UNIVERSIDADE FEDERAL DE GOIÁS
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PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA

ADESÃO DE PACIENTES COM CÂNCER ORAL A UM PROTOCOLO DE PREPARO ODONTOLÓGICO: IMPACTO NA INTERRUPÇÃO DA RADIOTERAPIA E NA SOBREVIDA

MARILIA OLIVEIRA MORAIS

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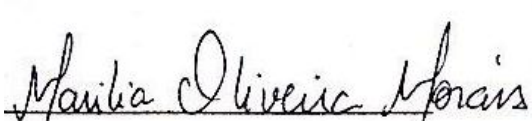

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MARILIA OLIVEIRA MORAIS

ADESÃO DE PACIENTES COM CÂNCER ORAL A UM PROTOCOLO DE PREPARO ODONTOLÓGICO: IMPACTO NA INTERRUPÇÃO DA RADIOTERAPIA E NA SOBREVIDA

Dissertação apresentada ao Programa de Mestrado em Odontologia, da Faculdade de Odontologia da Universidade Federal de Goiás como requisito para a obtenção do título de Mestre em Odontologia, área de concentração Clínica Odontológica.

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Adesão de pacientes com câncer oral a um protocolo de preparo odontológico: Impacto na interrupção da radioterapia e na sobrevida

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"A persistência é o caminho do êxito."
Charles Chaplin

RESUMO

Modalidades de tratamentos para o câncer de cavidade oral resultam em efeitos adversos locais que podem gerar interrupções da radioterapia e consequentemente influenciar na sobrevida do paciente. Para a redução e controle dos efeitos adversos, protocolos de preparo do paciente oncológico são estabelecidos por equipes odontológicas antes, durante e pós-tratamento radioterápico e quimioterápico.

Objetivo: Verificar a adesão dos pacientes portadores de câncer de cavidade oral ao protocolo preventivo odontológico e seu impacto na interrupção da radioterapia e sobrevida do paciente.

Pacientes e método: Neste estudo foram selecionados 133 casos de câncer de cavidade oral submetidos à radioterapia. Os pacientes foram classificados de acordo com o tempo de adesão odontológica: sem adesão (grupo I), adesão inferior ou igual a 6 meses (grupo II) e adesão superior a 6 meses (grupo III). Foram investigadas as características clínico-patológicas, ocorrência de interrupção da radioterapia, sobrevida livre de doença e sobrevida global.

Resultados: A ocorrência de interrupção por sintomas foi estatisticamente significante no grupo III quando comparado ao grupo I (p=0,01). A frequência e a duração de interrupção por sintomas não foram estatisticamente significante entre os grupos. A conclusão da radioterapia foi estatisticamente significante no grupo com adesão superior a 6 meses (p=0,02). A sobrevida dos pacientes foi maior no grupo III (p=0,01) quando comparado aos demais grupos.

Conclusão: A adesão ao protocolo não teve impacto sobre interrupção da radioterapia devido ocorrência da interrupção por sintomas, no entanto, pacientes que tiveram adesão ao protocolo preventivo odontológico apresentaram um melhor índice de sobrevida livre de doença e de sobrevida global.

Palavras-chaves: carcinoma espinocelular, odontologia preventiva, radioterapia, suspensão do tratamento e taxa de sobrevida.

ABSTRACT

Therapeutic modalities for the treatment of oral cancer result in local adverse effects that can cause interruptions of the radiotherapy and consequently to influence in the patient survival. For the reduction and control of the adverse effects, Dental Care Protocol is applied to patients with oral cancer by dental surgeon team before, during and after radiotherapy and chemotherapy.

Objective: The aim of this study was to investigate the adhesion of patients with oral cancer to a Dental Care Protocol and its Impact in the interruption and survival.

Patients and methods: In this study 133 cases of oral cancer undergoing radiotherapy were selected. The patients were classified according to the period of dental adhesion: no adhesion (group I), adhesion less than or equal to 6 months (group II) and adhesion higher than 6 months (group III). Clinic and pathological aspects, occurrence of interruption of radiotherapy, disease-free survival and overall survival were investigated.

Results: The incidence of radiotherapy interruption due to symptoms was statistically significant in group III compared to group I ($p = 0.01$). The frequency and duration of interruption due to symptoms were not statistically significant between groups. The conclusion of radiotherapy rate was statistically significant in the group that exceeded 6 months of dental adhesion ($p = 0.02$). Patient's survival was higher in group III ($p = 0.01$) when compared to the other groups.

Conclusion: The adhesion to a dental care protocol did not have any impact on the radiotherapy interruption due to the occurrence of symptoms, however, patients who had higher adhesion to the Dental Care Protocol showed a higher rate of disease-free survival and overall survival.

Keywords: squamous cell carcinoma, preventive dentistry, radiotherapy, withholding treatment and survival rate.

SÍMBOLOS, SIGLAS E ABREVIATURAS

α/β	Dose na qual os componentes linear e quadrático da morte celular são iguais. Para mucosa e o tumor valor α/β = 10.
BED	Dose Biológica Efetiva
CEC	Carcinoma Espinocelular
cTNM	Estadiamento clínico
d	Dose total de radioterapia em Gy/dia
DNA	Ácido desoxirribonucleico
DP	Desvio padrão
ECOG-PS	*Performance Status* Eastern Cooperative Oncology Group
Gy	Gray
HAJ/ACCG	Hospital Araújo Jorge - Associação de Combate ao Câncer de Goiás
HR	*Hazard Ratio*
IC 95%	Intervalo de confiança de 95%
INCA	Instituto Nacional de Câncer José Alencar Gomes da Silva
$iPLA_2$	Fosfolipase A_2 intracelular independente de Cálcio
MV	Megavoltagem
n	Número de aplicações de radioterapia em dias
OMS	Organização Mundial de Saúde
One-way ANOVA	Análise de Variância simples
PGE_2	Prostaglandina E_2
PPO	Protocolo Preventivo Odontológico
pTNM	Estadiamento patológico
QT	Quimioterapia
RT	Radioterapia

