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IMPACTO DE DOIS REGIMES DE EXERCÍCIOS PROFILÁTICOS À HIPOMOBILIDADE MANDIBULAR NA MEDIDA DE ABERTURA BUCAL, MUCOSA ORAL, DOR, CAPACIDADE FUNCIONAL E QUALIDADE DE VIDA DE PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO SUBMETIDOS À RADIOTERAPIA

PORTO ALEGRE

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Orientador: Prof. Dr. Geraldo Pereira Jotz
Coorientador: Prof. Dr. Rodrigo Della Méa Plentz

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“Os que se encantam com a prática sem a ciência são como os timoneiros que entram no navio sem timão nem bússola, nunca tendo certeza do seu destino”.

(Leonardo da Vinci)

RESUMO

Introdução: Trismo radioinduzido (TR) refere-se a hipomobilidade mandibular decorrente da fibrose na musculatura mastigatória, quando localizada no campo de radiação. O TR é uma complicação progressiva e tardia da radioterapia (RDT), tendo pico de incidência entre os 9 e 12 meses do término da RDT. Estudos prévios enfatizam que o TR é de difícil resolução e, portanto, esforços devem ser focados na prevenção dessa complicação, entretanto, até a atual data, nenhum protocolo de prevenção demonstrou-se efetivo para tal finalidade. **Objetivo:** Verificar o efeito de dois protocolos de exercícios terapêuticos na preservação da mobilidade mandibular de pacientes com câncer de cabeça e pescoço (CCP) submetidos a RDT e, secundariamente, verificar o impacto dos exercícios na mucosa oral, dor, capacidade funcional e qualidade de vida (QV). **Métodos:** Trata-se de um ensaio clínico de prevenção, randomizado-controlado, paralelo, duplo-cego, com três braços. Esta pesquisa está registrada no ClinicalTrials.gov e no Registro Brasileiro de Ensaios Clínicos, sob número de registro NCT02094690 e RBR-89mdvw, respectivamente. Noventa pacientes foram randomizados em três grupos: Grupo intervenção 1 (G1) – exercícios ativos da mandíbula, alongamento da musculatura mastigatória com o Therabite e treino de mastigação com hiperboloide; Grupo intervenção 2 (G2) - exercícios ativos da mandíbula e treino de mastigação com hiperboloide; e grupo controle (GC) – receberam apenas o protocolo padrão pré-radioterapia da instituição. Os grupos intervenção receberam o material necessário para realizar o protocolo em domicílio 4x/dia e, foi realizada 1x/semana, uma sessão de exercícios supervisionada pelo fisioterapeuta treinador, nas dependências do serviço de RDT, durante todo o tratamento radioterápico. A medida de abertura bucal máxima (ABM) foi mensurada com paquímetro digital antes do início da RDT (T0), imediatamente após a última sessão de RDT (T1) e 12 meses após o término da RDT (T2). A mucosite oral foi classificada de acordo com a Escala de Toxicidade Oral da Organização Mundial da Saúde (OMS). A dor foi avaliada usando a escala visual

analógica. A capacidade funcional foi medida pela *Karnofsky Performance Status* e a QV foi mensurada através do Questionário de Avaliação da Qualidade de Vida da Universidade de Washington (UW-QoL). **Resultados**: A ABM não apresentou diferença significativa entre os grupos nos três momentos avaliados (p=0.264). A variação na medida de abertura bucal do T0 para o T2 foi de -1 mm no GC (95% intervalo de confiança [IC], -4.0 a 2.0), 1.3 mm no G1 (95% IC, -1.7 a 4.3) e 0.5 mm no G2 (95% IC, -3.4 a 4.4). No T1 a dor e a mucosite foram significativamente maiores no G1 quando comparado ao GC (p<0.024 e p<0.001, respectivamente). A capacidade funcional reduziu em todos os grupos do T0 para o T1 (p<0.001) mas sem significância entre os grupos (p=0.737). O escore total do UW-QoL reduziu significativamente do T0 para o T1 (p<0.001) e apresentou melhora significativa do T1 para o T2 em todos os grupos (p<0.001), sem diferenças significativas entre os grupos (p=0.180). **Conclusão**: Não é possível concluir que os protocolos de exercícios propostos nesse estudo são mais eficazes para a prevenção do TR que a orientação padrão pré-radioterapia. Mais estudos são necessários para verificar a eficácia e o impacto na medida de ABM de exercícios profiláticos ao TR iniciados após o término da RDT, quando as alterações agudas da mucosa estiverem resolvidas, pois de acordo com este estudo iniciar os exercícios durante a RDT parece não ter benefício terapêutico na medida de ABM e pode aumentar a dor associada a mucosite. Nenhum dos protocolos apresentados nesse estudo foi capaz de evitar a redução na capacidade funcional e na QV dos pacientes.

Palavras-chave: Neoplasias de cabeça e pescoço. Trismo. Radioterapia. Amplitude de movimento articular. Modalidades de fisioterapia. Terapia por exercício.

ABSTRACT

Background: Radiation-induced trismus (RIT) is a reduction in mouth opening measurement due to fibrosis in the masticatory musculature when located in the radiation field. RIT is a late and progressive complication of radiotherapy treatment (RDT), has a peak incidence around 9 to 12 months after the end of the RDT. Previously studies emphasize that RIT is difficult to treat, and, therefore, efforts should focus on its prevention; however, so far, no clinical trial has been able to demonstrate an effective protocol for the prevention of RIT. **Objective:** To verify the effect of two preventive interventions consisting of therapeutic exercises performed during the RDT in the preservation of mandibular range of motion, and to ascertain whether associations exist between RIT outcomes and mucositis, pain, performance status and quality of life (QOL). **Methods:** This study was a randomized, controlled, double-blind, three-arm, parallel-group, prevention clinical trial. The trial is registered at ClinicalTrials.gov, number NCT02094690, and at the Brazilian Clinical Trials Registry, number RBR-89mdvw. Ninety patients were randomized into 3 groups: intervention group 1 (G1) – active exercises of the mandible, stretching exercise with Therabite and masticatory training with Hiperbolóide; intervention group 2 (G2) - active exercises of the mandible and masticatory training with Hiperbolóide, and control group (CG) - usual care guidance from the institution. The exercise groups received the instructions and the devices to perform the protocol exercises four times a day at home and throughout the course of RDT, patients performed one supervised exercise session per week, under the guidance of the trainer physiotherapist. Maximum mouth opening (MMO) was measured with a digital paquimeter before (T0), immediately after (T1), and at 12 months (T2) after completion of radiotherapy treatment. Oral mucositis was graded in accordance with the World Health Organization (WHO) Oral Toxicity Scale. Pain was assessed using a visual analog scale. Functional capacity was measured by the *Karnofsky Performance Status*. QOL was assessed

using the self-administered University of Washington Quality of Life (UW-QOL) Questionnaire. **Results**: There was no significant difference in mouth opening measure between the groups at the three assessment time points (p=0.264). The difference in mouth opening measure from baseline to 12 months after having completed radiotherapy was -1 mm in CG (95% confidence interval [CI], -4.0 to 2.0), 1.3 mm in G1 (95% CI, -1.7 to 4.3) and 0.5 mm in G2 (95% CI, -3.4 to 4.4). At T1 the grade of pain and the incidence of mucositis was significantly higher in G1 than CG (p<0.024 and p<0.001, respectively). There was a significantly reduction in performance status in all groups from T0 to T1 (p<0.001) but without differences between the groups (p=0.737). The composite score of the University of Washington Quality of Life (QOL) Questionnaire showed a significantly decreased from T0 to T1 (p<0.001) and presented a significant increase from T1 to T2 in all groups (p<0.001), without significant differences between the groups (p=0.180). **Conclusion**: It is not possible to conclude that the exercise protocols performed in this study are more effective in the prevention of RIT than the usual guidance for patients undergoing radiotherapy. Further studies are needed to verify the efficacy and the impact on MMO of prophylactic exercises for RIT initiated after RDT treatment, when the acute mucosal reactions are resolved, since according to our study, initiating exercises during RDT seems not to have a therapeutic benefit to MMO, and may increase the pain associated with mucositis. Neither of the prophylaxis protocols tested in this study was able to prevent declines in performance status and in QOL.

Keywords: head and neck neoplasms. Trismus. Radiotherapy. Joint range of motion. Physical therapy. Exercise therapy.

SUMÁRIO

APRESENTAÇÃO

Este trabalho consiste na Tese de Doutorado intitulada “Impacto de dois regimes de exercícios profiláticos ao trismo na abertura bucal, mucosa oral, dor, capacidade funcional e qualidade de vida de pacientes com câncer de cabeça e pescoço submetidos a radioterapia”, a ser apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Ciências da Saúde de Porto Alegre, em seis de junho de 2019. Essa pesquisa foi avaliada e aprovada pelo Comitê de Ética em Pesquisa (CEP) da Irmandade Santa Casa de Misericórdia de Porto Alegre e pelo CEP da Universidade Federal de Ciências da Saúde de Porto Alegre, conforme parecer consubstanciado número 259.691 e número 311.888, respectivamente. Essa pesquisa é uma continuação do estudo desenvolvido no mestrado, realizado nesta mesma instituição e programa de pós-graduação, resultando no artigo intitulado “Jaw mobility changes in patients with upper aerodigestive tract cancer undergoing radiation therapy”, publicado em novembro de 2015 na revista “Medicina Oral Patologia Oral y Cirugia Bucal” - doi:10.4317/medoral.20477 (Apêndice A).

Essa tese é composta pelas seguintes partes: apresentação, revisão da literatura, justificativa, objetivos e três manuscritos científicos. O primeiro, intitulado *“Effect of physiotherapy to prevent trismus in irradiated head and neck cancer patients: study protocol for a randomized, investigator-blinded, controlled, superiority trial”*, foi submetido para publicação na categoria “*Study Protocol”* no periódico *“BMC Cancer”*. O segundo manuscrito, intitulado “*Exercise therapy during radiotherapy treatment seems not to prevent radiation-induced trismus in head and neck cancer patients: a randomized controlled trial”*, será enviado para apreciação do corpo editorial do periódico *“Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology”,* na categoria *“Original Research”;* e o terceiro manuscrito, intitulado “*Health-related quality of life up to 1 year after radiotherapy in head and neck cancer patients with and without trismus”* será submetido para apreciação do corpo editorial do periódico *“Health and Quality of Life Outcomes”* na categoria *“Short Report”*.

1 REVISÃO DA LITERATURA

1.1 INTRODUÇÃO

A incidência de câncer de cabeça e pescoço (CCP) está aumentando e os avanços no tratamento oncológico contribuem significativamente para melhorias na sobrevida (HADDAD e DONG 2008, MINISTÉRIO DA SAÚDE 2018). No entanto, um número crescente de sobreviventes de CCP agora vive com as sequelas a longo prazo do tratamento do câncer (COUSINS et al. 2013). As modalidades terapêuticas para tratamento dos tumores malignos de cabeça e pescoço incluem procedimentos cirúrgicos, radioterápicos e quimioterápicos que podem ser utilizados isoladamente ou em conjunto (PANTVAIDYA et al. 2019). A radioterapia (RDT) desempenha um papel fundamental no tratamento de pacientes com CCP (BORRAS et al. 2015). Aproximadamente 80% (intervalo 73,9 - 84,4%) de todos os pacientes com CCP receberão RDT pelo menos uma vez durante o curso de sua doença (BORRAS et al. 2015).

O principal mecanismo de ação da RDT é restringir o potencial reprodutivo das células tumorais por induzir a morte celular por meio de apoptose, necrose, catástrofe mitótica, senescência e autofagia (DELOCH et al. 2016). Não somente as células tumorais são irradiadas durante o curso da RDT. Algum grau de dano é infligido nas células normais adjacentes ao tumor e aos volumes alvo associados (STROJAN et al. 2017). A manifestação clínica dos danos resultantes depende da sensibilidade à radiação e da organização celular dos tecidos irradiados, bem como do padrão de distribuição da dose de radiação acumulada nesses tecidos (BENTZEN et al. 2010).

Nenhuma tecnologia é capaz de proteger completamente os tecidos normais da irradiação e os pacientes sempre experimentarão algum grau de toxicidade associada à radiação (MACHTAY et al. 2008). As toxicidades da RDT para CCP são classificadas como agudas ou tardias com base no momento em que se desenvolvem em relação ao tratamento (STROJAN et al. 2017). A toxicidade aguda desenvolve-se durante ou logo após a conclusão do tratamento e é geralmente temporária. A toxicidade tardia surge meses a anos após a conclusão do tratamento e é frequentemente permanente (PAYAKACHAT et al. 2013). A relação entre a duração e severidade da reação aguda e efeitos tardios tem sido investigada na literatura, uma vez que efeitos colaterais tardios podem persistir como desfechos adversos dos efeitos colaterais agudos não totalmente reparados (VAN DER LAAN et al. 2015).

Trismo é um importante efeito colateral tardio da RDT, todavia a redução da abertura bucal pode já ser observada durante o tratamento radioterápico (GOLDSTEIN et al. 1999; BRAGANTE et al. 2012) principalmente se o paciente apresentar mucosite e capacidade funcional reduzida (JOHNSON et al. 2010; BRAGANTE et al. 2015).

1.2 TRISMO

A palavra trismo deriva da palavra grega "*trismos*" que significa ranger ou chiar (BASMAJIAN 1982). Historicamente, o termo era usado para referir-se à incapacidade de um paciente abrir a boca, devido a uma contração tônica dos músculos mastigatórios, resultante do tétano (DHANRAJANI e JONAIDEL 2002; RAPIDIS et al. 2015). Atualmente, o termo trismo é utilizado para indicar qualquer condição de hipomobilidade mandibular, de qualquer etiologia (ICHIMURA e TANAKA 1993; DHANRAJANI e JONAIDEL 2002; TEGUH et al. 2008; RAPIDIS et al. 2015).

Trismo tem uma série de possíveis causas. As principais condições predisponentes são: trauma; tratamento odontológico; distúrbios da articulação temporomandibular (ATM); cirurgias; medicamentos; problemas congênitos; perturbações psicológicas; tumores malignos; radioterapia e quimioterapia (DHANRAJANI e JONAIDEL 2002; COHEN et al. 2005; SHULMAN et al. 2008; RAPIDIS et al. 2015). Quando relacionado a neoplasias de cabeça e pescoço, esta complicação pode ocorrer por infiltração tumoral na musculatura mastigatória e na ATM, por obstrução mecânica, pelo tumor, do processo coronóide da mandíbula (BHRANY et al. 2007; STUBBLEFIELD et al. 2010); após intervenção cirúrgica em lesões tumorais que envolvam a musculatura mastigatória ou ATM (PANTVAIDYA et al. 2019) e, decorrente da radioterapia, em função da fibrose radioinduzida que ocorre na musculatura mastigatória e tecidos conjuntivo ao redor (JOHNSON et al. 2010; BENSADOUN et al. 2010; RAPIDIS et al. 2015; VAN DER GEER et al. 2019).

1.2.1 Trismo Radioinduzido

Trismo radioinduzido é decorrente da fibrose na musculatura mastigatória, quando localizada no campo de radiação, causando redução da mobilidade mandibular (DHANRAJANI e JONAIDEL 2002; KENT et al. 2008; TEGUH et al. 2008). A musculatura mastigatória, quando afetada pela irradiação, reage inicialmente através de uma proliferação anormal de fibroblastos que acentuam a síntese de colágeno levando à formação de tecido

fibroso espesso (TEGUH et al. 2008; BENSADOUN et al. 2010; STUBBLEFIELD 2011; HOJAN e MILECKI 2013).

A medida de mobilidade mandibular normal, descrita na literatura, para abertura bucal (AB) varia entre 40 a 70 mm (MEZITIS et al. 1989; KHARE et al. 2012). Esses valores variam de acordo com fatores como gênero, idade, peso corpóreo, estatura, condição dentária e presença de sinais e sintomas de disfunção temporomandibular (DHANRAJANI e JONAIDEL 2002; KHARE et al. 2012). Diferentes pontos de corte foram descritos para o trismo com base no estado dentário dos pacientes: 35 mm para pacientes dentados e 40 mm para pacientes edêntulos (KENT et al. 2008). Outros pontos de corte para o trismo são baseados na severidade da restrição, como 35 mm para trismo moderado e 20 ou 25 mm para trismo severo (STEINER et al. 2015). Dijkstra et al. (2006) em estudo transversal com amplo número amostral, padronizaram o ponto de corte funcional para trismo, com base nas restrições relatadas por pacientes com CCP, como sendo uma AB $\leq$35 mm, mensurada com paquímetro, independente da condição dentária e do gênero do paciente. O ponto de corte de 35 mm ou menos para o trismo foi confirmado em uma população com CCP pelo estudo de VAN DER GEER et al. (2019) e é recomendado para estudos futuros.

Na literatura, a incidência média do trismo radioinduzido em pacientes com CCP costuma oscilar em torno de 56% (GOLDSTEIN et al. 1999; KENT et al. 2008; BENSADOUN et al. 2010; JOHNSON et al. 2010; WEBER et al. 2010; BRAGANTE et al. 2015; VAN DER GEER et al. 2016). A prevalência do trismo pode ser reduzida com o uso da radioterapia com intensidade de feixe modulada (IMRT) (CHEN et al. 2011; GEBRE-MEDHIN et al. 2016), entretanto, essa modalidade de tratamento não está disponível em muitos hospitais no Brasil para o tratamento de pacientes no sistema público de saúde, levando a uma maior prevalência de trismo nesses pacientes (BRAGANTE et al. 2015).

Mesmo sob baixas doses de irradiação, a redução da abertura bucal pode ocorrer durante o tratamento radioterápico (GOLDSTEIN et al. 1999; BRAGANTE et al. 2012) principalmente se a funcionalidade do paciente estiver reduzida (JOHNSON et al. 2010; BRAGANTE et al. 2012) e os campos irradiados incluírem a boca e/ou a orofaringe (GOLDSTEIN et al. 1999; WEBER et al. 2010). Porém, a incidência do trismo radioinduzido aumenta proporcionalmente ao aumento da dosagem de irradiação (TEGUH et al. 2008, KAMSTRA et al. 2015, RAPIDIS et al. 2015, GEBRE-MEDHIN et al. 2016) e após o término do tratamento (ICHIMURA e TANAKA 1993; KAMSTRA et al. 2015). O trismo tem um pico de incidência entre os 9 e 12 meses após a RDT, porém pode continuar progredindo por vários anos após o término da terapia de irradiação (WANG et al. 2005;

TEGUH et al. 2008). Outros fatores de risco para o decréscimo da abertura bucal incluem: tumores avançados (KAMSTRA et al. 2015), menor AB prévia ao tratamento, mostrando-se esse um significante preditor para o desenvolvimento do trismo (JOHNSON et al. 2010, KAMSTRA et al. 2015; VAN DER GEER et al. 2016), gênero feminino (LEE et al.2012; KAMSTRA et al. 2015) e maior idade (KAMSTRA et al. 2015, VAN DER GEER et al. 2019), pois a medida que o paciente envelhece, a amplitude de movimento diminui devido às alterações micro e macro nas articulações e ligamentos, o que também inclui a articulação temporomandibular (HANDFORTH et al. 2015).

1.2.2 Fisioterapia no tratamento do trismo radioinduzido

A fisioterapia é considerada a primeira linha no tratamento conservador do trismo radioinduzido, porém para a prevenção deste indesejado efeito colateral da RDT a sua efetividade não foi ainda devidamente estabelecida na literatura (STUBBLEFIELD et al. 2010).

A abordagem mais comumente utilizada para tratar o trismo se dá através do alongamento da musculatura mastigatória, com ou sem a assistência de um dispositivo abridor de mordida, sendo considerado assim, alongamento passivo e ativo, respectivamente (PAULI et al. 2015). Exercício ativo ocorre quando o movimento é impulsionado pela musculatura ao redor da articulação. Já o exercício passivo ocorre quando uma força externa é aplicada causando movimento da articulação na ausência de atividade muscular (BENSADOUN et al. 2010).

