FUNDAÇÃO OSWALDO CRUZ
INSTITUTO GONÇALO MONIZ

Programa de Pós-Graduação em Pesquisa Clínica e Translacional

DISSERTAÇÃO DE MESTRADO PROFISSIONAL

USO DA FOTOBIOMODULAÇÃO EM PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO TRATADOS EM UM SERVIÇO DE ONCOLOGIA NO BRASIL

LARISSA MATOS ALMEIDA MOURA

Salvador – Bahia
2022

FUNDAÇÃO OSWALDO CRUZ

INSTITUTO GONÇALO MONIZ

Programa De Pós-Graduação em Pesquisa Clínica e Translacional

DISSERTAÇÃO DE MESTRADO PROFISSIONAL

USO DA FOTOBIOMODULAÇÃO EM PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO TRATADOS EM UM SERVIÇO DE ONCOLOGIA NO BRASIL

LARISSA MATOS ALMEIDA MOURA

Dissertação apresentada ao Curso de Pós-Graduação em Pesquisa Clínica e Translacional para a obtenção do grau de Mestra.

Orientador: Prof. Dr. Marcus Fernando da Silva Praxedes

Salvador – Bahia

2022

Ficha Catalográfica elaborada pela Biblioteca do
Instituto Gonçalo Moniz/ FIOCRUZ – Bahia - Salvador

M929u Moura, Larissa Matos Almeida

Uso da fotobiomodulação em pacientes com câncer de cabeça e pescoço tratados em um serviço de oncologia no Brasil / Larissa Matos Almeida Moura. _ Salvador, 2022.

99 f.: il.: 30 cm

Orientador: Prof. Dr. Marcus Fernando da Silva Praxedes

Dissertação (Mestrado Profissional em Pesquisa Clínica e Translacional) – Instituto Gonçalo Moniz, Fundação Oswaldo Cruz, Salvador, 2022.

1. Câncer de cabeça e pescoço. 2. Laserterapia de baixa potência. 3. Mucosite oral. 4. Quimiorradioterapia. I. Título.

CDU 616-006.6

“USO DA FOTOBIOMODULAÇÃO EM PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO TRATADOS EM UM SERVIÇO DE ONCOLOGIA NO BRASIL”.

LARISSA MATOS ALMEIDA MOURA

FOLHA DE APROVAÇÃO

Salvador, 29 de julho de 2022.

COMISSÃO EXAMINADORA

Dr. Paulo Celso Prado Telles Filho
Professor Associado IV
UFVJM

Pablo de Moura Santos:92526411572
Assinado de forma digital por Pablo de Moura Santos:92526411572
Dados: 2022.08.09 12:04:31 -03'00'

Dr. Pablo de Moura Santos
Professor Adjunto
UFBA

Dr. Marcus Fernando da Silva Praxedes
Professor Adjunto
UFRB

FONTES DE FINANCIAMENTO

O presente trabalho foi realizado com apoio da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES).

Universidade Aberta do Sistema Único de Saúde (UNASUS).

AGRADECIMENTOS

A Deus, por ter me dado saúde, força e coragem.

A minha amada mãe, Carmeneide, por ser o pilar mais forte da nossa família e meu maior exemplo de amor e dedicação.

Agradeço, em especial, ao meu pai, José Carlos Moura, que sempre será meu herói e me ensina diariamente o que é ser forte.

Ao meu marido, João Paulo, pelo carinho, amor, compreensão e companheirismo, mesmo nos momentos mais difíceis.

A minha filha, Alícia, por me ensinar o verdadeiro significado de amor incondicional.

Ao meu orientador, Marcus Praxedes, por todo suporte e incentivo.

A todos os meus pacientes, pela confiança que sempre depositaram em mim.

“Você nunca poderá atravessar o oceano até que tenha coragem de perder de vista a costa”

(**Cristóvão Colombo**)

MOURA, Larissa Matos Almeida. **Uso da fotobiomodulação em pacientes com câncer de cabeça e pescoço tratados em um serviço de oncologia no Brasil**. 2022. 99 f. Dissertação (Mestrado Profissional em Pesquisa Clínica e Translacional) – Instituto Gonçalo Moniz, Fundação Oswaldo Cruz, Salvador, 2022.

RESUMO

Introdução: O câncer de cabeça e pescoço (CCP) é a sétima neoplasia mais comum no mundo, sendo responsável por cerca de 800.000 novos casos e 270.000 mortes anualmente. O tratamento com Quimiorradioterapia (QRT), especialmente a com uso de platina em altas doses, é frequentemente utilizado nos pacientes com doença localmente avançada e está associado a um ganho significativo de sobrevida e maior controle de doença. Porém, esse tratamento ocasiona uma elevada toxicidade. A mucosite oral (MO) é um evento adverso frequente e potencialmente grave associado ao tratamento com QRT. Existem poucas terapias eficazes para tratamento e profilaxia da MO induzida por RT. A fotobiomodulação (FBM), também conhecida como laserterapia de baixa potência (LBP), é um tratamento não invasivo que auxilia na prevenção e tratamento da MO através da utilização de fontes de luz não-ionizantes, principalmente a luz vermelha ou quase-infravermelha. Estudos mostram que o uso da FBM pode prevenir, mesmo que parcialmente, o desenvolvimento de MO, além de reduzir a incidência de MO grave e apresentar ação analgésica local, com redução da necessidade de uso de opioides e de dieta enteral, com menor necessidade de interrupções do tratamento e menos internamentos devido a toxicidade. Além de seu efeito na redução da intensidade da MO, alguns estudos mostram que o seu uso pode reduzir a intensidade da perda ponderal nestes pacientes. **Objetivo:** Avaliar o uso da FBM profilática e sua relação na perda ponderal e no desenvolvimento da mucosite oral em pacientes com CCP que receberam tratamento oncológico com QRT em um serviço privado de oncologia no Brasil. **Métodos:** Este é um estudo de coorte retrospectiva, que incluiu pacientes com CCP submetidos a tratamento com radioterapia em concomitância com terapia sistêmica em um serviço privado de oncologia entre janeiro de 2017 e fevereiro de 2021. Foram incluídos pacientes com mais de 18 anos, com diagnóstico de CCP localizado ou localmente avançado, submetidos a tratamento com RT em associação com terapia sistêmica (cisplatina, carboplatina ou cetuximabe). Pacientes submetidos à QT de indução, que apresentavam metástases à distância ao diagnóstico e que iniciaram uso de terapia enteral antes do início da QRT foram excluídos. Os pacientes foram divididos em dois grupos: 1) pacientes que receberam tratamento com FMB e 2) pacientes que não receberam FMB. **Resultados:** 30 pacientes foram incluídos no estudo, sendo 15 em cada grupo. A média de idade foi de 62 anos no grupo PBM e 63,2 anos no grupo controle. A maioria dos pacientes era do sexo masculino, e apresentavam doença localmente avançada (estadiamento III ou IV), submetidos a tratamento com intenção radical com radioterapia concomitante a cisplatina em alta dose (100 mg/m² a cada 3 semanas). O uso de FBM apresentou efeito protetor em relação ao desenvolvimento de MO graus 3 ou 4 [Odds Ratio 0,22 (0.04-1.11)], independentemente do tamanho do tumor (p= 0.5508) e do acometimento linfonodal (p= 0.3564). A intensidade de perda ponderal foi mais acentuada no grupo controle, com uma redução no risco de perda ponderal maior que 5%, porém essa diferença não apresentou significância estatística. **Conclusão:** O uso da FBM profilática mostrou uma possível relação com menor risco de perda de peso e efeito protetor no desenvolvimento de MO grave na população estudada. Os resultados clínicos apontados são observados na assistência diária tendo impacto direto na qualidade de vida do paciente, além de possibilitar maior adesão ao tratamento, menor número de internações e, consequentemente, redução dos custos globais do tratamento.

Palavras-chave: Câncer de cabeça e pescoço. Laserterapia de baixa potência. Mucosite oral. Quimiorradioterapia.

MOURA, Larissa Matos Almeida. **Use of photobiomodulation in patients with head and neck cancer treated in an oncology service in Brazil**. 2022. 99 f. Dissertação (Mestrado Profissional em Pesquisa Clínica e Translacional) – Instituto Gonçalo Moniz, Fundação Oswaldo Cruz, Salvador, 2022.

ABSTRACT

Introduction: Head and neck cancer (HNC) is the seventh most common cancer worldwide, amount to more than 800.000 new cases and 270.000 deaths annually. Concurrent treatment with radiotherapy and chemotherapy (CRT) is one of the main approaches for locally advanced squamous-cell carcinoma of the head and neck and is associated with improvement in survival and a higher disease control rate. However, this treatment causes a significant increase in acute and late toxicity. Oral mucositis is a frequent and potentially severe acute adverse event. There are few effective therapies for treatment and prophylaxis of RT-induced OM. Photobiomodulation (PBM), also known as low-level laser therapy (LLLT), is a non-invasive treatment that shows effectiveness in the prevention and treatment of OM using non-ionizing light. Clinical trials show that the use of FBM can prevent, even partially, the development of OM, in addition to reducing the incidence of severe OM and reduction in opioid use and enteral diet, with fewer treatment interruptions and hospitalizations due to toxicity. In addition to its effect on reducing the intensity of OM, some studies show that its use can reduce the intensity of weight loss in these patients. **Objective:** To evaluate the use of prophylactic PBM and its relationship with weight loss and the development of oral mucositis in patients with HNC treated with CRT in a private oncology service in Brazil. **Methods:** This is a retrospective cohort study that included patients who received radiation therapy concomitantly with systemic therapy for the treatment of HNC in a private service in Brazil between January 2017 and February 2021. Patients aged 18 years old or more, diagnosed with localized or locally advanced HNC, who performed treatment with RT concurrent with cisplatin, carboplatin or cetuximab were included. Patients who had distant metastases at time of diagnosis, who received induction chemotherapy or who had started enteral diet before beginning of CRT were excluded. Patients were divided into two groups: 1) patients who received FMB treatment and 2) patients who did not receive FMB. **Results:** Thirty patients were included in the study, 15 in each group, with a mean age of 62 years in the PBM group and 63.2 years in the control group. Most patients were male, with locally advanced disease (clinical stage III or IV) and received radical intent treatment with concomitant radiotherapy to high doses of cisplatin (100 mg/m² every 3 weeks). In this analysis, the use of PBM had a protective effect against the development of grade 3 or 4 oral mucositis [Odds Ratio 0.22 (0.04-1.11)], regardless of tumor size (p= 0.5508) and nodal involvement (p) = 0.3564). The intensity of weight loss was more significant in the control group, with a reduced risk of developing weight loss > 5%, but this difference was not statistically significant. **Conclusion:** The prophylactic use of FBM showed a possible relationship with a lower risk of weight loss and a protective effect on the development of severe OM in the population studied. The clinical results found are observed in daily practical care, having a direct impact on the patient's quality of life, in addition to allowing greater adherence to treatment, fewer hospitalizations and, consequently, a reduction in the overall costs of treatment.

Keywords: Head and neck cancer. low-level laser therapy. Oral mucositis. Chemoradiotherapy.

LISTA DE TABELAS

Tabela 1	Graduação da mucosite oral pelo CTCAE 5.0	25
Tabela 2	Códigos utilizados para pesquisa no banco de dados	29
Table 1	Patient characteristics according to PBM and control groups	35
Table 2	Weight loss and oral mucositis according to PBM prophylactic and control groups	37

LISTA DE ABREVIATURAS E SIGLAS

Siglas	Significados
AJCC	*American Joint Committe on Cancer*
aRT	Radioterapia adjuvante
CCP	Câncer de cabeça e pescoço
CCP-LA	Câncer de cabeça e pescoço localmente avançado
CDDP	Cisplatina
CDDP-AD	Cisplatina em alta dose
CEC	Carcinoma escamocelular
CEP	Comitê de ética em pesquisa
ClCr	Clearence de creatinina
CLR	Controle locorregional
CNF	Carcinoma nasofaríngeo
CTCAE	*Common Terminology Criteria for Adverse Events*
ECOG	*Eastern Cooperative Oncologic Group*
EBV	*Epstein-Barr Virus*
EORTC	*European Organization for Research and Treatment of Cancer*
FBC	Fundação Baiana de Cardiologia
FMB	Fotobiomodulação
GGT	Gastrostomia
HPV	*Human Papiloma Virus*
IMC	Índice de massa corporal
IMRT	*Intensity-modulated radiation therapy*
ISOO	*International Society of Oral Oncology*
Kg	Quilogramas
LBP	Laserterapia de baixa potência
MASCC	*Mucositis Study Group of the Multinational Association of Supportive Care in Cancer*
MO	Mucosite oral
PAAF	Punção aspirativa por agulha fina
PP	Perda ponderal
PPC	Perda ponderal crítica

PS	*Performance status*
QRT	Quimiorradioterapia
QT	Quimioterapia
QdV	Qualidade de vida
RT	Radioterapia
RTOG	*Radiation TherapyOncology Group*
SG	Sobrevida global
SLD	Sobrevida livre de doença
SLP	Sobrevida livre de progressão
SNE	Sonda nasoenteral

SUMÁRIO

1	**INTRODUÇÃO**	13
2	**REVISÃO DA LITERATURA**	16
2.1	EPIDEMIOLOGIA	16
2.2	FATORES DE RISCO	16
2.3	DIAGNÓSTICO	18
2.4	ESTADIAMENTO ONCOLÓGICO	18
2.5	PRINCÍPIOS GERAIS DO TRATAMENTO	20
2.6	ESTADO NUTRICIONAL E PERDA PONDERAL	23
2.7	MUCOSITE ORAL	24
2.8	FOTOBIOMODULAÇÃO	26
3	**OBJETIVO**	27
4	**MÉTODOS**	28
4.1	CRITÉRIOS DE INCLUSÃO	28
4.2	CRITÉRIOS DE EXCLUSÃO	28
4.3	SELEÇÃO DA AMOSTRA	29
4.4	COLETA DE DADOS	29
4.5	ANÁLISE ESTATÍSTICA	30
4.6	ASPECTOS ÉTICOS	30
5	**RESULTADOS**	32
5.1	ARTIGO - USE OF PHOTOBIOMODULATION IN PATIENTS WITH HEAD AND NECK CANCER TREATED IN AN ONCOLOGY SERVICE IN BRAZIL	32
6	**DISCUSSÃO**	43
7	**CONCLUSÃO**	46
	REFERÊNCIAS	47
	APÊNDICES	54
	ANEXOS	55

1 **INTRODUÇÃO**

O câncer de cabeça e pescoço (CCP) é uma terminologia genérica utilizada para tumores que se desenvolvem nos revestimentos epiteliais do trato aerodigestivo superior, podendo surgir, entre outros sítios, na cavidade oral, orofaringe, nasofaringe, hipofaringe, laringe, cavidade nasal e seios paranasais (CONWAY et al., 2021; KFOURI et al., 2018). O tipo histológico mais comum destas neoplasias é o carcinoma escamocelular (CEC) e apresentam como principal fator de risco a exposição ao tabaco e ao álcool (BOSCOLO-RIZZO et al., 2018; KFOURI et al., 2018).

Em todo o mundo, o CCP é responsável por mais de 800.000 casos e 270.000 mortes anualmente (SUNG et al., 2021). Na Europa, é o sexto tipo de câncer mais comum com, aproximadamente, 150.000 novos casos diagnosticados em 2020 (BOSCOLO-RIZZO et al., 2018). Nos Estados Unidos, o CCP é responsável por 3% de todas as neoplasias malignas e 1,5% das mortes relacionadas ao câncer, com, aproximadamente, 66.000 casos e 15.000 mortes anualmente (SIEGEL et al., 2022).

Segundo a estimativa do Instituto Nacional do Câncer (INCA) para o triênio 2020-2022, cerca de 7.600 novos casos de câncer de laringe e 15.200 de câncer de cavidade oral serão anualmente no Brasil, com uma incidência estimada de 6,20 e 10,69 casos a cada 100 mil homens, respectivamente (MINISTÉRIO DA SAÚDE; INCA, 2019).

Além disso, devido à localização anatômica, é comum que os pacientes tenham que conviver com alterações da fala, dificuldades na mastigação e deglutição, desfiguração cosmética, alteração do paladar e xerostomia. Além disso, dado que os sobreviventes do CCP, devido a sequelas do tratamento, são frequentemente incapacitados e incapazes de retornar ao trabalho, tornando os custos econômicos e sociais associados ao CCP ainda mais elevados. Esses dados expressam a relevância da doença para a saúde pública (JETHWA; KHARIWALA, 2017).

A maioria dos pacientes apresentam tumores localmente avançados ao diagnóstico, com presença de lesões volumosas, seja por invasão importante de estruturas locais, metástases para linfonodos regionais ou ambos, o que torna o tratamento ainda mais desafiador. Além disso, entre 15 a 40% destes pacientes irão desenvolver recorrência local ou com metástase à distância, contribuindo para um prognóstico ainda mais reservado, com menos de 50% deles estando vivos em 5 anos (CHOW, 2020; IOCCA et al., 2018).

Nos casos de doença localmente avançada, o tratamento com a associação de quimioterapia e radioterapia (QRT) é frequentemente utilizado (IOCCA et al., 2018a). A cisplatina (CDDP) é o agente quimioterápico mais estudado e utilizado nesta associação, com nível de evidência 1A para

pacientes com bom *performance status* (PS) e tumores localmente avançados. Estudos mostraram que a associação de radioterapia (RT) com CDDP está associada a um ganho significativo de sobrevida quando comparado ao tratamento com radioterapia isolada (ANTUNES et al., 2017).

Porém, os regimes de tratamento com QRT induzem altos níveis de toxicidade aguda, significativamente maiores do que quando utilizamos a radioterapia isolada. A adição de quimioterapia associa toxicidade sistêmica, como toxicidade hematológica e nefrotoxicidade, além de, frequentemente, exacerbar reações teciduais locais quando usada concomitantemente à RT, como mucosite oral (MO) e radiodermite (ANTUNES et al., 2017b; BERNIER et al., 2004a; COOPER et al., 2004a).

A MO é uma complicação comum e potencialmente grave da QRT, sendo reconhecida como o principal fator limitante para a intensificação do tratamento nessas situações (LIU et al., 2021). Devido ao efeito deletério expressivo da MO na qualidade de vida (QdV) e nos custos do tratamento, diversas intervenções terapêuticas têm sido estudadas com intuito de prevenir e gerenciar este evento adverso (EA) (BLAKAJ et al., 2019).

Existem poucos tratamentos realmente eficazes para prevenção de MO nos pacientes com CCP tratados com QRT. As diretrizes da *Multinational Association of Supportive Care in Cancer* e *International Society of Oral Oncology* (MASCC/ISOO) recomendam um protocolo padrão para o manejo da MO em pacientes com câncer. Esse manejo inclui higiene bucal adequada para todos os pacientes, incluindo escovação com escova de dentes macia, uso de fio dental e o uso de enxaguantes não medicamentosos (solução salina ou lavagens com bicarbonato de sódio), eliminação de qualquer tipo de agente irritante e controle da proliferação da microflora patogênica bucal por meio da remoção mecânica. Exame oral minucioso e intervenções odontológicas, quando indicadas, são componentes importantíssimos e devem ser realizados em conjunto com tratamentos oncológicos nestes pacientes (ELAD et al., 2020).

Além do cuidado com a saúde bucal, vários agentes terapêuticos vêm sendo estudados para o manejo clínico e prevenção da MO em estudos de fase 2 ou 3, como uso da vitamina C oral, acetilcisteína e de anti-inflamatórios (BLAKAJ et al., 2019). A benzidamina exibe propriedades anti-inflamatórias através da inibição da produção de citocinas pró-inflamatórias, como como TNFα e IL-1β (ARIYAWARDANA et al., 2019). As diretrizes da MASCC/ISOO a recomendam o uso de benzidamina em pacientes que recebem radioterapia em doses até 50 Gy (nível de evidência I) e sugerem o seu uso em pacientes tratados com QRT (nível de evidência II) (ELAD et al., 2020).

A fotobiomodulação (FBM) utiliza laserterapia de baixa intensidade e, atualmente, é considerada uma das terapias mais efetivas para a prevenção e tratamento de MO em vários

cenários de tratamento oncológico, principalmente para pacientes com CCP submetidos à QRT (ANTUNES et al., 2013a; ELAD et al., 2020).

Vários estudos observaram que o tratamento profilático com FBM ajuda a prevenir o surgimento e diminuir a gravidade da MO nos pacientes com CCP tratados com terapia concomitante, estando associado à menor incidência e duração da MO, além de menor necessidade de uso de dieta enteral, melhor controle de dor, menor necessidade de analgesia com opioides e, consequentemente, menor taxa de interrupção de tratamento por toxicidade (ANTUNES et al., 2013, 2017; GAUTAM et al., 2012a; LEGOUTÉ et al., 2019). As diretrizes MASCC/ISOO recomendam o seu uso para a prevenção de MO em pacientes com CCP tratados com RT isolada ou QRT, com uso de protocolos com parâmetros específicos para garantir a terapia ideal (ELAD et al., 2020).

2 **REVISÃO DA LITERATURA**

2.1 EPIDEMIOLOGIA

Nos Estados Unidos, o CCP corresponde a cerca de 3-4% de todas as neoplasias, sendo esperado o diagnóstico de 66.470 novos casos (48.520 em homens e 17.950 em mulheres) em 2022 (SIEGEL et al., 2021). Segundo a estimativa do INCA para o triênio 2020-2022, no Brasil são diagnosticados, aproximadamente, 7.650 novos casos de neoplasia de laringe e 15.190 de cavidade oral anualmente (MINISTÉRIO DA SAÚDE; INCA, 2019).

Na região nordeste do Brasil, sem considerar os tumores de pele não melanoma, o câncer de laringe é o oitavo tumor mais incidente em homens (5,02 casos a cada 100 mil) e a décima sexta mais comum entre as mulheres (1,06 casos a cada 100 mil). Já o câncer da cavidade oral é o quinto mais frequente entre os homens (7,65 casos a cada 100 mil) e o décimo primeiro entre as mulheres (3,75 casos a cada 100 mil). Segundo a estimativa do INCA para o triênio 2020-2022, apenas no estado da Bahia, são diagnosticados, em média, 750 novos casos de neoplasias de laringe e 450 de cavidade oral anualmente, com uma incidência de 5,23 e 7,15 para cada 100 mil homens e 0,67 e 2,48 para cada 100 mil mulheres (MINISTÉRIO DA SAÚDE; INCA, 2019).

Apesar de um número crescente de CCP associado ao papilomavírus humano (HPV), que afetam particularmente pacientes mais jovens, a maioria dos CCP ainda ocorrem em pacientes com mais de 50 anos. A maioria dos CCP ocorre durante entre a quinta e sexta décadas de vida, com, aproximadamente, 25-40% dos pacientes apresentando 70 anos ou mais ao diagnóstico (FASANO et al., 2022).

