

SHEILLA DE OLIVEIRA FARIA

**Efeito do atendimento nutricional intensivo em pacientes com câncer
de cabeça e pescoço submetidos à radioterapia**

Tese apresentada à Faculdade de Medicina
da Universidade de São Paulo para obtenção
do título de Doutor em Ciências

Programa de Saúde Coletiva

Orientador: Prof. Dr. José Eluf Neto

SÃO PAULO

2020

SHEILLA DE OLIVEIRA FARIA

**Efeito do atendimento nutricional intensivo em pacientes com câncer
de cabeça e pescoço submetidos à radioterapia**

Tese apresentada à Faculdade de Medicina
da Universidade de São Paulo para obtenção
do título de Doutor em Ciências

Programa de Saúde Coletiva

Orientador: Prof. Dr. José Eluf Neto

SÃO PAULO

2020

Dados Internacionais de Catalogação na Publicação (CIP)

Preparada pela Biblioteca da
Faculdade de Medicina da Universidade de São Paulo

©reprodução autorizada pelo autor

Faria, Sheilla de Oliveira

Efeito do atendimento nutricional intensivo em
pacientes com câncer de cabeça e pescoço submetidos à
radioterapia / Sheilla de Oliveira Faria. -- São
Paulo, 2020.

Tese(doutorado)--Faculdade de Medicina da
Universidade de São Paulo.

Programa de Saúde Coletiva.

Orientador: José Eluf Neto.

Descritores: 1.Neoplasias de cabeça e pescoço
2.Qualidade de vida 3.Estado nutricional 4.Terapia
nutricional 5.Radioterapia 6.Cooperação do paciente

USP/FM/DBD-306/20

Responsável: Erinalva da Conceição Batista, CRB-8 6755

DEDICATÓRIA

À minhas filhas, Sophia e Luiza.

AGRADECIMENTOS

Ao meu querido orientador, professor José Eluf Neto, por ter acreditado na minha capacidade, e pelos ensinamentos e dedicação.

Aos meus pais, pelo amor, apoio e incentivo. Obrigada por serem os melhores pais do mundo e por não medirem esforços para que eu chegasse até aqui.

À minhas filhas, Sophia e Luiza, pela coragem enfrentando um novo idioma e país, por vibrarem comigo a cada conquista e entenderem as ausências nas inúmeras viagens à São Paulo.

Ao meu marido, Tozinho, pelo amor, suporte, incentivo e pela parceria.

A meus irmãos, fonte de inspiração.

À professora Doris Howell pela recepção e carinho durante minha estadia na Universidade de Toronto e valiosa contribuição.

Aos colaboradores dos manuscritos que compõem esta tese.

Às amigas que me ajudaram durante estes anos cuidando das minhas filhas sempre que eu precisava viajar para coletar os dados ou participar de disciplinas na FMUSP: Michely, Flavia, Cristiane, Daniela, Fabiana, Lívia, Marcela, Marília. Obrigada pelo carinho com as pequenas.

Às amigas de Toronto que também cuidaram das pequenas sempre que eu tinha compromisso na Universidade de Toronto fora do horário da escolinha: Lydia, Lisa, Thu, Mina e Tamara.

À equipe de radioterapia e nutrição do ICESP, que facilitaram todo o processo de coleta de dados, em especial Graziela e Renata, que participaram diretamente na preparação dos manuscritos.

Aos pacientes que fizeram parte deste estudo.

Aos alunos, professores e funcionários do Departamento de Medicina Preventiva da FMUSP.

À CAPES que financiou parte dos anos de estudos, inclusive o período sanduiche realizado na Universidade de Toronto, Ontario, Canada.

À Universidade de São Paulo.

EPÍGRAFE

*“A vida não é fácil para nenhum de nós. Temos que ter persistência e, acima de tudo,
confiança em nós mesmos”*

Marie Curie

Esta dissertação ou tese está de acordo com as seguintes normas, em vigor no momento desta publicação:

Referências: adaptado de International Committee of Medical Journals Editors (Vancouver).

Universidade de São Paulo. Faculdade de Medicina. Divisão de Biblioteca e Documentação. Guia de apresentação de dissertações, teses e monografias. Elaborado por Anneliese Carneiro da Cunha, Maria Julia de A. L. Freddi, Maria F. Crestana, Marinalva de Souza Aragão, Suely Campos Cardoso, Valéria Vilhena. 3a ed. São Paulo: Divisão de Biblioteca e Documentação; 2011.

Abreviaturas dos títulos dos periódicos de acordo com List of Journals Indexed in Index Medicus.

SUMÁRIO

LISTA DE TABELAS

LISTA DE FIGURAS

LISTA DE ABREVIATURAS

RESUMO

ABSTRACT

APRESENTAÇÃO

1. INTRODUÇÃO	1
2. REVISÃO DE LITERATURA	2
2.1. O CÂNCER NO BRASIL E NO MUNDO	2
2.1.1 Câncer de cabeça e pescoço.....	3
2.2. CÂNCER E QUALIDADE DE VIDA	5
2.2.1 Avaliação da qualidade de vida em pacientes com câncer.....	8
2.2.2 Diferença mínima importante.....	9
2.3. NUTRIÇÃO E CÂNCER	11
2.3.1 Estado nutricional e câncer	11
2.3.2 Avaliação do estado nutricional em pacientes com câncer	15
2.3.3 Intervenção nutricional em pacientes com câncer.....	17
2.4. EFEITO DO ACONSELHAMENTO NUTRICIONAL INTENSIVO EM PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO.....	19
3. JUSTIFICATIVAS.....	24
4. OBJETIVOS.....	25
4.1. OBJETIVOS ESPECÍFICOS	25
5. EFEITO DA IMPLEMENTAÇÃO DO CUIDADO NUTRICIONAL INTENSIVO NO ESTADO NUTRICIONAL DE PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO SUBMETIDOS A RADIOTERAPIA	26
6. PREVALÊNCIA E O EFEITO DO DA ADESÃO AO PROTOCOLO DE ATENDIMENTO NUTRICIONAL INTENSIVO E OS FATORES RELACIONADOS A ADESÃO	46
7. EVIDÊNCIA SOBRE O ESTUDO DA ADESÃO A INTERVENÇÃO NUTRICIONAL ORAL EM PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO	67
8. EFEITO DA ADESÃO APÓS A IMPLEMENTAÇÃO DE PROTOCOLO DE ATENDIMENTO NUTRICIONAL INTENSIVO NA QUALIDADE DE VIDA E NO ESTADO NUTRICIONAL DE PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO	92

9. CONSIDERAÇÕES FINAIS	119
10. REFERÊNCIAS	124
ANEXOS	

LISTA DE TABELAS

Tabela 1. Taxas relativas de sobrevida de 5 anos* (%) por estágio ao diagnóstico, EUA, 2009-2015.....	5
--	---

ARTIGO 1

Table 1. Participant characteristics before and after the implementation of the weekly contact protocol.....	34
Table 2. Energy and protein intake in patients with head and neck cancer.....	35
Table 3. Weight loss in patients meeting or not meeting the energy and protein recommendations at end of radiotherapy, n=370.....	36
Table 4. Multivariate logistic regression analysis of weight loss in patients with head and neck cancer during radiotherapy.....	37

ARTIGO 2

Table 1. Participants' characteristics of study sample by dietary adherence status.....	55
Table 2. Multivariate logistic regression analysis of weight loss in patients with head and neck cancer during radiotherapy.....	58

ARTIGO 3

Table 1. Summary of eligibility criteria.....	73
Table 2. Detailed summary of included articles.....	77
TS1. Medline search strategy.....	91

ARTIGO 4

Table 1. Participants' characteristics of study sample.....101

Table 2. Mean (SD) quality-of-life dimension's scores for the EORTC QLQ-C30 and the EORTC QLQ H&N35 at baseline (T1) and number (%) of participants that reported improved, stable or worsened HRQL at T2.....103

Table 3. Participants' characteristics of study sample by dietary adherence status.....106

Table 4. Mean (SD) quality-of-life dimension's scores for the EORTC QLQ-C30 and the EORTC QLQ H&N35 by adherence status at baseline (T1).....107

Table 5. Heat map, representing HRQL change over time to MCID ratio, by adherence.....108

LISTA DE FIGURAS

Figura 1. A pirâmide da caquexia do câncer representa a maioria dos fatores envolvidos na síndrome.....12

ARTIGO 1

Figure 1. Percent weight change before and after implementation of protocol.....35

ARTIGO 2

Figure 1. Place of residence of adherent (white) and non-adherent (black) patients.....56

Figure 2. Patients' capacity to accomplish estimated energy requirement (% of patients) by regular foods ($p=0.08$), oral nutritional supplements - ONS ($p=0.04$) and enteral nutrition - EN ($p=0.58$).....57

Figure 3. Kaplan-Meier curves for overall survival for adherent and non-adherent group. Log-rank test ($p=0.97$).....59

ARTIGO 3

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.....75

ARTIGO 4

Figure 1. Mean percentage weight loss by type of nutrition intervention. ONS- oral nutritional supplements; EN – enteral nutrition.....105

LISTA DE ABREVIATURAS

ASG	Avaliação Subjetiva Global
ASG- PPP	Avaliação Subjetiva Global Produzida pelo Próprio Paciente
BMI	Body mass index
CART	Cocaine-Amphetamine Regulated Transcript
CCP	Câncer de cabeça e pescoço
CI	Confidence interval
CRT	Chemoradioterapy
CWL	Critical weight loss
DALYs	Disability adjusted life years
DC	Dietary counselling
DP	Desvio padrão
DEXA	Densitometria por dupla emissão de raios-X
ECOG	Eastern Cooperative Oncology Group
EN	Enteral nutrition
EORTC	European Organization for Research and Treatment of Cancer
ESPEN	European Society for Enteral and Parenteral Nutrition
FACT	Functional Assessment of Cancer Therapy
GER	Gasto energético de repouso
HNC	Head and neck cancer
HPV	Papilomavírus humano
HRQL	Health-related quality of life
IBNO	Inquérito Brasileiro de Nutrição Oncológica
ICD-10	International Classification of Diseases 10th Revision
ICESP	Instituto do Câncer do Estado de São Paulo
IL	Interleucinas
IMC	Índice de massa corporal
INC	Intensive nutrition care
IQ	Intervalo interquartil

KPS	Karnofsky Performance Scale
MCID	Minimal clinically important difference
MeSH	Medical Subject Headings
MHDI	Municipal Human Development Index
NCCN	National Comprehensive Cancer Network
NLM	National Library of Medicine
NRS 2002	Nutritional Risk Screening
OMS	Organização Mundial de Saúde
ONS	Oral nutritional supplementation/ Oral nutritional supplements
OR	Odds ratio
PG-SGA	Patient Generated–Subjective Global Assessment
PIF	Proteolysis-inducing factor
POMC	Proopiomelanocortin
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-	Preferred Reporting Items for Systematic reviews and Meta-Analyses
ScR	extension for Scoping Reviews
QOL	Quality of life/Qualidade de vida
RCT	Randomized clinical trials
RT	Radioterapia/Radiotherapy
RWE	Real world evidence
SD	Standard Deviation
SEER	Surveillance, Epidemiology, and End Results
TNE	Terapia nutricional enteral
TNF-α	Tumour necrosis factor- α
TNM	Tumor, nódulos linfáticos, metástase
TNP	Terapia nutricional parenteral
WLG	Weight loss grade
ZAG	Zinco- α 2-glicoproteína

RESUMO

Faria SO. *Efeito do atendimento nutricional intensivo em pacientes com câncer de cabeça e pescoço submetidos à radioterapia* [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2020.

Guidelines recomendam contatos frequentes com nutricionistas durante o tratamento do câncer de cabeça e pescoço (CCP) para aumentar a ingestão alimentar e evitar a perda de peso. No entanto, poucos estudos examinaram a efetividade da implementação das recomendações nutricionais de *guidelines* e o papel da adesão à prescrição nutricional. Quatro manuscritos compõem essa tese. Em janeiro de 2013, o Instituto do Câncer do Estado de São Paulo implementou protocolo de cuidados nutricionais intensivos durante a radioterapia de CCP. Os objetivos desta pesquisa foram verificar o efeito da implantação do protocolo de atendimento nutricional intensivo no estado nutricional e na qualidade de vida (QOL) de pacientes com CCP submetidos à radioterapia, a importância da adesão ao protocolo, bem como investigar fatores associados à adesão. A pesquisa dividiu-se em uma parte retrospectiva, com análise de dados dos prontuários, e uma parte prospectiva. Foram incluídos pacientes com CCP submetidos à radioterapia. Os desfechos foram o estado nutricional (perda de peso e avaliação subjetiva global), ingestão alimentar, QOL e sobrevida. Pacientes que perderam mais de 25% das consultas com o nutricionista durante a radioterapia foram considerados não aderentes. Uma análise dos dados, em estudo retrospectivo com 472 pacientes, comparando os desfechos antes e após a implementação do protocolo de cuidado nutricional intensivo (primeiro manuscrito), encontrou maior perda de peso antes (-6,7%; intervalo interquartil (IQ) -10,5 / -1,9) do que após a implementação do protocolo (-5,0%; IQ -9,8 / -0,7), embora não estatisticamente significativa ($p = 0,06$). Também não houve diferença significativa em termos de atingir a ingestão nutricional recomendada. Em uma segunda análise, limitada aos 317 pacientes após a implementação do protocolo (segundo manuscrito), encontrou-se que menos da metade dos pacientes (45,7%) eram aderentes. Verificou-se menor perda de peso significativa no grupo de aderentes (42,8% vs 55,8%, $p = 0,02$), apesar de não haver diferença na ingestão nutricional. A sobrevida global não foi diferente entre os grupos. Em modelo de regressão logística, a adesão ao protocolo resultou em 43% (*odds ratio* 0,57, intervalo de 95% de confiança 0,34 - 0,97) de proteção para perda de peso

significativa. No terceiro manuscrito, foi realizada uma *scoping review* com intuito de mapear as evidências sobre a adesão à intervenção nutricional oral em pacientes com CCP. A revisão mostrou não haver uma base de evidências robustas sobre este tema. No quarto manuscrito, com dados prospectivos de 80 pacientes após implementação de protocolo de cuidados nutricionais intensivos, a maioria dos pacientes relatou QOL estável ou melhor em todos os domínios, exceto para fadiga, dor e sentidos durante a radioterapia. Apenas pacientes não aderentes tiveram uma piora clínica significativa na função física, cognitiva e social, e apresentaram aumento significativo da prevalência de desnutrição. Em conclusão, a implementação do protocolo cuidados nutricionais intensivos parece ter efeito positivo no estado nutricional e na qualidade de vida de pacientes com CCP submetidos à radioterapia, mas não na sobrevida e na ingestão alimentar. A adesão à intervenção nutricional parece ser importante para melhores desfechos e deveria receber atenção da equipe multiprofissional.

Descritores: Neoplasias de cabeça e pescoço; Qualidade de vida; Estado nutricional; Terapia nutricional; Radioterapia; Cooperação do paciente.

ABSTRACT

Faria SO. *Effect of intensive nutritional care in patients with head and neck cancer undergoing radiotherapy* [thesis]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2020.

Guidelines recommend frequent contacts with dietitians during the treatment of head and neck cancer (HNC) to increase food intake and prevent weight loss. However, few studies have examined the effectiveness of implementing nutritional guidelines recommendations and the role of adherence to nutritional prescription. Four manuscripts composed this thesis. In January 2013, the *Instituto do Câncer do Estado de São Paulo* implemented a protocol of intensive nutritional care during HNC radiotherapy. The objectives of this research were to verify the effect of the implementation of the protocol of intensive nutritional care on the nutritional status and quality of life (QOL) of patients with HNC undergoing radiotherapy, the importance of adhering to the protocol, as well as investigating factors associated with adherence. The research was divided into a retrospective part, with analysis of data from medical records, and a prospective part. Patients with HNC submitted to radiotherapy were included. The outcomes were nutritional status (weight loss and subjective global assessment), food intake, QOL and survival. Patients who missed more than 25% of appointments with the dietitian during radiotherapy were considered non-adherent. An analysis of the data, in a retrospective study with 472 patients, comparing the outcomes before and after the implementation of the intensive nutritional care protocol (first manuscript), showed greater weight loss before (-6.7%; interquartile range (IQR) -10.5 / -1.9) than after the implementation of the protocol (-5.0%; IQR -9.8 / -0.7), although not statistically significant ($p = 0.06$). There was also no significant difference in terms of capacity to accomplish nutritional intake recommendations. In a second analysis, limited to 317 patients after the implementation of the protocol (second manuscript), it was found that less than half of the patients (45.7%) were adherent. There was less significant weight loss in the group of adherents (42.8% vs 55.8%, $p = 0.02$), although there was no difference in nutritional intake. Overall survival was not different between groups. In a logistic regression model, adherence to the protocol resulted in 43% (odds ratio 0.57, 95% confidence interval 0.34 - 0.97) of protection for significant weight loss. In the third manuscript, a scoping review was

carried out to map the evidence on adherence to oral nutritional intervention in patients with HNC. The review showed that there is no robust evidence base on this topic. In the fourth manuscript, with prospective data from 80 patients after implementing the protocol of intensive nutritional care, most patients reported stable or better QOL in all domains, except for fatigue, pain and senses during radiotherapy. Only non-adherent patients had a significant clinical worsening in physical, cognitive and social function, and showed a significant increase in the prevalence of malnutrition. In conclusion, the implementation of the protocol of intensive nutritional care seems to have a positive effect on the nutritional status and quality of life of patients with HNC undergoing radiotherapy, but not on survival and food intake. Adherence to nutritional intervention seems to be important for better outcomes and should receive attention from the multidisciplinary team.

Descriptors: Head and neck neoplasms; Quality of life; Nutritional status; Nutrition therapy; Radiotherapy; Patient compliance.

APRESENTAÇÃO

Esta tese é composta por uma breve **Introdução**, que situa o tema da pesquisa, e uma **Revisão de Literatura**, na qual são apresentados os aspectos epidemiológicos do câncer de cabeça e pescoço, sua relação com a qualidade de vida e estado nutricional do paciente oncológico, e efeitos da intervenção nutricional nesta população.

Também são partes integrantes da tese a **Justificativa**, os **Objetivos** e **Resultados**, além das **Considerações Finais**.

Os Resultados estão organizados sob a forma de artigos, a saber:

Artigo 1: *Nutritional outcomes after radiotherapy of head and neck cancer: is intensive nutritional care during treatment worth it?*

Artigo 2: *Adherence to intensive nutrition care in head and neck cancer patients undergoing radiotherapy*

Artigo 3: *Adherence to nutritional interventions in head and neck cancer patients: a systematic scoping review of the literature*

Artigo 4: *Clinically significant changes in health-related quality of life in head and neck cancer patients following intensive nutritional care during radiotherapy*

Os artigos foram produzidos no idioma e formatação exigidos pelos periódicos científicos nos quais foram aceitos ou submetidos. Esta tese atende as recomendações do Guia de Apresentações de Teses da Faculdade de Medicina da Universidade de São Paulo. Na parte final são apresentados os **Anexos**.

1. INTRODUÇÃO

Pacientes com câncer de cabeça e pescoço (CCP) geralmente enfrentam vários desafios nutricionais antes, durante e após o tratamento devido à proximidade do câncer a órgãos vitais para a função normal da alimentação.^{1,2} Desta forma, prevenir o declínio no estado nutricional é essencial nesta população.

O suporte nutricional adequado durante a radioterapia pode diminuir o impacto dos efeitos colaterais do tratamento, minimizar a perda de peso e até melhorar a qualidade de vida.³ Na prática clínica atual, o aconselhamento nutricional com ou sem suplementos nutricionais orais em pacientes recebendo radioterapia para câncer de cabeça e pescoço é considerado adequado. *Guidelines* recomendam contatos frequentes com nutricionistas durante o tratamento do CCP para aumentar a ingestão alimentar e evitar a perda de peso.⁴⁻⁶

No entanto, embora seja importante incorporar recomendações de diretrizes na prática clínica, poucos estudos que examinaram a efetividade da implementação das recomendações nutricionais de *guidelines* foram realizados em pacientes com CCP. Muito pouco se sabe sobre o efeito do atendimento nutricional intensivo sobre a qualidade de vida nestes pacientes. Além disso, apesar da adesão à prescrição nutricional ser crucial para o sucesso da intervenção alimentar, a adesão é raramente abordada em estudos com pacientes com câncer de cabeça e pescoço.

Em janeiro de 2013, um hospital público oncológico do Brasil, o Instituto do Câncer do Estado de São Paulo (ICESP), implementou um novo protocolo nutricional para todos os pacientes com CCP, com cuidados nutricionais intensivos (aconselhamento nutricional individualizado semanal) durante a radioterapia.

Assim, o objetivo desta pesquisa foi verificar o efeito da implantação do protocolo de atendimento nutricional semanal no estado nutricional e na qualidade de vida de pacientes com câncer de cabeça e pescoço submetidos à radioterapia, bem como investigar fatores relacionados à adesão ao protocolo de atendimento nutricional semanal.

2. REVISÃO DE LITERATURA

2.1. O CÂNCER NO BRASIL E NO MUNDO

A carga de câncer global tem crescido de forma expressiva. De acordo com dados da Organização Mundial de Saúde (OMS) uma em cada seis mortes no mundo é atribuída ao câncer. Cerca de 18,1 milhões casos de câncer ocorreram em 2018 e 9,6 milhões de mortes foram registradas no mundo e estima-se que este cenário irá piorar consideravelmente em 2040.⁷ Além disso, o câncer impõe o maior ônus mundial em anos de vida ajustados por incapacidade (244,6 milhões de DALYs – Disability Adjusted Life Years), tanto em homens (137,4 milhões de DALYs) quanto em mulheres (107,2 milhões de DALYs). Assim, levando em conta o impacto das doenças malignas na carga de doença, nos padrões sociais e nos recursos econômicos, o câncer pode ser considerado o mais importante problema de saúde pública mundial.⁸

No entanto, diferenças notáveis em relação à incidência, tipos de câncer, mortalidade relacionadas ao câncer e estimativa de novos casos são observadas em diferentes partes do globo.⁷ Em países de baixa renda e, particularmente, nos países de média renda, a carga de câncer tem se tornado alarmante. Estima-se que 80% dos mais de 20 milhões de casos novos de câncer previstos para 2025 ocorram nos países em desenvolvimento.⁹ Este cenário é particularmente preocupante uma vez que, justamente nesses países, há uma profunda falta de modelos de prestação de cuidados de saúde disponíveis, acessíveis e sustentáveis.^{10, 11} Atualmente, devido ao acesso limitado à detecção precoce e tratamento curativo, a mortalidade ajustada por idade por câncer em países em desenvolvimento é maior, apesar da incidência dos tumores malignos ser relativamente menor do que países desenvolvidos.¹² A falta de investimento tanto em prevenção primária (redução da exposição a fatores de risco) quanto em prevenção secundária (detecção e intervenção precoce) é considerada um agravante.¹³

A adoção de comportamentos de estilo de vida que são conhecidos por aumentar o risco de câncer, como o tabagismo, má alimentação e sedentarismo levaram a um aumento da carga de câncer em países economicamente menos desenvolvidos, impulsionado pelo envelhecimento da população e reduções substanciais na mortalidade

por outras causas.^{10, 14} No Brasil, estudo recente constatou que aproximadamente um terço de todos os casos (26,5%, n=114.497 casos) e de todas as mortes de câncer (33,6%, n=63.371 mortes) poderiam ser potencialmente evitados com a eliminação de fatores de risco relacionados ao estilo de vida.¹⁵

No nosso país, a estimativa de câncer para o triênio 2020-2022 aponta a ocorrência de cerca de 450 mil casos novos de câncer por ano, excetuando-se o câncer de pele não melanoma. As taxas de incidência ajustadas por idade no Brasil, à exceção do câncer de pele não melanoma, são consideradas compatíveis com as apresentadas para países em desenvolvimento. Os tipos mais frequentes em homens serão próstata (29,2%), cólon e reto (9,1%), traqueia, brônquio e pulmão (7,9%), estômago (5,9%) e cavidade oral (5,0%), e nas mulheres, os cânceres de mama (29,7%), cólon e reto (9,2%), colo do útero (7,4%), traqueia, brônquio e pulmão (5,6%) e glândula tireoide (5,4%).¹⁶ Por ser um país de dimensões continentais, a distribuição e o padrão da incidência do câncer diferem por região geográfica no Brasil. Apesar da Região Sudeste concentrar mais de 60% da incidência, seguida pelas Regiões Nordeste (27,8%) e Sul (23,4%), a mortalidade ajustada por idade tem crescido nas regiões Norte e Nordeste enquanto tem predominantemente estabilizado ou decrescido nas demais regiões, refletindo as diferenças socioeconômicas e de acesso ao cuidado.^{16, 17}

2.1.1 Câncer de cabeça e pescoço

Entre os tipos de câncer mais frequentes no mundo, os cânceres de cabeça e pescoço afetam uma variedade de localizações anatômicas, incluindo cavidade oral, orofaringe, nasofaringe, hipofaringe, laringe, seios paranasais e glândulas salivares. A grande maioria dos CCP é composta por carcinomas espinocelulares.¹⁸ Em 2018, de acordo com dados do GLOBOCAN, estima-se que cerca de 834.000 casos novos de CCP foram diagnosticados e 431.000 mortes foram registradas no mundo.⁷ No Brasil, segundo uma estimativa do Instituto Nacional do Câncer, para o triênio 2020-2022, são previstos anualmente 17.650 novos casos de câncer de cavidade oral, lábio, orofaringe e laringe em homens e 5.190 em mulheres.¹⁶

A etiologia dos cânceres de cabeça e pescoço é multifatorial, sendo os fatores de risco principais o tabaco e o consumo excessivo de álcool. Quando fumo e ingestão alcoólica estão juntos, é observada a existência de um sinergismo aumentando o risco de

CCP.^{18, 19} Além do tabaco e do álcool, outros fatores associados aos CCP como infecção pelo papilomavírus humano - HPV, alimentação (pobre em frutas e vegetais), e má higiene bucal vêm sendo investigados.^{20, 21} Estudos demonstraram que os fumantes consomem menos frutas e vegetais do que os não fumantes, por sua vez, a baixa ingestão de carotenóides e outros componentes protetores de frutas e vegetais está associada ao aumento do risco de CCP.²²

A incidência é maior em homens do que em mulheres, ocorre na razão de 2:1 a 4:1, e está relacionada a diferentes exposições aos fatores de risco.¹⁶ Sabe-se, por exemplo, que a prevalência do hábito de fumar e consumo de bebida alcoólicas sempre foi maior entre homens.^{7,19}. Além disso, em homens jovens, há evidência na literatura de aumento importante dos CCP associados ao HPV.²³

O padrão de tratamento de CCP é baseado principalmente em considerações anatômicas e estágio TNM (tumor, nódulos linfáticos, metástase). A escolha depende do local do tumor e da extensão do mesmo, da taxa de cura prevista e do resultado funcional e estético.²⁴ A radioterapia (RT) exclusiva ou combinada com cirurgia é considerada o principal tratamento para câncer de cabeça e pescoço. Para muitos sítios primários de CCP, a RT produz melhores resultados funcionais e, portanto, é muitas vezes preferida quando a doença é localizada, ou seja, não apresenta comprometimento de estruturas adjacentes e nem metástase a distância. Para lesões loco-progressivamente avançadas, a RT é frequentemente usada em combinação com quimioterapia para preservação de função orgânica, ou após a cirurgia como adjuvante. Normalmente, a dose total de radioterapia é de 68-70 Gy, que são aplicados de forma fracionada (1.8-2.0 Gy diários), por cinco dias da semana.^{25, 26} O tratamento exige a participação de uma equipe multidisciplinar, com equipe médica (oncologista clínico, cirurgião, radioterapeuta), enfermeiro, nutricionista, fonoaudiólogo, entre outros.

O diagnóstico em estágios iniciais e o tratamento apropriado imediato é particularmente importante como prioridade de saúde pública.²⁷ A maioria dos casos no Brasil ainda são diagnosticados em estágios avançados e, portanto, implicam em tratamentos mais agressivos. Estudo transversal realizado a partir de dados secundários de base hospitalar, encontrou que 69,4% dos cânceres de cavidade oral foram diagnosticados em estágio III/IV, enquanto que para cânceres de orofaringe a ocorrência de estágios avançados (III/IV) chega a quase 90% dos casos.²⁸

A sobrevida do paciente com câncer de cabeça e pescoço varia de acordo com a localização do câncer, estágio, HPV *status* e tabagismo. Pacientes com câncer de cabeça e pescoço associados a HPV tem maior sobrevida, independentemente do estágio.^{29, 30}

Quanto à localização, de acordo com dados do SEER-*Surveillance, Epidemiology, and End Results*, nos EUA estima-se uma taxa relativa de sobrevida de 5 anos de 65% considerando todos os estágios câncer de cavidade oral e faringe e de 60% para câncer de laringe (Tabela 1).³¹ No Brasil, em estudo com dados de um registro hospitalar de câncer, no período entre 2001 e 2012, as taxas de sobrevida geral em 5 anos ficaram estáveis (52% para câncer de cavidade oral e 45% para câncer de orofaringe). O estágio da doença ao diagnóstico também influenciou a taxa de sobrevida. Pacientes em estágios iniciais da doença (I/II) apresentaram a taxa de sobrevida de 74% em pacientes com câncer de cavidade oral e 75.2% em pacientes com câncer de orofaringe, enquanto que em pacientes em estágios avançados (III/IV) foi de 36.2% e 42%, respectivamente.³²

Tabela 1. Taxas relativas de sobrevida de 5 anos* (%) por estágio ao diagnóstico, EUA, 2009-2015

	Todos os estágios	Localizado	Regional	Distante
Cavidade oral e faringe	65	84	66	39
Laringe	60	77	45	33

* Taxas são ajustadas para expectativa de vida normal e são baseadas em casos diagnosticados em 18 áreas do SEER de 2009-2015, seguidos até 2016. Localizado: um câncer maligno invasivo confinado inteiramente ao órgão de origem. Regional: um câncer maligno que 1) se estendeu além dos limites do órgão de origem para os órgãos ou tecidos circundantes; 2) envolve linfonodos regionais; ou 3) tem extensão regional e envolvimento de linfonodos regionais. Distante: um câncer maligno que se espalhou para partes do corpo distantes do tumor primário por extensão direta ou por metástase descontínua para órgãos distantes, tecidos, ou através do sistema linfático para linfonodos distantes. Fonte: Howlader 2018

31

2.2. CÂNCER E QUALIDADE DE VIDA

Apesar dos avanços na pesquisa do câncer e disponibilidade de tratamento eficazes para aumentar a sobrevida do paciente oncológico, o tratamento contra o câncer

ainda está associado a vários efeitos colaterais e sintomas indesejáveis, afetando negativamente a qualidade de vida do paciente. Apesar do grande impacto do câncer na qualidade de vida do indivíduo, geralmente oncologistas e pacientes discutem sobre o tema com ênfase apenas no tratamento e nos sintomas, com pouca atenção direcionada aos aspectos psicológicos, sociais e espirituais do indivíduo.^{33, 34}

No entanto, ser diagnosticado com uma doença com risco de vida, como o câncer, pode ser uma experiência profundamente perturbadora que pode suscitar preocupações nesses outros aspectos. Além das manifestações clínicas inerentes ao tumor que afetam a função física e funcional da pessoa com câncer, o diagnóstico e a incerteza da cura podem trazer grande impacto emocional, social e existencial, com depressão, tristeza e preocupação.³⁵ Mesmo com melhora gradual na qualidade de vida após o fim do tratamento, é possível dizer que, anos após o fim do tratamento do câncer, pacientes ainda precisam lidar com mudanças e desafios fundamentais em relação ao seu bem-estar físico, mental e psicossocial. Desta forma, frente à magnitude do câncer, alguns autores consideram a avaliação da qualidade de vida como um dos principais desfechos em pacientes oncológicos.^{36, 37}

Assim, nos últimos anos, houve um aumento expressivo de número de estudos na literatura nacional e internacional sobre qualidade de vida e câncer, principalmente pela necessidade de medir resultados dos tratamentos oncológicos para além da morbidade e funcionamento biológico. Todavia, embora as avaliações de rotina da qualidade de vida sejam recomendadas em diretrizes, raramente a avaliação da qualidade de vida é incorporada na prática clínica.³⁸

Há muitas definições para o termo “qualidade de vida” (QOL, em inglês). Por trata-se de um conceito abstrato, subjetivo e multidimensional que envolve a auto percepção do paciente na sociedade, o consenso na definição do termo qualidade de vida se torna um desafio. De toda forma, dois aspectos de grande relevância para o constructo de qualidade de vida devem ser considerados: a subjetividade e a multidimensionalidade.³⁹ A subjetividade refere-se à percepção do indivíduo sobre seu estado de saúde e, portanto, é composta pelo mundo interno, próprio e inerente de cada ser. Já o aspecto da multidimensionalidade da qualidade de vida inclui dimensões de ordem física, psicológica, social e espiritual, que interagem entre si. Alterações em uma ou mais dimensões podem ter importantes repercussões.⁴⁰ Características intrínsecas de

cada paciente, como crenças pessoais, expectativas e experiências pessoais podem influenciar a sua QOL.

Um dos conceitos mais utilizados na literatura, o do WHOQOL Group (1995)⁴⁰, define QOL como "a percepção do indivíduo de sua posição na vida, no contexto da cultura e sistemas de valores nos quais vive e em relação aos seus objetivos, expectativas, padrões e preocupações". Embora esta e muitas definições de QOL tenham como foco julgamentos subjetivos, alguns autores argumentam que fatores objetivos deveriam ser incluídos na QOL.⁴¹ Por exemplo, QOL foi definido por Felce 1995⁴², como "um bem-estar geral que inclui descritores objetivos e avaliações subjetivas do bem-estar físico, material, social e emocional além da extensão do desenvolvimento pessoal e com propósito, ponderados por um conjunto pessoal de valores". Assim, dois pacientes com problemas de saúde idênticos podem ter uma QOL muito diferente, dependendo de suas experiências subjetivas, expectativas e percepções sobre saúde.

Considerando todos estes aspectos da qualidade de vida, talvez em nenhum outro grupo de pacientes com câncer a qualidade de vida seja tão importante quanto para pacientes com câncer de cabeça e pescoço. No paciente com CCP, as manifestações clínicas do tumor podem levar a efeitos negativos na qualidade de vida do paciente. As disfunções significativas na fala, deglutição/mastigação, alteração da aparência estética, comprometimento sensorial, dor crônica, redução do apetite entre outros podem, secundariamente, afetar um amplo espectro de papéis e responsabilidades sociais, familiares e profissionais nestes pacientes.^{43, 44} Além disso, o tipo de tratamento empregado pode ter implicações na QOL. Pacientes que recebem tratamentos multimodais, apresentam mais problemas em domínios da qualidade de vida, principalmente relacionados a deglutição e xerostomia.^{45, 46} Apesar dos recentes avanços nas técnicas de radioterapia, principal modalidade de tratamento de pacientes com CCP, com redução dos efeitos colaterais associados a irradiação de áreas sensíveis, complicações ainda se fazem presentes e podem perdurar por longo período.^{47, 48}

Assim, a avaliação da qualidade de vida no paciente com CPP é crucial uma vez que está ligada a vários aspectos importantes relacionados à decisão e avaliação dos resultados do tratamento e da reabilitação física e funcional, além do dimensionamento do apoio social e emocional a estes pacientes. A avaliação da QOL deveria ser incorporada na prática clínica do médico e da equipe multidisciplinar. Ainda, pode desempenhar papel importante como medida de resultado em ensaios clínicos.⁴⁹

2.2.1 Avaliação da qualidade de vida em pacientes com câncer

Percebe-se nos últimos anos um aumento crescente de estudos com avaliação da qualidade de vida. Este fenômeno pode ser explicado por muitos fatores, entre eles o envelhecimento da população, que resultou no aumento da prevalência de doenças crônicas, o maior envolvimento dos pacientes no processo de decisão de tratamento, com interesse em aspectos não-clínicos como a qualidade de vida. Além disso, como em algumas doenças crônicas a cura não pode ser alcançada, a qualidade de vida destaca-se como importante desfecho a ser avaliado, como no caso do câncer.