Os exercícios ativos citados na literatura para tratamento do trismo incluem exercícios de abrir e fechar a boca, mover a mandíbula para direita e para esquerda e mover a mandíbula para frente e para trás, com frequências ao dia, número de repetições e tempo de sustentação do alongamento variados (RIDDER 1993; WHYTMYER et al. 1997; DHANRAJANI e JONAIDEL 2002; BENSADOUN et al. 2010; KAMSTRA et al. 2017).

O exercício passivo para alongamento da musculatura mastigatória pode ser realizado pelo fisioterapeuta, que, com luvas, após o paciente abrir a boca, posiciona o polegar nos incisivos centrais superiores, cruzando o indicador em direção aos incisivos centrais inferiores do paciente, o que permitirá a alavanca necessária para forçar a AB (RIDDER 1993); ou pelo próprio paciente realizando tal manobra (WHYTMYER et al. 1997); ou ainda através de dispositivos, chamados abridores de mordida, que permitem o alongamento passivo (BENSADOUN et al. 2010).

O estudo de MELCHERS et al. (2009) verificou que a utilização de um dispositivo abridor de mordida associado a um protocolo de exercícios, melhora a adesão do paciente ao tratamento do que apenas exercícios ativos sem auxílio de aparelhos.

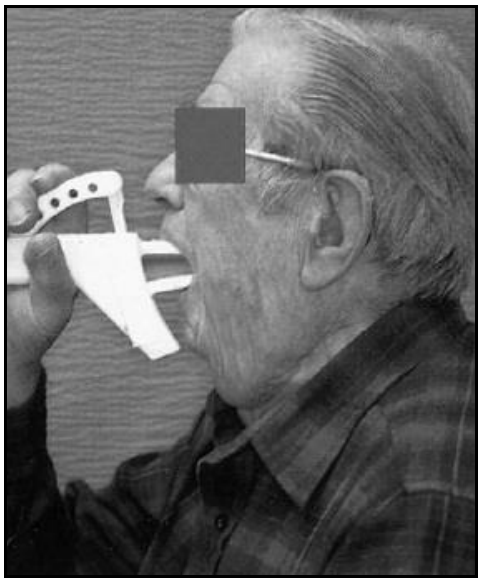
As duas principais ferramentas acessórias rotineiramente citadas na literatura para o alongamento passivo da musculatura mastigatória são:

1) *Dynasplint Trismus System* – DTS (Figura 1): É um dispositivo de mobilização da mandíbula, com bandejas bucais personalizadas, possibilitando mãos livres. Possui um sistema de tensão reprodutível, calibrado e modificável conforme a necessidade do paciente, produzindo um alongamento de baixo torque com o objetivo de atingir a duração de 90 minutos ao dia (SHULMAN et al. 2009; KAMSTRA et al. 2016; ZATARAIN et al. 2018). Não está disponível comercialmente no Brasil.

Fonte: Adaptado de DYNASPLINT SYSTEMS 2018

Figura 1- Foto ilustrativa do uso do *Dynasplint Trismus System*

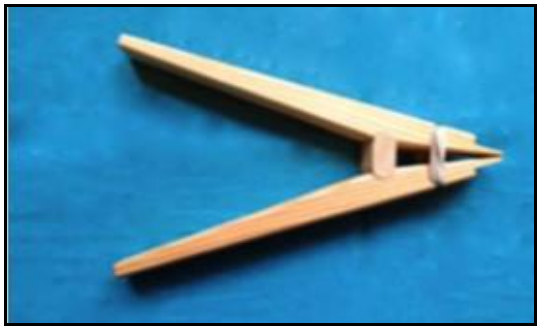
2) Therabite (Figura 2): é um dispositivo de plástico que é colocado na boca; possui *pads* que são ajustados conforme a dentição do paciente; e, atua com a aplicação de força manual conferindo abertura bucal proporcional ao quão rígidas às alavancas do dispositivo são apertadas. A força é normalmente feita próxima à tolerância máxima do paciente (STUBBLEFIELD et al. 2010) e a duração recomendada varia de sete a 30 segundos, realizando de sete a dez repetições, entre três a sete vezes por dia (TANG et al. 2011; PAULI et al. 2015). Este dispositivo está comercialmente disponível no Brasil, tendo registro ANVISA, nº 80911510012.



Fonte: Adaptado de COHEN et al. (2005)

Figura 2 – Foto ilustrativa do uso do Therabite

Outras ferramentas terapêuticas como o *"Engstrom Device"* (PAULI et al. 2014; PAULI et al. 2016) - não disponível comercialmente no Brasil – (Figura 3), a goma de mascar (GRANDI et al. 2007) e as espátulas de madeira (DIJKSTRA et al. 2006) também atuam em adjuvância com a fisioterapia convencional para tratamento do trismo radioinduzido.



Fonte: Adaptado de PAULI et al. (2015)

Figura 3 – *"Engstrom Device"*

Apesar do uso generalizado desses dispositivos no tratamento do trismo radioinduzido, ainda não há um tratamento padrão ouro para essa complicação (DIJKSTRA et al. 2006; TANG et al. 2011; KAMSTRA et al. 2013; PAULI et al. 2014; KAMSTRA et al. 2016). As revisões sistemáticas existentes sobre o assunto, sugerem que o trismo deveria ser prevenido ao invés de tratado, pois é uma complicação de difícil resolução, e, uma vez estabelecido o trismo, apenas um aumento limitado na abertura bucal pode ser alcançado

(BENSADOUN et al. 2010; COUSINS et al. 2013; SCHERPENHUIZEN et al. 2015; KAMSTRA et al. 2017). Tais revisões sistemáticas também afirmam que a qualidade metodológica dos artigos encontrados é baixa, o que impossibilita realizar metaanalise dos dados.

Uma distinção importante a ser feita é que o trismo cirúrgico não pode e não deve ser comparado com o trismo radioinduzido, pois o primeiro é de fácil resolução, já o segundo é, frequentemente, crônico e progressivo. Foi constatado no estudo de REN et al. (2013), em pacientes com trismo cirúrgico, um aumento de 14 mm após duas a seis semanas de exercícios com Therabite; COHEN et al. (2005), que também utilizou o Therabite (em pacientes com CCP após cirurgia), verificou um aumento de 10 mm na AB, resultados esses mantidos no follow-up tardio (seis meses após a cirurgia). Já VAN DER MOLEN et al. (2014) relataram, em seu estudo com pacientes com CCP irradiados, que também realizaram exercícios com o Therabite, uma redução média de 20,6 mm da AB no follow-up tardio (um ano após o tratamento oncológico).

Os protocolos de prevenção também diferem dos protocolos de tratamento do trismo radioinduzido, principalmente no quesito adesão, pois nos protocolos de prevenção ao objetivar-se manter a função, o paciente não observa ganho na medida de AB, como ocorre nos protocolos de tratamento, e, com isso, desmotiva-se em continuar o protocolo de prevenção, sendo esse um importante fator que limita à adesão aos protocolos preventivos (MELCHERS et al. 2009; ZATARAIN et al. 2018).

1.2.3 Prevenção do trismo radioinduzido.

Até o ano em que começamos a realizar nossa pesquisa, apenas um ensaio clínico randomizado e controlado que analisava exercícios na prevenção do trismo em pacientes irradiados havia sido publicado (LOORENTS et al. 2014), também havia um estudo quase experimental (GRANDI et al. 2007) e dois ensaios clínicos onde a medida de AB era desfecho secundário (VAN DER MOLLEN et al. 2011; CARNABY-MANN et al. 2012). Um ensaio clínico (HOGDAL et al. 2015) e um quase experimento (LEE et al. 2018) para prevenção do trismo radioinduzido foram publicados recentemente. Os resultados principais desses estudos (no que tange à medida de AB) serão relatados a seguir, por ordem cronológica.

O estudo quase experimental de GRANDI et al. (2007) teve como objetivo prevenir o trismo radioinduzido por meio de dois regimes terapêuticos diferentes. Cinquenta e quatro pacientes, foram distribuídos em três grupos: Grupo controle - não realizou exercícios; Grupo

1 - realizou o protocolo de BUCHBINDER et al. (1993) que consistia em seis vezes ao dia realizar 10 repetições de exercícios de abrir e fechar a boca, lateralização mandibular para direita e esquerda e protrusão mandibular; Grupo 2 - realizou o protocolo de SANTOS (2003) que consistia em três vezes ao dia realizar cinco repetições de: exercícios de abrir e fechar a boca, lateralização mandibular direita e esquerda, protrusão mandibular e após mascar dois Trident® por 15 min. Os exercícios foram realizados diariamente em domicílio, sem supervisão, durante todo tratamento com a terapia de irradiação. Como resultado, a AB mostrou uma tendência de redução em todos os grupos, mas sem significância estatística. Não houve diferença significativa na medida da AB entre os grupos, mas houve uma tendência (provável erro tipo II em função do reduzido número amostral) do grupo 2 ter melhores resultados. Não foi possível concluir que os exercícios de fisioterapia são eficazes para prevenir a redução da medida de AB.

O estudo de VAN DER MOLLEN et al. (2011) teve como objetivo avaliar o efeito de exercícios preventivos na deglutição e medida de AB em pacientes com CCP recebendo quimiorradioterapia. Quarenta e nove pacientes foram randomizados em: cuidados padrão (exercícios mandibulares sem ajuda de dispositivos tanto para deglutição quanto para o trismo) ou braço experimental (somente Therabite para treino da deglutição e trismo). Não houve diferença na AB entre os grupos e ao comparar as medidas de AB, pré e pós tratamento, de ambos grupos, houve uma redução significativa nessa medida (50 para 47mm, $p<0.01$). É importante frisar que uma significância estatística não necessariamente tem relevância clínica (SCHERPENHUIZEN et al. 2015). Estudos prévios indicam que uma diferença, na medida de AB, de no mínimo 5 mm é necessária para ser interpretada como uma alteração clinicamente relevante (JAGER-WITTENAAR et al. 2009; PAULI et al. 2016).

O estudo de CARNABY-MANN et al. (2012) teve como objetivo principal a profilaxia da função da deglutição analisando a AB como desfecho secundário em pacientes submetidos a quimiorradioterapia. Cinqüenta e oito pacientes foram divididos em três grupos: Grupo exercício com Therabite, que fez referência ao estudo de BUCHBINDER et al. (1993) onde os alongamentos foram realizados com o Therabite, seis vezes ao dia, cinco repetições de alongamento sustentando 30 segundos cada, grupo cuidados habituais que recebeu as orientações de rotina da instituição e grupo terapia placebo para a deglutição. O grupo Therabite mostrou um declínio significativamente menor da medida de AB (redução média de 1,6mm) em relação ao grupo placebo e cuidados habituais (redução de 5,1 mm e 4,3 mm, respectivamente, $p=0.046$).

No estudo de LOORENTS et al. (2014) sessenta e seis pacientes consecutivos de duas clínicas de radioterapia da Suécia foram randomizados em dois grupos para possível prevenção do trismo radioinduzido: exercícios com Therabite, que consistiam em realizar cinco vezes ao dia, cinco séries, sustentando 15 segundos o alongamento com o Therabite, ou grupo controle (não recebeu um protocolo de exercícios estruturados). Aos pacientes do grupo controle que reduzissem a AB mais de 15% da medida do baseline era oferecido trocar para o grupo treinamento. Os pacientes do grupo controle realizaram exercícios por conta própria que não foram padronizados nem especificados no estudo. A técnica radioterápica utilizada foi RT3D e IMRT. A medida de AB foi verificada semanalmente durante o curso da RDT e aos seis e 12 meses após o término do tratamento. Não foram incluídos no estudo dados sobre mucosite e tipo de alimentação. Como resultado, os pacientes do grupo controle tiveram aumento médio de 1,7% na AB aos 12 meses contra um decréscimo de 4,3% no grupo exercícios, mas sem significância estatística.

O tempo de alongamento de somente 15 segundos, no estudo de LOORENTS et al. (2014), pode justificar esse aparente melhor resultado no grupo controle, pois esta curta duração de tempo na ADM mandibular máxima resulta em espasmo dos músculos da mastigação (SHULMAN et al. 2009). Haja vista que no estudo de CARNABY-MANN et al. (2012) o grupo que manteve o tempo de alongamento com o uso do *Therabite* em 30 segundos, apresentou uma medida de AB significativamente maior do que os outros grupos. Tal fato pode ser explicado fisiologicamente segundo KISNER e COLBY (2005, p.149):

> "Quando um músculo é alongado muito rapidamente, as fibras aferentes primárias estimulam os motonêuronios alfa da medula espinhal e facilitam a contração das fibras extrafusais, aumentando a tensão no músculo. (....). Se uma força de alongamento lenta é aplicada ao músculo, os órgãos tendinosos de Golgi (OTGs) disparam e inibem a tensão no músculo, permitindo que o componente elástico paralelo (o sarcômero) do músculo permaneça relaxado e se alongue."

O estudo de HODGAL et al. (2015) teve como objetivo investigar os benefícios na AB de um regime de exercício profilático ao trismo em pacientes com CCP submetidos à RDT curativa. Cem pacientes foram randomizados em dois grupos: Grupo intervenção, realizava sete tipos de exercícios (o anexo suplementar com a cartilha de exercícios não estava disponível) cinco a seis vezes por dia e também deveria mascar um Trident® por 10 min,

cinco vezes por dia, durante todo o período da RDT e até 10 meses do término do tratamento oncológico; esse grupo também recebeu, durante o curso da RDT, uma sessão semanal de exercícios de 45 minutos, supervisionada por um fisioterapeuta; o grupo cuidado usual recebia informações sobre exercícios mandibulares (os quais não foram descritos no artigo) pela equipe de enfermagem uma semana antes de iniciar a RDT. O desfecho primário foi a mudança na medida de AB verificada aos 5 e 12 meses após a RDT.

Os autores, do estudo supracitado, verificaram que uma boa adesão ao tratamento ocorreu com somente 12 (24%) pacientes da amostra; não resultando em diferenças na medida de AB entre os grupos intervenção e controle e também sem diferença significativa na medida da AB entre os pacientes que aderiram e os que não aderiram ao protocolo de exercícios. Os autores relatam que realizar exercícios seis vezes ao dia pode ser oneroso para o paciente que está em tratamento oncológico, e que isso pode ter causado a baixa adesão. Os autores concluem que a prevenção através do autocuidado (exercícios domiciliares) com intervenção fisioterapêutica uma vez por semana não pareceu ser uma estratégia promissora para prevenção do trismo radioinduzido em pacientes com CCP; e, sugerem novos estudos com maior controle da adesão dos pacientes para esclarecer se os exercícios podem prevenir a fibrose radioinduzida e com isso evitar o trismo radioinduzido.

No estudo de LEE et al. (2018) a efetividade do Therabite na prevenção e alívio de trismo radioinduzido foi comparada com as espátulas de madeira; ambos os grupos (Therabite ou espátulas de madeira) deveriam realizar cinco séries diárias de cinco repetições cada, sustentando o alongamento por 30 segundos. O acompanhamento foi realizado por contato telefônico e o próprio paciente mensurava a medida de AB com a régua fornecida pelos pesquisadores. Dos 110 pacientes planejados no cálculo amostral, apenas 41 concluíram o estudo, reduzindo o poder estatístico da pesquisa. Esse estudo demonstrou que não há diferença em realizar os exercícios com espátulas ou com Therabite, na prevenção de redução da mobilidade mandibular.

Como observado nos estudos descritos anteriormente, a literatura demonstra dados contraditórios sobre o efeito dos exercícios terapêuticos na prevenção do trismo radioinduzido. Não há consenso de que a fisioterapia, através de exercícios e dispositivos de alongamento passivo, é capaz de prevenir o aparecimento do trismo radioinduzido; e, além disso, não há padronização de um protocolo de exercícios efetivos para atingir tal objetivo.

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2 JUSTIFICATIVA

Trismo é considerado o segundo efeito colateral mais oneroso da terapia oncológica na região da cabeça e pescoço, e, apesar do avanço tecnológico nos tratamentos radioterápicos ter aumentado sobremaneira a sobrevida dos pacientes portadores de CCP, os efeitos colaterais a longo prazo que afetam a qualidade de vida dos pacientes ainda são frequentes. Apropriada prevenção e tratamento das complicações da RDT são necessárias, reduzindo assim comorbidades nesses pacientes com maiores expectativas de vida.

A fisioterapia é considerada a primeira linha no tratamento conservador do trismo radioinduzido, através de exercícios ativos e passivos. Porém, devido a dados contraditórios e a falta de evidência na literatura científica quanto à efetividade de exercícios terapêuticos na prevenção do trismo radioinduzido, verifica-se a necessidade de melhor investigar a eficácia e o impacto de diferentes protocolos de exercícios profiláticos ao desenvolvimento do trismo radioinduzido em pacientes com CCP.

3 OBJETIVOS

3.1 OBJETIVO GERAL

Comparar o efeito de dois protocolos de exercícios fisioterapêuticos com a orientação padrão pré-RDT na prevenção da redução da amplitude de abertura bucal em pacientes com CCP submetidos à radioterapia.

3.2 OBJETIVOS ESPECÍFICOS

- Comparar os valores de abertura bucal obtidos no período pré RDT (baseline), imediatamente após a última sessão de RDT e um ano após o tratamento oncológico, entre os três grupos;
- Comparar os diferentes graus de mucosite encontrados entre os três grupos no período pré RDT (baseline), imediatamente após a última sessão de RDT e um ano após o tratamento oncológico;
- Comparar as diferenças na capacidade funcional entre os três grupos no período pré RDT (baseline), imediatamente após a última sessão de RDT e um ano após o tratamento oncológico;
- Comparar as diferenças na incidência e intensidade de dor entre os três grupos no período pré RDT (baseline), imediatamente após a última sessão de RDT e um ano após o tratamento oncológico;
- Comparar as diferenças na qualidade de vida entre os três grupos, no período pré RDT (baseline), imediatamente após a última sessão de RDT e um ano após o tratamento oncológico;
- Verificar quais variáveis demográficas e clínicas associam-se com a manutenção, redução ou aumento da medida AB;
- Analisar a adesão dos pacientes aos dois protocolos de exercícios.

4 DESENVOLVIMENTO

A seção de desenvolvimento será apresentada a seguir na forma de três manuscritos, que serão enviados para apreciação do corpo editorial dos periódicos *"BMC Cancer"*, *"Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology"* e *"Health and Quality of Life Outcomes"*, respectivamente.

4.1 MANUSCRITO I

Effect of physiotherapy to prevent trismus in irradiated head and neck cancer patients: study protocol for a randomized, investigator-blinded, controlled, superiority trial.

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Abstract:

Background: Radiotherapy treatment (alone or as adjunct to surgery and/or chemotherapy) is a well-established method for treating patients with head and neck cancer (HNC); however, side effects such as radiation-induced trismus can occur. This complication has a high

incidence and a negative effect on the quality of life of patients. The current evidence suggests that radiation-induced trismus is difficult to solve; therefore, efforts should focus on its prevention rather than its management. Physiotherapy resources have been used to treat mandibular hypomobility. The most widely used device for the treatment of reduced mouth opening is TheraBite; however, it is expensive, and its effect on prevention of trismus in irradiated HNC remains unclear. The aim of this study is to investigate the efficacy of two protocols of physiotherapy (with or without TheraBite) in order to prevent radiation-induced trismus in patients with HNC undergoing radiotherapy.

Methods: The study will be conducted as a clinical, investigator blinded, parallel-group, controlled, superiority trial with balanced randomization (1:1:1). The planned sample size is 90 participants (at a ratio of 1:1:1, 30 subjects in each group). Enrolled participants will be randomized into one of three groups: Intervention Group I (physiotherapy plus TheraBite device plus usual care); Intervention Group II (physiotherapy plus usual care); or control group (usual care). Participants in all groups will be evaluated before the beginning of radiotherapy (baseline), after the last radiotherapy session and at 12 months after radiotherapy treatment. The primary endpoint measure is the maintenance of mouth opening. Secondary endpoints include mucositis, performance status, pain, quality of life and protocol adherence.