2.2 FATORES DE RISCO

Historicamente, tabagismo e etilismo são os principais fatores de risco para desenvolver neoplasias de cavidade oral, faringe e laringe. Pelo menos 75% dos CCP são atribuíveis às combinações de álcool e tabaco e os fumantes têm um risco 10 vezes maior de desenvolver CCP do que os não fumantes, com este risco sendo diretamente proporcional à carga tabágica (relação entre quantidade de cigarros fumados por dia e anos de tabagismo) (JETHWA; KHARIWALA, 2017). Embora a cessação do tabagismo reduza o risco de desenvolver CCP, não está claro se é possível retornar ao de um paciente nunca fumante. Dados mostram benefício na redução do risco após 1-4 anos de abstinência e alguns sugerem que o risco pode se tornar semelhante à população geral após cerca de 20 anos de cessação do tabagismo (WINN et al., 2015).

Já o risco associado ao uso de cigarros eletrônicos ainda é incerto. Esses aparelhos contém uma associação de nicotina e várias outras substâncias, incluindo propilenoglicol, glicerol, aldeídos, nitrosaminas e metais e a inalação dessas substâncias pode levar a danos na mucosa das vias aéreas. Porém, poucos estudos clínicos examinaram o impacto da exposição ao cigarro eletrônico em seres humanos (AUPÉRIN, 2020; SZUKALSKA et al., 2020).

Estudos epidemiológicos conduzidos em diferentes populações evidenciaram relação direta entre o consumo de álcool e o risco de CCP, principalmente para neoplasia de orofaringe e hipofaringe. Com o risco aumentando conforme a intensidade do consumo. Aparentemente, o consumo de grandes quantidades de bebida alcoólica em um período mais curto é mais prejudicial do que o menor consumo por um período mais prolongado. Em pacientes que nunca fumaram, o uso de, pelo menos, três doses por dia é suficiente para aumentar o risco de CCP (OR 2,04). A cessação do consumo de álcool reduz o risco progressivamente, atingindo valores semelhantes a população geral após 20 anos de abstinência (AUPÉRIN, 2020; HASHIBE et al., 2007; KAWAKITA; MATSUO, 2017).

Infecções pelo HPV e Epstein-Barr vírus (EBV) são fatores de risco independente para desenvolvimento de câncer de orofaringe e nasofaringe, respectivamente (JOHNSON et al., 2020b). Como resultado das políticas globais para redução do tabagismo, nas últimas décadas tem-se observado uma redução dos novos diagnósticos de CCP nos países que reduziram o tabagismo, em contrapartida, a incidência de neoplasia de orofaringe associada ao HPV, tem aumentado de forma gradativa neste mesmo período (CHOW, 2020).

A incidência da neoplasia de orofaringe associada ao HPV varia consideravelmente a depender da região, mas é estimado entre 30 e 35% dos casos, sendo mais comum entre pacientes mais jovem, sem história de tabagismo etilismo ou imunossupressão. O HPV tipo 16 e, em menor escala, o tipo 18, são os principais subtipos associados ao CCP. Eles mediam seu efeito carcinogênico através das oncoproteínas virais E6 e E7, que inativam as proteínas supressoras de tumor, P53 e PRb, respectivamente (AUPÉRIN, 2020; JOHNSON et al., 2020b; TABERNA et al., 2017; VONSKY et al., 2019).

Além de ser um fator de risco independente, a associação com o HPV está relacionada a um prognóstico mais favorável, apresentando melhor resposta ao tratamento com RT, QT ou QRT que os tumores HPV-negativos, mesmo nos casos clinicamente mais avançados (CHOW, 2020a; JOHNSON et al., 2020b).

O vírus Epstein-Barr (EBV), também conhecido como vírus de herpes humano tipo 4 (HHV4), foi identificado pela primeira vez em linhas celulares de linfoma de Burkitt na década de 1960 (EPSTEIN; ACHONG; BARR, 1964; TSAO; TSANG; LO, 2017). Outra neoplasia muito

relacionada ao EBV é o carcinoma nasofaríngeo (CNF). Praticamente todos os casos de CNF não-queratinizante são associados ao EBV, especialmente em zonas endêmicas, como sul da China e sudeste da Ásia (TSAO; TSANG; LO, 2017).

2.3 DIAGNÓSTICO

Até o momento, não existe uma estratégia de *screening* eficaz para a detecção precoce dessas neoplasias. Embora uma proporção de lesões pré-malignas orais, que se apresentam como leucoplasia (manchas brancas) ou eritroplasia (manchas vermelhas), progrida para câncer invasivo, a maioria dos pacientes apresenta-se já com lesão invasiva em estágio avançado, sem relato prévio de lesões pré-malignas (JOHNSON et al., 2020).

Durante a avaliação inicial de pacientes com suspeita de CCP, deve ser realizada anamnese com coleta da história da doença, sinais e sintomas e exposição a possíveis fatores de risco, além de exame físico detalhado do trato aerodigestivo superior (preferencialmente com realização de exame endoscópico, como nasofibrolaringoscopia) (CHOW, 2020). Após esta primeira avaliação, devem ser realizados exames de imagem, com tomografia ou ressonância magnética, direcionados para identificação da lesão primária (caso a mesma não tenha sido visualizada na consulta), melhor caracterização da extensão da lesão e planejamento do melhor sítio de biópsia, além de estadiamento locorregional e à distância (CHOW, 2020). O diagnóstico definitivo deve ser feito através da biópsia da lesão primária (origem do tumor) ou do linfonodo cervical, com confirmação de neoplasia através de análise histopatológica. Normalmente, as lesões primárias são submetidas à biópsia com retirada de fragmento tumoral para análise histopatológica. Já os linfonodos suspeitos costumam ser avaliados por citologia após realização de punção aspirativa por agulha fina (PAAF) (TANDON et al., 2008).

Nos tumores de orofaringe, é mandatório a realização de teste para HPV em todos os pacientes, independente do método utilizado. Esse teste pode ser feito através de técnicas de hibridização ou reação de polimerase em cadeia (PCR) para determinar a presença do DNA do HPV ou por teste imuno-histoquímico para detectar expressão da proteína p16, que é um marcador substituto para positividade do HPV (CHOW, 2020).

2.4 ESTADIAMENTO ONCOLÓGICO

O estadiamento oncológico é uma classificação baseada na carga tumoral apresentada pelo paciente (GLASTONBURY, 2020). Nos manuais de estadiamento do câncer do *American Joint*

Committee on Cancer (AJCC), o estadiamento é descrito de acordo com o tumor primário, presença e extensão do comprometimento linfonodal e disseminação à distância (presença de metastáse), que são designados como T, N , e M, respectivamente (AMIN et al., 2017).

Cerca de dois terços dos pacientes com CCP apresentam doença em estágio avançado, geralmente envolvendo linfonodos regionais. A metástase à distância na apresentação inicial é incomum, surgindo em cerca de 10% dos pacientes, com 20-30% dos pacientes desenvolvendo metástases durante o curso de sua doença (PISANI et al., 2020).

Todo paciente com CCP deve ser submetido a um estadiamento oncológico adequado, com base na 8ª edição do AJCC (AMIN et al., 2017), antes do início do tratamento. Este estadiamento deve ser realizado com exames de imagem (preferencialmente tomografia computadorizada ou ressonância magnética), exame endoscópico (como fibronasofaringolaringoscopia) e anatomia patológica (biópsia e citologia) (ROLAND et al., 2016). Com base no estágio da doença, é possível selecionar a melhor opção de tratamento, planejar o mesmo e estimar o prognóstico (MACHIELS et al., 2020; ZANONI; PATEL; SHAH, 2019).

O estadiamento TNM para CCP varia de acordo com o sítio primário da lesão e, nos casos de tumores de orofaringe, se o tumor é relacionado ao HPV (GLASTONBURY, 2020). Geralmente, os estágios iniciais (I e II) envolvem tumores menores e sem envolvimento importante dos linfonodos. Os estágios III e IV são caracterizados por doença localmente avançada e invasão de estruturas vizinhas ou aumento do número de linfonodos envolvidos. Casos que apresentem disseminação metastática à distância são definidos como o estágio IVb (CHOW, 2020).

O estadiamento do câncer de orofaringe requer uma avaliação do status do HPV (CHOW, 2020). Por se comportar como uma doença completamente diferente quando comparada a p16-negativa, com melhor resposta ao tratamento e melhor prognóstico, um sistema de estadiamento separado foi desenvolvido para os tumores de orofaringe relacionado ao HPV (p16-positivo) (O'SULLIVAN et al., 2016; ZANONI; PATEL; SHAH, 2019).

Em geral, o paciente com CCP tem um prognóstico reservado, com uma sobrevida global em 5 anos variando entre 34% e 77%, a depender da localização, do estadiamento e da associação com o HPV. Os estágios iniciais (I ou II) apresentam alta chance de cura, com mais de 70% dos pacientes sobrevivendo a longo prazo (CHOW, 2020). Na doença localmente avançada, que apresenta alto risco de recorrência local e metástase à distância, o prognóstico é mais reservado, com menos de 50% dos pacientes vivos em 5 anos. Pacientes com doença metastática ou com recorrência locorregional que não pode ser tratada com cirurgia de resgate, radioterapia ou uma combinação dos dois, tem um pior prognóstico e apresentam uma sobrevida global (SG) média entre 6 e 9 meses (CHOW, 2020a; MACHIELS et al., 2020b).

Os pacientes com câncer de orofaringe HPV-positivos apresentam melhor prognóstico, com maior taxa de resposta ao tratamento e maior sobrevida. No estudo RTOG 0129, os pacientes com câncer de orofaringe localmente avançado associado ao HPV (p16-positivo) apresentaram resultados significativamente melhores do que os pacientes com doença HPV-negativa, com uma maior taxa de SG (70,9% vs. 30,2%) e sobrevida livre de progressão (SLP) (64.0% vs. 23.3%) em 8 anos (CHOW, 2020; NGUYEN-TAN et al., 2014).

2.5 PRINCÍPIOS GERAIS DO TRATAMENTO

Os três pilares da terapia do CCP são cirurgia, radioterapia e quimioterapia. É comum que essas modalidades de tratamento sejam realizadas em conjunto, como a quimiorradioterapia (QRT), ou de forma sequencial, com quimioterapia de indução (realizada antes do tratamento definitivo, seja cirúrgico ou radioterápico), e radioterapia ou QRT adjuvantes. O objetivo principal do tratamento é alcançar a maior taxa de cura possível e reduzir o risco de morbidade associado ao tumor, com a menor toxicidade possível. Devido a anatomia da região e sua associação com estruturas fundamentais para funções básicas de vida, como deglutição e respiração, o tratamento do CCP é associado a toxicidades importantes e bastante complexo, além de poder interferir de forma temporária ou definitiva na imagem corporal e fisionomia (LICITRA et al., 2016; MACHIELS et al., 2020).

Sempre que possível, esta terapêutica deve ser personalizada e levar em consideração os parâmetros tumorais objetivos (por exemplo, localização do tumor, histologia do tumor, estágio T, estágio N), as técnicas e tecnologias disponíveis em cada serviço e as características e preferências de cada paciente (por exemplo, idade fisiológica, comorbidades, história prévia de câncer, ocupação, resultado funcional esperado, preferência) (MACHIELS et al., 2020). É amplamente recomendado que as estratégias de tratamento sejam discutidas em uma equipe multidisciplinar especializada (EMD), que deve incluir, idealmente, cirurgiões de cabeça e pescoço, radio-oncologistas, oncologistas clínicos, radiologistas, médicos nucleares e patologistas, além das equipes de odontologia, nutrição, enfermagem, fisioterapia, fonoaudiologia e psicologia (LO NIGRO et al., 2017; MACHIELS et al., 2020).

Em tumores iniciais, com estadiamento I e II (T1-2N0), o tratamento com cirurgia conservadora ou com radioterapia aparenta resultar em controle locorregional semelhante (ANDERSON et al., 2021; KIM et al., 2022). Tumores classificados como estágio III ou IV são considerados como locorregionalmente avançados e podem ser tratadas com cirurgia seguida de radioterapia adjuvante (aRT) ou quimiorradioterapia concomitante (QRT) definitiva, que é

frequentemente utilizada quando objetiva-se a preservação do órgão e de sua funcionalidade. Dentro dessa classificação encontram-se os tumores da cavidade oral, laringe, hipofaringe e câncer de orofaringe p16-negativo. Os tumores de orofaringe associados ao HPV com estadiamento T3-T4 e N0-N3 ou T0-T4 e N1-N3 de acordo com o AJCC TNM 8ª edição, também entram neste grupo (ANDERSON et al., 2021; MACHIELS et al., 2020).

A RT consiste no uso de radiação de alta energia é usada para destruir as células cancerígenas, danificando o material genético das células e bloqueando sua capacidade de se dividir e proliferar ainda mais. A depender do estadiamento oncológico, a RT pode ser utilizada como tratamento curativo ou como terapêutica isolada associada à cirurgia, sendo administrado durante o intraoperatório, antes (neoadjuvante) ou após o ato cirúrgico (adjuvante), ou concomitante à terapia sistêmica. Além disso, pode ser utilizada no contexto paliativo, para proporcionar alívio dos sintomas de tumores localmente avançados ou disseminados (CHOW et al., 2012; GARIBALDI et al., 2017).

As técnicas de RT tem evoluído fortemente durante as últimas décadas, graças a melhorias na engenharia e na computação. A *Intensity-modulated radiation therapy* (IMRT) foi introduzida no início da década de 1990 como um refinamento adicional na entrega de radiação conformada tridimensional (3D-CRT), possibilitando fornecer simultaneamente diferentes níveis de dose para diferentes volumes-alvo em um único tratamento, através do uso de colimadores multifolhas controlados por computador (MLCs) e algoritmos avançados de otimização de planejamento de tratamento, que são capazes de criar a variação de dose desejada dentro do campo de radiação (GARIBALDI et al., 2017; LO NIGRO et al., 2017b; VAN GESTEL et al., 2011b).

Apesar da RT apresentar altas taxas de controle local e ganho de sobrevida, está associada a uma elevada incidência de efeitos adversos graves e sequelas tardias, com grande impacto na QdV, como xerostomia, disfagia, perda auditiva, necrose tardia do lobo temporal, neuropatia óptica e osteorradionecrose de mandíbula. Essas toxicidades são dose dependente, e o uso de técnicas de tratamento mais avançadas, como a IMRT, possibilita a redução destas toxicidades (NUTTING et al., 2011; WANG; HU; EISBRUCH, 2011).

A QRT é parte fundamental do tratamento do CCP localmente avançado, seja com objetivo adjuvante ou definitivo, com intuito de eliminar a doença macroscópica e microscópicamente. O uso de cisplatina em altas doses (CDDP-AD) (100 mg/m² a cada três semanas por três doses) é a terapia padrão ouro, com evidência de benefício clínico, aumento da taxa de controle loco-regional e ganho de sobrevida em comparação com a radioterapia isolada (ADELSTEIN et al., 2003a; BERNIER et al., 2004b; COOPER et al., 2004a; FORASTIERE et al., 2013; MASHHOUR; HASHEM, 2020).

No cenário adjuvante, o estudo *Radiation Therapy Oncology Group* (RTOG) 9501 o uso de CDDP-AD a cada três semanas foi associado a um prolongamento significativo do controle locorregional (CLR) em 5 anos (68 vs. 81%) e SLD (25 vs. 35%), mas sem ganho de SG (COOPER et al., 2004, 2012). O *European Organization for Research and Treatment of Cancer* (EORTC) 22931 evidenciou uma melhora estatisticamente significante no CLR (69 vs. 82%), SLP (36 vs. 47%) e, também, na SG (40 vs. 53%) (BERNIER et al., 2004). Em ambos os estudos, como esperado, a taxa de MO grave foi significativamente maior no grupo tratado com CDDP-AD, ocorrendo em mais de 40% dos pacientes no estudo RTOG 9501 (BERNIER et al., 2004; COOPER et al., 2004).

Similarmente ao tratamento adjuvante, no cenário de tratamento radical, dois estudos mostraram que o uso de CDDP-AD resultou em um claro aumento da sobrevida global mediana quando comparado ao tratamento com RT isolada, porém acompanhado por um aumento significativo de EA agudos graves, com 85% dos pacientes apresentando toxicidades grau 3 ou 4 e 43% apresentando MO grave no braço tratado com CDDP-AD. Cerca de 30% dos pacientes não conseguiram receber todos os três ciclos de CDDP planejados nestes estudos devido aos EAs (ADELSTEIN et al., 2003; FORASTIERE et al., 2003).

A dose e a concentração de CDDP aplicada é um fator determinante para a toxicidade aguda (náuseas, vômitos, elevações das transaminases, ototoxicidade, aumento da creatinina sérica). A QRT com uso de CDDP em doses menores, em infusão semanal, reduz os efeitos colaterais agudos relacionados à quimioterapia, facilita o ajuste de dose de acordo com as condições clínicas durante o tratamento e, portanto, auxilia o manejo ambulatorial destes pacientes, proporcionando menores taxas de internação, evitando interrupções da radioterapia, e aumentando a adesão ao tratamento, culminando na manutenção da intensidade da dose da CDDP (BUGLIONE et al., 2021).

Dois estudos de fase 3, JCOG1008 e ConCERT, evidenciaram que o uso de cisplatina semanal na dose de 40 mg/m² concomitante à RT foi não-inferior ao tratamento com CDDP-AD, tanto no cenário adjuvante (KIYOTA et al., 2022) como no tratamento definitivo (SHARMA et al., 2022), com um melhor perfil de toxicidade. Apesar do estudo JCOG1008 não ter evidenciado diferença na incidência de MO grave entre os dois tratamentos, no estudo ConCERT a cisplatina semanal foi associada a uma taxa significativamente menor de MO (40,6% vs 54,1%; p = 0,039), além de menor toxicidade renal (3,7% vs 18%; P <0,0001), vômitos (4,5% vs 12,7%; p = 0,019) e hiponatremia (21,8% vs 37,5%; p = 0,004), além de menor necessidade de hospitalização (20% vs 36,8%; p = 0,004) e interrupções do tratamento (57,8% vs 61,6%; p = 0,035) (KIYOTA et al., 2022; SHARMA et al., 2022).

Contudo, além da toxicidade associada a intensificação dos efeitos intrínsecos à radioterapia, existe o risco agregado de toxicidades inerentes ao uso da cisplatina, como nefrotoxicidade, otoxicidade e mielossupressão. Diante da preocupação com este alto efeito tóxico, foram desenvolvidos consensos, tanto a nível nacional como internacional, para definição de quais pacientes poderiam ser considerados elegíveis para uso de CDDP, especialmente CDDP-AD (SZTURZ et al., 2019).

Atualmente, considera-se como contraindicação absoluta ao uso de CDDP: baixo PS (ECOG >= 3), *Clearance de creatinina* (ClCr) menor que 50 mL/min, perda auditiva importante (redução do limiar maior que 25 dB em 2 frequências contíguas em pelo menos um ouvido) ou zumbido intenso, neuropatia periférica importante (que atrapalha atividades diárias comuns). Além destas, qualquer disfunção orgânica sintomática e que limite as atividades e a QdV (cardiovascular, hepática, respiratória ou de medula óssea), outras doenças graves ameaçadoras à vida, HIV/AIDS com CD4 < 200/µl[d], alergia ao agente ou ao manitol (comumente infundido junto com a cisplatina) (AHN et al., 2016; DE CASTRO et al., 2018; SZTURZ et al., 2019).

Nos pacientes considerados inelegíveis para realização de CDDP, independente da dose, os consensos recomendam tratamento com QRT com cetuximabe (MACHIELS et al., 2020) ou carboplatina. A QRT com cetuximabe demonstrou melhor controle locorregional e maior SG e SLD em comparação com RT isolada (categoria IIA) (BONNER et al., 2006). Devido a sua menor toxicidade e maior tolerância, a despeito de evidências científicas limitadas, alguns oncologistas têm substituído a cisplatina por carboplatina isolada no tratamento concomitante com RT para CCP-LA (categoria IIC) (SZTURZ et al., 2019).

2.6 ESTADO NUTRICIONAL E PERDA PONDERAL

A desnutrição é um problema comum em pacientes oncológicos, especialmente em pacientes com CCP, devido à história frequente de tabagismo excessivo, dieta irregular e abuso de álcool. Além disso, a localização anatômica do tumor costuma obstruir as vias superiores da deglutição, dificultando, ou até mesmo impedindo, a passagem do bolo alimentar, a anorexia induzida pelo tumor e a disfunção metabólica, como o catabolismo acelerado, contribuem para deterioração adicional do estado nutricional (CHASEN; BHARGAVA, 2009; MEKHAIL et al., 2001).

É fundamental que seja realizada avaliação adequada do *status* nutricional do paciente, além do *status* da funcionalidade da deglutição, tanto antes, como durante e após o tratamento (BOSSI; ALFIERI, 2016; LO NIGRO et al., 2017a; MACHIELS et al., 2020). Nos pacientes com

perda ponderal (PP) maior que 10% nos seis meses anteriores ao início do tratamento é recomendado início de dieta enteral, sendo a gastrostomia a via preferencial de alimentação (MACHIELS et al., 2020). Perda ponderal crítica (PPC) é definida por perda de peso corporal > 5% durante o tratamento (LANGIUS et al., 2016).

Estima-se que 35%-60% dos pacientes com CCP apresentam comprometimento nutricional no momento do diagnóstico (CURTIN et al., 2020) e que mais de 50% deles irão perder mais de 5% do peso corporal basal durante o tratamento com QRT devido aos EAs. Essa deficiência nutricional é associada a um pior prognóstico, com redução da sobrevida global e sobrevida doença específica, além de pior QdV, especialmente naqueles pacientes que apresentam redução maior que 10% do peso inicial (GHADJAR et al., 2015; LANGIUS et al., 2016; MEKHAIL et al., 2001).

2.7 MUCOSITE ORAL

A mucosite oral (MO) é uma complicação muito comum, ocorrendo em até 91% dos pacientes com CCP que recebem RT (BROWN; GUPTA, 2020). Está associado ao aumento do uso de recursos de saúde e custos excessivos de saúde, sendo o principal fator relacionado à piora do estado nutricional e PP durante e logo após o tratamento (ZECHA et al., 2016). É caracterizada por eritema e ulceração do revestimento da mucosa oral, associado a dor local intensa, odinofagia, disfagia, disgeusia, anorexia, desidratação, perda ponderal importante e maior susceptibilidade a infecções secundárias e sistêmicas (BLAKAJ et al., 2019; ELAD et al., 2020), podendo acarretar necessidade de nutrição enteral ou parenteral, além de interrupção, temporária ou definitiva, da terapia oncológica (ELAD et al., 2020).

