 USD while severe adverse events accounted for incremental costs of 20 279,12 USD [52]. Higher grades of OM in radiotherapy alone required an increased number of visits to dental oncologists and dieticians, as well as increased use of opioid analgesics, and gastrostomy tubes [3].

During chemotherapy cycles with mucositis, liquid diets, total parenteral nutrition, fluid replacement, antifungal and antiviral therapy, and prophylaxis were more common. The serious outcomes of mucositis led to more days of hospitalization per cycle (four days with no mucositis and six with mucositis): the average additional cost of hospitalization was 3443,55 USD per cycle with OM, 7567,44 USD per cycle with gastrointestinal mucositis, and 7609,33 per cycle with both oral/gastrointestinal mucositis [4].

In the radiotherapy/chemoradiotherapy setting, the following premise can explain why mucositis can become burdensome and implicates in a considerable amount of resource utilization that results in enhanced costs. The commonest symptom of mucositis is pain; which requires a shift from solid to soft food to nutritional supplements. Mucous production, altered

taste, and dry mouth result in weight loss, and eventually, the placement of feeding tubes becomes compulsory. This scenario represents an increased need for consultations with health professionals (e.g., physicians, nurses, nutritionists, speech therapists and dentists). Pain is also responsible for a change in opioid use patterns, from oral to transdermal/parenteral forms. Impaired swallowing can result in hospitalization for placement of a feeding tube, aspiration pneumonia with respiratory compromise, the need for intravenous fluids due to dehydration, and renal insufficiency due to failure to hydrate. Ulcers also act as a site for local infection and can cause septicemia. Hospitalizations may also be a requirement for intravenous analgesia and antibiotics [11,29,57].

Clinical implications

By exploring mucositis and its cost drivers, we aimed to identify ways in which we can reduce costs. The current medical care paradigm is mainly focused on treatment rather than on prevention [58], but preventive measures before cancer treatment appear to be one of the ways to reduce the costs associated with mucositis and includes high-quality clinical practice, good oral hygiene, nutritional support and adequate pain management [28]. As prolonged management of mucositis and its further complications carries additional clinical and economic costs, a therapy that reduces both the duration and the acuity of this condition would be beneficial [29].

The Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) has recently updated the guidelines on protocols for the management of mucositis [59]. They underscore the importance of basic oral care in the prevention of OM during chemotherapy, head and neck radiotherapy and HSCT; recommend the use of oral cryotherapy for bolus dosing of 5-fluorouracil and high-dose melphalan for autologous HSCT; and the usage of recombinant human keratinocyte growth factor-1 (palifermin) in autologous HSCT with high-dose chemotherapy and total body irradiation. Additionally, there is a recommendation for the prevention of OM with intraoral photobiomodulation therapy (PBMT) in patients who undergo HSCT and in patients receiving head and neck radiotherapy, with or without concomitant chemotherapy.

Although literature lacks studies that explore the economic benefits of a given treatment when preventing or treating mucositis, PBMT appears to be an effective tool for reducing the economic burden of mucositis. PBMT is known for its anti-inflammatory, analgesic and tissue repair properties and is considered one of the most effective forms of therapy for OM both as

treatment or prevention [60]. In the HSCT treatment setting, the introduction of PBM resulted in 30% fewer hospital costs [61], and it proved to be cost-effective with a reduction in costs of 5592,10 USD per grade 3-4 OM case prevented [25] and at 2979,95 USD for each severe case prevented [26].

Ongoing research on agents that can help reduce the incidence, severity, and duration of mucositis may help alleviate the costs associated with mucositis. Results from a phase IIb randomized trial show that superoxide dismutase mimetic GC4419, has the potential for safely achieving a clinically significant reduction in the incidence, severity, and duration of chemoradiation-induced severe mucositis [62]. Additionally, two mouthwashes, one containing doxepin and the other, diphenhydramine-lidocaine-antacid, were more effective than placebo in reducing OM pain in patients receiving radiotherapy with or without chemotherapy [63,64]. Additionally, it may be helpful to disseminate timely and accurate cost information, such as the information synthesized in this systematic review, to healthcare leaders, providers and payers to in order to inform decisions to lower costs while sustaining or improving outcomes, by favoring preventive measures. Stakeholders may also introduce more cost-effective processes, financing and investing in new research for preventive or therapeutic measures to reduce costs associated with mucositis.

Costs versus Charges

Charges are the amounts set by health systems for services before any discounts, which differs from actual costs of care. We could not combine the findings from all included studies, mainly due to variations in the methodology used for reporting mucositis and its related costs or charges. A few of the studies analyzed the charges of mucositis rather than costs and comparison among them is inappropriate because charges exceed the costs [65]. Regardless of whether studies observed actual costs or charges, mucositis is costly.

Limitations

Most studies evaluated costs on a retrospectively and some of the costs used in the economic evaluation were derived from phase III clinical trials that only reported the percentage of mucositis, without the utility data, which then was estimated through expert advice. These methods have shown limitations and bias as it is difficult to estimate the resource use and costs retrospectively and may result in under-reporting of costs [3,4, 43, 49, 50]. A few of the studies restricted their economic evaluation to severe grades 3/4 mucositis as authors believe grades 1

and 2 are associated with minor costs [49]. However, the costs associated with grades 1 and 2 mucositis should also be reported to evaluate the full constituent of costs. Studies also often combine grade 3 and 4 as only one cost, but therapeutic and economic consequences of grade 3 and 4 events can differ remarkably [49].

Despite the limitations highlighted, mucositis is associated with a substantial increase in costs independent of cancer treatment modality.

Conclusion

This systematic review demonstrated that mucositis is associated with increased use of resources, extra consultations, hospitalizations and extended hospitalizations. This leads to an increase in costs ranging from 4,18 USD in chemotherapy to 299 214,14 USD in HSCT. The aforementioned costs accumulate economic burden on the patient, health plan and health system across all cancer sites and treatments. More studies with a careful prospective evaluation of the economic costs associated with mucositis management are needed, and clinical trials should include the costs of adverse events management, including mucositis. Finally, therapies that prevent, reduce the incidence, severity, and duration of mucositis may help alleviate the economic burden of mucositis. In this scenario, PBMT is promising, but new therapies are needed to help with alleviating mucositis and to reduce economic burden on any health plan or health system.

Funding: This work was supported in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

References

[1] Buffery D. Health Economics in Oncology: A Necessary Tool for Value-Based Patient Care. Am Health Drug Benefits 2015;8(4):184.

[2] Miller JD, Foley KA, Russell MW. Current challenges in health economic modeling of cancer therapies: a research inquiry. Am Health Drug Benefits 2014;7(3):153-62.

[3] Elting LS, Cooksley CD, Chambers MS, Garden AS. Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. Int J Radiat Oncol Biol Phys 2007;68(4):1110-1120.
https://doi:10.1016/j.ijrobp.2007.01.053.

[4] Elting LS, Cooksley C, Chambers M, Cantor SB, Manzullo E, Rubenstein EB. The burdens of cancer therapy. Clinical and economic outcomes of chemotherapy-induced mucositis. Cancer 2003;98(7):1531-1539.
https://doi:10.1002/cncr.11671.

[5] Vera-Llonch M, Oster G, Ford CM, Lu J, Sonis S. Oral mucositis and outcomes of allogeneic hematopoietic stem-cell transplantation in patients with hematologic malignancies. Support Care Cancer 2007;15(5):491-496.
https://doi:10.1007/s00520-006-0176-9.

[6] Berger K, Staudenmaier T, Cenzer I, Crispin A, Strobach D, Ostermann H. Epidemiology, patient adherence, and costs of oral mucositis in routine care in stem cell transplantation. Support Care Cancer 2020;28(7):3113-3123.
https://doi:10.1007/s00520-019-05107-2.

[7] Lalla RV, Schubert MM, Bensadoun RJ, Keefe D. Anti-inflammatory agents in the management of alimentary mucositis. Support Care Cancer 2006;14(6):558-565.
https://doi:10.1007/s00520-006-0050-9.

[8] Wong W, Yim YM, Kim A, Cloutier M, Gauthier-Loiselle M, Gagnon-Sanschagrin P, et al. Assessment of costs associated with adverse events in patients with cancer. PLoS One 2018;13(4):e0196007.
https://doi:10.1371/journal.pone.0196007.

[9] Peterman A, Cella D, Glandon G, Dobrez D, Yount S. Mucositis in head and neck cancer: economic and quality-of-life outcomes. J Natl Cancer Inst Monogr 2001;(29):45-51.
https://doi:10.1093/oxfordjournals.jncimonographs.a003440.

[10] Lalla RV, Bowen J, Barasch A, Elting L, Epstein J, Keefe DM, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy [published correction appears in Cancer. 2015 Apr 15;121(8):1339]. Cancer 2014;120(10):1453-1461.
https://doi:10.1002/cncr.28592.

[11] Murphy BA, Beaumont JL, Isitt J, Garden AS, Gwede CK, Trotti AM, et al. Mucositis-related morbidity and resource utilization in head and neck cancer patients receiving radiation therapy with or without chemotherapy. J Pain Symptom Manage 2009;38(4):522-532.
https://doi:10.1016/j.jpainsymman.2008.12.004.

[12] Oronsky B, Goyal S, Kim MM, Cabrales P, Lybeck M, Caroen S, et al. A Review of Clinical Radioprotection and Chemoprotection for Oral Mucositis. Transl Oncol 2018;11(3):771-778.
https://doi:10.1016/j.tranon.2018.03.014.

[13] Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement [published correction appears in Int J Surg. 2010;8(8):658]. Int J Surg 2010;8(5):336-341.
https://doi:10.1016/j.ijsu.2010.02.007.