Discussion: This study will provide new information about physiotherapy for radiation-induced trismus. Once confirmed, these findings may help to avoid radiation-induced trismus in HNC patients, which would help to improve their quality of life, as well as provide a low-cost way to achieve that improvement.

Trial registration: The study is registered in ClinicalTrials.gov under accession number NCT02094690 and ReBEC under accession number RBR-89mdvw.

Keywords: Head and neck neoplasms; Radiotherapy; Trismus; Physical therapy modalities

Background

Trismus, defined as reduced mandibular mobility, is a common problem in patients with head and neck cancer (HNC) [1,2]. It can be caused by the tumor itself, or it can arise as a complication after HNC surgery and/or radiation therapy (RDT) [3]. Trismus has a negative impact on quality of life (QoL), as it can lead to impairment of speech and eating, malnutrition, poor oral hygiene and difficulties with intubation [4-6]. Studies have reported a prevalence of trismus between 38% and 56% among patients treated for HNC, and this restriction in mouth opening may become severe and irreversible over time [4,7,8]. This prevalence of trismus can be reduced by using intensity modulated radiotherapy (IMRT) [9,10]; however, this treatment modality is not available in many hospitals in Brazil for the treatment of patients in the public health system, leading to a higher prevalence of trismus in these patients [11].

Several studies have reported a good outcome in the treatment of postsurgical trismus with physical therapy [12-14]; however, studies reporting the treatment of radiation-induced trismus emphasize that it is difficult to treat, often progressive, and, therefore, efforts should focus on its prevention [15-18].

Radiation-induced trismus is a late complication of RDT that is due to the fibrosis generated in the masticatory muscles, ligaments, tendons and nerves located in the radiation field [19,20]. Current evidence suggests that physical therapy during RDT could prevent this complication, but to date, no well-designed study with long follow-up has been able to demonstrate an effective protocol for the prevention of radiation-induced trismus [21-24]; also, none of these studies controlled the degree of mucositis, and this is an important risk factor for trismus [11]. By causing pain, mucositis limits the functions of the stomatognathic system,

which also forces patients to change the consistency of their diet and, often, to adopt exclusive enteral feeding [25]. Thus, patients move their jaws less and less, which results in connective tissue contractures and deterioration of the muscles of mastication [26]. These muscles start to show signs of atrophy and fibrosis after as little as three days of restricted range of motion [27].

Some of the therapeutic options for trismus treatment and prevention cited in the literature include active jaw exercises, mouth openers – particularly the TheraBite® Jaw Motion Rehabilitation System™ (TheraBite) [15-18] – and chewing gum [21,24].

In the Grandi et al. study [21] patients were allocated across three groups: control (no exercise); Group 1 – free active exercises, which consisted of 10x maximum mouth opening (MMO), right lateral excursion (RLE), left lateral excursion (LLE), and mandibular protrusion (PR), six times a day; and Group 2, which consisted of 5x MMO, RLE, LLE, and PR, followed by chewing two pieces of Trident® gum for 15 minutes, three times a day. They observed a tendency of group 2 to have better results in MMO, but without significant between-group differences. We believe 15 minutes of mastication is an excessively long period and may have had a negative impact on the results of the study and a shorter mastication time should be tested. As the HNC patients often have poor dentition and mucositis, these patients are usually on a soft/semisolid diet or enteral feeding, which suppresses the proprioceptive mechanisms involved in preservation of muscle activity; therefore, their hypoactive muscles of mastication require shorter chewing periods to prevent fatigue [28]. The jaw elevator muscles are generally fatigue-resistant, a property attributed to their rich blood supply and high proportion of type I fibers [29]. However, RDT can affect local perfusion, and studies have shown that a progressive reduction in muscle activity, as measured by electromyography, occurs after three minutes of continuous mastication; even healthy patients report muscle fatigue with longer periods of chewing [30,31].

Edentulous patients do not benefit fully from therapeutic use of chewing gum. In Brazil, 20% of the population is completely edentulous, and HNC patients expected to undergo RDT often have several teeth extracted to remove foci of oral infection that might predispose them to complications [32]. Within this context, the Hiperboloide device, a low-cost chew tool used as an adjunct in the treatment of temporomandibular joint dysfunction [33], has the potential for therapeutic use in patients with HNC. The Hiperboloide device acts on immobility, as the patient is required to activate stomatognathic system components to chew the device, and, thus, we hypothesized that its use during RDT might prevent the development of trismus and sought to compare the results of its use with and without TheraBite, in view of the high cost of the latter device.

Methods and Design

Study aims

The primary aim of this study is to investigate the efficacy of two protocols of physiotherapy in order to preserve mandibular range of motion in HNC patients undergoing RDT. The secondary aims are to verify whether a difference in the adherence to treatment exists between patients who exercise with and without the aid of the TheraBite device; to evaluate the incidence of pain, mucositis, performance status and quality of life in each group.

Trial design and setting

This is a clinical, parallel group, randomized, controlled, superiority trial with follow-up, immediately after the last RDT and 12 months after RDT, that will be conducted at the Santa Casa de Porto Alegre. Patients will be recruited from the radiotherapy department of this hospital.

A brief standard protocol items: Recommendations for Interventional Trials (SPIRIT) flow diagram is provided in Fig. 1, and a populated SPIRIT checklist is provided in Additional file 1.

Participants

Inclusion Criteria

Participants satisfying the following inclusion criteria will be enrolled: either sex; age > 18 years; formal histopathological diagnosis of HNC; undergoing definitive or postoperative external beam RDT for HNC, either alone or in combination with chemotherapy or target therapy; Karnofsky Performance Status (KPS) > 60%.

Exclusion Criteria

If one of the following criteria is met, patients will be excluded from the study: tumor diagnosis not expected to develop trismus (i.e., the esophagus, the skin, the larynx and the hypopharynx); motor sequelae affecting the face or neck region, whether secondary to stroke, facial palsy, trauma and/or surgery that precluded completion of the exercise protocols; cognitive impairments, such as Alzheimer's disease, senile dementia, and/or Wernicke-Korsakoff syndrome, that could impair patient understanding of the exercise protocols; history of prior RDT to the head and neck region; history of surgical interventions involving resection of the mandible; current physical therapy or speech pathology interventions for trismus; initial mouth opening range < 10 millimeter (mm).

Discontinuation criteria for participants

Becoming too ill to continue; electing not to continue; and by medical orders.

Adverse events

Adverse events will be recorded as part of the data collection for each weekly supervised exercise session by training physiotherapist (PT) and will be reported to the clinical authorities and to the ethics committee. Participants suffering adverse events from physical therapy intervention will receive free hospital care to treat the adverse event.

Trial modifications

Important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) will be reported to the relevant parties (investigators, trial participants, trial registry, ethics committee) either immediately (investigators, trial participants) or at the time a report is due (trial registry, ethics committee, journal).

Sample Size

This study is powered to detect a modification, at least 5 mm, in the range of mouth opening motion. The sample size was calculated in PEPI (*Programs for Epidemiologists*) 4.0 software and was based on the studies of Tang et al. [15] and Jager-Wittenar et al. [34] to achieve a significance level of 5%, a statistical power of 90% and an acceptable between-group effect size of one standard deviation (Cohen's d). For the primary outcome, the minimum sample size was calculated as 23 patients per group, for a total of 69 patients. To enable multivariate analysis (10%) and to account for potential attrition (20%), we increased the sample by 30% for a total of 90 patients.

Randomization and blinding

Patients will be randomly allocated in three groups, at a ratio of 1:1:1, by random number generation with the RANDOM subroutine of the PEPI software suite. The

confidentiality of allocation will be ensured by using sealed, numbered, opaque brown paper envelopes. These enveloped will be stored and handled only by a nurse otherwise uninvolved in the study, who will be contacted by telephone, at the start of the intervention, by the physiotherapist (PT) responsible for patient training.

The PT responsible for outcome examination, the radiation oncologists and the statistician will be blinded to the patient allocation. Only the trainer PT and each patient will be aware of the allocation.

Data collection

Patients eligible for inclusion will be identified prior to the start of their radiation therapy regimens, during the weekly multidisciplinary team meetings of the Department of Radiation Oncology. On the day of radiation simulation (one or two weeks before starting RDT), the patients will be informed of the study and will be invited to participate. After providing written informed consent to evaluator PT, participants will be asked standardized questions about their demographic characteristics, socioeconomic status, smoking and drinking habits and medical history. Clinical data will be extracted from medical records regarding tumor site, histological type, concomitant chemotherapy, surgery, radiotherapy and tumor stage (according to the Union for International Cancer Control [UICC] TNM classification of malignant tumors).

Physical examination will be always performed by the same examiner – a trained PT with ample experience in the study protocols - at three time points: before the start of RT (T0), immediately after the last RT session (T1), and at 12 months after radiotherapy treatment (T2). These examinations are used to assess the following outcomes: opening mouth measure, oral mucositis, performance status, pain and quality of life.

Maximum mouth opening (MMO) will be measured using Digimess 100.179N digital calipers (resolution 0.01 mm/.0005", with a certificate of calibration provided by the manufacturer), expressed in mm. The patients will be seated in an upright position and will be asked to open their mouths as wide as possible, without excessive pain. The adaptations proposed by Goldstein et al. [35] and Dijkstra et al. [36] for assessment of completely and partially edentulous patients will be adopted, namely: in patients with an edentulous mandible and no dentures, the distance between the incisal edge of the most vertical maxillary central incisor and the opposing (i.e., corresponding mandibular) alveolar ridge will be measured; in patients with an edentulous maxilla and no dentures, the distance between the incisal edge of the most vertical mandibular central incisor and the opposing alveolar ridge was measured; in fully edentulous patients, MMO will be measured from the mandibular alveolar ridge to the maxillary alveolar ridge along the midline corresponding to the nasopalatine foramen. The condition of the teeth will be noted to enable correction in the event of changes.

Oral mucositis is defined as inflammation of the oral mucosa cavity and is clinically characterized by the presence of erythematous areas that subsequently merge with ulcerations [37]. A variety of assessment scales exist for the measurement of oral mucositis. The most commonly and widely utilized scales is the World Health Organization (WHO) Oral Toxicity Scale, and it will be used in this trial: Grade 0 = No oral mucositis; Grade 1 = Erythema and soreness; Grade 2 = Ulcers, able to eat solids; Grade 3 = Ulcers, requires liquid diet (due to mucositis); Grade 4 = Ulcers, alimentation not possible (due to mucositis) [37,38].

Performance status will be measured by using the *Karnofsky Performance Status* (KPS). The KPS is designed to measure general well-being and activities of daily life, and it is widely used in oncology patients [39,40]. The scores range from 100% to 0%, with 100% indicating normal function, and 0% indicating death [39].

Pain intensity will be assessed using a visual analog scale (VAS) [41]. The VAS for pain has been adapted and validated for use in Brazil [42]. It is a patient self-evaluation scale, ranging from 0 to 10, with 0 meaning no pain and 10 meaning maximum pain [42].

Assessment of quality of life will be through the University of Washington Quality of Life (UW-QOL) Questionnaire, version 4, which has been validated for the Brazilian population [43]. The UW-QOL questionnaire consists of 12 single question domains that have between 3 and 6 response options that are scaled evenly from 0 (worst) to 100 (best) according to the hierarchy of response. The domains are pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood and anxiety. Another question asks patients to choose up to three of these domains that have been the most important to them. There are also three global questions, one about how patients feel relative to before they developed their cancer, one about their health-related QoL and one about their overall QoL. The whole questionnaire focuses on current patient health and quality of life within the past 7 days [43].

Intervention

Exercise protocols

Each patient (always chaperoned by a family member) will receive a booklet containing written and illustrated instructions on the physical therapy protocol to be followed, as well as verbal guidance provided by the trainer PT.

The patients will be allocated randomly across three groups: Intervention Group I (G1), Intervention Group II (G2), and control group (CG). The protocols used in each group were as follows:

G1 (Figure 2): a) warm-up (exercises to enhance joint lubrication): 10x MMO, 10x RLE, 10x LLE and 10x PR; b) stretching: 6 sets of holding the TheraBite device at MMO for

30 seconds; c) masticatory training: 5 minutes of alternating bilateral chewing with Hiperboloide device. A new Hiperboloide device will be provided each week during the patient's training visit.

G2 (Figure 3): Same warm-up and masticatory training protocol as in G1, but without the TheraBite stretching step.

CG: Not exposed to either of the tested intervention protocols. However, just as patients in G1 and G2, controls will receive the usual care pre-RT guidance from the nursing team, which consists of: avoiding exposure of the irradiated area to sunlight, not shaving with a razor over the irradiated area, cleansing the irradiated area with neutral soap alone, drinking 2 L water daily, and five times per day of mouth rinses with chamomile (*Matricaria chamomilla*) tea, and Clorexidine digluconate 0.12% in attempt to prevent mucositis, according to department's protocol.

Patients in the exercise groups will be instructed to start the exercise protocols one day before the start of RDT and to continue until the end of RDT, performing the protocol exercises four times a day (after breakfast, lunch, dinner, and at bedtime, to prevent missed exercises). Throughout the course of RDT, patients will perform one supervised exercise session per week, under the guidance of the trainer PT. Controls will also meet with the PT for assessment of oral mucositis (the evaluation of oral mucositis is the same in all groups) and for assessment of potential adverse reactions to therapy.

The TheraBite (Figure 4a) is a portable, single-patient use plastic device equipped with mouthpieces that are placed between the maxilla and mandible. The mouthpiece forces the mouth open proportionally to the strength with which the user squeezes the lever of the device. Depending on the condition of the patient's teeth, different bite pads (regular bite pad, edentulous bite pad, or both) are used. These foam pads will be fitted to the TheraBite by the trainer PT, taking into account the patient's dentition.

The Hiperboloide (Figure 4b) is a peri-myofunctional exercise device consisting of a nontoxic, odorless, and tasteless silastic hyperboloid. To ensure the safety of therapy with this device, a length of dental floss will be threaded through the body of the device so that patients could hold it securely during chewing exercises, as recommended by the manufacturer.

Protocol adherence

To assess protocol adherence, at baseline, each patient will receive a training log on which to record his or her exercise progress. These logs were designed for easy completion to enable their use by patients with low educational attainment, and they covered the whole duration of the RDT course.

Adherence will be classified as high (patients who completed their protocol exercises at least twice daily), moderate (patients who completed their protocol exercises up to twice daily and missed their exercises no more than 1 day per week), low (patients who missed their exercises no more than 2 days per week), or absent (patients who missed or skipped their exercises on 3 or more days per week).

Oncologic Treatment

Patients will undergo external photon beam RDT, at a dose of 2 Gy per fraction per day, 5 days a week, according to the radiotherapy protocol of Santa Casa de Porto Alegre. Protocols will vary from 25 to 35 sessions of RDT, considering the need of sequential tumor bed boost in some patients.

Data management and confidentiality

The data will be entered twice by data entry personnel without identifying which are G1, G2 or CG data. A specific identification number (ID) will be generate for each patient.

All data will be recorded on paper and only one document will contain both the patient ID and the name and address of the patient. This document will be held by the hospital. All data entered into a computer will be in de-identified form and the data will be stored in a password-protected Microsoft Excel file. The electronic de-identified data will be held indefinitely by the researchers for future meta-analysis and will be made accessible from the corresponding author on reasonable request.

Endpoints

The primary endpoint is the difference in mouth opening range of motion, which will be measured using a digital caliper, from baseline to the last RDT treatment and after 12 months after the RDT treatment has been completed.

Secondary endpoints include between-group differences in the adherence to exercise protocol (Training log), pain (VAS), mucositis (WHO scale), performance status (KPS) and quality of life (UW-QoL).

Statistical Analysis

Quantitative variables will be expressed as the means and standard deviations or as medians and interquartile ranges, depending on the normality of distribution. Categorical variables will be expressed as absolute and relative frequencies. The *Kolmogorov-Smirnov* test will be used to assess the distribution of variables.

Generalized estimating equations (GEE) model complemented by the least significant difference (LSD) test will be applied to the intra and inter group comparisons.

One-way analysis of variance (ANOVA) with Tukey's *post hoc* test will be used to compare means across groups. In the case of asymmetric distribution, the Kruskal–Wallis test and Dunn's *post hoc* test will be used instead.

Pearson's chi-square test with adjusted residuals will be used to compare proportions across the study groups. Pearson's linear (r) or Spearman's (r_s) correlation coefficients will be used as appropriate, depending on data distribution, to test for associations between quantitative variables.

The significance level will be set at 5% ($p<0.05$), and all analyses will be performed using Statistical Package for Social Sciences (SPSS) software v.21 (SPSS Inc., Chicago Illinois, United States).

Unadjusted and adjusted analyses

For each outcome variable, the unadjusted analysis will be designated as the primary analysis; the covariate-adjusted analysis will be designated as the secondary analysis. The criterion for inclusion of variables in the adjusted analyses will be $p<0.20$ at bivariate analysis.

Missing data

Every effort will be made to obtain data, irrespective of whether the patient completed the treatment. The analyses will be based on available data only, because GEE model is robust to the "missing at random" missing data mechanism, hence meaningful results can be ascertained even when there are missing data and no substitution mechanism for missing data is needed.

Discussion

The number of cancer survivors has increased due to better diagnostic tools and more efficacious treatments [44]**.** However, a growing number of HNC survivors are met with the burden of long-term negative treatment-related side-effects [45]. Trismus can develop and/or

progress years after RDT. In the Lindblom study [46], 41% of 121 patients had trismus at 12 months follow-up.

Many late effects progress over time and can, in the long run, adversely impact the quality of patient´s lives [47]. Study results from Lee et al. [48] found that HNC patients with trismus had a worse QoL in terms of social contact, sexuality, feeling ill, nutritional deficiency, and weight loss compared with HNC patients without trismus and suggest that implementing measures to prevent trismus in HNC patients may contribute to enhanced quality of life over the long term in these patients.

Relative recovery progression of late effects may vary depending on the nature of the problem. The relationship between the duration and severity of acute side effects and late effects is also well established [47]. The classic concept of consequential late side effects persisting as adverse outcomes of severe acute side effects not completely repaired has also been supported in the literature, particularly in the area of acute mucositis in relationship to late trismus [47]. Then, evaluating mucositis during cancer treatment is essential to understand the risk of late development of trismus. However, to our knowledge, this is the first trial to pay attention to mucositis and to investigate its impact, in the long term, and to explore the effect of exercise-based treatment in mouth opening and in quality of life in HNC survivors.

The study has some limitations. First, blinding of patients and trainer PT is not possible; second, the research is to be conducted in just one hospital in Brazil. Nevertheless, the design also has important strengths: reproducibility, the blinding of the PT assessor and data analyst and the incorporation of control group as a comparator.

Trismus is considered the second most burdensome side effect of oncology therapy in the head and neck region [49]. Cost-effective interventions to prevent this disabling late

sequalae are required. If our research findings are positive, we will provide a new intervention for trismus in HNC patients.

Abbreviations

HNC: head and neck cancer; RDT: radiotherapy; QoL: quality of life; PT: physiotherapist; MMO: maximum mouth opening; RLE: right lateral excursion; LLE: left lateral excursion; PR: mandibular protusion; VAS: visual analogue scale; WHO: World and Health Organization; KPS: Karnofsky Performance Scale; UW-QoL: University of Washington Quality of Life Questionnaire; Gy: grays; IMRT intensity-modulated radiation therapy; G1: intervention group I; G2: intervention group II; CG: control group.

Ethics approval and consent to participate

The present study was approved by the Research Ethics Committee of Irmandade Santa Casa de Misericórdia de Porto Alegre with judgment number 259.691, in accordance with the ethical standards of the Declaration of Helsinki and with Brazilian National Health Council Resolution 466/12. The trial will obtain written informed consent from all participants in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used during the current study will be available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contribuitions

GPJ is the academic supervisor of KCB and had important input on the trial design. KCB is the main writer of the manuscript. CC is the second main writer of the manuscript. NWM and RCP provided logistic and administrative support. MFS and RP provided assistance in writing the manuscript.