Para a avaliação da qualidade de vida, questionários específicos são utilizados. Há diferentes métodos disponíveis na literatura e nenhum deles pode ser considerado como padrão-ouro. Como a qualidade de vida mede a percepção do indivíduo de sua posição na vida, medir essas variações requer uma avaliação de saúde complexa, que inclui domínios físico, funcional, fisiológico, social e espiritual. Assim, alguns instrumentos se concentram em um sintoma específico ou aspecto funcional do paciente, enquanto outros usam ferramentas de avaliação global de qualidade de vida.⁴³

A escolha do tipo de questionário deve levar em consideração os fundamentos conceituais de cada instrumento além da finalidade do estudo (prática clínica ou em pesquisa, população geral ou específica). Existem diversos instrumentos para a avaliação da qualidade de vida validados em diferentes línguas e culturas, sendo caracterizados geralmente em genéricos ou específicos. Entre os genéricos, o mais comum é o *36-Item Short Form Health Survey questionnaire - SF 36*.⁵⁰

Para pacientes oncológicos, os questionários do *European Organization for Research and Treatment of Cancer - EORTC* e do *Functional Assessment of Cancer Therapy – FACT* são alguns dos instrumentos mais utilizados com alta aceitabilidade e com validação em diversas línguas e culturas. Cada um deles tem o questionário geral para a avaliação da qualidade de vida de pacientes oncológicos, além de seus módulos específicos, contemplando as diferentes localizações do tumor.^{39, 51}

No Brasil, os três instrumentos mais utilizados em todo o mundo para avaliação da QOL em pacientes com câncer de cabeça e pescoço (*European Organization for Research and Treatment of Cancer (EORTC QLQ C30/H&N35, Functional Assessment*

of Cancer Therapy – FACT-H&N; University of Washington- Quality of Life Questionnaire) foram adaptados e revalidados psicometricamente em nosso meio. Os questionários são multidimensionais e variam quanto ao número de questões globais (referentes aos domínios físico, sócio familiar, funcional e emocional) e questões específicas ao CCP, relacionadas a mastigação, deglutição, paladar, aparência entre outras.^{49,52}

O EORTC QLQ- H&N35 desenvolvido pela *European Organization for Research and Treatment of Cancer*, é específico para pacientes com câncer de cabeça e pescoço e deve ser aplicado conjuntamente com o EORTC QLQ-C30. O EORTC QLQ-C30, que foi validado no Brasil por Ferreira (2008)⁵³, avalia vários fatores gerais que contribuem para a QOL, incluindo capacidade física, papel, status cognitivo, fatores emocionais e sociais, bem como sintomas (por exemplo, fadiga, dor, dispneia e insônia). Foi desenvolvido para ser utilizado em pacientes com câncer em pesquisas ou na prática clínica. Já o EORTC QLQ- H&N35 consiste em 35 perguntas sobre sintomas e efeitos colaterais do tratamento do CCP.⁵¹ Dezoito perguntas tratam de sintomas como dor, deglutição, sabor e aparência. As próximas 12 perguntas medem funções como comer, conversar, contato social e sexualidade e por fim, cinco itens são perguntas binárias sobre analgesia, alimentação suplementar e peso. O EORTC QLQ- H&N 35 também foi submetido à tradução e adaptação transcultural para o português.⁵² Escores mais altos nas escalas de saúde funcional e global indicam melhor qualidade de vida, enquanto escores mais altos nas escalas de sintomas representam mais sintomatologia.

2.2.2 Diferença mínima importante

A utilização dos instrumentos descritos acima destina-se a avaliar a qualidade de vida na perspectiva dos pacientes. Embora muitos profissionais de saúde concordem que tais medidas agreguem valor aos dados de qualidade de vida do paciente, ainda é difícil definir qual a magnitude de alteração nesses dados é clinicamente importante.⁵⁴

A grande maioria dos estudos na literatura usam a diferença estatisticamente significativa nos escores das escalas para avaliar as mudanças na QOL do paciente oncológico depois de uma intervenção. No entanto, uma diferença estatisticamente significativa pode não ser sinônimo de significado clínico para o paciente ou para o profissional de saúde. Ao mesmo tempo, a ausência de uma mudança estatisticamente

significante não significa uma ausência de mudança clinicamente significativa.⁵⁵ Da mesma forma, apenas o relato da diferença nos escores de QOL entre os momentos de avaliação raramente fornece ao profissional de saúde informações que podem ser úteis. 49,49, 54, 56

Assim, a diferença mínima clinicamente importante (*minimal clinically important difference –MCID*, em inglês) refere-se à menor diferença que reflete uma mudança clinicamente importante em uma pontuação de determinada escala.⁵⁷ A MCID é conceituada como "a menor diferença de pontuação no domínio de interesse que os pacientes consideram benéfico e que exigiria, na ausência de efeitos colaterais incômodos e custo excessivo, uma mudança no gerenciamento do paciente".⁵⁸

Levando em consideração que a diferença mínima pode estar relacionada a uma redução significativa dos sintomas ou melhora da função do ponto de vista do paciente ou a uma indicação de mudança no tipo tratamento ou no prognóstico da doença para o médico, devemos entender que nem sempre estas perspectivas estarão em concordância.⁵⁷

Desta forma, diferentes métodos de cálculo desta medida podem ser utilizados e dependendo do objetivo de determinada intervenção, diferentes abordagens podem ser utilizadas.

A MCID pode ser estimada estatisticamente ou por comparação com padrões aceitos (âncoras) e, ambos métodos, têm vantagens e limitações.

No método baseado em âncoras, no qual podem ser utilizados cortes transversais ou longitudinais, a mudança na qualidade de vida é comparada com outra medida ou fenômeno que tem importância clínica, chamada âncora.^{57,58} Entre as abordagens longitudinais baseadas em âncoras mais utilizadas para estabelecer mudanças clinicamente significativas estão o uso de classificações globais de mudança e abordagens que incluem uso de fator prognóstico em saúde, como mortalidade ou uso de serviços de saúde/custos.

Já o método baseado em distribuições para calcular a MICD utiliza características estatísticas da amostra estudada. Entre os métodos mais utilizados neste tipo de abordagem está o tamanho de efeito. O tamanho de efeito representa uma medida padronizada de mudança ao longo do tempo e é calculado dividindo-se a diferença entre as pontuações pré e pós-teste pelo desvio padrão (DP) no pré-teste.⁵⁷ Os valores de tamanho de efeito de 0,20, 0,50 e 0,80 foram propostos para representar pequenas, moderadas e grandes mudanças, respectivamente.⁵⁹ Yost et al.⁶⁰ propõe que o valor de

MCID seja calculado como 0,33, uma vez que consideram esse tamanho de efeito uma aproximação adequada da diferença mínima clinicamente importante por estar entre um tamanho de efeito pequeno e moderado.

Apesar do fato de que a MCID possa ser diferente entre grupos de pacientes de acordo com a doença, gravidade, status socioeconômico e nacionalidade, o uso de uma estimativa constante tem a vantagem de fornecer um ponto de referência fácil e clinicamente compreensível, além de permitir comparações entre os estudos.⁵⁴

Para alguns instrumentos já existem pontos de corte bem estabelecidos para a diferença mínima clinicamente importante na literatura. Para o EORTC QLQ-C30, a MCID é definida como uma alteração de 10 pontos na escala de 100 pontos.^{61, 62} Para o EORTC QLQ-HN, parece ainda não haver um consenso de qual é o melhor ponto de corte para a MCID.

2.3. NUTRIÇÃO E CÂNCER

2.3.1 Estado nutricional e câncer

As estatísticas de desnutrição de base populacional na maioria dos países não são disponíveis como as estatísticas de incidência e mortalidade de câncer e, portanto, não temos uma visão global deste problema no paciente oncológico.⁶³

A desnutrição é uma condição clínica causada pelo desequilíbrio de energia, proteína e outros nutrientes que provoca efeitos adversos mensuráveis sobre os tecidos, composição corporal, função e desfecho clínico.⁶⁴ Se não for devidamente tratada desde o início, a desnutrição avança à caquexia.⁶⁵

A caquexia do câncer, uma síndrome metabólica complexa associada à doença subjacente, é caracterizada por uma perda de massa magra, com ou sem perda de massa gorda, que pode ser parcialmente revertida pelo suporte nutricional convencional. De acordo Fearon et al, 2011⁶⁶, a caquexia do câncer pode ser dividida em três estágios distintos: (1) pré-caquexia, (2) caquexia e (3) caquexia refratária.

Em pacientes oncológicos, a caquexia é resultado de múltiplas causas, tanto fisiológicas, como psicológicas e sociais. A fisiopatologia da caquexia inclui uma série de mecanismos metabólicos complexos diretamente ligados à interação do tumor com o hospedeiro, associada ou não a fatores digestivos funcionais estruturais.

Anorexia, inflamação, resistência à insulina e aumento da quebra de proteínas musculares estão frequentemente associados à caquexia.^{63, 67, 68} Nesse contexto, as anormalidades no metabolismo de proteínas, carboidratos e lipídios são as principais bases para o hipercatabolismo observado. A figura 1 apresenta os fatores envolvidos na síndrome.

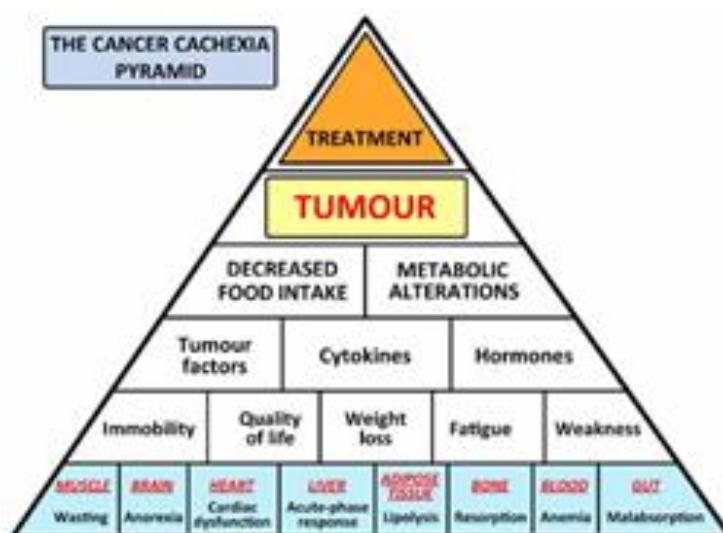


Figura 1. A pirâmide da caquexia do câncer representa a maioria dos fatores envolvidos na síndrome. Fonte: Argiles et al 2017 ⁶⁹.

As células tumorais, bem como a inflamação aumentada provocada pelo tumor, resultam na superexpressão e secreção de moléculas que podem diretamente induzir o catabolismo do músculo e do tecido adiposo.⁷⁰ Vários fatores pró-inflamatórios expressam ações catabólicas diretamente no músculo por meio de seus receptores específicos, incluindo prostaglandina E2, interleucinas (IL) IL-6 e IL-1, fator de necrose tumoral (*tumour necrosis factor- α* /*TNF- α* , em inglês) e interferon γ .^{63, 70, 71} O fator indutor de proteólise (*proteolysis-inducing factor- PIF*, em inglês) também é produzido pelas células tumorais e, como o próprio nome indica, promove a quebra de proteínas e induz a caquexia.⁷¹ Além disso, o controle da lipogênese e lipólise também é

profundamente alterado. A atividade de lipase sensível ao hormônio é duas vezes maior no tecido adiposo branco de pacientes com câncer.⁷² Além disso, vários produtos tumorais são fatores potentes de indução de lipólise, incluindo IL-6, TNF- α , zinco- α 2-glicoproteína (ZAG), adrenomedulina e proteína relacionada ao hormônio da paratireoide.^{63, 72, 73}

Além do catabolismo dos músculos e do tecido adiposo, as citocinas também induzem anorexia (falta de apetite) por ação específica no sistema nervoso central.⁷⁴ Particularmente, as citocinas podem induzir a expressão hipotalâmica do neurotransmissor anorexigênico serotonina e estimular a via anorexigênica POMC (*Proopiomelanocortin*, em inglês)/ CART (*Cocaine-Amphetamine Regulated Transcript*, em inglês), levando a uma redução da ingestão de energia e, conseqüentemente, ao balanço energético negativo.^{75, 76}

Além do efeito do próprio tumor, a desnutrição no paciente oncológico ainda pode estar relacionada à ingestão insuficiente de alimentos devido à localização do tumor e aos efeitos colaterais dos tratamentos contra o câncer (quimioterapia, radioterapia ou cirurgia).^{67, 75} Desta forma, a prevalência de desnutrição em pacientes oncológicos depende do tipo e do estágio do tumor, dos órgãos acometidos e da terapia anticâncer. É menos prevalente em pacientes com câncer de próstata e mama, e mais prevalente em pacientes com câncer do trato gastrointestinal (esôfago, estômago, pâncreas) e em tumores de cabeça e pescoço.^{63, 77, 78}

No câncer de cabeça e pescoço, estudos indicam que, no momento do diagnóstico, até 60% destes pacientes podem estar desnutridos.⁷⁹⁻⁸¹ No Inquérito Brasileiro de Nutrição Oncológica (IBNO), em que foram avaliados pacientes oncológicos, internados em 45 instituições brasileiras, a maioria dos pacientes com câncer de cabeça e pescoço, adultos ou idosos, apresentavam desnutrição moderada ou grave.⁸²

A localização do câncer, que pode gerar dificuldades na deglutição ou problemas de mastigação, e os efeitos metabólicos do próprio tumor (caquexia) somados à história de consumo abusivo de álcool ou tabagismo, entre outros fatores, levam os pacientes com CCP a terem risco aumentado de desnutrição antes mesmo do tratamento iniciar^{83, 84}. O álcool, além de ser um substituto energético, é desprovido de vitaminas e gorduras essenciais, e, além disso, esgota ainda mais os estoques de nutrientes por exigir que certos micronutrientes sejam utilizados durante sua metabolização.⁸⁵

Ao longo do tratamento oncológico, a desnutrição aumenta consideravelmente nos pacientes com CCP.^{81, 86-88} As sequelas nutricionais resultantes da radioterapia, por exemplo, ocorrem por efeitos diretos da radiação nos tecidos neoplásicos e normais e estão relacionadas ao local do tumor e às regiões irradiadas. Entre as toxicidades da RT em pacientes com câncer de cabeça e pescoço, que afetam a ingestão oral, estão mudança no sabor, secreções pegajosas, mucosite, xerostomia, odinofagia, trismo, disfagia entre outros.^{87, 89, 90} Além disso, os níveis baixos de pH da saliva são associados a uma maior incidência de cárie dentária. A alteração nas glândulas salivares e dentes, juntamente com a infecção, facilitam o desenvolvimento da radionecrose dos tecidos orais e resultam em menor ingestão oral e sequelas nutricionais.⁹¹

Mesmo após o término do tratamento, as sequelas da toxicidade podem continuar por semanas, ou até meses, aumentando a perda de peso nos pacientes com CCP.⁹² Disfagia tardia grave, por exemplo, ocorreu em 19,2% dos 99 pacientes tratados para câncer de laringe e hipofaringe com um período médio de acompanhamento de 72 meses.⁹³

Entre as consequências da desnutrição nos pacientes oncológicos estão o aumento da morbidade, maiores taxas de complicação pós-cirúrgica, baixa imunidade, e até mesmo a redução da tolerância ao próprio tratamento; além de aumento dos custos hospitalares.^{67, 94} Uma recente revisão sistemática da literatura encontrou que a desnutrição aumenta os custos dos cuidados de saúde por aumentar o tempo de internação hospitalar e UTI, pela maior incidência de complicações infecciosas e não infecciosas, por aumentar o número de readmissões e / ou necessidade de encaminhamento para cuidados continuados em centros de alta complexidade.⁹⁵ A caquexia também pode estar associada a maior depressão e ansiedade em pacientes com câncer.⁹⁶ A existência de depressão, ansiedade e outros distúrbios psicológicos podem induzir perda de apetite, o que poderia explicar a correlação indireta entre depressão, ansiedade e caquexia.⁹⁷

Outra consequência negativa da desnutrição é a redução da qualidade de vida.^{63, 98-101} Em estudo randomizado com 271 pacientes, Ravasco et al¹⁰² encontraram que apesar do estágio do câncer ter aparecido como principal determinante da qualidade de vida dos pacientes, em alguns diagnósticos o impacto da deterioração nutricional combinada com deficiências na ingestão nutricional foram mais importantes do que a fase do processo da doença. Em revisão sistemática para verificar a relação entre estado nutricional e qualidade de vida em pacientes com câncer, observou-se que o estado nutricional foi um

forte preditor de qualidade de vida.¹⁰³ Citak et al 2019², em estudo prospectivo com pacientes com CCP em radioterapia, encontraram que a qualidade de vida global foi pior nos pacientes desnutridos. Todavia, as evidências existentes sugerem que ainda não há uma associação consistente entre intervenção nutricional e melhoria da qualidade de vida de pessoas com câncer.¹⁰⁴ Uma revisão sistemática recente da literatura encontrou que intervenções nutricionais com prescrição adequada de energia e proteína parecem promover melhoria na qualidade de vida de pacientes oncológicos. Entretanto, a heterogeneidade observada no desenho dos estudos, das terapias nutricionais, medidas de qualidade de vida e tipos de câncer, impedem consenso sobre intervenções nutricionais definitivas para melhorar a qualidade de vida de pacientes com câncer.¹⁰⁵

Além do impacto negativo na qualidade de vida do paciente oncológico, acredita-se que a caquexia seja indiretamente responsável pela morte de pelo menos 20% de todos pacientes com câncer.⁷⁰ Alguns estudos sugerem que a perda de peso antes e durante a RT podem ser prognósticos de sobrevida em 5 anos em pacientes com CCP, demonstrando a importância de se prevenir esse efeito.^{70, 106, 107} Kubrak e colaboradores⁸⁰ encontraram em análise de uma coorte de 1756 pacientes com CCP, que mesmo controlando para idade, sexo, estágio e local do câncer e função física, as categorias de perda de peso ao diagnóstico (*weight loss grade –WLG*, em inglês) foram capazes de prever independentemente a sobrevida global ($p < 0,001$). No mesmo sentido, estudo que avaliou os valores prognósticos da composição corporal em pacientes com CCP avançado, encontrou que pacientes com sarcopenia tiveram um risco três vezes maior de recorrência do câncer ou morte¹⁰⁸. Orell e colaboradores¹⁰⁹ encontraram que pacientes com câncer de cabeça e pescoço considerados desnutridos ou caquéticos antes do início do tratamento tiveram pior sobrevida geral ou sobrevida livre da doença.

Um diagnóstico tardio de desnutrição em paciente com CCP pode resultar em atraso nutricional intervenção e, portanto, desfechos indesejados. Desta forma, a avaliação e a intervenção nutricional podem ser fatores chaves no cuidado efetivo ao paciente com câncer de cabeça e pescoço.^{107, 110-112}

2.3.2 Avaliação do estado nutricional em pacientes com câncer

Considerando que a desnutrição é problema importante antes, durante e após o tratamento, a avaliação adequada do estado nutricional é imprescindível. Embora vários

biomarcadores sanguíneos para pacientes com caquexia do câncer tenham sido sugeridos, como derivados de tumores, citocinas inflamatórias, proteínas de fase aguda e marcadores de degradação muscular esquelética, eles estão longe de serem universais e aplicáveis a todos os pacientes e, portanto, não são utilizados rotineiramente.^{63, 71, 73, 113} Desta forma, existem diferentes outras ferramentas na avaliação nutricional do paciente oncológico que são úteis e sugeridas como válidas por diferentes *guidelines*.

O rastreamento do risco nutricional, que deve ser realizado o mais cedo possível, permite a identificação de pacientes com risco de desnutrição. Para tal, a ferramenta *Nutritional Risk Screening* (NRS 2002) é considerada uma das mais recomendadas ferramentas de triagem do risco nutricional em âmbito hospitalar.¹¹⁴ É um método objetivo que se baseia em dados de ingestão alimentar, índice de massa corporal (IMC) e perda de peso, além de incluir idade do paciente e abranger várias condições patológicas. Pacientes com escore maior ou igual a três são considerados em risco nutricional.¹¹⁵

Quando o risco nutricional está presente, a triagem deve ser seguida de uma avaliação nutricional abrangente, para determinar a melhor intervenção nutricional.⁴ As recomendações atuais consagram a utilização da Avaliação Subjetiva Global Produzida pelo Próprio Paciente (ASG- PPP), considerada padrão-ouro para avaliação nutricional do paciente oncológico, por ser uma ferramenta de elevada sensibilidade e especificidade.^{3, 116} Maiores escores da ASG-PPP estão relacionados a pior estado nutricional, e o paciente é classificado categoricamente em “A” bem nutrido, “B” com suspeita ou desnutrição moderada, ou “C” severamente desnutrido. É composta por uma parte inicial, preenchida pelo próprio paciente e a parte subsequente, preenchida pelo profissional nutricionista. A ASG-PPP permite a identificação de sintomas de impacto nutricional, como falta de apetite, náusea, constipação, dores na boca, disgeusia (paladar alterado), dificuldade de engolir, vômito, diarreia, xerostomia (boca seca), empachamento, dor entre outros.¹¹⁷

Considerando que pacientes com câncer apresentam sintomas de impacto nutricional que afetam negativamente a ingestão alimentar, a avaliação da ingestão deve ser abordada precocemente. A ingestão deve ser avaliada pelo menos qualitativamente e, se possível, quantitativamente, usando registros alimentares, recordatórios de 24 horas ou questionários de frequência alimentar.^{4, 118}

Para detectar distúrbios nutricionais precocemente, além da avaliação regular da ingestão nutricional, *guidelines* também recomendam a avaliação de mudanças de peso e

IMC, começando desde o diagnóstico de câncer e repetindo as avaliações de acordo com situação clínica.^{4,6,118}

A mudança de peso é considerada um dos parâmetros mais úteis utilizados para descrever o estado nutricional na prática clínica, assim como o IMC, principalmente quando outras avaliações mais precisas de composição corporal não são possíveis.^{3,119}

Geralmente os pontos de corte para classificação do IMC (kg/m^2) adotados são os propostos pela Organização Mundial de Saúde (OMS)¹²⁰ que considera o paciente como—desnutrido ($\text{IMC} < 18,5 \text{ kg}/\text{m}^2$), eutrófico ($18,5 \leq \text{IMC} < 25,0 \text{ kg}/\text{m}^2$), sobrepeso ($25,0 \leq \text{IMC} < 30,0 \text{ kg}/\text{m}^2$), obeso ($\text{IMC} \geq 30,0 \text{ kg}/\text{m}^2$). A perda de peso crítica, definida como perda de peso não intencional de 5% é um indicador-chave usado no diagnóstico de desnutrição em pacientes com câncer.^{121,122} Vale destacar que medidas como IMC e perda de peso possuem baixa sensibilidade para detectar alterações na composição corporal, principalmente em pacientes obesos, devendo nestas situações serem utilizados apenas em combinação com outras ferramentas de avaliação.³ No entanto, medidas de avaliação de composição corporal consideradas altamente precisas (padrão-ouro), os exames de DEXA (densitometria por dupla emissão de raios-X) e tomografia computadorizada, geralmente não estão amplamente disponíveis para utilização na prática clínica.^{3,109}

2.3.3 Intervenção nutricional em pacientes com câncer

A fim de evitar a perda de peso e prevenir a desnutrição, a intervenção nutricional é considerada parte importante do tratamento do câncer. Embora a caquexia não possa ser completamente revertida com a intervenção nutricional convencional, a redução dos déficits de nitrogênio pode preservar as proteínas estruturais vitais.¹²³

Assim, intervenção nutricional em pacientes com câncer identifica, previne e trata a desnutrição.^{3,4,6} Para tal, a assistência nutricional deve ser individualizada, compreendendo a avaliação nutricional, o cálculo das necessidades nutricionais, a decisão da via de acesso da terapia nutricional, a alta e o seguimento ambulatorial.¹¹⁸

A escolha da via de acesso da nutrição deve ser determinada conforme o estado clínico e nutricional do paciente. Na prática clínica, o uso da via oral de alimentação, deve ser sempre prioridade, por ser a via mais fisiológica e de fácil acesso. Quando a ingestão oral não atinge as necessidades nutricionais, os suplementos nutricionais estão indicados.

Quando o paciente não consegue manter uma ingestão oral suficiente, mesmo com uso de suplementos nutricionais, mas apresenta funcionalidade do trato-gastrointestinal parcial ou total, a terapia nutricional enteral (TNE) pode ser indicada. Já a terapia nutricional parenteral (TNP) deve ser indicada quando o trato-gastrointestinal não está apto a receber nutrientes de forma total ou parcial. A TNP também pode ser indicada como complemento da TNE. Em todo caso, a terapia nutricional deve ser incorporada ao tratamento integral do paciente o mais cedo possível e, para tal, o nutricionista deve fazer parte da equipe multidisciplinar.^{67, 118}

A aceitação e à tolerância da terapia nutricional escolhida são aspectos importantes da intervenção nutricional do paciente oncológico. Tanto a terapia nutricional oral (suplementos) quanto a terapia nutricional enteral podem desencadear sintomas de impacto nutricional (como náuseas, vômitos, distensão abdominal, cólicas, flatulência, plenitude, diarreia e constipação intestinal). Assim, o monitoramento desses aspectos deve ser realizado com frequência pelo nutricionista.¹¹⁸

Em se tratando de pacientes com câncer de cabeça e pescoço, parece não existir uma maneira simples e única de alimentar estes pacientes e, portanto, uma abordagem individualizada é recomendada.^{107,124} O diagnóstico em estágios avançados e, conseqüentemente, a demanda por tratamentos mais complexos e agressivos faz com que um dos principais objetivos da intervenção nutricional do paciente com CCP seja minimizar as toxicidades do tratamento e evitar interrupções no mesmo.¹²⁵

Para tal, planos de nutrição personalizados, ou seja, o aconselhamento nutricional individualizado, devem ser desenvolvidos para pacientes com CCP durante o tratamento para auxiliar no controle dos sintomas e garantir que as recomendações de energia e proteína sejam atendidas e, assim, minimizar o catabolismo corporal. *Guidelines* recomendam ingestão calórica de 25 a 35 kcal/kg/dia e 1,0 a 1,5g proteína/kg/dia em pacientes recebendo radioterapia ou radio-quimioterapia.^{4, 6, 118} No entanto, vale ressaltar que não há nível de evidência robusto com relação às recomendações energéticas e proteicas, pois apenas alguns estudos com pequeno número de pacientes avaliaram esta questão em pacientes com câncer. Há pouca evidência de que o gasto energético de repouso (GER) possa estar elevado em alguns pacientes com câncer, no entanto, também já foi relatado que o GER pode estar inalterado ou reduzido em relação aos controles não portadores de câncer.⁴ Quanto à recomendação de proteínas, a ESPEN (*European Society for Enteral and Parenteral Nutrition*) recomenda que esta pode chegar até 2g

proteína/kg/dia, no entanto, deve-se ter atenção às funções renal e hepática e, portanto, o paciente deve ser acompanhado com mais cautela pelo nutricionista.

É imperativo que os pacientes com CCP sejam avaliados em tempo hábil e encaminhados para gerenciamento nutricional. Alguns *guidelines* ainda recomendam que o aconselhamento nutricional seja realizado com contatos semanais com nutricionistas, ou seja, os pacientes devem receber cuidado nutricional intensivo (*intensive nutrition care- INC*, em inglês) durante a radioterapia de câncer de cabeça e pescoço para evitar a deterioração nutricional durante o tratamento.^{5,6} O aconselhamento nutricional é considerado eficiente pois é um processo contínuo e repetitivo que oferece aos pacientes um entendimento de tópicos relacionados a nutrição de maneira a proporcionar mudanças efetivas dos hábitos alimentares. O profissional leva em consideração vários aspectos individuais do paciente como estilo de vida, ingestão atual, gasto energético, preferências alimentares, autonomia ou necessidade de ajuda para se alimentar e sintomas.^{3,4} O aconselhamento nutricional pode influenciar positivamente a qualidade de vida a partir de seu impacto sobre o estado nutricional, já que a redução da ingestão de alimentos e a perda de peso afetam negativamente a qualidade de vida.^{3, 4,102, 126-129}

2.4. EFEITO DO ACONSELHAMENTO NUTRICIONAL INTENSIVO EM PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO

Na literatura existe evidência de ensaios clínicos randomizados que investigaram os efeitos do aconselhamento nutricional intensivo durante a radioterapia no estado nutricional e na qualidade de vida das pessoas com câncer de cabeça e pescoço. A maioria destes estudos encontraram menor deterioração do peso, do estado nutricional e/ou da qualidade de vida e melhor ingestão alimentar nos pacientes do grupo intervenção quando comparados com aqueles que receberam prática padrão.^{127, 128, 130-133}

Isenring et al.¹²⁷ em ensaio controlado randomizado, com 60 pacientes oncológicos ambulatoriais, submetidos à radioterapia para área gastrointestinal ou cabeça e pescoço, investigaram o impacto da intervenção nutricional intensiva versus intervenção padrão (conselhos gerais pela enfermagem e livreto com informações nutricionais), sobre o estado nutricional (Avaliação Subjetiva Global - ASG) e qualidade de vida (EORTC-QLQC30). Os pacientes que receberam intervenção nutricional

intensiva experimentaram menor deterioração do peso (média de perda: -0,4kg vs -4,7 kg; $p<0,001$), do estado nutricional (média escore da ASG: 8,4 vs 4,8; $p=0,020$), e da qualidade de vida global (média escore EORTC-QLQC30: 72,7 vs 62,5; $p=0,009$), quando comparados com aqueles que receberam prática padrão. Em ambos os grupos, suplementos orais foram ofertados quando necessário.

Como parte do mesmo estudo, Isenring et al.¹²⁸ relataram os dados de ingestão alimentar desses 60 pacientes oncológicos ambulatoriais e procuraram determinar o impacto da intervenção nutricional intensiva (grupo intervenção) em comparação com a prática padrão (grupo controle) na ingestão dietética. Os pacientes no grupo intervenção apresentaram maior ingestão de energia média total (2190 ± 427 kcal vs 1953 ± 562 kcal; $p=0,029$) e maior ingestão de proteínas ($82,4\pm 17,2$ g vs $80,0\pm 25,3$ g; $p<0,001$) em comparação com o grupo controle.

De maneira semelhante, também em ensaio clínico controlado em pacientes com câncer de cavidade oral, orofaringe ou hipofaringe submetidos à radioterapia, van den Berg et al.¹³⁰ procuraram avaliar se o aconselhamento dietético individualizado intensivo seria melhor em manter o peso corporal do paciente em comparação com cuidados nutricionais padrão. Duas semanas após o tratamento, o número de pacientes com perda de peso $\geq 5\%$ no grupo intervenção era menor do que no grupo controle (0/20 vs 5/18, $p<0,02$).

Outro estudo realizado por Kang et al.¹³¹ também procurou avaliar o efeito da intervenção nutricional intensiva *versus* intervenção nutricional regular em pacientes com câncer de cabeça e pescoço. Ao final da radioterapia, pacientes do grupo intervenção quando comparados ao grupo controle apresentaram maior ingestão alimentar (1.691 ± 301 kcal vs 1.066 ± 312 kcal, $p<0.05$) e menor prevalência de desnutrição severa (20% dos pacientes vs 50%, $p<0.05$).

No mesmo sentido, Roussel et al.¹³² investigaram se a intervenção nutricional intensiva (seis consultas individualizadas com nutricionista, sendo duas durante a radioterapia e quatro depois da RT) seria mais efetiva em melhorar a qualidade de vida (EORTC QLQ-C30 e EORTC H&N35), peso e ingestão de energia e proteína do que intervenção nutricional padrão (duas consultas durante a radioterapia). Em ambos os grupos, os pacientes foram tratados com os mesmos protocolos de atendimento. No entanto, não encontraram diferença significativa dos desfechos entre os grupos, a não ser pela piora dos itens “sono” do EORTC QLQ-C30 ($\Delta m = 4$ vs 7 , $p=0.04$) e “fala” do

EORTC H&N35 ($\Delta m = 4$ vs 6 , $p=0.02$) no grupo controle em comparação com o intervenção. Também não encontraram diferença significativa na mudança no peso corpóreo ($-3.6\pm 4.8\text{kg}$ vs -4.4 ± 7.1 kg, $p=0.95$) entre grupo intervenção e grupo controle. Além disso, não houve nenhuma diferença na ingestão de energia ou proteína entre os grupos 1 mês após o término da RT ($p = 0.41$ e $p = 0.50$, respectivamente) ou 3 meses ($p = 0.07$ e $p = 0.79$, respectivamente).

Da mesma maneira, em estudo randomizado controlado, Orell e colaboradores¹³³ não encontraram diferença na perda de peso e outros parâmetros nutricionais entre pacientes que receberam o aconselhamento nutricional intensivo e aqueles que receberam aconselhamento nutricional por demanda.

Esses ensaios clínicos randomizados apresentaram algumas limitações, como pequeno tamanho da amostra, diferentes localizações tumorais (câncer gastrointestinal e de cabeça e pescoço) entre outros. Ainda, apesar do grande valor dos ensaios clínicos randomizados, eles são realizados em populações seletivas e podem não representar a realidade da maioria dos serviços de saúde.

Assim, incorporar recomendações de diretrizes baseadas em evidências na prática de rotina de serviços de saúde pode ser útil. Evidências do mundo real (*RWE, real world evidence*, em inglês) são valiosas, uma vez que contribuem para o estudo da efetividade de intervenções, tornando-as aplicáveis a populações heterogêneas. No entanto, existem poucas evidências do mundo real que examinaram a efetividade do cuidado nutricional intensivo em pacientes com CCP durante a radioterapia.¹³⁴⁻¹³⁶ Grande parte desses estudos reportaram que o contato mais frequente com o nutricionista não evitou a perda de peso na população CCP.

Vlooswijk et al.¹³⁶ analisaram retrospectivamente o prontuário de 276 pacientes com câncer de orofaringe que foram encaminhados para intervenção nutricional intensiva durante à radio quimioterapia. Apesar do suporte nutricional e consulta nutricional frequente, os pacientes perderam peso durante o tratamento (média de 6.5%) e continuaram a perder peso corporal até 1 ano após o mesmo.