A cascata de eventos biológicos responsáveis pela fisiopatologia da MO ocorre em cinco etapas: 1) Iniciação: quando ocorre danos celulares induzidos por radiação e/ou quimioterapia, que produzem espécies reativas de oxigênio dentro do epitélio basal e das células da submucosa; 2) Resposta ao dano primário: O dano celular ativa p53 e fator nuclear-kB (NF-kB); 3) Amplificação de sinal: a ativação de NF-kB resulta na produção das citocinas pró-inflamatórias fator de necrose tumoral-alfa (TNF-alfa), interleucina-1b (IL-1b) e interleucina-6 (IL-6), que levam a danos nos tecidos e morte celular; 4) Ulceração: O resultado do dano celular torna-se clinicamente aparente, com presença de lesões na mucosa e alto risco de colonização bacteriana e desenvolvimento de sepse; 5) Cura: ocorre quando há cessação de dano tecidual em curso que iniciou a mucosite e o tecido lesionado cicatriza (BROWN; GUPTA, 2020; LESSA et al., 2021; MARIA; ELIOPOULOS; MUANZA, 2017).

A MO geralmente surge na terceira semana de RT e tende a progredir gradativamente, podendo até gerar risco de vida, devido a grave redução da ingesta de alimentos e líquidos, com subsequente perda de peso, desidratação e complicações sépticas devido à perda das barreiras protetoras epiteliais e da membrana basal. Essas complicações graves podem gerar uma redução da efetividade do tratamento e menor controle local do tumor, uma vez que costumam acarretar na necessidade de interrupção do tratamento oncológico ou redução da dose de radiação (LESSA et al., 2021; MARIA; ELIOPOULOS; MUANZA, 2017).

A severidade da MO depende de diversos fatores inerentes ao tratamento (tipo de tratamento utilizado, dose cumulativa de radiação, volume e região tratada, fracionamento, uso de terapia citotóxica concomitante ou uso de quimioterapia de indução), e ao paciente (sexo, idade, estilo de vida, condição bucal, comorbidades, microbioma oral, suscetibilidades epigenéticas e genéticas) (BLAKAJ et al., 2019; ZECHA et al., 2016). A *National Cancer Institute-Common Terminology Criteria for Adverse Event* (CTCAE) é frequentemente usada em ensaios clínicos para documentar os efeitos colaterais causados por terapias antineoplásicas e classifica a gravidade da MO em uma escala de 1 a 5, baseada na gravidade da dor e alteração na capacidade de comer (Tabela 1) (BLAKAJ et al., 2019; NATIONAL CANCER INSTITUTE, 2017).

Tabela 1 - Graduação da mucosite oral pelo CTCAE 5.0

Grau	**Descrição dos sinais e sintomas**
1	Assintomático ou com sintomas leves
2	Dor moderada ou presença de úlceras que não interferem na ingesta oral; indicado modificação de dieta
3	Dor severa, interferindo na ingesta oral
4	Sintomas graves com risco de vida; indicado intervenção urgente
5	Morte

Fonte: (NATIONAL CANCER INSTITUTE, 2017)

Apesar do seu efeito deletério na QdV e associação com aumento no custo do tratamento, atualmente as opções para tratamento e prevenção MO são limitadas (ZECHA et al., 2016), se resumindo a uma miscelânea de terapias que buscam o controle e o alívio dos sintomas. Cuidados orais básicos, incluindo higiene oral adequada e tratamento dentário especializado, uso de agentes anti-inflamatórios, anestésicos tópicos e analgésicos são recomendados por guideline e serviços especializados, mas apresentam baixo nível de evidência (ELAD et al., 2020).

2.8 FOTOBIOMODULAÇÃO

A luz tem efeito direto nos sistemas e processos biológicos do corpo humano, como no ciclo sono-vigília, ritmo circadiano e na absorção de vitaminas (DOMPE et al., 2020). A fotobiomodulação (FBM), também conhecida como laserterapia de baixa potência (LBP), é um tratamento não invasivo que consiste na aplicação local de uma fonte de luz não-ionizantes, monocromática e de banda estreita, que já demonstrou ter ação na redução da inflamação e no alívio da dor (BENSADOUN et al., 2020; DOMPE et al., 2020).

A FBM tem capacidade de modular atividades moleculares e celulares em um tecido irradiado, gerando um efeito terapêutico não térmico (interação luz-tecido biológica). Embora a FBM tenha sido o foco de muitos grupos de pesquisa nos últimos anos, seu mecanismo real de ação ainda é desconhecido, mas sabe-se que sua eficácia depende dos parâmetros utilizados, como a fonte de luz, comprimento de onda, densidade de energia, estrutura de pulso de luz e a duração da aplicação do laser, além de mecanismos epigenéticos, que são regulados por estímulos ambientais. Os comprimentos de onda mais usados são a luz vermelha ou quase-infravermelha (600–1100 nm) (DOMPE et al., 2020; HANNA et al., 2020).

Nos últimos anos, a FBM tem sido amplamente utilizada nos cuidados de pacientes com câncer (BENSADOUN et al., 2020), sendo seu uso para prevenção e tratamento da MO a indicação mais estudada. Diversos ensaios clínicos e metanálises foram realizados com o uso da PBM em pacientes com CCP para prevenção e tratamento da MO, demonstrando eficácia significativa na redução da prevalência, gravidade e duração da MO, bem como da dor associada a esse EA, sem interferir no resultado do tratamento (ANTUNES et al., 2013b, 2017b; GAUTAM et al., 2012b, 2013a, 2015; WORTHINGTON et al., 2013). Dito isso, consensos internacionais recomendam o uso de FBM na prevenção da MO em pacientes com CCP que irão receber tratamento com QRT (BROWN; GUPTA, 2020; ELAD et al., 2020).

Outrossim, a FBM também tem demonstrado efeitos benéficos no manejo da necrose de tecidos moles e osteonecrose induzida pela terapia oncológica (EPSTEIN et al., 2017; SCOLETTA et al., 2010), além de aparente benefício para tratamento de xerostomia, disgeusia, radiodermatite, fibrose e linfedema pós-RT (DENG et al., 2021; EL MOBADDER et al., 2019; HEISKANEN; ZADIK; ELAD, 2020; ROBIJNS; LODEWIJCKX; MEBIS, 2019; ZECHA et al., 2016).

3 **OBJETIVO**

Avaliar o uso da FBM profilática e sua relação na perda ponderal e no desenvolvimento da mucosite oral em pacientes com CCP que receberam tratamento oncológico com QRT em um serviço de oncologia privado no Brasil.

4 **MÉTODOS**

Este é um estudo de coorte retrospectiva realizado através de análise de dados em prontuário. O desenho de coorte é um tipo de desenho de estudo não experimental ou observacional.

Em um estudo de coorte retrospectivo, os participantes são selecionados com base no status de exposição e, então, acompanhados ao longo do tempo para avaliar a ocorrência do resultado de interesse, por ser retrospectivo, os dados ocorreram no passado, sendo coletados através da análise de prontuários (SETIA, 2016).

4.1 CRITÉRIOS DE INCLUSÃO

Pacientes com ≥ 18 anos, com diagnóstico de neoplasia de cabeça e pescoço localizado ou localmente avançado pelo sistema Tumor (T), Linfonodo (N) e Metástase (M) da *American Joint Committe on Cancer* (AJCC) 8ª edição (Estadiamento I a IVA) (AMIN et al., 2017), que foram submetidos à tratamento com radioterapia em concomitância com quimioterapia baseada em cisplatina, cetuximabe ou carboplatina entre janeiro de 2017 e fevereiro de 2021.

4.2 CRITÉRIOS DE EXCLUSÃO

Foram excluídos pacientes submetidos à quimioterapia de indução (prévia ao tratamento concomitante), que apresentavam metástases à distância ao diagnóstico (estadiamento IVB pelo TNM AJCC 8ª edição) (AMIN et al., 2017) e que iniciaram uso de terapia enteral (via sonda nasoenteral ou gastrostomia) antes do início do tratamento oncológico.

4.3 SELEÇÃO DA AMOSTRA

A seleção da amostra foi realizada por conveniência e os dados foram obtidos através da análise retrospectiva dos prontuários eletrônicos de pacientes. Foi realizada uma seleção inicial através de busca por cadastro do código internacional de doenças (CID) (conforme descrito na Tabela 1). Após esta busca, um total de 82 pacientes foram pré-selecionados. Foi, então, realizada uma triagem dos prontuários através da aplicação dos critérios de inclusão e exclusão pré-determinados pelo estudo, sendo excluídos 52 prontuários. Todos os 30 prontuários

remanescentes, após análise final dos critérios de inclusão e exclusão, foram incluídos no estudo. Os participantes foram, então, divididos em dois grupos: 1) pacientes que receberam PBM (15 pacientes) e 2) pacientes que não receberam PBM, grupo controle (15 pacientes).

Tabela 2 - Códigos utilizados para pesquisa no banco de dados

CID	Descrição da doença
C00	Neoplasia Maligna do Lábio
C01	Neoplasia Maligna da Base da Língua
C02	Neoplasia Maligna de Outras Partes e de Partes Não Especificadas da Língua
C03	Neoplasia Maligna da Gengiva
C04	Neoplasia Maligna do Assoalho da Boca
C05	Neoplasia Maligna do Palato
C06	Neoplasia Maligna de Outras Partes e de Partes Não Especificadas da Boca
C09	Neoplasia Maligna da Amígdala
C10	Neoplasia Maligna da Orofaringe
C11	Neoplasia Maligna da Nasofaringe
C12	Neoplasia Maligna do Seio Piriforme
C13	Neoplasia Maligna da Hipofaringe
C14	Neoplasia Maligna de Outras Localizações e de Localizações Mal Definida, do Lábio, Cavidade Oral e Faringe
C31	Neoplasia Maligna Dos Seios da Face
C32	Neoplasia Maligna da Laringe

Fonte: Elaboração da autora

4.4 COLETA DE DADOS

Após a seleção da amostra, os dados foram obtidos através da análise retrospectiva dos prontuários eletrônicos de pacientes de uma clínica multidisciplinar de oncologia privada localizada na região nordeste do Brasil, pela pesquisadora responsável, seguindo formulário específico (APÊNDICE A). As seguintes variáveis foram coletadas: idade no momento do diagnóstico, sexo, *performance status* (PS) (pelo Eastern Cooperative Oncology Group – (ECOG), sítio primário da neoplasia, status p-16, histórico de tabagismo, estadiamento clínico e/ou patológico (pelo TNM AJCC 8ª edição ou versão anterior vigente no momento do tratamento)

(AMIN et al., 2017), caráter do tratamento (adjuvante ou radical), tipo de quimioterapia (cisplatina 40 mg/m², cisplatina 100 mg/m², cetuximabe, carboplatina), percentual de perda de peso durante o tratamento (– necessidade de uso de dieta enteral, grau de MO apresentado, conforme os Critérios de terminologia comum para eventos adversos (CTCAE 5.0 ou versão anterior vigente no momento do tratamento) (CANCER INSTITUTE, 2017).

4.5 ANÁLISE ESTATÍSTICA

A base de dados foi validada por dupla entrada no software EpiData (versão 3.1, EpiData Assoc., Dinamarca). A análise das variáveis foi realizada na linguagem de programação R versão 3.2.5. As variáveis categóricas foram descritas com frequências (absolutas e relativas) e as variáveis quantitativas por medidas de tendência central (média) e variabilidade (desvio padrão).

Foram realizados testes estatísticos bivariados e de correlação. Utilizou-se o *teste t de student* e o Teste Exato de Fisher para comparar as variáveis quantitativas e qualitativas categóricas entre os dois grupos, respectivamente. Foi utilizado o teste de Mann-Whitney (Wilcoxon Rank Sum Test) para verificar influência de variáveis independentes qualitativas nominais em variáveis dependentes qualitativas ordinais e a Correlação de Spearman para verificar a relação entre variáveis independentes qualitativas ordinais e variáveis dependentes de mesma classificação. Para análise da influência da FBM no grau de MO foi utilizado o Teste Exato de Fisher, e o teste qui-quadrado com correção Yates foi utilizado para análise da associação da FBM com a perda ponderal. Valores de p menores que 0.05 foram considerados para indicar significância estatística.

4.6 ASPECTOS ÉTICOS

Essa pesquisa é baseada em princípios científicos que a justificam e tem possibilidades concretas de responder questionamentos pertinentes, sendo fundamentada em resultados de estudos prévios publicados em revistas nacionais e internacionais.

Este estudo foi submetido e aprovado pelo Comitê de Ética em Pesquisa da Fundação Baiana de Cardiologia (FBC) (CAAE: 44689321.7.0000.5027) (ANEXO A), de acordo com a resolução 466 de 2012 e 510 de 2016, que orienta que todo projeto de pesquisa que envolva Seres Humanos (direta ou indiretamente, incluindo estudos retrospectivos) deve passar por apreciação de um Comitê de Ética em Pesquisa e somente poderá ser iniciado após sua aprovação.

Por se tratar de um estudo retrospectivo, com revisão de prontuários, não houve intervenção direta ao paciente, logo, não submeteu o mesmo a riscos. Foram utilizados métodos eficazes para garantir a confidencialidade dos dados de todos os participantes.

Na submissão ao CEP, foi solicitada e aprovada a isenção da aplicação do termo de consentimento livre e esclarecido (TCLE), pois este projeto foi baseado em análise retrospectiva de dados de prontuários, portanto, com caráter não intervencionista, o que dispensou a coleta de informação direta com o sujeito de pesquisa.

Considerando o acima exposto, não foram identificados riscos significativos aos sujeitos da pesquisa, sendo o projeto classificado como de risco mínimo, baseado na possibilidade de que toda pesquisa pode oferecer algum risco aos sujeitos envolvidos. Os dados coletados foram utilizados apenas para fins desta pesquisa. Não houve benefícios imediatos e diretos aos sujeitos desta pesquisa, considerando ser um estudo retrospectivo com dados colhidos de prontuários médicos, contudo, os resultados podem contribuir para o melhor entendimento sobre o benefício do uso da FBM em pacientes com neoplasia de cabeça e pescoço submetidos a tratamento com quimioterapia e radioterapia concomitantes.

5 **RESULTADOS**

Optou-se por apresentar os resultados na forma de artigo científico intitulado "**Use of photobiomodulation in patients with head and neck cancer treated in an oncology service in Brazil**", que será submetido à revista *Supportive Care in Cancer* – (ISSN 0941-4355) (fator de Impacto= 3.603 e Qualis capes A2), seguindo as normas específicas da mesma (Anexo B).

5.1 ARTIGO

USE OF PHOTOBIOMODULATION IN PATIENTS WITH HEAD AND NECK CANCER TREATED IN AN ONCOLOGY SERVICE IN BRAZIL

Abstract:

Purpose: The purpose of this study was to evaluate the use of prophylactic photobiomodulation and its relationship with weight loss and the development of oral mucositis in patients with head and neck cancer treated with chemoradiotherapy in an oncology service in Brazil.

Methods: This is a retrospective cohort study that included patients who received radiation therapy concomitantly with systemic therapy for treatment of head and neck cancer. Patients were divided into two groups: 1) who received photobiomodulation (PMB) treatment and 2) who did not receive PMB.

Results: Thirty patients were included in the study, 15 in each group, with a mean age of 62 years in the PBM group and 63.2 years in the control group. Most patients were male, with locally advanced disease (clinical stage III or IV), and received definitive intent treatment with concomitant radiotherapy to high-dose cisplatin (100 mg/m² every 3 weeks). In this analysis, the use of PBM shows a protective effect against the development of grade 3 or 4 oral mucositis [Odds Ratio 0.22 (0.04-1.11)], regardless of tumor size (p= 0.5508) and nodal involvement (p) = 0.3564). The intensity of weight loss was higher in the control group, but the difference was not statistically significant.

Conclusions: Use of prophylactic PBM showed a relation with lower risk of weight loss and a protective effect on the development of severe OM in this study population, even though the difference between two groups was not statistically significant. These results might have a direct impact on patient's quality of life, besides enabling a higher rate treatment compliance, fewer hospitalizations and, consequently, reducing global costs of treatment. The benefit of prophylatic

use of FBM is observed in daily clinical practice, with better control of severe OM and significant gain in quality of life, which step up the recommendation of prophylactic use in these patients.

Keywords: Head and Neck Cancer, Low-Level Laser Therapy, Oral Mucositis, Chemoradiotherapy.

Introduction

Head and neck cancer (HNC) are malignances originating from the upper aerodigestive tract, including the following locations: oral cavity, pharynx, larynx, nasal cavity, and paranasal sinus. Squamous cell carcinoma (SCC) is the predominant histology. They correspond to the seventh most common type of neoplasm worldwide, accounting for more than 800,000 cases and 270,000 deaths annually [1]. In Brazil, approximately 7,650 and 15,190 new cases of larynx and oral cavity carcinomas are diagnosed, annually [2]. The major risk factors associated with head and neck cancer (HNC) are smoking, alcohol consumption and human papillomavirus (HPV) infection, the latter having an important role in the pathophysiology of oropharynx neoplasms [3,4].

Cisplatin (CDDP) based concurrent chemo-radiotherapy (CRT) protocols are the standard of care in treating locally advanced head and neck squamous cell carcinoma [5,6]. In patients considered ineligible to treatment with CDDP [7,8], it is possible to administer other drugs in concurrent treatment, like carboplatin or cetuximab [9]. The concurrent treatment is more effective than radiotherapy (RT) alone in patients with locally advanced HNC, with significant survival improvement and higher locoregional control. However, this treatment resulted in a higher incidence of severe adverse events (SAE), particularly high-grade oral mucositis (OM), radiodermatitis and nephrotoxicity. This SAE may become limiting factors for the treatment compliance and resulted in a significant worsening of quality of life [6,10-12], in addition to being associated with an increase in the cost of treatment, with a greater need for analgesic and opioid medications and, frequently, hospitalizations [13].

Therefore, effective prevention and treatment strategies for OM are necessary. The use of photobiomodulation (PBM) currently is considered one of the most effective therapies for the prevention and treatment of OM in various cancer treatment scenarios, especially for patients with HNC submitted to CRT [14,15]. PBM is associated with lower incidence and duration of OM, less need for the use of enteral diet, better pain control, less need for analgesia with opioids, and, consequently, lower rate of treatment interruption and hospitalizations due to acute toxicity [6,16].

The aim of this study was to evaluate the use of prophylactic PBM and its relationship with weight loss and development of oral mucositis in patients with HNC treated with chemoradiotherapy in a private oncologic service in Brazil.

Methods

This is a retrospective cohort study with patients diagnosed with HNC, with primary tumor originating from the nasopharynx, pharynx, oropharynx, oral cavity, hypopharynx and larynx, treated from January 2015 to February 2021, in a private oncological service in Salvador-Bahia/Brazil. Participants were divided into two groups: 1) patients who received PBM; 2) patients who did not receive PBM (named as control group).

The sample selection was for convenience and the data were collected through the retrospective analysis of the electronic medical records of patients from January 2019 to February 2021. Patients ≥ 18 years old, diagnosed with localized or locally advanced HNC by the Tumor (T), Lymph node (N), and Metastasis (M) system by the American Joint Committee on Cancer (AJCC) 8th edition or previous version (Staging I to IVa) [17], submitted to treatment with CRT with cisplatin, cetuximab or carboplatin were included. Patients who received induction chemotherapy, with distant metastasis at diagnosis and who started enteral diet therapy (by nasoenteric tube or gastrostomy) prior to initiation of cancer treatment were excluded.

The following variables were collected: age at diagnosis, gender, performance status (PS) (by the Eastern Cooperative Oncology Group – (ECOG), primary site of neoplasia, status p-16, smoking history, clinical and/or pathological staging (by TNM AJCC 8th edition or previous version) [17], intent of treatment (adjuvant or definitive), type of chemotherapy (weekly cisplatin 40 mg/m², cisplatin 100 mg/m², cetuximab, carboplatin), percentage of weight loss during treatment (0%, 0.1-5%, 5.1-10%, >10%), need to use enteral diet, presence and grade of OM, according to the Common Terminology Criteria for adverse events (CTCAE 5.0 or previous version in force at the time of treatment) [18].

The database was validated by double entry in EpiData software (version 3.1, EpiData Assoc., Denmark). The variables were analyzed in the programming language R version 3.2.5. Categorical variables were described with frequencies (absolute and relative) and quantitative variables by measures of central tendency (mean) and variability (standard deviation).

Bivariate and correlation statistical tests were performed. The Mann-Whitney test (Wilcoxon Rank Sum Test) was used to verify the influence of nominal qualitative independent variables on qualitative ordinal dependent variables and spearman's correlation to verify the

relationship between ordinal qualitative independent variables and variables dependent on the same classification Student's t-test and Fisher's exact test were used to comparing quantitative and qualitative categorical variables between the two groups, respectively. Fisher's exact test was used to analyze the influence of FBM on the degree of BM, and the chi-square test with Yates correction was used to analyze the association between FBM and weight loss. P values less than 0.05 were considered to indicate statistical significance.

Results

Eighty-two patients were selected initially and thirty were included in the study according to eligibility criteria, 15 in each group (PBM and control). All participants were evaluated by the specialized dentistry team of the service and PBM was indicated, but the 15 patients in the control group did not undergo PBM for personal or financial reasons.

The mean age was 62 years in the PBM group and 63.2 years in the control group. Most patients were male, ECOG 0 or 1 and with locally advanced disease (staging III or IV) at the time of diagnosis, with a higher percentage of stage III in the control group.

It was not possible to obtain information about the dose, quantity, and frequency of PBM applications in three patients, because they underwent treatment in other dental services. In the remaining 12 patients, an important variation in relation to the number of PBM sessions applied, were observed, with a median of 22 applications (ranging from 3 to 32). The daily dose of PBM applied was similar among patients.

Fourteen patients allocated in each group received treatment with definitive intent. Thirteen patients in PBM group (86.6%) and 10 in the control group underwent systemic therapy with high-dose cisplatin (HD-CDDP). The other significant features are described in Table 1.