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	STUDY PERIOD						
	Enrollment	Allocation	Post-allocation			Close- out	Follow- up
TIMEPOINT**	*SE*	Baseline	*Week 1-2*	*Week 3-4*	*Week 5,6-7*	*Last RDT*	*12 Months*
ENROLLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation	X						
INTERVENTIONS:							
Group 1 (G1)			◆	—	◆		
Group 2 (G2)			◆	—	◆		
Control-group (CG)							
ASSESSMENTS:							
Mouth opening measure		G1+G2+CG				G1+G2+CG	G1+G2+CG
Oral mucositis		G1+G2+CG				G1+G2+CG	G1+G2+CG
Pain		G1+G2+CG				G1+G2+CG	G1+G2+CG
Performance status		G1+G2+CG				G1+G2+CG	G1+G2+CG
Quality of life		G1+G2+CG				G1+G2+CG	G1+G2+CG

SE: study entry

Figure 1. SPIRIT flow diagram of the “Effect of physiotherapy to prevent trismus in irradiated head and neck cancer patients” study.

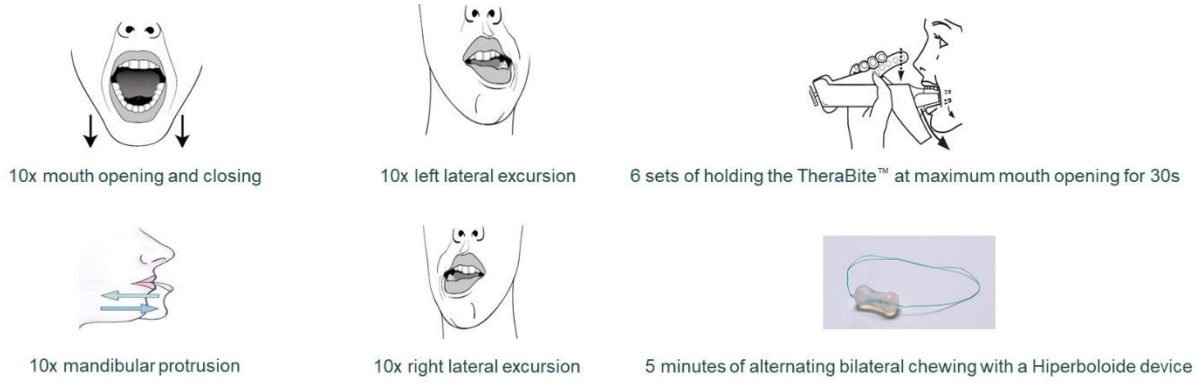

Figure 2. Intervention group I exercises

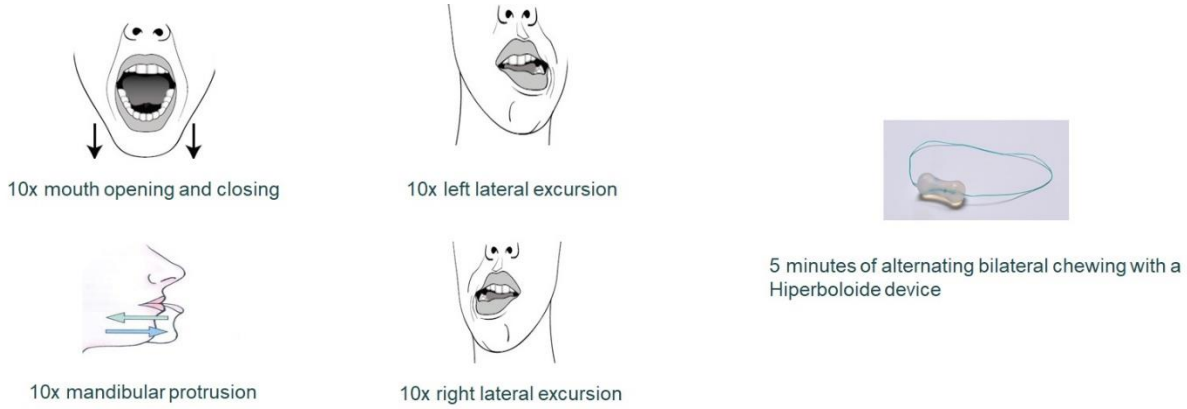

Figure 3. Intervention group II exercises

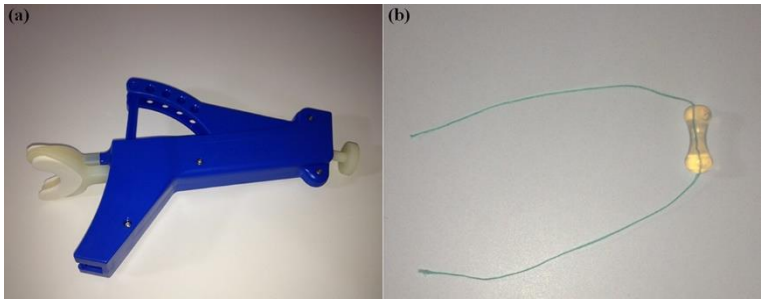

Figure 4. Jaw exercise devices.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Pg.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Pg. 3
	2b	All items from the World Health Organization Trial Registration Data Set	Pgs. 3, 17-18
Protocol version	3	Date and version identifier	Study protocol, page 1 (version 3, modified in July, 2015)
Funding	4	Sources and types of financial, material, and other support	Pg. 18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Pgs. 1-2, 18
	5b	Name and contact information for the trial sponsor	N/A (No sponsor)

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Pg. 18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Trial is overseen by academic advisor in charge of the radiotherapy department.
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Pgs. 4-5
	6b	Explanation for choice of comparators	Pgs. 5-6, 13
Objectives	7	Specific objectives or hypotheses	Pg. 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Pgs. 6-7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Pgs 7, 9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Pg 7

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pgs. 12-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Pg. 8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Pgs. 13-14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Mucositis treatment is permitted according to department's protocol
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Pgs. 10-11, 14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Pgs. 7, 12-13 SPIRIT flow diagram
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Pgs. 8-9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Pg. 9

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Pg. 9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Pg. 9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Pg. 9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Pg. 9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A as training physiotherapist and participants are not blinded
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Pgs. 9-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Pgs. 13-14, 16

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Pg. 14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Pgs.15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Pg. 16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Pg. 16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	No DMC as small trial. Safety is overseen by the medical doctor in charge of the radiotherapy department.

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Only if serious adverse events due to treatment pg. 8 Hospital staff and treatment personnel will report to medical doctor in charge of the radiotherapy department.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Pgs. 8, 13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	None
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Pg. 18 Ethical approval received
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Pg. 8
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Pg. 9

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	No ancillary studies.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Pg. 14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Pg. 18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Pg. 14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	No special provisions for care, compensation: pg. 8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Via publication
	31b	Authorship eligibility guidelines and any intended use of professional writers	Pg. 18, no professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Pg. 18

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available on request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

4.2 MANUSCRITO II

Exercise therapy during radiotherapy treatment seems not to prevent radiation-induced trismus in head and neck cancer patients: a randomized controlled trial

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ABSTRACT

Objective: To compare the efficacy of two protocols of exercise therapy with the usual care guidance pre-RDT to avoid reduction in mouth opening (MO) in patients with head and neck cancer undergoing radiotherapy. **Study design**: A randomized, controlled, double-blind, three-arm, parallel-group, prevention clinical trial. Ninety patients were randomized into 3 groups to perform exercises during radiotherapy treatment: intervention group 1 (G1) – active exercises of the mandible, stretching exercise with Therabite and masticatory training with Hiperbolóide; intervention group 2 (G2) - active exercises of the mandible and masticatory training with Hiperbolóide, and control group (CG) - usual care guidance from the institution. Maximum mouth opening was measured before (T0), immediately after (T1), and at 12 months (T2) after completion of radiotherapy treatment. Generalized estimating equations model complemented by the least significant difference (LSD) test was applied to group comparisons. **Results**: There was no significant difference in mouth opening measure between the groups at the three assessment time points (p=0.264). The difference in MO measure from baseline to 12 months after having completed radiotherapy was -1 mm in CG (95% confidence interval [CI], -4.0 to 2.0), 1.3 mm in G1 (95% CI, -1.7 to 4.3) and 0.5 mm in G2 (95% CI, -3.4 to 4.4). **Conclusion**: It is not possible to conclude that the exercise

protocols performed in this study are more effective to prevent reduction in MO than the usual guidance for patients undergoing radiotherapy.

Keywords: head and neck neoplasms, trismus, radiotherapy, mucositis, exercise therapy

Clinical trial registration number: ClinicalTrials.gov, NCT02094690;
ReBEC, RBR-89mdvw.

INTRODUCTION

The incidence of head and neck cancer (HNC) is increasing and advances in cancer treatment contribute significantly to improve survival rates.[1,2] However, an increasing number of HNC survivors must deal with the long-term sequelae of cancer treatment.[3]

Radiotherapy (RDT), alone or combined with surgery and chemotherapy, plays a key role in the treatment of patients with HNC.[4] Despite the modernization of irradiation techniques, no technology can completely protect normal tissues from irradiation and patients will always experience some degree of toxicity associated with radiation.[5, 6] Oral mucositis and oral infections, both resulting in pain, are common acute side effects, while xerostomia and trismus are late side effects of RDT.[6, 7]

Radiation-induced trismus (RIT), a reduction in mouth opening measurement due to fibrosis in the masticatory musculature when located in the radiation field,[8, 9] has a peak incidence around 9 to 12 months after the end of the RDT,[10-12] however, reduction in mouth opening may occur during the irradiation period particularly in patients with reduced performance status,[13, 14] when the tumor is located at the maxilla, mandible or cheek,[15] when radiation is administered postoperatively[16] or in case of reduced masticatory muscle function due to exclusive enteral tube feeding.[17] The development of trismus has a negative impact on patient quality of life (QoL), as it

causes changes in facial appearance, difficulty speaking, problems with denture use and oral hygiene, and difficulty feeding, potentially leading to malnutrition.[9,18]

Studies reporting the treatment of RIT emphasize that it is difficult to treat, often progressive, and, therefore, efforts should focus on its prevention.[19-21] Current evidence suggests that physical therapy during RDT could prevent this complication, being TheraBite the most widely used device for this function.[3,22] However, to our knowledge, so far, no well-designed clinical trial has been able to demonstrate an effective protocol for the prevention of RIT;[23-25] also, none of these studies verified whether a chewing training with hyperboloid (a piece of silicon, also known as mechanical sialogogue) during RDT could prevent the development of trismus.

As the hyperboloid device avoids mandibular immobility because the patient is required to activate stomatognathic system components to chew the device, we hypothesized that its use during RDT might prevent the development of RIT and the results of its use with and without the TheraBite should be compared.

The primary objective of this study was to assess whether a preventive intervention consisting of therapeutic exercises performed during the RDT preserves mandibular range of motion, and whether a difference in mandibular mobility exists among patients who exercise with and without the aid of the TheraBite device. The secondary objective was to ascertain whether associations exist between RIT outcomes and mucositis, pain, performance status and adherence to the study interventions.

MATERIALS AND METHODS

This was a randomized, controlled, double-blind, three-arm, parallel-group, prevention clinical trial. The trial is registered at ClinicalTrials.gov, number NCT02094690, and at the Brazilian Clinical Trials Registry, number RBR-89mdvw.

Study setting and participants

This trial was carried out at the Department of Radiation Oncology of a university hospital in the city of Porto Alegre, Brazil. The recruitment period was between May 1, 2014, and November 30, 2015, the last follow-up was in March 2017. We screened all consecutive patients with HNC (neoplasms of the oral cavity, oropharynx, nasopharynx, salivary glands and nasal fossae) undergoing RDT who met the following eligibility criteria: either sex; age > 18 years; formal histopathological diagnosis of HNC; undergoing definitive or postoperative external beam RDT for HNC, either alone or in combination with chemotherapy or target therapy; Karnofsky Performance Status (KPS) > 60%.[26]

The criteria for exclusion were: motor sequelae affecting the face or neck region, whether secondary to stroke, facial palsy, trauma and/or surgery that precluded completion of the exercise protocols; cognitive impairments, such as Alzheimer's disease, senile dementia, and/or Wernicke-Korsakoff syndrome, that could impair patient understanding of the exercise protocols; history of prior RDT to the head and neck region; history of surgical interventions involving resection of the mandible; current physical therapy or speech pathology interventions for trismus; initial mouth opening range < 10 millimeter (mm).

Sample size calculation

This study is powered to detect a modification, at least 5 mm, in the range of mouth opening motion.[27] The sample size was calculated in PEPI (Programs for Epidemiologists) 4.0 software and was based on the studies of Tang et al.[19] and Jager-Wittenar et al.[27] to achieve a significance level of 5%, a statistical power of 90% and an acceptable between-group effect size of one standard deviation (Cohen's d). For the

primary outcome, the minimum sample size was calculated as 23 patients per group, for a total of 69 patients. To enable multivariate analysis (10%) and to account for potential attrition (20%), we increased the sample by 30% for a total of 90 patients.

Randomization

Patients were randomly allocated in three study groups, at a ratio of 1:1:1, by random number generation with the RANDOM subroutine of the PEPI software suite (Programs for Epidemiologists, version 4.0). The statistician generated the random allocation sequence. The confidentiality of allocation was ensured by using sealed, numbered, opaque brown paper envelopes. These enveloped were stored and handled only by a nurse otherwise uninvolved in the study, who was contacted by telephone, at the start of the intervention, by the physiotherapist (PT) responsible for patient training.

Blinding

The PT responsible for outcome examination, the radiation oncologists and technologists, and the statistician were all blinded to patient allocation. Only the trainer PT and each patient were aware of allocation.

Data collection

Patients eligible for inclusion were identified, prior to the start of their RDT regimens, during the weekly multidisciplinary team meetings of the Department of Radiation Oncology. On the day of radiation simulation (one or two weeks before starting RDT), patients were informed of the study and invited to participate. After each patient agreed to take part and provided verbal and written informed consent, data collection was begun.

A history and physical examination were obtained from each patient, individually. Physical examination was always performed by the same examiner – a trained PT with ample experience in the study protocols – and sought to collect data on the following variables:

Demographic: age, sex, skin color, educational attainment, smoking, drinking, and type of diet.

Clinical: tumor site, histological type, concomitant chemotherapy or target therapy, surgery, tumor stage (according to the Union for International Cancer Control [UICC] TNM classification of malignant tumors),[28] modality and dose of RDT. These data were extracted from patient records.

Physical examination was performed at three time points: before the start of RDT (T0), immediately after the last RDT session (T1), and at 12 months (T2) after RDT treatment; and sought to assess the following outcomes: mouth opening measure, oral mucositis, pain, and functional capacity.

Maximum mouth opening (MMO) was measured using Digimess 100.179N digital calipers (resolution 0.01 mm/.0005", with a certificate of calibration provided by the manufacturer), expressed in mm. The patients were seated in an upright position and were asked to open their mouths as wide as possible. The recommendations and instructions proposed by Goldstein et al.[29] and Dijkstra et al.[30] were followed for the assessment of completely and partially edentulous patients, namely: in patients with an edentulous mandible and no dentures, the distance between the incisal edge of the most vertical maxillary central incisor and the opposing (i.e., corresponding mandibular) alveolar ridge was measured; in patients with an edentulous maxilla and no dentures, the distance between the incisal edge of the most vertical mandibular central incisor and the opposing alveolar ridge was measured; in fully edentulous patients, MMO was

measured from the mandibular alveolar ridge to the maxillary alveolar ridge along the midline corresponding to the nasopalatine foramen. Dental health condition was assessed to enable correction in the event of changes.

Oral mucositis was graded in accordance with the World Health Organization (WHO) Oral Toxicity Scale.[31] Pain was assessed using a visual analogue scale.[32] Functional capacity was measured by the KPS.[26,33]

Exercise protocols

After assessment, each patient – always chaperoned by a family member – was given a booklet containing written and illustrated instructions on the physical therapy protocol to be followed, as well as verbal guidance provided by the trainer PT.

Patients were allocated randomly across three groups: Intervention Group 1 (G1), Intervention Group 2 (G2), and control group (CG). The protocols used in each group were as follows:

G1: a) warm-up (exercises to enhance joint lubrication): 10x mouth opening and closing, 10x right lateral excursion, 10x left lateral excursion and 10x mandibular protrusion; b) stretching: 6 sets of holding the TheraBite device at MMO for 30 seconds, resting 30 seconds between each set; c) masticatory training: 5 minutes of alternating bilateral chewing with the hyperboloid device. A new hyperboloid device was provided each week during the patient's training visit.

G2: Same warmup and masticatory training protocol as in G1, but without the TheraBite stretching step.

CG: Not exposed to either of the tested intervention protocols. However, just as patients in G1 and G2, controls received the usual care guidance from the nursing team, which consists of: avoiding exposure of the irradiated area to sunlight, not shaving with

a razor over the irradiated area, cleansing the irradiated area with neutral soap alone, drinking 2 L water daily, and five times per day of mouth rinses with chamomile (*Matricaria chamomilla*) tea, and chlorhexidine digluconate 0.12% in attempt to prevent mucositis, according to department's protocol.

Patients in the exercise groups were instructed to start the exercise protocols one day before the start of RDT and continue until the end of RDT, performing the protocol exercises four times a day (after breakfast, lunch, dinner, and at bedtime, to prevent missed exercises). Throughout the course of RDT, patients performed one supervised exercise session per week, under the guidance of the trainer PT. Controls also met with the trainer PT for assessment of potential adverse reactions to therapy.

Protocol adherence

To assess protocol adherence, at T0, each patient was given a training log on which to record his or her exercise progress. These logs were designed for easy completion, so enable their use by patients with low educational attainment and covered the whole duration of the RDT course. The patient was also instructed to take notes of any discomfort perceived during the exercises and possible doubts to be cleared out during the weekly consultation with the trainer PT. The control group received a different booklet from the rehabilitation groups to take notes on possible side effects of RDT to report on the weekly meeting with the trainer PT.

Adherence was classified as "adherent" (patients who completed their protocol exercises at least twice daily and missed their exercises no more than 1 day per week), or "non-adherent" (patients who missed or skipped their exercises on 2 or more days per week).

Oncologic treatment

All patients underwent external photon beam RDT, at a dose of 2 Gy per fraction per day, 5 days a week, over a 5- to 7-week course of therapy, for a final dose ranging from 50 to 70 Gy. Overall, 61 patients (68.5%) received concomitant chemotherapy (50 mg cisplatin once weekly), and one (1.1%) received targeted therapy (cetuximab) in addition to chemotherapy. Treatment regimens were individualized according to tumor site, size, and stage.

The present study was conducted in accordance with the ethical standards of the Declaration of Helsinki and with Brazilian National Health Council Resolution 466/12 and was approved by the Research Ethics Committee of Irmandade Santa Casa de Misericórdia de Porto Alegre (approval number 259.691).

Statistical Analysis

Quantitative variables were expressed as means and standard deviations/standard errors or as medians and interquartile ranges, depending on the normality of distribution. Categorical variables were expressed as absolute and relative frequencies. The Kolmogorov Smirnov test was used to assess the distribution of variables.

Generalized estimating equations (GEE) model complemented by the least significant difference (LSD) test was applied to the intra- and intergroup comparisons. All randomized patients were included in the intent-to-treat analysis. GEE is a robust model for the missing-at-random assumption in the missing data mechanism, obviating the need for data imputation.

One-way analysis of variance (ANOVA) with Tukey's post-hoc test or t-test was used to compare means across groups. In case of asymmetric distribution, the Kruskal–Wallis test and Dunn's post hoc test or Mann-Whitney test was used instead.

Pearson's chi-square test with adjusted residuals was used to compare proportions across the study groups. Pearson's linear (r) or Spearman's (rs) correlation coefficients were used as appropriate, depending on data distribution, to test for associations between quantitative variables.