Jeffery e colaboradores¹³⁴ encontraram que a porcentagem de perda de peso para pacientes com CCP submetidos à radioterapia não diferiu após a implementação de protocolo de atendimento nutricional semanal. Da mesma maneira, Hofto e colaboradores¹³⁵ relataram que perda de peso significativa e desnutrição ainda ocorreram

em pacientes com CCP, apesar da implementação de protocolo de atendimento nutricional intensivo.

Nenhum destes estudos avaliou se a adesão do paciente ao cuidado nutricional intensivo implicou em diferentes desfechos ou se o paciente foi capaz de atingir as necessidades nutricionais calculadas. Ainda, nenhum estudo verificou se a implantação de diretrizes de *guidelines* apresentou impacto na qualidade de vida dos pacientes.

Bicakli et al.¹³⁷ avaliaram os efeitos da assiduidade ao aconselhamento dietético individual em pacientes com cancer de cabeça e pescoço submetidos a radioterapia, e verificaram que naqueles pacientes que foram assíduos ao aconselhamento, praticamente não ocorreu mudança na composição corporal, enquanto que naqueles pacientes que não compareceram ao aconselhamento, houve uma diminuição significativa no índice de massa corporal, massa gorda, massa livre de gordura, e massa muscular no período estudado. Da mesma maneira, Kabarriti et al.¹³⁸ encontrou que pacientes com câncer de laringe e orofaringe tratados com radioterapia que foram aderentes ao aconselhamento nutricional intensivo tiveram menor progressão da doença.

A adesão dos pacientes a qualquer intervenção nutricional, pode influenciar a efetividade do tratamento nutricional. A adesão representa a tomada de decisão fundamentada com base em escolhas relacionadas ao tratamento e intervenções.^{139, 140}

De acordo com a Organização Mundial de Saúde, a adesão é definida como a "medida em que o comportamento de uma pessoa - tomar medicamentos, seguir uma dieta e / ou realizar mudanças no estilo de vida, corresponde às recomendações acordadas com um profissional de saúde".

De acordo com o *Medical Subject Headings (MeSH)* da *US National Library of Medicine (NLM)*, a definição de "Adesão ao tratamento e conformidade" ("*Treatment Adherence and Compliance*", em inglês) seria: "a extensão em que o paciente segue o tratamento prescrito, como consultas, horários e medicação para atingir um resultado terapêutico desejado".

A preocupação com a adesão ganhou importância na segunda metade do século 20.¹⁴¹ Apesar da adesão à intervenção nutricional representar um problema que merece atenção de pesquisadores e profissionais de saúde da prática clínica, o assunto é pouco abordado.^{141,142} Vários fatores podem complicar a adesão de pacientes oncológicos, principalmente pacientes com CCP, como escolaridade, falta de recursos, sofrimento psíquico, sintomas, etc.¹⁴³⁻¹⁴⁶ A escassez na literatura de divulgação da adesão aos

protocolos de intervenção nutricional limita recomendações práticas para pacientes com câncer de cabeça e pescoço.

3. JUSTIFICATIVAS

Apesar da indicação de atendimento nutricional semanal durante a radioterapia de cabeça e pescoço preconizada por *guidelines* internacionais, com eficácia demonstrada por alguns ensaios clínicos randomizados, existem poucas evidências baseadas em mundo real para apoiá-las. Ainda, não há nenhum estudo brasileiro sobre o efeito deste tipo de atendimento no país.

Vale ressaltar que o perfil do paciente brasileiro que chega aos serviços é diferente do encontrado na maioria dos estudos publicados sobre o efeito do aconselhamento nutricional e, portanto, não se sabe se o número de consultas preconizados é adequado ou suficiente à nossa população.

Outra questão a ser considerada é a pouca evidência sobre o impacto da adesão a intervenção nutricional intensiva. Considerando a escassez de recursos humanos e financeiros da maioria das instituições brasileiras, é necessário justificar recursos e demonstrar a importância de serviços nutricionais eficazes. Desta maneira, verificar as taxas de adesão ao protocolo e os fatores relacionados a mesma, poderia ajudar a otimizar os recursos financeiros e de recursos humanos e, caso necessário, possibilitar que seja proposto um modelo de atendimento mais adequado.

Além disso, embora exista alguma evidência de que o estado nutricional é preditor de qualidade de vida em pacientes com câncer e algumas indicações de uma relação direta entre intervenções nutricionais e qualidade de vida, poucas pesquisas investigaram se QOL é afetada pela intervenção nutricional intensiva durante a radioterapia de câncer de cabeça e pescoço e seu verdadeiro papel ainda precisa ser claramente definido.

Desta forma, um estudo para investigar os efeitos do atendimento nutricional intensivo no estado nutricional e na qualidade de vida de pacientes com câncer de cabeça e pescoço submetidos à radioterapia no Brasil é relevante.

4. OBJETIVOS

O objetivo desta pesquisa foi verificar o efeito da implementação do protocolo de atendimento nutricional intensivo no estado nutricional e na qualidade de vida de pacientes com câncer de cabeça e pescoço submetidos à radioterapia, bem como investigar fatores relacionados à adesão ao protocolo de atendimento nutricional intensivo.

4.1. OBJETIVOS ESPECÍFICOS

- Investigar o efeito da implementação do cuidado nutricional intensivo no estado nutricional de pacientes com câncer de cabeça e pescoço submetidos a radioterapia;
- Avaliar a prevalência e o efeito do da adesão ao protocolo de atendimento nutricional intensivo e os fatores relacionados a adesão;
- Avaliar a evidência sobre o estudo da adesão a intervenção nutricional oral em pacientes com câncer de cabeça e pescoço;
- Verificar o efeito da implementação de protocolo de atendimento nutricional intensivo na qualidade de vida e no estado nutricional de pacientes com câncer de cabeça e pescoço e comparar o efeito da adesão ao protocolo nos desfechos.

5. EFEITO DA IMPLEMENTAÇÃO DO CUIDADO NUTRICIONAL INTENSIVO NO ESTADO NUTRICIONAL DE PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO SUBMETIDOS A RADIOTERAPIA

Este capítulo apresenta o artigo '*Nutritional outcomes after radiotherapy of head and neck cancer: is intensive nutritional care during treatment worth it?*' de autoria de Sheilla de Oliveira Faria, Doris Howell, Marco Aurélio Vamondes Kulcsar e Jose Eluf-Neto. O artigo foi originalmente publicado na revista *Cancer Treatment and Research Communications* e pode ser acessado em <https://www.sciencedirect.com/science/article/pii/S246829422030068X?via%3Dihub>.

Para citação: De Oliveira Faria, S., Howell, D., Vamondes Kulcsar, M.A., Eluf-Neto, J., 2020. Nutritional outcomes in head and neck cancer patients: is intensive nutritional care worth it?. *Cancer Treatment and Research Communications* 25, 100233. doi:10.1016/j.ctarc.2020.100233.

Nutritional outcomes in head and neck cancer patients: is intensive nutritional care worth it?

Sheilla de Oliveira Faria MS ^{a,b,c}, Doris Howell PhD ^{b,c}, Marco Aurélio Vamondes Kulcsar PhD ^d and Jose Eluf-Neto PhD ^a

^a Departamento de Medicina Preventiva, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

^b Princess Margaret Cancer Centre Research Institute, Toronto, Ontario, Canada.

^c Lawrence S. Bloomberg Faculty of Nursing, University of Toronto, Toronto, Ontario, Canada.

^d Cirurgia de Cabeça e Pescoço, Instituto do Câncer do Estado de São Paulo (ICESP), Hospital das Clinicas HCFMUSP, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil.

Correspondence: Sheilla de Oliveira Faria; Departamento de Medicina Preventiva, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil, Av. Dr Arnaldo, 455 2ºandar, Sao Paulo, 01246-903, Brazil, 55 11 3061-8278, sheilla.faria@usp.br, <https://orcid.org/0000-0002-6426-932X>

Funding source -This study was supported in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001”

CRedit authorship contribution statement

Sheilla de Oliveira Faria: Conceptualization; Data collection, data analysis; Roles/Writing - original draft; Writing - review & editing. Marco Aurélio Vamondes Kulcsar: Writing - review & editing. Doris Howell: Supervision; Writing - review & editing. Jose Eluf-Neto: Conceptualization; Supervision; Writing - review & editing.

Declaration of Competing Interests

There are no conflicts of interests.

Abstract

Objective: This study aimed to compare nutritional outcomes before and after implementation of weekly dietetic counseling (intensive nutritional care) in head and neck cancers patients. **Methods:** A retrospective study with all head and neck patients, who received radiotherapy between January 2010 and December 2017 were performed. The main outcome was significant weight loss. Compliance to caloric and protein recommendations were also evaluated. **Results:** In all, 472 patients were included. Weight loss was not different between before and after implementation (-6.7%; IQ -10.5/-1.9 vs -5.0%; IQ -9.8/-0.7;p=0.06). There were no significant difference in terms of meeting the recommended intake. Higher baseline body mass index and oral nutritional support predicted significant weight loss. **Conclusion:** Implementation of intensive nutritional care did not have an impact on weight loss and energy and protein intake in head and neck cancer patients. Further research would be of value to determine the appropriate service-delivery model to achieve optimal patient outcomes.

Keywords: head and neck cancer, nutrition support, implementation, radiotherapy

Abbreviations

BMI, body mass index; EN, enteral nutrition; ONS, oral nutritional supplementation;

Introduction

Multimodal treatment has been shown to be the most effective approach in head and neck cancer (HNC) patients, for enhancing disease-free survival and loco regional control.¹ However, treatment toxicities such as mucositis, dysphagia, xerostomia, dermatitis, pain and other distressing side-effects can cause weight loss, and consequently, increase morbidity and has a negative impact on the patient's quality of life.²⁻⁵ In addition to treatment toxicities, other problems can predispose patients with HNC to an increased risk of involuntary weight loss: difficulty of swallowing or chewing problems, metabolic effects of the tumor (cachexia), history of alcohol abuse or smoking, among other factors.⁶⁻⁹

Weight loss is a burdensome problem in patients with head and neck cancer.¹⁰⁻¹² A meta-analysis of the literature reported that 20 to 30% of HNC patients have a significant weight loss at the time of diagnosis/just before initiation of cancer treatment.¹³ In addition, up to half of patients lose more than 5% of their body weight during treatment.^{14, 15}

Preventing weight loss in HNC patients is complex and therefore an individualized approach is recommended.^{16, 17} To avoid nutritional deterioration and maintain intake, the European Society for Enteral and Parenteral Nutrition (ESPEN) recommends that an adequate nutritional intake should be ensured for HNC patients primarily by individualized nutritional counseling and/or with use of oral nutritional supplements (ONS).¹⁸ Guidelines recommend weekly contacts by dietitians (intensive nutritional care) during radiotherapy of HNC to increase dietary intake.^{19, 20}

A number of randomized clinical trials (RCT) have evaluated the effect of intensive nutritional care in HNC patients, demonstrating that regular dietary counseling during treatment was associated with less weight loss during treatment. However, the RCTs had some limitations, including small sample size and different tumor locations (gastrointestinal and head and neck cancers).²¹⁻²⁴ In addition, despite the great value of RCT, they are conducted on selective populations. Thus, real world evidence is valuable for estimating effectiveness of interventions that may be applicable to heterogeneous HNC populations.²⁵ Most real world studies that have examined the effectiveness of more frequent contact with the dietitian in HNC patients during radiotherapy, reported that best practice failed to avoid weight loss in HNC population. The majority of those studies did not measure if patients accomplished with recommended nutritional intake.²⁶⁻²⁹

Therefore, there is a lack of evidence available to support the need for weekly dietetic counseling in HNC patients receiving radiotherapy.

In January 2013, a public oncology hospital in Brazil implemented a nutritional protocol for all HNC patients, with intensive nutritional care (weekly individualized nutritional counseling) during radiotherapy. The aim of this study was to compare nutritional outcomes before and after the implementation of intensive nutritional care for HNC patients. The hypothesis was that patients that had received intensive nutritional care (after implementation) would have less weight loss and better energy and protein intake.

Materials and Methods

Study design

Retrospective data were collected from electronic medical records of HNC patients that received radiotherapy treatment in a tertiary hospital in Brazil. We did not perform a sample size and power calculation before the data collection; instead, we used convenience sampling: all suitable charts between January 2010 and December 2017 were included. The primary outcome variable was weight loss during treatment. Secondary outcomes were protein and energy intake after treatment.

The study was conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki (version 2002) and was approved by the Research Center of Sao Paulo Cancer Institute (NP 1313/18) and the Committee for Ethics in Research of School of Medicine of the University of São Paulo (CEP-FMUSP – CAAE 93676618.0.0000.0065).

Study population

The charts of all HNC patients, who received radiotherapy treatment between January 2010 and December 2017, were assessed for inclusion. Patients were included in this study if they were adults (18 years or more), had cancer of oral cavity, oropharynx or larynx (International Statistical Classification of Diseases and Related Health Problems 10th Revision ICD-10)³⁰, any disease stage and received radiotherapy as primary or adjuvant treatment (total dose 50–70 Gray in the cervical area for 5–7 weeks). Patients were excluded if they did not complete treatment or received palliative radiotherapy. Patients with no weight record were also excluded.

Nutritional care

Nutritional care consisted of appointments with the dietitian, which corresponded to nutritional advice (use of regular foods). Dietitians also provided tips of how to deal with the impact of symptoms on nutrition and a diet plan. When necessary, dietitians prescribed oral nutritional supplementation (ONS) and/or enteral nutrition (EN), according to nutritional status. The hospital provided free ONS or EN until the next appointment with the dietitian. The main goal of nutritional interventions was to enable patients to achieve their calculated energy and protein requirements (30kcal/kg/day and 1.5 g/kg/day, respectively).

Before protocol implementation

Prior to the implementation of the protocol HNC patients received nutritional care only when referred by the multiprofessional team to the outpatient nutrition clinic or by patient's own request (before protocol group). The patient had contact with the dietitian once a month or fortnightly during radiotherapy, depending on nutritional status.

After protocol implementation

After the implementation of the protocol, before the beginning of treatment, all HNC patients treated with curative-intent radiotherapy were referred to the multidisciplinary education session. All patients received nutritional care during radiotherapy provided by the dietitian at the beginning of treatment and thereafter on a weekly basis (after protocol group), as recommend by guidelines

Study measures

All data were abstracted from the patient's electronic medical chart. Demographics characteristics were recorded from the beginning of radiation therapy and consisted of gender, age, race/color and education level, and clinical characteristics were location of the tumor, staging, treatment, Karnofsky Performance Scale. Tumor stage was grouped as stage I/II, III and IV using the AJCC 8th edition.³¹ Treatment modality consisted of radiotherapy alone; adjuvant radiotherapy (RT plus surgery) or combination treatment of

radio(chemo)therapy. Karnofsky Performance Scale was divided into two groups: ≥ 70 (good performance status; care of self) and ≤ 60 (worse performance status; requires assistance).

Nutritional assessment

Weight, height and body mass index (BMI) were obtained from chart reviews of dietitians, physicians and nursing staff at baseline (beginning of radiotherapy treatment) and 12 weeks after treatment started (± 1 week). BMI (kg / m^2) was classified according to cut-off points proposed by the World Health Organization³²: underweight (BMI $< 18.5 \text{kg}/\text{m}^2$); normal weight (BMI $\geq 18.5 \text{kg}/\text{m}^2 \leq 24.9 \text{kg}/\text{m}^2$); overweight (BMI $\geq 25.0 \text{kg}/\text{m}^2$). The percentage of weight loss was calculated according to the following formula: $[(\text{weight after} - \text{weight before}) / (\text{weight before})] * 100$. Weight loss of $\geq 5\%$ was considered significant and measured as a binary variable (yes/no).

Dietary assessment

Nutritional intake (total calorie and protein) was derived from 24-hour recall food questionnaire, assessed from the chart at baseline (beginning of radiotherapy treatment) and 12 weeks after treatment started (± 1 week), when available. After abstracted from chart, the analysis of nutritional intake was done on the program for food intake analysis Avanutri® online (Avanutri Assessment Equipment Ltda, Três Rios, RJ). Nutrition support provided was classified as regular foods, oral nutritional supplementation or enteral nutrition. Patients' capacity to accomplish caloric and protein recommendations were calculated for each patient based on kilograms of body weight at baseline and end of treatment. Patients were categorized according to meeting or not meeting the dietitian energy recommendations intakes of $\geq 30 \text{ kcal}/\text{kg}/\text{d}$; and meeting or not meeting the dietitian protein recommendations intakes of $\geq 1.5 \text{ g}/\text{kg}/\text{d}$.

Data analysis

Statistical analysis was performed using Stata 12 (Stata Corp LP, College Station, Texas). Chi-square tests were used to compare categorical variables, and t test or a Mann-Whitney U test, depending on normality of the data were used for continuous variables.

For model building, the first step was to test which of the independent variables predicted weight loss, using a logistic regression model, with $\geq 5\%$ weight loss (yes/no) as the

outcome/dependent variable. Each variable with a p value ≤ 0.2 , was then included in a multivariate logistic model. Independent variables were then checked for multicollinearity. The results are reported as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was reported at the $p < 0.05$ level.

Results

A total of 688 patients' files were reviewed. Fifty-five patients did not have a weight record, 50 patients had interrupted RT for different reasons and 111 patients receiving palliative radiotherapy were excluded. Four hundred and seventy-two patients were included, with a higher percentage included in the after-implementation period (N=317, 67.2%). Patient characteristics at baseline are summarized in Table 1. In baseline comparison of the before and after protocol group, there were significant differences in treatment modality and race/color ($p < 0.05$). In both groups the oral cavity was the most common location of tumor and more than 60% of patients had advanced disease (stage IV). Median age was not different between before (median=59; IQ=53/65) and after protocol group (median=58; IQ=52/66), $p=0.82$, Mann-Whitney U test.

Table 1. Participant characteristics before and after the implementation of the weekly contact protocol.

Patient Characteristics	Before protocol group (n=155)		After protocol group (n=317)		p*
	N	%	N	%	
Sex					.31
Male	119	76.8	256	80.8	
Female	36	23.2	61	19.2	
Race/Color					<0.05
White Caucasian	128	82.6	221	69.7	
Others	27	17.4	96	30.3	
Education†					.32
Primary school or less education	77	85.6	155	80.7	
Secondary school or higher education	13	14.4	37	19.3	
Tumor site					.08
Oral cavity	68	43.9	144	45.4	
Oropharynx	50	32.2	74	23.4	
Larynx	37	23.9	99	31.2	
Overall Cancer Stage					0.99
I/II	19	12.3	39	12.4	
III	33	21.3	66	21.0	
IV	103	66.4	210	66.6	
Treatment modality					<0.05
Radiotherapy alone	7	4.5	11	3.4	
Adjuvant Radiotherapy	45	29.0	134	42.3	
Radio(chemo)therapy	103	66.5	172	54.3	
BMI					.49
Underweight	22	14.2	47	14.8	
Normal	95	61.3	177	55.8	
Overweight	38	24.5	93	29.4	
KPS‡					.16
≥70	124	93.2	264	96.4	
≤60	9	6.8	10	3.6	
Nutrition support					.26
Regular foods	41	32.5	61	28.9	
Oral nutritional supplementation	36	28.6	49	23.2	
Enteral nutrition	49	38.9	101	47.9	

*X² test between groups; † 190 missing values; ‡ 65 missing values

Median weight loss was higher before (-6.7%; IQ -10.5/-1.9) than after implementation (-5.0%; IQ -9.8/-0.7), although not statistically significant (p=0.06, *Mann-Whitney U test*) (Figure 1). Almost fifty percent (n=158, 49.8%) of patients in the after-protocol group

experienced a significant weight loss ($\geq 5\%$ of pre-treatment weight) during radiotherapy, which was not different from the before protocol group ($n=88$, 56.8%), $\chi^2= 2.00$, $p=0.16$.

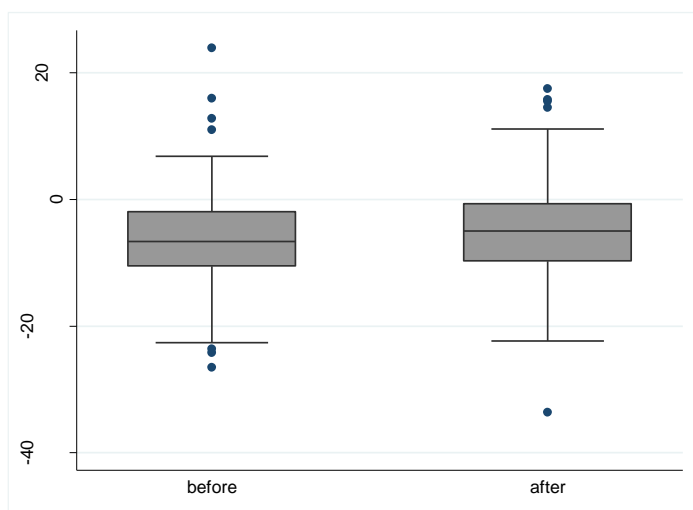


Figure 1. Percent weight change before and after implementation of protocol.

Nutritional intake data were available for 337 patients (71.4%) at baseline and for 370 (78.4%) at the end of treatment.

At baseline and the end of treatment, energy and protein intake were not significantly different between the before and after protocol group. Likewise, there were not significant differences between the before and after protocol group in terms of meeting the recommended intake for energy and protein (Table 2).

Table 2. Energy and protein intake in patients with head and neck cancer

	Baseline (n=337, 126 before; 211 after)		End of treatment (n=370, 133 before; 237 after)	
	Energy (kcal/kg/d)	Protein (g/kg/d)	Energy (kcal/kg/d)	Protein (g/kg/d)
Before protocol	29.0±10.8	1.27±0.50	29.7±10.9	1.28±0.49
After protocol	30.3±11.4	1.29±0.51	32.0±12.8	1.39±0.57
<i>p</i>	0.32	0.72	0.07	0.06
	% of patients meeting the dietitian recommendations			
	Energy	Protein	Energy	Protein
Before protocol	51.6%	32.5%	51.9%	36.1%
After protocol	52.6%	34.1%	58.6%	44.3%
<i>p</i>	0.86	0.77	0.21	0.12

p-value for t-test or χ^2 test between groups

Regarding type of nutrition support, there was no significant difference between groups (43.2% before and 39.4% after protocol received enteral nutrition and 28.8% before and 30.1% after protocol received oral nutritional supplementation, $p=0.77$).

About fifty percent (42.2% before and 54.7% after protocol) of the patients with BMI ≤ 24.9 kg/m², received enteral nutrition support, compared to 25.0% and 26.9% of patients with BMI 25 kg/m² or above.

Seventy-seven and 85% of patients receiving enteral nutrition achieved the caloric goal before and after the protocol implementation, respectively. Patients receiving regular foods or oral nutritional supplementation had less success at meeting nutritional recommendations.

Patients not meeting the recommendations of energy intake had a median weight loss of approximately twice that of patients achieving nutritional goals. Patients meeting the recommendations of energy and protein had less significant weight loss (Table 3).

Table 3. Weight loss in patients meeting or not meeting the energy and protein recommendations at end of radiotherapy, n= 370.

	Energy		Protein	
	Meeting(n =208)	Not Meeting (n=162)	Meeting (n=153)	Not Meeting (n=217)
Weight loss (median %, IQ)*	-3.9 (-8.5/0)	-6.3 (-10.2/-2.1)‡	-4.4 (-9.1/-0.6)	-5.8 (-9.9/-1.0)
Patients with significant weight loss†	42.8%	59.9%‡	43.8%	54.8%§

* Mann-Whitney; † X² test; ‡ $p<0.01$; § $p<0.05$

According to the univariate logistic regression analyses, age, sex and KPS had a p value >0.2 , and thus, these variables were not included in the multivariate analysis. The multivariate logistic regression analysis showed that baseline BMI and nutrition support predicted significant weight loss (Table 4). The odds of significant weight loss in patients with BMI 25 kg/m² or above were more than two times higher (OR: 2.25, CI: 1.28 – 3.95) compared with patients with BMI ≤ 24.9 kg/m². The odds of significant weight loss were

almost two times higher (OR: 1.93, CI: 1.21 – 3.08) in patients not receiving enteral nutritional support compared with patients receiving tube feeding.

Table 4. Multivariate logistic regression analysis of weight loss in patients with head and neck cancer during radiotherapy.

	OR	95 % CI	p
BMI (<25 Kg/m ² omitted as reference)	2.25	1.28 – 3.95	< 0.01
Nutrition support (Enteral nutrition omitted as reference)	1.93	1.21 – 3.08	< 0.01
Nutrition protocol (not weekly contact omitted as reference)	0.79	0.49 – 1.27	0.33
Location of tumor (Larynx omitted as reference)	1.34	0.79 – 2.26	0.28
Treatment modality (exclusive RT omitted as reference)			
Adjuvant radiotherapy	2.11	0.47 – 9.47	0.32
Chemoradiotherapy	3.38	0.76 – 15.0	0.11
Stage (early stage – I/II omitted as reference)	1.84	0.86 – 3.93	0.12
Education (Primary school or less education omitted as reference)	1.05	0.99 – 1.11	0.10
Race (White Caucasian omitted as reference)	0.93	0.54 – 1.58	0.77

Discussion

The present study shows that, in patients with head and neck cancer, intensive care (weekly dietetic counseling during RT) did not have an impact on weight loss and energy and protein intake. Our study highlights predictors associated with higher percent of weight loss in HNC during radiotherapy, as higher BMI and oral nutritional support.

Patients in both the before and the after-protocol groups had significant weight loss during radiotherapy. Our results are similar to a study that compared percent weight loss during radiotherapy before and after the implementation of weekly dietetic counseling in a large hospital in Australia.²⁷ Likewise, in a two-year retrospective cohort study of 209 HNC patients, significant weight loss was observed in HNC patients, regardless of the introduction of best-practice nutritional guidelines (weekly contacts with dietitians).²⁶

Vlooswijk et al.²⁹ also reported that even with weekly dietary counselling during treatment for oropharyngeal cancer, weight loss remained high.

In contrast to these findings, a study about implementation of early and intensive nutrition intervention in patients with HNC receiving chemoradiotherapy reported less weight loss and improved treatment tolerance and fewer admissions to hospital with intensive nutrition intervention. However, the proportion of patients in that study with early disease (stage I/II) was higher and more patients received enteral nutritional.²⁸ A possible explanation for not finding an effect of nutritional interventions even after the implementation of best practice in our study is the prevalence of patients with stage IV disease. It is already known that patients with advanced-stage disease are more likely to develop weight loss³³. Unfortunately, most patients are diagnosed with advanced stage³⁴, therefore the development of new strategies and an appropriate service-delivery model to enhance advanced stage patient outcomes is of utmost importance.

Hofto²⁶ and Jeffery²⁷ raised the question of patient noncompliance to dietetic recommendations being the reason for failure after implementation, as this was not evaluated in either study. We didn't observe any differences in the proportion of patients receiving nutritional support (oral nutritional supplementation or enteral nutrition) between the before and after period. It seemed that the nutritional care delivered prior to protocol implementation provided good access to nutrition support and therefore, the frequency of contact with the dietitian made no difference.

In our study, we did measure if patients accomplished nutritional recommendation of energy and protein. However, regardless of the implementation of a weekly protocol, the proportion of patients that met the dietetic recommendations were not significantly different from before the implementation. Strategies to achieve compliance to nutritional recommendations and consequently improve nutrition outcomes in cancer patients is crucial. Bicakli³⁵ et al., in a prospective study to evaluate the effects of compliance of patients with individual dietary counselling on nutritional parameters in HNC patients under RT, reported that only 37.5% of patients complied with the recommended plan for energy and protein intake. In their study, the nature of living conditions of patients during RT was important in relation to their food consumption, i.e., patients staying at home or staying with relatives had significantly more energy intake. This might suggest that some factors are related to compliance with dietetic recommendations and therefore it should be assessed in future studies.

As expected, patients not meeting the protein and energy recommendations experienced more weight loss. Giles et al.³⁶ reported that patients not meeting ESPEN energy recommendations (<30 kcal/kg/d) lost more weight than those meeting ESPEN energy recommendations ≥ 30 kcal/kg/d. Bicakli et al.³⁵ observed no significant weight loss in patients that met $\geq 75\%$ of the recommended energy and protein intake during RT.

However, even patients meeting the nutritional recommendations lost weight, suggesting the energy requirements were not enough. Energy requirements, generally recommended by guidelines, can be imprecise when compared with more accurate measures, as indirect calorimetry.³⁷ A study about requirements for attenuation of weight loss in patients with HNC patients found that for maintaining their weight throughout treatment patients had to have a minimum energy intake of 33.3 kcal/kg/d and 1.6 g protein/kg/d.³⁶ Jager-Wittenaar et al.³⁸ also reported that HNC patients with an intake of ≥ 35 kcal/kg/d and ≥ 1.5 g protein/kg/d lost significantly less body weight. Additionally, Della Valle et al.³⁹ suggested that for HNC patients who were candidates for chemoradiotherapy to have a stable body weight, it was necessary to give at least 35kcal/kg. Besides, weight loss in cancer patients is associated with an energy imbalance, not only from anorexia but also from increase in energy expenditure induced by tumor and host's factors and therefore adequate energy and protein intake may still be inadequate to meet this demand. Nevertheless, an adequate nutritional support is the best way of preventing weight loss up to now, whereas multimodal intervention (with drug therapies and exercise) are under investigation.^{40,41}

The current data demonstrate that patients with overweight or obesity according to the BMI classification ($BMI \geq 25$ Kg/m²) had significantly greater weight loss than did patients with normal or underweight as reported by previous studies.⁴²⁻⁴⁶ As a result of the belief that patients with a higher BMI might be in better nutritional balance, sometimes healthcare professionals and patients themselves, fail to prioritize nutritional support for these patients. Enteral nutrition, for example, is often initiated only for patients with a low BMI before treatment.⁴⁶ In our study, overweight patients received less nutritional support compared with patients with $BMI < 25$ kg/m².

Patients receiving enteral nutrition were more likely to achieve nutritional recommendation of energy and protein intake in both pre and post-implementation period and presented less weight loss than those not on tube feeding. An intensive debate remains

about the decision to use a nasogastric tube or percutaneous endoscopic gastrostomy to provide nutrition to HNC and this remains an area requiring further research^{16, 47}.

Previous research in the field raised the question as to whether all HNC patients should have intensive care (weekly contacts with dietitian) or if routine weekly counseling for all patients could be over-servicing.^{27, 48} Maybe patients at a lower risk of significant weight loss (as those receiving enteral nutrition) should have a less intensive timeframe of contacts with the dietitian. It is important to note that weekly dietetic counseling for all HNC patients undergoing radiotherapy as recommended in the guidelines require more human resources and organizational support. In some hospitals, especially at low- and medium-income countries, this may not be practicable.⁴⁹

Finally, non-compliance to nutrition recommendations may have had an impact in the delivery of intervention, and this should be an avenue for further study.

Some limitations should be considered when interpreting our results. First, the current study is limited by its retrospective design, which cannot infer causation or temporal relationship. Furthermore, given that data rely on chart reviews, some variables were not systematically collected, and we must rely on others for accurate recordkeeping; thus variance in the quality of information recorded by medical professionals can compromise data quality. We do not have data on nutritional intake of all patients across the time points, thus making it difficult to draw stronger conclusions. Second, the use of 24-hour recall may not represent an adequate food intake for the patient or represent long-term dietary habits. Finally, we did not have data on history of alcohol abuse or smoking. Although we did not perform a sample size and power calculation, we included all patients undergoing radiotherapy. Taking into consideration that a minimum of 5–10 charts per variable is required to obtain results that are likely to be both true and clinically useful, we can assume that our sample was sufficient.

In conclusion, our study provides evidence that implementation of intensive nutritional care (weekly dietetic counseling) for HNC patients during radiotherapy did not have an impact on weight loss and energy and protein intake. The results of this study add important information about effectiveness of intensive nutrition intervention, but they do not allow us to conclude that guidelines are not worthwhile. Further research is required to clarify which patients benefit from weekly counseling, especially in the context of limited resources. In addition, future studies for understanding the problem of continued

weight loss despite frequent access to dietetic care would be of value to determine the appropriate service-delivery model to achieve optimal patient outcomes.

References

1. Nilsen ML, Mady LJ, Hodges J, Wasserman-Wincko T, Johnson JT. Burden of treatment: Reported outcomes in a head and neck cancer survivorship clinic. *The Laryngoscope* 2019;129(12):E437-E44.
2. Kubrak C, Martin L, Gramlich L, Scrimger R, Jha N, Debenham B, et al. Prevalence and prognostic significance of malnutrition in patients with cancers of the head and neck. *Clin Nutr* 2019. Article in press.
3. Kubrak C, Olson K, Jha N, Scrimger R, Parliament M, McCargar L, et al. Clinical determinants of weight loss in patients receiving radiation and chemoradiation for head and neck cancer: a prospective longitudinal view. *Head Neck* 2013;35(5):695-703.
4. Arribas L, Hurtos L, Taberna M, Peiro I, Vilajosana E, Lozano A, et al. Nutritional changes in patients with locally advanced head and neck cancer during treatment. *Oral Oncol* 2017;71:67-74.
5. Crowder SL, Douglas KG, Yanina Pepino M, Sarma KP, Arthur AE. Nutrition impact symptoms and associated outcomes in post-chemoradiotherapy head and neck cancer survivors: a systematic review. *J Cancer Surviv* 2018;12(4):479-94.
6. Pezdirec M, Strojjan P, Boltezar IH. Swallowing disorders after treatment for head and neck cancer. *Radiol Oncol* 2019;53(2):225-30.
7. Alterio D, Gerardi MA, Cella L, Spoto R, Zurlo V, Sabbatini A, et al. Radiation-induced acute dysphagia : Prospective observational study on 42 head and neck cancer patients. *Strahlenther Onkol.* . 2017;193(11):971-81.
8. Aguilar ML, Sandow P, Werning JW, Brenneman L, Psoter WJ. The Head and Neck Cancer Patient Concern Inventory© : Patient Concerns' Prevalence, Dental Concerns' Impact, and Relationships of Concerns with Quality of Life Measures. *J Prosthodont* 2017;26(3):186-95.
9. Martin L, de van der Schueren MAE, Blauwhoff-Buskermolen S, Baracos V, Gramlich L. Identifying the Barriers and Enablers to Nutrition Care in Head and Neck and Esophageal Cancers. *JPEN J Parenter Enteral Nutr* 2016;40(3):355-66.