SPSS	*Statistical Package for the Social Sciences*
TNM	Tamanho do tumor/Metástase regional/Metástase à distância
T1	Tumor de até 2 cm em sua maior dimensão
T2	Tumor maior que 2 cm e até 4 cm em sua maior dimensão
T3	Tumor maior que 4 cm em sua maior dimensão
T4	Tumor invade estruturas adjacentes
UICC	União Internacional Contra Câncer

SUMÁRIO

1 CARACTERIZAÇÃO DO PROBLEMA

O câncer de cavidade oral apresenta alta taxa de mortalidade e morbidade (RAZAK et al., 2009; WARNAKULASURIYA, 2009), e atualmente representa o décimo-primeiro tipo de neoplasia mais comum no mundo, tendo sua maior incidência em países como Índia, Austrália, Brasil, França e África do Sul (WARNAKULASURIYA, 2009; PODLODOWSKA et al., 2012). De acordo com os dados do Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA), no Brasil, o câncer de cavidade oral é o quinto e o décimo primeiro tipo de neoplasia mais comum em homens e mulheres, respectivamente. Em Goiás, foram estimados 370 novos casos em 2012 (INCA, 2011).

A etiologia é complexa e está associada ao tabagismo, etilismo, infecção pelo papiloma vírus humano, deficiência de vitamina A, riboflavina e ferro, má higiene bucal, terapia imunossupressora e até fatores genéticos tem sido demonstrados no processo de carcinogênese (BALAGOPAL et al., 2012; BREW et al., 2012; PODLODOWSKA et al., 2012).

No processo de diagnóstico do câncer de cavidade oral é fundamental caracterizar clinicamente a lesão determinando o seu estadiamento clínico na primeira consulta do paciente (KATO et al., 2008). Este sistema, também conhecido por Sistema TNM da União Internacional Contra Câncer (UICC) tem sido amplamente utilizado para o estabelecimento do prognóstico e condutas terapêuticas para o tratamento do câncer (SOBIN e WITTEKIND, 2002; OLIVEIRA et al., 2008; MOTTA RDA et al., 2009; KREPPEL et al., 2010).

Entretanto, este estadiamento é definido pela extensão anatômica do tumor e é estabelecido por três características distintas: **T** que representa o tamanho do tumor; **N**, envolvimento de linfonodo regional e **M**, metástase à distância (SOBIN e WITTEKIND, 2002). Essa classificação é baseada a partir da observação clínica e de exames por imagens (estadiamento clínico, **cTNM**) assim como pelos achados histopatológicos após a ressecção cirúrgica do tumor (estadiamento patológico, **pTNM**), sendo esse último, mais preciso quando comparado ao cTNM (GREENE e SOBIN, 2008; KREPPEL et al., 2010).

O tipo histológico mais frequente é carcinoma espinocelular (CEC) que representa cerca de 90% a 95% das neoplasias malignas de cavidade oral (MOTTA RDA et al., 2009; PONTES et al., 2011; PODLODOWSKA et al., 2012). De acordo

com a Organização Mundial de Saúde (OMS), baseada na análise do grau de queratinização, pleomorfismo nuclear e atividade mitótica, essa neoplasia é classificada em gradações histológicas que foram inicialmente descritas por Brothers (PINDBORG et al., 1997; WOOLGAR, 2006).

Usualmente, o CEC pode ser considerado **grau I** ou bem diferenciado quando se observa a queratinização proeminente, poucas figuras mitóticas e mitoses atípicas ou células epidermóides multinucleadas e, raramente pleomorfismo celular e nuclear. O **grau II** ou moderadamente diferenciado é intermediário ao grau I e grau III. Há menos queratinização, quando comparado ao CEC bem diferenciado, presença de mais pleomorfismo celular e nuclear, figuras mitóticas e mitoses atípicas além da perda de adesão intracelular. Já em **grau III** ou pobremente diferenciado, a queratinização é extremamente rara com intensa perda de adesão intracelular além de frequentes mitoses atípicas, pleomorfismo celular e nuclear e, ainda, presença de células epidermóides multinucleadas (PINDBORG et al., 1997).

Além do sistema de classificação histológico preconizado pela OMS, outros parâmetros microscópicos se fazem necessário com a finalidade tornar a classificação mais acurada para determinar o prognóstico de pacientes diagnosticado com CEC e obter um adequado planejamento terapêutico (LIAO et al., 2007; 2008; CAMISASCA et al., 2009; MOTTA RDA et al., 2009). Dentre eles, destaca-se padrão de invasão tumoral, tumores satélites, invasão linfovascular e perineural, infiltração muscular, extravasamento extracapsular, e por fim, reação desmoplásica e inflamação peritumoral (FAN et al., 2011). Todos esses parâmetros histológicos têm sido associados a menores taxas de sobrevida, com maior índice de recorrência e metástase regional e um pior prognóstico em CEC de cavidade oral (LEHN e RAPOPORT, 1994; FUKANO et al., 1997; PURI et al., 2003; PIMENTA AMARAL et al., 2004; SPARANO et al., 2004; BRANDWEIN-GENSLER et al., 2005; YANG, KO, et al., 2008; YANG, WANG, et al., 2008; HUANG et al., 2010; DE MATOS et al., 2012)

Além disso, pacientes com metástase clínica ou histopatológica possuem um pobre prognóstico, sendo a metástase, um fator determinante na sobrevida e recorrência de câncer na região de cabeça e pescoço (PURI et al., 2003). Quando envolvimento linfonodal regional se faz presente, há uma redução de sobrevida de 50% em 5 anos (PURI et al., 2003). O contrário também é observado em pacientes com linfonodos cervicais clinicamente ou histologicamente negativos no diagnóstico,

apresentando maior chance de sobrevivência (ZWETYENGA et al., 2003). Quando comparado o envolvimento de linfonodo, a sobrevida é significativamente maior em pacientes com linfonodo negativo em CEC de cavidade oral (LAYLAND et al., 2005).

Baseado nesses aspectos acima descritos, o estadiamento clínico e patológico da lesão associada aos parâmetros histopatológicos, sítio anatômico envolvido, idade, gênero, opção do paciente pelo tratamento e recursos institucionais oferecidos, a decisão terapêutica será estabelecida e consequentemente determinará a cura e/ou aumentos de sobrevida do paciente (PRIETO et al., 2005; PATRA et al., 2009; RAZAK et al., 2009; HOFFMANNOVA et al., 2010).