For each outcome variable, the unadjusted analysis was designated as the primary analysis, and the covariate-adjusted analysis was designated as the secondary analysis/additional analysis. The criterion for inclusion of variables in the adjusted analyses was $p<0.20$ in the bivariate analysis.

For control of confounding factors, the hierarchical Poisson regression model was used. According to this model blocks are created according to the proximity of the outcome. In the distal block were included characterization and lifestyle of the patient variables. In the intermediate block were used the variables that evaluated the immediate post-treatment and in the proximal block the variations that considered all follow up. The criterion for inclusion of the variable in its respective block was that it presented a *P*-value < 0.20 in the univariate analysis.

The significance level was set at 5% ($P < 0.05$), and all analyses were carried out in Statistical Package for Social Sciences (SPSS) software v.23 (SPSS Inc., Chicago, IL, USA).

Endpoints

The primary endpoint was the difference in MMO range of motion, which was measured using a digital caliper, from baseline to the last RDT session and after 12 months of completion of RDT treatment.

Secondary endpoints include between-group differences in mucositis (WHO scale), pain (VAS), performance status (KPS) and adherence to exercise protocol (Training log).

The normal range of jaw mobility is 40–70 mm for mouth opening.[34] These ranges may vary according to factors such as sex, age, body weight, height, dentition, and presence of signs and symptoms of temporomandibular dysfunction.[35] The 35mm cutoff measure for trismus in patients with HNC is widely used in literature[30,36] and was used in this study. However, supporting the view presented by Loorents et al.[23] that it is necessary to focus on the individual's normal variation in MMO to detect a clinically relevant impairment of MMO (because not necessarily a statistical significance has clinical relevance),[21] we considered in this study a difference of at least 5 mm in mouth opening to be interpreted as a clinically relevant alteration.[20,27]

RESULTS

During the enrolment period, 133 patients with HNC were treated at our Department of Radiation Oncology. Of these, 43 were ultimately excluded, as shown in the CONSORT[37] flow diagram (Figure 1).

All three study groups were homogeneous in terms of demographic and clinical variables at baseline (Table I).

Table II gives an overview of all pre- and post-treatment outcomes.

MMO: There was no difference in MMO between the groups at the three assessment time points, although the CG showed a significant reduction of MMO

measurement from T0 to T1, there was a normalization of MMO measurement at T2. When checking how many patients met criteria for trismus (mouth opening ≤35mm), no significant differences were found between the groups (Figure 2).

Mucositis: There was a significant increase in mucositis from T0 to T1 in all groups, and this increase was significantly higher in G1 than CG. Regarding the degree of mucositis there were no significant differences between the groups (Table III).

VAS: Pain increased significantly from T0 to T1 in the two exercise groups, and this increase was significantly higher in G1 than CG. There was a statistically significant direct association between increased mucositis grade and increased pain at T1 (rs = 0.463, $P < 0.001$).

KPS: There was a significant reduction in KPS, in CG and G1, from T0 to T1, and significant improve in KPS in all groups from T1 to T2, but without differences between groups at three time points ($P = 0.737$).

Adherence: The analysis of adherence to the exercise protocol showed no significant differences between G1 and G2 patients ($P = 0.730$).

Additional analysis

When analyzing MMO measurement between adherent and non-adherent patients in G1 (Figure 3a), there was no significant effect of interaction between adherence and time ($P = 0.094$), despite the decrease in MMO in the non-adherent group -5.7 mm (95% confidence interval [CI], -13.6 to 2.3; $P = 0.162$). In the adherent group, there was an average increase of 1 mm but not significant (95% CI, -0.8 to 2.9; $P = 0.259$).

In G2 (Figure 3b), there was a statistically significant interaction between adherence and time ($P < 0.001$). There was a significant reduction in mouth opening in

the non-adherent group of -8.6 mm (95% CI, -12.4 to -4.7; $P < 0.001$), while in the adherent group the MMO measurement of -0.8 mm at T0 remained at T1 (95% CI, -3.3 to 1.8; $P = 0.564$).

The following variables were associated with clinical worsening in MMO measurements: post-treatment mucositis, grade of mucositis, reduction in KPS, and VAS (Table IV).

After adjusting for the multivariate model, they remained statistically associated with the clinical worsening in MMO, the degree of mucositis in the immediate post-treatment period and the variation of the KPS score throughout the follow-up (Table V). Patients with grade III and IV mucositis present a 3.66x greater risk of clinically significant reduction in MMO measurement when compared to patients without mucositis. Also, for each additional point in the KPS score, there is a 4% reduction in the risk of clinical worsening.

DISCUSSION

This randomized clinical trial showed no significant benefits from the preventive exercise protocols to RIT at 12 months after the RDT treatment, indicating that both patients who performed exercises and those who did not had the same outcome regarding MMO at 12 months of follow-up. These results corroborate the findings of the quasi-experiment of Loorents et al.,[23] in which no difference was found in the MMO measure between the usual care and the group that performed a protocol of prophylactic exercises to the RIT during and up to 12 months after RDT; and the clinical trial of Hodgal et al.[25] where there were also no differences in the measure of MMO, in the 12-month follow-up, between the usual care and the group that performed prophylactic exercises to RIT during RDT.

In our study, the incidence of oral mucositis ranged from 40% to 66.7% across groups and was significantly higher in G1 patients than in CG. This incidence of mucositis found in our study is within the normal range reported in the literature of oral mucositis in patients with HNC who were irradiated,[38] but we believe this greater increase in oral mucositis in G1 can be attributed to the stretching exercises performed only in this group during RDT. The quality of oral hygiene was not measured in this study, and poor oral hygiene in G1 could also be a possible cause of the higher incidence of mucositis in this group. Nevertheless, we suggest that future studies on RIT should pay more attention to the impact of the exercises and the TheraBite device on the oral mucosa during RDT and not only to the MMO measurement.

A significant increase in G1 pain was observed in relation to CG, and this pain was associated with a higher incidence of mucositis in G1. Exercise may worsen the pain of mucositis due to tissue stretching that was performed with TheraBite in G1. In the study of prevention of dysphagia and trismus in irradiated patients with HNC of van der Molen et al.,[39] male patients in the exercise group with TheraBite also experienced significantly more pain, probably due to mucositis, considering that the exercises were performed during RDT treatment, but the incidence and degree of mucositis were not reported in the study.

Studies that analyzed KPS[14,18,40] in irradiated patients with HNC found reductions in this variable after cancer treatment. Likewise, in our sample, patients in all groups demonstrated a tendency of reductions in this variable after cancer treatment with long term improvement. Further research should investigate whether early, comprehensive physical rehabilitation can have beneficial effects on the functional capacity of patients with HNC.

We found no differences in adherence between G1 and G2. Although training schedules were not filled under supervision, our study showed a high adherence rate (G1: 78% and G2: 84%) when compared to the study by Hodgal et al.,[25] in which patients were instructed to perform seven exercises five times daily and it was found that only 24% of the patients showed high adherence and 36% showed medium adherence, but the authors did not make clear what criteria were used for this classification of adherence to the exercise.

In a study by van der Molen et al.,[39] patients were encouraged to exercise three times daily, but on average, patients in their study only practiced four days per week. Van der Molen et al.[39] found this adherence acceptable considering the burdensome chemo-radiotherapy, demonstrating that, in this way, 69% of the patients adhered to the prophylactic protocol. As such, in our study, we aimed to attain the best result with the least possible burden to the patients. This greater adherence of the patients in our study also can be explained by the fact that patients received a weekly session of supervised exercises, always with the same PT, which may have supported and encouraged the home exercise program. Melchers et al.,[41] in their qualitative study on the adherence of patients to the use of TheraBite, verified that physiotherapy sessions not only acted as motivator, but also influenced adherence by reducing fear of exercising and sometimes by evoking a feeling of obligation in the patient.

Treatment adherence is an essential determinant of the success of any preventive exercise protocol. We observed that in G2 non-adherent patients presented a significant reduction of the MMO measure, but due to the reduced number of participants for subgroup analysis, we cannot infer that this reduction occurred only because of non-adherence to the exercises, since after multivariate analysis the main factors for late reduction of mouth opening were the degree of acute mucositis and the

variation in KPS throughout the follow-up. By causing pain, grade III and IV mucositis limits the functions of the stomatognathic system, forcing the patients to change the consistency of their diet and, often, to adopt exclusive enteral feeding,[42] which leads to a greater risk of malnutrition, loss of functional capacity and depression.[13,43] Further studies should investigate whether prevention of mucositis has an impact on the range of MMO and KPS of patients undergoing RDT for head and neck neoplasms.

The relationship between the duration and severity of acute side and late effects of RDT has been investigated in the literature.[6] The classic concept of consequential late side effects persisting as adverse outcomes of severe acute side effects has been supported in the literature.[6] The higher the time of mandibular hypomobility generated by mucositis, pain and consequent exclusive enteral feeding, the greater the damage to the masticatory muscles and temporomandibular joint difficult to be completely reversed in later phases, especially if a process of radiation-induced fibrosis in the masticatory musculature or in the temporomandibular joint is being developed.[44] Tang et al.[19] treated patients with trismus several years after their RDT treatment. They noticed that exercise with the TheraBite or manual stretching may prevent trismus from progressing but cannot reverse the installed deficit, because the older the fibrotic contracture is or the more the muscular and normal connective tissue is replaced by non-extensible adhesions, the more difficult it is to recover soft tissue mobility and the higher the likelihood of the contracture becoming irreversible.[44]

The study by Pauli et al.[20] compared the usual care with two different devices (TheraBite and Egstrom) for the treatment of trismus, demonstrating that both devices significantly increased the measure of MMO, and patients were included at a mean of 2.5 (TheraBite) and 2.7 (Engstrom) months after the end of RDT. Early start of exercise has been shown to increase the possibility of improving MMO. The study by Kamstra et

al.,[45] also supports that early detection of trismus and the start of exercise therapy are important for a better outcome of MMO. Early detection seems to be a promising approach in the management of trismus, however early start of exercise requires regular follow-up and surveillance of MMO and trismus-related symptoms,[20] therefore all professionals involved in the care and treatment of patients with HNC should be trained on the early recognition of potential patients to the development of RIT in order to refer them to the PT, enabling immediate and early interventions.

Further studies are needed to verify the efficacy and the impact on MMO of prophylactic exercises for RIT initiated after RDT treatment, when the acute mucosal reactions are resolved, since according to our study, initiating exercises during RDT seems not to have a therapeutic benefit to MMO, and may increase the pain associated with mucositis.

One major limitation of this study was the lack of supervision of home exercises. However, training schedules and a weekly therapy session with the trainer PT were used to mitigate this limitation. Blinding of patients and trainer PT was not possible. Nevertheless, this study design also has important qualities: reproducibility, the blinding of the examiner PT and data analyst and the incorporation of control group as a comparator.

Based on the results obtained in this study, it is not possible to conclude that the exercise protocols presented here are more effective than the usual care for trismus prevention. Studies assessing whether implementation of mucositis prevention protocols have an impact in the short and long term on MMO are advised.

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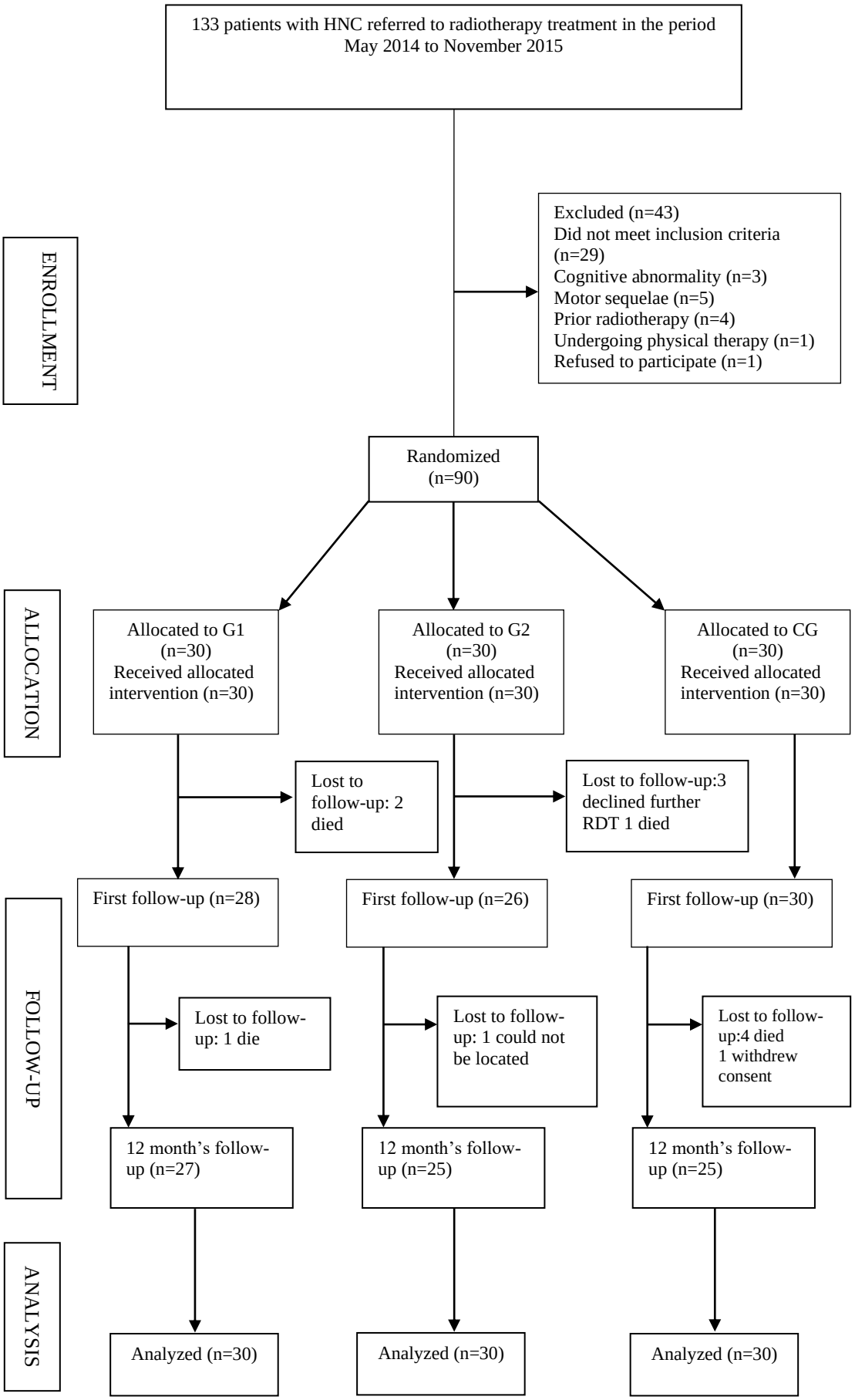

Figure 1. CONSORT flow diagram.

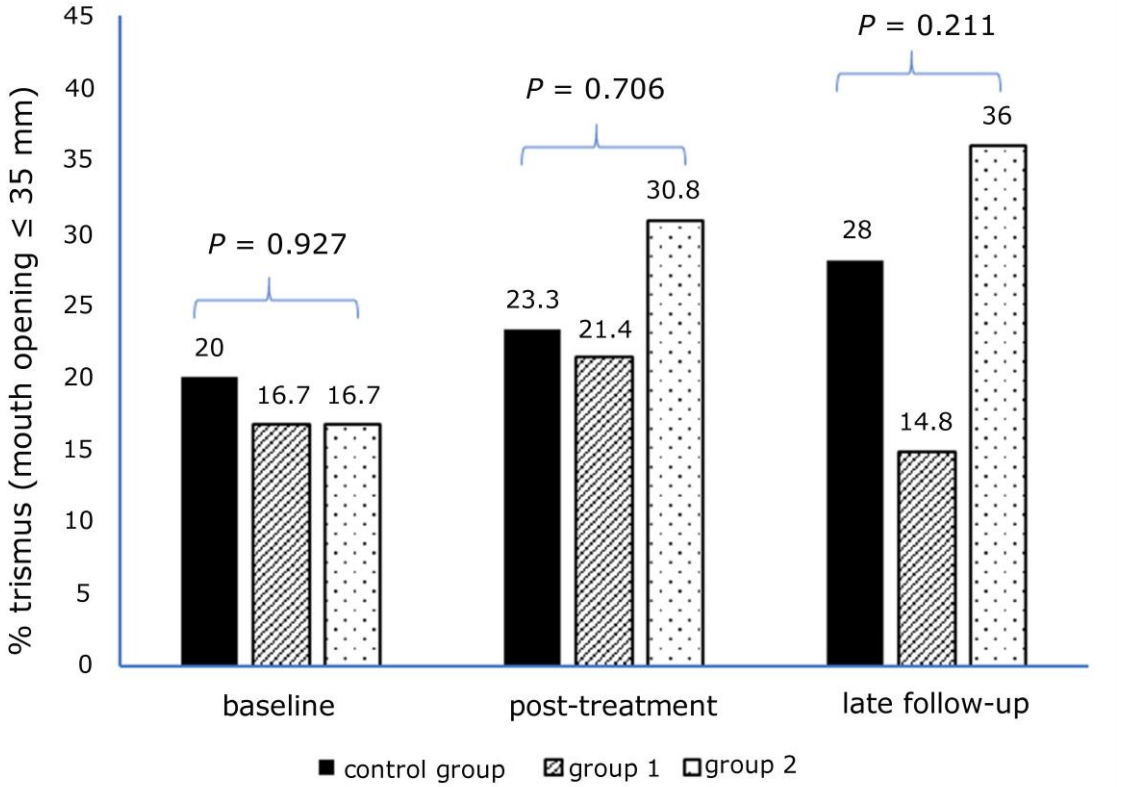

Figure 2. Percentage of trismus in individuals assessed at the three different time points.

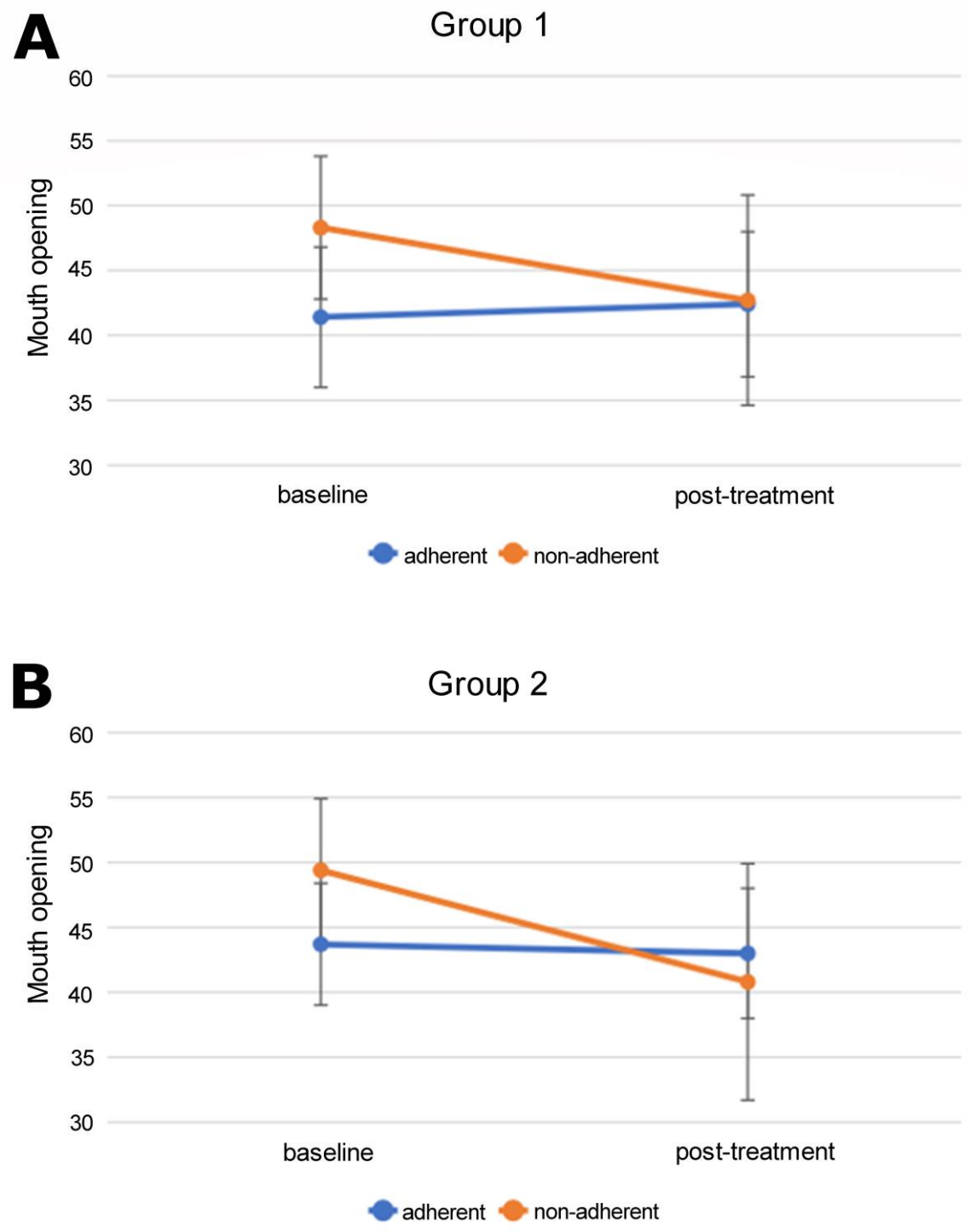

Figure 3. Measurement of maximum mouth opening in adherent and non-adherent patients. **A**) Evaluation of mouth opening measurement according to adherence in group 1. **B**) Evaluation of mouth opening measurement according to adherence in group 2.