[14] National Institute for Health Research. PROSPERO International prospective register of systematic reviews. Available from: https://www.crd.york.ac.uk/prospero/. [Accessed 29 October 2020].
[15] Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5(1):210.
https://doi:10.1186/s13643-016-0384-4.
[16] Shemilt I, Thomas J, Morciano M. A web-based tool for adjusting costs to a specific target currency and price year. Evid Policy 2010; 6:51–9.
https://doi.org/10.1332/174426410X482999.
[17] Campbell and cochrane economics methods group and the evidence for policy and practice information and coordinating centre. CCEMG–EPPI - centre cost converter (v.1.6). Available from: http://eppi.ioe.ac.uk/costconversion/default.aspx. [Accessed 29 October 2020].
[18] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
https://doi:10.1136/bmj.d5928.
[19] Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
https://doi:10.1136/bmj.i4919.
[20] Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. Int J Technol Assess Health Care 2005;21(2):240-245.
[21] van Mastrigt GA, Hiligsmann M, Arts JJ, Broos PH, Kleijnen J, Evers SM, et al. How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: a five-step approach (part 1/3). Expert Rev Pharmacoecon Outcomes Res 2016;16(6):689-704.
https://doi:10.1080/14737167.2016.1246960
[22] National Cancer Institute (NCI), National Cancer Health (NIH), Common Toxicity Criteria (CTCAE). Version 5.0. Available from: https://ctep.cancer.gov. [Accessed 29 October 2020].
[23] Parulekar W, Mackenzie R, Bjarnason G, Jordan RC. Scoring oral mucositis. Oral Oncol 1998;34(1):63-71.
https://doi:10.1016/s1368-8375(97)00065-1.
[24] Nonzee NJ, Dandade NA, Patel U, Markossian T, Agulnik M, Argiris A, et al. Evaluating the supportive care costs of severe radiochemotherapy-induced mucositis and pharyngitis : results from a Northwestern University Costs of Cancer Program pilot study with head and neck and nonsmall cell lung cancer patients who received care at a county hospital, a Veterans Administration hospital, or a comprehensive cancer care center [published correction appears in Cancer. 2009 Jun 15;115(12):2805. Patel, Urjeet [added]]. Cancer 2008;113(6):1446-1452.
https://doi:10.1002/cncr.23714
[25] Antunes HS, Schluckebier LF, Herchenhorn D, Small IA, Araújo CM, Viégas CM, et al. Cost-effectiveness of low-level laser therapy (LLLT) in head and neck cancer patients receiving concurrent chemoradiation. Oral Oncol 2016;52:85-90.
https://doi:10.1016/j.oraloncology.2015.10.022.
[26] Lopes Martins AF, Nogueira TE, Morais MO, de Sousa-Neto SS, Oton-Leite AF, Valadares MC, et al. Cost-effectiveness randomized clinical trial on the effect of photobiomodulation therapy for prevention of radiotherapy-induced severe oral mucositis in a

Brazilian cancer hospital setting [published online ahead of print, 2020 Jul 3]. Support Care Cancer 2020.
https://doi:10.1007/s00520-020-05607-6.
[27] Brown B, Diamantopoulos A, Bernier J, Schöffski P, Hieke K, Mantovani L, et al. An economic evaluation of cetuximab combined with radiotherapy for patients with locally advanced head and neck cancer in Belgium, France, Italy, Switzerland, and the United Kingdom. Value Health 2008;11(5):791-799.
https://doi:10.1111/j.1524-4733.2007.00302.x.
[28] Cho SK, McCombs J, Punwani N, Lam J. Complications and hospital costs during hematopoietic stem cell transplantation for non-Hodgkin lymphoma in the United States. Leuk Lymphoma 2019;60(10):2464-2470.
https://doi:10.1080/10428194.2019.1581932.
[29] Sonis ST, Oster G, Fuchs H, Bellm L, Bradford WZ, Edelsberg J, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. J Clin Oncol 2001;19(8):2201-2205.
https://doi:10.1200/JCO.2001.19.8.2201.
[30] Jones JA, Qazilbash MH, Shih YC, Cantor SB, Cooksley CD, Elting LS. In-hospital complications of autologous hematopoietic stem cell transplantation for lymphoid malignancies: clinical and economic outcomes from the Nationwide Inpatient Sample. Cancer 2008;112(5):1096-1105.
https://doi:10.1002/cncr.23281.
[31] Lafuma A, Cotté FE, Le Tourneau C, Emery C, Gaudin AF, Torreton E, et al. Economic burden of chemotherapy-treated recurrent and/or metastatic squamous cell carcinoma of the head and neck in France: real-world data from the permanent sample of national health insurance beneficiaries. J Med Econ 2019;22(7):698-705.
https://doi:10.1080/13696998.2019.1594837.
[32] Fragoulakis V, Roncato R, Fratte CD, Ecca F, Bartsakoulia M, Innocenti F, et al. Estimating the Effectiveness of DPYD Genotyping in Italian Individuals Suffering from Cancer Based on the Cost of Chemotherapy-Induced Toxicity. Am J Hum Genet 2019;104(6):1158-1168.
https://doi:10.1016/j.ajhg.2019.04.017.
[33] Smith DH, Adams JR, Johnston SR, Gordon A, Drummond MF, Bennett CL. A comparative economic analysis of pegylated liposomal doxorubicin versus topotecan in ovarian cancer in the USA and the UK. Ann Oncol 2002;13(10):1590-1597.
https://doi:10.1093/annonc/mdf275.
[34] Weiner MG, Ross SJ, Mathew JI, Millman AM, Even-Shoshan O, Fox KR, et al. Estimating the costs of chemotherapy-associated adverse event clusters. Health Serv Outcomes Res Method 2007;(7)1–21.
[35] Elting LS, Shih YC. The economic burden of supportive care of cancer patients. Support Care Cancer 2004;12(4):219-226.
https://doi:10.1007/s00520-003-0513-1.
[36] Rashid N, Koh HA, Baca HC, Lin KJ, Malecha SE, Masaquel A. Economic burden related to chemotherapy-related adverse events in patients with metastatic breast cancer in an integrated health care system. Breast Cancer (Dove Med Press) 2016;8:173-181.
https://doi:10.2147/BCTT.S105618.
[37] Mittmann N, Verma S, Koo M, Alloul K, Trudeau M. Cost effectiveness of TAC versus FAC in adjuvant treatment of node-positive breast cancer. Curr Oncol 2010;17(1):7-16.
https://doi:10.3747/co.v17i1.445.

[38] Dranitsaris G, Yu B, King J, Kaura S, Zhang A. Nab-paclitaxel, docetaxel, or solvent-based paclitaxel in metastatic breast cancer: a cost-utility analysis from a Chinese health care perspective. Clinicoecon Outcomes Res 2015;7:249-256.
https://doi:10.2147/CEOR.S82194.
[39] Xie Q, Wen F, Wei YQ, Deng HX, Li Q. Cost analysis of adjuvant therapy with XELOX or FOLFOX4 for colon cancer. Colorectal Dis 2013;15(8):958-962.
https://doi:10.1111/codi.12216.
[40] Groener MG, van Ineveld BM, Byttebier G, van Hout BA, Rutten FF. An economic evaluation of Tomudex (raltitrexed) and 5-fluorouracil plus leucovorin in advanced colorectal cancer. Anticancer Drugs 1999;10(3):283-288.
https://doi:10.1097/00001813-199903000-00005.
[41] Berger K, Schopohl D, Rieger C, Ostermann H. Economic and clinical aspects of intravenous versus oral busulfan in adult patients for conditioning prior to HSCT. Support Care Cancer 2015;23(12):3447-3454.
https://doi:10.1007/s00520-015-2695-8.
[42] Ojeda B, de Sande LM, Casado A, Merino P, Casado MA. Cost-minimisation analysis of pegylated liposomal doxorubicin hydrochloride versus topotecan in the treatment of patients with recurrent epithelial ovarian cancer in Spain. Br J Cancer 2003;89(6):1002-1007.
https://doi:10.1038/sj.bjc.6601228.
[43] Frías C, Cortés J, Seguí MÁ, Oyagüez I, Casado MÁ. Cost-effectiveness analyses of docetaxel versus paclitaxel once weekly in patients with metastatic breast cancer in progression following anthracycline chemotherapy, in Spain. Clin Transl Oncol 2010;12(10):692-700.
https://doi:10.1007/s12094-010-0579-4.
[44] Capri S, Cattaneo G. Cost-minimization analysis of pegylated liposomal doxorubicin versus topotecan for the treatment of ovarian cancer in Italy. Clin Ther 2003;25(6):1826-1845.
https://doi:10.1016/s0149-2918(03)80172-8.
[45] Giuliani G, Lucioni C, Mazzi S, de Carli C, Jamieson C. Valutazione di convenienza economica comparata tra un farmaco orale (capecitabina) e una chemioterapia parenterale a base di 5-FU (regime Mayo) nel trattamento del carcinoma del colon retto metastatizzato. PharmacoEconomics - Ital Res Artic 2002;4(1):31–8.
[46] Mickisch G, Gore M, Escudier B, Procopio G, Walzer S, Nuijten M. Costs of managing adverse events in the treatment of first-line metastatic renal cell carcinoma: bevacizumab in combination with interferon-alpha2a compared with sunitinib. Br J Cancer 2010;102(1):80-86.
https://doi:10.1038/sj.bjc.6605417.
[47] Doral Stefani S, Giorgio Saggia M, Vicino dos Santos EA. Cost-minimisation analysis of erlotinib in the second-line treatment of non-small-cell lung cancer: a Brazilian perspective. J Med Econ 2008;11(3):383-396.
https://doi:10.3111/13696990802208186.
[48] Kotowa W, Gatzemeier U, Pirk O, Gabriel A HD. A comparison of the estimated costs of erlotinib, docetaxel and pemetrexed for the second-line treatment of non-small cell lung cancer from the German healthcare perspective. J Med Econ 2007;255–71.
[49] Banz K, Bischoff H, Brunner M, Chouaid C, de Castro Carpeño J, de Marinis F, et al. Comparison of treatment costs of grade 3/4 adverse events associated with erlotinib or pemetrexed maintenance therapy for patients with advanced non-small-cell lung cancer (NSCLC) in Germany, France, Italy, and Spain. Lung Cancer 2011;74(3):529-534.
https://doi:10.1016/j.lungcan.2011.04.010.
[50] Riesco-Martínez MC, Berry SR, Ko YJ, Mittmann N, Giotis A, Lien K, et al. Cost-Effectiveness Analysis of Different Sequences of the Use of Epidermal Growth Factor Receptor Inhibitors for Wild-Type KRAS Unresectable Metastatic Colorectal Cancer. J Oncol Pract 2016;12(6):e710-e723.

https://doi:10.1200/JOP.2015.008730.
[51] Del Río-Valencia JC, Asensi-Díez R, Villalobos-Torres L, Clopés-Estela A, Fraga-Fuentes MªD. Economic evaluation of the GENESIS-SEFH report of olaratumab with doxorubicin in soft tissue sarcoma in advanced stages. Evaluación económica del informe GENESIS-SEFH de olaratumab con doxorrubicina en el sarcoma de tejidos blandos en estadios avanzados. Farm Hosp 2018;42(5):204-211.
https://doi:10.7399/fh.10917.
[52] Wong W, Yim YM, Kim A, Cloutier M, Gauthier-Loiselle M, Gagnon-Sanschagrin P, et al. Assessment of costs associated with adverse events in patients with cancer. PLoS One 2018;13(4):e0196007.
https://doi:10.1371/journal.pone.0196007.
[53] Zhang X, Song X, Lopez-Gonzalez L, Jariwala-Parikh K, Cong Z. Economic burden associated with adverse events of special interest in patients with relapsed Philadelphia chromosome-negative B-cell acute lymphoblastic leukemia in the United States. Expert Rev Pharmacoecon Outcomes Res 2018;18(5):573-580.
https://doi:10.1080/14737167.2018.1490645.
[54] Bermejo de Las Heras B, Cortes Ramon Y Cajal J, Galve Calvo E, de la Haba Rodriguez J, Garcia Mata J, Moreno Anton F, et al. The economic burden of metastatic breast cancer in Spain. Eur J Hosp Pharm 2020;27(1):19-24.
https://doi:10.1136/ejhpharm-2017-001453.
[55] Harvard Business Review. The big idea: how to solve the cost crisis in health care. Available from:
https://hbr.org/2011/09/how-to-solve-the-cost-crisis-in-health-care. [Accessed 29 October 2020].
[56] Broder MS, Quock TP, Chang E, Reddy SR, Agarwal-Hashmi R, Arai S, et al. The Cost of Hematopoietic Stem-Cell Transplantation in the United States. Am Health Drug Benefits 2017;10(7):366-374.
[57] Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer. 2004;100(9 Suppl):1995-2025.
https://doi:10.1002/cncr.20162.
[58] Loeppke R. The value of health and the power of prevention. Int J Work Heal Manag 2008;1(2):95–108.
[59] Elad S, Kin K, Cheng F, Lalla R V, Yarom N, Hong C, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy [published online ahead of print, 2020 Jul 28]. Cancer. 2020;126(19):4423-4431.
https://doi:10.1002/cncr.33100.
[60] Sandoval RL, Koga DH, Buloto LS, Suzuki R, Dib LL. Management of chemo- and radiotherapy induced oral mucositis with low-energy laser: initial results of A.C. Camargo Hospital. J Appl Oral Sci 2003;11(4):337-341.
https://doi:10.1590/s1678-77572003000400012.
[61] Bezinelli LM, de Paula Eduardo F, da Graça Lopes RM, Biazevic MG, de Paula Eduardo C, Correa L, et al. Cost-effectiveness of the introduction of specialized oral care with laser therapy in hematopoietic stem cell transplantation. Hematol Oncol 2014;32(1):31-39.
https://doi:10.1002/hon.2050.
[62] Anderson CM, Lee CM, Saunders DP, Curtis A, Dunlap N, Nangia C, et al. Phase IIb, Randomized, Double-Blind Trial of GC4419 Versus Placebo to Reduce Severe Oral Mucositis Due to Concurrent Radiotherapy and Cisplatin For Head and Neck Cancer [published correction appears in J Clin Oncol. 2020 Jan 20;38(3):288]. J Clin Oncol 2019;37(34):3256-3265.
https://doi:10.1200/JCO.19.01507.