A terapia oncológica tem por finalidade a remoção do processo neoplásico com o objetivo de cura e/ou controle da doença no indivíduo, entretanto, na dependência da extensão da doença e, também, das modalidades terapêuticas empregadas, tais como cirurgia, radioterapia (RT) e/ou quimioterapia (QT), podem-se manifestar efeitos adversos locais e sistêmicos (CHAMBERS et al., 2004; PATRA et al., 2009; RAZAK et al., 2009).

Dentre esses tratamentos, destaca-se a possibilidade de ressecções cirúrgicas amplas com potencial para desfiguração facial do paciente gerando instabilidade emocional e social durante todo o processo de diagnóstico e cura do paciente (SPECHT, 2002; DE CASTRO e GUINDALINI, 2010). Não há dúvida que o melhor tratamento a ser instituído para o paciente com câncer em cavidade oral é o cirúrgico e que na dependência dos fatores acima citados pode ser associado às terapias adjuvantes como a RT e QT (DIRIX et al., 2006; GLENNY et al., 2010).

A RT constitui uma técnica de alta precisão que usa raio-x de alta tensão através de um acelerador linear de fótons ou elétrons que promove a quebra do ácido desoxirribonucleico celular (DNA), liberação de radicais livres e morte do tumor na região irradiada (LESTER e YANG, 2012). Entretanto, diferentes regiões adjacentes ao tumor de cavidade oral também são afetadas pela irradiação de acordo com o modelo linear de Dose Biológica Efetiva (BED). Alguns tecidos como tumor e mucosa, respondem rapidamente. Outros tecidos, tais como tecido conjuntivo, respondem lentamente a RT, tendo efeitos menos severos (MACIEJEWSKI et al., 1990; COOPER et al., 1995). Tecidos de mucosa possuem alta renovação celular, mas são susceptíveis a ulcerações com doses superiores a 50 Gy em RT convencional (COOPER et al., 1995; VERA-LLONCH et al., 2006).

Em glândulas salivares os efeitos da irradiação podem ser observados histologicamente em média 10 a 12 semanas após doses de 50 a 70 Gy. Esse dano ocorre principalmente em células serosas, presentes em glândulas parótidas e submandibulares, onde resultará em morte celular seguida de atrofia glandular (STEPHENS et al., 1986). Os vasos sanguíneos também têm a sua permeabilidade alterada pela irradiação. Doses únicas e superiores a 20 Gy promovem o aumento de permeabilidade vascular que subsequentemente leva a maior deposição de fibrina e posterior substituição por colágeno (COOPER et al., 1995). Esses eventos levam a formação tardia de fibrose tanto em vasos quanto nos espaços intersticiais perivasculares. Além disso, o extravasamento de proteínas do plasma e deposição de fibrina leva a uma resposta inflamatória local que ocasiona no aumento de síntese de colágeno e proliferação de fibroblastos que clinicamente resulta em fibrose local (COOPER et al., 1995).

O tipo e a severidade destas alterações relacionam-se diretamente com a dose da radiação, tamanho da fração e a duração do tratamento (OLMI et al., 2003; CHAMBERS et al., 2004; BOURHIS et al., 2006; FALLAI et al., 2006; KELLY et al., 2007). Os efeitos adversos ou complicações provenientes da ação da RT sobre o tumor e tecidos adjacentes, portanto, variam desde um leve desconforto, quando apenas pequenas partes da boca são irradiadas até lesões mais agressivas com sinais e sintomatologias mais severos, quando áreas de maior extensão estão incluídas no campo a ser irradiado (SPECHT, 2002).

Quanto aos efeitos adversos mais comuns resultantes da terapia oncológica podem ser destacados: mucosite, candidose, xerostomia, dor, disfagia, dermatite, rouquidão, osteorradionecrose, fibrose, trismo, perda do paladar, disfunção da tireóide, estenose esofágica, destruição dentária ou “cárie de radiação”, desnutrição, perda de peso, dentre outros (COOPER et al., 1995; TROTTI, 2000; SPECHT, 2002; CHAMBERS et al., 2004; DIRIX et al., 2006; DE CASTRO e GUINDALINI, 2010). Alguns desses efeitos são considerados agudos, transitórios e tardios. Dentre os efeitos agudos, podem ser observados os danos ou ulcerações em mucosa de revestimento da cavidade oral, como a mucosite, além da xerostomia e perda de paladar, que pode ser transitória (COOPER et al., 1995; SONIS, 2011).

A xerostomia pode ser irreversível e de difícil controle principalmente quando as glândulas salivares maiores estão incluídas na área a ser irradiada, consequentemente interferindo na qualidade de vida do paciente (SPECHT, 2002;

DIRIX et al., 2006). Outras toxicidades podem ser observadas tardiamente, após a RT como, por exemplo, o trismo e osteorradionecrose (COOPER et al., 1995).

Neste contexto, é importante considerar que dentre os efeitos agudos, na dependência da sua severidade, a mucosite pode comprometer a saúde geral do indivíduo pela dificuldade de alimentação causando um maior comprometimento sistêmico e, consequentemente pode ocasionar a interrupção da terapia adjuvante (NAIDU et al., 2004; VERA-LLONCH et al., 2006; BESE et al., 2007; RUSSO et al., 2008; SONIS, 2011; TOLENTINO EDE et al., 2011). A mucosite oral ou orofarigenana tem sido associada com maior possibilidade de interrupção de RT no tratamento do câncer na região de cabeça e pescoço (VERA-LLONCH et al., 2006; RUSSO et al., 2008).

Outros fatores têm sido relatados na interrupção da RT. Esses fatores podem ser categorizados em interrupções programada as quais constituem RT em curso descontínuo para maior controle do tumor com reações teciduais em níveis aceitáveis, e interrupções não programadas na qual se destaca quadro de mucosite severa, defeito e manutenção do aparelho radioterápico, feriados e outras complicações clínicas, como por exemplo, hemorragias (AMDUR et al., 1989; DUNCAN et al., 1996; KWONG et al., 1997; TARNAWSKI et al., 2002; BESE et al., 2007). Todavia, independente do motivo que levou a interrupção e do tempo da mesma, constituem um problema na prática clínica de pacientes com câncer na região de cabeça e pescoço. (MACIA et al., 2009).