TABLES

Table I. Characterization of the sample.

Variables*	**Control**	**Group 1**	**Group 2**	***P***
Age (years)	58.5 ± 12.5	54.7 ± 9.8	58.7 ± 8.0	0.243
Gender				0.919
Female	4 (13.3)	5 (16.7)	5 (16.7)	
Male	26 (86.7)	25 (83.3)	25 (83.3)	
Ethnicity				0.626
Caucasian	22 (73.3)	19 (63.3)	23 (76.7)	
Black	4 (13.3)	3 (10.0)	3 (10.0)	
Mixed	4 (13.3)	8 (26.7)	4 (13.3)	
Education (years)	6.3 ± 3.1	5.9 ± 2.8	7.0 ± 3.5	0.360
Smoking	27 (90.0)	26 (86.7)	25 (83.3)	0.749
Amount (packs/year)	39 (32-60)	53 (29-77)	46 (25-76)	0.974
Alcoholism	19 (63.3)	20 (66.7)	20 (66.7)	0.952
Time (years)	30 (20-40)	30 (24-35)	30 (21-40)	0.931
Feeding				0.494
Normal	15 (50.0)	22 (73.3)	18 (60.0)	
Soft	7 (23.3)	6 (20.0)	7 (23.3)	
Liquid	2 (6.7)	1 (3.3)	1 (3.3)	
Enteral	6 (20.0)	1 (3.3)	4 (13.3)	
Chemotherapy	18 (60.0)	20 (66.7)	23 (79.3)	0.269
Surgery	14 (46.7)	18 (60.0)	10 (33.3)	0.117
Neck Dissection	14 (46.7)	12 (40.0)	9 (30.0)	0.411
Diagnosis				0.761
Oral cavity	14 (46.7)	11 (36.7)	9 (30.0)	
Oropharynx	10 (33.3)	14 (46.7)	12 (40.0)	
Nasal cavity	4 (13.3)	3 (10.0)	4 (13.3)	
Salivary Glands	2 (6.7)	2 (6.7)	4 (13.3)	
Primary hidden	0 (0.0)	0 (0.0)	1 (3.3)	
Histology				0.305
Squamous cell carcinoma	29 (96.7)	28 (93.3)	26 (92.9)	
Adenoid cystic carcinoma	0 (0.0)	0 (0.0)	2 (7.1)	
Acinic cell carcinoma	1 (3.3)	1 (3.3)	0 (0.0)	
Verrucous carcinoma	0 (0.0)	1 (3.3)	0 (0.0)	
Staging				0.542
I and II	3 (10.0)	4 (13.3)	6 (20.0)	
III	8 (26.7)	11 (36.7)	6 (20.0)	
IVa and IVb	19 (63.3)	15 (50.0)	18 (60.0)	
RDT modality				0.426
IMRT	2 (6.7)	1 (3.3)	4 (13.8)	
2D	25 (83.3)	28 (93.3)	23 (75.9)	
3D	3 (10.0)	1 (3.3)	3 (10.3)	

IMRT, intensity-modulated radiation therapy; RDT, radiation therapy; 3D, three-dimensional conformed radiation therapy; 2D, two-dimensional conventional radiation therapy.

*Described as mean ± standard deviation, median (25th-75th percentiles), or n (%).

Table II. Data on maximum mouth opening, pain, mucositis, performance status and adherence.

Variables	Control	Group 1	Group 2	Effects (*P*-value)*		
	Mean ± SE	Mean ± SE	Mean ± SE	Time	Group	Time x group
Maximum mouth opening (mm)				0.053	0.748	0.264
Baseline	42.9 ± 1.9	42.4±2.2	43.3 ±2.0			
Post-treatment	39.2 ±1.9	42.5 ±2.4	42.6 ±2.3			
Late follow-up	41.9 ± 2.0	43.7 ± 2.1	43.8 ± 2.4			
Difference baseline − post (95% CI)	-3.7 (-6.1 to -1.4)	0.1 (-2.5 to 2.7)	-0.7 (-3.6 to 2.2)			
Difference baseline − follow-up (95% CI)	-1.0 (-4 to 2.0)	1.3 (-1.7 to 4.3)	0.5 (-3.4 to 4.4)			
Difference post – follow-up (95% CI)	2.7 (-0.8 to 6.3)	1.2 (-1.1 to 3.6)	1.2 (-1.6 to 3.9)			
Presence of mucositis				<0.001	<0.001	<0.001
Baseline	2 (6.7)[a]	0 (0.0)[a]	2 (6.7)[a]			
Post-treatment	11 (37.9)[a]	20 (71.4)[b]	14 (53.8)[a,b]			
Late follow-up	0 (0.0)[a]	0 (0.0)[a]	1 (4.2)[a]			
Difference baseline − post (95% CI)	31 (11 to 52)	71 (55 to 88)	47 (25 to 70)			
Difference baseline − follow-up (95% CI)	-7 (-16 to 2)	0 (0 to 0)	-3 (-15 to 10)			
Difference post – follow-up (95% CI)	-38 (-56 to -20)	-71 (-88 to -55)	-50 (-69 to -30)			
VAS				<0.001	0.874	0.024
Baseline	2.6 ± 0.6[a]	2.5 ± 0.5[a]	2.8 ± 0.5[a]			
Post-treatment	3.0 ± 0.6[a]	5.1 ± 0.7[b]	4.3 ±0.7[a,b]			
Late follow-up	1.8 ± 0.5[a]	0.7 ± 0.4[a]	1.0 ±0.4[a]			
Difference baseline − post (95% CI)	0.4 (-0.6 to 1.6)	2.6 (1.3 to 3.9)	1.5 (0.1 to 2.8)			
Difference baseline − follow-up (95% CI)	-0.7 (-2.1 to 0.6)	-1.8 (-3 to -0.6)	-1.8 (-2.9 to -0.7)			
Difference post – follow-up (95% CI)	-1.2 (-2.6 to 0.2)	-4.4 (-5.7 to -3)	-3.2 (-4.5 to -2)			

Variables	Control	Group 1	Group 2	Effects (*P*-value)*		
	Mean ± SE	Mean ± SE	Mean ± SE	Time	Group	Time x group
KPS				<0.001	0.054	0.737
Baseline	83.0 ± 2.6	89.7 ± 2.1	87.7 ± 2.7			
Post-treatment	75.7 ± 2.9	81.8 ± 2.8	81.5 ± 3.1			
Late follow-up	83.6 ± 3.7	94.8 ± 2.1	93.2 ± 2.8			
Difference baseline − post (95% CI)	-7.3 (-11.6 to -3.1)	-7.9 (-13.4 to -2.4)	-6.1 (-12.5 to 0.2)			
Difference baseline − follow-up (95% CI)	0.6 (-4.9 to 6.1)	5.2 (0.2 to 10.1)	5.5 (-1.7 to 12.7)			
Difference post – follow-up (95% CI)	7.9 (0.9 to 15)	13 (7.3 to 18.8)	11.7 (4.5 to 18.9)			
Adherence	-	22/28 (78.6)	22/26 (84.6)		0.730**	

MMO, maximum mouth opening; VAS, visual analogue scale; KPS, Karnofsky Performance Status; Values are expressed in mean and standard error. For mucositis, n (%) was used.

** Fisher's exact test.

* Model of generalized estimating equations (GEE);

a, b comparison between groups where equal letters do not differ statistically by the Least Significant Difference (LSD) test with $P < 0.05$.

Table III. Different grades of mucositis presented in T1.

Variables[#]	**CG** **n (%)**	**G1** **n (%)**	**G2** **n (%)**	***P****
T1				0.165
None	18 (60.0)	8 (28.6)	12 (46.2)	
Grade I	5 (16.7)	9 (32.1)	3 (11.5)	
Grade II	4 (13.3)	6 (21.4)	4 (15.4)	
Grade III	1 (3.3)	3 (10.7)	5 (19.2)	
Grade IV	2 (6.7)	2 (7.1)	2 (7.7)	

CG, control group; G1, group 1; G2, group 2; T1, post radiotherapy.

[#] Data are expressed as absolute and relative frequencies.

* Pearson's chi-square test.

Table IV. Associations with clinical worsening during follow-up (baseline-follow).

Variables[#]	**Reduced > 5 mm (n = 19)**	**Not reduced > 5 mm (n = 58)**	***P***
Age (years)	56.2 ± 12.4	57.9 ± 9.5	0.589
Gender			0.719
Female	2 (10.5)	10 (17.2)	
Male	17 (89.5)	48 (82.8)	
Education (years)	6.7 ± 2.9	6.4 ± 3.5	0.692
Smoking	14 (73.7)	51 (87.9)	0.157
Amount (packs/year)	55 (30 to 92)	39 (28 to 72)	0.228
Alcoholism	12 (63.2)	35 (60.3)	1.000
Time (years)	34 (21 to 45)	30 (20 to 45)	0.193
Feeding			0.239
Normal	4 (21.1)	26 (44.8)	
Soft	7 (36.8)	12 (20.7)	
Liquid	5 (26.3)	10 (17.2)	
Enteral	3 (15.8)	10 (17.2)	
Chemotherapy	12 (63.2)	37 (63.8)	1.000
Surgery	12 (63.2)	27 (46.6)	0.321
Neck dissection	9 (47.4)	22 (37.9)	0.647
Diagnosis			0.677
Oral cavity	7 (36.8)	22 (37.9)	
Oropharynx	9 (47.4)	22 (37.9)	
Nasal cavity	1 (5.3)	9 (15.5)	
Salivary glands	2 (10.5)	5 (8.6)	
Staging			0.375
I and II	2 (10.5)	10 (17.2)	
III	4 (21.1)	19 (32.8)	
IVa and IVb	13 (68.4)	29 (50.0)	
RDT modality			0.282
IMRT	1 (5.3)	6 (10.3)	
2D	15 (78.9)	49 (84.5)	
3D	3 (15.8)	3 (5.2)	
Trismus baseline	2 (10.5)	9 (15.5)	0.722
Trismus post	7 (36.8)	11 (19.0)	0.127
Mucositis post	15 (78.9%)	27 (46.6%)	0.028
Grade mucositis post			0.015
No mucositis	4 (21.1)	31 (53.4)*	
I-II	8 (42.1)	20 (34.5)	
III-IV	7 (36.8)*	7 (12.1)	
KPS (post)	78.4±15.0	82.2±15.1	0.341
KPS (delta)	-13.2 ± 16.3	5.2 ± 8.4	<0.001
VAS post	7 (0-9)	3.5 (0-7)	0.042
VAS (delta)	-0.4 ± 3.1	-1.3 ± 3.1	0.284
Group			0.528
Control group	6 (31,6)	19 (32,8)	
Group 1	5 (26,3)	22 (37,9)	
Group 2	8 (42,1)	17 (29,3)	
Adherence	10 (76.9)	32 (82.1)	0.697

RDT, radiation therapy; IMRT, intensity-modulated radiation therapy; 3D, three-dimensional conformed radiation therapy; 2D, two-dimensional conventional radiation therapy; VAS: visual analogue scale, KPS: Karnofsky Performance Status.

Described as mean ± standard deviation, median (25th-75th percentiles), or n (%).

* Statistically significant association through the test of adjusted residuals at 5% significance.

Table V. Variables independently associated with clinical worsening throughout the follow-up.

Bloc	**Variables**	**Relative Risk**	**95% CI**	***P****
Distal	Smoking	0.52	0.23-1.17	0.112
Intermediate	Trismus post	1.50	0.72-3.13	0.282
	Mucositis grade post			
	No mucositis	1.00	-	-
	I-II	1.96	0.70-5.49	0.200
	III-IV	3.66	1.31-10.3	0.014
	VAS post	1.03	0.91-1.17	0.653
Proximal	KPS (delta)	0.96	0.94-0.98	0.001

95% CI, 95% confidence interval; VAS, visual analogue scale; KPS, Karnofsky Performance Status.

* Hierarchical Poisson regression analysis.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	4 (trial design and methods are together according to the journal instructions)
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5 and 6
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6 and 8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	6 and 7
	4b	Settings and locations where the data were collected	6 and 8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10 and 11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8, 9, 10, 13 and 14
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			

Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	8
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12 and 13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	13
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	14
	13b	For each group, losses and exclusions after randomisation, together with reasons	14
Recruitment	14a	Dates defining the periods of recruitment and follow-up	14
	14b	Why the trial ended or was stopped	Ao atingir o número amostral
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	14 (table1)
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	14 and 15
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	14, 15 and 16
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	15 and 16
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	We found no adverse events

Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	20
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	20
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	19 and 20
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org]

4.3 MANUSCRITO III

Health-related quality of life up to 1 year after radiotherapy in head and neck cancer patients with and without trismus

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Short Report

Background

Trismus, or mandibular hypomobility, is defined as a mouth opening (MO) of 35 mm or less (either the interincisal distance or the distance between the upper and lower alveolus) [1,2]. The most common cause of oncology-related trismus is radiation-induced fibrosis in the masticatory musculature when located in the radiation field [3]. Trismus significantly impacts activities of daily living as well as vital oral function; it can lead to impairment of speech and eating, malnutrition, poor oral hygiene and difficulty with dental treatment and intubation [4,5]. However, despite these issues, trismus does not receive sufficient attention in the literature and in clinical practice [5].

Health-related quality of life (HRQOL) instruments are becoming increasingly important and reliable measures of how patients experience their symptoms and are an important part of modern cancer research [5]. The number of cancer survivors has increased due to better diagnostic tools and more efficacious treatments [6]. Although treatment prolongs survival, many patients with head and neck cancer (HNC) continue to experience complications related to trismus [7]. For example, Lee et al. [4] found that head and neck cancer (HNC) survivors with trismus had a worse quality of life in terms of social contact, sexuality, feeling ill, nutritional deficiency, and weight loss compared to HNC survivors without trismus.

The aim of the present study was to investigate HRQOL in patients with HNC up to 1 year after radiotherapy treatment (RDT) and verify whether there are differences in HRQOL between patients with and without trismus in order to offer more specific care based on related deficits in HRQOL.

Methods

This is a longitudinal descriptive study including patients with HNC receiving RDT. The data of the present study were collected in a randomized, prospective study investigating the effectiveness of training interventions to prevent trismus in patients undergoing RT and up to 12 months after completed RT (primary endpoint). No statistically significant differences in trismus and in quality of life were found between the intervention and control groups [8]. Ninety consecutive patients from the Department of Radiation Oncology of a charitable hospital in Porto Alegre, were initially included between May 1, 2014, and November 30, 2015. Of these, 77 completed the 12-month follow-up time period and were therefore included in the present study.

Inclusion criteria

Patients were included if they met the following criteria: willing to participate; age greater than 18 years; formal histopathological diagnosis of HNC; undergoing definitive or postoperative external beam RDT for HNC, either alone or in combination with chemotherapy; and cognitive ability to complete the quality of life questionnaire.

Oncologic treatment

All patients underwent external photon beam radiotherapy, at a dose of 2 Gy per fraction per day, 5 days a week, over a 5- to 7-week course of therapy, for a final dose ranging from 50 to 70 Gy. Overall, 49 patients (63.6%) received concomitant chemotherapy (50 mg cisplatin once weekly). Treatment regimens were individualized according to tumor site, size, and stage.

Data collection

On the day of radiation simulation (two weeks before starting RDT), patients were informed of the study and invited to participate. All patients provided verbal and written informed consent. Demographic variables were collected in a written questionnaire and clinical data were extracted from patient medical records.

HRQOL and the mouth opening measure were assessed at three different time points: baseline, after the last RDT and 12 months after completed RDT. HRQOL was assessed using the self-administered University of Washington Quality of Life (UW-QOL) Questionnaire, version 4, which is validated for the Brazilian population [9]. The UW-QOL questionnaire consists of 12 single question domains that have between 3 and 6 response options that are scaled evenly from 0 (worst) to 100 (best) according to the hierarchy of response. The domains are pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood and anxiety. From these domains, a composite score is calculated (a simple average of all 12 domain scores). The whole questionnaire focuses on current patient health and quality of life within the past 7 days [9].

Maximum mouth opening (MMO) was measured using Digimess 100.179N (São Paulo/SP, Brazil) digital calipers (resolution 0.01 mm/.0005", with a certificate of calibration provided by the manufacturer), and MMO is expressed in mm. The patients were seated in an upright position and were asked to open their mouths as wide as possible. The recommendations and instructions proposed by Goldstein et al. [10] and Dijkstra et al. [1] for assessment of completely and partially edentulous patients were adopted, namely: in patients with an edentulous mandible and no dentures, the distance between the incisal edge of the most vertical maxillary central incisor and the opposing (i.e., corresponding mandibular) alveolar ridge was measured; in patients with an edentulous maxilla and no dentures, the distance between the incisal edge of the most vertical mandibular central incisor and the opposing alveolar ridge was measured; in fully edentulous patients, MMO was measured from

the mandibular alveolar ridge to the maxillary alveolar ridge along the midline corresponding to the nasopalatine foramen. Dental health condition was assessed to enable correction in the event of changes.

The present study was conducted in accordance with the ethical standards of the Declaration of Helsinki and with Brazilian National Health Council Resolution 466/12 and was approved by the Research Ethics Committee of Irmandade Santa Casa de Misericórdia de Porto Alegre (approval number 259.691).

Statistical Analysis

The sample size was calculated from the main outcome reported previously [8]. Quantitative variables were expressed as the means and standard deviations or as medians and interquartile ranges, depending on the normality of distribution. Categorical variables were expressed as absolute and relative frequencies. The Kolmogorov-Smirnov test was used to assess the distribution of variables.

A generalized estimating equations (GEE) model complemented by the least significant difference (LSD) test was applied to the comparisons over the time. The T-test was used to compare means across groups. In cases of asymmetric distribution, the Mann-Whitney test was used instead.

The significance level was set at 5% ($P < 0.05$), and all analyses were carried out in Statistical Package for Social Sciences (SPSS) software v.23 (SPSS Inc., Chicago, IL, USA).

Results

During the study period, 90 patients were eligible for inclusion, and all agreed to participate in this study. However, only 77 fulfilled the 12-month assessment and were therefore included in the present analysis of HRQOL. The 13 dropouts were a result of death

(n = 8), failure to comply (n = 4) or withdrawal due to patient request (n = 1). The demographic and clinical characteristics of the included patients are given in Table 1. The scores of 12 disease-specific domains and the composite score are listed in Table 2.