10. Gorenc M, Kozjek NR, Strojjan P. Malnutrition and cachexia in patients with head and neck cancer treated with (chemo)radiotherapy. *Rep Pract Oncol Radiother.* 2015;20(4):249-58.
11. Langius JA, van Dijk AM, Doornaert P, Kruizenga HM, Langendijk JA, Leemans CR, et al. More than 10% weight loss in head and neck cancer patients during radiotherapy is independently associated with deterioration in quality of life. *Nutr Cancer* 2013;65(1):76-83.
12. Jager-Wittenaar H, Dijkstra PU, Dijkstra G, Bijzet J, Langendijk JA, van der Laan BFAM, et al. High prevalence of cachexia in newly diagnosed head and neck cancer patients: An exploratory study. *Nutr* 2017;35:114-8.
13. Couch ME, Dittus K, Toth MJ, Willis MS, Guttridge DC, George JR, et al. Cancer cachexia update in head and neck cancer: Definitions and diagnostic features. *Head Neck* 2015;37(4):594-604.
14. Ghadjar P, Hayoz S, Zimmermann F, Bodis S, Kaul D, Badakhshi H, 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). *Radiol Oncol* 2015;10(1):21.
15. Lee SC, Wang TJ, Chu PY. Predictors of weight loss during and after radiotherapy in patients with head and neck cancer: A longitudinal study. *Eur J Oncol Nurs* 2019;39:98-104.
16. Langius JAE, Zandbergen MC, Eerenstein SEJ, van Tulder MW, Leemans CR, Kramer MHH, et al. Effect of nutritional interventions on nutritional status, quality of life and mortality in patients with head and neck cancer receiving (chemo)radiotherapy: a systematic review. *Clin Nutr* 2013;32(5):671-8.
17. Bossola M. Nutritional interventions in head and neck cancer patients undergoing chemoradiotherapy: a narrative review. *Nutrients* 2015;7(1):265-76.
18. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr* 2017;36(1):11-48.
19. Findlay M, Bauer J, Brown T, Committee. HaNGS. Evidence-based practice guidelines for the nutritional management of adult patients with head and neck cancer. Sydney: Cancer Council Australia. [cited 2020 Jan 10]. Available from: https://wiki.cancer.org.au/australia/COSA:Head_and_neck_cancer_nutrition_guidelines

20. Talwar B, Donnelly R, Skelly R, Donaldson M. Nutritional management in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol* 2016;130:S32-S40.
21. Isenring EA, Bauer JD, Capra S. Nutrition Support Using the American Dietetic Association Medical Nutrition Therapy Protocol for Radiation Oncology Patients Improves Dietary Intake Compared with Standard Practice. *J Am Diet Assoc* 2007;107(3):404-12.
22. Isenring EA, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. *Br J Cancer* 2004;91(3):447-52.
23. van den Berg MG, Rasmussen-Conrad EL, Wei KH, Lintz-Luidens H, Kaanders JH, Merkx MA. Comparison of the effect of individual dietary counselling and of standard nutritional care on weight loss in patients with head and neck cancer undergoing radiotherapy. *Br J Nutr* 2010;104(6):872-7.
24. Kang W-X, Li W, Huang S-G, Dang Y, Gao H. Effects of nutritional intervention in head and neck cancer patients undergoing radiotherapy: A prospective randomized clinical trial. *Mol Clin Oncol* 2016;5(3):279-82.
25. Dreyer NA. Advancing a Framework for Regulatory Use of Real-World Evidence: When Real Is Reliable. *Ther Innov Regul Sci* 2018;52(3):362-8.
26. Hofto S, Abbott J, Jackson JE, Isenring E. Investigating adherence to Australian nutritional care guidelines in patients with head and neck cancer. *Cancers of the Head & Neck* 2018;3(1):6.
27. Jeffery E, Young P, Sherriff J. Nutritional outcomes with radiotherapy for head and neck cancer: a before and after comparison of 'best practice guidelines' implementation. *Asia Pac J Clin Nutr* 2018;27(5):955-61.
28. Paccagnella A, Morello M, Da Mosto MC, Baruffi C, Marcon ML, Gava A, et al. Early nutritional intervention improves treatment tolerance and outcomes in head and neck cancer patients undergoing concurrent chemoradiotherapy. *Support Care Cancer* 2010;18(7):837-45.
29. Vlooswijk CP, van Rooij PHE, Kruize JC, Schuring HA, Al-Mamgani A, de Roos NM. Dietary counselling and nutritional support in oropharyngeal cancer patients treated with radiotherapy: persistent weight loss during 1-year follow-ups. *Eur J Clin Nutr* 2016;70(1):54-9.

30. World Health O. ICD-10 : international statistical classification of diseases and related health problems : tenth revision. 2nd ed ed. Geneva: World Health Organization; 2004.
31. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, 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 Cancer J Clin* 2017;67(2):93-9.
32. WHO WHO-. Obesity: Preventing and managing the Global Epidemic. Geneva: World Health Organization - WHO; 2000.
33. Iftikhar H, Suhail A, Nathani K, Urooba A, Shahzad N, Awan S, et al. Determination of Factors Associated with Critical Weight Loss in Oral Cavity Carcinoma Patients: A Retrospective Cohort Study. *International Archives of Otorhinolaryngology*. 2018. 10.1055/s-0038-1641131
34. Faria SO, Nascimento MCD, Kulcsar MAV. Malignant neoplasms of the oral cavity and oropharynx treated in Brazil: what do hospital cancer records reveal? *Braz J Otorhinolaryngol*. 2020. 10.1016/j.bjorl.2020.05.019
35. Hopanci Bicakli D, Ozkaya Akagunduz O, Meseri Dalak R, Esassolak M, Uslu R, Uyar M. The Effects of Compliance with Nutritional Counselling on Body Composition Parameters in Head and Neck Cancer Patients under Radiotherapy. *J Nutr Metab* 2017;2017:7.
36. Giles KH, Kubrak C, Baracos VE, Olson K, Mazurak VC. Recommended European Society of Parenteral and Enteral Nutrition protein and energy intakes and weight loss in patients with head and neck cancer. *Head Neck* 2016;38(8):1248-57.
37. Souza MTP, Singer P, Ozorio GA, Rosa VM, Alves MMF, Mendoza López RV, et al. Resting energy expenditure and body composition in patients with head and neck cancer: An observational study leading to a new predictive equation. *Nutrition* 2018;51-52:60-5.
38. Jager-Wittenaar H, Dijkstra PU, Vissink A, Langendijk JA, Van Der Laan BFAM, Pruim J, et al. Changes in nutritional status and dietary intake during and after head and neck cancer treatment. *Head Neck* 2011;33(6):863-70.
39. Della Valle S, Colatruglio S, La Vela V, Tagliabue E, Mariani L, Gavazzi C. Nutritional intervention in head and neck cancer patients during chemo-radiotherapy. *Nutrition* 2018;51-52:95-7.

40. Schcolnik-Cabrera A, Chavez-Blanco A, Dominguez-Gomez G, Duenas-Gonzalez A. Understanding tumor anabolism and patient catabolism in cancer-associated cachexia. *Am J Cancer Res* 2017;7(5):1107-35.
41. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. *Nat Rev Dis Primers* 2018;4(1):17105.
42. Lonbro S, Petersen GB, Andersen JR, Johansen J. Prediction of critical weight loss during radiation treatment in head and neck cancer patients is dependent on BMI. *Support Care Cancer* 2016;24(5):2101-9.
43. Zhang Z, Zhu Y, Zhang L, Wang Z, Wan H. Prediction model of critical weight loss in cancer patients during particle therapy. *Jpn J Clin Oncol* 2018;48(1):75-81.
44. Ottosson S, Zackrisson B, Kjöellén E, Nilsson P, Laurell G. Weight loss in patients with head and neck cancer during and after conventional and accelerated radiotherapy. *Acta Oncol* 2013;52(4):711-8.
45. Silander E, Nyman J, Hammerlid E. An exploration of factors predicting malnutrition in patients with advanced head and neck cancer. *Laryngoscope* 2013;123(10):2428-34.
46. Zhao J-Z, Zheng H, Li L-Y, Zhang L-Y, Zhao Y, Jiang N. Predictors for Weight Loss in Head and Neck Cancer Patients Undergoing Radiotherapy: A Systematic Review. *Cancer Nurs* 2015;38(6):E37-45.
47. McClelland S, Andrews JZ, Chaudhry H, Teckie S, Goenka A. Prophylactic versus reactive gastrostomy tube placement in advanced head and neck cancer treated with definitive chemoradiotherapy: A systematic review. *Oral Oncol* 2018;87:77-81.
48. Wall LR, Cartmill B, Ward EC, Hill AJ, Isenring E, Porceddu SV. Evaluation of a weekly speech pathology/dietetic service model for providing supportive care intervention to head and neck cancer patients and their carers during (chemo)radiotherapy. *Support Care Cancer* 2016;24(3):1227-34.
49. McCarter K, Baker AL, Britton B, Beck AK, Carter G, Bauer J, et al. Effectiveness of clinical practice change strategies in improving dietitian care for head and neck cancer patients according to evidence-based clinical guidelines: a stepped-wedge, randomized controlled trial. *Transl Behav Med* 2018;8(2):166-74.

6. PREVALÊNCIA E O EFEITO DO DA ADESÃO AO PROTOCOLO DE ATENDIMENTO NUTRICIONAL INTENSIVO E OS FATORES RELACIONADOS A ADESÃO

Este capítulo apresenta o artigo “*Adherence to intensive nutrition care in head and neck cancer patients undergoing radiotherapy*” de autoria de Sheilla de Oliveira Faria, Doris Howell, André Lopes Carvalho, Rafael de Oliveira Faria e Jose Eluf Neto. O artigo foi aceito e será publicado na revista *European Archives of Oto-Rhino-Laryngology*.

Para citação: Faria SO, Howell D, Carvalho AL, Faria RO, Eluf Neto J. Adherence to intensive nutrition care in head and neck cancer patients undergoing radiotherapy Eur Arch Oto-Rhino-L. In preparation.

Adherence to intensive nutrition care in head and neck cancer patients undergoing radiotherapy

Authors: Sheilla de Oliveira Faria ^{a,b,c}, Doris Howell ^{b,c}, André Lopes Carvalho^d, Rafael de Oliveira Faria^e and Jose Eluf Neto PhD^a

Affiliations of all authors

^a Departamento de Medicina Preventiva, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

^b Princess Margaret Cancer Centre Research Institute, Toronto, Ontario, Canada.

^c Lawrence S. Bloomberg Faculty of Nursing, University of Toronto, Toronto, Ontario, Canada.

^d Head and Neck Surgery, Barretos Cancer Hospital, Barretos, SP, Brazil

^e Departamento de Engenharia Agrícola, Universidade Federal de Lavras, Lavras, MG, Brazil

Correspondence: Sheilla de Oliveira Faria; Departamento de Medicina Preventiva, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil, Av. Dr Arnaldo, 455 2ºandar, Sao Paulo, 01246-903, Brazil, 55 11 3061-8278, shefaria@hotmail.com, <https://orcid.org/0000-0002-6426-932X>

DECLARATIONS:

Conflict of interest: The authors declare that they have no conflict of interest.

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

Ethics approval: 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 Research Center of Instituto do Câncer do Estado de São Paulo (NP 1313/18) and the Committee for Ethics in Research of School of Medicine

of the University of São Paulo (CEP-FMUSP – CAAE 93676618.0.0000.0065) approved this study.

Consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and material: Not applicable.

Code availability: Not applicable

Authors' contributions: Sheilla O Faria and Jose Eluf Neto contributed to the study conception and design. Doris Howell and Andre Carvalho revised it critically for important intellectual content. Material preparation, data collection and analysis were performed by Sheilla O Faria and Rafael O Faria. The first draft of the manuscript was written by Sheilla O Faria and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

ABSTRACT

Purpose: The aim of this study was to determine the prevalence and effect of adherence to intensive nutritional care on nutritional outcomes and survival in head and neck cancer patients undergoing radiotherapy. **Methods:** Three-hundred and seventeen head and neck cancer patients referred to intensive nutrition support during radiotherapy were retrospectively analyzed. Patients who missed less than 25% of their appointments with the dietitian were considered adherent. Primary outcome was percentage weight loss during treatment. Secondary outcomes were overall survival and patients' capacity to accomplish to their caloric and protein recommendations. Logistic regression was used to examine predictors of weight loss and Kaplan-Meier to estimate survival. **Results:** Less than half of patients (n = 145, 45.7%) were adherent. Statistically significant less weight loss in the adherent group (42.8% vs 55.8%; p =0.02) was found, despite no difference in energy or protein intake. Logistic regression models after adjusting for other variables demonstrated that adherence resulted in 43% protection from significant weight loss (Odds Ratio 0.57, 95% CI 0.34 - 0.97). Overall survival was not different between groups. **Conclusion:** Findings demonstrated that patients who were adherent to weekly contacts with the dietitian had less weight loss, but not better survival or nutritional intake. Additional investigation of factors that may act as barriers or enablers for adherence could help improve the outcomes in this population.

Keywords: head and neck cancer; oral cancer; diet; nutrition; adherence; compliance.

INTRODUCTION

Malnutrition is common in head and neck cancer (HNC) patients. At the time of diagnosis, 30%–50% of HNC patients are malnourished and malnutrition increases considerably during cancer treatment [1-4]. Significant weight loss during treatment can lead to increased treatment toxicity, infections, hospital admissions and early mortality [1, 5-7].

Individualized nutritional counseling and/or oral nutritional supplements (ONS) can help HNC patients to maintain an adequate nutritional intake [8]. Evidence-based guidelines recommend frequent contacts with dietitians during treatment of HNC to increase dietary intake and avoid weight loss [9-11].

Although a useful method of knowledge translation is to incorporate evidence-based guideline recommendations into routine practice, few studies examining the effectiveness of nutrition guideline implementation have been conducted with HNC patients. Most studies reported that best practices failed to avoid weight loss in HNC population, but did not measure the capacity of patients to accomplish their recommended nutritional intake [12-15].

In addition, another concern that can influence negatively the effectiveness of nutrition guideline implementation is the adherence of patients to the nutritional intervention. Adherence is “the extent to which patients follow through with decisions about physician orders”, and represents reasoned decision-making based on choices regarding treatment/interventions [16-17]. Adherence to nutritional intervention may influence treatment efficacy, but a range of factors can complicate adherence of patients with HNC, such as education level, lack of resources, psychological distress, symptom burden and specifically dysphagia, etc.[18-21].

Adherence is an important part of assessing the extent of the uptake of the intervention delivered to patients, however very few studies have evaluated the extent to which HNC patients may be able to adhere to weekly contact with the dietitian during radiotherapy and/or recommended nutritional intake. Two studies reported that up to 49% of patients missed appointments with the dietitian, resulting in poor survival and disease progression and higher rates of malnutrition and significant weight loss [12, 22].

Therefore, the aims of this study were to determine the prevalence and effect of adherence to intensive nutrition care on nutritional outcomes, functional outcome and survival and investigate sociodemographic and clinical factors associated with adherence.

MATERIALS AND METHODS

Study design

Data were retrieved from medical records of all HNC patients treated with radiotherapy at an oncology hospital in Brazil, between January 2013 and December 2017. The Research Center of *Instituto do Câncer do Estado de São Paulo* (NP 1313/18) and the Committee for Ethics in Research of School of Medicine of the University of São Paulo (CEP-FMUSP – CAAE 93676618.0.0000.0065) approved the study.

Population

Adults patients with cancer of the oral cavity, oropharynx or larynx (CID 10) [23] that received radiotherapy as primary or adjuvant treatment to the head and neck area at a public oncology hospital in Brazil were included. HNC patients received a total dose of 50–70 Gray (Gr) daily for 5–7 weeks. Patients were excluded if they were identified as palliative care, did not complete treatment, were receiving parenteral nutrition or had diagnosis of nasopharynx, hypopharynx, lips, sinus or salivary gland cancer.

Intensive Nutrition Care

Before the beginning of treatment, all HNC patients treated with curative-intent radiotherapy were referred to the multidisciplinary education session. All patients received nutritional counselling during radiotherapy provided by the dietitian at the beginning of treatment and thereafter on a weekly basis (intensive nutrition care). The individualized nutritional counselling focused on use of regular foods, and if necessary oral supplements or tube feeding were prescribed. The aim was to enable patients to achieve their calculated energy and protein requirements (30kcal/kg/day and 1.5 g/kg/day, respectively). Dietitians also provided tips on how to deal with nutrition impact symptoms and a diet plan, with modified soft texture when necessary (patients with dysphagia, sore mouth, etc.). In order to standardize nutrition intervention, dietitians prescribed oral nutritional supplementation (ONS) and/or enteral nutrition (EN)

according to a nutritional protocol, considering intake and nutritional status. The hospital provided free ONS or EN.

Data collection

Study assessments were tabulated from medical records at baseline (before radiotherapy) and 12 weeks after the beginning of treatment.

Demographics characteristics (sex, age, race/color and education level) and clinical characteristics (tumour site, staging and treatment) were collected only at baseline from medical records. Clinical stage was categorized into three groups, stage I/II; stage III; and stage IV [24]. Treatment modality consisted of radiotherapy alone; adjuvant radiotherapy and or combination treatment of radio(chemo)therapy. Time of treatment (in days) was calculated between the first and last day of radiotherapy.

Karnofsky Performance Scale (KPS) was divided into two groups: ≥ 70 (good performance status) and ≤ 60 (worse performance status). Body mass index (BMI) was calculated and classified according to the cut-off points proposed by the World Health Organization [25]. Evaluation of total energy (kcal/day) and protein (g/day) intake derived from 24-hour food records.

Adherence

This was defined as patients who attend $\geq 75\%$ of their appointments with the dietitian were considered adherent (adherent group) and those who missed $>25\%$ of their appointments with the dietitian were considered non-adherent (non-adherent group).

Primary and Secondary Outcomes

The primary outcome was percentage weight loss. It was calculated according to: $(\text{weight after treatment} - \text{weight at baseline}) / (\text{weight before}) * 100$ and considered significant when $\geq 5\%$ of baseline weight.

The secondary outcomes included overall survival, functional outcome and patients' capacity to accomplish their caloric and protein recommendations.

Survival time was defined as the time between the first day of the radiotherapy treatment until date of death or censored to last day of data updating on death (January 1, 2019), whichever came first. Each patient's overall functional state was analyzed according

to the KPS, which indicates a person's ability to work, perform physical activity, and care for the self.

Food consumption were recorded with portions described in household measures (cups, spoons, etc). The analysis of the total calories and proteins consumed was done in the Avanutri online food intake analysis program (*Avanutri Equipamentos de Avaliação Ltda, Três Rios, RJ*). Patient's capacity to accomplish their energy and protein recommendations were calculated for each patient based on kilograms of body weight at baseline and end of treatment. Patients were categorized according to meeting or not meeting the dietitian energy recommendations intake of ≥ 30 kcal/kg/day; and meeting or not meeting the dietitian protein recommendations intake of ≥ 1.5 g/kg/day.

Factors related to adherence

Demographics characteristics, clinical characteristics and place of residence were compared between adherent and non-adherent group.

For place of residence, we calculated the distance in kilometers between patient's home and the hospital where treatment was being delivered. Also, we performed an exploratory analysis of the spatial distribution of patients, using a thematic map prepared by the proportional geometric figure method, with QGIS 3.12 software (Open Source Geospatial Foundation). We extracted the Municipal Human Development Index (MHDI) for the neighborhood or city (whatever was available) from the patient's address. The MHDI is an important indicator that evaluates well-being from three dimensions: income, health and education [26].

Statistical analyses

Comparisons between groups were conducted using Chi-square test, t test and Mann-Whitney test. The risk factors for significant weight loss were analyzed using logistic regression models. All covariates that reached 20% level of significance in the univariate regression model were considered for the final model. We used Kaplan-Meier procedure to estimate the distribution of time to death and log rank tests for the difference in survival time. Significance level was set at $p < 0.05$. All data were analyzed using Stata 12 statistical software.

RESULTS

The cohort consisted of 317 head and neck patients. Less than half of patients (n = 145, 45.7%) were considered adherent to the weekly nutritional protocol. The average number of contacts with the dietitian during radiotherapy was 6.2 ± 1.1 for the adherent group and 2.5 ± 1.4 for the non-adherent group, $p < 0.01$.

Median age was not statistically different between the adherent (median=60; IQ=53/65) and non-adherent group (median=58; IQ=52/66), $p=0.07$, Mann-Whitney U test). Table 1 presents the baseline characteristics of the study participants. There was no significant difference between the adherent and non-adherent group. A majority were male, white and had less education. Most patients had oral cavity cancer, received radio-chemotherapy and had normal weight before treatment starts. Moreover, despite more than sixty percent of the study participants having stage IV cancer, they had good performance status (KPS ≥ 70).

Table 1. Participants' characteristics of study sample by dietary adherence status

Patient Characteristics	Adherent group (n=145)		Non-adherent group (n=172)		P ^d
	N	%	N	%	
Sex					.80
Male	118	81.4	138	80.2	
Female	27	18.6	34	19.8	
Race/color					.45
White Caucasian	98	67.6	123	71.5	
Others	47	32.4	49	28.5	
Education^a					.05
Primary school or less education	78	86.7	77	75.5	
Secondary school or higher education	12	13.3	25	24.5	
Tumor site					.91
Oral cavity	65	44.8	79	45.9	
Oropharynx	33	22.8	41	23.9	
Larynx	47	32.4	52	30.2	
Overall Cancer Stage					.76
I/II	17	11.7	22	12.8	
III	28	19.3	38	22.1	
IV	100	69.0	112	65.1	
Treatment modality					.67
Radiotherapy alone	6	4.1	5	2.9	
Adjuvant Radiotherapy	58	40.0	76	44.2	
Radio(chemo)therapy	81	55.9	91	52.9	
BMI					.78
Underweight	23	15.9	24	13.9	
Normal	78	53.8	99	57.6	
Overweight	44	30.3	49	28.5	
KPS^b					.13
≥70	120	94.5	144	98.0	
≤60	7	5.5	3	2.0	
Nutrition support^c					.21
Regular foods	24	23.3	37	34.3	
Oral nutritional supplementation	26	25.2	23	21.3	
Enteral nutrition	53	51.5	48	44.4	

(a) 125 missing values; (b) 43 missing values; (c) 106 missing values; (d) X² test between groups

Mean distance from patient's home to the hospital was not significantly different between adherent and non-adherent group (17.27 ± 9.80 vs 17.34 ± 8.80 km, $p=0.47$) (Figure 1).

There was also no significant difference in the Municipal Human Development Index (MHDI) between adherent and non-adherent group (0,784 vs 0,785, $p=0.88$).

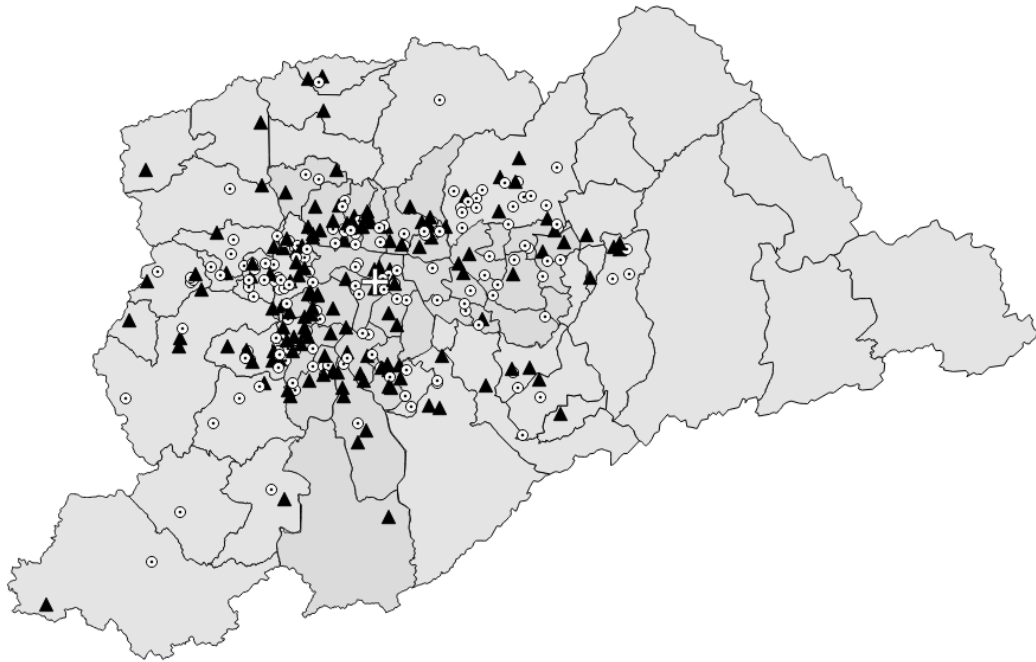


Fig. 1 Place of residence of adherent (white) and non-adherent (black) patients

Mean weight loss of patients from the adherent group was significantly lower than from the non-adherent group ($-3.94\% \pm 6.77$ vs $-6.24\% \pm 7.40$, $p < 0.01$). Patients from the adherent group had less significant weight loss ($\geq 5\%$) during radiotherapy when compared with patients from the non-adherent group - 62 (42.8%) vs 96 (55.8%), $p=0.02$. The mean treatment time was significantly different for adherent (48.8 ± 0.6 days) and non-adherent (51.5 ± 0.7 days) patients ($p < 0.01$).

Twenty-four-hour recall was available for 211 (66.6%) patients at baseline and 237 (74.8%) patients at end of treatment. At baseline and the end of treatment, energy intake was not significantly different between the adherent and non-adherent group. In detail, at baseline mean energy intake was 31.3 ± 11.1 kcal/kg in the adherent group (1818.8 ± 53.8 kcal/day) and 29.2 ± 11.7 kcal/kg (1754.0 ± 59.9 kcal/day) in the non-adherent group ($p=0.19$). At the end of radiotherapy, mean energy intake was 32.0 ± 13.2 kcal/kg in the adherent group (1843.7 ± 60.3 kcal/day) and 32.1 ± 12.3 kcal/kg (1781.0 ± 55.6 kcal/day) in the non-adherent group ($p=0.97$). Protein intake was also not significantly different between the adherent and non-adherent group at baseline (1.34 ± 0.49 g/kg/day vs

1.25±0.53 g/kg/day, $p=0.21$) and end of treatment (1.41±0.62 g/kg/day vs 1.37±0.51 g/kg/day, $p=0.64$).

Moreover, regarding capacity to accomplish dietary recommendations, at the end of treatment, 58.2% vs 59.1% ($p=0.88$) and 41.8% vs 46.9% ($p=0.42$) of adherent and non-adherent patients met the recommended intake for calorie and protein, respectively, with no significant differences between groups.

Furthermore, we did not find significant differences between the two study groups regarding reaching estimated energy needs for patients receiving regular foods or enteral nutrition. However, we found a significant difference for patients receiving oral nutrition supplements support (Figure 2).

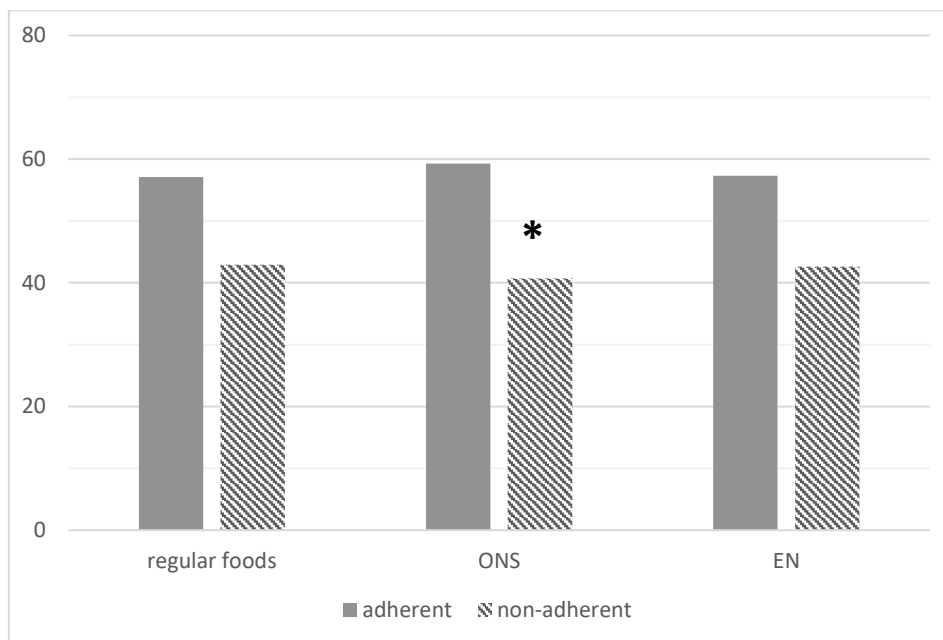


Fig. 2 Patients' capacity to accomplish estimated energy requirement (% of patients) by regular foods ($p=0.08$), oral nutritional supplements - ONS ($p=0.04$) and enteral nutrition - EN ($p=0.58$)

Logistic regression models after adjusting for nutritional and clinical variables including stage, tumor site, treatment, pre-treatment BMI, nutritional support and capacity to accomplish energy and protein recommendations, demonstrated that adherence with the nutritional protocol resulted in 43% (OR 0.57, 95% CI 0.34 - 0.97) protection from significant weight loss (Table 2). Patients receiving adjuvant radiotherapy or chemoradiotherapy had twice the risk for significant weight loss than patients receiving

exclusive radiotherapy (OR 2.01, 95% CI 1.23 – 3.29). Patients receiving oral nutrition had twice the risk for significant weight loss than patients receiving enteral nutrition (OR 2.01, 95% CI 1.15 – 3.50). Patients with stage III/IV had almost three times the risk for significant weight loss than patients with stage I/II (OR 2.89, 95% CI 1.21 – 6.90).

Table 2. Multivariate logistic regression analysis of weight loss in patients with head and neck cancer during radiotherapy

Variable	OR	95% CI	P value
Adherence to weekly review (non-adherent omitted as reference)	0.57	0.34 - 0.97	0.04
BMI (<25 Kg/m ² omitted as reference)	1.61	0.89 – 2.92	0.12
Nutrition support (Tube feeding omitted as reference)	2.01	1.15 – 3.50	<0.01
Age (≥65 years omitted as reference)	0.74	0.44 – 1.27	0.28
Sex (female omitted as reference)	1.07	0.54 – 2.10	0.85
Treatment modality (exclusive RT omitted as reference)	2.01	1.23 – 3.29	<0.01
Tumor site (Larynx omitted as reference)	1.40	0.79– 2.47	0.25
Stage (stage I/II omitted as reference)	2.89	1.21 – 6.90	0.02

The mean follow-up for the cohort was 35.2 (\pm 18.9) months. Overall survival was not different between groups regarding dietary adherence status (Kaplan-Meier curves - Figure 3). Most patients in both groups maintained a good performance status during radiotherapy of head and neck. Meanwhile, two patients from adherent group experience a decreased of functional outcomes (KPS score <70), while four patients from non-adherent group did so.

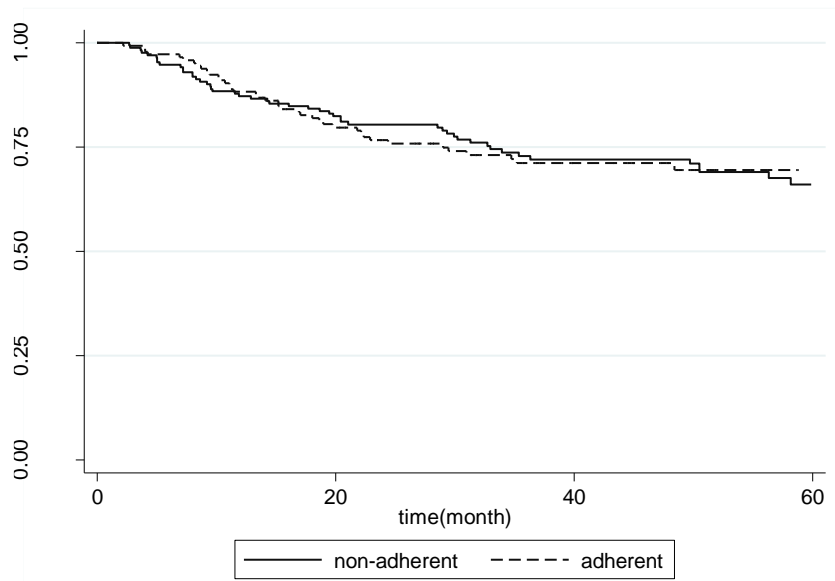


Fig. 3 Kaplan-Meier curves for overall survival for adherent and non-adherent group. Log-rank test ($p=0.97$)

DISCUSSION

Despite being crucial to the success of dietary interventions, adherence is rarely addressed. Our study shows that patients who were adherent to weekly contacts with the dietitian had less weight loss, but not better survival or nutritional intake.

We demonstrated that HNC cancer patients that were adherent to intensive nutritional care had less significantly weight loss. A study performed by Hofto et al. (2018) found that in spite of high adherence to Australian nutritional care guidelines in HNC patients, significant weight loss and malnutrition were still prevalent, but they did not address patient compliance to dietary recommendations at home [12].

Further analyses showed that patients receiving adjuvant radiotherapy or chemoradiotherapy, patients receiving oral nutrition and patients with stage III/IV had more risk for significant weight loss. In the context of limited resources, to provide intensive nutritional care for all patients may be not possible; therefore, the development of new strategies or adaptation of the appropriate service-delivery model is of utmost

importance. For example, the multidisciplinary team could pay more attention to the management of this subset of HNC patients.

We found that, despite adherence to intensive nutrition care, only 58% of patients met their energy requirements and less than half did achieve protein goals. Two retrospective chart review of HNC patients reported similar rates of patients that achieved a total oral diet. They found that the rate of total oral diet achievement was lower in patients who had prior radiation history, among other factors [27-28].

In our study, frequent contact with dietitian did not translate into more nutritional intake, with the exception of patients receiving oral nutrition supplements. However, as we did not access dietary intake during treatment, we cannot make assumptions for nutritional intake during treatment, and the adherent group may have had better nutritional intake through radiotherapy. The less weight loss of the adherent group may be due to a more individualized approach, ensuring an appropriate diet that was able to deal with nutritional impact symptoms [29].

The difficulty in achieving the dietary recommendations also suggests that the counseling approach of dietitians should focus on behaviour change, like motivational interviewing, thereby strengthening commitment and promoting adherence to nutritional intervention [18]. In addition, we need to keep in mind that nutritional interventions undertaken in uncontrolled conditions, i.e., free-living, assume that patients will strictly follow the dietary advice recommended. However, in those conditions, as in our real world-evidence study, cultural, socioeconomic, familiar and personal factors may determine the capacity to accomplish the dietary recommendations [30]. As the hospital provided free ONS and diet for EN until next contact with the dietitian, we assumed that financial issues were not a problem for our patients to have access to those types of nutrition. Understanding reasons for not accomplishing dietary recommendations despite implementation of guidelines recommendation should be an aim of future prospective studies.

In our study, adherence to intensive nutrition care did not have an effect on overall survival or functional outcome. On the other hand, a retrospective study by Kabarriti et al. found that laryngeal and oropharyngeal cancer patients who were compliant with regular diet counseling had 27% (HR 0.73, 95% CI 0.43 – 1.26) protection from death (not significant) and 31% (HR 0.69, 95% CI 0.50 – 0.94) protection for disease progression ($p < 0.05$) [22].

Most studies about weekly reviews with dietitian, although reporting that best practice failed to avoid weight loss, they did not report on adherence to the intervention [13, 15]. We found that only about half of patients were considered adherent to the weekly nutritional protocol. Similarly, on Kabarriti's study, 49% of patients missed > 25% of appointments with the dietitian [22]. However, Hofto et al. in a study to investigate adherence to Australian guidelines, found a higher rate (80%) of adherence [12].

There was no significant difference between the adherent and non-adherent groups in relation to age, gender, race/color, educational level, place of residence, cancer type, staging, type of nutrition (regular foods vs oral supplementation / enteral nutrition) or Karnofsky Performance Status (KPS). We were expecting that non-adherent patients would have less education or poor living conditions [31]. Kabarriti's study also did not find differences between compliant and non-compliant patients, except for disease location [22]. In the intensive care setting, patients' characteristics (as poor prognosis, unstable clinical condition, and other priorities of care) influenced negatively guideline adherence [32]. Hofto et al. reported that the main reason for not being compliant was difficulty in attending scheduled arrangement [12]. Time and logistical difficulty are often reported problems by patients for attending regular clinical consultations [33].