[63] Sio TT, Le-Rademacher JG, Leenstra JL, Loprinzi CL, Rine G, Curtis A, et al. Effect of Doxepin Mouthwash or Diphenhydramine-Lidocaine-Antacid Mouthwash vs Placebo on Radiotherapy-Related Oral Mucositis Pain: The Alliance A221304 Randomized Clinical Trial. JAMA 2019;321(15):1481-1490.
https://doi:10.1001/jama.2019.3504.
[64] Leenstra JL, Miller RC, Qin R, Martenson JA, Dornfeld KJ, Bearden JD, et al. Doxepin rinse versus placebo in the treatment of acute oral mucositis pain in patients receiving head and neck radiotherapy with or without chemotherapy: a phase III, randomized, double-blind trial (NCCTG-N09C6 [Alliance]). J Clin Oncol 2014;32(15):1571-1577.
https://doi:10.1200/JCO.2013.53.2630.
[65] Finkler SA. The distinction between cost and charges. Ann Intern Med 1982;96(1):102-109.
https://doi:10.7326/0003-4819-96-1-102

Appendix 1: Search strategy

The following search strategy was designed to identify studies that report costs on mucositis.

Database	Search
PubMed October, 31st, 2020	#1 ((mucositis[MeSH Terms]) OR (stomatitis[MeSH Terms])) OR (mucositis OR stomatitis OR oropharyngitis OR "oral ulcer" OR "oral ulcers" OR aphthous) #2: ("costs and cost analysis"[MeSH Terms]) OR (hospital costs[MeSH Terms]) OR (cost OR costs OR "cost-effectiveness" OR economic) #3: (neoplasms[MeSH Terms]) OR (neoplas* OR tumors OR tumours OR tumor OR tumour OR cancer OR cancers OR malignant OR malignancies OR malignancy) #4: (("antineoplastic protocols"[MeSH Terms]) OR (therapeutics[MeSH Terms])) OR ("cancer treatment" OR therapeutic OR therapy OR therapies OR treatment OR treatments) #1 AND #2 AND #3
EMBASE October, 31st, 2020	#1: (mucositis OR stomatitis OR oropharyngitis OR "oral ulcer" OR "oral ulcers" OR aphthous) #2: ("cost and cost analysis" OR cost OR costs OR "cost-effectiveness" OR economic) #3: (neoplas* OR tumors OR tumours OR tumor OR tumour OR cancer OR cancers OR malignant OR malignancies OR malignancy) #4: ("antineoplastic protocols" OR therapeutics OR "cancer treatment" OR therapeutic OR therapy OR therapies OR treatment OR treatments) #1 AND #2 AND #3

SCOPUS October, 30st, 2020	#1: (mucositis OR stomatitis OR oropharyngitis OR "oral ulcer" OR "oral ulcers" OR aphthous) #2: ("cost and cost analysis" OR cost OR costs OR "cost-effectiveness" OR economic) #3: (neoplas* OR tumors OR tumours OR tumor OR tumour OR cancer OR cancers OR malignant OR malignancies OR malignancy) #4: ("antineoplastic protocols" OR therapeutics OR "cancer treatment" OR therapeutic OR therapy OR therapies OR treatment OR treatments) #1 AND #2 AND #3

Table 1: Baseline characteristics of the included studies.

Treatment modality				Condition evaluated				Study type		
	Country	Cancer type	Treatment	Oral mucositis	Mucositis	Stomatitis	Other	Prospective	Retrospective	Resource utilization
- RT/ CRT/ molecular targeted therapy										
Elting et al., 2007 [3]	USA	HNC	RT or CRT	X	-	-	-	-	Chart review	Chart review
Peterman et al., 2001 [9]	USA	HNC	RT or CRT	-	X	-	-	-	Chart review	Panel of experts
Murphy et al., 2009 [11]	USA	HNC	RT or CRT	-	X	-	-	Longitudinal multicenter noninterventional	-	Chart review/ Patient interview
Nonzee et al., 2008 [24]	USA	HNC/ NSCLC	CRT	-	X	-	Pharyngitis	-	Chart review	Chart review
Antunes et al., 2016 [25]	Brazil	HNC	CRT	X	-	-	-	Randomized, double-blind, placebo-controlled phase III clinical trial	-	Brazil's public health system
Lopes Martins et al., 2020 [26]	Brazil	HNC	RT or CRT	X	-	-	-	Randomized, double-blind, placebo-controlled trial	-	Chart review
Brown et al., 2008 [27]	Belgium, France, Italy, SWI and UK	HNC (locally advanced)	RT alone or in combination with weekly Cetuximab	-	X	X	Dysphagia	-	Phase III clinical trial	Panel of experts
- HSCT										
Vera-Llonch et al., 2007 [5]	USA	Leukemia, lymphoma and myelodysplasia	Allogeneic	X	-	-	-	-	Chart review	Chart review
Berger et al., 2020 [6]	Germany	Hematological	Autologous and Allogeneic	X	-	-	-	Noninterventional single-center observational study	-	Database
Cho et al., 2019 [28]	USA	Non-Hodgkin lymphoma	Autologous and Allogeneic	-	X	-	-	-	Database	Database
Sonis et al., 2001 [29]	USA	Hematologic, lymphatic or solid tumors	Autologous and Allogeneic	X	-	-	-	-	Chart review	Chart review
Jones et al., 2008 [30]	USA	M.M., lymphomas	Autologous	-	-	X	-	-	Database	Database
- Chemotherapy										
Elting et al., 2003 [4]	USA	Solid tumors or lymphomas	Chemotherapy-induced myelosuppression	X	-	-	Gastrointestinal	-	Database/ Chart review	Database/ Chart review
Lafuma et al.,2019 [31]	France	HNC (Recurrent or metastatic)	CT	-	X	X	-	-	Database	Database

Fragoulakis et al., 2019 [32]	Italy	Not specified	Fluoropyrimidines	-	-	X	-	-	Database	Database
Smith et al., 2002 [33]	USA and UK	Ovarian cancer	PLD versus Topotecan	-	-	X	Pharyngitis	-	Phase III clinical trial	Panel of experts
Weiner et al., 2007 [34]	USA	All cancer patients that received CT*	CT not specified	-	X	-	-	-	Database	Database
Elting and Shih, 2004 [35]	USA	No specific type of cancer	CT	-	X	X	-	-	Database	Database
Rashid et al., 2016 [36]	USA	Breast cancer (metastatic)	Capecitabine, Taxane, Cyclophosphamide, Doxorubicin, Gemcitabine, Epirubicin, Vinorelbine, Ixabepilone, or Eribulin.	-	-	X	-	-	Database/ Chart review	Database costs/ Cost of drugs
Mittmann et al., 2010 [37]	Canada	Breast cancer	Docetaxel plus Doxorubicin and Cyclophosphamide compared with 5FU, Doxorubicin and Cyclophosphamide	-	-	X	-	-	Data from previous study	Data from previous study
Dranitsaris et al., 2015 [38]	China	Breast cancer (metastatic)	Nab-paclitaxel, Docetaxel, or solvent-based Paclitaxel	-	-	X	-	-	Phase III clinical trial	Panel of experts
Xie et al., 2013 [39]	China	Colon cancer	XELOX or FOLFOX-4	-	-	X	-	-	Chart review	Chart review
Groener et al., 1999 [40]	Netherlands	Colorectal cancer (advanced)	Tomudex versus 5FU + Leucovorin	-	X	-	-	-	Data from previous study	Data from previous study
Berger et al., 2015 [41]	Germany	Not specified	Busulfan for conditioning prior to HSCT	X	-	-	-	-	Data from previous study	Panel of experts
Ojeda et al., 2003 [42]	Spain	Ovarian cancer (recurrent)	PLD hydrochloride versus Topotecan	-	-	X	Pharyngitis	-	Phase III clinical trial	Panel of experts
Frías et al., 2010 [43]	Spain	Breast cancer (metastatic)	Docetaxel versus weekly Paclitaxel	-	-	X	-	-	Phase III clinical trial	Panel of experts
Capri and Cattaneo, 2003 [44]	Italy	Ovarian cancer	PLD and Topotecan	-	-	X	-	-	Phase III clinical trial	Panel of experts
Giuliani et al., 2002 [45]	Italy	Colorectal cancer (advanced)	Oral Capecitabine versus intravenous 5FU + Leucovorin	-	-	X	-	-	Phase III clinical trial	Data from previous study
- Molecular targeted therapy										
Mickisch et al., 2010 [46]	UK, Germany, France and Italy	Renal carcinoma (metastatic)	Bevacizumab + IFN versus Sunitinib	-	-	X	-	-	Phase III clinical trials	Data from previous study
- Multimodal therapy										

Doral Stefani et al., 2008 [47]	Brazil	NSCLC	Erlotinib versus Docetaxel or Pemetrexed	-	-	X	-	-	Clinical trial	Panel of experts
Kotowa et al., 2007 [48]	Germany	NSCLC	Erlotinib, Docetaxel and Pemetrexed	-	-	X	-	-	Phase III clinical trial	Data from previous study
Banz et al., 2011 [49]	Germany, France, Italy and Spain	NSCLC	Erlotinib or Pemetrexed	-	X	X	-	-	Clinical trial	Panel of experts
Riesco-Martínez et al., 2016 [50]	Canada	Colorectal cancer (unresectable wild-type KRAS metastatic)	Fluoropyrimidines, Oxaliplatin, Irinotecan, Bevacizumab, and Epithelial growth factor receptor inhibitors.	-	-	X	-	-	Database/ Chart review	Database/ Chart review
Del Río-Valencia et al., 2018 [51]	Spain	Soft tissue sarcoma	Olaratumab + Doxorubicin versus Doxorubicin alone	-	X	-	-	-	Phase IIb/II clinical trial	Database
- Not specified treatment										
Wong et al., 2018 [52]	USA	Most prevalent types of cancer**	Not specified	-	X	X	-	-	Database	Database
Zhang et al., 2018 [53]	USA	Acute lymphocytic leukemia	Not specified	-	X	X	-	-	Database	Database
Bermejo de Las Heras et al., 2020 [54]	Spain	Breast cancer (metastatic)	Not specified	-	X	X	-	-	Cost-of-illness model Estimates	Panel of experts