Table 1 - *Patient characteristics according to PBM and control groups*

	Frequencies in groups n(%)		
Characteristics	**PBM**	**CONTROL**	**p-value**
Age (years) Mean ± standard deviation	62 ± (8.65)	63.2 ± (10.22)	0,7311[a]
Sex			
Male	14 (46.7%)	12 (40.0%)	0,5977[b]
Female	1 (3.3%%)	3 (10.0%)	
Performance status (ECOG)			0,0033[b]

0	13 (86.7%)	4 (26.0%)	
1	2 (13.3%)	9 (60%)	
2	0	1 (7.0%)	
3	0	1 (7.0%)	
Smoking History			
Non-smoking	7 (46.5%)	3 (20%)	0,1056[b]
Active smoker	1 (7.0%)	6 (40%)	
Former-smoker	7 (46.5%)	6 (40%)	
Primary site			
Oral cavity	2 (13.0%)	3 (20%)	
Oropharynx	6 (40%)	3 (20%)	
Nasopharynx	1 (7.0%)	3 (20%)	0,2845[b]
Hypopharynx	1 (7.0%)	1 (7.0%)	
Larynx	2 (13.0%)	5 (33.0%)	
Unknown	3 (20%)	0	
p-16			
Positive	9 (60%)	2 (13.0%)	0,0984[b]
Negative	2 (13.0%)	1 (7.0%)	
Not reported	4 (27.00%)	12 (80%)	
T (TNM)			
1	3 (20%)	4 (27.0%)	
2	3 (20%)	2 (13.0%)	0,3636[b]
3	4 (27.0%)	8 (53.0%)	
4	2 (13.0%)	1 (7.0%)	
x	3 (20%)	0	
N(TNM)			
0	1 (7.0%)	2 (13.0%)	
1	5 (33.0%)	5 (33.0%)	1,0[b]
2	8 (53.0%)	7 (47.0%)	
3	1 (7.0%)	1 (7.0%)	
Staging			
I	3 (20%)	1 (7.0%)	
II	4 (27.0%)	1 (7.0%)	0,1028[b]
III	1 (7.0%)	6 (40%)	
IV	7 (46.0%)	7 (46.0%)	
Treatment			
Adjuvant	1 (7.0%)	1 (7.0%)	1,0[b]
Deffinitive	14 (93.0%)	14 (93.0%)	
Systemic therapy			
CDDP 100 mg/m²	13 (87.0%)	10 (66.0%)	0,4770[b]
CDDP 40 mg/m²	2 (13.0%)	3 (20%)	
Carboplatin	0	1 (7.0%)	

Cetuximab	0	1 (7.0%)	
Use of enteral diet			
Yes	14 (93.33%)	14 (93.33%)	1,0[b]
No	1 (6.66%)	1 (6.66%)	

[a]Student's t test
[b]Fisher's exact test
Abbreviations: PBM: photobiomodulation; CDDP: Cisplatin; ECOG: Eastern Cooperative Oncology Group; TNM: tumor (T), lymph node (N) and metastasis (M)

Specific analyses of PBM with OM and weight loss are presented in Table 2. Although not statistically significant, the use of PBM showed a protective effect in relation to the development of severe OM (grades 3 or 4) [Odds Ratio 0.22 (0.04-1.11)], regardless of tumor size (p= 0.5508) and lymph node involvement (p= 0.3564).

The majority of patients in both groups presented moderate (5-10%) or severe weight loss (>10%), with more patients in the control group presenting weight loss greater than 10% (66.6% vs. 40%). Although this difference was not statistically significant, the use of PBM was associated with a risk reduction of weight loss higher than 5% of 8% (relative risk, 0.92; 95% CI, 0.62 – 1.36). In this sample, the use of PBM showed no reduction in the rate of weight loss in the global population (p= 0.2198), regardless the smoking history (p = 0.6470), patient age (p= 0.2905), tumor size (p= 0.5388) or lymph node involvement (p= 0.8258).

Table 2 - *Weight loss and oral mucositis according to PBM prophylactic and control groups*

	Frequency in groups n(%)		
Characteristics	**PBM (15)**	**Control Group (15)**	**p-value**
Weight Loss			
0%	2 (13.33%)	1 (6.66%)	
0.1% ⊦ 5.0%	2 (13.33%)	2 (13,33%)	0.6535[a]
5.0% ⊦ 10.0%	5 (33,33%)	2 (13,33%)	
>10.0%	6 (40%)	10 (66,66%)	
Mucositis			
No mucositis	3 (20%)	0	
Grade 1	0	1 (6.66%)	
Grade 2	5 (33.33%)	2 (13.33%)	
Grade 3	7 (46.67%)	10 (66.67%)	0.0821[b]
Grade 4	0	2 (13.33%)	

[a] Fisher's Exact Test
[b] Chi-square test with Yates correction

Discussion

It was possible to evaluate the use of PBM in the selected sample. Specific analyses related to the presence of OM and weight loss were highlighted, which are significant AE of CRT in the HNC. Such effects can significantly compromise the expected results of treatment, generating a worsening of the quality of life of patients, and, unfortunately, there are few effective strategies. Due to the variability among specialized professionals and the high cost of material purchasing and training the team, there are few clinical trials testing PBM available and their results are difficult to compare [15].

The characteristics of the population of this study are in accordance with the literature. The majority of patients were male, smokers or former smokers, with locally advanced tumors (staging III or IV) and primary site in oral cavity or oropharynx and with good PS. The mean age of both groups was slightly higher than that found in the literature [10,12,14,19,20].

Weight loss is very common during treatment with CRT in HNC patients, being an important cause of concern for the team. Up to 60% of patients with HNC already have nutritional impairment at the time of diagnosis, and at least half of them will experience weight loss greater than 5% during CRT treatment due to AE. This nutritional deficiency is associated with a worse prognosis, with reduced overall survival and specific disease survival, besides worse quality of life, especially in those patients who have a reduction greater than 10% of the initial weight. Some clinical trials endorse the benefit of PBM in reducing weight loss in these patients, since it is able to reduce the intensity and duration of OM, in addition to generating a significant increase in swallowing functionality [16,20-24]

In line with the literature, in the present study, a positive clinical result associated with the use of PBM was observed, indicating a protective effect against the presence of severe OM in relation to the control group and an 8% risk reduction of losing more than 5% of weight during the treatment, even though statistical significance was not reached between two groups. In a randomized prospective study conducted by Antunes et al., 94 patients with HNC undergoing CRT treatment were randomized to receive PBM or placebo treatment. It was evidenced that PBM effectively prevented the occurrence of OM in grades 3-4. Furthermore, the update of this study in 2017 showed that patients who received PBM had a better response and increased progression-free survival [6,14].

In the present study there was no significant difference between the groups in relation to the intensity of weight loss, as well as in the study conducted by Antunes et al. [6,14]. However, in another essay conducted by Gautam et. al, 221 patients were randomized to PBM or placebo,

with use of PBM resulting in a significant reduction in the incidence of severe OM (p<0,0001), pain associated with OM (p<0.0001), dysphagia (p<0.0001), opioid use (p<0.0001), in addition to a significant reduction in weight loss intensity and need for enteral diet when compared to placebo [19,20]. This benefit was also evidenced in an essay that included only elderly patients with HNC [16].

A Brazilian study evaluated the impact of FBM use on the weight and BMI of patients with HNC. Patients were divided into two groups, according to the use or not of PBM. All patients showed significant differences in weight and BMI throughout the study period, but patients in the PBM group showed less weight loss ($p < 0.01$) and lower BMI loss ($p < 0.01$. Although, in this study, PBM did not prevent the onset of oral mucositis, it decreased its severity ($p < 0.01$) [25].

In addition to a significant reduction in local AE, the use of PBM is also associated with significant improvement in the quality of life, both the short and long term [18,26], besides significant reduction in the overall cost of treatment [13]. A study conducted in the United States of America showed that OM increased the cost of treatment of patients with HNC between US$ 1,700.00 and 6,000.00, mainly due to increased use of resources, days of hospitalization, use of opioids, among other factors. Another trial, conducted in Brazil, also shows a high cost-effectiveness of PBL prophylactic use in this population of patients [27,28].

Despite the proven benefits, PBM treatment is difficult to implement, and it is not available in most oncologic centers in Brazil, since it requires expensive equipment and staff with specialized training [15]. Moreover, PBM's costs are not widely covered by the Brazilian public health system or by most private health insurances, making it an expensive treatment for patients who perform it. Nevertheless, considering the short- and long-term benefit for patients, besides being a cost-effective treatment, it is highly recommended that PBM should be used prophylactically in patients with HNC who are receiving CRT treatment.

There are potential limitations in this study. It was conducted in a single private oncology service in Brazil. Because of the differences in the care system and standard of practice of usual care among health services, besides the convenience sampling utilized, generalization of the results found is limited. Finally, data was collected from medical records, which can generate limitations in information retrieval.

Conclusion

Use of prophylactic PBM showed a relation with lower risk of weight loss and a protective effect on the development of severe OM in this study population, even though the difference between

two groups was not statistically significant. These results might have a direct impact on patient's quality of life, besides enabling a higher rate treatment compliance, fewer hospitalizations and, consequently, reducing global costs of treatment. The benefit of prophylactic use of FBM is observed in daily clinical practice, with better control of severe OM and significant gain in quality of life, which step up the recommendation of prophylactic use in these patients.

References

1. Sung H, Ferlay J, Siegel RL, et al (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians 71:209–249. https://doi.org/10.3322/caac.21660
2. Ministério da saúde, INCA (2019) Estimativa 2020 incidência de cancer no Brasil. Rio de Janeiro
3. Habbous S, Chu KP, Qiu X, et al (2013) The changing incidence of human papillomavirus-associated oropharyngeal cancer using multiple imputation from 2000 to 2010 at a Comprehensive Cancer Centre. Cancer Epidemiology 37:820–829. https://doi.org/10.1016/j.canep.2013.09.011
4. Fasano M, D'Onofrio I, Belfiore MP, et al (2022) Head and Neck Squamous Cell Carcinoma in Elderly Patients: Role of Radiotherapy and Chemotherapy. Cancers (Basel) 14:472. https://doi.org/10.3390/cancers14030472
5. Pignon J-P, Maître A le, Maillard E, Bourhis J (2009) Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiotherapy and Oncology 92:4–14. https://doi.org/10.1016/j.radonc.2009.04.014
6. Antunes HS, Herchenhorn D, Small IA, et al (2017) Long-term survival of a randomized phase III trial of head and neck cancer patients receiving concurrent chemoradiation therapy with or without low-level laser therapy (LLLT) to prevent oral mucositis. Oral Oncology 71:11–15. https://doi.org/10.1016/j.oraloncology.2017.05.018
7. Ahn MJ, D'Cruz A, Vermorken JB, et al (2016) Clinical recommendations for defining platinum unsuitable head and neck cancer patient populations on chemoradiotherapy: A literature review. Oral Oncology 53:10–16. https://doi.org/10.1016/j.oraloncology.2015.11.019
8. Szturz P, Cristina V, Gómez RGH, et al (2019) Cisplatin eligibility issues and alternative regimens in locoregionally advanced head and neck cancer: Recommendations for clinical practice. Frontiers in Oncology 9:. https://doi.org/10.3389/fonc.2019.00464
9. Machiels JP, René Leemans C, Golusinski W, et al (2020) Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Annals of Oncology 31:1462–1475. https://doi.org/10.1016/j.annonc.2020.07.011
10. Bernier J, Domenge C, Ozsahin M, et al (2004) Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer. New England Journal of Medicine 350:1945–1952. https://doi.org/10.1056/NEJMoa032641
11. Cooper JS, Pajak TF, Forastiere AA, et al (2004) Postoperative Concurrent Radiotherapy and Chemotherapy for High-Risk Squamous-Cell Carcinoma of the Head and Neck. New England Journal of Medicine 350:1937–1944. https://doi.org/10.1056/NEJMoa032646

12. Forastiere AA, Goepfert H, Maor M, et al (2003) Concurrent Chemotherapy and Radiotherapy for Organ Preservation in Advanced Laryngeal Cancer. New England Journal of Medicine 349:2091–2098. https://doi.org/10.1056/NEJMoa031317
13. Antunes HS, Schluckebier LF, Herchenhorn D, et al (2016) Cost-effectiveness of low-level laser therapy (LLLT) in head and neck cancer patients receiving concurrent chemoradiation. Oral Oncology 52:85–90. https://doi.org/10.1016/j.oraloncology.2015.10.022
14. Antunes HS, Herchenhorn D, Small IA, et al (2013) Phase III trial of low-level laser therapy to prevent oral mucositis in head and neck cancer patients treated with concurrent chemoradiation. Radiotherapy and Oncology 109:297–302. https://doi.org/10.1016/j.radonc.2013.08.010
15. Migliorati C, Hewson I, Lalla R v., et al (2013) Systematic review of laser and other light therapy for the management of oral mucositis in cancer patients. Supportive Care in Cancer 21:333–341. https://doi.org/10.1007/s00520-012-1605-6
16. Gautam AP, Fernandes DJ, Vidyasagar MS, et al (2015) Low level laser therapy against radiation induced oral mucositis in elderly head and neck cancer patients-a randomized placebo controlled trial. Journal of Photochemistry and Photobiology B: Biology 144:51–56. https://doi.org/10.1016/j.jphotobiol.2015.01.011
17. Amin MB, Greene FL, Edge SB, et al (2017) The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA: A Cancer Journal for Clinicians 67:93–99. https://doi.org/10.3322/caac.21388
18. National Cancer Institute (2017) Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE) v5.0
19. Gautam AP, Fernandes DJ, Vidyasagar MS, et al (2013) Effect of low-level laser therapy on patient reported measures of oral mucositis and quality of life in head and neck cancer patients receiving chemoradiotherapy - A randomized controlled trial. Supportive Care in Cancer 21:1421–1428. https://doi.org/10.1007/s00520-012-1684-4
20. Gautam AP, Fernandes DJ, Vidyasagar MS, et al (2012) Low level laser therapy for concurrent chemoradiotherapy induced oral mucositis in head and neck cancer patients - A triple blinded randomized controlled trial. Radiotherapy and Oncology 104:349–354. https://doi.org/10.1016/j.radonc.2012.06.011
21. Langius JAE, Bakker S, Rietveld DHF, et al (2013) Critical weight loss is a major prognostic indicator for disease-specific survival in patients with head and neck cancer receiving radiotherapy. British Journal of Cancer 109:1093–1099. https://doi.org/10.1038/bjc.2013.458
22. Langius JAE, van Dijk AM, Doornaert P, et al (2013) More than 10% weight loss in head and neck cancer patients during radiotherapy is independently associated with deterioration in quality of life. Nutrition and Cancer 65:76–83. https://doi.org/10.1080/01635581.2013.741749
23. Curtin P, Akbar A, Kramer H, et al (2020) The Status of Nutritional Management Guidelines for Head and Neck Cancer Patients. Cureus. https://doi.org/10.7759/cureus.11309
24. Ghadjar P, Hayoz S, Zimmermann F, et al (2015) Impact of weight loss on survival after chemoradiation for locally advanced head and neck Cancer: secondary results of a randomized phase III trial (SAKK 10/94). Radiation Oncology 10:21. https://doi.org/10.1186/s13014-014-0319-y

25. de Sousa Melo A, Andrade CL, de Lima Dantas JB, et al (2022) Impact of photobiomodulation for oral mucositis on body weight and BMI of patients with head and neck cancer. Supportive Care in Cancer 30:4897–4904. https://doi.org/10.1007/s00520-022-06899-6
26. Oton-Leite AF, Corrêa De Castro AC, Morais MO, et al (2012) Effect of intraoral low-level laser therapy on quality of life of patients with head and neck cancer undergoing radiotherapy. Head and Neck 34:398–404. https://doi.org/10.1002/hed.21737
27. Elting LS, Cooksley CD, Chambers MS, Garden AS (2007) Risk, Outcomes, and Costs of Radiation-Induced Oral Mucositis Among Patients With Head-and-Neck Malignancies. International Journal of Radiation Oncology Biology Physics 68:1110–1120. https://doi.org/10.1016/j.ijrobp.2007.01.053
28. Lopes Martins AF, Nogueira TE, Morais MO, et al (2021) 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. Supportive Care in Cancer 29:1245–1256. https://doi.org/10.1007/s00520-020-05607.

6 **DISCUSSÃO**

O uso de terapia sistêmica concomitante ao tratamento com RT está associado a uma melhor resposta ao tratamento, com maior SG, SLD e redução da recidiva locorregional. Porém, esses ganhos de sobrevida e o controle da doença vieram à custa do aumento significativo da toxicidade aguda, principalmente MO, náusea e/ou vômito e mielossupressão (BERNIER et al., 2004; COOPER et al., 2004; SZTURZ et al., 2019).

Historicamente, a QRT com associação de CDDP-AD à RT é a combinação mais utilizada. Porém, esta combinação está associada a uma maior incidência de EA graves, tanto agudos como crônicos, com redução significativa da QdV, o que resulta em uma menor adesão ao tratamento (MASHHOUR; HASHEM, 2020; SZTURZ et al., 2019). Em estudos clínicos, cerca de 30 a 40% dos pacientes não conseguem completar o tratamento planejado com três doses de CDDP-AD (BERNIER et al., 2004; COOPER et al., 2004). Uma vez que é necessária uma dose cumulativa mínima de 200 mg/m² de CDDP para alcançar um efeito antitumoral adequado, a alta taxa de descontinuação do tratamento pode comprometer a eficácia do mesmo (SZTURZ et al., 2019), ademais, interrupções prolongadas das sessões de radioterapia podem favorecer um repovoamento de células cancerígenas (GONZÁLEZ FERREIRA et al., 2015; HAN et al., 2020).

Essa alta incidência de EA graves é motivo de grande preocupação para a equipe multidisciplinar, especialmente naqueles pacientes com condição clínica ruim, idade avançada ou que apresentem comorbidades prévias significativas (SZTURZ et al., 2019). Como evidenciado neste trabalho, e em consonância com a literatura, a MO é um EA muito comum nos pacientes com CCP submetidos a tratamento com RT ou QRT, com, virtualmente, todos os pacientes apresentando algum grau de mucosite durante o tratamento e até metade deles cursando com MO grave (graus 3 e 4) (ADELSTEIN et al., 2003; SZTURZ et al., 2019).

Além da interferência negativa na QdV associada aos sintomas da MO, como odinofagia e disfagia, esta resulta em uma piora considerável na aceitação da alimentação por via oral e, consequentemente, em perda de peso. Estima-se que metade dos pacientes irão apresentar uma PP maior que 5% do peso corporal basal durante o tratamento com QRT. Como a incidência de desnutrição nos indivíduos com CCP ao diagnóstico é elevada, a PP durante o tratamento é motivo de grande preocupação para a equipe, uma vez que é associada uma maior deterioração da QdV e pior prognóstico (CURTIN et al., 2020; GHADJAR et al., 2015; LANGIUS et al., 2016).

As diretrizes da MASCC/ISOO sugerem medidas para prevenção e tratamento da MO grave em pacientes em tratamento oncológico. Dentre elas, a manutenção de saúde e higiene bucal

adequadas, bochechos com agentes anti-inflamatórios e enxaguantes suaves, como solução com bicarbonato de sódio, uso de medicações anti-inflamatórias e analgésicas tópicas e uso da fotobiomodulação, tanto com intuito profilático como terapêutico (ELAD et al., 2020). Existem evidências consistentes que sugerem que a FBM pode prevenir parcialmente o desenvolvimento de MO, reduzir a incidência de MO grave, além de apresentar ação analgésica local (HANNA et al., 2020).

A FBM é um tratamento não invasivo que auxilia na prevenção e tratamento da MO através da utilização de fontes de luz não-ionizantes, principalmente a luz vermelha ou quase-infravermelha. Os mecanismos de ação da FBM ainda não são completamente conhecidos, mas estudos comprovam que o PBM tem um impacto significativo nas atividades celulares e moleculares, e o modo de ação difere entre várias aplicações, podendo sofrer influência das propriedades de cada tecido. Durante o tratamento com FBM, é importante considerar a natureza da lesão em termos de consistência, composição e localização (profunda ou superficial) (DOMPE et al., 2020; HANNA et al., 2020).

Em estudo prospectivo randomizado, 94 pacientes com CCP em tratamento com QRT foram randomizados para receber tratamento com FBM ou placebo (ANTUNES et al., 2013). Evidenciou-se que a FBM foi eficaz em prevenir a ocorrência de MO de graus 3-4, porém sem diferença na intensidade de perda ponderal. Ademais, a atualização desse estudo em 2017 mostrou que os pacientes que receberam PBM apresentaram uma melhor resposta e aumento da sobrevida livre de progressão (ANTUNES et al., 2017).

Em outro ensaio, 221 pacientes foram randomizados para FBM ou placebo, sendo evidenciado redução significativa na incidência de MO grave ($p<0.0001$), dor associada a OM ($p<0.0001$), disfagia ($p<0.0001$), uso de opioides ($p<0.0001$), além de redução significativa na perda ponderal e na necessidade de dieta enteral no grupo FBM em comparação com placebo (GAUTAM et al., 2012).

Um estudo brasileiro avaliou, especificamente, o impacto do uso da FBM no peso e IMC de pacientes com CCP. Os pacientes foram alocados em dois grupos, de acordo com o uso ou não de FBM. Todos os pacientes apresentaram redução significativa de peso e IMC ao longo do período do estudo, porém os pacientes do grupo FBM perderam menos peso ($p < 0,01$) e tiveram menor perda de IMC ($p < 0,01$). Embora neste estudo a FBM não tenha prevenido o surgimento de mucosite oral, diminuiu significativamente a gravidade da mesma ($p < 0,01$) (DE SOUSA MELO et al., 2022).

Em aditamento a uma redução significativa dos EA, o uso da FBM também está associado ao ganho significativo na QdV a curto e longo prazo (GAUTAM et al., 2013; OTON-LEITE et

al., 2012) e a redução significativa do custo geral em pacientes submetidos a tratamentos com alto risco de desenvolver MO grave (ANTUNES et al., 2016). Um estudo realizado nos EUA evidenciou que a MO elevou o custo do tratamento de pacientes com CCP entre US$ 1.700,00 e 6.000,00, principalmente devido ao aumento do uso de recursos, dias de hospitalização, uso de opioides, entre outros fatores (ELTING et al., 2007). Em outro estudo randomizado conduzido no Brasil o uso da FBM foi mais custo-efetivo do que o cuidado oral preventivo isolado na prevenção de MO grave, da piora da qualidade de vida e foi associado a redução nas interrupções da RT (LOPES MARTINS et al., 2021).

Em consonância com a literatura, no presente estudo foi observado um resultado clínico positivo associado ao uso da FBM, indicando um possível efeito protetor contra a presença de MO grave em relação ao grupo controle. Apesar dos benefícios já comprovados, o tratamento com FBM é de difícil implementação no Brasil, uma vez que requer equipamentos caros e equipe com treinamento especializado (MIGLIORATI et al., 2013). Em um estudo, o custo médio considerado para aquisição do equipamento foi de US$ 3.349,75 e o custo para aquisição da licença para realização do tratamento foi de US$ 1.418,72 (LOPES MARTINS et al., 2021). Esses valores não são cobertos pela rede pública de saúde (SUS) brasileira ou pela grande maioria das operadoras de saúde do setor privado, se tornando um tratamento dispendioso para os pacientes que a realizam. Nada obstante, considerando o benefício a curto e longo prazo para os pacientes, além de ser um tratamento custo-efetivo, é altamente recomendado que a FBM deva ser usada profilaticamente em pacientes com CCP que estejam recebendo tratamento com QRT.