Although a commonly held presumption exists that non-adherent patients are clients who are "non-cooperative" or "unable to follow instructions", it is important to highlight that the involvement of patients in treatment decision-making, i.e., the increased autonomy in patient's health care, recognizes the patient's right to choose whether to follow or not the advice. In this case, activist patients can be mindful to their non-adherence if they disagree with the health care provider treatment regimen, depending on the patients' level of knowledge or medical information about their condition [17]. Thus, this raises questions about what factors drive patients to be non-adherent to intensive nutritional interventions and if some non-adherent patients understand the importance of nutritional management. Some troublesome factors, including tumour and treatment side effects alongside elevated rates of mental health problems, can also affect adherence of HNC patients with nutritional interventions [18]. A study about the relationship between psychological status and compliance in HNC patients, reported that anxiety was the only significant predictor to diet compliance [21]. Understanding the factors associated with adherence may help to improve outcomes by adapting implementation strategies to local circumstances within

different institutions and should be the subject of future scientific inquiry. The use of apps to monitor and evaluate patient adherence to INC, for example, could be a solution [34]. This study has some limitations. First, the current study is limited by its retrospective design, which cannot infer causation or temporal relationship. Furthermore, given that data rely on chart reviews, some variables were not systematically collected. Second, the dietary intake as assessed by 24-hour recall may not be an accurate description of nutritional intake. In addition, as mentioned above, we only accessed nutritional intake in two time points, therefore we cannot make assumptions about nutritional intake during treatment. Third, we did not investigate reasons for patient non-attendance to nutritional reviews. Finally, we did not have data on history of alcohol abuse or smoking.

CONCLUSION

In conclusion, about half of patients were considered adherent to intensive nutrition care and there were no sociodemographic or clinical factors associated with adherence. Adherence to intensive nutritional care resulted in less weight loss, but not better survival, functional outcome or nutritional intake during head and neck radiotherapy. Additional investigation of factors that may act as barriers or enablers to attendance at weekly contact appointments with dietitians and reasons for not meeting nutrition recommendations could help improve the outcomes in this population.

REFERENCES

- [1] Kaderbay A, Atallah I, Fontaine E et al. Malnutrition and refeeding syndrome prevention in head and neck cancer patients: from theory to clinical application. *Eur Arch Otorhinolaryngol* 2018;275:1049–1058.
- [2] Langius JAE, Doornaert P, Spreeuwenberg MD, Langendijk JA, Leemans CR, Schueren MAEvB-dvd. Radiotherapy on the neck nodes predicts severe weight loss in patients with early stage laryngeal cancer. *Radiother Oncol* 2010;97(1):80-5.
- [3] Arribas L, Hurtos L, Taberna M, Peiro I, Vilajosana E, Lozano A, et al. Nutritional changes in patients with locally advanced head and neck cancer during treatment. *Oral Oncol* 2017;71:67-74.
- [4] Kubrak C, Martin L, Gramlich L, Scrimger R, Jha N, Debenham B, et al. Prevalence and prognostic significance of malnutrition in patients with cancers of the head and neck. *Clin Nutr* 2020;39(3):901-909.
- [5] Capuano G, Grosso A, Gentile PC, Battista M, Bianciardi F, Di Palma A, et al. Influence of weight loss on outcomes in patients with head and neck cancer undergoing concomitant chemoradiotherapy. *Head Neck* 2008;30(4):503-8.
- [6] Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. *Clin Nutr* 2017;36(5):1187-96.
- [7] Crowder SL, Douglas KG, Yanina Pepino M, Sarma KP, Arthur AE. Nutrition impact symptoms and associated outcomes in post-chemoradiotherapy head and neck cancer survivors: a systematic review. *J Cancer Surviv* 2018;12(4):479-94.
- [8] Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr* 2017;36(1):11-48.
- [9] Talwar B, Donnelly R, Skelly R, Donaldson M. Nutritional management in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol* 2016;130(S2):S32-s40.
- [10] Isenring EA, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. *Br J Cancer* 2004;91(3):447-52.
- [11] Findlay M, Bauer J, Brown T. Evidence-based practice guidelines for the nutritional management of adult patients with head and neck cancer. [cited 2020 Apr 28]. Available

from: https://wiki.cancer.org.au/australia/COSA:Head_and_neck_cancer_nutrition_guidelines.

[12] Hofto S, Abbott J, Jackson JE, Isenring E. Investigating adherence to Australian nutritional care guidelines in patients with head and neck cancer. *Cancers Head Neck* 2018;3(1):6.

[13] Jeffery E, Young P, Sherriff J. Nutritional outcomes with radiotherapy for head and neck cancer: a before and after comparison of 'best practice guidelines' implementation. *Asia Pac J Clin Nutr* 2018;27(5):955-61.

[14] Kiss NK, Krishnasamy M, Loeliger J, Granados A, Dutu G, Corry J. A dietitian-led clinic for patients receiving (chemo)radiotherapy for head and neck cancer. *Support Care Cancer*. 2012;20(9):2111-20.

[15] Paccagnella A, Morello M, Da Mosto MC, Baruffi C, Marcon ML, Gava A, et al. Early nutritional intervention improves treatment tolerance and outcomes in head and neck cancer patients undergoing concurrent chemoradiotherapy. *Supportive Care Cancer* 2010;18(7):837-45.

[16] Cases MG, Frugé AD, Daniel M. Head and Neck Cancer Adherence to Dietary Recommendations using Theory-Based Tools: Future Research Directions. *J Food Nutr Disor* 2015;4(5):181.

[17] Vahdat S, Hamzehgardeshi L, Hessam S, Hamzehgardeshi Z. Patient involvement in health care decision making: a review. *Iranian Red Crescent medical journal* 2014;16(1):e12454-e.

[18] Beck AK, Britton B, Baker A, Odelli C, Wratten C, Bauer J, et al. Preliminary report: training head and neck cancer dietitians in behaviour change counselling. *Psychooncology* 2017;26(3):405-7.

[19] Verhulst S RLQ. Developing Theory-Based Measurement Tools for Improving Diet Compliance in Head and Neck Cancer Patients. *J Food Nutr Disor* 2015;04(02).

[20] Kubrak C, Olson K, Jha N, Jensen L, McCargar L, Seikaly H, et al. Nutrition impact symptoms: Key determinants of reduced dietary intake, weight loss, and reduced functional capacity of patients with head and neck cancer before treatment. *Head Neck* 2010;32(3):290-300.

[21] McDonough EM, Boyd JH, Varvares MA, Maves MD. Relationship between psychological status and compliance in a sample of patients treated for cancer of the head and neck. *Head Neck* 1996;18(3):269-76.

- [22] Kabarriti R, Bontempo A, Romano M, McGovern KP, Asaro A, Viswanathan S, et al. The impact of dietary regimen compliance on outcomes for HNSCC patients treated with radiation therapy. *Support Care Cancer* 2018;26(9):3307-13.
- [23] World Health Organization- WHO. ICD-10 : international statistical classification of diseases and related health problems : tenth revision. 2nd ed ed. Geneva: World Health Organization; 2004.
- [24] Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, 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 Cancer J Clin* 2017;67(2):93-9.
- [25] World Health Organization- WHO. Obesity: Preventing and managing the Global Epidemic. Geneva: World Health Organization - WHO; 2000.
- [26] PNUD Brasil. Atlas do Desenvolvimento Humano no Brasil [cited 2020 March 13]. Available from: <http://www.atlasbrasil.org.br/2013/pt/consulta/>.
- [27] Kansara S, Wang T, Koochakzadeh S, Liou NE, Graboyes EM, Skoner JM et al. Prognostic factors associated with achieving total oral diet following osteocutaneous microvascular free tissue transfer reconstruction of the oral cavity. *Oral Oncol* 2019; 98:1-7.
- [28] Chen DW, Wang T, Ni JSS, Sandulache VC, Graboyes EM, Worley M et al. Prognostic factors associated with achieving total oral diet after glossectomy with microvascular free tissue transfer reconstruction. *Oral Oncol* 2019; 92: 59-66.
- [29] Volpe S, Marvaso G, Alterio D, Ciardo D, Sabbatini A, Zagallo E, et al. Nutritional Intervention for Nonsurgical Head and Neck Cancer Patients Treated with Radiation Therapy: Results from a Prospective Stepped-Wedge Clinical Protocol. *Nutr Cancer* 2018;70(7):1051-9.
- [30] Beck AK, Baker A, Britton B, Wratten C, Bauer J, Wolfenden L, et al. Fidelity considerations in translational research: Eating As Treatment — a stepped wedge, randomised controlled trial of a dietitian delivered behaviour change counselling intervention for head and neck cancer patients undergoing radiotherapy. *Trials* 2015;16(1):465.
- [31] Mathes T, Jaschinski T, Pieper D. Adherence influencing factors – a systematic review of systematic reviews. *Archives of Public Health* 2014;72(1):37.

- [32] Cahill NE, Suurdt J, Ouellette-Kuntz H, Heyland DK. Understanding Adherence to Guidelines in the Intensive Care Unit. *JPEN J Parenter Enteral Nutr* 2010;34(6):616-24.
- [33] McCarter K, Baker AL, Britton B, Beck AK, Carter G, Bauer J, et al. Effectiveness of clinical practice change strategies in improving dietitian care for head and neck cancer patients according to evidence-based clinical guidelines: a stepped-wedge, randomized controlled trial. *Transl Behav Med* 2018;8(2):166-74.
- [34]. Chen J, Gemming L, Hanning R, Allman-Farinelli M. Smartphone apps and the nutrition care process: Current perspectives and future considerations. *Patient Educ Couns*. 2018;101(4):750-7. <https://doi.org/10.1016/j.pec.2017.11.011>

7. EVIDÊNCIA SOBRE O ESTUDO DA ADESÃO A INTERVENÇÃO NUTRICIONAL ORAL EM PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO

Este capítulo apresenta o artigo "*Adherence to nutritional interventions in head and neck cancer patients: a systematic scoping review of the literature*" de autoria de Sheilla de Oliveira Faria, Renata Alvim Moravia, Doris Howell e Jose Eluf Neto. O artigo foi aceito e será publicado na revista *Journal of Human Nutrition and Dietetics*.

Para citação: Faria SO, Moravia RA, Howell D, Faria RO, Eluf Neto J. Adherence to nutritional interventions in head and neck cancer patients: a systematic scoping review of the literature. *J Hum Nutr Diet*. In preparation.

Adherence to nutritional interventions in head and neck cancer patients: a systematic scoping review of the literature

Sheilla de Oliveira Faria^a, Renata Alvim Moravia^b, Doris Howell^c and Jose Eluf-Neto^d

Affiliations:

^a Departamento de Medicina Preventiva, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil; Princess Margaret Cancer Centre Research Institute, Toronto, Ontario, Canada; Lawrence S. Bloomberg Faculty of Nursing, University of Toronto, Toronto, Ontario, Canada. sheila.faria@usp.br

^b Departamento de Nutrição, Instituto do Câncer do Estado de São Paulo (ICESP), Hospital das Clinicas HCFMUSP, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil. Renata.alvim@hc.fm.usp.br

^c Princess Margaret Cancer Centre Research Institute, Toronto, Ontario, Canada; Lawrence S. Bloomberg Faculty of Nursing, University of Toronto, Toronto, Ontario, Canada. Doris.Howell@uhn.ca

^d Departamento de Medicina Preventiva, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil. jelufnet@usp.br

Correspondence: Sheilla de Oliveira Faria; Departamento de Medicina Preventiva, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil, Av. Dr Arnaldo, 455 2ºandar, São Paulo, 01246-903, Brazil, 55 11 3061-8278, shefaria@hotmail.com

ABSTRACT

Background: Dietary counseling provided by a dietitian, with or without oral nutritional supplements, can impact on nutritional and clinical outcomes in head and neck cancer (HNC) patients undergoing radiotherapy. However, little is known about the role of adherence to oral nutritional interventions in this population. This review aimed to map the literature for evidence of adherence to oral nutritional interventions in HNC patients undergoing radiotherapy and to identify gaps in knowledge in this field. **Methods:** Scoping review methodology was used to identify studies, extract data, collate and summarise results. We searched Medline, Embase, Cochrane Central, CINAHL, from the earliest available time to 8 January 2020. **Results:** A total of 2,315 unique articles were identified, 163 studies were assessed in full, and 9 were included in the scoping review. Use of different measures to assess adherence and variability in the timing of the assessments was noted across studies. Despite identifying studies that have measured adherence to oral nutritional interventions, very few studies monitored its influence on clinical and nutritional outcomes in head and neck cancer patients or reported factors related to adherence. **Conclusions:** A robust evidence base is lacking for adherence to oral nutritional intervention in head and neck cancer patients. Overall, further studies evaluating the impact of oral nutritional interventions in head and neck cancer patients undergoing radiotherapy should measure adherence to the intervention. Early recognition of non-adherence and the contributing factors could ensure intensification of nutritional support and better health outcomes.

INTRODUCTION

Worldwide, the global incidence of head and neck cancer (HNC) patients is growing. GLOBOCAN estimates more than 1.2 million new cases of head and neck cancer will be diagnosed and about 680 thousand deaths are anticipated worldwide in 2040⁽¹⁾.

Tumor location and treatment can induce poor nutritional intake and weight loss in HNC patients. Most of them experience symptoms that impact on nutritional status inclusive of mucositis, xerostomia, trismus, dysphagia, dysgeusia, lack of appetite among others^(2,3). Given that undernutrition and weight loss can increase risk of delay in treatment, complications and mortality, nutritional interventions should be encouraged. More important, cancer cachexia, a complex and multifactorial metabolic syndrome, can be partially reversed by nutritional interventions⁽⁴⁾. International guidelines support the benefits of nutrition counselling, with or without oral nutritional supplements (ONS) for improving nutritional status and quality of life in head and neck cancer patients receiving radiotherapy (RT)⁽⁵⁾.

Nutrition interventions should be comprised of the prescription component and the implementation of that prescription, for example use of ONS, including follow-up and monitoring to ensure adherence. In terms of oral nutritional interventions, adherence can be measured as the proportion of clients achieving the recommended dietary intake, participation in individual counselling or group sessions and regular use of prescribed oral nutritional supplements⁽⁶⁾. The World Health Organization (WHO) describes adherence as the *“the extent to which a person's behaviour - taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider”*⁽⁷⁾.

Monitoring and optimizing adherence with the oral nutritional prescription could maximize the benefits of the nutrition interventions and may have a critical impact on health outcomes. However, adherence is rarely addressed, despite being crucial to the success of dietary interventions⁽⁸⁻¹⁰⁾. Two recent systematic reviews have been conducted to synthesize the effect of nutritional interventions in head and neck cancer patients^(11,12). However, those reviews did not measure adherence to the dietary intervention or determined if the effect on patient health outcomes differed by level of adherence.

While the literature is abundant on studies evaluating the role of oral nutrition interventions in HNC, the lack of attention on adherence to oral nutritional interventions

in this population limits our understanding of the extent of the research in this field. Describing the adherence rates and factors that can influence adherence to oral nutritional interventions in HNC is an important step for developing an evidence base that could be used to improve the care of HNC patients. Exploring and clarifying this issue could increase the awareness of adherence role within nutrition interventions and help to engage discussions regarding changes in the delivery of such interventions. Thus, the aim of this review was to systematically identify and map the research on adherence to oral nutritional interventions in head and neck cancer, as well as to identify existing gaps in knowledge.

MATERIALS AND METHODS

As the purpose of our review was to identify knowledge gaps, identify and map the research on adherence and clarify concepts, we decided to conduct a systematic scoping review of literature instead of a systematic review⁽¹³⁾. We followed the scoping review methods outlined by Arksey and O'Malley⁽¹⁴⁾. The following steps were undertaken: (1) development of the research question, (2) location of relevant publications, (3) screening and selection of publications, (4) data charting, (5) analyzing data, and summarizing and reporting the results. We conducted a search according to an unpublished protocol. We reported this scoping review using the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist⁽¹⁵⁾, and, as such, the protocol is not registered. The reference management software End Note® was used to manage all citations.

Step 1: Development of the research question

This scoping review focused on mapping the literature on adherence to oral nutritional interventions in HNC patients undergoing radiotherapy. The specific aims were to: (a) Identify the types of studies on adherence; (b) Determine the most common methods used to assess adherence; (c) Estimate adherence rates to oral nutritional intervention in this population; (d) Determine periodicity of measuring adherence; (e) Identify the factors that influence adherence (f) Identify if observed outcomes were assessed according to adherence.

Step 2: Location of relevant publications

The search was carried out using four databases (Medline, Embase, Cochrane Central, CINAHL), from the earliest available time to 8 January, 2020. The search was developed for MEDLINE and then adapted for other databases. The search strategy was developed in consultation with a health sciences librarian to ensure an appropriate and thorough search of the literature. Key terms included head and neck neoplasms, nutrition support, dietary counselling and nutrition therapy. The Medline search strategy is presented in the Supporting information, Table S1. We decided not to include adherence terms to our search strategy in order to decrease the chance of missing relevant references. We also included studies in other types of cancer if two-thirds or more of the participants were HNC patients and if data for HNC was provided separately. Reference lists of previous systematic reviews were manually searched for additional articles referring to head and neck cancer. Finally, we included publications addressing any variation of topics related to adherence to oral nutritional intervention in HNC population.

Step 3: Screening and selection of publications

First, SOF screened each reference title for eligibility against the agreed inclusion and exclusion criteria (Table 1). Next, two reviewers (SOF/RAM) screened all included abstracts independently using the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Reference lists of identified studies were evaluated for other relevant sources. Finally, the resulting full text copies of all studies considered to be of potential relevance were retrieved and screened similarly. Disagreement between the reviewers were resolved through discussion.

Table 1 - Summary of eligibility criteria

	Inclusion criteria	Exclusion criteria
Population	Adult patients aged ≥ 18 years Head and neck cancer Received radiotherapy or radio-chemotherapy as the primary treatment	Children Patients with thyroid, esophagus, skin or skull base cancer. Not received radiotherapy or radio-chemotherapy
Intervention	Oral nutrition care	Enteral or Parenteral nutrition
Publication	Full text article in the English Language Any type of quantitative study Any sample size (at least 2/3 HNC)	Language other than English

HNC; Head and Neck Cancer

Step 4: Charting the data

After reading the full article of each study included in the scoping review, two reviewers (SOF, RAM) extracted the data using a standardised form. Data extracted included the following summary data: author (year), country, study type and design, type of HNC included, stage, treatment, sample size, nutrition intervention, definition for adherence, how adherence was measured, adherence rates, periodicity of measuring, factors related to adherence and outcomes. The data charting form was piloted on the first two articles and reviewed to ensure it was clear and comprehensive.

Step 5: Analyzing data, and summarizing and reporting the result

First, the data was extracted based on the general characteristics of the studies as described above (publication date, country of origin, etc.). Second, results were summarized based on the specific objectives: information on adherence measurement

methods, periodicity of measuring adherence, adherence rates, factors related to adherence and outcomes.

RESULTS

Study characteristics

A total of 3,526 studies were retrieved from all sources. Duplicates were removed (n=1,211), yielding 2,315 records for eligibility screening. Titles were screened by SOF resulting in 1,942 records excluded. SOF and RAM screened three hundred and seventy-three abstracts independently with 88.6% inter-reviewer agreement; 163 articles were read in full and assessed for eligibility, and an additional 154 were excluded. Nine studies met our inclusion criteria. The numbers of articles reviewed and retrieved in each stage are shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (Figure 1).

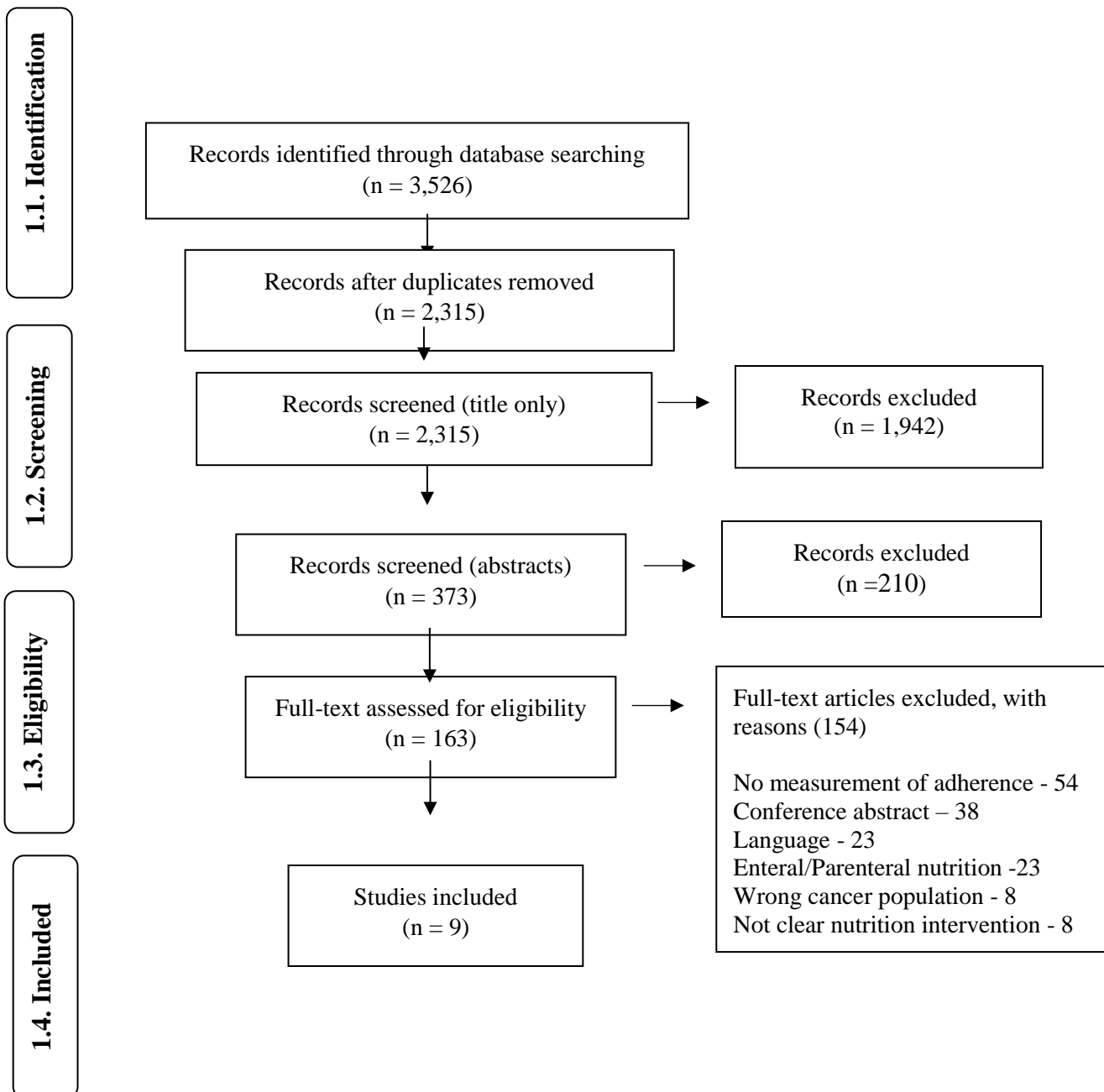


Figure 1 - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram

The studies were published between 1989 and 2018, with 44% ($n = 4$) of the studies published in the last 5 years. Two studies were by researchers from United States, two from Italy, and one from Canada, Turkey, Portugal, Spain and Egypt respectively.

Five studies (56%) were randomized clinical trials⁽¹⁶⁻²⁰⁾. There were three prospective cohort studies⁽²¹⁻²³⁾ and one retrospective cohort study⁽²⁴⁾. In accordance with the scoping

review protocol guiding this review, a summary of the extent, nature and distribution of the studies is presented (Table 2).

Eight hundred and twenty one participants were included in total across all the studies, 316 males, 109 females. Two studies did not specify the sex of the participants^(19, 24). The disease site varied across studies. All studies included patients with cancer stage I-IV, with exception of Valentini et al.⁽²³⁾ which included patients with stage II-IV (Table 2).

Table 2- Detailed summary of included articles

Author, year, location	Study design, sample size, age, sex, disease site and stage, treatment (oncology)	Aim	Description of nutrition intervention and follow-up	Adherence Measurement Methods	Adherence Rates	Periodicity of measuring	Outcomes
Arnold & Richter (1989), USA	Randomized Controlled Trial, sample size: 50, M=29, F=21, ONS n=23/ age 34-88; CG n=27/age 43-80, oral cavity, oropharynx, nasopharynx, hypopharynx, larynx and cervical esophagus, stage I-IV, planned for RT	To investigate the role of nutritional supplements in maintaining nutritional status and the effect on tolerance to therapy and treatment outcome.	ONS + DC 960 or 1080 kcal/day of Sustacal® liquid for 10 days + intensive nutritional counselling Delivered by: no mention Follow-up: patients were seen on a weekly basis. Control group: DC	mean consumption of recommended volume of supplement No mention how it was measured.	Males- 67% of recommended volume Females- 56% of recommended volume	Not specified.	No significant difference between groups in weight loss. Did not analyze outcomes between adherent and non-adherent patients
Cereda et al (2018), Italy	Randomized Controlled Trial, sample size: 159, M=114, F=45, ONS n = 78/age 66.5±14.5; CG n=81/age 63.8±12.7), nasopharynx, oral	To evaluate the effect of ONS consumption on body weight and other predefined outcomes (nutritional parameters, QOL,	ONS +DC 2 bottles/day (250 mL) of a ready-to-use energy-dense, high-protein, omega-3 enriched oral formula	recording with a diary the number of bottles consumed (approximating up to half a bottle)	Mean (SD) - 1.2 (0.6)bottles/day	Daily	Mean change in body weight at the end of RT in the ONS group was significant lower than control group (All patients consuming at least one bottle of ONS were included in safety analysis)

	cavity oropharynx, parotid, hypopharynx, supraglottis, larynx, laterocervical, thyroid, stage I-IV, candidates for RT ±chemotherapy	functional status and tolerance to anti-cancer treatment) during and for 3 months after RT, in HNC patients receiving nutritional counseling as standard of care.	Delivered by: registered dietitian Follow-up: weekly during RT, 1 month and 3 months after the end of RT Control group: DC				
Giles et al (2016), Canada	Prospective cohort study, sample size: 38, M=31, F=7, age 54 (24–79), lip/oral cavity,pharynx, larynx, salivary gland,primary site unknown, stage I-IV, scheduled to receive RT and surgery ±chemotherapy	To compare weight loss of orally fed patients with head and neck cancer consuming greater than or equal to the recommended ESPEN intake for energy (30 kcal/kg/d) and protein (1.2 g/kg/d) with those who were consuming less than the minimum recommended ESPEN intakes during and after treatment.	DC General recommendations based on nutritional issues Delivery by: dietitian Follow-up: after RT, posttreatment (chemo/surgery); 2.5 months after completion of treatment Control group: NA	number of patients achieving ≥ 30 kcal/kg/d (energy) and 1.2 g/kg/d (protein), - 3-day diet records	For energy: 32% (posttreat) and 50% (follow-up) For protein: 29% (posttreat) and 71% (follow-up)	Twice (Posttreatment and follow-up)	Mean percentage of weight loss patterns were similar between adherent and non-adherent at posttreatment and follow-up

Bicakli et al (2017), Turkey	Prospective cohort study, sample size: 59, M=47, F= 12, age 61.0±13.8, larynx-hypopharynx, oral cavity, Nasopharynx, paranasal sinus, oropharynx, other, stage I-IV, referred to RT (± Surgery ±chemotherapy).	To evaluate the effect of compliance with individual dietary counselling provided by the dietitian on body composition and anthropometry in HNC patients under RT.	<p>DC + ONS</p> <p>nutritional counselling during RT or CRT</p> <p>Oral hypercaloric/protein nutritional supplements (no mention if powder or bottle or volume prescribed)</p> <p>Follow-up: before, in the middle of, and at the end of RT with approximately two-week intervals.</p> <p>Delivered by: the same dietitian</p> <p>Control group: NA</p>	number of patients consumed ≥75% of the recommended energy and protein; number of patients that consumed regularly the ONS; food consumption from three-day food recall (diary)	38% met ≥75% of the recommended energy and protein; 55.4% consumed regularly ONS	Once (middle of the treatment)	No significant change was noted in anthropometric values over the time in compliant patients, whereas in noncompliant patients all these indices decreased significantly (p < 0.001).
Kabarriti et al (2018), USA	Retrospective cohort study, sample size: 352, age 61, sex unknown, oropharynx, larynx, stage I-IV, before definitive RT	To examine the association of nutritional counseling and	<p>DC + ONS</p> <p>Nutritional counseling ONS – homemade or commercial supplements of at least 1.5kcal/ml</p> <p>Follow up: during treatment(weekly)</p>	not canceled > 25% of their appointments, accepted nutritional counseling, or followed recommendations as	51% went to ≥ 75% of appointments, 96 % accepted nutritional counselling, 84% followed	Weekly	Compliance led to a 31% (HR 0.69, 95% CI 0.50, 0.94) protection in disease progression, but not resulted in protection from death (HR 0.73, 95%CI 0.43, 1.26). Non-compliant - significantly longer treatment durations than

		compliance with overall survival (OS) and progression-free survival (PFS).	Delivered by: registered dietitian Control group: NA	documented in dietitian's note.	recommendations		compliant participants (26.5 vs 14.8%, P=0.03).
Ravasco et al (2005), Portugal	Randomized Controlled Trial, sample size: 75, M=60, F=15, age 36-79, (DC=25, ONS=25, CG=25), base of the tongue, nasopharynx, oropharynx, and larynx, stage I-IV, referred for preoperative RT, having been previously treated with chemotherapy	To investigate whether, and to what extent, dietary counseling or oral nutrition commercial supplements during RT affected oral intake.	Group 1 (DC) Therapeutic diet that used regular foods Group 2 (ONS) High-protein, energy-dense liquid polymeric formulations (two cans 200ml/ day) Delivered by: no mention Follow up: end of RT and 3 months Control group: Ad Libitum intake	Compliance with dietary recommendations; sequential 24-hour recall evaluations (2 weekdays and 1 weekend day) ONS: supplement consumption record kept by patients and verified by a caretaker/ relative	All patients in group 1 still complied with dietary recommendations (maintained their energy and protein intake)	Weekly (For ONS - Daily)	Group 1: 8 of 16 malnourished patients at baseline improved their nutritional status, None of the patients in groups 2 and 3 improved their nutritional status. Incidence of symptoms was not different between groups (p < .08). All group 1 patients maintained or improved their overall QOL
Valentini et al (2012), Italy	Prospective cohort study, sample size:21, M=18, F=3, age 56.1 ±9.9, pharynx, larynx,	To determine the frequency of CRT-related toxicity in	DC + ONS individualized dietetic DC in the form of regular and intensive nutrition counselling	Number of patients consuming the prescribed diet for 6days/week, 4	19 (90.4%)- 6 days/week 1(4.7%) 4 days/week	Weekly	Mean (SD) weight changed significantly over time (P < 0.001). They did not analyze outcomes between adherent and non-adherent patients

	stage II-IV, referred for CRT	patients with head and neck cancer undergoing CRT and receiving NC associated with ONS, as well as to measure energy and protein intakes, nutritional status and body composition.	A weekly supply of powder ONS (Protifar®) for up to 3 months Follow up: the first 4 days of RT and weekly during RT Delivered by: dietitian Control group: NA	days/week and <3days/week; diary (means of 3day diet diaries) No mention for adherence to ONS	1(4.7%) <3 days		
Macia et al (1991), Spain	Randomized Controlled Trial, sample size: 44, age unknown, sex unknown, (DC=13, CG=31), pharynx, larynx, oral cavity, parotid gland, stage not specified, referred for RT	To detect malnutrition at an early stage and investigate the efficiency of special oral diets suited for each case.	DC oral and written instructions, individually) Follow up: beginning and the end of RT Delivered by: by the same two doctor from the Nutrition and Dietetic Unit Control group: Ad Libitum intake	Compliance with dietary recommendations No mention how it was measured.	100% of patients belonging to experimental group followed the instructions correctly	Not specified	Patients from DC group had less declined at anthropometric parameters.

Nayel et al (1992), Egypt	Randomized Controlled Trial, sample size: 23(ONS=11, CG=12), age 29-79, M= 17, F=6, supraglottic, nasopharyngeal, tonsillar, oropharyngeal, oral cavity, stage not specified, referred for RT (± Surgery)	To access the frequency of nutritional consequences of tumors of the head and neck before and during radiotherapy. To study the impact of nutritional supplementation in patients with head and neck cancer treated with radiotherapy on treatment delay and mucosal reaction	<p>ONS</p> <p>High protein nutritional powder (Ensure®) - prescribed individually</p> <p>Follow up: beginning of RT and weekly for 6 weeks (during RT)</p> <p>Delivered by: no mention</p> <p>Control group: No ONS</p>	Record the amount of ONS actually taken and any side effect that may be attribute to ONS	No patient experienced symptoms related to ONS	Not specified	Patients from ONS group experienced an increase in body weight and in triceps skinfold
---------------------------	---	---	--	--	--	---------------	--

M- male; F- Female; CG – Control Group; DC -Dietary counselling; ONS -Oral Nutritional Supplements ; QOL- quality of life; RT- Radiotherapy;CRT- Chemoradioterapy

Methods for measuring adherence

The definitions for adherence were diverse and heterogeneous between studies. The most commonly used method to assess adherence (n=6) included self-reported consumption (use of a diary).

Most studies (n=5, 56%) defined adherence as compliance with dietary recommendations, either as a minimum calorie/protein requirement^(21, 22) or with no defined range of intake^(18, 19, 23).

In general, 3 out of 5 studies measuring the adherence of ONS defined adherence as the number of patients consuming ONS on a regular basis, as recommended by the study protocol^(18, 20, 22), with the exception of Cereda et al., who defined adherence as the number of bottles consumed⁽¹⁷⁾ and Arnold & Richter, who defined adherence as mean consumption of recommended volume of supplement⁽¹⁶⁾.

Finally, one study defined adherence as the number of patients that canceled < 25% of their appointments with the dietitian, accepted nutritional counselling, or followed recommendations as documented in the dietitian's note⁽²⁴⁾.

Adherence Rates

Four studies measuring the adherence of dietary counselling, reported variability in adherence rates, with rates ranging from 32% to 100%^(19, 21-23). Adherence rates were lowest post-treatment (at completion of RT), and increased at follow-up (2.5 months after completion of treatment)⁽²¹⁾.

Bicakli et al. reported that 55.4% of patients regularly consumed ONS⁽²²⁾. Additionally, one study suggested that male individuals had better adherence to consumption of ONS than females.⁽¹⁶⁾

Kabarriti et al. reported that 62.6% of patients were adherent with the nutritional program. The distribution for reasons patients were scored adherent were as follows: 51% attended appointments, 96 % accepted nutritional counselling, 84% followed the dietary prescription⁽²⁴⁾.

Three of the studies reviewed did not provide quantitative data on the adherence rates to oral nutritional intervention.