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; FOLFOX-4, Oxaliplatin, Folinic Acid and 5-Fluorouracil; HNC, head and neck cancer; HSCT, hematopoietic stem cell transplantation; IFN, Interferon; KRAS, Kirsten rat sarcoma viral oncogene homolog; M.M., multiple myeloma; NSCLC, non-small cell lung cancer; PLD, Pegylated Liposomal Doxorubicin; RT, radiotherapy; SWI, Switzerland; UK, United Kingdom; USA, United States of America; XELOX, Capecitabine plus Oxaliplatin; 5-FU, 5-Fluorouracil;
* Leukemia/lymphoma, breast, colon, lung, gynecologic, non-colon gastrointestinal, head and neck, urinary tract, brain, melanoma, prostate, unspecified, bone/soft tissues, testes, pleura, mediastinum, endocrine and non-melanoma skin.
** Bladder, breast, digestive organs and peritoneum, ovary and other uterine adnexa, other genitourinary organs, lung, lymphatic and hematopoietic tissue and skin.

Table 2. Characteristics of included studies reporting costs.

Treatment modality - RT/ CRT/ molecular targeted therapy	Country	Cancer type	Treatment	OM/M/S	Grading system	Sample size	Cost perspective	Year/ Currency/ Cost type	Reported cost (cost estimates in 2021 USD)
Elting et al., 2007 [3]	USA	HNC	RT or CRT	OM	NCI	204 patients (109 RT and 95 CRT)	Provider's perspective	2006; USD; Costs	Mean incremental cost: **- Average:** Grade 1-2: 1700 (2209,80) Grade 3-4: 3600 (4679,57) **- OM RT = 5978 (7770,68)** Grade 1-2: 1900 (2469,77) Grade 3-4: 2100 – 2200 (2469,77– 2469,77) **- OM CRT = 6046 (7859,08)** Grade 1-2: 2200 – 2400 (2859,74– 3119,71) Grade 3-4: 2400-2500 (3119,71– 3249,70)
Nonzee et al., 2008 [24]	USA	HNC/ NSCLC	CRT	M+P	N.I.	139 patients (99 HNC and 40 NSCLC)	Payer's/ Provider's perspective	2005; USD; Costs	Mean Incremental cost for each resource use: - Inpatient hospitalization: 12 600 (16 874,03) - Tests and procedures: 2325 (3113,66) - Imaging procedures: 1119 (1498,57) - Clinic visits: 420 (562,47) - M/P related medications: 110 (147,31) - Laboratory diagnostic tests: 101 (135,26) **- Total: 18 515 (24 795,46)** HNC – incremental costs - Inpatient hospitalization: 14 000 (18 748,93) - Tests and procedures: 2226 (2981,08) - Imaging procedures: 2092 (2801,63) - Clinic visits: 510 (683) - M/P related medications: 90 (120,53) - Laboratory diagnostic tests: 90 (120,53) **- Total: 17 244 (23 093,32)** NSCLC – incremental costs - Inpatient hospitalization: 11 200 (14 999,14) - Tests and procedures: 780 (1044,58)

									- Imaging procedures: 4146 (5552,36) - Clinic visits: 960 (1285,64) - M/P related medications: 3 (4,02) - Laboratory diagnostic tests: 208 (278,56) **- Total: 25 060 (33 560,58)**
Antunes et al., 2016 [25]	Brazil	HNC	CRT	OM	WHO, NCI, OMAS	94 patients (47 PBMT and 47 placebo group)	Societal perspective Perspective of Brazil's public health care system (SUS)	2013; USD; Costs	Grade 3-4 OM - Cost per patient - Hospitalization: 77,03 (88,63) - Opioids use: 44,28 (50,95) - Gastrostomy 129,86 (149,41) **- Total: 251,17 (288,99)**
Lopes Martins et al., 2020 [26]	Brazil	HNC	RT or CRT	OM	WHO, NCI	48 patients (25 PBMT and 23 control)	Provider's perspective	2018; USD; Costs	Grade 3-4 (WHO) and grade 3-4-5 (NCI) - Visits to the emergency service: 185,17 (196,40) - Nasoenteral tube: 36,25 (38,45) - Opioids: 4,44 (4,71) - NSAIDS: 1,35 (1,43) - Corticosteroids: 2,11 (2,24) - Electrolyte replacement/ polyvitamins: 15,63 (16,58) - Hospitalization: 253,49 (268,86) **- Final cost: 48,30 (51,23)**
Brown et al., 2008 [27]	Belgium, France, Italy, SWI and the UK	HNC (locally advanced)	RT alone or in combination with weekly Cetuximab	M+S+D	N.I.	Based on a phase III randomized trial	Societal/ Payer's perspective	2005; Euros; Costs	**Belgium:** Grade 2/3/4: 4408 (6987,79) **France:** Grade 2/3: 1756 (2716,62); Grade 4: 3236 (5006,26) **Italy:** Grade 2/3/4: 3605 (6214,38) **SWI:** Grade 3: 3349 (4485,01); Grade 4: 26 790* (35 877,41*) **UK:** Grade 2: 2710 (4192,51), Grade 3/4: 4524 (6998,86) *estimated inpatient length of stay of 28 days.
- HSCT									
Berger et al., 2020 [6]	Germany	Hematological	Autologous and Allogeneic	OM	WHO	45 patients (25 allogenic and 25 autologous)	Provider's perspective	2018; Euros; Costs	Autologous patients: 824 euros higher (1124,47 higher) Incremental - Nutrition: 23 (31,39) - Analgesia: 14 (19,11)

									- Anti-infectives [prophylaxis: 5 (6,82), antiviral: 3 (4,09), antibiotics 84 (114,63), antifungal: 696 (949,80)] Allogenic patients: not all costs reported (no anti-infectives) Incremental - analgesia: 8 (10,92)
Cho et al., 2019 [28]	USA	Non-Hodgkin lymphoma	Autologous and Allogeneic	M	N.I.	1,832 patients (406 allogeneic and 1426 autologous)	Provider's perspective	2014; USD; Costs	Additional mean hospital costs (unadjusted): - Autologous: 22 269 (25 146,06) - Allogeneic: 50 217 (56 704,82)
Jones et al., 2008 [30]	USA	M.M., lymphomas	Autologous	S	N.I.	6,918 patients	Payer's perspective	2003; USD; Costs	Increased hospital costs range 15 000 to 50 000 (21 271,67 to 70 905,56)
- Chemotherapy									
Elting et al., 2003 [4]	USA	Solid tumors or lymphomas	Chemotherapy-induced myelosuppression	OM + G	NCI	599 patients who developed chemotherapy-induced myelosuppression (thrombocytopenia and neutropenia)	Provider's perspective	2002; USD; Costs	Average cost of hospitalization: Additional - Oral mucositis: 2384 (3443,55) - Gastrointestinal mucositis: 5239 (7567,44) - Oral + gastrointestinal mucositis: 5268 (7609,33) Grade 1-2: 2725 (3936,11) Grade 3-4: 5565 (8038,33)
Lafuma et al.,2019 [31]	France	HNC (Recurrent or metastatic)	CT	M + S	N.I.	267 patients	Societal perspective	2018; Euros; Costs	- Ambulatory setting: 213 (284,98)
Fragoulakis et al., 2019 [32]	Italy	Not specified	Fluoropyrimidines	S	NCI	571 patients	Payer's perspective	2018; Euros; Costs	Grade IV and V: supportive therapy for 1 week – 17 (24,64)
Smith et al., 2002 [33]	USA and UK	Ovarian cancer	PLD versus Topotecan	S + P	N.I.	Randomized clinical trial 239 patients treated in Europe and 235 in North America	Payer's perspective	2001; USD; Costs	Grade 3-4: - USA: T = 30 (44,02) and PLD = 101(148,20) - Europe: T = 70 (102,71) and PLD = 175 (256,78)
Weiner et al., 2007 [34]	USA	All cancer patients that received CT*	CT not specified	M	N.I.	2,067 patients	Payer's perspective	2004, USD; Costs	Inpatient: - Mucositis alone no additional cost as compared to no adverse events -MUPLUS*** – 465 (642,13) additional

									Outpatient - Mucositis 126 (174) additional
Elting and Shih, 2004 [35]	USA	No specific type of cancer	CT	M + S	N.I.	Based on 55,7281 inpatient claims	Payer's perspective	2002; USD; Costs	- 7,895 (11 403,88) - Average reimbursement – charges 3 451(4 984,77)
Rashid et al., 2016 [36]	USA	Breast cancer (metastatic)	Capecitabine, Taxane, Cyclophosphamide, Doxorubicin, Gemcitabine, Epirubicin, Vinorelbine, Ixabepilone, or Eribulin.	S	N.I.	1,682 patients	Payer's/ Provider's perspective	2013; USD; Costs	Grade 3-4: - Single episodes: Outpatient: 5 096 (5 863,24) Hospital: 27 781 (31 963,64) - Multiple episodes ER + hospital: 71 708 (82 504,19)
Mittmann et al., 2010 [37]	Canada	Breast cancer	Docetaxel plus Doxorubicin and Cyclophosphamide compared with 5FU, Doxorubicin and Cyclophosphamide	S	N.I.	1480 patients (744 TAC, 736 FAC)	Societal perspective	2006; Canadian dollars; Costs	Grade 3/4: 3151,18 (3 371,28)
- Chemotherapy									
Dranitsaris et al., 2015 [38]	China	Breast cancer (metastatic)	Nab-paclitaxel, Docetaxel, or solvent-based Paclitaxel	S	N.I.	Phase III trials	Societal perspective	2014; USD; Costs	- Grade 3/4: 5 (5,65) Supportive care of symptoms, hydration if necessary
Xie et al., 2013 [39]	China	Colorectal cancer	XELOX or FOLFOX-4	S	N.I.	50 patients in each group of treatment	Provider's perspective	2012, USD; Costs	One event = 3,57 (4,18)
Groener et al., 1999 [40]	Netherlands	Colorectal cancer (advanced)	Tomudex versus 5FU + Leucovorin	M	WHO	Randomized clinical trial – 439 patients (220 raltitrexed and 212 5FU + LV)	Societal perspective	1998; USD; Costs	Grade 3-4: 531 (825,78)
Berger et al., 2015 [41]	Germany	Not specified	Busulfan for conditioning prior to HSCT	OM	N.I.	Model of cost	Provider's perspective	2014; Euros; Costs	- Grade 1–2: 50 (72,96)
Ojeda et al., 2003 [42]	Spain	Ovarian cancer (recurrent)	PLD hydrochloride versus Topotecan	S + P	N.I.	Phase III clinical trial (474 patients – 239 PLD and 235 T)	Provider's perspective	2001; Euros; Costs	- Grade 1: 0 (0) - Grade 2: 106,90 (233,38) - Grade 3 724,45 (1581,59) - Grade 4 1330,53 (2904,76)
Frías et al., 2010 [43]	Spain	Breast cancer (metastatic)	Docetaxel versus weekly Paclitaxel	S	N.I.	Phase III trial	Societal perspective	2009; Euros; Costs	Grade 3-4: 475,49 (805,76)
Capri and Cattaneo, 2003 [44]	Italy	Ovarian cancer	PLD and Topotecan	S	NCI	Phase III clinical trial	Societal perspective	2002, Euros; Costs	Grade 1 – 14 (26,01) Grade 2 – 28 (52,02)