Já é do conhecimento que a interrupção da RT, mesmo em poucos dias, é suficiente para que as células tumorais presentes ou remanescentes em tumores ressecados possam entrar em processo de diferenciação e proliferação celular propiciando o crescimento tumoral e, por sua vez, aumentando as chances de recidivas regionais. E dessa maneira reduzindo a chance de cura e sobrevida de pacientes com CEC de cabeça e pescoço (HOLSTI e TASKINEN, 1964; LEIPZIG et al., 1978; AMDUR et al., 1989; COX et al., 1992; ZELEFSKY et al., 1992; HERRMANN et al., 1994; SKLADOWSKI et al., 1994; DUNCAN et al., 1996; NISHIMURA et al., 1996; KWONG et al., 1997; BHATTATHIRI, 2002; SUWINSKI et al., 2003; LOHYNSKA et al., 2005; RUSSO et al., 2008; XU et al., 2010).

Há estudos que afirmam que em um dia de interrupção, há perda de controle local de 1,4% a 3,3%, com aumento de recorrência local e redução de sobrevida (BARTON et al., 1992; RUDOLTZ et al., 1993; HERRMANN et al., 1994; DUNCAN et

al., 1996; KWONG et al., 1997; ROBERTSON, C. et al., 1998; BESE et al., 2007). Essa interrupção, por sua vez, resulta em prolongamento global da RT com consequente perda de controle locorregional (MACIEJEWSKI et al., 1983; AMDUR et al., 1989; MACIEJEWSKI et al., 1989; BARTON et al., 1992; WITHERS et al., 1995; FEIN et al., 1996; VAN DER VOET et al., 1998; ROSENTHAL et al., 2002; RADES et al., 2008).

A perda de controle locorregional em consequência da interrupção da RT tem sido relatada em CEC bem e moderadamente diferenciados do ponto de vista do grau histológico de malignidade e em tumores T2. Tumores bem e moderadamente diferenciados tiveram taxas aumentadas de perda de controle do tumor quando comparado ao grau III (HANSEN et al., 1997). Em pacientes com tumores glóticos T2 houve maior perda de controle locorregional que T1 (VAN DEN BOGAERT et al., 1995; LE et al., 1997; GROOME et al., 2006)

Além da perda de controle locorregional em pacientes com câncer de cabeça e pescoço, com a ocorrência de interrupção de RT foi observada uma redução de 50% nas taxas de sobrevida e a sobrevida reduz ainda mais quando a quebra ocorre durante as últimas semanas de RT (HERRMANN et al., 1994). Pacientes com tumores em laringe tem risco de morte aumentado em 68% quando comparado aos pacientes sem interrupção radioterápica e uma tendência estatística para o risco de morte de 41% para pacientes com neoplasia de glândulas salivares (FESINMEYER et al., 2010).

Este fato é explicado pelo repovoamento de clones do tumor a partir da apoptose em células tumorais induzidas pela RT e, também pela sobrevida de células com ciclo celular acelerado enquanto não há a aplicação da RT ou QT (HERRMANN et al., 1994; VAN DEN BOGAERT et al., 1995; SUWINSKI et al., 2003; LOHYNSKA et al., 2005; MURPHY et al., 2007; LAUBER et al., 2011).

Este processo, entretanto, a nível molecular ainda é pouco compreendido. Huang e colaboradores (2011), em um estudo in vitro, demonstrou que a Caspase 3 faz a mediação direta das células tumorais sobreviventes com as células em apoptose no estroma tumoral irradiado. Os autores explicam que as células mortas, resultante da ação da RT e QT, liberam sinais como a Fosfolipase A_2 intracelular independente de Cálcio ($iPLA_2$) e Prostaglandina E_2 (PGE_2) ativadas pela Caspase 3. Esses sinais estimulam as células sobreviventes a proliferarem no microambiente tumoral. Adicionalmente, esses autores também verificaram a presença das células

guardiãs do sistema imunológico, os macrófagos, que foram presumivelmente recrutados pelos sinais da Caspase 3, também facilitam o repovoamento e consequentemente, a recorrência do tumor (HUANG et al., 2011).

Tarnawski e colaboradores (2002) demonstraram que durante a RT a taxa de repovoamento é maior durante os dias de interrupções não planejadas quando comparado aos dias de irradiação ininterruptos. E esses valores tendem a elevar quando se observa a dose perdida nos finais de semana e durante a interrupção não planejada após 2 semanas de tratamento. Overgaard et al (1988) em seus estudos demonstraram em carcinoma de laringe, um aumento de cerca de 100 vezes o número de células tumorais durante a quebra da RT. Somado a isso, deve-se considerar que tumores de cabeça e pescoço apresentam alto potencial de duplicação que varia de 2 a 30 dias reduzindo ainda mais a chance de controle do tumor em decorrência da interrupção da RT (FOWLER e LINDSTROM, 1992; LOCHRIN et al., 1992; MARGARINO et al., 1992; BOURHIS et al., 1993; ROBERTSON, A. G. et al., 1998; TARNAWSKI et al., 2002).

Além da possibilidade do repovoamento celular durante a suspensão da RT, há estudos demonstrando também a associação do nível de hemoglobina com tratamento prolongado de pacientes que fazem RT/QT concomitante (DENIS et al., 2004; RADES et al., 2008; MCCLOSKEY et al., 2009). Mccloskey e colaboladores (2009) revelam que quanto maior a interrupção, menor a taxa de hemoglobina. Isso pode ser explicado pela hipóxia levar à formação de mecanismos subsequentes como a redução de oxigênio reativo, estimulação da angiogênese, aumento de resistência a apoptose e desestabilização do genoma, promovendo dessa forma a perda de controle do tumor (FEIN et al., 1995; CHO et al., 2004; VARLOTTO e STEVENSON, 2005; MCCLOSKEY et al., 2009) e redução da sobrevida (FEIN et al., 1995; CHO et al., 2004; LOHYNSKA et al., 2005; XU et al., 2010).