Periodicity of Monitoring Adherence

The frequency of monitoring adherence was heterogeneous across studies. In general (n=4), the frequency was monitored daily or weekly^(17, 18, 23, 24). Giles et al. performed two single measurements, one at the end of treatment and one at follow-up⁽²¹⁾, while Bicakli et al. performed one single measurement in the middle of treatment⁽²²⁾. Three studies did not specify the periodicity of measuring adherence^(16, 19, 20). No study evaluated if follow-ups had an impact on adherence.

Factors that influence adherence

Most studies (n=7, 77.8%) did not assess factors related to adherence^(16-21, 23).

Bicakli et al. reported that nature of living conditions of the patients during RT had an impact on energy intake⁽²²⁾. Additionally, they reported reasons for non-consumption of ONS, as loss of appetite, nausea & diarrhoea (50%); personal reasons (bad taste, not believing the importance of it) (17.8%) or pain during swallowing (17.8%).

Kabarriti et al. reported that oropharynx patients were at higher risk for non-adherence than larynx cancer patients. They did not find any other demographic or clinical difference between adherent and non-adherent patients⁽²⁴⁾.

Outcomes

Four studies did not analyze the difference in outcomes between adherent and non-adherent patients^(16, 19, 20, 23). Similarly, Cereda et al. did not examine the impact of adherence and non-adherence on outcomes, but included only patients consuming at least one bottle of ONS in their safety analysis to compare outcomes with a control group⁽¹⁷⁾.

Two studies reported that adherent patients had less weight loss than non-adherent patients^(18, 22). However, Giles et al. found that the mean percentage of weight loss patterns were similar between adherent and non-adherent patients at posttreatment and follow-up⁽²¹⁾.

Adherence to the nutrition intervention led to a 31% (HR 0.69, 95% CI 0.50, 0.94) protection in disease progression, but did not result in protection from death (HR 0.73, 95% CI 0.43, 1.26)⁽²⁴⁾.

DISCUSSION

The purpose of this scoping review was to map the research that has examined adherence to oral nutritional interventions in head and neck cancer, as well as to identify existing gaps in knowledge. To the best of our knowledge, this study represents the first scoping review addressing this issue in HNC patients, providing researchers and clinicians with a summary of what is currently known in this field of research.

The adherence rates were variable among included studies. First, there were heterogeneous definitions of adherence to nutritional interventions. Some studies defined it as compliance with dietary recommendations but did not specify how it was measured (minimum or range of recommended intake). For adherence to ONS, while some measured proportion of patients that consumed ONS on a regular basis, as recommended by study protocol, one study defined adherence as the number of bottles consumed.

In addition, variability in timing of the assessments may also explain variation in rates of adherence. There is no ideal periodicity of measurement, since adherence is a dynamic behavior⁽²⁵⁾. The best time to assess and monitor adherence would be when it is possible to allow adjustments in the delivery of interventions to improve adherence⁽²⁶⁾.

Not surprising, the most commonly used assessment method for adherence was self-report. In other words, dietary or ONS consumption was assumed and not verified. In all studies, few details on the measure used were provided, specifically psychometric quality. Measurement of adherence in clinical nutrition studies are challenging, specifically with outpatients, as they may not report their real intake, either influenced by negligence or by lack of understanding of the importance of surveillance^(25, 27, 28).

Two of three studies that performed analyses comparing adherent to non-adherent patients, reported better outcomes in patients that accomplished the nutrition intervention. Most studies did not examine the impact of adherence and non-adherence on outcomes. A failure in monitoring adherence to interventions could be responsible for negative results from some dietary studies^(6, 10, 29, 30).

Furthermore, factors related to adherence were not addressed in most studies. Other studies reported that patient behaviors and different characteristics including educational level, financial and clinical characteristics may influence the ability to adhere to oral nutritional interventions⁽³⁰⁾. A number of factors such as flavour, smell, viscosity, form, tolerance and volume, have been identified as predominant elements influencing

adherence with ONS in general cancer population^(18, 31, 32). In addition, satisfaction with nutrition services, adaptation to patient preferences, dietary surveillance, use of behavioral change techniques by dietitians and engagement of multiprofessional team members may be important factors related with adherence to nutritional interventions^(9, 27, 33-37).

Important findings from this study were the identification of knowledge gaps, which represent areas for future research. Overall, it seems that the limited number of publications assessing adherence and the lack of those providing determinants of adherence to oral nutritional interventions in HNC are important areas for future research. Future efforts should be directed at validation of daily diaries, for example, or development of other specific questionnaires. In addition, future research and clinical efforts like developing technology-based applications (“telehealth”), increasing the periodicity of monitoring, with reinforcement strategies including reminders, should also be a priority. Further, future research should focus on the reasons for non-adherence, so that strategies could be developed and implemented to enhance adherence to nutritional interventions and promoting better outcomes in HNC patients.

Some limitations should be considered. No quantitative synthesis of data was performed, since, by design, a scoping study does not address this issue. In addition, no methodological limitations were placed on the studies included and quality assessment was not undertaken for this study. There is controversy in the literature about whether a quality appraisal should be done in a scoping review⁽¹³⁾. Finally, we did not search grey literature and only studies in English were included.

CONCLUSION

The results of this scoping review highlight the lack of robust evidence about adherence to oral nutritional interventions in head and neck cancer patients. Overall, further studies evaluating the impact of oral nutritional interventions in head and neck cancer patients undergoing radiotherapy should measure adherence to the intervention. Early recognition of non-adherence and the contributing factors could ensure intensification of nutritional support and better health outcomes.

TRANSPARENCY DECLARATION

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported. The reporting of this work is compliant with PRISMA guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68(6):394-424.
2. Kubrak C, Martin L, Gramlich L, Scrimger R, Jha N, Debenham B, et al. Prevalence and prognostic significance of malnutrition in patients with cancers of the head and neck. *Clin Nutr* 2019.
3. Ganzer H, Touger-Decker R, Parrott JS, Murphy BA, Epstein JB, Huhmann MB. Symptom burden in head and neck cancer: impact upon oral energy and protein intake. *Support Care Cancer* 2013;21(2):495-503.
4. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;12(5):489-95.
5. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr* 2017;36(1):11-48.
6. De Van Der Schueren MAE, Laviano A, Blanchard H, Jourdan M, Arends J, Baracos VE. Systematic review and meta-analysis of the evidence for oral nutritional intervention on nutritional and clinical outcomes during chemo(radio)therapy: current evidence and guidance for design of future trials. *Ann Oncol* 2018;29(5):1141-53.
7. E. S. WHO Adherence Meeting Report. Geneva: World Health Organization 2011.
8. Ravasco P. Nutrition in Cancer Patients. *Journal of Clinical Medicine* 2019;8(8):13.
9. Talwar B, Donnelly R, Skelly R, Donaldson M. Nutritional management in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol* 2016;130(S2):S32-s40.

10. Capra S, Bauer J, Davidson W, Ash S. Nutritional Therapy for Cancer-Induced Weight Loss. *Nutr Clin Pract* 2002;17(4):210-3.
11. Langius JAE, Zandbergen MC, Eerenstein SEJ, van Tulder MW, Leemans CR, Kramer MHH, et al. Effect of nutritional interventions on nutritional status, quality of life and mortality in patients with head and neck cancer receiving (chemo)radiotherapy: a systematic review. *Clinical nutrition (Edinburgh, Scotland)* 2013;32(5):671-8.
12. Roussel LM, Micault E, Peyronnet D, Blanchard D, Guarnieri S, Choussy O, et al. Intensive nutritional care for patients treated with radiotherapy in head and neck cancer: a randomized study and meta-analysis. *Eur Arch Otorhinolaryngol* 2017;274(2):977-87.
13. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol* 2018;18(1):143.
14. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *International Journal of Social Research Methodology* 2005;8(1):19-32.
15. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med* 2018;169(7):467-73.
16. Arnold C, Richter MP. The effect of oral nutritional supplements on head and neck cancer. *Int J Radiat Oncol Biol Phys* 1989;16(6):1595-9.
17. Cereda E, Cappello S, Caccialanza R. The use of oral nutritional supplements in patients with head and neck cancer receiving (chemo)radiotherapy. *Clin Nutr* 2014;33(2):370.
18. Ravasco P, Monteiro-Grillo I, Marques Vidal P, Camilo ME. Impact of nutrition on outcome: a prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. *Head Neck* 2005;27(8):659-68.
19. Macia E, Moran J, Santos J, Blanco M, Mahedero G, Salas J. Nutritional evaluation and dietetic care in cancer patients treated with radiotherapy: prospective study. *Nutrition (Burbank, Los Angeles County, Calif.)* 1991;7(3):205-9.
20. Nayel H, el-Ghoneimy E, el-Haddad S. Impact of nutritional supplementation on treatment delay and morbidity in patients with head and neck tumors treated with irradiation. *Nutrition (Burbank, Los Angeles County, Calif.)* 1992;8(1):13-8.

21. Giles KH, Kubrak C, Baracos VE, Olson K, Mazurak VC. Recommended European Society of Parenteral and Enteral Nutrition protein and energy intakes and weight loss in patients with head and neck cancer. *Head Neck* 2016;38(8):1248-57.
22. Hopanci Bicakli D, Ozkaya Akagunduz O, Meseri Dalak R, Esassolak M, Uslu R, Uyar M. The Effects of Compliance with Nutritional Counselling on Body Composition Parameters in Head and Neck Cancer Patients under Radiotherapy. *J Nutr Metab* 2017;2017:7.
23. Valentini V, Marazzi F, Bossola M, Micciche F, Nardone L, Balducci M, et al. Nutritional counselling and oral nutritional supplements in head and neck cancer patients undergoing chemoradiotherapy. *Journal of human nutrition and dietetics : the official journal of the British Dietetic Association* 2012;25(3):201-8.
24. Kabarriti R, Ohri N, Bontempo A, Romano M, Modi C, Viswanathan S, et al. The impact of dietary regimen compliance and sarcopenia in head and neck cancer patients treated with definitive radiation therapy. *International Journal of Radiation Oncology Biology Physics* 2015;93(3 SUPPL. 1):E332-E3.
25. Davidson W, Isenring E, Brown T, Riddle B. Nutritional management of patients with head and neck cancer: Integrating research into practice. *Cancer Forum* 2006;30(3):183-7.
26. Ravasco P, Monteiro-Grillo I, Camilo ME. Does nutrition influence quality of life in cancer patients undergoing radiotherapy? *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2003;67(2):213-20.
27. Isenring EA, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. *Br J Cancer* 2004;91(3):447-52.
28. Cabrera AG, Sanz-Lorente M, Sanz-Valero J, Lopez-Pintor E. Compliance and adherence to enteral nutrition treatment in adults: A systematic review. *Nutrients* 2019;11(11):2627.
29. Balstad TR, Solheim TS, Strasser F, Kaasa S, Bye A. Dietary treatment of weight loss in patients with advanced cancer and cachexia: A systematic literature review. *Crit Rev Oncol Hematol* 2014;91(2):210-21.
30. Jeffery E, Young P, Sherriff J. Nutritional outcomes with radiotherapy for head and neck cancer: a before and after comparison of 'best practice guidelines' implementation. *Asia Pac J Clin Nutr* 2018;27(5):955-61.

31. Chitapanarux I, Pisprasert V, Tharavichitkul E, Jakrabhandu S, Klunklin P, Onchan W, et al. Randomized study of nutritional status and treatment toxicities of oral arginine, glutamine, and omega-3 fatty acids during concurrent chemoradiotherapy for head and neck cancer patients. *Functional foods in health and disease* 2016;6(3):121-32.
32. Hubbard GP, Elia M, Holdoway A, Stratton RJ. A systematic review of compliance to oral nutritional supplements. *Clin Nutr* 2012;31(3):293-312.
33. Laviano A, Meguid MM. What's new in nutrition therapy for cancer patients. *Med Princ Pract* 2011;20(5):395-6.
34. Dawson ER, Morley SE, Robertson AG, Soutar DS. Increasing dietary supervision can reduce weight loss in oral cancer patients. *Nutr Cancer* 2001;41(1/2):70-4.
35. Bozzetti F. Nutritional support of the oncology patient. *Crit Rev Oncol Hematol* 2013;87(2):172-200.
36. Jin T, Li KX, Li PJ, Huang S, Chen XZ, Chen M, et al. An evaluation of nutrition intervention during radiation therapy in patients with locoregionally advanced nasopharyngeal carcinoma. *Oncotarget* 2017;8(48):83723-33.
37. Hopkinson J. Psychosocial Support in Cancer Cachexia Syndrome: The Evidence for Supported Self-Management of Eating Problems during Radiotherapy or Chemotherapy Treatment. *Asia-Pacific journal of oncology nursing* 2018;5(4):358-68.

TS1 -Medline search strategy

1	"head and neck neoplasms"/ or "squamous cell carcinoma of head and neck"/ or exp mouth neoplasms/ or exp otorhinolaryngologic neoplasms/ or parathyroid neoplasms/ or tracheal neoplasms/
2	((head or neck or otorhinolaryngologic or parathyroid or oral or mouth or pharyn* or laryn* or hypopharyn* or oropharyn* or tracheal or tongue or ear or nose) adj3 (neoplasm* or tumor* or tumour* or cancer or carcinoma or malignan* or squamous cell carcinoma)).tw,kf.
3	1 or 2
4	Nutritional Support/
5	Nutrition Therapy/
6	((nutrition* or dietary or dietetic* or diet*) adj3 (therap* or support* or counseling or counselling or advice or recommendation or prescription or care or supplement* or intervention*)).tw,kf.
7	(oral adj2 supplement*).tw,kf.
8	4 or 5 or 6 or 7
9	3 and 8

8. EFEITO DA ADESÃO APÓS A IMPLEMENTAÇÃO DE PROTOCOLO DE ATENDIMENTO NUTRICIONAL INTENSIVO NA QUALIDADE DE VIDA E NO ESTADO NUTRICIONAL DE PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO

Este capítulo apresenta o artigo “*Clinically significant changes in health-related quality of life in head and neck cancer patients following intensive nutritional care during radiotherapy*” de autoria de Sheilla de Oliveira Faria, Grazielle Aparecida Simões Lima, André Lopes Carvalho, Gustavo Nader Marta, Doris Howell e Jose Eluf Neto. O artigo será submetido a publicação em revista indexada.

Para citação: Faria SO, Lima GAS, Carvalho AL, Marta GN, Howell D, Eluf Neto J. Clinically significant changes in health-related quality of life in head and neck cancer patients following intensive nutritional care during radiotherapy. In preparation.

Clinically significant changes in health-related quality of life in head and neck cancer patients following intensive nutritional care during radiotherapy

Sheilla de Oliveira Faria MS ^{a,b}, Grazielle Aparecida Simões Lima MS^c, André Lopes Carvalho, MD, PhD, MPH^d, Gustavo Nader Marta PhD^e, Doris Howell PhD ^b and Jose Eluf-Neto PhD^a

^a Departamento de Medicina Preventiva, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

^b Princess Margaret Cancer Centre Research Institute, Toronto, Ontario, Canada; Lawrence S. Bloomberg Faculty of Nursing, University of Toronto, Toronto, Ontario, Canada.

^c Departamento de Nutrição, Instituto do Câncer do Estado de São Paulo (ICESP), Hospital das Clinicas HCFMUSP, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil.

^d Head and Neck Surgery, Barretos Cancer Hospital, Barretos, SP, Brazil

^e Department of Radiation Oncology, Hospital Sírio-Libanês, São Paulo, Brazil; Department of Radiology and Oncology, Division of Radiation Oncology, Instituto do Câncer do Estado de São Paulo (ICESP), Hospital das Clinicas HCFMUSP, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

Acknowledgment of grant support: This study was supported in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001.

Correspondence: Sheilla de Oliveira Faria; Departamento de Medicina Preventiva, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil, Av. Dr Arnaldo, 455 2ºandar, Sao Paulo, 01246-903, Brazil, +55 11 3061-8278, sheila.faria@usp.br, <https://orcid.org/0000-0002-6426-932X>

ABSTRACT

Background: This study aimed to explore whether intensive nutritional care during radiotherapy would avoid a meaningful worsening in health-related quality of life in head and neck cancer patients; and whether adherence was associated with better outcomes.

Methods: Observational prospective study with head and neck cancer patients planned for radiotherapy. The main outcome was minimal clinically important difference in health-related quality of life between baseline and 12 weeks (T2). We also evaluated nutritional outcomes and adherence to intensive nutritional care. **Results:** 80 patients were included. Most of them reported stable or improved health-related quality of life in all domains at T2, except for fatigue, pain and senses. Only non-adherent patients had a clinically significant worsening in physical, cognitive and social function and experienced a significant increase in the prevalence of malnutrition. **Conclusion:** Intensive nutritional care may be able to avoid a meaningful worsening in health-related quality of life in head and neck cancer patients. Adherence may result in better outcomes and should be assessed in research and clinical practice.

INTRODUCTION

Head and neck cancer (HNC) is the eighth most common cancer worldwide and one of the most susceptible group of cancer patients to malnutrition^{1,2}. The tumor location increases risk of malnutrition as patients may experience difficulty with swallowing or chewing problems, while the metabolic effects of the tumor, history of alcohol abuse and/or smoking, among other factors may also complicate oral intake³⁻⁵. Treatment toxicities, like mucositis, dysgeusia, trismus, xerostomia, dermatitis, fatigue and pain, and reduced nutritional intake negatively affect patient's weight and health-related quality of life (HRQL)^{1, 6-8}.

HRQL is an important outcome in cancer patients and measures patients' perspectives on physical health, psychological state, independence, and social relationships⁹. Whether statistically significant changes in HRQL measures are meaningful for the patient is unknown and therefore, determining clinically meaningful differences is of utmost importance to evaluate the effect of an intervention^{10, 11}. The minimal clinically important difference (MCID) is defined as "the smallest difference in score which patients perceive as beneficial and which would, therefore, mandate a change in the patient's management"¹². To positively influence HRQL, increase dietary intake and prevent weight loss of HNC patients, guidelines recommend weekly follow-ups by dietitians during radiotherapy (RT)^{13, 14}. Previous studies have shown nutritional interventions play an important role in the maintenance of nutritional status of HNC patients, however, evidence for the effects of nutritional interventions on clinical outcome is inconclusive¹⁵⁻¹⁷. The potential effect of individualized intensive nutritional care (INC) given by a dietician in minimal clinically important difference in HRQL in head and neck patients has not been previously explored.

Therefore, the purpose of this observational prospective study prospective, single arm pilot intervention was to explore whether INC during RT would result in meaningful change in HRQL and nutritional outcomes in head and neck cancer patients. Our hypothesis was that INC during RT would avoid a clinically meaningful worsening in HRQL, reduce deterioration of nutritional status and improve nutritional intake. Our specific aims were to determine whether: (1) INC was associated with a clinically significant change in HRQL; (2) patient demographic, clinical, and nutritional factors were associated with clinically significant change in HRQL; (3) INC was able to enhance nutritional outcomes; and (4) adherence to INC was associated with a clinically significant change in HRQL and better nutritional outcomes.

MATERIALS AND METHODS

This was a single-institution, observational prospective study with all HNC patients planned for RT at *Instituto do Câncer do Estado de Sao Paulo- ICESP*, Brazil, who were recruited between August 2018 and April 2019. The Research Center of *ICESP* (NP 1313/18) and the Committee for Ethics in Research of School of Medicine of the University of Sao Paulo (CEP-FMUSP – CAAE 93676618.0.0000.0065) approved the study. This study proceeded according to the Declaration of Helsinki and all the participants gave their signed consent after being fully informed of the purpose and requirements for the study.

Patient eligibility

We enrolled patients 18 years or older, diagnosed with cancer of the oral cavity, oropharynx or larynx, and planned to received radiotherapy as primary, adjuvant with or

without concomitant chemotherapy. All patients were treated according to the National Comprehensive Cancer Network (NCCN) guideline recommendations¹⁸.

Patients were excluded if they had a previous cancer in any location, or if they were recommended for palliative treatment with no curative therapeutic options or had distant metastases. Patients not able to understand the questionnaires were also excluded.

Nutritional intervention

All patients received nutritional care provided by a dietitian at the beginning of treatment and thereafter on a weekly basis (INC) during radiotherapy, as recommended by guidelines. According to the patient's nutritional status and dietary habits, the dietitian designed a tailored diet plan. The dietitians also provided tips on how to deal with the impact of symptoms on nutrition. Total energy and protein intake were calculated according to the guidelines for patients with cancer¹⁷. Deficiencies were addressed with the use of oral nutritional supplementation (ONS) or enteral nutrition (EN), considering intake and nutritional status. The hospital provided free ONS or EN until the next appointment with dietitian.

As per our institution protocol, all HNC receive INC, we did not have a control group, as it would result in an unethical design. However, we decided to compare adherent patients to INC and non-adherent patients. The participants were classified as adherent (patients who attend $\geq 75\%$ of their appointments with the dietitian) and non-adherent (those who missed $>25\%$ of their appointments with the dietitian).

Data collection

Data including sex, age, race/color, education level, tumour site, staging and type of treatment were collected at baseline from medical records. Clinical stage was

categorized into three groups, stage I/II; stage III; and stage IV¹⁹. Eastern Cooperative Oncology Group (ECOG) Performance Status was used to categorize patients into two groups: good performance status (ECOG 1 or 2) and worse performance status (ECOG 3 or 4).

Nutritional status assessed by Patient Generated–Subjective Global Assessment (PG-SGA) and Body Mass Index (BMI) were measured at baseline (before RT- T1) and 3 months (12 weeks - T2) after the initiation of treatment. Patients were classified as well-nourished (PG-SGA A) or malnourished (PG-SGA B or C)²⁰. BMI was categorized using the World Health Organization criteria: underweight (BMI <18.5kg/m²); normal weight (BMI ≥18.5 kg/m² ≤ 24.9 kg/m²); overweight (BMI ≥25.0kg/m²)²¹. Weight change referred to the percentage weight loss during treatment and was calculated using weight at T1 and T2. Critical weight loss (CWL) was defined as ≥5% weight loss²².

Twenty-four hour food records were collected to assess energy and protein intake. Mean energy (kcal/kg/d) and protein (g/ kg/d) intakes were expressed per kilogram (kg) of body weight. Participants' capacity to accomplish their energy and protein recommendations were calculated for each participant and participants were categorized according to their ability to meet or not the energy recommendations intake of ≥25 kcal/kg/day; and meeting or not meeting the protein recommendations intake of ≥1.0 g/kg/day¹⁷.

Health-Related Quality of Life Assessment

The main outcome was minimal clinically important difference in HRQL. We used the EORTC QLQ-C30 version 3 (European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire version 3.0)²³ plus the EORTC QLQ H&N35 (European Organization for the Research and Treatment of Cancer Quality of

Life Questionnaire-Head and Neck³⁵)²⁴ to measure HRQL. Higher scores on the functional and global health scales indicated better functioning, whereas higher scores on the symptom scales represent more symptomatology.

For the EORTC QLQ-C30, MCID is defined as a difference of 10 points on the 100-point scale²⁵⁻²⁷. There is no MCID defined in literature for EORTC- HN35, therefore we used a distribution-based method to determine MCID for this questionnaire. The MCID was calculated as 0.33 SD, as proposed by Yost et al., who consider this effect size to be an adequate approximation of an MCID - it falls between a small and moderate effect size²⁸. MCID was calculated as follows: Standard Deviations (SD) for the different HRQL domains were extracted for each point of time (T1 e T2) and the MCID was determined to be one third that value.

Statistical analysis

The data were analysed using Stata (version 13.0) and were reported as mean and standard deviation or frequencies and percentages. The mean scores (\pm SD) of the HRQL scales were calculated according to the scoring manual. Participants' HRQL was classified as "improved" or "worsened" if the HRQL score improved or declined, respectively, by more than the MCID, or "stable" otherwise²⁵. The distribution of participants' characteristics by adherence to INC was assessed by using Student's t-test for continuous variables and chi-square test for categorical variables. To illustrate clinically significant changes in HRQL (improved, worsened, and stable) over time by adherence to INC, we performed a heat map analysis. It presents the ratio between the domain changes in HRQL over the course of RT and the corresponding MCID values. On this scale, a ratio ± 1 represents a minimal significant change, a ratio ± 2 , a significant moderate change, and a ratio ± 3 , a significant large change. A ratio between -1 and 1

indicates a nonsignificant clinical change¹⁰. A p-value below 0.05 was considered statistically significant.

RESULTS

Participants Demographics and Clinical Variables

The cohort consisted of 86 head and neck patients. Two (2.3%) participants died and 4 (4.6%) were lost to follow-up and therefore were excluded. Thus, 80 patients were included for analyses. The average number of contacts with the dietitian during RT was 5.0 ± 2.1 (0-8). The subject characteristics at baseline are detailed in Table 1. A majority were male, white and had primary education or less. Most participants had oropharynx cancer, received radio-chemotherapy and had normal weight before treatment started. Moreover, despite more than sixty percent of the study participants having stage IV cancer, they had good performance status (ECOG 1 or 2). Most participants had normal weight by BMI, but were classified as malnourished by the PG-SGA. Most of them received only regular foods.

Table 1. Participants' characteristics of study sample

Participants' characteristics	N	%
Sex		
Male	65	81.2
Female	15	18.8
Race/color		
White Caucasian	49	61.2
Others	31	38.8
Education		
Primary school or less education	67	83.7
Secondary school or higher education	13	16.3
Tumor site		
Oral cavity	25	31.2
Oropharynx	35	43.8
Larynx	20	25.0
Overall Cancer Stage		
I/II	12	15.0
III	16	20.0
IV	52	65.0
Treatment modality		
Radiotherapy alone	15	18.7
Adjuvant radiotherapy	22	27.5
Radio(chemo)therapy	43	53.8
BMI		
Underweight	13	16.2
Normal	50	62.5
Overweight	17	21.3
PG-SGA global rating		
Well nourished (A)	22	27.5
Malnourished (B or C)	58	72.5
ECOG		
1 or 2	63	78.8
2 or 3	17	21.3
Nutrition support		
Regular foods	40	50.0
Oral nutritional supplementation	13	16.2
Enteral nutrition	27	33.8

BMI- Body mass Index; PG-SGA -Patient Generated–Subjective Global Assessment;
 ECOG- Eastern Cooperative Oncology Group (ECOG) Performance Status

Minimal Clinically Important Difference

Mean (SD) quality-of-life dimension's scores for the EORTC QLQ-C30 and the EORTC QLQ H&N35 at baseline (T1) and the number (%) of participants that reported worsened, stable or improved HRQL at T2 are summarised in Table 2. Most participants reported stable or improved HRQL at the T2 in all domains of EORTC-QLQ, except for fatigue and pain. For domains measured by EORTC QLQ H&N35, most participants reported stable or improved HRQL, with the exception of senses.

Table 2- Mean (SD) quality-of-life dimension's scores for the EORTC QLQ-C30 and the EORTC QLQ H&N35 at baseline (T1) and number (%) of participants that reported improved, stable or worsened HRQL at T2.

Items	T1	Worsened N(%)	T2	
	Mean(SD)		Stable N(%)	Improved N(%)
EORTC QLQ-C30				
<i>Function scales</i>				
Global QOL	75.1 ± 20.7	33 (41.2)	28 (35.0)	19 (23.8)
Physical function	73.0 ± 23.6	35 (43.7)	31 (38.8)	14 (17.5)
Role function	52.1 ± 39.4	34 (42.5)	18 (22.5)	28 (35.0)
Emotional function	73.4 ± 27.7	28 (35.0)	39 (48.7)	13(16.3)
Cognitive function	90.6 ± 16.9	29 (36.2)	38 (47.5)	13(16.3)
Social function	84.4 ± 24.3	27 (33.7)	35 (43.8)	18(22.5)
<i>Symptoms scales</i>				
Fatigue	19.6 ± 17.6	47 (58.7)	13 (16.3)	20 (25.0)
Nausea and vomiting	17.9 ± 32.6	11 (13.7)	47 (58.8)	22 (27.5)
Pain	17.3 ± 20.6	41 (51.2)	23 (28.8)	16 (20.0)
Sleep disturbance	30.4 ± 36.3	24 (30.0)	33 (41.3)	23 (28.7)
Dyspnea	15.0 ± 27.5	13 (16.2)	54 (67.5)	13 (16.3)
Appetite	27.8 ± 36.8	19 (23.7)	39 (48.8)	22 (27.5)
Constipation	24.2 ± 37.1	13 (16.2)	47 (58.8)	20 (25.0)
Diarrhea	5.4 ± 18.7	1 (1.2)	73 (91.3)	6(7.5)
Finance	35.8 ± 42.0	22 (27.5)	40 (50.0)	18 (22.5)
EORTC QLQ H&N35				
Pain	15.3 ± 17.7	32 (40.0)	21 (26.2)	27 (33.8)
Swallowing	34.9 ± 36.0	39 (48.7)	28 (35.0)	13 (16.3)
Senses	26.5 ± 36.2	44 (55.0)	18 (22.5)	18 (22.5)
Speech	37.8 ± 33.2	32 (40.0)	26 (32.5)	22 (27.5)
Social eating	45.8 ± 40.9	31 (38.8)	28 (35.0)	21 (26.2)
Social contact	15.0 ± 22.0	32 (40.0)	33 (41.2)	15 (18.8)
Sexuality	44.2 ± 43.7	31 (38.8)	32 (40.0)	17 (21.2)
Teeth	53.3 ± 43.3	30 (37.5)	32 (40.0)	18 (22.5)
Opening mouth	26.2 ± 37.8	18 (22.5)	48 (60.0)	14 (17.5)
Dry mouth	31.2 ± 40.5	36 (45.0)	29 (36.3)	15 (18.7)
Sticky saliva	52.1 ± 42.4	34 (42.5)	31 (38.7)	15 (18.8)
Coughing	29.6 ± 34.8	21 (26.2)	41 (51.3)	18 (22.5)
Feeling ill	15.4 ± 30.0	28 (35.0)	42 (52.5)	10 (12.5)

Further analyses showed that age, sex, education level, tumor site, performance status (ECOG) and nutritional status (BMI) at baseline were not associated with MCID

in HRQL in any of the domains. Clinically significant worsening was associated with participants' characteristics such as nutritional status, race/color, stage, type of treatment and nutrition support. More non-white Caucasian participants than white Caucasian participants reported worsened HRQL in the physical (51.6% vs 38.8%, $p=0.047$), financial (35.5% vs 22.5%, $p<0.01$) and appetite (43.3% vs 12.2%, $p<0.01$) domains. More participants receiving radio-(chemo)therapy reported worsened HRQL in the fatigue and pain (HN35) domains than participants receiving radiotherapy alone or adjuvant radiotherapy: 80.0% vs 51.2% vs 59.1%, $p=0.02$ and 39.5% vs 26.7% vs 50%, $p=0.02$, respectively. More participants with stage IV disease (26.9%) than participants with stage III (18.8%) or stage I/II (8.3%) reported worsening of the 'opening mouth' domain. More participants classified as malnourished by PG-SGA than nourished participants reported worsened HRQL in cognitive (43.1% vs 18.2%, $p=0.02$), sleep disturbance (31.6% vs 27.2%, $p=0.02$), appetite (28.1% vs 13.6%, $p<0.01$), social contact (48.3% vs 18.2%, $p<0.01$) and feeling ill (39.7% vs 22.7%, $p=0.01$) domains. More participants receiving only regular foods reported worsened physical functional than those receiving ONS or EN (55% vs 23% vs 37%, $p=0.04$, respectively).

Nutritional Outcomes

There was a significant decrease for body weight and BMI between T1 and T2 ($p<0.01$). Mean percentage weight loss was $-4.9 \pm 8\%$, and almost half of participants ($n=38$, 47.5%) experienced CWL. A statistically significant difference in mean percentage weight loss was found between type of nutrition support (regular foods= $-8.1 \pm 7.4\%$; ONS = $-3.9 \pm 3.3\%$; EN= $-0.6 \pm 8.4\%$, $p=0.01$) (Figure 1).

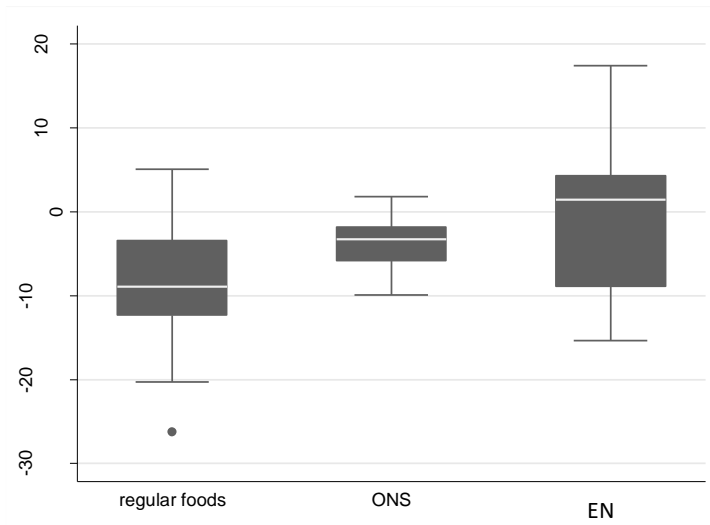


Figure 1- Mean percentage weight loss by type of nutrition intervention. ONS- oral nutritional supplements; EN – enteral nutrition.

According to PG-SGA, the prevalence of malnutrition increased significantly at T2, $p < 0.01$. There was an increase in energy and protein intake during RT, although not significant ($p = 0.08$ and $p = 0.09$, respectively). Regarding the capacity to accomplish dietary recommendations, at the end of treatment, most of the participants met the recommended intake of energy ($n = 53$, 66.3%) and protein ($n = 57$, 71.3%).

Adherence to Intensive Nutritional Care

About half of participants ($n = 43$, 53.7%) were considered adherent to the weekly nutritional protocol. No significant differences were found between the adherent and non-adherent participants regarding any demographic or clinical characteristic at baseline ($p > 0.05$) (Table 3).

Table 3. Participants' characteristics of study sample by dietary adherence status

Participants's Characteristics	Adherent (n=43)		Non-adherent (n=37)		p ^a
	N	%	N	%	
Sex					0.97
Male	35	81.4	30	81.1	
Female	8	18.6	7	18.9	
Race/Color					0.28
White Caucasian	24	55.8	25	67.6	
Others	19	44.2	12	32.4	
Education					0.54
Primary school or less education	35	81.4	32	86.5	
Secondary school or higher education	8	18.6	5	13.5	
Tumor site					0.78
Oral cavity	12	27.9	13	35.1	
Oropharynx	20	46.5	15	40.6	
Larynx	11	25.6	9	24.3	
Overall Cancer Stage					0.14
I/II	5	11.6	7	18.9	
III	12	27.9	4	10.8	
IV	26	60.5	26	70.3	
Treatment modality					0.53
Radiotherapy alone	7	16.3	8	21.6	
Adjuvant radiotherapy	14	32.6	8	21.6	
Radio(chemo)therapy	22	51.1	21	56.8	
BMI					0.99
Underweight	7	16.3	6	16.2	
Normal	27	62.8	23	62.2	
Overweight	9	20.9	8	21.6	
PG-SGA global rating					0.36
Well nourished (A)	10	23.3	12	32.4	
Malnourished (B or C)	33	76.7	25	67.6	
ECOG					0.53
1 or 2	35	81.4	28	75.7	
2 or 3	8	18.6	9	24.3	
Nutrition support					0.46
Regular foods	19	44.2	21	56.8	
Oral nutritional supplementation	7	16.3	6	16.2	
Enteral nutrition	17	39.5	10	27.0	

BMI- Body mass Index; PG-SGA -Patient Generated-Subjective Global Assessment
 ECOG- Eastern Cooperative Oncology Group (ECOG) Performance Status; (a)X² test between groups

We did not find a significant difference between the adherent and non-adherent groups at baseline regarding the mean scores of EORTC QLQ-C30 and EORTC QLQ H&N35, with the exception of swallowing ($p=0.029$) and coughing ($p<0.01$) (Table 4).