								Grade 3 – 908 (1687,06) Grade 4 – 1385 (2573,32)
Giuliani et al., 2002 [45]	Italy	Colorectal cancer (advanced)	Oral Capecitabine versus intravenous 5FU + Leucovorin	S	N.I.	Phase III trial 602 patients	Societal perspective	2001; Euros; Costs	Average hospitalization cost: 2073 (3980,81)
- Molecular targeted therapy									
Mickisch et al., 2010 [46]	UK, Germany, France and Italy	Renal carcinoma (metastatic)	Bevacizumab + IFN versus Sunitinib	S	N.I.	Phase III trials	Provider's perspective	2007; Euros; Costs	Grade 3-4 / grade 2 UK - 495 /88 (730,95 / 187,90) Germany - 1614 / 65 (2591,99 / 104,39) France - 31 / 2360 (45,78 / 3484,91) Italy – no data
- Multimodal therapy									
Doral Stefani et al., 2008 [47]	Brazil	NSCLC	Erlotinib versus Docetaxel or Pemetrexed	S	N.I.	Phase III trial	Provider's perspective	2007; Reais; Costs	Grade 3-4 – 152,49 (169,60) Total costs associated with adverse event management Erlotinib = 10,23 (11,38) Pemetrexed = 0 (0) Docetaxel = 14,25 (15,85)
Kotowa et al., 2007 [48]	Germany	NSCLC	Erlotinib, Docetaxel and Pemetrexed	S	NCI	Phase III trial	Societal perspective	2005; Euros; Costs	Grade 3-4 Mouthwash 7,60 (12,42)
Banz et al., 2011 [49]	Germany, France, Italy and Spain	NSCLC	Erlotinib or Pemetrexed	M + S	N.I.	Phase III trial	Payer's perspective	2008; Euros; Costs	Grade 3-4 Germany – 312 (495,57) France 441 (636,15) Italy 45 (72,52) Spain 102 (173,28)
Riesco-Martinez et al., 2016 [50]	Canada	Colorectal cancer (unresectable wild-type KRAS metastatic)	Fluoropyrimidines, Oxaliplatin, Irinotecan, Bevacizumab,and Epithelial growth factor receptor inhibitors	S	N.I.	65 patients	Societal perspective	2012; Canadian dollars; Costs	Grade 3-4: 1170,41 (1110,67)
Del Río-Valencia, et al., 2018 [51]	Spain	Soft tissue sarcoma	Olaratumab + Doxorubicin versus Doxorubicin alone	M	N.I.	Phase IIb/II trial	Societal perspective	2017; Euros; Costs	3429,05 (5670,46)
- Treatment not specified									
Wong et al., 2018 [52]	USA	Most prevalent types of cancer**	Not specified	M+S	N.I.	412,005 patients – 6,538 episodes of S/M (14% severe)	Payer's perspective	2015; USD; Costs	- Any severity: 1695 (1893,73) - Severe 18 151 (20 279,12)

									Incremental by any cancer type: - Breast 961 (1073,67) - Lung 3288 (3673,50) - Lymphatic and hematopoietic tissue 6690 (7474,37) - Digestive organs and peritoneum 2451 (2738,37)
Zhang et al., 2018 [53]	USA	Acute lymphocytic leukemia	Not specified	M+S	N.I.	370 patients	Payer's perspective	2016; USD; Costs	- Total costs 8868 (9800,64) - Inpatient costs 8355 (9233,69) - Outpatient costs 512 (565,85)
Bermejo de Las Heras et al., 2018 [54]	Spain	Breast cancer (metastatic)	Not specified	M+S	N.I.	Estimates	Societal perspective	2016; Euros; Costs	968 (1620,47)

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; D, dysphagia; E.R., emergency room; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; FOLFOX-4, Oxaliplatin, Folinic Acid and 5-Fluorouracil; G, gastrointestinal mucositis; HNC, head and neck cancer; HSCT, hematopoietic stem cell transplantation; IFN, Interferon; KRAS, Kirsten rat sarcoma viral oncogene homolog; M, mucositis; M.M., multiple myeloma; NCI, National Cancer Institute; N.I., not informed; NSAIDS, nonsteroidal anti-inflammatory drugs; NSCLC, non-small cell lung cancer; OM, oral mucositis; OMAS, Oral Mucositis Assessment Scale; P, pharyngitis; PBMT, Photobiomodulation therapy; PLD, Pegylated Liposomal Doxorubicin; RT, radiotherapy; S, stomatitis; SUS, Brazilian unified health system; SWI, Switzerland; TAC, doxorubicin and cyclophosphamide; UK, United Kingdom; USA, United States of America; USD, United States Dollar; T, Topotecan; WHO, World Health Organization; XELOX, Capecitabine plus Oxaliplatin; 5-FU, 5-Fluorouracil;
* Leukemia/lymphoma, breast, colon, lung, gynecologic, non-colon gastrointestinal, head and neck, urinary tract, brain, melanoma, prostate, unspecified, bone/soft tissues, testes, pleura, mediastinum, endocrine and non-melanoma skin.
** Bladder, breast, digestive organs and peritoneum, ovary and other uterine adnexa, other genitourinary organs, lung, lymphatic and hematopoietic tissue and skin.
*** A—Anemia; N—Neutropenia; T—Thrombocytopenia; M—Mucositis; D—Dehydration, Diarrhea Vomiting and/or Nausea

Table 2b: Characteristics of included studies reporting charges.

Treatment modality	Country	Cancer type	Treatment	OM/M/S	Grading system	Sample size	Cost perspective	Year/ Currency/ Cost type	Reported cost (cost estimates in 2021 USD)
- RT/ CRT/ molecular targeted therapy									
Peterman et al., 2001 [9]	USA	HNC	RT or CRT	M	N.I.	45 patients	Low: payer's perspective High: provider's perspective	1996; USD; Charges and reimbursements	Mean Incremental cost for each resource use (low - high): - Hospitalizations: 1840–1966 (2943,55–2943,55) - Outpatient support: 534–828 (854,27–1324,60) - Prescription medication: 452–1049 (723,09–1678,14) - Incremental professional time: 122–194 (195,17–310,35) **Average 3000 ± 1000 (4799,27 ± 1599,76)**
Murphy et al., 2009 [11]	USA	HNC	RT or CRT	M	N.I.	75 patients	Payer's perspective	2004; USD; Charges	Additional cost of: 2500/patient (3452,32/patient)
- HSCT									
Vera-Llonch et al., 2007 [5]	USA	Leukemia, lymphoma and myelodysplasia	Allogeneic	OM	Specific scoring system	281 patients	Provider's perspective	2005; USD; Charges	- Grade 0: 213 995 (286 584,05) - Grade 1: 251 805 (337 219,55) - Grade 2: 313 565 (419 929,11) - Grade 3: 279 769 (374 669,19) - Grade 4: 305 368 (408 951,61) - Grade 5: 437 421 (585 798,19) - Grade 0 to 5: 223 426 (299 214,14)
Sonis et al., 2001 [29]	USA	Hematologic, lymphatic or solid tumors	Autologous and Allogeneic	OM	OMAS	92 patients	Provider's perspective	2000; USD; Charges	Total hospital charges OMAS score: 0-0.99 – 73 095 (109 603,18) 1-1.99 – 96 825 (145 185,42) 2-2.99 – 123 446 (185 102,60) 3-5 – 162 228 (243 254,73) - Outcomes Associated With Presence of Ulceration: 42 749 (64 100,50) -One point increase in OMAS score is followed by additional hospital charges of 25 405 (38 093,83)

Abbreviations: CRT, chemoradiotherapy; HNC, head and neck cancer; HSCT, hematopoietic stem cell transplantation; M, mucositis; N.I., not informed; OM, oral mucositis; OMAS, Oral Mucositis Assessment Scale; RT, radiotherapy; USA, United States of America; USD, United States Dollar;

Table 3. Costs attributable to mucositis by cancer treatment modality.

Cancer treatment modality	Number of included studies	Cost-range (2021 USD) [per patient]	Charge-range (2021 USD) [per patient]	Grades 1 - 2 (2021 USD) [per patient]	Grades 3 - 4 (2021 USD) [per patient]
- HSCT	5	1124,47– 299 214,14	50 635,5 - 70 905,56	109 603,18 – 133 345,06	243 254,73 – 299 214,14
- RT/ CRT/ molecular targeted therapy	7	51,23 – 33 560,58	3199,51 - 6399,03	2209,80 – 4192,51	51,23 – 35 877,41
- CT	16	4,18 – 31 963,64	-	26,01 – 3936,11	5,65 – 31 963,64
- Treatment not specified	3	565,85– 20 279,12	-	-	-
- Multimodal therapy	5	12,42 – 5670,46	-	-	12,42 – 1110,67
- Molecular targeted therapy	1	45,78 - 3484,91	-	104,39 – 3484,91	45,78 – 2591,99

Abbreviation: CRT, chemoradiotherapy; CT, chemotherapy; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; USD, United States Dollar.

Figure 1. Flow diagram of literature search and selection criteria adapted from PRISMA.