A fim de evitar a perda de controle do tumor com consequente redução de sobrevida devido ao prolongamento do tempo de tratamento, há necessidade de reduzir ao mínimo a severidade dos efeitos adversos decorrentes de terapias adjuvantes, portanto, é fundamental o preparo do paciente antes, durante e após o início destas terapias adjuvantes, em especial a RT. (VAN DEN BOGAERT et al., 1995; LOHYNSKA et al., 2005). Para que isso ocorra, faz-se necessário a integração de equipes transdisciplinares de saúde que buscam minimizar e controlar os efeitos adversos decorrentes das terapias cirúrgicas e adjuvantes como RT e QT (SCHIODT

e HERMUND, 2002; SPECHT, 2002). Como parte integrante dessas equipes, a odontologia tem um papel essencial na composição das equipes que atuam no câncer da região de cabeça e pescoço, em especial a cavidade oral. A equipe odontológica atua colaborando para a redução das complicações orais no intuito de promover a qualidade de vida do paciente oncológico (JANSMA et al., 1992; KO e CITRIN, 2009; ROGERS, 2010; MAINALI et al., 2011; TOLENTINO EDE et al., 2011; OTON-LEITE et al., 2012; PATEL et al., 2012).

Neste contexto, em geral há um Protocolo Preventivo Odontológico (PPO) utilizado para prevenir e controlar estas complicações como o emprego da fluorterapia em pacientes dentados, anestésicos tópicos, anti-inflamatórios, analgésicos sistêmicos, sialogogos, laserterapia, acupuntura e prevenção de infecções secundárias com agentes antimicrobianos e anti-fúngicos, além dos procedimentos restauradores comuns à odontologia. (CHO et al., 2008; LANGENDIJK et al., 2009; OTON-LEITE et al., 2012). Nos estudos de Oton-leite e colaboradores (2012), por exemplo, foi observado que pacientes que receberam laserterapia por meio do laser de baixa potência tiveram menos interrupção do tratamento radioterápico quando comparado ao grupo que recebeu apenas os procedimentos básicos sem a ação da do laser de baixa potência.

Acredita-se, portanto, que quanto menor a severidade dos efeitos adversos ou complicações na cavidade oral, menos chance haverá de ocorrer a interrupção decorrente das terapias adjuvantes como a RT e/ou QT, o que certamente, resultará em uma maior efetividade desses tratamentos oncológicos no controle e/ou cura da doença, possibilitando um aumento da sobrevida e melhor qualidade de vida.

Baseado na literatura atual não há estudo que tenha investigado o impacto da adesão a um PPO sobre a interrupção da RT e na sobrevida dos pacientes portadores de câncer de cavidade oral submetidos a RT e/ou QT.

E neste contexto, o Hospital Araújo Jorge da Associação de Combate ao Câncer de Goiás (HAJ/ACCG), por agregar equipes transdisciplinares de saúde, desde 1988, conta com uma equipe de Cirurgiões-Dentistas que integram a equipe transdisciplinar, constituída por Médicos, Enfermeiros, Nutricionistas, Fonoaudiólogos, Psicólogos, Assistentes Sociais, Fisioterapeutas e Assistentes Espirituais, para o tratamento do câncer de cavidade oral. Nesta equipe o Cirurgião-Dentista participa do processo de prevenção, diagnóstico e tratamento dessas complicações orais durante as terapias adjuvantes e isto torna possível a

investigação do impacto da adesão dos pacientes oncológicos ao PPO (Anexo A) na redução da interrupção da RT por sintomas e da associação dessa adesão a sobrevida dos pacientes.

2 JUSTIFICATIVA

Diante do exposto, este trabalho se justifica pelos seguintes aspectos:

- Alta taxa de mortalidade e morbidade de câncer de cavidade oral (RAZAK et al., 2009).
- Modalidades terapêuticas empregadas como RT e/ou QT, em especial a RT, podem promover alterações na mucosa de revestimento, na dentição, no fluxo salivar, na microbiota oral, e comprometer a nutrição do paciente (AGUIAR et al., 2009). Em consequência dessas alterações, o paciente irradiado tem um risco aumentado de apresentar alterações como mucosite, xerostomia, destruição dentária ou “cárie de radiação” e outros (AGUIAR et al., 2009; DE CASTRO e GUINDALINI, 2010).
- Cuidados preventivos são necessários a fim de reduzir esses efeitos que podem interferir no tratamento resultando em interrupções das terapias e consequente perda do controle do tumor (HERRMANN et al., 1994; VAN DEN BOGAERT et al., 1995; LOHYNSKA et al., 2005).
- Redução de sobrevida de pacientes com câncer de cabeça e pescoço que interrompem a RT (FESINMEYER et al., 2010).
- A escassez de estudos investigando o impacto da adesão da terapia odontológica em relação às interrupções da RT e à sobrevida dos pacientes portadores de câncer de cavidade oral.

3 OBJETIVOS

3.1 OBJETIVO GERAL

Verificar a adesão dos pacientes portadores de câncer de cavidade oral ao PPO e seu impacto na interrupção da radioterapia e sobrevida do paciente.

3.2 OBJETIVOS ESPECÍFICOS

- Verificar a associação dos dados clínico-patológicos com o tempo de adesão ao PPO, interrupção da terapia adjuvante e sobrevida global e sobrevida livre de doença dos pacientes;
- Verificar a associação da interrupção do tratamento com a sobrevida global e sobrevida livre de doença dos pacientes submetidos à RT.

4 PACIENTES E MÉTODO

4.1 TIPO DE ESTUDO

Este é um estudo de coorte retrospectivo entre 1989 a 2009, de pacientes diagnosticados com câncer de cavidade oral. Aprovado pelos Comitês de Ética em Pesquisa da Universidade Federal de Goiás e HAJ/ACCG - (protocolos número 415/11 e 012/12 respectivamente – Anexo B).

4.2 OBTENÇÃO, SELEÇÃO E CARACTERIZAÇÃO DA AMOSTRA.

Para obtenção da amostra foram consultados 825 prontuários clínicos, selecionados pelo Registro Hospitalar de Câncer do HAJ/ACCG, de indivíduos com diagnóstico histológico de CEC de tumores primários em cavidade oral. Ao final, de acordo com os critérios de inclusão e exclusão deste estudo foram selecionados 133 pacientes.