7 CONCLUSÃO

Este foi o primeiro estudo a analisar a ação da FBM na prevenção de MO e da perda ponderal em pacientes da Bahia/Brasil com CCP tratados com QRT. Foram observados resultados interessantes do ponto de vista clínico, com um possível efeito protetor da FBM no desenvolvimento de MO grave, além de redução do risco de perda ponderal moderada a grave. Os benefícios do uso da FBM são observados na prática clínica diária, com um melhor controle da MO grave e ganho expressivo na qualidade de vida, o que ratifica a recomendação de seu uso nestes doentes, além de reforçar a importância da realização de estudos adicionais, com inclusão de uma maior amostragem, especialmente na população brasileira, para confirmar nossos achados de forma significativa.

REFERÊNCIAS

ADELSTEIN, D. J. et al. Simultaneous Versus Sequential Combined Technique Therapy for Squamous Cell Head and Neck Cancer. **Cancer**, v. 65, p. 1685–1691, 1990.

ADELSTEIN, D. J. et al. An Intergroup Phase III Comparison of Standard Radiation Therapy and Two Schedules of Concurrent Chemoradiotherapy in Patients With Unresectable Squamous Cell Head and Neck Cancer. **J Clin Oncol.**, v. 21, n. 1, p. 92–98, 1 jan. 2003.

AHN, M. J. et al. Clinical recommendations for defining platinum unsuitable head and neck cancer patient populations on chemoradiotherapy: A literature review. **Oral Oncology**, v. 53, p. 10–16, 1 fev. 2016.

AMIN, M. B. et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. **CA: A Cancer Journal for Clinicians**, v. 67, n. 2, p. 93–99, mar. 2017.

ANDERSON, G. et al. An updated review on head and neck cancer treatment with radiation therapy. **Cancers**, v. 13, n. 19, 1 out. 2021.

ANTUNES, H. S. et al. Phase III trial of low-level laser therapy to prevent oral mucositis in head and neck cancer patients treated with concurrent chemoradiation. **Radiotherapy and Oncology**, v. 109, n. 2, p. 297–302, nov. 2013.

ANTUNES, H. S. et al. Cost-effectiveness of low-level laser therapy (LLLT) in head and neck cancer patients receiving concurrent chemoradiation. **Oral Oncology**, v. 52, p. 85–90, 1 jan. 2016.

ANTUNES, H. S. et al. Long-term survival of a randomized phase III trial of head and neck cancer patients receiving concurrent chemoradiation therapy with or without low-level laser therapy (LLLT) to prevent oral mucositis. **Oral Oncology**, v. 71, p. 11–15, 1 ago. 2017.

AUPÉRIN, A. Epidemiology of head and neck cancers: An update. **Current Opinion in Oncology**, v. 32, n. 3, p. 178–186, 1 maio 2020.

BENSADOUN, R. J. et al. Safety and efficacy of photobiomodulation therapy in oncology: A systematic review. **Cancer Medicine**, v. 9, n. 22, p. 8279–8300, 1 nov. 2020.

BERNIER, J. et al. Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer. **N Engl J Med.**, v. 350, n. 19, p. 1945–1952, 6 maio 2004.

BLAKAJ, A. et al. Oral mucositis in head and neck cancer: Evidence-based management and review of clinical trial data. **Oral Oncology**, v. 95, p. 29–34, 1 ago. 2019.

BONNER, J. et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. **N Engl J Med.**, v. 354, n. 6, p. 567–78, 2006.

BOSCOLO-RIZZO, P. et al. The evolution of the epidemiological landscape of head and neck cancer in Italy: Is there evidence for an increase in the incidence of potentially HPV-related carcinomas? **PLoS ONE**, v. 13, n. 2, 1 fev. 2018.

Bossi P, Alfieri S. The Benefit of a Multidisciplinary Approach to the Patient Treated with (Chemo) Radiation for Head and Neck Cancer. **Curr Treat Options Oncol**. 2016 Oct;17(10):53.

BROWN, T. J.; GUPTA, A. Management of Cancer Therapy–Associated Oral Mucositis. **JCO Oncology Practice**, v. 16, n. 3, p. 103–109, mar. 2020.

BUGLIONE, M. et al. Three weekly versus weekly concurrent cisplatin: safety propensity score analysis on 166 head and neck cancer patients. **Radiation Oncology**, v. 16, n. 1, 1 dez. 2021.

CHASEN, M. R.; BHARGAVA, R. A descriptive review of the factors contributing to nutritional compromise in patients with head and neck cancer. **Supportive Care in Cancer**, v. 17, n. 11, p. 1345–1351, 18 nov. 2009.

CHOW, E. et al. Update on the Systematic Review of Palliative Radiotherapy Trials for Bone Metastases. **Clinical Oncology**, v. 24, n. 2, p. 112–124, mar. 2012.

CHOW, L. Q. M. Head and Neck Cancer. **N Engl J Med.**, v. 382, n. 1, p. 60–72, 2 jan. 2020.

CLARKSON, J. E. et al. Interventions for treating oral mucositis for patients with cancer receiving treatment. **Cochrane Database of Systematic Reviews**, 4 ago. 2010.

CONWAY, D. I. et al. Occupational socioeconomic risk associations for head and neck cancer in Europe and South America: Individual participant data analysis of pooled case–control studies within the INHANCE Consortium. **Journal of Epidemiology and Community Health**, v. 75, n. 8, p. 779–787, 1 ago. 2021.

COOPER, J. S. et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. **N Engl J Med.**, v. 350, p. 1937–1981, 2004.

COOPER, J. S. et al. Long-term Follow-up of the RTOG 9501/Intergroup Phase III Trial: Postoperative Concurrent Radiation Therapy and Chemotherapy in High-Risk Squamous Cell Carcinoma of the Head and Neck. ***Int'l J. of Medical Physics, Clinical Eng. and Radiation Oncology***, v. 84, n. 5, p. 1198–1205, dez. 2012.

CURTIN, P. et al. The Status of Nutritional Management Guidelines for Head and Neck Cancer Patients. **Cureus**, 3 nov. 2020.

DE CASTRO, G. et al. Criteria for eligibility to cisplatin in the curative treatment of head and neck cancer: Consensus opinion from a panel of experts. **Critical Reviews in Oncology/Hematology**, v. 131, p. 30–34, 1 nov. 2018.

DE SOUSA MELO, A. et al. Impact of photobiomodulation for oral mucositis on body weight and BMI of patients with head and neck cancer. **Supportive Care in Cancer**, v. 30, n. 6, p. 4897–4904, 15 jun. 2022.

DENG, J. et al. Photobiomodulation Therapy in Head and Neck Cancer-Related Lymphedema: A Pilot Feasibility Study. **Integrative Cancer Therapies**, v. 20, 2021.

DOMPE, C. et al. Photobiomodulation—underlying mechanism and clinical applications. **Journal of Clinical Medicine**, v. 9, n. 6, p. 1–17, 1 jun. 2020.

EL MOBADDER, M. et al. Photobiomodulation therapy in the treatment of oral mucositis, dysphagia, oral dryness, taste alteration, and burning mouth sensation due to cancer therapy: A case series. **International Journal of Environmental Research and Public Health**, v. 16, n. 22, 2 nov. 2019.

ELAD, S. et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. **Cancer**, v. 126, n. 19, p. 4423–4431, 1 out. 2020.

ELTING, L. S. et al. Risk, Outcomes, and Costs of Radiation-Induced Oral Mucositis Among Patients With Head-and-Neck Malignancies. **International Journal of Radiation Oncology Biology Physics**, v. 68, n. 4, p. 1110–1120, 15 jul. 2007.

EPSTEIN, J. B. et al. Photobiomodulation therapy: management of mucosal necrosis of the oropharynx in previously treated head and neck cancer patients. **Supportive Care in Cancer**, v. 25, n. 4, p. 1031–1034, 1 abr. 2017.

EPSTEIN, M. A.; ACHONG, B. G.; BARR, Y. M. VIRUS PARTICLES IN CULTURED LYMPHOBLASTS FROM BURKITT'S LYMPHOMA. **The Lancet**, v. 283, n. 7335, p. 702–703, mar. 1964.

FASANO, M. et al. Head and Neck Squamous Cell Carcinoma in Elderly Patients: Role of Radiotherapy and Chemotherapy. **Cancers**, v. 14, n. 3, p. 472, 18 jan. 2022.

FORASTIERE, A. A. et al. Concurrent Chemotherapy and Radiotherapy for Organ Preservation in Advanced Laryngeal Cancer. **N Engl J Med.**, v. 349, n. 22, p. 2091–2098, 27 nov. 2003.

FORASTIERE, A. A. et al. Long-term results of RTOG 91-11: A comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. **J Clin Oncol**, v. 31, n. 7, p. 845–852, 1 mar. 2013.

GARIBALDI, C. et al. Recent advances in radiation oncology. ecancermedicalscience, v. 11, 30 nov. 2017.

GAUTAM, A. P. et al. Low level laser therapy for concurrent chemoradiotherapy induced oral mucositis in head and neck cancer patients - A triple blinded randomized controlled trial. **Radiotherapy and Oncology**, v. 104, n. 3, p. 349–354, set. 2012.

GAUTAM, A. P. et al. Effect of low-level laser therapy on patient reported measures of oral mucositis and quality of life in head and neck cancer patients receiving chemoradiotherapy - A randomized controlled trial. **Supportive Care in Cancer**, v. 21, n. 5, p. 1421–1428, maio 2013.

GAUTAM, A. P. et al. Low level laser therapy against radiation induced oral mucositis in elderly head and neck cancer patients-a randomized placebo controlled trial. **J Photochem Photobiol B**, v. 144, p. 51–56, 2015.

GHADJAR, P. et al. Impact of weight loss on survival after chemoradiation for locally advanced head and neck Cancer: secondary results of a randomized phase III trial (SAKK 10/94). **Radiation Oncology**, v. 10, n. 1, p. 21, 17 dez. 2015.

GLASTONBURY, C. M. Critical changes in the staging of head and neck cancerRadiology: Imaging Cancer. **Radiol Imaging Cancer**. 2020 Jan 31;2(1):e190022.

HABBOUS, S. et al. The changing incidence of human papillomavirus-associated oropharyngeal cancer using multiple imputation from 2000 to 2010 at a Comprehensive Cancer Centre. **Cancer Epidemiology**, v. 37, n. 6, p. 820–829, dez. 2013.

HANNA, R. et al. Photobiomodulation Therapy in Oral Mucositis and Potentially Malignant Oral Lesions: A Therapy Towards the Future. **Cancers**, v. 12, n. 7, p. 1949, 18 jul. 2020.

HASHIBE, M. et al. Alcohol Drinking in Never Users of Tobacco, Cigarette Smoking in Never Drinkers, and the Risk of Head and Neck Cancer: Pooled Analysis in the International Head and Neck Cancer Epidemiology Consortium. **J Natl Cancer Inst.**, v. 99, n. 10, p. 777–789, 16 maio 2007.

HEISKANEN, V.; ZADIK, Y.; ELAD, S. Photobiomodulation Therapy for Cancer Treatment-Related Salivary Gland Dysfunction: A Systematic Review. **Photobiomodul Photomed Laser Surg**, v. 38, n. 6, p. 340–347, 1 jun. 2020.

IOCCA, O. et al. Locally advanced squamous cell carcinoma of the head and neck: A systematic review and Bayesian network meta-analysis of the currently available treatment options. **Oral Oncology**, v. 80, p. 40–51, 1 maio 2018.

JETHWA, A. R.; KHARIWALA, S. S. Tobacco-related carcinogenesis in head and neck cancer. **Cancer and Metastasis Reviews**, v. 36, n. 3, p. 411–423, 1 set. 2017.

JOHNSON, D. E. et al. Head and neck squamous cell carcinoma. **Nat Rev Dis Primers.**, v. 6, n. 1, p. 92, 26 dez. 2020.

KAWAKITA, D.; MATSUO, K. Alcohol and head and neck cancer. **Cancer and Metastasis Reviews**, v. 36, n. 3, p. 425–434, 16 set. 2017.

KFOURI, S. A. et al. Fraction of head and neck cancer attributable to tobacco and alcohol in cities of three Brazilian regions. **Revista Brasileira de Epidemiologia**, v. 21, 2018.

KIM, D.-Y. et al. Radiotherapy versus Surgery in Early-Stage HPV-Positive Oropharyngeal Cancer. **Cancer Research and Treatment**, v. 54, n. 2, p. 406–416, 15 abr. 2022.

KIYOTA, N. et al. Weekly Cisplatin Plus Radiation for Postoperative Head and Neck Cancer (JCOG1008): A Multicenter, Noninferiority, Phase II/III Randomized Controlled Trial. **J Clin Oncol**, v. 40, p. 1980–1990, 2022.

LANGIUS, J. A. E. et al. Prediction model to predict critical weight loss in patients with head and neck cancer during (chemo)radiotherapy. **Oral Oncology**, v. 52, p. 91–96, jan. 2016.

LEGOUTÉ, F. et al. Low-level laser therapy in treatment of chemoradiotherapy-induced mucositis in head and neck cancer: Results of a randomised, triple blind, multicentre phase III trial. **Radiation Oncology**, v. 14, n. 1, 22 maio 2019.

LESSA, R. C. et al. Oral Mucositis in Cancer and Potential Use of Omega-3 Free Fatty Acids in Its Management: A Review. **Biomedicines**, v. 9, n. 11, p. 1531, 25 out. 2021.

LICITRA, L. et al. Evaluation of the benefit and use of multidisciplinary teams in the treatment of head and neck cancer. **Oral Oncology**, v. 59, p. 73–79, 1 ago. 2016.

LO NIGRO, C. et al. Head and neck cancer: Improving outcomes with a multidisciplinary approach. **Cancer Management and Research**, v. 9, p. 363–371, 18 ago. 2017.

LOPES MARTINS, A. F. 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. **Supportive Care in Cancer**, v. 29, n. 3, p. 1245–1256, 1 mar. 2021.

MACHIELS, J. P. et al. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. **Annals of Oncology**, v. 31, n. 11, p. 1462–1475, 1 nov. 2020.

MARIA, O. M.; ELIOPOULOS, N.; MUANZA, T. Radiation-Induced Oral Mucositis. **Frontiers in Oncology**, v. 7, 22 maio 2017.

MASHHOUR, K.; HASHEM, W. Cisplatin weekly versus every 3 weeks concurrently with radiotherapy in the treatment of locally advanced head and neck squamous cell carcinomas: What is the best dosing and schedule? **Asian Pacific Journal of Cancer Prevention**, v. 21, n. 3, p. 799–807, 1 mar. 2020.

MEKHAIL, T. M. et al. Enteral Nutrition during the Treatment of Head and Neck Carcinoma: Is a Percutaneous Endoscopic Gastrostomy Tube Preferable to a Nasogastric Tube? **Cancer**, v. 91, n. 9, p. 1785–1790, 2001.

MIGLIORATI, C. et al. Systematic review of laser and other light therapy for the management of oral mucositis in cancer patients. **Supportive Care in Cancer**, v. 21, n. 1, p. 333–341, 2013.

MINISTÉRIO DA SAÚDE; INCA. Estimativa 2020 incidência de câncer no Brasil. Rio de Janeiro, 2019.

MÜNGER, K.; HOWLEY, P. M. Human papillomavirus immortalization and transformation functions. **Virus Research**, v. 89, n. 2, p. 213–228, nov. 2002.

NATIONAL CANCER INSTITUTE. Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE) v5.0, 2017. Disponível em: <https://www.meddra.org/> Acesso em 7 de maio de 2022.

NGUYEN-TAN, P. F. et al. Randomized Phase III Trial to Test Accelerated Versus Standard Fractionation in Combination With Concurrent Cisplatin for Head and Neck Carcinomas in the

Radiation Therapy Oncology Group 0129 Trial: Long-Term Report of Efficacy and Toxicity. **J Clin Oncol**, v. 32, n. 34, p. 3858–3867, 1 dez. 2014.

NUTTING, C. M. et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. **Lancet Oncol**. 2011 Feb;12(2):127-36.

O'SULLIVAN, B. et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study. **Lancet Oncol.**, v. 17, n. 4, p. 440–451, abr. 2016.

OTON-LEITE, A. F. et al. Effect of intraoral low-level laser therapy on quality of life of patients with head and neck cancer undergoing radiotherapy. **Head and Neck**, v. 34, n. 3, p. 398–404, mar. 2012.

PIGNON, J.-P. et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. **Radiotherapy and Oncology**, v. 92, n. 1, p. 4–14, jul. 2009.

ROBIJNS, J.; LODEWIJCKX, J.; MEBIS, J. Photobiomodulation therapy for acute radiodermatitis. **Current Opinion in Oncology**, v. 31, n. 4, p. 291–298, 1 jul. 2019.

ROLAND, N. et al. Tumour assessment and staging: United Kingdom National Multidisciplinary Guidelines. **The Journal of laryngology and otology**, v. 130, n. S2, p. S53–S58, 1 maio 2016.

SCOLETTA, M. et al. Effect of Low-Level Laser Irradiation on Bisphosphonate-Induced Osteonecrosis of the Jaws: Preliminary Results of a Prospective Study. **Photomedicine and Laser Surgery**, v. 28, n. 2, p. 179–184, 2010.

SETIA, M. Methodology series module 1: Cohort studies. **Indian Journal of Dermatology**, v. 61, n. 1, p. 21, 2016.

SIEGEL, R. L. et al. Cancer Statistics, 2021. **CA Cancer J Clin**, v. 71, n. 1, p. 7–33, 2021.

SIEGEL, R. L. et al. Cancer statistics, 2022. **CA Cancer J Clin**, v. 72, n. 1, p. 7–33, jan. 2022.

SUNG, H. et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. **CA Cancer J Clin**, v. 71, n. 3, p. 209–249, maio 2021.

SZTURZ, P. et al. Cisplatin eligibility issues and alternative regimens in locoregionally advanced head and neck cancer: Recommendations for clinical practice. **Frontiers in Oncology**, v. 9, n. JUN, 2019.

SZUKALSKA, M. et al. Electronic Cigarettes and Head and Neck Cancer Risk—Current State of Art. **Cancers**, v. 12, n. 11, p. 3274, 5 nov. 2020.

TABERNA, M. et al. Taberna M, Mena M, Pavón MA, Alemany L, Gillison ML, Mesía R. Human papillomavirus-related oropharyngeal cancer. **Ann Oncol**. 2017 Oct 1;28 (10):2386-2398.

TANDON, S. et al. Fine-needle aspiration cytology in a regional head and neck cancer center: Comparison with a systematic review and meta-analysis. **Head and Neck**, v. 30, n. 9, p. 1246–1252, set. 2008.

TSAO, S. W.; TSANG, C. M.; LO, K. W. Epstein–Barr virus infection and nasopharyngeal carcinoma. **Philosophical Transactions of the Royal Society B: Biological Sciences**, v. 372, n. 1732, p. 20160270, 19 out. 2017.

VAN GESTEL, D. et al. Intensity-modulated radiotherapy in patients with head and neck cancer: A European single-centre experience. **British Journal of Radiology**, v. 84, n. 1000, p. 367–374, abr. 2011.

WANG, X.; HU, C.; EISBRUCH, A. Organ-sparing radiation therapy for head and neck cancer. **Nature Reviews Clinical Oncology**, v. 8, n. 11, p. 639–648, nov. 2011.

WINN, D. M. et al. The INHANCE consortium: Toward a better understanding of the causes and mechanisms of head and neck cancer. **Oral Diseases**, v. 21, n. 6, p. 685–693, 1 set. 2015.

WORTHINGTON, H. et al. Interventions for preventing oral mucositis for patients with cancer receiving treatment (Review). **Cochrane Database of Systematic Reviews**, 2013.

ZANONI, D. K.; PATEL, S. G.; SHAH, J. P. Changes in the 8th Edition of the American Joint Committee on Cancer (AJCC) Staging of Head and Neck Cancer: Rationale and Implications. **Current Oncology Reports**, v. 21, n. 6, p. 52, 17 jun. 2019.

ZECHA, J. A. E. M. et al. Low-level laser therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 2: proposed applications and treatment protocols. **Supportive Care in Cancer**, v. 24, n. 6, p. 2793–2805, 1 jun. 2016.

Apêndice A - Formulário padrão para coleta de dados nº paciente

1. **Idade ao diagnóstico (anos)**
   _____
2. **Sexo**
   a. Masculino
   b. Feminino
3. **ECOG ao diagnóstico**
   a. 0
   b. 1
   c. 2
   d. 3
   e. 4
4. **Tipo histológico**
   a. Carcinoma escamocelular
   b. Outros
5. **Sítio primário**
   _____
6. **p16**
   a. Positivo
   b. Negativo
   c. Desconhecido
7. **Tabagismo**
   a. Não-fumante
   b. Ex-fumante
   c. Fumante ativo
8. **Estadiamento clínico (AJCC)**
   a. I
   b. II
   c. III
   d. IVA
9. **T (TNM)**
   a. T1
   b. T2
   c. T3
   d. T4
10. **N (TNM)**
    a. N1
    b. N2
    c. N3
11. **Intenção do tratamento**
    a. Adjuvante
    b. Radical / curativo
12. **Tratamento sistêmico concomitante**
    a. CDDP 40 mg/m² semanal
    b. CDDP 100 mg/m² D1, 22, 43
    c. Carboplatina
    d. Cetuximabe
13. **Peso ao diagnóstico (Kg)**
    _____
14. **Peso após término do tratamento (Kg)**_____
15. **% perda ponderal**
    a. 0%
    b. 0.1-5%
    c. 5.1-10%
    d. >10%
16. **Necessidade de uso de SNE ou GGT**
    a. Sim
    b. Não
17. **Grau de mucosite apresentado**
    a. 0
    b. 1
    c. 2
    d. 3
    e. 4
    f. 5

Anexo A - Parecer consubstanciado do CEP

DADOS DA EMENDA

Título da Pesquisa: EFEITO DA LASERTERAPIA PROFILÁTICA NA PERDA PONDERAL EM PACIENTES COM NEOPLASIA DE CABEÇA E PESCOÇO **Pesquisador:** LARISSA MATOS ALMEIDA MOURA **Área Temática:**

Versão: 2

CAAE: 44689321.7.0000.5027

Instituição Proponente:IPD-CAM INSTITUTO DE PESQUISA E DESENVOLVIMENTO CARLOS

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.991.395

Apresentação do Projeto:

As informações elencadas nos campos "Apresentação do Projeto", "Objetivo da Pesquisa" e "Avaliação dos Riscos e Benefícios" foram retiradas do arquivo Informações Básicas da Pesquisa (PB_INFORMACOES_BASICAS_1778819_E1.pdf, de 21/06/2021).