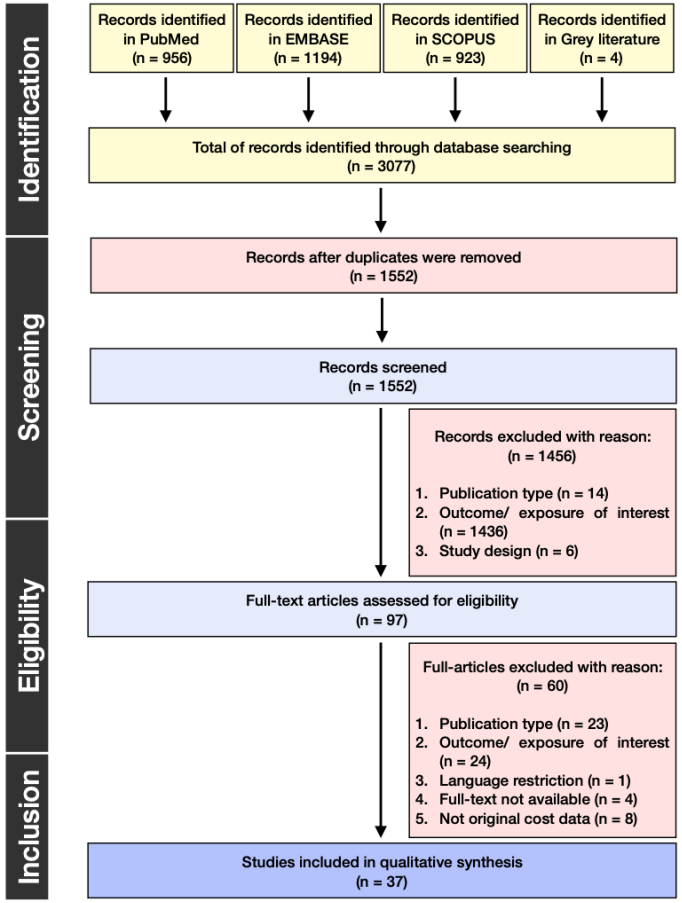
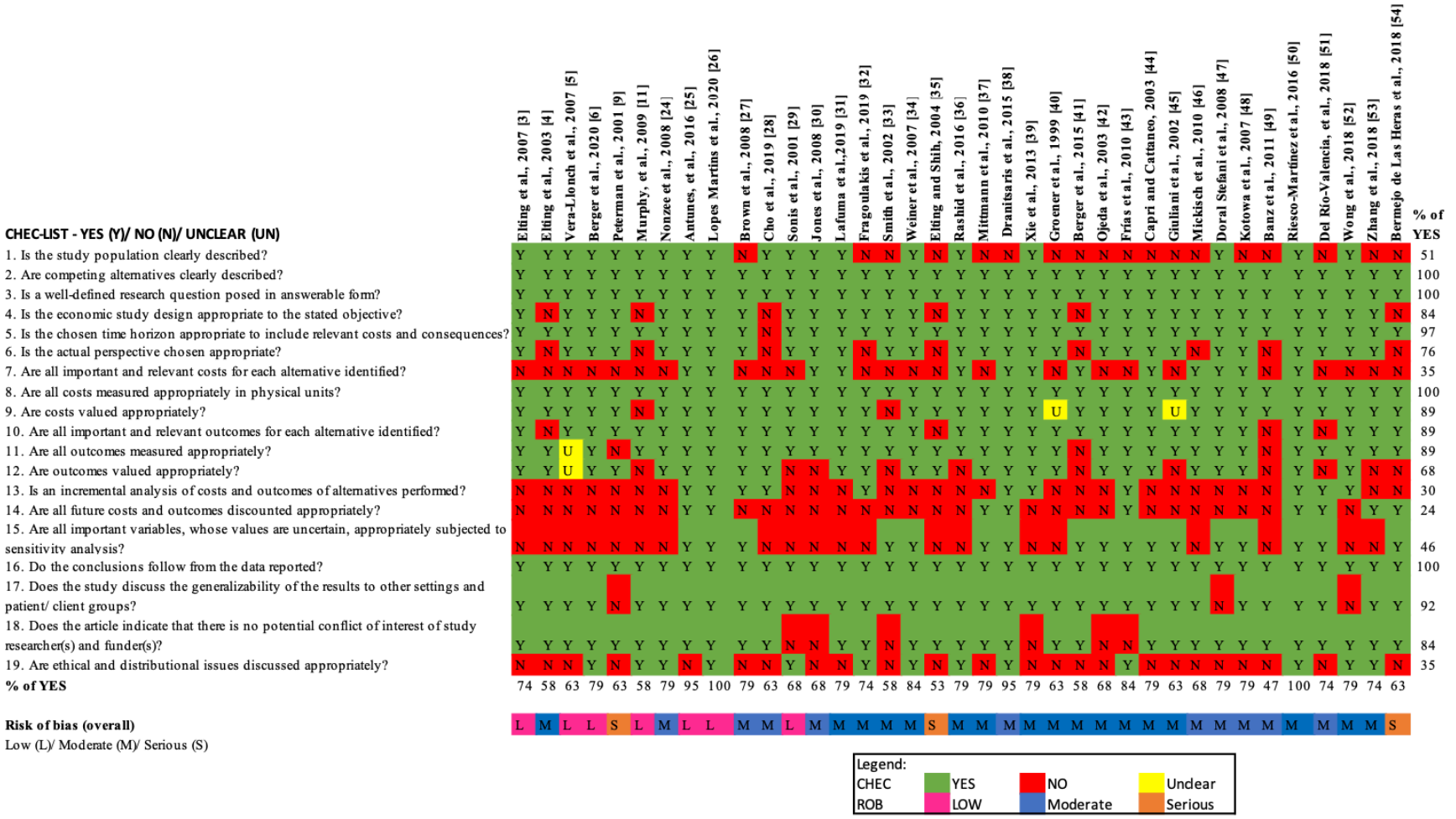


Figure 2. CHEC-list for economic appraisal and overall risk of bias evaluation of the included studies.



DISCUSSÃO

O tratamento odontológico de pacientes diagnosticados com câncer de boca e orofaringe representa um desafio para os cirurgiões-dentistas, pois requer um plano de tratamento individualizado baseado no histórico médico e odontológico do paciente, estadiamento do tumor, protocolo de tratamento oncológico e prognóstico e status hematológico, físico e nutricional.[9, 14-15]

De acordo com o protocolo de recomendação internacional da Multinational Association for Supportive Care in Cancer (MASCC),[18] todo paciente diagnosticado com câncer de cabeça e pescoço deve ser avaliado de forma abrangente por um cirurgião-dentista e receber tratamento odontológico previamente a qualquer tratamento oncológico. Este tratamento deve se iniciar logo após o diagnóstico do câncer para que não haja impacto sobre o tratamento oncológico e para que haja tempo necessário para a cicatrização óssea e dos tecidos moles.[14, 19-20.]

No artigo 1 apresentado, os resultados sugerem que, embora os pacientes com câncer de boca e orofaringe apresentem diversas comorbidades e vários resultados de exames laboratoriais alterados, o tratamento odontológico nesta população pode ser realizado com segurança pelo cirurgião-dentista. Observamos também que o diagnóstico de câncer de boca e orofaringe não representou um desafio adicional, uma vez que complicações adicionais como sangramento ou infecção não foram identificadas.

A literatura cientifica pertinente destaca que a frequência de comorbidades em pacientes com câncer de boca e orofaringe é alta em comparação com a população em geral e está associada principalmente ao tabagismo crônico e exposição ao álcool.[21-23] De forma semelhante, observamos em nosso estudo que 85,4% dos participantes relataram exposição ao tabaco e consumo de álcool; e ainda 63,6% dos pacientes apresentavam comorbidades prévias.

As comorbidades apresentadas pelos pacientes, no presente estudo, impactam não somente no diagnóstico, prognóstico, sobrevida e tratamento de pacientes com câncer, mas também dita o tratamento odontológico e a maneira a ser realizado.[22, 24]

As alterações laboratoriais mais frequentes encontradas em nosso estudo foram valores elevados de proteína C reativa (PCR), hemoglobina, gama-glutamiltransferase, 25-hidroxi vitamina D, neutrófilos e glicose. Nossos resultados sugerem, em concordância com a literatura vigente, que essas mudanças não requerem modificações no tratamento odontológico e podem não gerar complicações relacionadas aos procedimentos odontológicos invasivos.

A literatura afirma que os cirurgiões-dentistas clinico gerais podem ter uma experiência limitada no atendimento ao paciente oncológico e que um cirurgião-dentista especialista deve realizar este atendimento.[20] Embora o acima mencionado possa ser verdadeiro para pacientes em tratamento ou que já tenham concluído o tratamento oncológico, o tratamento odontológico anterior ao tratamento do câncer pode ser realizado por dentistas clínico gerais. Tal afirmação pode ser reforçada pelos resultados do presente estudo, em que embora comorbidades e alterações laboratoriais tenham sido observadas em pacientes com câncer de boca e orofaringe, nenhum dos pacientes avaliados apresentou alterações laboratoriais que contraindicasse o tratamento odontológico; mesmo submetidos a uma ampla gama de procedimentos odontológicos, nenhum complicação durante ou após os procedimentos foi observada.

Em relação ao segundo capítulo dessa dissertação de mestrado, procuramos sintetizar os custos da mucosite em uma revisão sistemática, trabalho inédito na literatura, pois considerou os custos incrementais diretos associados à mucosite em todas as modalidades terapêuticas de câncer em que a mucosite pudesse estar envolvida. O tratamento da mucosite é desafiador e os custo, podendo levar a uma carga financeira desfavorável para hospitais, seguros de saúde, governos e os próprios pacientes.[25-29] Desta forma,

A mucosite associada a radioterapia / quimiorradioterapia / radioterapia mais terapia alvo molecular, transplante de células-tronco hematopoiéticas, quimioterapia, terapia alvo molecular, terapia multimodal e tratamento não especificado leva a um aumento na utilização de recursos, resultando em aumento de custos que variaram de 4,18 USD[30] a 299.214,14 USD.[26]

Os custos mais altos de mucosite foram observados no transplante de medula óssea, inclusive associado a um aumento no tempo de internação hospitalar. Piores graus de mucosite foram preditores significativos de dias febris, dias de nutrição parenteral total, dias de analgesia injetáveis, resultando em um aumento do tempo de internação hospitalar e despesas totais de internação.[26]

No contexto do tratamento radioterápico ou quimiorradioterápico em pacientes com câncer de cabeça e pescoço, a toxicidade mais frequente é a mucosite. Devido a dor associada às lesões de mucosite, há uma mudança na dieta – de alimentos sólidos para alimentos de consistência macia a até necessidade de suplementos nutricionais. A produção de muco, alteração do paladar e boca seca resultam em perda de peso e, pode haver a necessidade de introdução de alimentação enteral. Esse cenário representa um aumento da necessidade de consultas com profissionais de saúde (médicos, enfermeiros, nutricionistas, fonoaudiólogos e dentistas). A dor também é responsável por uma mudança nos padrões de uso de opióides, das

formas oral para transdérmica ou parenteral. As úlceras orais também atuam como um fator preditor para infecção local que podem em casos mais severos evoluir para um quadro de septicemia.[31-33]

Como demostrado, no estudo conduzido por nossa equipe, a mucosite está associada a um aumento substancial nos custos, independente da modalidade de tratamento oncológico. Por meio dessa revisão sistemática, buscamos maneiras para identificação de estratégias de redução de custos. Medidas preventivas prévias ao tratamento oncológico parecem ser uma das mais efetivas estratégias para a redução dos custos associados à mucosite. De acordo com o protocolo publicado no ano de 2020 pela MASSC, as medidas de prevenção incluem adequação do meio bucal e tratamento odontológico prévio ao oncológico, orientações de higiene oral, suporte nutricional adequado e manejo da dor.[34] Neste contexto de redução de custos associados a mucosite, o cirurgião-dentista pode ter papel fundamental por meio da realização da terapia de fotobiomodulação (FBM) que é conhecida por suas propriedades antiinflamatórias, analgésicas e de reparo tecidual.[35] Estudo prévio demostrou um decréscimo em de 30% nos custos hospitalares[36] em pacientes transplantados de medula óssea e provou ser custo-efetiva com uma redução de custos de 5.592,10 USD por caso de mucosite grau 3-4 evitado[37] e redução de 2979,95 USD para cada caso grave evitado[38] em pacientes em pacientes com câncer de cabeça e pescoço.