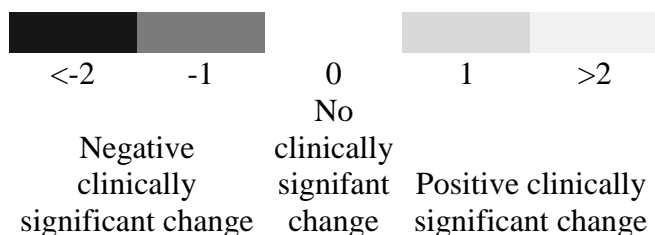
Table 4- Mean (SD) quality-of-life dimension's scores for the EORTC QLQ-C30 and the EORTC QLQ H&N35 by adherence status at baseline (T1)

Items	Adherent (n=43)	Non-adherent (n=37)	P
EORTC QLQ-C30			
<i>Function scales</i>			
Global QOL	76.7(20.6)	73.2(20.9)	0.448
Physical function	72.9 (24.4)	73.1 (23.0)	0.957
Role function	53.1 (38.5)	50.9 (40.8)	0.805
Emotional function	75.8(27.3)	70.7(28.2)	0.419
Cognitive function	88.8 (16.5)	92.8(17.4)	0.291
Social function	82.9(27.3)	86.0(20.6)	0.575
<i>Symptoms scales</i>			
Fatigue	20.4(18.3)	18.6(17.0)	0.652
Nausea and vomiting	13.9(28.1)	22.5(36.9)	0.243
Pain	14.3(18.4)	20.8(22.7)	0.118
Sleep disturbance	27.9(35.6)	33.3(37.4)	0.580
Dyspnea	18.6 (32.0)	10.8 (20.9)	0.208
Appetite	27.9(34.1)	27.8(40.2)	0.830
Constipation	27.9(38.4)	19.8(35.5)	0.334
Diarrhea	5.4(19.1)	5.4(18.4)	0.996
Finance	34.9(41.1)	36.9(43.6)	0.829
EORTC QLQ H&N35			
Pain	13.9 (15.0)	16.9 (20.5)	0.462
Swallowing	43.0(38.4)	25.4(30.9)	0.029
Senses	24.0 (34.0)	29.3(39.0)	0.522
Speech	38.2(33.0)	37.2(34.0)	0.894
Social eating	46.9 (43.2)	44.6 (38.6)	0.803
Social contact	15.2(20.8)	14.8(23.6)	0.933
Sexuality	43.8 (43.3)	44.6 (44.8)	0.936
Teeth	58.1(42.5)	47.7(44.1)	0.287
Opening mouth	27.9(39.1)	24.3(36.5)	0.675
Dry mouth	34.1(40.2)	27.9(41.2)	0.500
Sticky saliva	53.5 (41.2)	50.4(44.2)	0.751
Coughing	41.1(37.0)	16.2(26.8)	<0.01
Feeling ill	14.7(27.5)	16.2(33.0)	0.826

The heat map demonstrates that adherent participants reported nonsignificant clinical change in function scales, while non-adherent participants reported a clinically significant worsening in physical function, cognitive function and social function at T2. Participants reported a clinically significant worsening in most symptom domains at T2, especially non-adherent participants (Table 5).

Table 5- Heat map, representing HRQL change over time to MCID ratio, by adherence.

	Non-Adherent (n=37)	Adherent (n=43)
QLQ C30		
Fatigue	-1.56	-1.37
Cognitive function	-1.42	-0.64
Pain	-1.28	-1.02
Physical function	-1.12	-0.92
Social function	-1.10	-0.88
Emotional function	-0.68	-0.70
Dyspnea	-0.56	0.30
Finance	-0.56	0.05
Role function	-0.40	-0.58
Constipation	0.08	0.96
Appetite	0.21	0.06
Sleep disturbance	0.82	-0.53
Diarrhea	0.88	0.76
Global QOL	0.95	-0.84
Nausea and vomiting	1.07	0.87
QLQ H&N35		
Dry mouth	-1.78	-1.27
Senses	-1.69	-2.00
Teeth	-1.46	-0.40
Sticky saliva	-1.45	-0.79
Feeling ill	-1.37	-1.30
Swallowing	-1.31	-1.10
Coughing	-1.01	0.12
Social contact	-0.63	-1.49
Speech	-0.63	-0.54
Social eating	-0.24	-0.42
Pain	-0.15	-0.39
Opening mouth	0.22	-0.06



According to PG-SGA, the prevalence of malnutrition (PG-SGA B or C) increased significantly in the non-adherent group ($p < 0.01$), but not in the adherent group ($p = 0.18$). Mean percentage weight loss was higher in the non-adherent group ($-6.2 \pm 7.8\%$) in comparison to the adherent group ($-3.8 \pm 8.1\%$), although not statistically significant ($p=0.18$). The proportion of participants that experienced CWL was not different between groups ($p= 0.37$).

Regarding capacity to accomplish dietary recommendations, more participants in the adherent group met the recommended intake of calories compared to the non-adherent group, although this was not statistically significant ($p=0.23$). Furthermore, there was no difference regarding capacity to accomplish protein intake between groups ($p=0.50$).

DISCUSSION

Within oncology, there is an increased interest in defining meaningful patient outcomes after any intervention. This prospective cohort study evaluated whether INC during RT would provide a meaningful change in HRQL and affect nutritional outcomes in HNC patients. Additionally, we sought to analyze whether adherence was related with better outcomes.

To our knowledge, our study was the first to evaluate if INC during RT was associated with MICD in HRQL for HNC patients. In our study, most participants

reported stable or improved HRQL at the T2 in almost all domains. This may imply that INC during RT was able to avoid a meaningful worsening in HRQL in most of HNC patients. On the other hand, response shift (change in internal standards) may also be one reason for these findings. A recent meta-analysis of the effect of INC on HRQL in HNC during RT, reported that regardless of whether the group was control or intervention, global QOL and physical function were maintained²⁹. On the other hand, Cereda et al. reported better HRQL in patients receiving nutrition counselling plus ONS when compared with counselling alone³⁰. Those studies used statistically significant difference to assess HRQL changes. However, a statistically significant difference may be not synonymous with clinically important change and the absence of a statistically significant change does not mean an absence of clinically significant change³¹. Likewise, only reporting the difference in HRQL scores between time points rarely gives the health care professional information that can be useful³²⁻³⁴.

In the same way, despite frequent contact with the dietitian during RT, participants had a significant decrease in weight and BMI and there was a significant increase in malnutrition by PG-SGA at T2. Significant improvement in energy and protein intake was also not significant. This observation is consistent with the findings of Roussel et al. who reported in a recent meta-analysis that there was no significant global combined effect of nutrition on weight change, regardless of patients being in the intervention or control group²⁹. Orell et al. also did not find a difference in CWL between patients that received INC or on-demand nutritional counseling³⁵. Those findings illustrate the challenge of nutritional management in HNC patients during RT and how implementation of best practice does not always translate into better outcomes. There is a need to further identify individual patient risks that increase their vulnerability to CWL and intensity early proactive support to address.

Despite INC, participants in our study classified as malnourished by PG-SGA, non-white Caucasian participants, receiving radio(chemo)therapy, stage IV disease reported worsened QOL in some domains. This may indicate that the dietitian and multiprofessional team should follow this subset of patients closely during the course of RT or maybe have a different approach.

We found that the type of nutrition intervention was related with percentage of weight loss between T1 and T2. Cereda et al. also reported that the use of ONS resulted in better weight maintenance when compared with patient that received only counselling and regular foods³⁰. There is a debate at the literature about whether to use or not prophylactic percutaneous endoscopic gastrostomy (PEG) in HNC patients to increase nutritional intake and avoid weight loss. However, prophylactic PEG complications can be a problem and should be avoid as much as possible.³⁶⁻³⁸ When reviewing nutrition therapy options, it is important that dietitians keep track of outcomes and involve the caregivers in that discussion with the patient.

There is little evidence regarding the effect of adherence to INC on HRQL or nutritional outcomes during RT of HNC³⁹⁻⁴¹. We found that only half of our participants were adherent to INC. There was no difference in any sociodemographic or clinical characteristics between adherent and non-adherent participants at baseline. However, the worse swallowing and coughing problems reported by adherent participants at baseline may explain why they decided to be adherent to the INC, since it may be related to feeding difficulties, and therefore the patient felt the need for closer monitoring by the nutritionist.

Albeit at baseline HRQL and nutritional status were similar between groups, we found that less participants from the adherent group reported worsened HRQL. In the same way, less patients from the adherent group presented deterioration of nutritional status by PG-SGA at 12 weeks. However, despite adherence to intensive nutrition care,

patients experience CWL and had difficulty accomplishing recommended calories and protein intake. This may indicate that the counselling approach needs further intensification or deterioration is unavoidable due to disease and treatment morbidity.⁴²

With the increased participation of patients in decision-making in health, we need to recognize the patient's right to choose whether or not to follow advice⁴³. However, it is important to guide our patients to make better choices as adherence may have a critical impact on research outcomes; and patients may be unaware that self-care actions focused on nutrition can improve their health^{13, 44, 45}. Our findings emphasize the importance of measuring adherence to a nutrition intervention and the need for discussion with the patients at the beginning of treatment, about how their choices about adherence with the INC may impact on their outcomes.

This study has some limitations. First, we did not include a control group with no nutritional intervention. On the other hand, the results of our observational study in real-world cancer care produced valuable insights into INC and its outcomes in daily oncology practice. Second, this study is primarily limited in the sample size and analysis of a larger cohort may lead to results that are more robust. Third, we only evaluated HRQL at two time points thus, future trials with longer follow-up periods should evaluate if patients reported MCID differently through the course of therapy. In addition, we know that risk factors including tobacco smoking and alcohol consumption, may worsen malnutrition, but we did not have data on this subject. The use of effect size to determine MCID may have some limitation, as it may vary widely among samples. Despite these limitations, this study provides useful data about the MCID in HRQL and adherence to INC and may inspire future larger trials.

In conclusion, our study suggests that intensive nutrition care may be able to avoid a meaningful worsening in health-related quality of life in HNC patients. Some patient's

characteristics may contribute to worsening in health-related quality of life despite INC; therefore, this subset of patients should receive more attention during treatment. Adherence may result in better outcomes and clarification of this subject is important to support guidelines for nutritional support in head and neck oncology patients. Our results may help to increase the awareness of the assessment of MCID in HRQL and adherence assessment for research purposes and the importance of integrate such measures in clinical practice.

REFERENCES

1. Pandit P, Patil R, Palwe V, Yasam VR, Nagarkar R. Predictors of Weight Loss in Patients With Head and Neck Cancer Receiving Radiation or Concurrent Chemoradiation Treated at a Tertiary Cancer Center. *Nutr Clin Pract*:6.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68(6):394-424.
3. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;12(5):489-95.
4. Pezdirec M, Strojjan P, Boltezar IH. Swallowing disorders after treatment for head and neck cancer. *Radiology and Oncology* 2019;53(2):225-30.
5. Mulasi U, Vock DM, Jager-Wittenaar H, Teigen L, Kuchnia AJ, Jha G, et al. Nutrition Status and Health-Related Quality of Life Among Outpatients With Advanced Head and Neck Cancer. *Nutr Clin Pract* 2020.
6. Arribas L, Hurtos L, Taberna M, Peiro I, Vilajosana E, Lozano A, et al. Nutritional changes in patients with locally advanced head and neck cancer during treatment. *Oral Oncol* 2017;71:67-74.
7. Sandmæl JA, Sand K, Bye A, Solheim TS, Oldervoll L, Helvik A-S. Nutritional experiences in head and neck cancer patients. *European Journal of Cancer Care* 2019;28(6):e13168.
8. Marta GN, Saad ED. Assessment of quality of life in phase III trials of radiotherapy in localized or locally advanced head and neck cancer over the past 17 years. *Annals of Palliative Medicine* 2017;6(1):73-80.
9. The World Health Organization quality of life assessment (WHOQOL): Position paper from the World Health Organization. *Soc Sci Med* 1995;41(10):1403-9.
10. Binenbaum Y, Amit M, Billan S, Cohen JT, Gil Z. Minimal clinically important differences in quality of life scores of oral cavity and oropharynx cancer patients. *Ann Surg Oncol* 2014;21(8):2773-81.
11. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol* 2003;56(5):395-407.

12. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989;10(4):407-15.
13. Talwar B, Donnelly R, Skelly R, Donaldson M. Nutritional management in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol* 2016;130(S2):S32-s40.
14. Findlay M, Strange E, Bauer J. Maintaining evidence-based guidelines online: Update on nutritional management of patients with head and neck cancer. *Asia Pac J Clin Oncol* 2013;9(SUPPL. 3):70.
15. Langius JAE, Zandbergen MC, Eerenstein SEJ, van Tulder MW, Leemans CR, Kramer MHH, et al. Effect of nutritional interventions on nutritional status, quality of life and mortality in patients with head and neck cancer receiving (chemo)radiotherapy: a systematic review. *Clinical nutrition (Edinburgh, Scotland)* 2013;32(5):671-8.
16. Kristensen MB, Isenring E, Brown B. Nutrition and swallowing therapy strategies for patients with head and neck cancer. *Nutrition* 2020;69:110548.
17. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr* 2017;36(1):11-48.
18. Network NCC. NCCN Guidelines - Head and Neck Cancers 2020 [updated June 9, 2020. version 2:[Available from: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf.
19. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, 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 Cancer J Clin* 2017;67(2):93-9.
20. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. *Nutrition* 1996;12(1 Suppl):S15-9.
21. WHO WHO-. Obesity: Preventing and managing the Global Epidemic. Geneva: World Health Organization - WHO; 2000.
22. White JV, Guenter P, Jensen G, Malone A, Schofield M, Group AMW, et al. Consensus Statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition. *Journal of Parenteral and Enteral Nutrition* 2012;36(3):275-83.
23. Bjordal K, Ahlner-Elmqvist M, Tolleson E, Jensen AB, Razavi D, Maher EJ, et al. Development of a European Organization for Research and Treatment of Cancer

(EORTC) questionnaire module to be used in quality of life assessments in head and neck cancer patients. EORTC Quality of Life Study Group. *Acta Oncol* 1994;33(8):879-85.

24. Bjordal K, Hammerlid E, Ahlner-Elmqvist M, de Graeff A, Boysen M, Evensen JF, et al. Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35. *J Clin Oncol* 1999;17(3):1008-19.

25. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998;16(1):139-44.

26. Maringwa JT, Quinten C, King M, Ringash J, Osoba D, Coens C, et al. Minimal important differences for interpreting health-related quality of life scores from the EORTC QLQ-C30 in lung cancer patients participating in randomized controlled trials. *Support Care Cancer* 2011;19(11):1753-60.

27. Musoro JZ, Coens C, Singer S, Tribius S, Oosting SF, Groenvold M, et al. Minimally important differences for interpreting European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 scores in patients with head and neck cancer. *Head Neck* 2020;42(11):3141-52.

28. Yost KJ, Eton DT. Combining distribution- and anchor-based approaches to determine minimally important differences: the FACIT experience. *Eval Health Prof* 2005;28(2):172-91.

29. Roussel LM, Micault E, Peyronnet D, Blanchard D, Guarnieri S, Choussy O, et al. Intensive nutritional care for patients treated with radiotherapy in head and neck cancer: a randomized study and meta-analysis. *Eur Arch Otorhinolaryngol* 2017;274(2):977-87.

30. Cereda E, Cappello S, Colombo S, Klersy C, Imarisio I, Turri A, et al. Nutritional counseling with or without systematic use of oral nutritional supplements in head and neck cancer patients undergoing radiotherapy. *Radiother Oncol* 2018;126(1):81-8.

31. Funk GF, Karnell LH, Smith RB, Christensen AJ. Clinical Significance of Health Status Assessment Measures in Head and Neck Cancer: What Do Quality-of-Life Scores Mean? *Archives of Otolaryngology–Head & Neck Surgery* 2004;130(7):825-9.

32. Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA. Interpreting clinically significant changes in patient-reported outcomes. *Cancer* 2007;110(1):196-202.

33. Hong F, Bosco JL, Bush N, Berry DL. Patient self-appraisal of change and minimal clinically important difference on the European organization for the research and

treatment of cancer quality of life questionnaire core 30 before and during cancer therapy. *BMC Cancer* 2013;13:165.

34. Vartanian JG, Rogers SN, Kowalski LP. How to evaluate and assess quality of life issues in head and neck cancer patients. *Curr Opin Oncol* 2017;29(3):159-65.

35. Orell H, Schwab U, Saarilahti K, Österlund P, Ravasco P, Mäkitie A. Nutritional Counseling for Head and Neck Cancer Patients Undergoing (Chemo) Radiotherapy—A Prospective Randomized Trial. *Frontiers in Nutrition* 2019;6(22).

36. Kimura H, Hamauchi S, Kawai S, Onozawa Y, Yasui H, Yamashita A, et al. Pretreatment predictive factors for feasibility of oral intake in adjuvant concurrent chemoradiotherapy for patients with locally advanced squamous cell carcinoma of the head and neck. *Int J Clin Oncol* 2020;25(2):258-66.

37. Axelsson L, Silander E, Nyman J, Bove M, Johansson L, Hammerlid E. Effect of prophylactic percutaneous endoscopic gastrostomy tube on swallowing in advanced head and neck cancer: A randomized controlled study. *Head Neck* 2017;39(5):908-15.

38. Silander E, Nyman J, Bove M, Johansson L, Larsson S, Hammerlid E. Impact of prophylactic percutaneous endoscopic gastrostomy on malnutrition and quality of life in patients with head and neck cancer: a randomized study. *Head Neck* 2012;34(1):1-9.

39. Hopanci Bicakli D, Ozkaya Akagunduz O, Meseri Dalak R, Esassolak M, Uslu R, Uyar M. The Effects of Compliance with Nutritional Counselling on Body Composition Parameters in Head and Neck Cancer Patients under Radiotherapy. *J Nutr Metab* 2017;2017:8631945.

40. Hofto S, Abbott J, Jackson JE, Isenring E. Investigating adherence to Australian nutritional care guidelines in patients with head and neck cancer. *Cancers of the Head & Neck* 2018;3(1):6.

41. Jeffery E, Young P, Sherriff J. Nutritional outcomes with radiotherapy for head and neck cancer: a before and after comparison of 'best practice guidelines' implementation. *Asia Pac J Clin Nutr* 2018;27(5):955-61.

42. Van Den Berg MGA, Rasmussen-Conrad EL, Gwasara GM, Krabbe PFM, Naber AHJ, Merks MA. A prospective study on weight loss and energy intake in patients with head and neck cancer, during diagnosis, treatment and revalidation. 2006;25(5):765-72.

43. Vahdat S, Hamzehgardeshi L, Hessam S, Hamzehgardeshi Z. Patient involvement in health care decision making: a review. *Iranian Red Crescent medical journal* 2014;16(1):e12454-e.

44. Ravasco P. Nutrition in Cancer Patients. *Journal of Clinical Medicine* 2019;8(8):13.
45. de van der Schueren MAE, Laviano A, Blanchard H, Jourdan M, Arends J, Baracos VE. Systematic review and meta-analysis of the evidence for oral nutritional intervention on nutritional and clinical outcomes during chemo(radio)therapy: current evidence and guidance for design of future trials. *Ann Oncol* 2018;29(5):1141-53.

9. CONSIDERAÇÕES FINAIS

Apesar da indicação de atendimento nutricional semanal durante a radioterapia de câncer de cabeça e pescoço preconizada por *guidelines* internacionais, com eficácia demonstrada por alguns ensaios clínicos randomizados, poucos estudos de mundo real haviam sido realizados e não havia nenhum estudo brasileiro sobre o efeito deste tipo de cuidado nutricional no país. Assim, trata-se do primeiro estudo que avaliou a efetividade do atendimento nutricional intensivo no Brasil, e que avaliou o efeito da adesão à referida intervenção nutricional.

O conjunto de manuscritos apresentados nesta tese traz importantes implicações práticas para as instituições brasileiras com relação às diretrizes atuais de periodicidade semanal do atendimento nutricional em pacientes com câncer de cabeça e pescoço, e instiga futuras investigações.

Em primeiro lugar, a partir da análise dos manuscritos é possível inferir que apenas a implementação de um cuidado nutricional intensivo parece não implicar benefícios aos pacientes com câncer de cabeça e pescoço submetidos à radioterapia. Fica claro que a adesão ao protocolo é importante. Apesar da adesão não ter impactado na sobrevida ou na ingestão alimentar, ou ainda apresentar resultados divergentes quanto à proteção para perda de peso significativa durante o tratamento, a adesão parece reduzir a prevalência de desnutrição e o declínio da qualidade de vida dos pacientes. Vale ressaltar que em nosso estudo, houve adesão limitada à revisão dietética durante a radioterapia.

A implementação de protocolo de atendimento nutricional intensivo exige alocação de recursos, como necessidade de um local para a realização do atendimento nutricional, equipamentos (computadores, balança, etc.), nutricionista disponível para os atendimentos, entre outros recursos. Sendo assim, considerando a escassez de recursos humanos e financeiros da maioria das instituições brasileiras, seria importante que as mesmas, caso decidam por implementar protocolos de atendimento nutricional intensivo, realizem auditorias frequentes para determinar as taxas de adesão e, caso necessário, façam intervenções a fim de promover serviços nutricionais eficazes. Para aumentar a adesão dos pacientes à intervenção nutricional, o nutricionista e o time multidisciplinar deveriam reforçar sobre a lógica e os benefícios da realização do protocolo de atendimento semanal, a fim de otimizar e melhorar os resultados dos pacientes.

Não encontramos diferenças nas características sociodemográficas ou clínicas investigadas entre pacientes aderentes e não aderentes, e nem diferença entre os grupos com relação à distância entre o domicílio e o hospital. Esperávamos que pacientes aderentes teriam pior condição clínica ou maior escolaridade, ou que residiriam mais próximos ao hospital onde o tratamento era realizado. Não investigamos em nosso estudo os motivos pelos quais os pacientes decidiram ser aderentes ou não ao protocolo de atendimento nutricional intensivo. É possível que as consultas semanais sejam consideradas inconvenientes ou cansativas para os pacientes, uma vez que geralmente eles já apresentam uma quantidade considerável de consultas, exames e tratamentos a serem realizados. Em estudo sobre a prestação de serviço semanal para pacientes com CCP, avaliando a percepção da necessidade de comparecer à consulta dietética (combinada com a fonoaudiologia), 41% dos pacientes avaliados relataram que não precisavam comparecer à consulta, e 58,5% das vezes isso estava de acordo com a percepção do médico.¹⁴⁷ Assim, futuras investigações deveriam avaliar como os pacientes e médicos brasileiros percebem a necessidade de atendimento nutricional intensivo e investigar por que os pacientes não comparecem às consultas nutricionais.

Seria lógico supor que a adesão às recomendações dos *guidelines* tenha um impacto positivo nos resultados e que a adesão deveria ser avaliada rotineiramente nos serviços e em pesquisas. No entanto, de acordo com a revisão de literatura realizada como parte desta tese, com intuito de mapear as evidências sobre a adesão à intervenção nutricional oral em pacientes com CCP, não há uma base de evidências robustas sobre este tema e mais estudos deveriam ser conduzidos nesta temática.

Encontramos ainda que algumas características dos pacientes, como índice de massa corporal basal mais alto, uso de suporte nutricional oral durante a radioterapia, tratamento multimodal (radioterapia adjuvante ou radioquimioterapia) e estágio avançado da doença foram preditores de perda de peso significativa durante o tratamento. Além disso, nosso estudo prospectivo destacou que a piora clinicamente significativa na qualidade de vida para participantes que se encontravam desnutridos antes do início da RT, ou participantes que receberam apenas alimentação via oral durante a RT, sem uso de suplementação, incentiva a atenção em tais pacientes durante o tratamento.

Como já mencionado, a implementação de protocolo de atendimento semanal para todos os pacientes com CCP que recebem radioterapia exige muitos recursos. Ainda, os efeitos combinados do crescente número de pacientes e serviços especializados

insuficientes desafiam a implementação de evidências dos *guidelines* para a prática clínica.¹⁴⁷ Desta forma, identificar o grupo de pacientes em maior risco e realizar a intervenção nutricional intensiva apenas nesses pacientes poderia ser uma alternativa caso a oferta deste tipo de intervenção nutricional a todos os pacientes não seja viável devido ao contexto de recursos finitos. É preciso entender que uma abordagem única para a prestação de serviços pode não ser a maneira mais adequada e/ou possível de fornecer intervenção nutricional.

Kiss e colaboradores,¹⁵⁵ em estudo sobre intervenção com uso de assistentes de nutrição (técnicos em nutrição), encontraram que a implementação do novo modelo de cuidado liberou o tempo do nutricionista para pacientes com necessidades mais complexas, como intolerância à alimentação enteral ou múltiplos sintomas que afetam a ingestão nutricional. Assim, a exploração de modelos alternativos de prestação de serviços e o uso de meios assistidos por tecnologia, para fornecer um complemento clínico para serviços presenciais, podem ajudar na triagem de pacientes com CCP que requerem intervenção de cuidados de suporte face a face pela equipe multidisciplinar. Isso poderia, em última análise, melhorar a eficiência dos serviços durante o tratamento de radioterapia. Esta deveria ser uma área de pesquisas futuras no país.

Vale destacar que, assim como em outros estudos,¹⁴⁸⁻¹⁵² encontramos que pacientes com excesso de peso ou obesidade, tiveram risco aumentando de perda de peso. Geralmente, por causa da crença de que pacientes com IMC mais elevado podem estar em melhor equilíbrio nutricional, os próprios profissionais de saúde e até os próprios pacientes deixam de priorizar o suporte nutricional. Como resultado o suporte nutricional enteral, por exemplo, costuma ser iniciado apenas para pacientes com IMC baixo antes do tratamento. Este achado deveria ser levado em consideração pela equipe multiprofissional que atende pacientes com CCP, para que pacientes com excesso de peso e obesidade não sejam negligenciados.

A dificuldade dos pacientes em atingir as recomendações de proteína e energia também traz importantes implicações de ordem prática e de pesquisa e sugere que a abordagem de aconselhamento dos nutricionistas deva ser revista e talvez deva concentrar na mudança de comportamento, como por exemplo, a entrevista motivacional. Por outro lado, é preciso considerar que, em se tratando de pacientes ambulatoriais, existe uma dificuldade em monitorar e garantir que o paciente atinja as recomendações nutricionais.

Alguns fatores podem influenciar a capacidade do paciente em atingir as recomendações, entre eles estão sintomas decorrentes do tratamento ou da localização do tumor, inúmeros exames e consultas, questões financeiras e de suporte social, problemas psicológicos, entre outros.^{123,144, 153-156} O crescente aumento do uso de radioquimioterapia em pacientes com CCP culminou em uma maior carga de cuidados recaindo sobre os pacientes e suas famílias para gerenciar os efeitos colaterais em casa¹⁴⁷. O impacto da falta de apoio social e recursos financeiros limitados sobre os resultados nutricionais no CCP foi pouco estudado, portanto, deveria ser objeto de futuras investigações.

A periodicidade e o instrumento de avaliação também podem influenciar na avaliação da ingestão alimentar dos indivíduos. No nosso estudo, por exemplo, utilizamos o recordatório de 24 horas para avaliar a ingestão alimentar dos pacientes, mas este instrumento pode não representar a ingestão alimentar habitual dos indivíduos e ainda ser passível de viés de recordação. Ainda, fizemos a avaliação da ingestão alimentar em apenas dois momentos. Neste sentido, pode ter ocorrido uma mudança na ingestão alimentar ao longo das semanas da radioterapia. Geralmente a ingestão energética reduz de acordo com a progressão natural dos efeitos colaterais causados pela radioterapia.¹²⁸

Sugerimos que futuras investigações incluam dados de avaliação da ingestão alimentar não apenas em dois momentos, mas ao longo do tratamento, além de investigar os fatores e barreiras que possam atuar na adesão às recomendações nutricionais. Também seria interessante que pesquisas futuras desenvolvam aplicativos para monitorar, de forma remota e simples, a ingestão alimentar dos pacientes ao longo do tratamento.

Todavia, encontramos que mesmo pacientes que conseguiram atingir a recomendações energéticas e proteicas perderam peso. Apesar de *guidelines* apresentarem as faixas de recomendações de energia e proteína para pacientes oncológicos, sabe-se que as pesquisas nesta área ainda precisam avançar muito, uma vez que a perda de peso em pacientes oncológicos não é apenas resultados da baixa ingestão alimentar ou baixa oferta de energia e calorias pela terapia nutricional, mas também ocorre por problemas metabólicos inerentes ao tumor.^{66, 71}

Alguns aspectos devem ser considerados quando se interpreta os resultados desta tese. O primeiro deles, diz respeito ao significado da adesão. O termo pode implicar responsabilidade ativa compartilhada pelo paciente e pelos profissionais de saúde.¹⁴⁰ No caso da implementação do protocolo de atendimento nutricional intensivo, a responsabilidade recai sobre o nutricionista em transmitir as recomendações, mas, em

última instância, são os pacientes que tomam a decisão final. Cada vez mais na literatura tem se discutido a questão da autonomia do paciente em decidir seguir ou não as recomendações dos profissionais de saúde.^{157, 158} Outro aspecto importante está relacionado ao método utilizado para medir a adesão. Escolhemos neste estudo utilizar a proporção de encontros com o nutricionista durante a radioterapia, mas não sabemos se a proporção adotada (presença em 75% ou mais dos encontros) é adequada.

O uso do IMC e perda de peso como indicadores do estado nutricional pode ser considerado uma limitação do estudo, uma vez que não é possível inferir sobre a composição corporal do sujeito utilizando apenas estas medidas. No entanto, são os indicadores mais utilizados na prática clínica, uma vez que não são caros nem complexos, e podem ser úteis em detectar pacientes em risco de piores desfechos clínicos.^{3, 106} Além disso, apesar da DEXA e da tomografia computadorizada serem considerados padrão-ouro na avaliação nutricional, são medidas consideradas complexas e que não são disponíveis na maioria dos hospitais brasileiros.

Por fim, o fato de ter sido realizado em um centro de referência do tratamento oncológico pode comprometer a generalização dos resultados.

Como mensagem final, concluímos que nossos resultados corroboram as diretrizes atuais de cuidado nutricional em pacientes com câncer de cabeça e pescoço, que recomendam a periodicidade semanal do atendimento nutricional como uma das estratégias para a prevenção da perda de peso e melhoria da qualidade de vida. Todavia, a adesão à intervenção nutricional parece ser importante para melhores desfechos e deveria receber atenção da equipe multiprofissional e ser avaliada rotineiramente nas instituições e também na pesquisa. É imperativo continuar a examinar a oferta de serviços de nutrição no país, a fim de ajudar a otimizar sua entrega a pacientes e cuidadores com CCP dentro das limitações atuais da maioria das equipes e serviços. O desenvolvimento de estratégias para abordar as dificuldades de adesão pode ser fundamental para alcançar melhores resultados de nutrição neste grupo de pacientes.

10. REFERÊNCIAS

1. Huh G, Ahn SH, Suk JG, Lee MH, Kim WS, Kwon SK, et al. Severe late dysphagia after multimodal treatment of stage III/IV laryngeal and hypopharyngeal cancer. *Jpn J Clin Oncol* 2020;50(2):185-92.
2. Citak E, Tulek Z, Uzel O. Nutritional status in patients with head and neck cancer undergoing radiotherapy: a longitudinal study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2019;27(1):239-47.
3. Ravasco P. Nutrition in Cancer Patients. *Journal of Clinical Medicine* 2019;8(8):13.
4. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr* 2017;36(1):11-48.
5. Findlay M, Bauer J, Brown T, Committee. HaNGS. Evidence-based practice guidelines for the nutritional management of adult patients with head and neck cancer. . Sydney: Cancer Council Australia.
6. Talwar B, Donnelly R, Skelly R, Donaldson M. Nutritional management in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol* 2016;130(S2):S32-s40.
7. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68(6):394-424.
8. Mattiuzzi C, Lippi G. Current Cancer Epidemiology. *J Epidemiol Glob Health* 2019;9(4):217-22.
9. Stewart B, Wild C. *World Cancer Report 2014*. International Agency for Research on Cancer; 2014.
10. Gelband H, Sankaranarayanan R, Gauvreau CL, Horton S, Anderson BO, Bray F, et al. Costs, affordability, and feasibility of an essential package of cancer control interventions in low-income and middle-income countries: key messages from Disease Control Priorities, 3rd edition. *The Lancet* 2016;387(10033):2133-44.
11. Are C, Colburn L, Rajaram S, Vijayakumar M. Disparities in cancer care between the United States of America and India and opportunities for surgeons to lead. *J Surg Oncol* 2010;102(1):100-5.

12. Lortet-Tieulent J, Georges D, Bray F, Vaccarella S. Profiling global cancer incidence and mortality by socioeconomic development. *Int J Cancer* 2020;147(11):3029-36.
13. Song M, Vogelstein B, Giovannucci EL, Willett WC, Tomasetti C. Cancer prevention: Molecular and epidemiologic consensus. *Science* 2018;361(6409):1317-8.
14. Torre LA, Siegel RL, Ward EM, Jemal A. Global Cancer Incidence and Mortality Rates and Trends--An Update. *Cancer Epidemiol Biomarkers Prev* 2016;25(1):16-27.
15. Rezende LFMd, Lee DH, Louzada MLdC, Song M, Giovannucci E, Eluf-Neto J. Proportion of cancer cases and deaths attributable to lifestyle risk factors in Brazil. *Cancer Epidemiol* 2019;59:148-57.
16. Instituto, INCA. NdC-. Estimativa 2020 : incidência de câncer no Brasil Rio de Janeiro: Instituto Nacional de Câncer José Alencar Gomes da Silva. ; 2019.
17. Bigoni A, Ferreira Antunes JL, Weiderpass E, Kjærheim K. Describing mortality trends for major cancer sites in 133 intermediate regions of Brazil and an ecological study of its causes. *BMC Cancer* 2019;19(1):940.
18. Cohen N, Fedewa S, Chen AY. Epidemiology and Demographics of the Head and Neck Cancer Population. *Oral and Maxillofacial Surgery Clinics* 2018;30(4):381-95.
19. Kfoury SA, Eluf Neto J, Koifman S, Curado MP, Menezes A, Daudt AW, et al. Fração de câncer de cabeça e pescoço atribuível ao tabaco e ao álcool em cidades de três regiões brasileiras. *Revista Brasileira de Epidemiologia* 2018;21.
20. Ribeiro KB, Levi JE, Pawlita M, Koifman S, Matos E, Eluf-Neto J, et al. Low human papillomavirus prevalence in head and neck cancer: results from two large case-control studies in high-incidence regions. *Int J Epidemiol* 2011;40(2):489-502.
21. Society AC. *Cancer Facts & Figures 2014*. Atlanta: American Cancer Society; 2014.
22. Bradshaw PT, Siega-Riz AM, Campbell M, Weissler MC, Funkhouser WK, Olshan AF. Associations Between Dietary Patterns and Head and Neck Cancer: The Carolina Head and Neck Cancer Epidemiology Study. *Am J Epidemiol* 2012;175(12):1225-33.
23. Petito G, Carneiro MADS, Santos SHDR, Silva AMTC, Alencar RDC, Gontijo AP, et al. Human papillomavirus in oral cavity and oropharynx carcinomas in the central region of Brazil. 2016.