Introdução:

As neoplasias de cabeça e pescoço correspondem ao sétimo câncer mais comum em todo o mundo, com uma incidência anual de aproximadamente 700.000 e uma taxa de mortalidade estimada em 350.000 em 2018 [1]. Essas neoplasias podem surgir na cavidade oral, faringe, laringe, cavidade nasal, seios paranasais e incluem uma variedade de tipos histopatológicos, sendo o carcinoma escamocelular (CEC) a histologia predominante.No Brasil, estima-se que em 2020 6.470 em homens e de 1.180 em mulheres foram diagnosticados com neoplasia de laringe e 11.180 homens e 4.010 em mulheres com neoplasia de cavidade oral [2]. Entre os principais fatores de risco associados ao câncer de cabeça e pescoço (CCP) estão o tabagismo, etilismo e, mais recentemente, a infecção pelo papiloma vírus humano (HPV), que desempenha um papel cada vez mais

proeminente como fator etiológico associado às neoplasias de orofaringe e cavidade oral [3,4]. Cerca de 75% a 85% dos CECs de cabeça e pescoço estão relacionados ao uso de tabaco e consumo de álcool, com a prevalência de câncer de orofaringe associado ao HPV variando amplamente em todo o mundo, mas estimada em cerca de 30% e 35% [5].O tratamento dessas patologias é baseado em três modalidades principais: cirurgia, quimioterapia e radioterapia, sendo fundamental a realização de uma abordagem multidisciplinar para a definição da melhor abordagem terapêutica, com planejamento de tratamento e avaliação da resposta pós-tratamento [6,7]. Sempre que possível, essa equipe deve ser formada por cirurgiões, oncologistas e radio-oncologistas, bem como de dentistas, fonoaudiólogos, nutricionistas, psicólogos e terapeutas de reabilitação. Dados mostram que esta abordagem multidisciplinar pode resultar em mudança no diagnóstico, estágio ou plano de tratamento do tumor em cerca de 27% dos pacientes [6].Os principais fatores a serem considerados para definição da melhor estratégia terapêutica incluem o local do tumor primário e a extensão da doença, os fatores individuais do paciente (idade, comorbidade, preferências quanto ao tipo de tratamento) e as prováveis consequências funcionais e morbidade de cada abordagem de tratamento [24].Nos indivíduos com doença localizada ou localmente avançada, o tratamento com radioterapia ou quimiorradioterapia concomitantes é frequentemente utilizado, seja como tratamento adjuvante ou como tratamento radical com intuito curativo, principalmente nos casos em que é possível realizar a preservação funcional do órgão [23]. A combinação de quimioterapia à base de platina e radioterapia é considerada segura e eficaz, com nível de evidência 1A, sendo o tratamento padrão ouro para pacientes com tumores localmente avançados [6,8] e nos casos que há indicação de preservação de órgão [9]. Apesar desta combinação de tratamento estar associada a um ganho de sobrevida quando comparado ao tratamento com radioterapia isolada, ela está associada a um aumento significativo de toxicidade maior ou igual a grau 3, principalmente de mucosite oral, radiodermatite e nefrotoxicidade, que podem ser fatores limitantes para a conclusão do tratamento [10,11,12]. Essas toxicidades podem culminar em interrupções não planejadas de tratamento e / ou reduções de dose de quimioterapia, aumentando as chances de recorrências locorregionais, reduzindo a taxa de cura e sobrevivência nestes pacientes [9,13]. Além disso, devido a limitações funcionais significativas relacionadas à própria doença e ao tratamento, a qualidade de vida (QV) a longo prazo em sobreviventes de CCP é pior em comparação com a população oncológica em geral [14]. Vários fatores foram identificados como possíveis influenciadores na QV, como gravidade da doença, tipo e localização do câncer, rede de suporte

pessoal e nível socioeconômico [14,15,16].Durante o tratamento e após a conclusão do mesmo, é muito comum que os pacientes apresentem perda ponderal acentuada. Estudos mostram que existe uma associação significativa entre a perda de peso e deterioração da QV global, funcionamento físico, funcionamento social, alimentação social e contato social, principalmente nos pacientes com redução superior a 10% [17]. Possíveis fatores de risco para o emagrecimento acentuado nos pacientes com CCP submetidos à radioterapia incluem estadiamentos mais avançados do tumor, índice de massa corporal (IMC) elevado ao diagnóstico, dose total de radioterapia, grau de mucosite apresentado, tratamento concomitante com quimioterapia (QRT), xerostomia, disfagia e disgeusia. [21]. Atualmente, a Laserterapia de Baixo Nível (LLLT) é considerada uma terapia promissora e tem sido usado na prevenção e tratamento de mucosite oral em vários cenários de tratamento oncológico, principalmente na radioterapia para pacientes com câncer de cabeça e pescoço [18,19]. Estudos mostram que o uso de laser de baixa intensidade para a prevenção e tratamento da mucosite oral induzida por tratamento oncológico está associado a uma menor incidência de mucosite oral e menor duração da mesma, além de menos necessidade de gastrostomia ou uso de sondas enteral, melhor controle de dor, com menor necessidade de tratamento antiálgico com opióides e menor taxa de interrupção de tratamento por toxicidade [10,18,20]. O mecanismo de ação da LLLT ainda não é bem definido, mas estudos demonstraram que a LLLT é segura e tem ação antiinflamatória, efeitos analgésicos e biomoduladores [13].Até o presente momento, não identificamos estudos nos bancos de dados nacionais e internacionais que associam o uso da LLLT profilática com a perda ponderal nos pacientes com CCP tratados com QRT. Como a LLT também apresenta funções antiflamatórias e analgésicas, esse estudo pretende gerar a hipótese que o uso da LLLT profilática está associada a uma menor taxa de perda ponderal durante o tratamento com QRT, mesmo nos pacientes que apresentam mucosite oral importante.

Objetivo da Pesquisa:

Objetivo Primário:

O objetivo deste estudo é avaliar o papel da laserterapia de baixa dosagem na prevenção da perda ponderal moderada (5-10%) e acentuada (> 10% do peso corporal basal) em pacientes com neoplasia de cabeça e pescoço tratados com tratamento oncológico sistêmico (quimioterapia baseada em cisplatina, carboplatina ou cetuximabe) e radioterapia concomitantes.

Metodologia Proposta:

DESENHO DO ESTUDO: Este é um estudo de coorte retrospectivo, realizado através de análise de dados em prontuário.

POPULAÇÃO: Pacientes com neoplasia de cabeça e pescoço, com tumor primário localizado na nasofaringe, faringe, orofaringe, cavidade oral, hipofaringe e laringe.

LOCAL DO ESTUDO: Este estudo será realizado no serviço da Clínica de Oncologia (CLION/Grupo CAM), que é formado por três unidades (CLION- Hospital Português, CLION-Unidade Rio Vermelho).

AMOSTRAGEM: A amostra será realizada por conveniência e serão incluídos todos os pacientes que se enquadrem nos critérios de elegibilidade do estudo. Os pacientes serão divididos em dois grupos, de acordo com o uso ou não de laserterapia profilática, sendo que um grupo exposto será formado pelos pacientes selecionados que foram submetidos a laserterapia profilática (iniciada até o 1o dia do tratamento) e o grupo não exposto será formado pelos pacientes que não foram submetidos à laserterapia profilática. COLETA DE DADOS: Os dados serão obtidos através da análise retrospectiva dos prontuários eletrônicos de pacientes da CLION - Grupo CAM, pela pesquisadora responsável. A coleta de dados será realizada através de ficha padrão (Apêndice 1) e as seguintes variáveis serão avaliadas: idade ao diagnóstico, sexo, performance status ao diagnóstico (pelo Eastern Cooperative Oncology Group - ECOG), tipo histológico, estadiamento clínico e/ou patológico (pelo TNM AJCC 8a edição), caráter do tratamento (adjuvante ou radical), dose total de radioterapia, tipo de quimioterapia (cisplatina 40 mg/m2, cisplatina 100 mg/m2, cetuximabe, carboplatina), uso de LLLT profiática, quantidade total de sessões de LLLT durante o tratamento, peso ao diagnóstico, peso ao final do tratamento, IMC ao diagnóstico, IMC ao final do tratamento, percentual de perda de peso (0%, 0.1- 5%, 5.1-10%, >10%), necessidade de uso de dieta enteral, grau de mucosite oral apresentado (pelo CTCAE 5.0) [26], uso de suplemento alimentar via oral e acompanhamento regular com nutricionista (2 consultas durante o tratamento).

Critério de Inclusão:

CRITÉRIOS DE INCLUSÃO: Pacientes com 18 anos, com diagnóstico de neoplasia de cabeça e pescoço localizado ou localmente avançado pelo sistema Tumor (T), Linfonodo (N) e Metástase (M) da American Joint Committe on Cancer (AJCC) 8a edição (Estadiamento I a IVA) [24], que foram submetidos à tratamento com radioterapia em concomitância com quimioterapia baseada em cisplatina, cetuximabe ou carboplatina entre Janeiro/2017 e Fevereiro/2021, que tiveram indicação, após avaliação com grupo de odontologia, para realização de laserterapia profilática.

Critério de Exclusão:

CRITÉRIOS DE EXCLUSÃO: Pacientes submetidos à quimioterapia de indução (prévia ao tratamento concomitante), que apresentem metástases à distância ao diagnóstico (estadiamento IVB pelo TNM AJCC 8a edição) [25], que iniciaram uso de terapia enteral (via sonda nasoenteral ou gastrostomia) antes do início do tratamento oncológico.

Metodologia de Análise de Dados:

ANÁLISE ESTATÍSTICA: A base de dados será validada por dupla entrada no software EpiData (versão 3.1,

EpiData Assoc., Dinamarca). Os dados serão exportados para uma única planilha no Excel e a análise das variáveis será realizada no ambiente de programação R versão 3.2.5. Variáveis categóricas serão descritas com frequências (absolutas e relativas) e variáveis quantitativas, por medidas de tendência central (média) e variabilidade (desvio padrão).As diferenças nas variáveis contínuas serão analisadas por meio do teste U de Mann-Whitney bicaudal. Para as variáveis categóricas, as diferenças serão analisadas por meio do teste do qui-quadrado ou teste exato de Fisher. A análise de regressão de riscos proporcionais de Cox será utilizada para avaliar análises univariadas e multivariadas papel preditivo do tratamento administrado e de variáveis clínicas que possam interferir na resposta ao tratamento com laserterapia. A razão de verossimilhança será usada para avaliar a significância das covariáveis incluídas em cada modelo. Valores de p menores que 0,05 serão considerados para indicar significância estatística. Desfecho Primário: Percentual de perda de peso (0%, 0.1-5%, 5.1-10%, >10%) durante o tratamento Desfecho Secundário: 1. Necessidade de uso de dieta enteral (via gastrostomia ou sonda nasoenteral). 2. Grau de mucosite oral.

Avaliação dos Riscos e Benefícios:

Riscos:

Por se tratar de um estudo retrospectivo, com revisão de prontuários, não haverá intervenção direta ao paciente, logo, não submeterá o mesmo a riscos diretos. Será garantido a confidencialidade dos dados de todos os participantes.

Benefícios:

Não haverá benefício imediato e direto aos sujeitos da pesquisa, considerando ser um estudo retrospectivo com dados colhidos de prontuários médicos, contudo os resultados serão divulgados em eventos e periódicos científicos, e poderão assim, contribuir para o melhor entendimento sobre

o benefício do uso da laserterapia profilática em pacientes com neoplasia de cabeça e pescoço submetidos a tratamento definitivo com quimioterapia e radioterapia concomitantes.

Comentários e Considerações sobre a Pesquisa:

Trata-se de um estudo de coorte retrospectiva avaliando perda ponderal (desfecho primário), necessidade de uso de dieta enteral e grau de mucosite oral (desfechos secundários) em pacientes com câncer de cabeça e pescoço que receberam profilaxia de mucosite com laserterapia oral antes do início do tratamento concomitante de quimioterapia e radioterapia, comparado com pacientes que não receberam laserterapia profilática. Aparentemente há um erro tipográfico no primeiro critério de inclusão: onde se lê "pacientes com 18 anos"(nosso destaque), deve ter havido a intenção de escrever "pacientes com idade igual ou superior a 18 anos" (nosso destaque).

Considerações sobre os Termos de apresentação obrigatória:

Os pesquisadores apresentam carta com solicitação de isenção de aplicação do Termo de Consentimento Livre e Esclarecido (TCLE). Foram apresentadas quatro razões para justificar o pleito: 1 - "por ser um estudo observacional, analítico ou descritivo retrospectivo, que empregará apenas informações clínicas disponíveis na instituição sem previsão de utilização de material biológico" (destaque nosso); 2 - "porque todos os dados serão manejados e analisados de forma anônima, sem identificação nominal dos participantes de pesquisa" (nosso destaque); 3 - "porque os resultados do estudo serão apresentados de forma agregada, não permitindo a identificação individual dos participantes"; e 4 - porque se trata de um estudo não intervencionista (sem intervenções clínicas) e sem alterações/influências na rotina/tratamento do participante de pesquisa, e consequentemente sem adição de riscos ou prejuízos ao bem-estar dos mesmos" (nosso destaque). As Resoluções do Conselho Nacional de Saúde de número 466/2012 (item IV.8) e 510/2016 (Art 14) contemplam dispensação do TCLE nos casos em que seja inviável a obtenção do TCLE (p. ex. por morte ou perda de contato com a instituição) ou que a obtenção do TCLE signifique riscos substanciais à privacidade e confidencialidade dos dados dos participantes. Assim sendo, não restou claro nas justificativas mencionadas a existência de uma ou outra das razões contempladas nas Resoluções mencionadas acima. Não obstante essas observações, considerando-se a natureza verdadeiramente retrospectiva do estudo, acredito ser razoável a dispensação do TCLE.

Conclusões ou Pendências e Lista de Inadequações:

Não foram observados óbices éticos.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1778819_E1.pdf	21/06/2021 12:34:07		Aceito
Projeto Detalhado / Brochura Investigador	Protocolo_versao_Brasil_2_0_de_08_de_junho_de_2021_Controle_de_Alteracoes.pdf	21/06/2021 12:33:17	LARISSA MATOS ALMEIDA MOURA	Aceito
Projeto Detalhado / Brochura Investigador	Protocolo_versao_Brasil_2_0_de_08_de_junho_de_2021_Versao_Final.pdf	21/06/2021 12:32:48	LARISSA MATOS ALMEIDA MOURA	Aceito
Outros	Of_030_2021_Submissao_Emenda_Laserterpia_DraLarissa.pdf	21/06/2021 12:31:58	LARISSA MATOS ALMEIDA MOURA	Aceito
Folha de Rosto	FolhadeRosto.pdf	09/03/2021 12:22:10	JAMILE SANTOS FERREIRA	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Solicitacao_de_Dispensa_de_TCLE.pdf	08/03/2021 12:37:05	LARISSA MATOS ALMEIDA MOURA	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SALVADOR, 22 de Setembro de 2021

Assinado por:
Lísia Marcílio Rabelo
(Coordenador(a)

ANEXO B - Submission guidelines Contents

- Instructions for Authors
    - Peer Review Taxonomy
    - Scope
    - Ethical Responsibilities of Authors
    - Authorship principles
    - Compliance with Ethical Standards
    - Competing Interests
    - Research involving human participants, their data or biological material
    - Informed consent
    - Types of Papers
    - Title Page
    - Structured Abstract
    - Review procedure
    - Manuscript preparation
    - Manuscript Submission
    - Text
    - Scientific style
    - References
    - Statements & Declarations
    - Tables
    - Supplementary Information (SI)
    - Research Data Policy
    - After acceptance
    - Open Choice
    - Artwork and Illustrations Guidelines
    - English Language Editing
- Open access publishing

Instructions for Authors

Peer Review Taxonomy

Supportive Care in Cancer and Springer Nature are participating in a pilot of STM's Working Group on Peer Review Taxonomy.

STM, the International Association of Scientific, Technical and Medical Publishers, has recognized a need to identify and standardize definitions and terminology in peer review practices in order to help align nomenclature as more publishers use open peer review models.

A peer review taxonomy that is used across publishers will help make the peer review process for articles and journals more transparent, and will enable the community to better assess and compare peer review practices between different journals.

Taxonomy:

1. Identity transparency: Single anonymized
2. Reviewer interacts with: Editor
3. Review information published: None

We would welcome your feedback on the Peer Review Taxonomy Pilot - please can you take the time to fill this short survey

Scope

Supportive Care in Cancer publishes papers devoted to medical, technical and surgical topics as they relate to supportive therapy and care that supplements or substitutes basic cancer treatment at all stages of the disease. The journal focuses on papers and reviews that report on intervention studies and policy-related issues to manage treatment-related toxicities and other supportive care endpoints.

Papers devoted to nursing, rehabilitative, psychosocial and spiritual issues of support are also considered for publication.

The journal's Editorial Board has placed a low priority on pilot research of interventions or instrument development studies. Due to the large, existing base of literature concerning cancer patients' needs for supportive care, papers reporting on these issues will no longer be considered. The journal is dedicated to publishing supportive care intervention studies that address patients' needs. The journal does not publish papers that focus on tumor outcomes.

Ethical Responsibilities of Authors

This journal is committed to upholding the integrity of the scientific record. As a member of the Committee on Publication Ethics (COPE) the journal will follow the COPE guidelines on how to deal with potential acts of misconduct.

Authors should refrain from misrepresenting research results which could damage the trust in the journal, the professionalism of scientific authorship, and ultimately the entire scientific endeavour. Maintaining integrity of the research and its presentation is helped by following the rules of good scientific practice, which include*:

- The manuscript should not be submitted to more than one journal for simultaneous consideration.
- The submitted work should be original and should not have been published elsewhere in any form or language (partially or in full), unless the new work concerns an expansion of previous work. (Please provide transparency on the re-use of material to avoid the concerns about text-recycling ('self-plagiarism').
- A single study should not be split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time (i.e. 'salami-slicing/publishing').
- Concurrent or secondary publication is sometimes justifiable, provided certain conditions are met. Examples include: translations or a manuscript that is intended for a different group of readers.
- Results should be presented clearly, honestly, and without fabrication, falsification or inappropriate data manipulation (including image based manipulation). Authors should adhere to discipline-specific rules for acquiring, selecting and processing data.
- No data, text, or theories by others are presented as if they were the author's own ('plagiarism'). Proper acknowledgements to other works must be given (this includes material that is closely copied (near verbatim), summarized and/or paraphrased), quotation marks (to indicate words taken from another source) are used for verbatim copying of material, and permissions secured for material that is copyrighted.

Important note: the journal may use software to screen for plagiarism.

- Authors should make sure they have permissions for the use of software, questionnaires/(web) surveys and scales in their studies (if appropriate).
- Research articles and non-research articles (e.g. Opinion, Review, and Commentary articles) must cite appropriate and relevant literature in support of the claims made. Excessive and inappropriate self-citation or coordinated efforts among several authors to collectively self-cite is strongly discouraged.
- Authors should avoid untrue statements about an entity (who can be an individual person or a company) or descriptions of their behavior or actions that could potentially be seen as personal attacks or allegations about that person.
- Research that may be misapplied to pose a threat to public health or national security should be clearly identified in the manuscript (e.g. dual use of research). Examples include creation of harmful consequences of biological agents or toxins, disruption of immunity of

vaccines, unusual hazards in the use of chemicals, weaponization of research/technology (amongst others).

- Authors are strongly advised to ensure the author group, the Corresponding Author, and the order of authors are all correct at submission. Adding and/or deleting authors during the revision stages is generally not permitted, but in some cases may be warranted. Reasons for changes in authorship should be explained in detail. Please note that changes to authorship cannot be made after acceptance of a manuscript.

*All of the above are guidelines and authors need to make sure to respect third parties rights such as copyright and/or moral rights.

Upon request authors should be prepared to send relevant documentation or data in order to verify the validity of the results presented. This could be in the form of raw data, samples, records, etc. Sensitive information in the form of confidential or proprietary data is excluded.

If there is suspicion of misbehavior or alleged fraud the Journal and/or Publisher will carry out an investigation following COPE guidelines. If, after investigation, there are valid concerns, the author(s) concerned will be contacted under their given e-mail address and given an opportunity to address the issue. Depending on the situation, this may result in the Journal's and/or Publisher's implementation of the following measures, including, but not limited to:

- If the manuscript is still under consideration, it may be rejected and returned to the author.
- If the article has already been published online, depending on the nature and severity of the infraction:
  - an erratum/correction may be placed with the article
  - an expression of concern may be placed with the article
  - or in severe cases retraction of the article may occur.

The reason will be given in the published erratum/correction, expression of concern or retraction note. Please note that retraction means that the article is **maintained on the platform**, watermarked "retracted" and the explanation for the retraction is provided in a note linked to the watermarked article.

- The author's institution may be informed
- A notice of suspected transgression of ethical standards in the peer review system may be included as part of the author's and article's bibliographic record.

Fundamental errors

Authors have an obligation to correct mistakes once they discover a significant error or inaccuracy in their published article. The author(s) is/are requested to contact the journal and explain in what sense the error is impacting the article. A decision on how to correct the literature will depend on

the nature of the error. This may be a correction or retraction. The retraction note should provide transparency which parts of the article are impacted by the error.

Suggesting / excluding reviewers

Authors are welcome to suggest suitable reviewers and/or request the exclusion of certain individuals when they submit their manuscripts. When suggesting reviewers, authors should make sure they are totally independent and not connected to the work in any way. It is strongly recommended to suggest a mix of reviewers from different countries and different institutions. When suggesting reviewers, the Corresponding Author must provide an institutional email address for each suggested reviewer, or, if this is not possible to include other means of verifying the identity such as a link to a personal homepage, a link to the publication record or a researcher or author ID in the submission letter. Please note that the Journal may not use the suggestions, but suggestions are appreciated and may help facilitate the peer review process.

Authorship principles

These guidelines describe authorship principles and good authorship practices to which prospective authors should adhere to.

Authorship clarified

The Journal and Publisher assume all authors agreed with the content and that all gave explicit consent to submit and that they obtained consent from the responsible authorities at the institute/organization where the work has been carried out, **before** the work is submitted.