CONCLUSÃO

A partir dos dois capítulos apresentados, concluímos, que:

- Pacientes com câncer de boca e orofaringe apresentam diversas comorbidades previamente ao diagnostico oncológico e os resultados dos exames laboratoriais alterados, no entanto, o tratamento odontológico prévio ao tratamento oncológico pode ser realizado com segurança;
- Alterações laboratoriais prévias ao tratamento oncológico podem ser preditivas de toxicidades como a mucosite, disgeusia, disfagia, radiodermite, trismo, candidose e xerostomia;
- A mucosite, uma das principais toxicidades relacionadas ao tratamento oncológico está associada a um aumento significativo dos custos do tratamento do câncer; devido ao aumento da necessidade consultas médicas e com equipe multiprofissional, maior número de internações e internações por período prolongado acarretando em um aumento nos custos do tratamento;
- Os custos associados à mucosite são variáveis e estão diretamente relacionados com a modalidade de tratamento oncológico e as estratégias de custo empregadas em cada artigo avaliado; no entanto, os valores que podem chegar a 299.214,14 dólares americanos.
- O emprego de estratégias que previnam e reduzam a incidência, gravidade e duração da mucosite são fundamentais para redução do custo global do tratamento associado à mucosite.

REFERÊNCIAS*

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71(3): 209-249. doi:10.3322/caac.21660

2. de Oliveira Santos M. Estimativas 2020: Incidência de Câncer no Brasil [Instituto Nacional de Câncer José Alencar (INCA)]. Ves Bras Cancerol. 2020; 66(1): e-00927.

3. Omran AR. The epidemiologic transition: a theory of the epidemiology of population change. 1971. Milbank Q. 2005; 83(4): 731-757. doi:10.1111/j.1468-0009.2005.00398.x

4. Marur S, Forastiere AA. Head and Neck Squamous Cell Carcinoma: Update on Epidemiology, Diagnosis, and Treatment. Mayo Clin Proc. 2016; 91(3): 386-396. doi:10.1016/j.mayocp.2015.12.017

5. Vigneswaran N, Williams MD. Epidemiologic trends in head and neck cancer and aids in diagnosis. Oral Maxillofac Surg Clin North Am. 2014; 26(2): 123-141. doi:10.1016/j.coms.2014.01.001

6. Kowalski LP, Carvalho AL, Martins Priante AV, Magrin J. Predictive factors for distant metastasis from oral and oropharyngeal squamous cell carcinoma. Oral Oncol. 2005; 41(5): 534-541. doi:10.1016/j.oraloncology.2005.01.012

7. Homer JJ, Fardy MJ. Surgery in head and neck cancer: United Kingdom National Multidisciplinary Guidelines [published correction appears in J Laryngol Otol. 2016 Aug;130(8):792]. J Laryngol Otol. 2016; 130(S2): S68-S70. doi:10.1017/S0022215116000475

8. Hong CHL, Hu S, Haverman T, et al. A systematic review of dental disease management in cancer patients. Support Care Cancer. 2018; 26(1): 155-174. doi:10.1007/s00520-017-3829-y

9. Epstein JB, Güneri P, Barasch A. Appropriate and necessary oral care for people with cancer: guidance to obtain the right oral and dental care at the right time. Support Care Cancer. 2014; 22(7): 1981-1988. doi:10.1007/s00520-014-2228-x

10. Brennan MT, Woo SB, Lockhart PB. Dental treatment planning and management in the patient who has cancer. Dent Clin North Am. 2008;52(1):19-vii. doi:10.1016/j.cden.2007.10.003

11. Santos-Silva AR, Rosa GB, Eduardo CP, Dias RB, Brandao TB. Increased risk for radiation-related caries in cancer patients using topical honey for the prevention of oral mucositis. Int J Oral Maxillofac Surg. 2011;40(11):1335-1235. doi:10.1016/j.ijom.2011.05.006

*De acordo com as normas da UNICAMP/FOP, baseadas na padronização do Internacional Commitee of Medical Journal Editors – Vancouver Group. Abreviaturas dos periódicos em conformidade com o PubMed.

12. Silva AR, Alves FA, Antunes A, Goes MF, Lopes MA. Patterns of demineralization and dentin reactions in radiation-related caries. Caries Res. 2009;43(1):43-49. doi:10.1159/000192799

13. Silva AR, Alves FA, Berger SB, Giannini M, Goes MF, Lopes MA. Radiation-related caries and early restoration failure in head and neck cancer patients. A polarized light microscopy and scanning electron microscopy study. Support Care Cancer. 2010;18(1):83-87. doi:10.1007/s00520-009-0633-3

14. Levi LE, Lalla RV. Dental Treatment Planning for the Patient with Oral Cancer. Dent Clin North Am. 2018;62(1):121-130. doi:10.1016/j.cden.2017.08.009

15. Carvalho CG, Medeiros-Filho JB, Ferreira MC. Guide for health professionals addressing oral care for individuals in oncological treatment based on scientific evidence. Support Care Cancer. 2018;26(8):2651-2661. doi:10.1007/s00520-018-4111-7

16. Rahman SS, Faruque M, Khan MHA, Hossain SA. Dental management of COPD patient. Bang Med J (Khulna). 2011; 44: 21-24

17. Miller CS, Westgate PM. Implications of medical screenings of patients arriving for dental treatment: the results of a comprehensive laboratory screening. J Am Dent Assoc. 2014;145(10):1027-1035. doi:10.14219/jada.2014.69

18. Elad S, Kin K, Cheng F, Lalla R V, Yarom N, Hong C, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy [published online ahead of print, 2020 Jul 28]. Cancer. 2020;126(19):4423-4431.

19. Jawad H, Hodson NA, Nixon PJ. A review of dental treatment of head and neck cancer patients, before, during and after radiotherapy: Part 1. Br Dent J [Internet]. 2015;218(2):65–8. Available from: http://dx.doi.org/10.1038/sj.bdj.2015.28

20. Samim F, Epstein JB, Zumsteg ZS, Ho AS, Barasch A. Oral and dental health in head and neck cancer survivors. Cancers Head Neck [Internet]. 2016;1(1):1–7. Available from: http://dx.doi.org/10.1186/s41199-016-0015-8

21. Paleri V, Wight RG, Silver CE, Haigentz M, Takes RP, Bradley PJ, et al. Comorbidity in head and neck cancer: A critical appraisal and recommendations for practice. Oral Oncol. 2010;46(10):712–9.

22. Steven Habbous MSc, Luke T. G. Harland BSc, Anthony La Delfa BSc, Ehab Fadhel MD, Wei Xu PhD, Fei-Fei Liu MD, David Goldstein MD, John Waldron MD, Shao-Hui Huang MD, Brian O'Sullivan MD GL. Comorbidity and prognosis in head and neck cancers: Differences by subsite, stage, and human papillomavirus status. Head Neck. 2014;36(10):1391.

23. Ribeiro K de CB, Kowalski LP, Latorre M do RDDO. Perioperative complications, comorbidities, and survival in oral or oropharyngeal cancer. Arch Otolaryngol - Head Neck Surg. 2003;129(2):219–28.

24. Schimansky S, Lang S, Beynon R, Penfold C, Davies A, Waylen A, et al. Association between comorbidity and survival in head and neck cancer: Results from Head and Neck 5000. Head Neck. 2019;41(4):1053–62.

25. Elting LS, Cooksley CD, Chambers MS, Garden AS. Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. Int J Radiat Oncol Biol Phys 2007;68(4):1110-1120. doi:10.1016/j.ijrobp.2007.01.053.

26. Vera-Llonch M, Oster G, Ford CM, Lu J, Sonis S. Oral mucositis and outcomes of allogeneic hematopoietic stem-cell transplantation in patients with hematologic malignancies. Support Care Cancer 2007;15(5):491-496. doi:10.1007/s00520-006-0176-9.

27. Berger K, Staudenmaier T, Cenzer I, Crispin A, Strobach D, Ostermann H. Epidemiology, patient adherence, and costs of oral mucositis in routine care in stem cell transplantation. Support Care Cancer 2020;28(7):3113-3123. doi:10.1007/s00520-019-05107-2.

28. Parulekar W, Mackenzie R, Bjarnason G, Jordan RC. Scoring oral mucositis. Oral Oncol 1998;34(1):63-71. doi:10.1016/s1368-8375(97)00065-1.

29. Dranitsaris G, Yu B, King J, Kaura S, Zhang A. Nab-paclitaxel, docetaxel, or solvent-based paclitaxel in metastatic breast cancer: a cost-utility analysis from a Chinese health care perspective. Clinicoecon Outcomes Res 2015;7:249-256. doi:10.2147/CEOR.S82194.

30. Xie Q, Wen F, Wei YQ, Deng HX, Li Q. Cost analysis of adjuvant therapy with XELOX or FOLFOX4 for colon cancer. Colorectal Dis 2013;15(8):958-962. doi:10.1111/codi.12216.

31. Murphy BA, Beaumont JL, Isitt J, Garden AS, Gwede CK, Trotti AM, et al. Mucositis-related morbidity and resource utilization in head and neck cancer patients receiving radiation therapy with or without chemotherapy. J Pain Symptom Manage 2009;38(4):522-532. doi:10.1016/j.jpainsymman.2008.12.004.

32. Wong W, Yim YM, Kim A, Cloutier M, Gauthier-Loiselle M, Gagnon-Sanschagrin P, et al. Assessment of costs associated with adverse events in patients with cancer. PLoS One 2018;13(4):e0196007. doi:10.1371/journal.pone.0196007.

33. Sonis ST, Oster G, Fuchs H, Bellm L, Bradford WZ, Edelsberg J, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. J Clin Oncol 2001;19(8):2201-2205. doi:10.1200/JCO.2001.19.8.2201.

34. Cho SK, McCombs J, Punwani N, Lam J. Complications and hospital costs during hematopoietic stem cell transplantation for non-Hodgkin lymphoma in the United States. Leuk Lymphoma 2019;60(10):2464-2470. doi:10.1080/10428194.2019.1581932.

35. Sandoval RL, Koga DH, Buloto LS, Suzuki R, Dib LL. Management of chemo- and radiotherapy induced oral mucositis with low-energy laser: initial results of A.C. Camargo Hospital. J Appl Oral Sci 2003;11(4):337-341. doi:10.1590/s1678-77572003000400012.

36. Bezinelli LM, de Paula Eduardo F, da Graça Lopes RM, Biazevic MG, de Paula Eduardo C, Correa L, et al. Cost-effectiveness of the introduction of specialized oral care with laser therapy in hematopoietic stem cell transplantation. Hematol Oncol 2014;32(1):31-39. doi:10.1002/hon.2050.

37. Antunes HS, Schluckebier LF, Herchenhorn D, Small IA, Araújo CM, Viégas CM, et al. Cost-effectiveness of low-level laser therapy (LLLT) in head and neck cancer patients receiving concurrent chemoradiation. Oral Oncol 2016;52:85-90. doi:10.1016/j.oraloncology.2015.10.022.