Como critérios de inclusão para este estudo, foram selecionados os pacientes com diagnóstico de CEC sem metástase regional e à distância na data do diagnóstico do tumor e que foram submetidos a RT. Para o tratamento radioterápico, os pacientes foram tratados através de um acelerador linear do HAJ, com feixes de fótons de 600 MV, da Varian, do modelo CLINAC 600 C. Todos os pacientes selecionados receberam irradiação individualizada em leito tumoral abrangendo os campos cérvico-facial direito e esquerdo até três fases da RT. A dose total programada variou até 70 Gy com frações de 1,5 a 3 Gy durante o período de 5 dias por semana. As doses recebidas foram expressas de acordo com o modelo quadrático linear de BED:

$$BED = nd\,[1 + d/(\alpha/\beta)]$$

Sendo:

BED= Dose Biológica Efetiva

n= número de aplicações de radioterapia em dias

d= dose total de radioterapia em Gy/dia

α/β = dose na qual os componentes linear e quadrático da morte celular são iguais. Para mucosa e o tumor valor α/β = 10.

A localização do tumor (Anexo C) foi definida, de acordo com os critérios da União Internacional contra o Câncer (UICC), como mucosa bucal (superfície das mucosas dos lábios superiores e inferiores, bochechas); áreas retromolares; sulcos buco-alveolares, gengiva e alvéolos (superiores e inferiores); palato duro, língua (dorso e bordas laterais anteriores a papilas caliciformes – dois terços anteriores e superfície inferior) - e assoalho da boca (SOBIN e WITTEKIND, 2002).

Como critério de exclusão, não fizeram parte da amostra os prontuários que não foram encontrados no arquivo médico do HAJ/ACCG e aqueles nos quais não foi possível coletar os dados que constituíram o banco de dados estabelecido para o desenvolvimento da investigação.

Os dados coletados dos prontuários compreenderam dados da escala de capacidade funcional, *performance status* Eastern Cooperative Oncology Group – ECOG-PS-(OKEN et al., 1982) - Anexo D; dados demográficos dos pacientes (idade, gênero e etnia) e clínicos-patológicos como: fatores de risco (tabagismo e etilismo), localização do tumor, estadiamento (tamanho – T; linfonodos regionais – N; metástase à distância – M; Anexo C), graduação histológica (bem diferenciado, moderadamente diferenciado, pouco diferenciado, ou não avaliado), tipo de tratamento realizado (cirúrgico, radioterápico ou quimioterápico) e necessidade de suporte nutricional. Foi registrado o tipo (interrupção por sintomas ou por outras causas), a frequência e duração interrupção de RT, e complicações decorrentes da RT, recidiva e metástase à distância do tumor. Para análise da sobrevida foi considerada a data de diagnóstico e data da primeira recidiva para sobrevida livre de doença; e data do último registro ou data do óbito para sobrevida global. Os dados coletados estão representados no Apêndice A.

Nesse estudo, foi considerada como interrupção da RT, independente se por sintomas ou outras causas, aquele paciente que excedeu tempo programado da terapia proposta a partir da primeira ausência do paciente à terapia adjuvante até o dia que antecedeu a próxima dose de RT.

Em relação à adesão do paciente ao PPO, a amostra foi dividida em três grupos:

- **Grupo I** – sem adesão ao PPO;
- **Grupo II** – adesão dos pacientes ao PPO inferior ou igual a 6 meses (0¬6 meses);
- **Grupo III** – adesão dos pacientes ao PPO maior que seis meses (>6 meses).

O tempo mínimo de acompanhamento de seis meses estabelecido nesta pesquisa foi equivalente à soma do tempo do diagnóstico (primeira consulta), preparo do paciente, tratamento cirúrgico, RT/QT e avaliação da resposta ao tratamento indicado. Esse é o tempo necessário para avaliação adequada da resposta em neoplasias de cabeça e pescoço (KWONG et al., 1997; MALONE et al., 2009). Esta fase corresponde a fase de controle dos efeitos adversos agudos (presentes nos primeiros 3 meses a partir das primeiras semanas da RT). O controle superior a 6 meses visa o controle dos efeitos tardios da RT.

Embora todos os pacientes tenham recebido informação sobre a importância do preparo odontológico, apenas os grupos que tiveram adesão ao PPO foram atendidos pela equipe da odontologia e receberam orientações conforme o PPO vigente do setor de Odontologia do HAJ/ACCG. O PPO é baseado na orientação dos efeitos adversos, na remoção dos focos de infecção, procedimentos operatórios restauradores, fluorterapia (bochecho de fluoreto de sódio a 0,05%); hidratação oral e manutenção de uma boa higiene oral supervisionada semanalmente; antes, durante e após o tratamento radioterápico enquanto recebendo acompanhamento pelas equipes transdisciplinares de saúde do hospital (Anexo A).

4.3 ANÁLISE ESTATÍSTICA DOS DADOS

Os dados clínicos patológicos foram apresentados na forma de uma análise descritiva exploratória. O teste qui-quadrado foi utilizado para investigar a associação das variáveis clínicas entre os grupos de pacientes. Análise de Variância simples (One-way ANOVA) foi utilizada para comparação das médias entre os grupos. O método de Kaplan-Meier para análise de sobrevida livre de doença e global. O teste log-rank para comparação entre os grupos e modelo de regressão de Cox para análise múltipla da sobrevida. Para análise estatística foi utilizado o software SPSS 17.0. O nível de significância estatística foi definido em $p < 0,05$.

5 ARTIGO

Título da publicação:

The effect of preventive oral care on treatment outcomes of a cohort of oral cancer patients

Formatação da publicação de acordo com as normas do periódico *Supportive Care in Cancer* (Anexo E).
Artigo aceito pelo periódico *Supportive Care in Cancer* em 12/09/15 (Anexo F).

The effect of preventive oral care on treatment outcomes of a cohort of oral cancer patients

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Abstract

Purpose: To assess patient adherence to an oral preventive measures (OPM) protocol and its impact on cancer treatment outcomes.

Methods: A retrospective cohort of oral cancer of 133 patients submitted to RT was selected, excluding those with metastasis. Patients were grouped according to their local tumor response after finishing RT (favorable or unfavorable) and adherence to an OPM (none, ≤ 6 months, and > 6 months). OPM included education and counseling about adverse effects, elimination of infection foci, restorative procedures, fluoride therapy, oral rehydration, and maintenance and supervision of oral hygiene throughout treatment. Clinical and pathological characteristics were recorded and patient outcomes (frequency of adverse effects, RT interruption and overall survival) were analyzed.