Of the included patients 19 (25%) showed trismus (AB ≤ 35 mm) at the 12 month follow-up. In a comparison of HRQOL scores of patients who develop trismus and those who do not, a significant statically difference was observed in 9 of 12 disease-specific domains and in the composite score, as shown in Table 3.

Discussion

The incidence of trismus in our study after 12 months of head and neck oncology treatment was 25%; the same incidence of trismus at the same period after RDT has been reported in previous studies [11-13]. The results of this study show an overall decrease in HRQOL at the completion of RDT and recovery at the 12 month follow-up. Our data reflect the published evidence, which supports the premise that the HRQOL returns to preillness levels by 12 months after treatment [14,15]. However, in our study at 1 year after completing RDT, there were remaining significant problems in the taste and saliva domains.

In the current study, patients with trismus had significantly poorer HRQOL in pain, appearance, activity, recreation, swallowing, chewing, speech, taste, mood domains and in the composite score compared with patients who did not have trismus. The negative impact of trismus on patient quality of life is not unexpected, considering its effect on speech, nutrition and oral hygiene [16]. However, despite the great impact on quality of life, trismus is frequently overlooked, neglected and under reported long-term complication of therapy [17]. Health care providers need to pay more attention to this devastating and progressive complication of oncologic treatment. To improve the patients' HRQOL, it is of utmost importance that caregivers manage strategies for early detection and appropriate treatment of

trismus. We believe consistent early intervention is important in the amelioration of trismus and may improve HRQOL.

Study strengths

One of the strengths of this study is its prospective design, and the fact that the data for mouth opening and HRQOL were collected before treatment began. These data ensured that the differences evaluated were attributed to the oncologic treatment given and not to the tumor.

Study limitations

Even though prospective data were used in the data collection, the original study design was to verify differences in mouth opening between groups. There may not be enough power in the analysis to support the secondary aim of this study group, although this may be justified by the significant differences found.

Future studies

Future studies should aim to determine to what extent increased morbidity contributes to the deterioration in HRQOL. A qualitative research approach may increase the understanding of the impact of trismus in HNC patients.

Conclusion

Overall, 25% of the patients had trismus twelve months after finishing their oncological treatment in this prospective study. Furthermore, we found that patients with trismus had greater negatively affected HRQOL in pain, appearance, activity, recreation, swallowing, chewing, speech, taste, mood and in the overall quality of life than patients

without trismus. Advances in trismus prevention and treatment are needed to improve HRQOL in HNC patients.

Abbreviations

HNC: head and neck cancer; RDT: radiotherapy treatment; HRQOL: healthe-related quality of life; MO: mouth opening; MMO: maximum mouth opening; UW-QoL: University of Washington Quality of Life Questionnaire; Gy: grays; GEE: Generalized estimating equations model; LSD: least significant difference.

Ethics approval and consent to participate

The present study was approved by the Research Ethics Committee of Irmandade Santa Casa de Misericórdia de Porto Alegre under approval number 259.691 in accordance with the ethical standards of the Declaration of Helsinki and with Brazilian National Health Council Resolution 466/12. Written informed consent was obtained from all participants in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contribuitions

GPJ is the academic supervisor of KCB and had important input on the trial design. KCB is the main writer of the manuscript. CC is the second main writer of the manuscript. NWM provided logistic and administrative support. MD and RP provided assistance in writing the manuscript.

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Table 1: Characterization of the sample.

Variables[#]	**n=77**
Age (years)	57.5 ± 10.2
Gender	
Female	12 (15.6)
Male	65 (84.4)
Ethnicity	
Caucasian	56 (72.7)
Black	8 (10.4)
Mixed	13 (16.9)
Education (years)	6.5 ± 3.3
Smoking	65 (84.4)
Amount (packs/year)	45 (30-75)
Alcoholism	47 (61.0)
Time (years)	30 (20-38)
Feeding	
Normal	52 (67.5)
Soft	15 (19,5)
Liquid	3 (3.9)
Enteral	7 (9.1)
Chemotherapy	49 (63.6)
Surgery	39 (50.6)
Neck Dissection	31 (40.3)
Diagnosis	
Oral cavity	29 (37.7)
Oropharynx	31 (40.3)
Nasopharynx	10 (13.0)
Salivary Glands	7 (9.1)
Histology	
Squamous cell carcinoma	72 (93.5)
Adenoid cystic carcinoma	2 (2.6)
Acinic cell carcinoma	2 (2.6)
Verrucous carcinoma	1 (1.3)
Staging	
I and II	12 (15.6)
III	23 (29.9)
IVa and IVb	42 (54.5)
RDT modality	
IMRT	7 (9.1)
2D	64 (83.1)
3D	6 (7.8)

IMRT, intensity-modulated radiation therapy; RDT, radiation therapy; 3D, three-dimensional conformed radiation therapy; 2D, two-dimensional conventional radiation therapy.

[#]Described as mean ± standard deviation, median (25th-75th percentiles), or n (%).

Table 2: University of Washington quality of life scores of the entire cohort

Domains	Baseline	Post-treatment	12 months follow-up	P*
	Mean ± SE	Mean ± SE	Mean ± SE	
Pain	77.6 ± 2.5[b]	64.9 ± 3,3[a]	86.7 ±2.4[c]	**<0.001**
Difference baseline- post (CI 95%)		-12.7 (-19.5 to -5.8)		
Difference baseline- follow-up (CI 95%)		9.1 (4.3 to 1.9)		
Difference post - follow-up (CI 95%)		21.8 (14.5 to 29.0)		
Appearence	68.8 ± 2.9[b]	61.0 ± 3.3[a]	82.8 ± 2.8[c]	**<0.001**
Difference baseline- post (CI 95%)		-7.8 (-14.6 to -1)		
Difference baseline- follow-up (CI 95%)		13.9 (7.4 to 20.7)		
Difference post - follow-up (CI 95%)		21.8 (14.9 to 28.6)		
Activity	69.5 ± 3.0[b]	56.8 ±3.5[a]	79.2 ± 2.9[c]	**<0.001**
Difference baseline- post (CI 95%)		-12.7 (-19.7 to -5.7)		
Difference baseline- follow-up (CI95%)		9.7 (4.2 to 15.3)		
Difference post - follow-up (CI 95%)		22.4 (15.4 to 29.4)		
Recreation	68.2 ± 3.7[b]	54.6 ± 4.1[a]	79.6 ± 3.2[c]	**<0.001**
Difference baseline- post (CI 95%)		-13.6 (-21.1 to -6.1)		
Difference baseline- follow-up (CI 95%)		11.4 (4.5 to 18.2)		
Difference post - follow-up (CI 95%)		25.0 (17.5 to 32.5)		
Swallowing	78.5 ± 3.2[b]	51.2 ± 3.7[a]	79.3 ± 3.2[b]	**<0.001**
Difference baseline- post (CI 95%)		-27.4 (-34.5 to -20.2)		
Difference baseline- follow-up (CI 95%)		0.8 (-6.6 to 8.2)		
Difference post - follow-up (CI 95%)		28.1 (20.6 to 35.7)		
Chewing	77.6 ± 3.8[b]	67.5 ±4.1[a]	80.5 ± 3.6[b]	**0.024**
Difference baseline- post (CI 95%)		-10.1 (-19.3 to -0.8)		
Difference baseline- follow-up (CI 95%)		2.9 (-5.5 to 11.4)		
Difference post - follow-up (CI 95%)		12.9 (3.4 to 22.6)		
Speech	65.4 ± 3.3[b]	56.5 ± 3.4[a]	73.7 ± 3.1[b]	**<0.001**
Difference baseline- post (CI 95%)		-8.9 (-15.8 to -2)		
Difference baseline- follow-up (CI 95%)		8.3 (2.4 to 14.2)		

Difference post - follow-up (CI 95%)		17.2 (10.5 to 23.9)		
Shoulder	78.8 ± 3.2	82.3 ± 3.0	84.4 ± 2.7	0.084
Difference baseline- post (CI 95%)		3.5 (-2.4 to 9.3)		
Difference baseline- follow-up (CI 95%)		5.7 (0.5 to 10.8)		
Difference post - follow-up (CI 95%)		2.2 (-1.9 to 6.2)		
Taste	90.1 ± 3.0[c]	26.8 ± 4.0[a]	73.2 ± 3.3[b]	**<0.001**
Difference baseline- post (CI 95%)		-63.3 (-73.1 to -53.4)		
Difference baseline- follow-up (CI 95%)		-16.9 (-24.1 to -9.7)		
Difference post - follow-up (CI 95%)		46.4 (37.9 to 54.9)		
Saliva	89.7 ± 2.0[c]	54.6 ± 2.5[a]	72.4 ± 3.1[b]	**<0.001**
Difference baseline- post (CI 95%)		-35.1 (-41.1 to -29.1)		
Difference baseline- follow-up (CI 95%)		-17.3 (-23.9 to -10.7)		
Difference post - follow-up (CI 95%)		17.8 (10.4 to 25.2)		
Mood	64.3 ± 3.4[a]	57.1 ± 3.7[a]	75.3 ± 3.2[b]	**<0.001**
Difference baseline- post (CI 95%)		-7.1 (-15.1 to 0.8)		
Difference baseline- follow-up (CI 95%)		11.0 (3.2 to 18.9)		
Difference post - follow-up (CI 95%)		18.2 (11.2 to 25.1)		
Anxiety	53.7 ± 4.0[a]	56.3 ± 3.9[a]	69.3 ± 3.4[b]	**<0.001**
Difference baseline- post (CI 95%)		2.6 (-6.5 to 11.7)		
Difference baseline- follow-up (CI 95%)		15.6 (7.1 to 24.1)		
Difference post - follow-up (CI 95%)		13.0 (5.3 to 20.7)		
Composite score	73.5 ± 1.7[b]	57.5 ± 2.2[a]	78.2 ± 2.1[c]	**<0.001**
Difference baseline- post (CI 95%)		-15.9 (-20.1 to -11.9)		
Difference baseline- follow-up (CI 95%)		4.7 (0.6 to 8.8)		
Difference post - follow-up (CI 95%)		20.7 (16.0 to 25.3)		

SE, standard error, CI 95%, Confidence interval 95%

* Model of generalized estimating equations (GEE);

a, b, c comparison between groups where equal letters do not differ statistically by the Least Significant Difference (LSD) test with $P < 0.05$.

Table 3. Association between quality of life and trismus during follow-up (baseline-follow).

Variation in QoL scores[#] (Basal-Follow)	**MO ≤ 35mm (N=19)**	**MO > 35 mm (N=58)**	**P[*]**
	Mean ± SD	**Mean ± SD**	
Pain	-6.6 ± 16.3	14.2 ± 21	<0.001
Appearence	-3.9 ± 31.5	19.8 ± 27.6	0.002
Activity	-6.6 ± 26.1	15.1 ± 22.4	0.001
Recreation	-7.9 ± 38.2	17.7 ± 25.2	0.012
Swalloing	-28.1 ± 42	10.2 ± 23.4	0.001
Chewing	-23.7 ± 38.6	11.6 ± 33.8	<0.001
Speech	-10.5 ± 33.5	14.4 ± 20.8	0.006
Shoulder	-3.6 ± 19.1	8.7 ± 23.9	0.056
Taste	-35.1 ± 35.9	-10.9 ± 29.1	0.004
Saliva	-31.6 ± 37.7	-12.6 ± 25.6	0.052
Mood	-13.2 ± 28.1	18.9 ± 33.9	<0.001
Anxiety	1.8 ± 41	20.1 ± 36.4	0.069
Composite scores	-14.1 ± 20.8	10.8 ± 12.6	<0.001

MO, mouth opening;

[#]Described as mean ± standard deviation

* T-studant test.

5 CONCLUSÃO

Não é possível concluir que os protocolos de exercícios aqui apresentados são mais eficazes para evitar redução da medida de AB do que as orientações padrão pré-radioterapia da instituição onde a pesquisa foi realizada, pois aos 12 meses do término do tratamento radioterápico tanto os pacientes que realizaram exercícios quanto os que não realizaram apresentaram o mesmo desfecho na medida de abertura bucal. Apesar de não haver contra-indicações ao uso do Therabite durante o tratamento radioterápico, chama-se atenção ao aumento significativo da dor (mensurada pela EVA) e mucosite (mensurada pelo Critério de toxicidade oral da OMS) nos pacientes que utilizaram este dispositivo, devendo ser futuramente analisado o impacto do Therabite na mucosa oral durante o tratamento radioterápico.

Não foram encontradas diferenças entre os grupos na capacidade funcional, mensurada pela KPS, e na qualidade de vida, mensurada pelo UW-QOL, todos os grupos apresentaram uma redução significativa dessas variáveis no pós-radioterapia imediato e uma melhora significativa aos 12 meses após o término da RDT.

As variáveis independentemente associadas com a redução clinicamente relevante da AB foram o grau III e IV de mucosite no pós-RDT imediato e a redução da KPS ao longo do seguimento, devendo ser investigado se a prevenção da mucosite tem um impacto na amplitude de AB e KPS de pacientes submetidos a RDT para neoplasias de cabeça e pescoço.

Pacientes sobreviventes ao CCP com trismo apresentam uma redução significativa da qualidade de vida quando comparados aos pacientes sem trismo. Dado o relevante impacto do trismo na QV desses pacientes sugere-se que protocolos para prevenção do trismo radioinduzido iniciados após o término da RDT sejam investigados.

6 APÊNDICES

6.1 PUBLICAÇÃO REFERENTE A ESTA TEMÁTICA

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Jaw mobility changes in patients with upper aerodigestive tract cancer undergoing radiation therapy

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Abstract

Background: Radiation therapy is a therapeutic modality widely used for treatment of upper aerodigestive tract (UADT) neoplasms. However, its action is not restricted to tumor cells, and it may cause a variety of adverse reactions, including reduced jaw mobility.

Material and Methods: A prospective cohort study was conducted to assess changes in jaw mobility in patients with UADT cancer undergoing radiation therapy.

Results: Fifty-six patients completed the study. The results showed a significant reduction in mouth opening (p<0.001), right lateral excursion (p=0.038) and left lateral excursion (p=0.035) of the jaw, a significant increase in the presence (p<0.001) and severity of oral mucositis (p<0.001), and a significant decrease in performance status (p<0.001) after radiation therapy. Thirty-six patients (64.3%) exhibited reduction in mouth opening after treatment. The variables significantly associated with mouth opening reduction on bivariate analysis were: modification of diet (p=0.037), radiation field (p=0.024), presence of mucositis (p=0.003), and reduction in performance status (p=0.007). After adjustment by the multivariate model, the only variables that remained significantly associated with reduction in mouth opening were presence of mucositis (p=0.018) and reduction in performance status (p=0.47).

Conclusions: These findings indicate that patients with upper aerodigestive tract cancer experience reduced jaw mobility after radiation therapy, which is strongly correlated with mucositis and reduced functional ability.

Key words: *Head and neck neoplasms, vertical dimension, radiation therapy, mucositis, temporomandibular joint, joint range of motion, trismus.*

Introduction

Over 1 million cases of upper aerodigestive tract (UADT) cancer are diagnosed worldwide each year, a number that is expected to increase (1). Oral cavity cancer is the seventh most common type of cancer in the Brazilian population (2), and the male population of Brazil has the third-highest risk of oral cancer in the world, after those of France and India (2).

According to the literature, normal jaw mobility ranges from 40 to 70 mm for mouth opening and from 8 to 12 mm for lateral excursion (3,4). However, these values can vary with factors such as gender, age, body weight, height, dental conditions, and signs and symptoms of temporomandibular disorders (4). UADT cancer-related reduced jaw mobility, or trismus, may occur due to tumor infiltration into the muscles of mastication or into the temporomandibular joint (TMJ). Other causes include mechanical obstruction of the coronoid process of the mandible by the tumor, surgical approaches to tumors involving the muscles of mastication or TMJ, adhesions and scar-related fibrosis, and radiation-induced fibrosis (5).

The incidence of mandibular hypomobility among UADT cancer patients treated with radiation therapy ranges from 6% to 85% (6-9). This broad range seems to be related with biases in retrospective collections, lack of uniform criteria to measure this complication, different anatomy sites and tumor sizes, and application of different forms of treatment and irradiation modes (5,7,10). Reduction in jaw mobility negatively impacts patient quality of life, as it changes facial appearance, hinders food intake and use of dental prostheses, compromises oral hygiene and speech, and may induce anxiety and depression (7-9).

In view of the lack of reliable data on the incidence of mandibular hypomobility among irradiated UADT cancer patients, the primary objective of this study was to assess jaw mobility in a cohort of patients with UADT cancer undergoing radiation therapy at a charitable hospital in Porto Alegre, state of Rio Grande do Sul, Brazil. The secondary objective was to ascertain whether changes in jaw mobility are associated with selected demographic and clinical variables.

Material and Methods

This prospective cohort consecutively assessed all patients with UADT cancer - defined for the purposes of this study as cancer of the oral cavity, oropharynx, nasopharynx, hypopharynx, or larynx - who attended the Department of Radiation Oncology of a charitable hospital in Porto Alegre, Brazil, between January 1st and June 30th, 2013.

Subjects included persons over 18 years of age, of either gender, who had received an anatomopathological diagnosis of UADT cancer and were undergoing radiation therapy (RT) exclusively or in association with chemotherapy and/or surgery. Patient selection was limited to those whose TMJ and/or muscles of mastication were in the radiation field and who were receiving RT with curative intent. The following exclusion criteria were applied: Surgical interventions that involved removal of the jaw or any of the muscles of mastication, facial palsy, trigeminal neuralgia, previous irradiation of the head and neck region, current physical therapy or speech therapy for jaw mobility, baseline mouth opening (MO) less than 10 mm, score below 50 on the Karnofsky Performance Status (KPS) scale (11), and refusal to take part in the study.

Sample size calculation was based on a previous study by Grandi *et al.* (12). We estimated that at least 43 patients would be required to detect an effect size of at least 0.6 standard deviations between assessments, at the 5% significance level, with 90% power.

- Data Collection

Eligible patients were identified before the start of RT, during the weekly multidisciplinary team meeting of the Department of Radiation Oncology. On the day of the patient's treatment simulation, the study was explained and patients were invited to participate. After each patient provided written informed consent, data collection was begun.

All patients underwent individual history-taking and physical examination, always performed by the same examiner, who was qualified and experienced with the research protocols at hand. Data on the following variables were collected: age, gender, skin color, occupation, family history of cancer, tobacco and alcohol intake, and consistency of diet (solid, semisolid, liquid, or enteral nutrition).

Occupational exposure to carcinogenic substances was assessed according to the description of the Union for International Cancer Control (UICC) (13). When the patient had a positive family history of cancer, the disease was classified into UADT cancer, tobacco-related can-

cer (lung, esophageal, liver, stomach, spleen, kidney, bladder, cervix, and myeloid leukemia), or other cancer types (14).

The clinical data collected were: tumor site, histologic type, concomitant chemotherapy, surgery, modality of RT, radiation field and dosage and tumor staging. These data were collected from patient records.

Physical examination was performed prior to the start of RT (pre-treatment) and immediately after the last RT session (post-treatment), and assessed maximum mouth opening (MMO), right lateral excursion (RLE), left lateral excursion (LLE), and protrusion (PR) of the jaw, oral mucositis, and functional ability.

Jaw MMO, RLE, LLE, and PR were measured with a Digimess 100.179N digital caliper (resolution 0.01 mm/.0005", with a certificate of calibration provided by the manufacturer), following the guidelines and specifications for clinical examination defined by the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) (15). The adaptations proposed by Goldstein *et al.* (6) for the assessment of partially and completely edentulous patients were adopted. In patients with an edentulous mandible who did not wear dentures, the distance from the incisal edge of the vertical most maxillary central incisor to the opposing alveolar ridge in the mandible was measured. In patients with an edentulous maxilla who did not wear dentures, the distance from the incisal edge of the vertical most mandibular central incisor to the opposing alveolar ridge was measured. In completely edentulous patients, MMO was measured from the mandibular alveolar ridge to the maxillary alveolar ridge at the midline corresponding to the nasopalatine foramen.