38. Lopes Martins AF, Nogueira TE, Morais MO, de Sousa-Neto SS, Oton-Leite AF, Valadares MC, et al. Cost-effectiveness randomized clinical trial on the effect of photobiomodulation therapy for prevention of radiotherapy-induced severe oral mucositis in a Brazilian cancer hospital setting [published online ahead of print, 2020 Jul 3]. Support Care Cancer 2020. doi:10.1007/s00520-020-05607-6.

Anexo 1. Certificado de Aprovação do Comitê de Ética em Pesquisa (Faculdade de Odontologia de Piracicaba).

UNICAMP - FACULDADE DE ODONTOLOGIA DE PIRACICABA DA UNIVERSIDADE DE CAMPINAS - FOP/UNICAMP

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Perfil sistêmico de pacientes com necessidade de adequação bucal prévia ao tratamento oncológico do câncer de boca e orofaringe. Estudo exploratório.

Pesquisador: Leticia Rodrigues de Oliveira

Área Temática:

Versão: 2

CAAE: 23671019.1.1001.5418

Instituição Proponente: Faculdade de Odontologia de Piracicaba - Unicamp

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.730.092

Situação do Parecer:
Aprovado

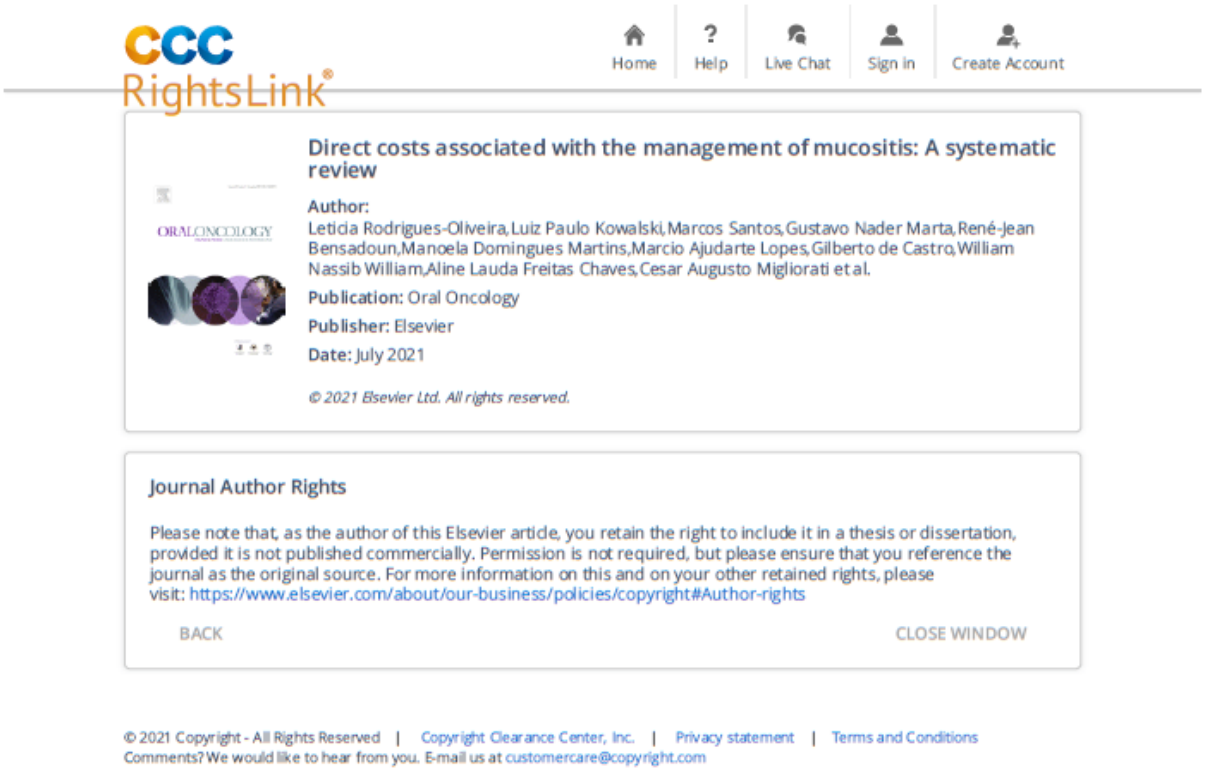
Necessita Apreciação da CONEP:
Não

PIRACICABA, 27 de Novembro de 2019

Assinado por:
Fernanda Miori Pascon
(Coordenador(a))

Endereço: Av.Limeira 901 Caixa Postal 52
Bairro: Areião **CEP:** 13.414-903
UF: SP **Município:** PIRACICABA
Telefone: (19)2106-5349 **Fax:** (19)2106-5349 **E-mail:** cep@fop.unicamp.br

Anexo 2. Consentimento para uso de artigo publicado na Oral Oncology - Editora Elsevier



CCC RightsLink®

Home | Help | Live Chat | Sign in | Create Account

Direct costs associated with the management of mucositis: A systematic review

Author:
Leticia Rodrigues-Oliveira, Luiz Paulo Kowalski, Marcos Santos, Gustavo Nader Marta, René-Jean Bensadoun, Manoela Domingues Martins, Marcio Ajudarte Lopes, Gilberto de Castro, William Nassib William, Aline Lauda Freitas Chaves, Cesar Augusto Migliorati et al.

Publication: Oral Oncology

Publisher: Elsevier

Date: July 2021

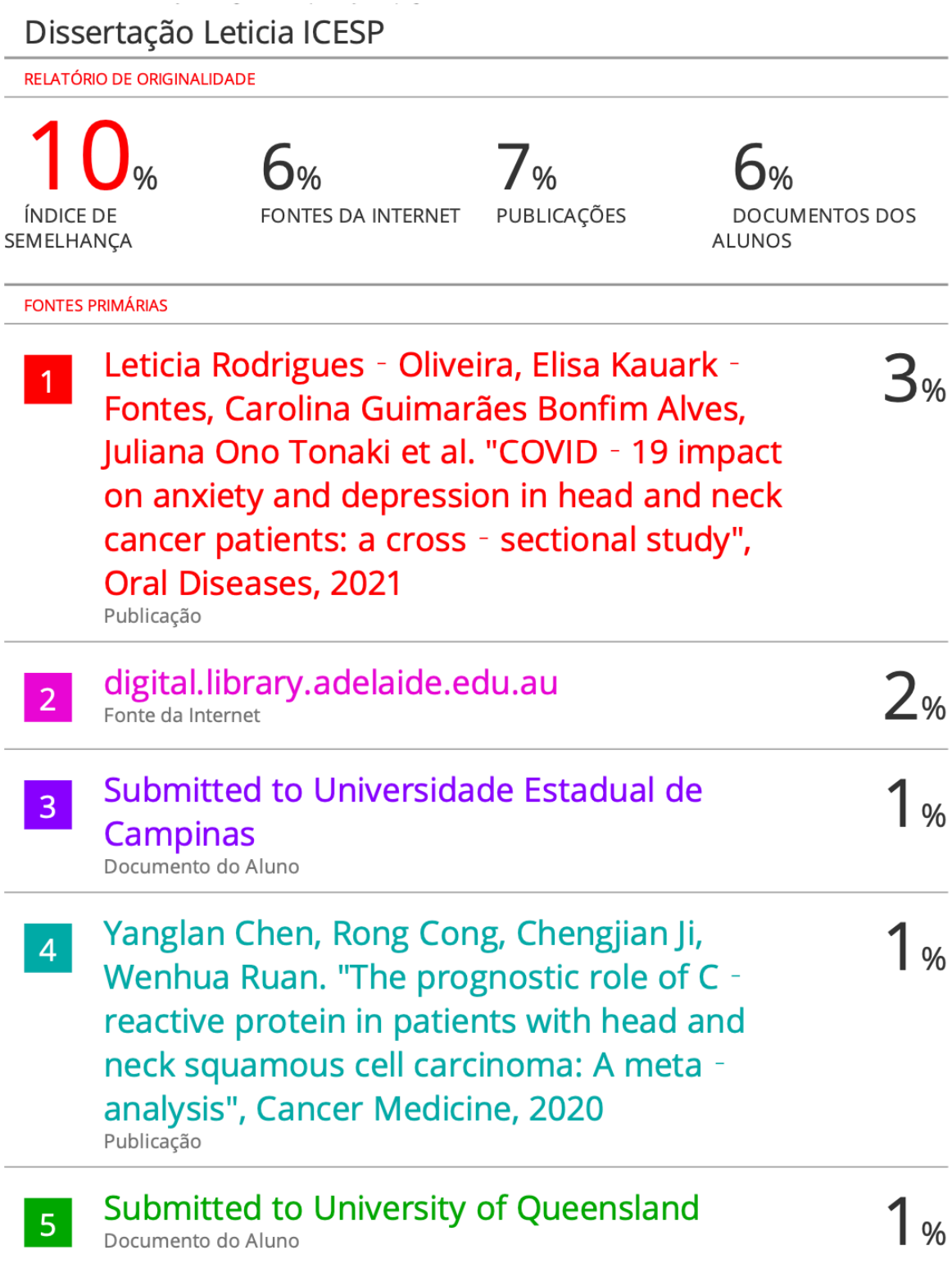
© 2021 Elsevier Ltd. All rights reserved.

Journal Author Rights

Please note that, as the author of this Elsevier article, you retain the right to include it in a thesis or dissertation, provided it is not published commercially. Permission is not required, but please ensure that you reference the journal as the original source. For more information on this and on your other retained rights, please visit: https://www.elsevier.com/about/our-business/policies/copyright#Author-rights

BACK CLOSE WINDOW

Anexo 3. Verificação de originalidade e prevenção de plágio.



Dissertação Leticia ICESP

RELATÓRIO DE ORIGINALIDADE

10%	6%	7%	6%
ÍNDICE DE SEMELHANÇA	FONTES DA INTERNET	PUBLICAÇÕES	DOCUMENTOS DOS ALUNOS

FONTES PRIMÁRIAS

1	Leticia Rodrigues - Oliveira, Elisa Kauark - Fontes, Carolina Guimarães Bonfim Alves, Juliana Ono Tonaki et al. "COVID - 19 impact on anxiety and depression in head and neck cancer patients: a cross - sectional study", Oral Diseases, 2021 Publicação	3%
2	digital.library.adelaide.edu.au Fonte da Internet	2%
3	Submitted to Universidade Estadual de Campinas Documento do Aluno	1%
4	Yanglan Chen, Rong Cong, Chengjian Ji, Wenhua Ruan. "The prognostic role of C - reactive protein in patients with head and neck squamous cell carcinoma: A meta - analysis", Cancer Medicine, 2020 Publicação	1%
5	Submitted to University of Queensland Documento do Aluno	1%

6	www.tandfonline.com Fonte da Internet	1 %
7	Submitted to Instituto Israelita de Ensino e Pesquisa Documento do Aluno	1 %
8	ikee.lib.auth.gr Fonte da Internet	1 %
9	journals.lww.com Fonte da Internet	1 %
10	clinicaltrials.gov Fonte da Internet	1 %

Excluir citações	Desligado	Excluir correspondências	< 1%
Excluir bibliografia	Em		