Results: Patients with higher adherence to the OPM had greater occurrence of RT interruption as a consequence of symptoms (p=0.01), however these patients were more likely to complete the established RT protocol (p=0.02). Overall survival (p=0.01) was higher in the group with higher adherence.

Conclusions: This study suggests that the implementation of oral preventive measures may contribute to improving the prognosis of SCC treatment by reducing the negative impact of oral complications.

Keywords: Oral cancer, preventive dentistry, radiotherapy, survival.

Introduction

Radiotherapy (RT) is one of the therapies used for oral cancer, used as an exclusive, adjuvant or palliative treatment, depending on the patient's clinical and histopathological features [1-3]. However, RT results in local and systemic side-effects which affect the patient's quality of life, especially when major salivary glands are included in the area to be irradiated [4,5].

Adverse effects such as acute mucositis (OM), dysphagia, odynophagia, pain, dermatitis have been reported as causes of interruption of the RT in head and neck cancer patients [6-8]. OM is the main adverse effect of RT in oral cancer patients (SCC) [9]. Depending on its severity, OM can make food intake extremely difficult, compromising the patient's general health and, in many cases, lead to interruption of RT adjuvant therapy [7,9,10]. RT interruption, even for a few days, is enough for the remaining cancer cells to begin the processes of differentiation, proliferation, migration and tumor growth [11], thereby increasing the risk of local recurrence and reducing the likelihood of disease and patient survival [12-14,8].

For patients undergoing oral cancer treatment, early oral preventive measures (OPM) are recommended as a standard of care, since the patient's ability to maintain effective and regular oral care will be impaired due to the expected harmful consequences of the disease and treatment, mostly when combined surgery and chemo-radiotherapy are used [15,10]. Hence, patients should adhere to an oral preventive program that covers all stages of treatment, from initial preparation until treatment follow-up. Early oral care includes general preventive measures such as treatment of active caries lesions, repair of defective restorations and prostheses, supportive periodontal therapy and the use of fluoride [16,10]. Preventive measures should also be continued as palliative strategies during chemo-radiotherapy for control of oral signs and symptoms, such as the use of anti-inflammatory drugs, topical anesthetics, systemic analgesics, sialogogues, laser therapy, acupuncture, and the prevention of secondary infections with antimicrobial and anti-fungal agents [17-19] which reduce the severity of oral pain and discomfort in SCC [20].

Previous studies have stressed the importance of OPM on the reduction of the adverse effects of oral cancer treatment [21,22,20,23-25]. Despite the variability of OPM across studies, overall results showed a reduction in severity of oral acute effects due to RT when OPM are effectively performed. However, these studies did not evaluate the influence of different adherence levels to OPM on interruption of RT and patient survival.

Conversely, there is scarce information about how OPM may influence the radio-chemotherapy treatment protocol and patient overall adherence to treatment. We hypothesize that a lower severity of adverse

effects or oral complications will reduce the likelihood of interruption of adjuvant therapies, which could result in higher survival rates. Similarly, higher adherence to OPM would also minimize the occurrence of severe acute symptoms, decrease the likelihood of RT interruption due to symptoms, and would improve RT effectiveness and patient survival rates. Hence, the aim of this study was to investigate the impact of patient adherence to an OPM program on the interruption of RT and on the survival of patients with oral cancer.

Materials and Methods

This was a retrospective cohort study covering a 20-year period between 1989 and 2009, including patients diagnosed with oral cancer at the Araujo Jorge Hospital, a regional reference hospital for cancer treatment in Goiania, Goias, Brazil. The research protocol was previously approved by the local Research Ethics Committee (Protocol #012/12).

A total of 825 charts from patients diagnosed with squamous cell carcinoma (SCC) of the oral cavity were initially retrieved from the hospital files. Subsequently, patient data were assessed to include only (1) patients without metastasis (regional or distant) diagnosed by clinical or pathological examination at the time of tumor diagnosis, and (2) patients who submitted to RT, irrespective of having surgical or chemotherapy treatment. Patients with lip SCC were excluded due to the differences in biological behavior of the tumor compared to oral cavity tumors. Cases without an initial TMN classification were also excluded, resulting in a study sample of 133 patients.

The RT protocol included radiation of the tumor area and the right and left cervicofacial regions. The total radiation dose was approximately 70 Gy, ranging from 1.5 to 3.0 Gy a day, on five consecutive days a week. RT treatment doses were planned according to the Biological Effective Dose (BED) linear quadratic model:

$$BED = nd\,[1 + d/(\alpha/\beta)]$$

where: BED = Biological Effective Dose; n = number of RT applications per day; d = total dose of radiation in Gy/day; α/β = dose at which the linear and quadratic components of cell death are equal, with α/β = 10 for mucosa and tumor.

Collected data included the functional capacity scale scores, Performance Status according to the Eastern Cooperative Oncology Group - ECOG-PS [26], demographic data (age, gender and ethnicity), risk factors (smoking and drinking habits), and clinico-pathological features (anatomic site of the tumor, TMN

clinical stage, histological type, histological grade of malignancy, type of treatment undergone and need for nutritional support). The ECOG-PS instrument is divided into five categories according to the daily abilities of the cancer patient, as follows: 0 – Fully active, able to carry on all pre-disease performance without restriction; 1 – Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2 – Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours; 3 – Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4 – Completely disabled; cannot carry on any selfcare; totally confined to bed or chair; and 5 – Dead [26].

Disruptions in the regular RT protocol were assessed, including the occurrence of RT interruptions, reasons (due to symptoms or not), frequency, duration of RT discontinuation, changes in BED, and tumor recurrence with or without local or distant metastasis. Time data were calculated for the analysis of patient disease-free and overall survival.

SCC submitted to RT were previously included in an oral care prevention program that included chairside information about the importance of oral care during RT treatment, instruction about oral adverse effects, elimination of infection foci, restorative procedures, fluoride therapy (0.05% sodium fluoride mouthwash), measures for rehydration of the oral mucosa, and regular supervision and maintenance of oral hygiene throughout the entire treatment period.