The Publisher does not prescribe the kinds of contributions that warrant authorship. It is recommended that authors adhere to the guidelines for authorship that are applicable in their specific research field. In absence of specific guidelines it is recommended to adhere to the following guidelines*:

All authors whose names appear on the submission

1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work;

2) drafted the work or revised it critically for important intellectual content;

3) approved the version to be published; and

4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

* Based on/adapted from:

ICMJE, Defining the Role of Authors and Contributors,

Transparency in authors' contributions and responsibilities to promote integrity in scientific publication, McNutt at all, PNAS February 27, 2018

Disclosures and declarations

All authors are requested to include information regarding sources of funding, financial or non-financial interests, study-specific approval by the appropriate ethics committee for research involving humans and/or animals, informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals (as appropriate).

The decision whether such information should be included is not only dependent on the scope of the journal, but also the scope of the article. Work submitted for publication may have implications for public health or general welfare and in those cases it is the responsibility of all authors to include the appropriate disclosures and declarations.

Data transparency

All authors are requested to make sure that all data and materials as well as software application or custom code support their published claims and comply with field standards. Please note that journals may have individual policies on (sharing) research data in concordance with disciplinary norms and expectations.

Role of the Corresponding Author

One author is assigned as Corresponding Author and acts on behalf of all co-authors and ensures that questions related to the accuracy or integrity of any part of the work are appropriately addressed.

The Corresponding Author is responsible for the following requirements:

- ensuring that all listed authors have approved the manuscript before submission, including the names and order of authors;
- managing all communication between the Journal and all co-authors, before and after publication;*
- providing transparency on re-use of material and mention any unpublished material (for example manuscripts in press) included in the manuscript in a cover letter to the Editor;
- making sure disclosures, declarations and transparency on data statements from all authors are included in the manuscript as appropriate (see above).

* The requirement of managing all communication between the journal and all co-authors during submission and proofing may be delegated to a Contact or Submitting Author. In this case please make sure the Corresponding Author is clearly indicated in the manuscript.

Author contributions

In absence of specific instructions and in research fields where it is possible to describe discrete efforts, the Publisher recommends authors to include contribution statements in the work that specifies the contribution of every author in order to promote transparency. These contributions should be listed at the separate title page.

Examples of such statement(s) are shown below:

• Free text:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [full name], [full name] and [full name]. The first draft of the manuscript was written by [full name] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Example: CRediT taxonomy:

• Conceptualization: [full name], …; Methodology: [full name], …; Formal analysis and investigation: [full name], …; Writing - original draft preparation: [full name, …]; Writing - review and editing: [full name], …; Funding acquisition: [full name], …; Resources: [full name], …; Supervision: [full name],….

For **review articles** where discrete statements are less applicable a statement should be included who had the idea for the article, who performed the literature search and data analysis, and who drafted and/or critically revised the work.

For articles that are based primarily on the **student's dissertation or thesis**, it is recommended that the student is usually listed as principal author:

A Graduate Student's Guide to Determining Authorship Credit and Authorship Order, APA Science Student Council 2006

Affiliation

The primary affiliation for each author should be the institution where the majority of their work was done. If an author has subsequently moved, the current address may additionally be stated. Addresses will not be updated or changed after publication of the article.

Changes to authorship

Authors are strongly advised to ensure the correct author group, the Corresponding Author, and the order of authors at submission. Changes of authorship by adding or deleting authors, and/or

changes in Corresponding Author, and/or changes in the sequence of authors are **not** accepted **after acceptance** of a manuscript.

- **Please note that author names will be published exactly as they appear on the accepted submission!**

Please make sure that the names of all authors are present and correctly spelled, and that addresses and affiliations are current.

Adding and/or deleting authors at revision stage are generally not permitted, but in some cases it may be warranted. Reasons for these changes in authorship should be explained. Approval of the change during revision is at the discretion of the Editor-in-Chief. Please note that journals may have individual policies on adding and/or deleting authors during revision stage.

Author identification

Authors are recommended to use their ORCID ID when submitting an article for consideration or acquire an ORCID ID via the submission process.

Deceased or incapacitated authors

For cases in which a co-author dies or is incapacitated during the writing, submission, or peer-review process, and the co-authors feel it is appropriate to include the author, co-authors should obtain approval from a (legal) representative which could be a direct relative.

Authorship issues or disputes

In the case of an authorship dispute during peer review or after acceptance and publication, the Journal will not be in a position to investigate or adjudicate. Authors will be asked to resolve the dispute themselves. If they are unable the Journal reserves the right to withdraw a manuscript from the editorial process or in case of a published paper raise the issue with the authors' institution(s) and abide by its guidelines.

Confidentiality

Authors should treat all communication with the Journal as confidential which includes correspondence with direct representatives from the Journal such as Editors-in-Chief and/or Handling Editors and reviewers' reports unless explicit consent has been received to share information.

Compliance with Ethical Standards

To ensure objectivity and transparency in research and to ensure that accepted principles of ethical and professional conduct have been followed, authors should include information regarding

sources of funding, potential conflicts of interest (financial or non-financial), informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals.

Authors should include the following statements (if applicable) in a separate section entitled "Compliance with Ethical Standards" when submitting a paper:

- Disclosure of potential conflicts of interest
- Research involving Human Participants and/or Animals
- Informed consent

Please note that standards could vary slightly per journal dependent on their peer review policies (i.e. single or double blind peer review) as well as per journal subject discipline. Before submitting your article check the instructions following this section carefully.

The corresponding author should be prepared to collect documentation of compliance with ethical standards and send if requested during peer review or after publication.

The Editors reserve the right to reject manuscripts that do not comply with the above-mentioned guidelines. The author will be held responsible for false statements or failure to fulfill the above-mentioned guidelines.

Competing Interests

Authors are requested to disclose interests that are directly or indirectly related to the work submitted for publication. Interests within the last 3 years of beginning the work (conducting the research and preparing the work for submission) should be reported. Interests outside the 3-year time frame must be disclosed if they could reasonably be perceived as influencing the submitted work. Disclosure of interests provides a complete and transparent process and helps readers form their own judgments of potential bias. This is not meant to imply that a financial relationship with an organization that sponsored the research or compensation received for consultancy work is inappropriate.

Editorial Board Members and Editors are required to declare any competing interests and may be excluded from the peer review process if a competing interest exists. In addition, they should exclude themselves from handling manuscripts in cases where there is a competing interest. This may include – but is not limited to – having previously published with one or more of the authors, and sharing the same institution as one or more of the authors. Where an Editor or Editorial Board Member is on the author list they must declare this in the competing interests section on the submitted manuscript. If they are an author or have any other competing interest regarding a

specific manuscript, another Editor or member of the Editorial Board will be assigned to assume responsibility for overseeing peer review. These submissions are subject to the exact same review process as any other manuscript. Editorial Board Members are welcome to submit papers to the journal. These submissions are not given any priority over other manuscripts, and Editorial Board Member status has no bearing on editorial consideration.

Interests that should be considered and disclosed but are not limited to the following:

Funding: Research grants from funding agencies (please give the research funder and the grant number) and/or research support (including salaries, equipment, supplies, reimbursement for attending symposia, and other expenses) by organizations that may gain or lose financially through publication of this manuscript.

Employment: Recent (while engaged in the research project), present or anticipated employment by any organization that may gain or lose financially through publication of this manuscript. This includes multiple affiliations (if applicable).

Financial interests: Stocks or shares in companies (including holdings of spouse and/or children) that may gain or lose financially through publication of this manuscript; consultation fees or other forms of remuneration from organizations that may gain or lose financially; patents or patent applications whose value may be affected by publication of this manuscript.

It is difficult to specify a threshold at which a financial interest becomes significant, any such figure is necessarily arbitrary, so one possible practical guideline is the following: "Any undeclared financial interest that could embarrass the author were it to become publicly known after the work was published."

Non-financial interests: In addition, authors are requested to disclose interests that go beyond financial interests that could impart bias on the work submitted for publication such as professional interests, personal relationships or personal beliefs (amongst others). Examples include, but are not limited to: position on editorial board, advisory board or board of directors or other type of management relationships; writing and/or consulting for educational purposes; expert witness; mentoring relations; and so forth.

Primary research articles require a disclosure statement. Review articles present an expert synthesis of evidence and may be treated as an authoritative work on a subject. Review articles therefore require a disclosure statement. Other article types such as editorials, book reviews, comments (amongst others) may, dependent on their content, require a disclosure statement. If you are unclear whether your article type requires a disclosure statement, please contact the Editor-in-Chief.

Please note that, in addition to the above requirements, funding information (given that funding is a potential competing interest (as mentioned above)) needs to be disclosed upon submission of the manuscript in the peer review system. This information will automatically be added to the Record of CrossMark, however it is **not added** to the manuscript itself. Under 'summary of requirements' (see below) funding information should be included in the '**Declarations**' section.

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Funding' and/or 'Competing interests'. Other declarations include Ethics approval, Consent, Data, Material and/or Code availability and Authors' contribution statements.

Please see the various examples of wording below and revise/customize the sample statements according to your own needs.

When all authors have the same (or no) conflicts and/or funding it is sufficient to use one blanket statement.

Examples of statements to be used when funding has been received:

- Partial financial support was received from [...]
- The research leading to these results received funding from […] under Grant Agreement No[…].
- This study was funded by […]
- This work was supported by […] (Grant numbers […] and […]

Examples of statements to be used when there is no funding:

- The authors did not receive support from any organization for the submitted work.
- No funding was received to assist with the preparation of this manuscript.
- No funding was received for conducting this study.
- No funds, grants, or other support was received.

Examples of statements to be used when there are interests to declare:

- **Financial interests:** Author A has received research support from Company A. Author B has received a speaker honorarium from Company Wand owns stock in Company X. Author C is consultant to company Y.

  Non-financial interests: Author C is an unpaid member of committee Z.
- **Financial interests:** The authors declare they have no financial interests.

  Non-financial interests: Author A is on the board of directors of Y and receives no compensation as member of the board of directors.

- **Financial interests:** Author A received a speaking fee from Y for Z. Author B receives a salary from association X. X where s/he is the Executive Director.
  Non-financial interests: none.
- **Financial interests:** Author A and B declare they have no financial interests. Author C has received speaker and consultant honoraria from Company M and Company N. Dr. C has received speaker honorarium and research funding from Company M and Company O. Author D has received travel support from Company O.
  Non-financial interests: Author D has served on advisory boards for Company M, Company N and Company O.

Examples of statements to be used when authors have nothing to declare:

- The authors have no relevant financial or non-financial interests to disclose.
- The authors have no competing interests to declare that are relevant to the content of this article.
- All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.
- The authors have no financial or proprietary interests in any material discussed in this article.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

Important remark

All authors must complete a copy of the ICMJE Conflict of Interest form; the forms should be uploaded alongside the manuscript when submitting to the journal. The ICMJE Conflict of Interest form can be downloaded directly from the ICMJE website

here.

Research involving human participants, their data or biological material

Ethics approval

When reporting a study that involved human participants, their data or biological material, authors should include a statement that confirms that the study was approved (or granted exemption) by the appropriate institutional and/or national research ethics committee (including the name of the ethics committee) and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical

standards. If doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards, the authors must explain the reasons for their approach, and demonstrate that an independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study. If a study was granted exemption from requiring ethics approval, this should also be detailed in the manuscript (including the reasons for the exemption).

Retrospective ethics approval

If a study has not been granted ethics committee approval prior to commencing, retrospective ethics approval usually cannot be obtained and it may not be possible to consider the manuscript for peer review. The decision on whether to proceed to peer review in such cases is at the Editor's discretion.

Ethics approval for retrospective studies

Although retrospective studies are conducted on already available data or biological material (for which formal consent may not be needed or is difficult to obtain) ethics approval may be required dependent on the law and the national ethical guidelines of a country. Authors should check with their institution to make sure they are complying with the specific requirements of their country.

Ethics approval for case studies

Case reports require ethics approval. Most institutions will have specific policies on this subject. Authors should check with their institution to make sure they are complying with the specific requirements of their institution and seek ethics approval where needed. Authors should be aware to secure informed consent from the individual (or parent or guardian if the participant is a minor or incapable) See also section on **Informed Consent**.

Cell lines

If human cells are used, authors must declare in the manuscript: what cell lines were used by describing the source of the cell line, including when and from where it was obtained, whether the cell line has recently been authenticated and by what method. If cells were bought from a life science company the following need to be given in the manuscript: name of company (that provided the cells), cell type, number of cell line, and batch of cells.

It is recommended that authors check the NCBI database for misidentification and contamination of human cell lines. This step will alert authors to possible problems with the cell line and may save considerable time and effort.

Further information is available from the International Cell Line Authentication Committee (ICLAC).

Authors should include a statement that confirms that an institutional or independent ethics committee (including the name of the ethics committee) approved the study and that informed consent was obtained from the donor or next of kin.

Research Resource Identifiers (RRID)

Research Resource Identifiers (RRID) are persistent unique identifiers (effectively similar to a DOI) for research resources. This journal encourages authors to adopt RRIDs when reporting key biological resources (antibodies, cell lines, model organisms and tools) in their manuscripts.

Examples:

Organism: *Filip1*$^{tm1a(KOMP)Wtsi}$ **RRID:MMRRC_055641-UCD**

Cell Line: RST307 cell line **RRID:CVCL_C321**

Antibody: Luciferase antibody DSHB Cat# LUC-3, **RRID:AB_2722109**

Plasmid: mRuby3 plasmid **RRID:Addgene_104005**

Software: ImageJ Version 1.2.4 **RRID:SCR_003070**

RRIDs are provided by the Resource Identification Portal. Many commonly used research resources already have designated RRIDs. The portal also provides authors links so that they can quickly register a new resource and obtain an RRID.

Clinical Trial Registration

The World Health Organization (WHO) definition of a clinical trial is "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes". The WHO defines health interventions as “A health intervention is an act performed for, with or on behalf of a person or population whose purpose is to assess, improve, maintain, promote or modify health, functioning or health conditions” and a health-related outcome is generally defined as a change in the health of a person or population as a result of an intervention.

To ensure the integrity of the reporting of patient-centered trials, authors must register prospective clinical trials (phase II to IV trials) in suitable publicly available repositories. For example www.clinicaltrials.gov or any of the primary registries that participate in the WHO International Clinical Trials Registry Platform.

The trial registration number (TRN) and date of registration should be included as the last line of the manuscript abstract.

For clinical trials that have not been registered prospectively, authors are encouraged to register retrospectively to ensure the complete publication of all results. The trial registration number

(TRN), date of registration and the words 'retrospectively registered' should be included as the last line of the manuscript abstract.

Standards of reporting

Springer Nature advocates complete and transparent reporting of biomedical and biological research and research with biological applications. Authors are recommended to adhere to the minimum reporting guidelines hosted by the EQUATOR Network when preparing their manuscript.

Exact requirements may vary depending on the journal; please refer to the journal's Instructions for Authors.

Checklists are available for a number of study designs, including:

Randomised trials (CONSORT) and Study protocols (SPIRIT)

Observational studies (STROBE)

Systematic reviews and meta-analyses (PRISMA) and protocols (Prisma-P)

Diagnostic/prognostic studies (STARD) and (TRIPOD)

Case reports (CARE)

Clinical practice guidelines (AGREE) and (RIGHT)

Qualitative research (SRQR) and (COREQ)

Animal pre-clinical studies (ARRIVE)

Quality improvement studies (SQUIRE)

Economic evaluations (CHEERS)

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Ethics approval'.

Examples of statements to be used when ethics approval has been obtained:

• All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical University of A (No. ...).

• This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University B (Date.../No. ...).

• Approval was obtained from the ethics committee of University C. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

• The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the University of D (Ethics approval number: ...).

Examples of statements to be used for a retrospective study:

• Ethical approval was waived by the local Ethics Committee of University A in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

• This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of XYZ who determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted from the IRB of XYZ.

• This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of University B approved this study.

Examples of statements to be used when no ethical approval is required/exemption granted:

• This is an observational study. The XYZ Research Ethics Committee has confirmed that no ethical approval is required.

• The data reproduced from Article X utilized human tissue that was procured via our Biobank AB, which provides de-identified samples. This study was reviewed and deemed exempt by our XYZ Institutional Review Board. The BioBank protocols are in accordance with the ethical standards of our institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

Informed consent

All individuals have individual rights that are not to be infringed. Individual participants in studies have, for example, the right to decide what happens to the (identifiable) personal data gathered, to what they have said during a study or an interview, as well as to any photograph that was taken. This is especially true concerning images of vulnerable people (e.g. minors, patients, refugees, etc) or the use of images in sensitive contexts. In many instances authors will need to secure written consent before including images.

Identifying details (names, dates of birth, identity numbers, biometrical characteristics (such as facial features, fingerprint, writing style, voice pattern, DNA or other distinguishing characteristic)

and other information) of the participants that were studied should not be published in written descriptions, photographs, and genetic profiles unless the information is essential for scholarly purposes and the participant (or parent/guardian if the participant is a minor or incapable or legal representative) gave written informed consent for publication. Complete anonymity is difficult to achieve in some cases. Detailed descriptions of individual participants, whether of their whole bodies or of body sections, may lead to disclosure of their identity. Under certain circumstances consent is not required as long as information is anonymized and the submission does not include images that may identify the person.

Informed consent for publication should be obtained if there is any doubt. For example, masking the eye region in photographs of participants is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic profiles, authors should provide assurance that alterations do not distort meaning.

Exceptions where it is not necessary to obtain consent:

• Images such as x rays, laparoscopic images, ultrasound images, brain scans, pathology slides unless there is a concern about identifying information in which case, authors should ensure that consent is obtained.

• Reuse of images: If images are being reused from prior publications, the Publisher will assume that the prior publication obtained the relevant information regarding consent. Authors should provide the appropriate attribution for republished images.

Consent and already available data and/or biologic material

Regardless of whether material is collected from living or dead patients, they (family or guardian if the deceased has not made a pre-mortem decision) must have given prior written consent. The aspect of confidentiality as well as any wishes from the deceased should be respected.

Data protection, confidentiality and privacy

When biological material is donated for or data is generated as part of a research project authors should ensure, as part of the informed consent procedure, that the participants are made aware what kind of (personal) data will be processed, how it will be used and for what purpose. In case of data acquired via a biobank/biorepository, it is possible they apply a broad consent which allows research participants to consent to a broad range of uses of their data and samples which is regarded by research ethics committees as specific enough to be considered “informed”. However, authors should always check the specific biobank/biorepository policies or any other type of data provider policies (in case of non-bio research) to be sure that this is the case.

Consent to Participate

For all research involving human subjects, freely-given, informed consent to participate in the study must be obtained from participants (or their parent or legal guardian in the case of children under 16) and a statement to this effect should appear in the manuscript. In the case of articles describing human transplantation studies, authors must include a statement declaring that no organs/tissues were obtained from prisoners and must also name the institution(s)/clinic(s)/department(s) via which organs/tissues were obtained. For manuscripts reporting studies involving vulnerable groups where there is the potential for coercion or where consent may not have been fully informed, extra care will be taken by the editor and may be referred to the Springer Nature Research Integrity Group.

Consent to Publish

Individuals may consent to participate in a study, but object to having their data published in a journal article. Authors should make sure to also seek consent from individuals to publish their data prior to submitting their paper to a journal. This is in particular applicable to case studies.

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Consent to participate' and/or 'Consent to publish'. Other declarations include Funding, Competing interests, Ethics approval, Consent, Data and/or Code availability and Authors' contribution statements.

Please see the various examples of wording below and revise/customize the sample statements according to your own needs.

Sample statements for **"Consent to participate"**:

Informed consent was obtained from all individual participants included in the study.

Informed consent was obtained from legal guardians.

Written informed consent was obtained from the parents.

Verbal informed consent was obtained prior to the interview.

Sample statements for **"Consent to publish"**:

The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) 1a, 1b and 1c.

The participant has consented to the submission of the case report to the journal.

Patients signed informed consent regarding publishing their data and photographs.

Sample statements if identifying information about participants is available in the article:

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

Images will be removed from publication if authors have not obtained informed consent or the paper may be removed and replaced with a notice explaining the reason for removal.

Types of Papers

- Research – body text is limited to 3500 words. There may be 45 references and no more than six figures/tables.
- Review – generally solicited by the editors but unsolicited proposals containing an abstract and outline can be sent to the editors for consideration. The word limit for Review Articles is up to 4,000 words for body text (excludes figures, charts, references, abstract). There may be up to 65 references. Methodological guidelines include:
  • CONSORT for randomised clinical trials (e.g. report refusals and drop outs to evaluate bias)
  • STARD for studies of diagnostic accuracy
  • PRISMA or MOOSE for systematic reviews and meta-analysis
  • STROBE for epidemiology
  • COREQ for qualitative research
- Correspondence – SCC occasionally accepts Correspondence (formerly Letters to the Editor) pertaining to articles published within the last 12 months in the Journal. These should not exceed 1000 words body text and will be passed to the authors of the article to which the comment applies to solicit a response. There may be up to 10 references.
- Comment – articles should be on innovative areas or opportunities for further research. The body text is limited to 1,000 words. There may be up to 20 references, and one figure or chart.

Important Note:

Supportive Care in Cancer **does not** normally accept papers reporting on unmet needs, pilot/feasibility studies, or instrument development studies. SCC no longer considers **case studies** for acceptance, nor **study protocol manuscripts**. Authors are encouraged to use the Springer Nature Journal Suggester to find a suitable journal for your manuscript: https://journalsuggester.springer.com

Title Page

Title Page

Please make sure your title page contains the following information.

Title

The title should be concise and informative.

Author information

- The name(s) of the author(s)
- The affiliation(s) of the author(s), i.e. institution, (department), city, (state), country
- A clear indication and an active e-mail address of the corresponding author
- If available, the 16-digit ORCID of the author(s)

If address information is provided with the affiliation(s) it will also be published.

For authors that are (temporarily) unaffiliated we will only capture their city and country of residence, not their e-mail address unless specifically requested.

Abstract

Please provide a structured abstract of 150 to 250 words which should be divided into the following sections:

- Purpose (stating the main purposes and research question)
- Methods
- Results
- Conclusion

For life science journals only (when applicable)

- Trial registration number and date of registration for prospectively registered trials
- Trial registration number and date of registration followed by "retrospectively registered", for retrospectively registered trials

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

Structured Abstract

Authors are asked to state the relevance of their manuscript to inform research, policies and/or programs.

Review procedure

All manuscripts undergo strict peer review. Manuscripts are initially considered by the Editor-in-Chief. Any manuscript that does not meet the general certain criteria of the journal, e.g.

• relevance to the aims of the journal with the topic being of overall general interest

• sufficiently original and contributing to the advancement of the field,

• clearly written with appropriate study methods, well-supported data and conclusions which are supported by the data

will be returned to the author without review.