Oral mucositis was graded according to the oral toxicity criteria of the World Health Organization (WHO) (16), while functional ability was assessed using the KPS scale (11).

All patients were treated with external photon beam RT. All received a daily dose of 2 Gy per fraction, 5 days a week, over a 5-to-7-week course of therapy. The total RT dose ranged from 50 to 70 Gy. Thirty-one (55.4%) patients received concomitant chemotherapy (50 mg cisplatin weekly). Twenty-two (39.3%) patients underwent surgical resection of the primary tumor. The treatment regimens were defined according to the tumor site and size and the disease stage.

The present study complied with the ethical standards of the Declaration of Helsinki and with Brazilian National Health Council Resolution no. 196/96, and was approved by the Research Ethics Committee of Irmandade Santa Casa de Misericórdia de Porto Alegre under protocol 031.12.

- Statistical Analysis

Quantitative variables were described as means and standard deviations or, if asymmetrically distributed, as medians and interquartile ranges. Categorical variables were described as absolute and relative frequencies.

The Shapiro-Wilk test was used to assess the distribution of variables, while Student's T-test was used to compare means among groups.

To assess the association among quantitative variables, Pearson's (r) or Spearman's (rs) linear correlation coefficients were used for symmetrically and asymmetrically distributed data respectively.

Student's T-test for paired samples was used to compare pre- and post-RT parameters. In case of distribution asymmetry, the Wilcoxon test was used instead. McNemar's test was used to compare the proportions.

To control for confounding factors, a multivariate multiple linear regression model was applied. The criterion for inclusion of variables in the multivariate regression model was $p<0.20$ at bivariate analysis.

The significance level was set at 5% ($p<0.05$). All analyses were carried out in the SPSS 21.0 software environment.

Results

Data were collected from 58 patients, two of whom were lost to follow-up (one deceased, one discontinued treatment as advised by physician). The demographic and clinical profiles of the 56 patients that completed the study are shown in tables 1 and 2 respectively.

Comparison of the pre- and post-treatment physical examination variables of the 56 patients who completed the study showed a statistically significant reduction in MO, RLE, and LLE, a statistically significant increase in the presence and severity of mucositis, and a statistically significant decline in functional ability (Table 3). After RT, MO decreased in 36 (64.3%) patients, increased in 12 (21.4%), and remained stable in eight (14.3%).

Bivariate analysis of clinical and demographic variables and physical examination findings showed that the following variables were significantly associated with change in MO: change in diet consistency (solid, -1.35±5.17 vs. modified, -5.17±7.00; $p=0.037$); radiation field (oral cavity/oropharynx, -5.64±6.42 vs. nasopharynx/hypopharynx/larynx, -1.68±6.27; $p=0.024$); presence of mucositis (present, -5.86±6.58 vs. absent, -0.62±5.34; $p=0.003$); and reduction in KPS score ($r=0.438$, $p=0.007$).

Patients who had mucositis had a significantly higher rate of modified diet as compared with those who had no mucositis (82.4% vs. 20.6%, $p=0.003$).

After adjustment using the multivariate model (Table 4), the only variables that remained significantly associated with MO reduction were presence of mucositis at post-RT assessment and reduction in KPS score. Patients with mucositis had an average reduction of 4.19 mm in MO after RT (b=-4.19; 95%CI -7.62 to -0.8). Pa-

Table 1. Sample profile.

Variables	n=56
Age (years) – Mean ± SD	58.7 ± 10.8
Gender – n (%)	
Male	52 (92.9)
Female	4 (7.1)
Skin color – n (%)	
White	42 (75.0)
Black	5 (8.9)
Brown	9 (16.1)
Occupational exposure – n (%)	
Yes	42 (75.0)
No	14 (25.0)
Family history of cancer – n (%)	
Yes	29 (51.8)
No	27 (48.2)
Type of cancer in family – n (%)	
UADT	0 (0.0)
Tobacco-related	17 (58.6)
Others	12 (41.4)
Smokers – n (%)	53 (94.6)
Duration of smoking (years) – Mean ± SD	38.1 ± 12.3
Pack-years – Median (IQR)	44 (30 – 86)
Alcohol intake – n (%)	38 (67.9)
Duration of alcohol intake (years) – Mean ± SD	29.8 ± 14.2
Continues to smoke – n (%)	12 (21.4)
Continues to drink – n (%)	2 (3.6)
Diet – n (%)	
Normal/Solid	41 (73.2)
Semisolid	7 (12.5)
Liquid	2 (3.6)
Enteral feeding/gastrostomy	6 (10.7)

UADT, upper aerodigestive tract.

Table 2. Clinical characteristics.

Variables	n=56
Primary site – n (%)	
OC, tongue	6 (10.7)
OC, floor of mouth	7 (12.5)
OC, retromolar trigone	1 (1.8)
Larynx, supraglottic	17 (30.4)
Oropharynx, tonsils	2 (3.6)
Oropharynx, base of tongue	5 (8.9)
Oropharynx, soft palate	9 (16.1)
Nasopharynx	4 (7.2)
Hypopharynx, pyriform sinus	5 (8.9)
Histologic type – n (%)	
Squamous cell carcinoma	55 (98.2)
Acinar cell adenocarcinoma	1 (1.8)
Chemotherapy – n (%)	31 (55.4)
Surgery – n (%)	22 (39.3)
RT modality – n (%)	
IMRT	2 (3.6)
2D	51 (91.1)
3D	3 (5.4)
Radiation field – n (%)	
Bilateral mouth	14 (25.0)
Bilateral nasopharynx	4 (7.2)
Bilateral oropharynx	16 (28.6)
Bilateral larynx	17 (30.4)
Bilateral hypopharynx	5 (8.9)
RT dose – Mean ± SD	5,746 ± 1,048
Disease stage – n (%)	
I	2 (3.6)
II	5 (8.9)
III	13 (23.2)
IV	36 (64.36)

IMRT, intensity-modulated radiation therapy; OC, oral cavity; RT, radiation therapy; 2D, two-dimensional conventional radiation therapy; 3D, three-dimensional conformal radiation therapy.

tients whose KPS score decreased by 1 point also had a mean reduction of 0.12 mm in MO (b=0.12; 95%CI 0.02 to 0.24). On analysis of the standardized regression coefficient (β), the variable most strongly associated with reduction in MO was presence of mucositis.

Discussion

Regarding sociodemographic and clinical variables, the results of the present study are consistent with the existing literature, which reports a higher incidence of UADT cancer among men, with a predominance of individuals in the 6th and 7th decades of life and white males (2,8,12,17). Habits and social factors reported in other studies, such as alcohol and tobacco intake, tobacco-related cancers in the family, occupational exposure to carcinogenic substances, and low socioeconomic level (16,18,19), were also found in the present investigation. All patients who underwent two-dimensional conventional radiation therapy (2D-RT) (91%) were treated through the public healthcare system, in contrast with the 9% who used private health insurance or paid out of pocket and had access to three-dimensional conformal

Table 3. Pre- and post-radiation therapy comparison.

Variables	Pre	Post	*p*
Mouth opening – Mean ± SD	39.8 ± 10.9	36.0 ± 10.9	<0.001**
RLE (mm)*	5 (4 – 10)	5 (2 – 10)	0.038#
LLE (mm)*	8 (4 – 10)	6.5 (3 – 10)	0.035#
PR (mm)*	4 (1 – 6)	3 (1 – 5)	0.083#
Mucositis – n (%)	2 (3.6)	34 (60.7)	<0.001***
Mucositis severity – n (%)			<0.001***
I	1 (50.0)	12 (35.3)	
II	1 (50.0)	12 (35.3)	
III	0 (0.0)	8 (23.5)	
IV	0 (0.0)	2 (5.9)	
KPS – Mean ± SD	83.0 ± 14.0	74.1 ± 15.9	<0.001**

KPS, Karnofsky Performance Status; LLE, left lateral excursion; PR, protrusion; RLE, right lateral excursion.
* Described as median (interquartile range).
** Student's T-test for paired samples;
*** Pearson chi-squared test; # Mann-Whitney U test.

Table 4. Multivariate linear regression analysis of factors associated with a reduction in mouth opening.

Variables	b (95% CI)	Beta (β)	*p*
Post-RT diet – Changed	-0.29 (-4.27 to 3.69)	-0.021	0.885
Radiation field – OC/oropharynx	-2.83 (-6.61 to 0.96)	-0.215	0.140
Post-RT mucositis	-4.19 (-7.62 to -0.8)	-0.313	0.018
Δ KPS	0.12 (0.02 to 0.24)	0.260	0.047
Stage III/IV disease	-0.90 (-4.26 to 6.07)	0.046	0.727

OC, Oral cavity; KPS, Karnofsky Performance Status.
b, angular coefficient.
95%CI, 95% confidence interval.
β, standardized regression coefficient.

radiation therapy (3D-RT) and intensity-modulated radiation therapy (IMRT). The most prevalent histologic tumor type in this sample was squamous cell carcinoma, which is in accordance with the Brazilian cancer registry (2). Most patients were at an advanced stage at the time of clinical diagnosis, as also reported in other studies (8,17).

The patients in this study experienced a high incidence (64.3%) of reduced jaw mobility after RT, which corroborates the reports of previous studies with the same prospective design (6,20). A high incidence of mandibular hypomobility was also found in two retrospective studies (17,21) and one cross-sectional study (8). However, none of those studies assessed mucositis (which was the variable most strongly associated with hypomobility in this study) or the occurrence of mucositis in relation to the reduction in MO.

By causing pain, mucositis limits the functions of the stomatognathic system, which also forces patients to change the consistency of their diet and, often, to adopt exclusive enteral feeding (22). Patients thus move their jaws less and less, which results in connective tissue contractures and deterioration of the muscles of mastication (23). Muscles start to show signs of atrophy after as little as 3 days of restricted range of motion (5). It is important to remember that immobile joints also undergo rapid degenerative changes, including thickening of the synovial fluid and thinning of the cartilage (5). Thus, patients fed via the nasoenteral route may not notice the slow and progressive onset of trismus until they try to resume solid food intake, since trismus is a complication often neglected by staff involved in patient care and follow-up (5).

The incidence of mucositis is around 80% among irradiated UADT cancer patients. Both the incidence and severity of mucositis may increase if chemotherapy is administered concomitantly with RT (24), which will decrease jaw mobility. Nevertheless, concomitant chemotherapy was not associated with a reduction in MO in the present study, a finding that corroborates previous reports (21,23).

Mucositis requires early intervention, as the mucous membranes are the first structures to be harmed by radiation and, despite 90-95% of patients recovering from mucositis within 4 weeks of treatment completion (25), the effect of mandibular hypomobility caused by mucositis will have a negative impact on the muscles of mastication and TMJ. This impact is difficult to reverse completely at later stages, especially if fibrosis develops in the affected muscles. As noted above, immobile joints rapidly undergo degenerative changes that can make remobilization difficult (5).

Radiation-induced fibrosis of the muscles of mastication as a cause of late post-RT mandibular hypomobility usually occurs 9 weeks after the end of the treatment and progresses over a period of 6 to 9 months (6,9). It has been detected as late as 4 years after the end of treatment (26), which is explained by the fact that muscles are slow-responding tissues that exhibit signs of damage long after RT (27). However, as the present study demonstrated, jaw mobility may also decrease during RT, particularly if mucositis occurs.

Studies assessing reduction in jaw mobility during RT have found that range of MO had not recovered at 6 months after treatment (9,20), while one study showed that MO remains reduced over several years (26). Protocols for prevention of mucositis and radiation-induced trismus must be tested to ascertain whether prophylactic interventions are able to preserve jaw mobility during RT or, at least, mitigate loss of range of motion, thus leading to MO values closer to those found prior to treatment.

The present study did not set a cutoff point for trismus. We believed that assessment of the change in jaw mobility at different points in time would be more reliable, as it would enable identification of any restriction of range of jaw motion (whether inherent to the patient or resulting from the tumor or surgery) before the start of RT, thus ensuring that only RT-related changes would be analyzed. Many patients with UADT cancer exhibit limited MO prior to RT, whether as a result of surgery, due to extension of the tumor into the muscles of mastication, or due to reflex spasm of these muscles (17,28). This symptom tends to improve or resolve during RT, but it can gradually return as an adverse effect of RT (28).

This study corroborates the existing literature (17,23) in that patients with decreased functional ability exhibited a greater reduction in MO. We also found that, unlike in some studies (20,21), mandibular hypomobility can develop regardless of radiation field and disease stage if the patient has reduced functional ability and develops mucositis during treatment. Therefore, although patients with hypopharyngeal and laryngeal cancer have a lower incidence of mandibular hypomobility (8), they must not be excluded from studies and prevention protocols,

as they are likely to develop this complication during RT due to onset of mucositis and changes in diet.

Given the small number of patients who underwent IMRT and 3D-RT in our sample, no inferences could be drawn. Some studies (5,10) have suggested a lower incidence of mandibular hypomobility with IMRT, but there is no consensus on this matter (21). We recommend that prospective studies with larger samples and longer follow-up be conducted to assess different modalities of RT and their impacts on jaw mobility. Protocols for prevention of mucositis and mandibular hypomobility must be tested to ascertain whether they have a positive impact on jaw mobility and patient quality of life.

Conclusion

The findings of this study suggest that patients with UADT cancer undergoing radiation therapy experience reduced jaw mobility. This complication occurs most frequently in patients with mucositis and reduced functional ability.

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Financial disclosure

The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest

The authors have no conflicts of interest to disclose.

7 ANEXOS

7.1 APROVAÇÃO DO COMITÊ DE ETICA EM PESQUISA DA ISCMPA

IRMANDADE DA SANTA CASA DE MISERICORDIA DE PORTO ALEGRE - ISCMPA

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Fisioterapia Profilática ao Desenvolvimento do Trismo Radioinduzido em Pacientes com Câncer de Cabeça e Pescoço

Pesquisador: Geraldo Pereira Jotz

Área Temática:

Versão: 3

CAAE: 11738213.0.0000.5335

Instituição Proponente: Irmandade da Santa Casa de Misericordia de Porto Alegre - ISCMPA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 259.691

Data da Relatoria: 17/04/2013

Apresentação do Projeto:

Trata-se de um ensaio clínico randomizado e controlado. A randomização será realizada no programa PEPI (Programs for Epidemiologists), subprograma RANDOM, para realização do sorteio dos números aleatórios em cada grupo. O sigilo da alocação será garantido por uma lista de randomização que ficará em um lugar remoto. A seqüência dos números a ser utilizada para randomização será mantida em sigilo ate o momento exato do inicio da intervenção. O avaliador estará cegado quanto ao protocolo de exercícios que o paciente estará realizando, apenas coletará os dados sem saber a qual grupo o paciente pertence. Um pesquisador Colaborador entregará e explicará ao paciente o seu devido protocolo conforme a randomização.A coleta será realizada sempre pelo mesmo avaliador, o qual realizará duas avaliações com o paciente,sendo a primeira antes do início do tratamento radioterápico preferencialmente no dia em que o paciente realizar a simulação (momento 0 ¿ M0) e a segunda imediatamente após a última sessão de radioterapia (momento 1 ¿ M1) . Para isso, todos os pacientes serão submetidos a uma breve anamnese, individualmente, nas dependências do Serviço de Radioterapia do HSR. Dados como sítio tumoral, tipo histológico neoplásico,estadiamento do tumor, campo de radiação, dosagem por sessão de radioterapia, se exposição uni ou bilateral. Serão aplicados exercícios e question de tratamento (curativo ou paliativo) serão coletados do prontuário do paciente. Amostra de 66 pacientes, 3 grupos, GEA, GEB, GEC. Serão aplicados exercícios e questionário.

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IRMANDADE DA SANTA CASA DE MISERICORDIA DE PORTO ALEGRE - ISCMPA

Objetivo da Pesquisa:

Objetivo Primário:

Verificar o efeito de dois protocolos de exercícios fisioterapêuticos na manutenção e/ou ganho da amplitude de movimento mandibular de pacientes com câncer de boca, de faringe, ou ambos em tratamento radioterápico.

Objetivo Secundário:

Comparar os valores de abertura, protusão e excursões laterais da mandíbula obtidos no pré e pós-RT entre os grupos intervenção; Comparar os valores de abertura, protusão e excursões laterais da mandíbula obtidos no pré e pós-RT entre os grupos intervenção e o grupo controle; Comparar os valores de abertura,protusão e excursões laterais da mandíbula obtidos no pré e pós-RT em cada grupo; Comparar os valores de capacidade

funcional obtidos no pré e pós RT entre os três grupos; Analisar qual o domínio do questionário de qualidade de vida foi mais acometido em cada grupo; Verificar se existe correlação entre abertura bucal e qualidade de vida; Verificar se existe correlação entre abertura bucal e capacidade funcional.

Avaliação dos Riscos e Benefícios:

Riscos:

Os procedimentos propostos envolvem um risco considerado mínimo de sentir desconforto na musculatura mastigatória ou na articulação temporomandibular durante a realização do exame físico e/ou do protocolo de xercícios. Essa pesquisa não traz riscos para saúde.

Benefícios:

Benefícios prováveis promover melhora na fala, na aparência facial, na mastigação e na ingestão de alimentos, possibilitar o uso de próteses dentária, facilitar a higienização oral, melhorando o convívio social e a qualidade de vida dos pacientes.

Comentários e Considerações sobre a Pesquisa:

Trata-se de um estudo de relevancia com possíveis melhorias para o convívio social e a qualidade de vida dos pacientes.

Considerações sobre os Termos de apresentação obrigatória:

Apresenta os termos exigidos pela RDC 196/96.

Recomendações:

Não se aplica.

Conclusões ou Pendências e Lista de Inadequações:

Após a reanálise do projeto acima descrito recomenda-se aprovar. A pesquisa atende as exigências, em seus aspectos éticos e metodológicos, as Diretrizes e Normas, especialmente as

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Plataforma Brasil

Resoluções 196/96, 251/97, 292/99, 346/05, 347/05 do Conselho Nacional de Saúde.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

Após reavaliação do protocolo acima descrito, o presente comitê não encontrou óbices quanto ao desenvolvimento do estudo em nossa Instituição e poderá ser iniciado a partir da data deste parecer.

Obs.: 1 - O pesquisador responsável deve encaminhar à este CEP, Relatórios de Andamento dos Projetos desenvolvidos na ISCMPA. Relatórios Parciais (pesquisas com duração superior à 6 meses), Relatórios Finais (ao término da pesquisa) e os Resultados Obtidos (cópia da publicação).

2 - Para o início do projeto de pesquisa, o investigador deverá apresentar a chefia do serviço (onde será realizada a pesquisa), o Parecer Consubstanciado de aprovação do protocolo pelo Comitê de Ética.

PORTO ALEGRE, 30 de Abril de 2013

Assinador por:
Claudio Teloken
(Coordenador)

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7.2 Normas das revistas (endereços eletrônicos)

Artigos	Revista, Fator de impacto (IF)/Qualis	Normas
Effect of physiotherapy to prevent trismus in irradiated head and neck cancer patients: study protocol for a randomized, investigator-blinded, controlled, superiority trial	BMC CANCER, IF: 3.679 Qualis - Medicina II: A2 Interdisciplinar: A1	https://bmccancer.biomedcentral.com/submission-guidelines
Exercise therapy during radiotherapy treatment seems not to prevent radiation-induced trismus in head and neck cancer patients: a randomized controlled trial	Oral Surgery, Oral Medicine Oral Pathology, Oral Radiology, IF: 1.718 Qualis - Medicina II: B2 Interdisciplinar: B1	https://www.oooojournal.net/content/authorinfo
Health-related quality of life up to 1 year after radiotherapy in head and neck cancer patients with and without trismus	Health and Quality of Life Outcomes, IF: 2.911 Qualis - Medicina II: B1 Interdisciplinar: A2	https://hqlo.biomedcentral.com/submission-guidelines