24. Cohen EEW, Lamonte SJ, Erb NL, Beckman KL, Sadeghi N, Hutcheson KA, et al. American Cancer Society Head and Neck Cancer Survivorship Care Guideline. *CA Cancer Journal for Clinicians* 2016;66(3):203-39.
25. Lin A. Radiation Therapy for Oral Cavity and Oropharyngeal Cancers. *Dent Clin North Am* 2018;62(1):99-109.
26. Iyer NG, Tan DSW, Tan VK, Wang W, Hwang J, Tan N-C, et al. Randomized trial comparing surgery and adjuvant radiotherapy versus concurrent chemoradiotherapy in patients with advanced, nonmetastatic squamous cell carcinoma of the head and neck: 10-year update and subset analysis. *Cancer* 2015;121(10):1599-607.
27. World Health O. WHO report on cancer: setting priorities, investing wisely and providing care for all. . Switzerland: WHO; 2020.
28. Faria SDO, Nascimento MCD, Kulcsar MAV. Malignant neoplasms of the oral cavity and oropharynx treated in Brazil: what do hospital cancer records reveal? *Braz J Otorhinolaryngol* 2020.
29. Li H, Torabi SJ, Yarbrough WG, Mehra S, Osborn HA, Judson B. Association of Human Papillomavirus Status at Head and Neck Carcinoma Subsites With Overall Survival. *JAMA Otolaryngology–Head & Neck Surgery* 2018;144(6):519.
30. Du E, Mazul AL, Farquhar D, Brennan P, Anantharaman D, Abedi-Ardekani B, et al. Long-term Survival in Head and Neck Cancer: Impact of Site, Stage, Smoking, and Human Papillomavirus Status. *The Laryngoscope* 2019;129(11):2506-13.
31. Howlader N N, Krapcho M, et al, editors. SEER cancer statistics review, 1975-2014. 2018 [11 dec 2019]. Available from: https://seer.cancer.gov/archive/csr/1975_2014/.
32. Kowalski LP, Oliveira MMd, Lopez RVM, Silva DRMe, Ikeda MK, Curado MP. Survival trends of patients with oral and oropharyngeal cancer treated at a cancer center in São Paulo, Brazil. *Clinics* 2020;75.
33. Rodriguez KL, Bayliss N, Alexander SC, Jeffreys AS, Olsen MK, Pollak KI, et al. How oncologists and their patients with advanced cancer communicate about health-related quality of life. *Psychooncology* 2010;19(5):490-9.
34. Loorents V, Rosell J, Salgado Willner H, Börjeson S. Health-related quality of life up to 1 year after radiotherapy in patients with head and neck cancer (HNC). *SpringerPlus* 2016;5(1):669.

35. Lee V, Loisel CG. The salience of existential concerns across the cancer control continuum. *Palliat Support Care* 2012;10(2):123-33.
36. Sosnowski R, Kulpa M, Ziętalewicz U, Wolski JK, Nowakowski R, Bakula R, et al. Basic issues concerning health-related quality of life. *Cent European J Urol* 2017;70(2):206-11.
37. Ringash J, Bernstein LJ, Devins G, Dunphy C, Giuliani M, Martino R, et al. Head and Neck Cancer Survivorship: Learning the Needs, Meeting the Needs. *Semin Radiat Oncol* 2018;28(1):64-74.
38. Wintner LM, Sztankay M, Aaronson N, Bottomley A, Giesinger JM, Groenvold M, et al. The use of EORTC measures in daily clinical practice—A synopsis of a newly developed manual. *Eur J Cancer* 2016;68:73-81.
39. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The functional assessment of cancer therapy scale: Development and validation of the general measure. *J Clin Oncol* 1993;11(3):570-9.
40. WHOQOL. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. *Soc Sci Med* 1995;41(10):1403-9.
41. Karimi M, Brazier J. Health, Health-Related Quality of Life, and Quality of Life: What is the Difference? *Pharmacoeconomics* 2016;34(7):645-9.
42. Felce D, Perry J. Quality of life: Its definition and measurement. *Res Dev Disabil* 1995;16(1):51-74.
43. Valdez JA, Brennan MT. Impact of Oral Cancer on Quality of Life. *Dent Clin North Am* 2018;62(1):143-54.
44. Koyfman SA, Ismaila N, Crook D, D'Cruz A, Rodriguez CP, Sher DJ, et al. Management of the neck in squamous cell carcinoma of the oral cavity and oropharynx: ASCO clinical practice guideline. *J Clin Oncol* 2019;37(20):1753-74.
45. Guenzel T, Walliczek-Dworschak U, Teymoortash A, Singer S, Eichler M, Wilhelm T, et al. Health-related quality of life in oropharyngeal cancer survivors - a population-based study. *Otolaryngol Pol* 2018;72(2):30-5.
46. Broglie MA, Soltermann A, Haile SR, Rösli C, Huber GF, Schmid S, et al. Quality of life of oropharyngeal cancer patients with respect to treatment strategy and p16-positivity. *Laryngoscope* 2013;123(1):164-70.

47. Wan Leung S, Lee TF, Chien CY, Chao PJ, Tsai WL, Fang FM. Health-related quality of life in 640 head and neck cancer survivors after radiotherapy using EORTC QLQ-C30 and QLQ-H&N35 questionnaires. *BMC Cancer* 2011;11:128.
48. Rathod S, Gupta T, Ghosh-Laskar S, Murthy V, Budrukkar A, Agarwal J. Quality-of-life (QOL) outcomes in patients with head and neck squamous cell carcinoma (HNSCC) treated with intensity-modulated radiation therapy (IMRT) compared to three-dimensional conformal radiotherapy (3D-CRT): evidence from a prospective randomized study. *Oral Oncol* 2013;49(6):634-42.
49. Vartanian JG, Rogers SN, Kowalski LP. How to evaluate and assess quality of life issues in head and neck cancer patients. *Curr Opin Oncol* 2017;29(3):159-65.
50. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: Scoping review. *SAGE Open Medicine* 2016;4(0):205031211667172.
51. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European organization for research and treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85(5):365-76.
52. Vartanian JG, Carvalho AL, Furia CLB, Junior GdC, Rocha CN, Sinitcovisky IML, et al. Questionários para a avaliação de Qualidade de Vida em pacientes com câncer de cabeça e pescoço validados no Brasil. *Rev. Bras. Cir. Cabeça Pescoço* 2007;36(2):108-15.
53. Ferreira K. Dor e qualidade de vida relacionada à saúde em pacientes com câncer: influência das citocinas pró-inflamatórias TNF- α , IL-6, IL-8 e IL-1 β . São Paulo: Universidade de São Paulo; 2008.
54. Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA. Interpreting clinically significant changes in patient-reported outcomes. *Cancer* 2007;110(1):196-202.
55. Funk GF, Karnell LH, Smith RB, Christensen AJ. Clinical Significance of Health Status Assessment Measures in Head and Neck Cancer: What Do Quality-of-Life Scores Mean? *Archives of Otolaryngology–Head & Neck Surgery* 2004;130(7):825-9.
56. Hong F, Bosco JL, Bush N, Berry DL. Patient self-appraisal of change and minimal clinically important difference on the European organization for the research and treatment of cancer quality of life questionnaire core 30 before and during cancer therapy. *BMC Cancer* 2013;13:165.

57. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol* 2003;56(5):395-407.
58. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989;10(4):407-15.
59. J. C. Statistical power analysis for the behavioral sciences. . 2nd edition ed. New York: Academic Press; 1988.
60. Yost KJ, Eton DT. Combining distribution- and anchor-based approaches to determine minimally important differences: the FACIT experience. *Eval Health Prof* 2005;28(2):172-91.
61. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998;16(1):139-44.
62. Maringwa JT, Quinten C, King M, Ringash J, Osoba D, Coens C, et al. Minimal important differences for interpreting health-related quality of life scores from the EORTC QLQ-C30 in lung cancer patients participating in randomized controlled trials. *Support Care Cancer* 2011;19(11):1753-60.
63. Baracos VE. Cancer-associated malnutrition. *Eur J Clin Nutr* 2018;72(9):1255-9.
64. Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clin Nutr* 2010;29(2):154-9.
65. Santarpia L, Contaldo F, Pasanisi F. Nutritional screening and early treatment of malnutrition in cancer patients. *J Cachexia Sarcopenia Muscle* 2011;2(1):27-35.
66. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;12(5):489-95.
67. Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. *Clin Nutr* 2017;36(5):1187-96.
68. Casbarien O, Fabios E, Perris P, Feliu MS, Slobodianik NH. Perfil bioquímico nutricional en un grupo de pacientes con cáncer de cabeza y cuello. *Acta Bioquímica Clínica Latinoamericana* 2016;50(4):623-7.
69. Argilés JM, López-Soriano FJ, Stemmler B, Busquets S. Novel targeted therapies for cancer cachexia. *Biochem J* 2017;474(16):2663-78.

70. Argilés JM, Busquets S, Stemmler B, López-Soriano FJ. Cancer cachexia: understanding the molecular basis. *Nature Reviews Cancer* 2014;14(11):754-62.
71. Tisdale MJ. Catabolic mediators of cancer cachexia. *Curr Opin Support Palliat Care* 2008;2(4):256-61.
72. Agustsson T, Rydén M, Hoffstedt J, van Harmelen V, Dicker A, Laurencikiene J, et al. Mechanism of increased lipolysis in cancer cachexia. *Cancer Res* 2007;67(11):5531-7.
73. Argilés JM, Busquets S, Toledo M, López-Soriano FJ. The role of cytokines in cancer cachexia. *Curr Opin Support Palliat Care* 2009;3(4):263-8.
74. Molino A, Laviano A, Fanelli FR. Contribution of anorexia to tissue wasting in cachexia. *Current Opinion in Supportive and Palliative Care* 2010;4(4):249-53.
75. Argilés JM, Stemmler B, López-Soriano FJ, Busquets S. Inter-tissue communication in cancer cachexia. *Nature Reviews Endocrinology* 2019;15(1):9-20.
76. Laviano A, Inui A, Marks DL, Meguid MM, Pichard C, Rossi Fanelli F, et al. Neural control of the anorexia-cachexia syndrome. *Am J Physiol Endocrinol Metab* 2008;295(5):E1000-8.
77. Pressoir M, Desne S, Berchery D, Rossignol G, Poiree B, Meslier M, et al. Prevalence, risk factors and clinical implications of malnutrition in french comprehensive cancer centres. *Br J Cancer* 2010;102(6):966-71.
78. Hebuterne X, Lemarie E, Michallet M, De Montreuil CB, Schneider SM, Goldwasser F. Prevalence of malnutrition and current use of nutrition support in patients with cancer. *Journal of Parenteral and Enteral Nutrition* 2014;38(2):196-204.
79. Mulasi U. Nutritional status, body composition, and psychosocial outcomes among individuals with advanced head and neck cancers: A prospective investigation in an outpatient setting. *Dissertation Abstracts International: Section B: The Sciences and Engineering* 2016;77(3-B(E)):No-Specified.
80. Kubrak C, Martin L, Gramlich L, Scrimger R, Jha N, Debenham B, et al. Prevalence and prognostic significance of malnutrition in patients with cancers of the head and neck. *Clin Nutr* 2019.
81. Arribas L, Hurtos L, Taberna M, Peiro I, Vilajosana E, Lozano A, et al. Nutritional changes in patients with locally advanced head and neck cancer during treatment. *Oral Oncol* 2017;71:67-74.

82. INCA INdC-. Inquérito brasileiro de nutrição oncológica. Rio de Janeiro: INCA; 2013.
83. Chasen MR, Bhargava R. A descriptive review of the factors contributing to nutritional compromise in patients with head and neck cancer. *Support Care Cancer* 2009;17(11):1345-51.
84. Martin L, de van der Schueren MAE, Blauwhoff-Buskermolen S, Baracos V, Gramlich L. Identifying the Barriers and Enablers to Nutrition Care in Head and Neck and Esophageal Cancers. *Journal of Parenteral and Enteral Nutrition* 2016;40(3):355-66.
85. Alshadwi A, Nadershah M, Carlson ER, Young LS, Burke PA, Daley BJ. Nutritional considerations for head and neck cancer patients: a review of the literature. *J Oral Maxillofac Surg* 2013;71(11):1853-60.
86. Vangelov B, Smee RI. Clinical predictors for reactive tube feeding in patients with advanced oropharynx cancer receiving radiotherapy ± chemotherapy. *Eur Arch Otorhinolaryngol* 2017;274(10):3741-9.
87. Citak E, Tulek Z, Uzel O. Nutritional status in patients with head and neck cancer undergoing radiotherapy: a longitudinal study. *Support Care Cancer* 2019;27(1):239-47.
88. Gorenc M, Kozjek NR, Strojan P. Malnutrition and cachexia in patients with head and neck cancer treated with (chemo)radiotherapy. *Reports of Practical Oncology & Radiotherapy* 2015;20(4):249-58.
89. Chen DW, Wang T, Shey-Sen Ni J, Sandulache VC, Graboyes EM, Worley M, et al. Prognostic factors associated with achieving total oral diet after glossectomy with microvascular free tissue transfer reconstruction. *Oral Oncol* 2019;92:59-66.
90. Bressan V, Bagnasco A, Aleo G, Catania G, Zanini MP, Timmins F, et al. The life experience of nutrition impact symptoms during treatment for head and neck cancer patients: a systematic review and meta-synthesis. *Support Care Cancer* 2017;25(5):1699-712.
91. Donaldson SS. Nutritional support as an adjunct to radiation therapy. *JPEN. Journal of parenteral and enteral nutrition* 1984;8(3):302-10.
92. Langius JAE, Bakker S, Rietveld DHF, Kruijenga HM, Langendijk JA, Weijs PJM, et al. Critical weight loss is a major prognostic indicator for disease-specific survival in patients with head and neck cancer receiving radiotherapy. *Br J Cancer* 2013;109(5):1093-9.

93. Huh G, Ahn SH, Suk JG, Lee MH, Kim WS, Kwon SK, et al. Severe late dysphagia after multimodal treatment of stage III/IV laryngeal and hypopharyngeal cancer. *Jpn J Clin Oncol* 2019.
94. Jager-Wittenaar H, Dijkstra PU, Vissink A, van der Laan BF, van Oort RP, Roodenburg JL. Critical weight loss in head and neck cancer--prevalence and risk factors at diagnosis: an explorative study. *Support Care Cancer* 2007;15(9):1045-50.
95. Palma Milla S, Meneses D, Valero M, Calso M, García Vázquez N, Ruiz Garrido M, et al. [Costs associated to disease-related malnutrition and treatment: a literature review]. *Nutr Hosp* 2018;35(2):442-60.
96. Sun H, Sudip T, Fu X, Wen S, Liu H, Yu S. Cachexia is associated with depression, anxiety and quality of life in cancer patients. *BMJ Supportive & Palliative Care* 2020:bmjpcare-2019-.
97. Fysekidis M, Bouchoucha M, Mary F, Airinei G, Bon C, Benamouzig R. Change of appetite in patients with functional digestive disorder. Association with psychological disorders: A cross-sectional study. *J Gastroenterol Hepatol* 2018;33(1):195-202.
98. Barajas Galindo DE, Vidal-Casariago A, Calleja-Fernández A, Hernández-Moreno A, Pintor de la Maza B, Pedraza-Lorenzo M, et al. Appetite disorders in cancer patients: Impact on nutritional status and quality of life. *Appetite* 2017;114:23-7.
99. Wallengren O, Lundholm K, Bosaeus I. Diagnostic criteria of cancer cachexia: relation to quality of life, exercise capacity and survival in unselected palliative care patients. *Support Care Cancer* 2013;21(6):1569-77.
100. Blum D, Omlin A, Baracos VE, Solheim TS, Tan BH, Stone P, et al. Cancer cachexia: a systematic literature review of items and domains associated with involuntary weight loss in cancer. *Crit Rev Oncol Hematol* 2011;80(1):114-44.
101. Wanden-Berghe C, Sanz-Valero J, Arroyo-Sebastián A, Cheikh-Moussa K, Moya-Forcen P. [Effects of a nutritional intervention in a fast-track program for a colorectal cancer surgery: systematic review]. *Nutr Hosp* 2016;33(4):402.
102. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Cancer: disease and nutrition are key determinants of patients' quality of life. *Support Care Cancer* 2004;12(4):246-52.
103. Lis CG, Gupta D, Lammersfeld CA, Markman M, Vashi PG. Role of nutritional status in predicting quality of life outcomes in cancer--a systematic review of the epidemiological literature. *Nutr J* 2012;11:27.

104. Kassianos AP, Raats MM, Gage H, Peacock M. Quality of life and dietary changes among cancer patients: a systematic review. *Qual Life Res* 2015;24(3):705-19.
105. Baguley BJ, Skinner TL, Wright ORL. Nutrition therapy for the management of cancer-related fatigue and quality of life: a systematic review and meta-analysis. *Br J Nutr* 2019;122(5):527-41.
106. Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. *J Clin Oncol* 2015;33(1):90-9.
107. Langius JAE, Zandbergen MC, Eerenstein SEJ, van Tulder MW, Leemans CR, Kramer MHH, et al. Effect of nutritional interventions on nutritional status, quality of life and mortality in patients with head and neck cancer receiving (chemo)radiotherapy: a systematic review. *Clinical nutrition (Edinburgh, Scotland)* 2013;32(5):671-8.
108. Jung AR, Roh JL, Kim JS, Kim SB, Choi SH, Nam SY, et al. Prognostic value of body composition on recurrence and survival of advanced-stage head and neck cancer. *Eur J Cancer* 2019;116:98-106.
109. Orell-Kotikangas H, Österlund P, Mäkitie O, Saarilahti K, Ravasco P, Schwab U, et al. Cachexia at diagnosis is associated with poor survival in head and neck cancer patients. *Acta Otolaryngol* 2017;137(7):778-85.
110. Um MH, Choi My Fau - Lee SM, Lee Sm Fau - Lee IJ, Lee Ij Fau - Lee CG, Lee Cg Fau - Park YK, Park YK. Intensive nutritional counseling improves PG-SGA scores and nutritional symptoms during and after radiotherapy in Korean cancer patients. 2014(1433-7339 (Electronic)).
111. Ravasco P, Monteiro Grillo I, Camilo M. Cancer wasting and quality of life react to early individualized nutritional counselling! *Clinical nutrition (Edinburgh, Scotland)* 2007;26(1):7-15.
112. Ravasco P. Nutritional support in head and neck cancer: how and why? *Anticancer Drugs* 2011;22(7):639-46.
113. Bruggeman AR, Kamal AH, LeBlanc TW, Ma JD, Baracos VE, Roeland EJ. Cancer Cachexia: Beyond Weight Loss. *J Oncol Pract* 2016;12(11):1163-71.
114. Raslan M, Gonzalez MC, Dias MCG, Paes-Barbosa FC, Ceconello I, Waitzberg DL. Aplicabilidade dos métodos de triagem nutricional no paciente hospitalizado. *Revista de Nutrição* 2008;21:553-61.

115. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. *Clin Nutr* 2003;22(4):415-21.
116. Leuenberger M, Kurmann S, Stanga Z. Nutritional screening tools in daily clinical practice: the focus on cancer. *Support Care Cancer* 2010;18 Suppl 2:S17-27.
117. Gonzalez MC, Borges LR, Silveira DH, Assunção MCF, Orlandi SP. Validação da versão em português da avaliação subjetiva global produzida pelo paciente *Rev Bras Nutr Clin* 2010;25(2):102-8.
118. (INCA) INdCJAGdS. Consenso nacional de nutrição oncológica. Rio de Janeiro: INCA; 2015.
119. Ottosson S, Zackrisson B, Kjellén E, Nilsson P, Laurell G. Weight loss in patients with head and neck cancer during and after conventional and accelerated radiotherapy. *Acta oncologica (Stockholm, Sweden)* 2013;52(4):711-8.
120. WHO WHO-. Obesity: Preventing and managing the Global Epidemic. Geneva: World Health Organization - WHO; 2000.
121. Vangelov B, Venchiarutti RL, Smee RI. Critical Weight Loss in Patients With Oropharynx Cancer During Radiotherapy (\pm Chemotherapy). *Nutr Cancer* 2017;69(8):1211-8.
122. White JV, Guenter P, Jensen G, Malone A, Schofield M. Consensus Statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition. *Journal of Parenteral and Enteral Nutrition* 2012;36(3):275-83.
123. Bozzetti F. Nutritional support of the oncology patient. *Crit Rev Oncol Hematol* 2013;87(2):172-200.
124. Garg S, Yoo J, Winquist E. Nutritional support for head and neck cancer patients receiving radiotherapy: a systematic review. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2010;18(6):667-77.
125. Bossola M. Nutritional interventions in head and neck cancer patients undergoing chemoradiotherapy: a narrative review. *Nutrients* 2015;7(1):265-76.
126. Dahele M, Fearon K. Research methodology: cancer cachexia syndrome. *Palliat Med* 2004;18(5):409-17.
127. Isenring EA, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. *Br J Cancer* 2004;91(3):447-52.

128. Isenring EA, Bauer JD, Capra S. Nutrition support using the American Dietetic Association medical nutrition therapy protocol for radiation oncology patients improves dietary intake compared with standard practice. *J Am Diet Assoc* 2007;107(3):404-12.
129. Isenring E, Loeliger J, Hodgson B. Nutritional management of patients with cancer improves nutritional and quality of life outcomes. *Cancer Forum* 2011;35(2):88-91.
130. Van Den Berg MGA, Rasmussen-Conrad EL, Wei KH, Lintz-Luidens H, Kaanders JHAM, Merks MAW. Comparison of the effect of individual dietary counselling and of standard nutritional care on weight loss in patients with head and neck cancer undergoing radiotherapy. *Br J Nutr* 2010;104(6):872-7.
131. Kang W-X, Li W, Huang S-G, Dang Y, Gao H. Effects of nutritional intervention in head and neck cancer patients undergoing radiotherapy: A prospective randomized clinical trial. *Molecular and clinical oncology* 2016;5(3):279-82.
132. Roussel L-M, Micault E, Peyronnet D, Blanchard D, Guarnieri S, Choussy O, et al. Intensive nutritional care for patients treated with radiotherapy in head and neck cancer: a randomized study and meta-analysis. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery* 2017;274(2):977-87.
133. Orell H, Schwab U, Saarilahti K, Osterlund P, Ravasco P, Makitie A. Nutritional Counseling for Head and Neck Cancer Patients Undergoing (Chemo) Radiotherapy-A Prospective Randomized Trial. *Frontiers in nutrition* 2019;6:22.
134. Jeffery E, Young P, Sherriff J. Nutritional outcomes with radiotherapy for head and neck cancer: a before and after comparison of 'best practice guidelines' implementation. *Asia Pac J Clin Nutr* 2018;27(5):955-61.
135. Hofto S, Abbott J, Jackson JE, Isenring E. Investigating adherence to Australian nutritional care guidelines in patients with head and neck cancer. *Cancers of the head & neck* 2018;3:6.
136. Vlooswijk CP, van Rooij PHE, Kruize JC, Schuring HA, Al-Mamgani A, de Roos NM. Dietary counselling and nutritional support in oropharyngeal cancer patients treated with radiotherapy: persistent weight loss during 1-year follow-ups. *Eur J Clin Nutr* 2016;70(1):54-9.

137. Hopanci Bicakli D, Ozkaya Akagunduz O, Meseri Dalak R, Esassolak M, Uslu R, Uyar M. The Effects of Compliance with Nutritional Counselling on Body Composition Parameters in Head and Neck Cancer Patients under Radiotherapy. *J Nutr Metab* 2017;2017:8631945.
138. Kabarriti R, Bontempo A, Romano M, McGovern KP, Asaro A, Viswanathan S, et al. The impact of dietary regimen compliance on outcomes for HNSCC patients treated with radiation therapy. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2018;26(9):3307-13.
139. Cases MG, Frugé AD, Daniel M. Head and Neck Cancer Adherence to Dietary Recommendations using Theory-Based Tools: Future Research Directions. *Journal of food & nutritional disorders* 2015;4(5):181.
140. Vahdat S, Hamzehgardeshi L, Hessam S, Hamzehgardeshi Z. Patient involvement in health care decision making: a review. *Iranian Red Crescent medical journal* 2014;16(1):e12454-e.
141. Cabrera AG, Sanz-Lorente M, Sanz-Valero J, Lopez-Pintor E. Compliance and adherence to enteral nutrition treatment in adults: A systematic review. *Nutrients* 2019;11(11):2627.
142. Capra S, Bauer J, Davidson W, Ash S. Nutritional Therapy for Cancer-Induced Weight Loss. *Nutr Clin Pract* 2002;17(4):210-3.
143. Verhulst S RLQ. Developing Theory-Based Measurement Tools for Improving Diet Compliance in Head and Neck Cancer Patients. *Journal of Food & Nutritional Disorders* 2015;04(02).
144. McDonough EM, Boyd JH, Varvares MA, Maves MD. Relationship between psychological status and compliance in a sample of patients treated for cancer of the head and neck. *Head Neck* 1996;18(3):269-76.
145. Kubrak C, Olson K, Jha N, Jensen L, McCargar L, Seikaly H, et al. Nutrition impact symptoms: Key determinants of reduced dietary intake, weight loss, and reduced functional capacity of patients with head and neck cancer before treatment. *Head Neck* 2010;32(3):290-300.
146. Beck A, Passchier E, Retèl V, Stuiver M, Hilgers F, Van Harten W, et al. A tailored multidisciplinary head and neck cancer rehabilitation program compared to usual supportive care for patients treated with concomitant chemoradiotherapy: The design of

an “assessment of effectiveness and cost-effectiveness in a multicenter prospective observational study”. *Eur J Cancer* 2017;72:S101.

147. Wall LR, Cartmill B, Ward EC, Hill AJ, Isenring E, Porceddu SV. Evaluation of a weekly speech pathology/dietetic service model for providing supportive care intervention to head and neck cancer patients and their carers during (chemo)radiotherapy. *Support Care Cancer* 2016;24(3):1227-34.

148. Lonbro S, Petersen GB, Andersen JR, Johansen J. Prediction of critical weight loss during radiation treatment in head and neck cancer patients is dependent on BMI. *Support Care Cancer* 2016;24(5):2101-9.

149. Zhang Z, Zhu Y, Zhang L, Wang Z, Wan H. Prediction model of critical weight loss in cancer patients during particle therapy. *Jpn J Clin Oncol* 2018;48(1):75-81.

150. Ottosson S, Zackrisson B, Kjellén E, Nilsson P, Laurell G. Weight loss in patients with head and neck cancer during and after conventional and accelerated radiotherapy. *Acta Oncol* 2013;52(4):711-8.

151. Silander E, Nyman J, Hammerlid E. An exploration of factors predicting malnutrition in patients with advanced head and neck cancer. *Laryngoscope* 2013;123(10):2428-34.

152. Zhao JZ, Zheng H, Li LY, Zhang LY, Zhao Y, Jiang N. Predictors for weight loss in head and neck cancer patients undergoing radiotherapy: A systematic review. *Cancer Nurs* 2015;38(6):E37-E45.

153. Dixon S. Head and neck management: importance of nutrition intervention. *Oncology Nutrition Connection* 2004;12(3):1-11.

154. Dawson ER, Morley SE, Robertson AG, Soutar DS. Increasing dietary supervision can reduce weight loss in oral cancer patients. *Nutr Cancer* 2001;41(1-2):70-4.

155. Kiss N, Gilliland S, Quinn P, Atkins L, Black J, Frowen J. Evaluating the effectiveness of a nutrition assistant role in a head and neck cancer clinic. *Nutr Diet* 2019;76(1):21-7.

156. Beck AK, Britton B, Baker A, Odelli C, Wratten C, Bauer J, et al. Preliminary report: training head and neck cancer dietitians in behaviour change counselling. *Psychooncology* 2017;26(3):405-7.

157. Arrieta Valero I. Autonomies in Interaction: Dimensions of Patient Autonomy and Non-adherence to Treatment. *Front Psychol* 2019;10(1857).

158. Herlitz A, Munthe C, Törner M, Forsander G. The Counseling, Self-Care, Adherence Approach to Person-Centered Care and Shared Decision Making: Moral Psychology, Executive Autonomy, and Ethics in Multi-Dimensional Care Decisions. *Health Communication* 2016;31(8):964-73.

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Efeito do atendimento nutricional intensivo em pacientes com câncer de cabeça e pescoço submetidos à radioterapia

Pesquisador: José Eluf Neto

Área Temática:

Versão: 1

CAAE: 93676618.0.0000.0065

Instituição Proponente: Faculdade de Medicina da Universidade de São Paulo

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.786.166

Apresentação do Projeto:

Projeto para obtenção de título - Doutorado.

Estudo observacional retrospectivo e prospectivo.

Parte retrospectiva (coleta de dados clínicos, sociodemográficos e do estado nutricional - prontuário) / parte prospectiva (aplicação de 2 escalas de Qualidade de vida).

Objetivo da Pesquisa:

Verificar o efeito do protocolo de atendimento nutricional semanal (intensivo) no estado nutricional e na qualidade de vida de pacientes com câncer de cabeça e pescoço submetidos à radioterapia;

Investigar fatores relacionados à aderência ao protocolo de atendimento nutricional intensivo.

Avaliação dos Riscos e Benefícios:

Quanto aos riscos da pesquisa, pode-se classificá-la como pesquisa de riscos mínimos, pois não oferece aos participantes nenhuma exposição diferente daquelas que já vivenciam em suas atividades cotidianas. Além disso, os pesquisadores se comprometem em manter sigilo sobre a identidade dos participantes.

Não há benefício direto para o participante. Trata-se de estudo observacional testando a hipótese

Endereço: DOUTOR ARNALDO 251 21º andar sala 36

Bairro: PACAEMBU

CEP: 01.246-903

UF: SP

Município: SAO PAULO

Telefone: (11)3893-4401

E-mail: cep.fm@usp.br

Continuação do Parecer: 2.786.166

de que o aconselhamento nutricional intensivo melhora o estado nutricional e a qualidade de vida de pacientes. Somente no final do estudo poderemos concluir a presença de algum benefício.

Comentários e Considerações sobre a Pesquisa:

Comparação entre dados de pacientes de janeiro de 2010 a dezembro 2012 (período pré) x dados de pacientes de janeiro 2013 a dezembro de 2017 (período pós)*

*protocolo de atendimento nutricional semanal no setor de radioterapia do ICESP foi implantado no final de dezembro de 2012.

Grupo aderente (até 2 faltas) x grupo não aderente (+ de 2 faltas) - análise do período pós.

Considerações sobre os Termos de apresentação obrigatória:

Solicitado dispensa do TCLE para a parte retrospectiva do estudo - de acordo.

TCLE para a parte retrospectiva - de acordo com a Resolução 466.

Conclusões ou Pendências e Lista de Inadequações:

Aprovado.

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_DO_PROJETO_1116291.pdf	13/07/2018 09:18:07		Aceito
Outros	formulario_cep_Sheilla_OK.pdf	13/07/2018 09:16:07	José Eluf Neto	Aceito
Declaração de Instituição e Infraestrutura	parecer_departamentoFMUSP.pdf	02/07/2018 22:54:11	José Eluf Neto	Aceito
Folha de Rosto	folha_de_rosto.pdf	02/07/2018 22:53:23	José Eluf Neto	Aceito
Outros	Dispensa_de_TCLE.pdf	29/06/2018 10:38:33	José Eluf Neto	Aceito
TCLE / Termos de Assentimento /	TCLE_projetoICESP_Ok.pdf	29/06/2018 09:27:37	José Eluf Neto	Aceito

Endereço: DOUTOR ARNALDO 251 21º andar sala 36

Bairro: PACAEMBU

CEP: 01.246-903

UF: SP

Município: SAO PAULO

Telefone: (11)3893-4401

E-mail: cep.fm@usp.br

USP - FACULDADE DE
MEDICINA DA UNIVERSIDADE
DE SÃO PAULO - FMUSP



Continuação do Parecer: 2.786.166

Justificativa de Ausência	TCLE_projetoICESP_Ok.pdf	29/06/2018 09:27:37	José Eluf Neto	Aceito
Declaração de Instituição e Infraestrutura	Parecer_nucleo_icesp.pdf	29/06/2018 09:27:12	José Eluf Neto	Aceito
Orçamento	ORCAMENTO_ok.pdf	29/06/2018 09:25:40	José Eluf Neto	Aceito
Cronograma	Cronograma_OK.pdf	29/06/2018 09:21:55	José Eluf Neto	Aceito
Projeto Detalhado / Brochura Investigador	projeto_doc_ICESP_29jun_ok.pdf	29/06/2018 09:21:13	José Eluf Neto	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

SAO PAULO, 26 de Julho de 2018

Assinado por:

**Maria Aparecida Azevedo Koike Folgueira
(Coordenador)**

Endereço: DOUTOR ARNALDO 251 21º andar sala 36

Bairro: PACAEMBU

CEP: 01.246-903

UF: SP

Município: SAO PAULO

Telefone: (11)3893-4401

E-mail: cep.fm@usp.br

São Paulo, 04 de junho de 2018.

Registro: NP 1313/18

Ref. Solicitação de execução de estudo: **Efeito do atendimento nutricional intensivo em pacientes com câncer de cabeça e pescoço submetidos à radioterapia.**

Pesquisador Responsável: Dr. José Eluf Neto
Pesquisador Executante: Dra. Sheila de Oliveira Faria

CONSIDERAÇÕES

Trata-se de um estudo prospectivo e retrospectivo com a finalidade de obtenção de título. O estudo visa verificar o efeito do protocolo de atendimento nutricional intensivo no estado nutricional e na qualidade de vida de pacientes com câncer de cabeça e pescoço submetidos à radioterapia e investigar fatores relacionados à aderência ao protocolo de atendimento nutricional intensivo. Esse projeto será desenvolvido no Instituto do Câncer do Estado de São Paulo – Icesp.

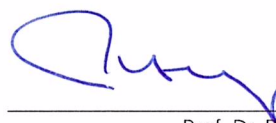
RESPONSABILIDADES DO PESQUISADOR

Antes do início das atividades relacionadas ao estudo:

- Apresentar a aprovação do Comitê de Ética em Pesquisa da FMUSP para execução no ICESP conforme a Resolução 466/12 do Conselho Nacional de Saúde, Ministério da Saúde;
- Enviar anualmente o *status* ou relatório do estudo. Projetos sem informações por mais de 1 ano serão cancelados automaticamente e impedirá a submissão de novos projetos pelos investigadores;
- Enviar resultados do projeto (publicações, defesa de tese, apresentação em congressos e outros);

Informamos que sua solicitação foi DEFERIDA

Atenciosamente,



Prof. Dr. Paulo M. Hoff
Diretor Geral

Prof. Dr. Paulo M. Hoff
Diretor Geral
ICESP

Versão 2.0 28 de Dezembro de 2017.