All other submitted manuscripts are assigned to an Associate Editor who will manage the external peer review process and editorial decision. The Journal encourages authors to recommend individuals who could be considered as reviewers, providing the editorial office with full names and contact details. Authors are also given the opportunity to request the exclusion of a specific reviewer. In this case, authors should provide justification for their request.

Each manuscript is reviewed by a minimum of two expert referees who will provide unbiased, critical and independent assessment of the submission. The (corresponding) author is notified by email of the editorial decision, which will include any applicable criticisms and comments from the reviewers and managing editor. The decision to accept with/without revision or otherwise, will be made by the Editor-in-Chief based on the critical assessments of the experts.

Manuscripts which are returned to the authors for minor or major modifications should be resubmitted online within four weeks; otherwise, they will be considered withdrawn. Normally, revised manuscripts are reassessed by the same reviewers to determine if the authors have satisfactorily addressed their criticisms and comments. Depending upon this evaluation, the manuscript may be accepted or rejected. Any questions or concerns regarding the editorial decision on a manuscript must be submitted directly to the editorial office within 3 months.

Confidentiality

All manuscripts are treated by the assigned reviewers as privileged and confidential information. Reviewers may request advice from another party, subject to the general principles of confidentiality and permission of the managing editor. Reviewers' comments are not published or made available publicly except with the prior written permission of the reviewer, author and editor. However, reviewers' comments are shared with the other reviewers of the same paper, and reviewers will be notified of the editor's decision. The reviewers' identity remains anonymous. All reviewers are asked to disclose any potential conflict that could influence their opinions of manuscripts, prior to review of manuscript.

Manuscript preparation

We urge authors to follow the guidelines for authors to speed up the review and publication process.

All manuscripts are subject to copyediting upon acceptance, however, authors are asked to ensure that manuscripts from non-native English language speakers should have the language and

grammar checked by a native speaker or a professional agency. Poorly written articles cannot be reviewed and will be returned to the authors.

- Authorship Criteria and Contributions

  All listed authors should have seen and approved the final version of the manuscript.

  All authors of accepted articles must sign an authorship form affirming that they have met all three of the following criteria for authorship, thereby accepting public responsibility for appropriate portions of the content:

  1. substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;

  2. drafting the article or revising it critically for important intellectual content;

  3. approval of the version to be published and all subsequent versions.

  If authorship is attributed to a group (such as for multi-center trials), the group must designate one or more individuals as authors or members of a writing group who meet full authorship criteria and who accepts direct responsibility for the manuscript.

  Other group members who are not authors should be listed in the Acknowledgment section of the manuscript as participating investigators.

  Individuals who do not meet the criteria for authorship but who have made substantial, direct contributions to the work (e.g., purely technical help, writing assistance, general or financial or material support) should be acknowledged in the

  Acknowledgments section of the manuscript, with a brief description of their contributions.

  Authors should obtain written permission from anyone they wish to list in the Acknowledgments section.

- Redundant, Duplicate or Fraudulent Publication

  Authors must not simultaneously submit their manuscripts to another publication if that manuscript is under consideration by Supportive Care in Cancer.

  Redundant or duplicate publication is a paper that overlaps substantially with one already published in print or electronic media. At the time of manuscript submission, authors must inform the editor about all submissions and previous publications that might be regarded as redundant or duplicate publication of the same or very similar work. Any such publication must be referred to and referenced in the new paper.

  Copies of such material should be included with the submitted paper as a supplemental file.

  Authors must not:

  • Willfully and knowingly submit false data

• Submit data from source not the authors' own

• Submit previously published material (with the exception of abstracts) without correct and proper citation

• Omit reference to the works of other investigators which established a priority

• Falsely certify that the submitted work is original

• Use material previously published elsewhere without prior written approval of the copyright holder

Manuscript Submission

Manuscript Submission

Submission of a manuscript implies: that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out. The publisher will not be held legally responsible should there be any claims for compensation.

Permissions

Authors wishing to include figures, tables, or text passages that have already been published elsewhere are required to obtain permission from the copyright owner(s) for both the print and online format and to include evidence that such permission has been granted when submitting their papers. Any material received without such evidence will be assumed to originate from the authors.

Online Submission

Please follow the hyperlink "Submit manuscript" and upload all of your manuscript files following the instructions given on the screen.

Source Files

Please ensure you provide all relevant editable source files at every submission and revision. Failing to submit a complete set of editable source files will result in your article not being considered for review. For your manuscript text please always submit in common word processing formats such as .docx or LaTeX.

Conflict of Interest form

Text

Text Formatting

Manuscripts should be submitted in Word.

- Use a normal, plain font (e.g., 10-point Times Roman) for text.
- Use italics for emphasis.
- Use the automatic page numbering function to number the pages.

- Do not use field functions.
- Use tab stops or other commands for indents, not the space bar.
- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Manuscripts with mathematical content can also be submitted in LaTeX. We recommend using Springer Nature's LaTeX template.

Headings

Please use no more than three levels of displayed headings.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

Scientific style

- Please always use internationally accepted signs and symbols for units (SI units).
- Genus and species names should be in italics.
- Generic names of drugs and pesticides are preferred; if trade names are used, the generic name should be given at first mention.

References

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].
2. This result was later contradicted by Becker and Seligman [5].
3. This effect has been widely studied [1-3, 7].

Reference list

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text.

The entries in the list should be numbered consecutively.

If available, please always include DOIs as full DOI links in your reference list (e.g. “https://doi.org/abc”).

- Journal article

  Gamelin FX, Baquet G, Berthoin S, Thevenet D, Nourry C, Nottin S, Bosquet L (2009) Effect of high intensity intermittent training on heart rate variability in prepubescent children. Eur J Appl Physiol 105:731-738. https://doi.org/10.1007/s00421-008-0955-8

  Ideally, the names of all authors should be provided, but the usage of “et al” in long author lists will also be accepted:

  Smith J, Jones M Jr, Houghton L et al (1999) Future of health insurance. N Engl J Med 965:325–329

- Article by DOI

  Slifka MK, Whitton JL (2000) Clinical implications of dysregulated cytokine production. J Mol Med. https://doi.org/10.1007/s001090000086

- Book

  South J, Blass B (2001) The future of modern genomics. Blackwell, London

- Book chapter

  Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) The rise of modern genomics, 3rd edn. Wiley, New York, pp 230-257

- Online document

  Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. http://physicsweb.org/articles/news/11/6/16/1. Accessed 26 June 2007

- Dissertation

  Trent JW (1975) Experimental acute renal failure. Dissertation, University of California

Always use the standard abbreviation of a journal’s name according to the ISSN List of Title Word Abbreviations, see

ISSN.org LTWA

If you are unsure, please use the full journal title.

Authors preparing their manuscript in LaTeX can use the bibliography style file sn-basic.bst which is included in the Springer Nature Article Template.

Statements & Declarations

The following statements must be included in your submitted manuscript under the heading 'Statements and Declarations'. This should be placed after the References section. Please note that submissions that do not include required statements will be returned as incomplete.

Funding

Please describe any sources of funding that have supported the work. The statement should include details of any grants received (please give the name of the funding agency and grant number).

Example statements:

"This work was supported by […] (Grant numbers […] and […]). Author A.B. has received research support from Company A."

"The authors declare that no funds, grants, or other support were received during the preparation of this manuscript."

Competing Interests

Authors are required to disclose financial or non-financial interests that are directly or indirectly related to the work submitted for publication. Interests within the last 3 years of beginning the work (conducting the research and preparing the work for submission) should be reported. Interests outside the 3-year time frame must be disclosed if they could reasonably be perceived as influencing the submitted work.

Example statements:

"Financial interests: Author A and B declare they have no financial interests. Author C has received speaker and consultant honoraria from Company M. Dr. C has received speaker honorarium and research funding from Company M and Company N. Author D has received travel support from Company O. Non-financial interests: Author D has served on advisory boards for Company M and Company N."

"The authors have no relevant financial or non-financial interests to disclose."

Please refer to the "Competing Interests" section below for more information on how to complete these sections.

Author Contributions

Authors are encouraged to include a statement that specifies the contribution of every author to the research and preparation of the manuscript.

Example statement:

"All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [full name], [full name] and [full name]. The first draft of the

manuscript was written by [full name] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript."

Please refer to the "Authorship Principles " section below for more information on how to complete this section.

In addition to the above, manuscripts that report the results of studies involving humans and/or animals should include the following declarations:

Ethics approval

Authors of research involving human or animal subjects should include a statement that confirms that the study was approved (or granted exemption) by the appropriate institutional and/or national research ethics committee (including the name of the ethics committee and reference number, if available). For research involving animals, their data or biological material, authors should supply detailed information on the ethical treatment of their animals in their submission. If a study was granted exemption or did not require ethics approval, this should also be detailed in the manuscript.

"This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University B (Date.../No....)."

"This is an observational study. The XYZ Research Ethics Committee has confirmed that no ethical approval is required."

For detailed information on relevant ethical standards and criteria, please refer to the sections on "Research involving human participants, their data or biological material", "Research involving animals, their data or biological material".

Consent to participate

For all research involving human subjects, freely-given, informed consent to participate in the study must be obtained from participants (or their parent or legal guardian in the case of children under 16) and a statement to this effect should appear in the manuscript.

Example statement:

"Informed consent was obtained from all individual participants included in the study."

"Written informed consent was obtained from the parents."

Please refer to the section on "Informed Consent" for additional help with completing this information.

Consent to publish

Individuals may consent to participate in a study, but object to having their data published in a journal article. If your manuscript contains any individual person's data in any form (including any individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. This is in particular applicable to

case studies. A statement confirming that consent to publish has been received from all participants should appear in the manuscript.

Example statement:

"The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) 1a, 1b and 1c."

Please refer to the section on "Informed Consent" for additional help with completing this information.

Tables

- All tables are to be numbered using Arabic numerals.
- Tables should always be cited in text in consecutive numerical order.
- For each table, please supply a table caption (title) explaining the components of the table.
- Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.
- Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

Supplementary Information (SI)

Springer accepts electronic multimedia files (animations, movies, audio, etc.) and other supplementary files to be published online along with an article or a book chapter. This feature can add dimension to the author's article, as certain information cannot be printed or is more convenient in electronic form.

Before submitting research datasets as Supplementary Information, authors should read the journal's Research data policy. We encourage research data to be archived in data repositories wherever possible.

Submission

- Supply all supplementary material in standard file formats.
- Please include in each file the following information: article title, journal name, author names; affiliation and e-mail address of the corresponding author.
- To accommodate user downloads, please keep in mind that larger-sized files may require very long download times and that some users may experience other problems during downloading.
- High resolution (streamable quality) videos can be submitted up to a maximum of 25GB; low resolution videos should not be larger than 5GB.

Audio, Video, and Animations

- Aspect ratio: 16:9 or 4:3

- Maximum file size: 25 GB for high resolution files; 5 GB for low resolution files
- Minimum video duration: 1 sec
- Supported file formats: avi, wmv, mp4, mov, m2p, mp2, mpg, mpeg, flv, mxf, mts, m4v, 3gp

Text and Presentations

- Submit your material in PDF format; .doc or .ppt files are not suitable for long-term viability.
- A collection of figures may also be combined in a PDF file.

Spreadsheets

- Spreadsheets should be submitted as .csv or .xlsx files (MS Excel).

Specialized Formats

- Specialized format such as .pdb (chemical), .wrl (VRML), .nb (Mathematica notebook), and .tex can also be supplied.

Collecting Multiple Files

- It is possible to collect multiple files in a .zip or .gz file.

Numbering

- If supplying any supplementary material, the text must make specific mention of the material as a citation, similar to that of figures and tables.
- Refer to the supplementary files as “Online Resource”, e.g., "... as shown in the animation (Online Resource 3)", “... additional data are given in Online Resource 4”.
- Name the files consecutively, e.g. “ESM_3.mpg”, “ESM_4.pdf”.

Captions

- For each supplementary material, please supply a concise caption describing the content of the file.

Processing of supplementary files

- Supplementary Information (SI) will be published as received from the author without any conversion, editing, or reformatting.

Accessibility

In order to give people of all abilities and disabilities access to the content of your supplementary files, please make sure that

- The manuscript contains a descriptive caption for each supplementary material
- Video files do not contain anything that flashes more than three times per second (so that users prone to seizures caused by such effects are not put at risk)

Research Data Policy

This journal operates a type 1 research data policy. The journal encourages authors, where possible and applicable, to deposit data that support the findings of their research in a public repository. Authors and editors who do not have a preferred repository should consult Springer Nature's list of repositories and research data policy.

List of Repositories

Research Data Policy

General repositories - for all types of research data - such as figshare and Dryad may also be used. Datasets that are assigned digital object identifiers (DOIs) by a data repository may be cited in the reference list. Data citations should include the minimum information recommended by DataCite: authors, title, publisher (repository name), identifier.

DataCite

If the journal that you're submitting to uses double-blind peer review and you are providing reviewers with access to your data (for example via a repository link, supplementary information or data on request), it is strongly suggested that the authorship in the data is also blinded. There are data repositories that can assist with this and/or will create a link to mask the authorship of your data.

Authors who need help understanding our data sharing policies, help finding a suitable data repository, or help organising and sharing research data can access our Author Support portal for additional guidance.

After acceptance

Upon acceptance, your article will be exported to Production to undergo typesetting. Once typesetting is complete, you will receive a link asking you to confirm your affiliation, choose the publishing model for your article as well as arrange rights and payment of any associated publication cost.

Once you have completed this, your article will be processed and you will receive the proofs.

Offprints

Offprints can be ordered by the corresponding author.

Color illustrations

Publication of color illustrations is free of charge.

Proof reading

The purpose of the proof is to check for typesetting or conversion errors and the completeness and accuracy of the text, tables and figures. Substantial changes in content, e.g., new results, corrected values, title and authorship, are not allowed without the approval of the Editor.

After online publication, further changes can only be made in the form of an Erratum, which will be hyperlinked to the article.

Online First

The article will be published online after receipt of the corrected proofs. This is the official first publication citable with the DOI. After release of the printed version, the paper can also be cited by issue and page numbers.

Back to top

Open Choice

In addition to the normal publication process (whereby an article is submitted to the journal and access to that article is granted to customers who have purchased a subscription), Springer provides an alternative publishing option: Springer Open Choice. A Springer Open Choice article receives all the benefits of a regular subscription-based article, but in addition is made available publicly through Springer's online platform SpringerLink.

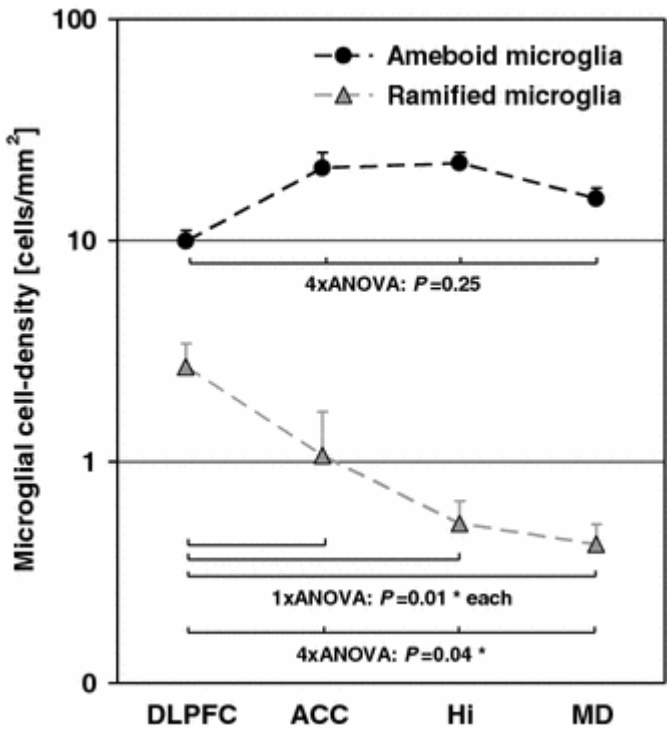
Open Choice

Artwork and Illustrations Guidelines

Electronic Figure Submission

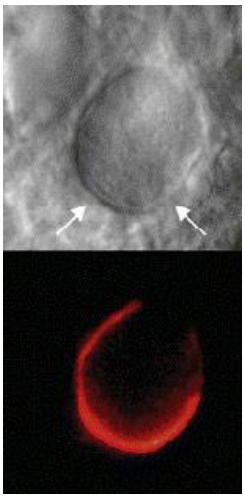
- Supply all figures electronically.
- Indicate what graphics program was used to create the artwork.
- For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MSOffice files are also acceptable.
- Vector graphics containing fonts must have the fonts embedded in the files.
- Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

Line Art



- Definition: Black and white graphic with no shading.
- Do not use faint lines and/or lettering and check that all lines and lettering within the figures are legible at final size.
- All lines should be at least 0.1 mm (0.3 pt) wide.
- Scanned line drawings and line drawings in bitmap format should have a minimum resolution of 1200 dpi.
- Vector graphics containing fonts must have the fonts embedded in the files.

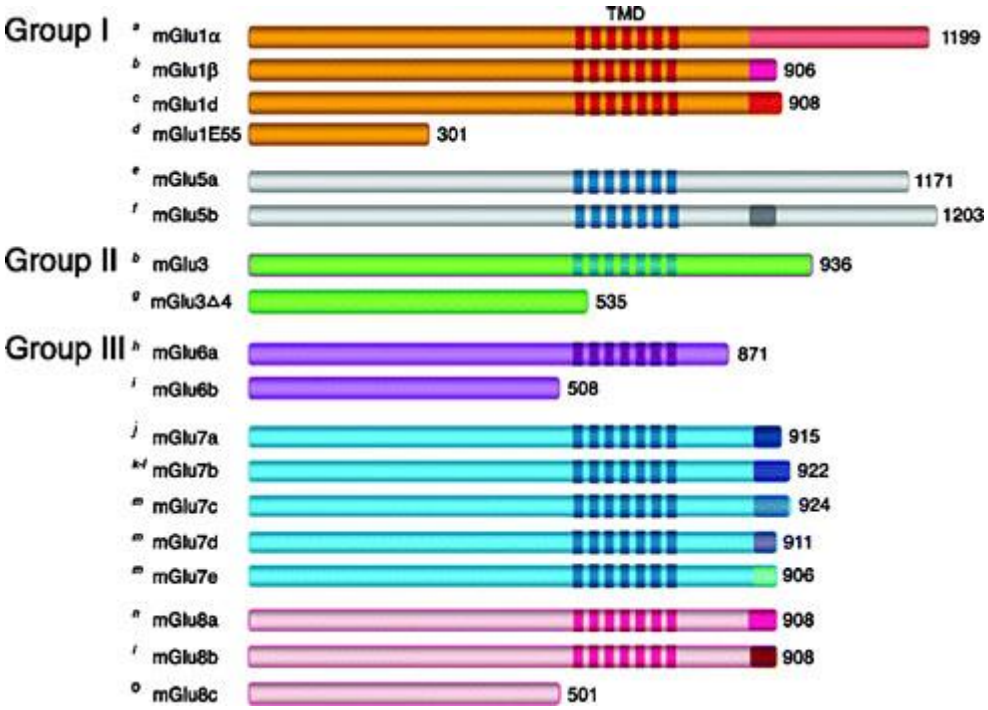
Halftone Art



- Definition: Photographs, drawings, or paintings with fine shading, etc.

- If any magnification is used in the photographs, indicate this by using scale bars within the figures themselves.
- Halftones should have a minimum resolution of 300 dpi.

Combination Art



- Definition: a combination of halftone and line art, e.g., halftones containing line drawing, extensive lettering, color diagrams, etc.
- Combination artwork should have a minimum resolution of 600 dpi.

Color Art

- Color illustrations should be submitted as RGB (8 bits per channel).

Figure Lettering

- To add lettering, it is best to use Helvetica or Arial (sans serif fonts).
- Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt).
- Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.
- Avoid effects such as shading, outline letters, etc.
- Do not include titles or captions within your illustrations.

Figure Numbering

- All figures are to be numbered using Arabic numerals.
- Figures should always be cited in text in consecutive numerical order.
- Figure parts should be denoted by lowercase letters (a, b, c, etc.).

- If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures,"A1, A2, A3, etc." Figures in online appendices [Supplementary Information (SI)] should, however, be numbered separately.

Figure Captions

- Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.
- Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type.
- No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.
- Identify all elements found in the figure in the figure caption; and use boxes, circles, etc., as coordinate points in graphs.
- Identify previously published material by giving the original source in the form of a reference citation at the end of the figure caption.

Figure Placement and Size

- Figures should be submitted within the body of the text. Only if the file size of the manuscript causes problems in uploading it, the large figures should be submitted separately from the text.
- When preparing your figures, size figures to fit in the column width.
- For large-sized journals the figures should be 84 mm (for double-column text areas), or 174 mm (for single-column text areas) wide and not higher than 234 mm.
- For small-sized journals, the figures should be 119 mm wide and not higher than 195 mm.

Permissions

If you include figures that have already been published elsewhere, you must obtain permission from the copyright owner(s). Please be aware that some publishers do not grant electronic rights for free and that Springer will not be able to refund any costs that may have occurred to receive these permissions. In such cases, material from other sources should be used.

Accessibility

In order to give people of all abilities and disabilities access to the content of your figures, please make sure that

- All figures have descriptive captions (blind users could then use a text-to-speech software or a text-to-Braille hardware)

- Patterns are used instead of or in addition to colors for conveying information (colorblind users would then be able to distinguish the visual elements)
- Any figure lettering has a contrast ratio of at least 4.5:1

Copyright transfer

Authors will be asked to transfer copyright of the article to the Publisher (or grant the Publisher exclusive publication and dissemination rights). This will ensure the widest possible protection and dissemination of information under copyright laws.

Open Choice articles do not require transfer of copyright as the copyright remains with the author. In opting for open access, the author(s) agree to publish the article under the Creative Commons Attribution Noncommercial License.

English Language Editing

For editors and reviewers to accurately assess the work presented in your manuscript you need to ensure the English language is of sufficient quality to be understood. If you need help with writing in English you should consider:

- Getting a fast, free online grammar check.
- Asking a colleague who is proficient in English to review your manuscript for clarity.
- Visiting the English language tutorial which covers the common mistakes when writing in English.
- Using a professional language editing service where editors will improve the English to ensure that your meaning is clear and identify problems that require your review. Two such services are provided by our affiliates Nature Research Editing Service and American Journal Experts. Springer authors are entitled to a 10% discount on their first submission to either of these services, simply follow the links below.

Please note that the use of a language editing service is not a requirement for publication in this journal and does not imply or guarantee that the article will be selected for peer review or accepted. If your manuscript is accepted it will be checked by our copyeditors for spelling and formal style before publication.