Considering the wide variation in the levels of adherence to OPM, individuals were classified according to their compliance with the oral care program. Patients were divided into three groups according to the levels of long-term adherence to the OPM administered by the dental team: no adherence (Group 1), low to moderate adherence for less than six months of supervised OPM (Group 2), and high adherence for more than six months of supervised OPM (Group 3). The six-month follow-up was selected for the cut-off classification of patient levels of adherence because it is the time period equivalent to the period between the time of tumor diagnosis (first visit), initial oral care measures, cancer surgical treatment, RT/CT protocol, and evaluation of response to the overall treatment. This period corresponds to the control phase of the RT acute adverse effects, which usually occur in the first three months after the first weeks of RT [27]. The continuation of supervised OPM for periods longer than six months (Group 3) aimed to control the delayed oral effects of RT.

Clinical and imaging evaluations of patients were performed 60 days after RT to assess the patient response to treatment. Patients with a poor response to RT, such as tumor growth or disease recurrence, as well

as patients who abandoned treatment were excluded from analysis. Hence, only individuals with no clinical and imaging signs of the tumor at the primary site were included in further analysis (n=81).

The clinical and pathological data were presented in the descriptive analysis. One-way ANOVA and chi-square tests were used to investigate the association of clinical variables between patient groups. Kaplan-Meier plots were used for survival analysis, followed by log-rank tests for comparisons between groups. Statistical analysis was performed using MedCalc 13.1 software. Statistical significance was set at $p < 0.05$.

Results

Patients were predominantly male (75.2%), smokers (69.2%) and alcohol consumers (45.1%). T-stage was graded as T4 in 54.9% and histological grade II of malignancy was observed in 60.9%. Demographic and clinic-pathological features of the study sample for each group (n=133) are summarized in Tables 1 and 2.

The classification of the overall patient sample (n=133) according to the level of adherence to the oral preventive measures resulted in the following group sizes: Group 1 (n =58), Group 2 (n=42) and Group 3 (n=33). No differences were observed between groups regarding demographic and clinical features, except for a difference in the patient mean age in years. Mean age in Group 1 (65.1±13.0) was significantly higher (p=0.001) compared to Groups 2 (57.3±11.3) and 3 (54.3±11.1). Concerning clinical features, Group 1 had a greater frequency of patients with adjuvant RT (77.6%) and a lower frequency of chemotherapy in the treatment protocol (8.6%) (p=0.001). Group 3 showed a greater frequency of patients who completed RT (90.0%), compared to groups 1 (72.4%) and 2 (64.3%) (p=0.021).

Five-year overall patient survival was 60.9% (81/133) and survival rate was significantly higher in Group 3 (84.8%) compared to Groups 1 (51.7%) and 2 (54.8%) (χ^2=10.66; p=0.005). The Kaplan-Meier analysis (and log-rank test) showed that the estimated survival was significantly higher in Group 3 compared to the overall patient sample (n=133) (p=0.001).

Subsequently, only patients with a favorable response to RT (evaluated 60 days after RT) showing no clinical and imaging signs of the tumor at the primary site were analyzed (n=81), comprising 37 out of 58 patients in Group 1, 16 out of 42 patients in Group 2, and 28 out of 33 patients in Group 3. The remaining 52 patients were excluded from this analysis due to adverse evolution of the disease, such as tumor progression (n=26), cancer treatment dropout (n=9), recurrence of the tumor (n=8), death (n=7), or local and/or distant metastasis (n=2).

Only 3.7% of patients (n= 3/81) did not interrupt RT, and of those only one patient had adhered to the OPM. Interruption of RT due to symptoms was observed in 41.9% (n= 34/81). Interruption due to symptoms was statistically significant higher in group 3 (82.1%) and group 2 (87.5%) when compared to group 1 (32.4%) (p=0.01). Table 3 summarizes the main reasons for the discontinuation of RT. The main reason for interruption was cancelled appointments due to holidays or disruption at the hospital (n=55), and the most common reason due to symptoms was OM (n=27). The overall distribution of interruption events was 176, and the proportions of interruption per patients in Groups 1, 2 and 3 were 72/37, 38/16, and 66/28, respectively.

The prevalence of oral and cutaneous complications is detailed in Table 4. Odynophagia and dysphagia were the most common occurrence (n=57), followed by OM (n=49), xerostomy (n=43), and dermatitis (n=35).

The Kaplan-Meier analysis (and log-rank test) showed that the estimated 5-year survival was significantly higher in Group 3 compared to the patient sample who showed favorable response to RT (n=81) (p=0.006), as depicted in Fig. 1.

Discussion

This is the first investigation to verify the effect of adherence to an OPM protocol on the interruption of RT and survival of SCC without any clinical or microscopic evidence of locoregional or distant metastasis. The findings suggest greater overall survival rates in patients with higher adherence and a favorable response to RT. However, the results did indicate that greater adherence to OPM had an indirect impact on a reduction in the occurrence of RT interruption due to signs and symptoms.

It was hypothesized that adherence to OPM, supervised by a dental team, would have a positive effect on patient outcomes. None or low adherence may be associated with factors such as advanced age, barriers to accessibility, progressive systemic involvement, nutritional deficiencies, or even emotional conditions such as fatigue and depression. In our study there was a higher incidence of older individuals and advanced stage of disease in groups 1 and 2, respectively. Hamaker et al [28] observed that older patients tend to show lower adherence to oncology treatment, mainly due to clinical factors such as comorbidities and advanced tumor stage, as well as negative attitudes expressed as a deliberate lack of cooperation and treatment refusal. Additionally, group 2 had a lower incidence of completion of RT prescription, which can be explained by the smaller number

of surgical procedures. Fesinmeyer et al [29] also found that failure to complete uninterrupted RT is common among head and neck cancer patients, and surgery before RT is a strong predictor of completing RT.

A lower occurrence of RT interruption was not observed when adherence to OPM was higher. When the causes of interruption due to symptoms were investigated it was found that OM was the main cause of interruption of RT in all three groups. Group 3 had a higher occurrence of discontinuation due to OM, which could be associated with the dose received and the patient's systemic conditions. Acute adverse effects were the main cause of RT interruption due to symptoms, similarly to previous studies that observed that a great number of interruptions were due to severe degrees of OM [7,19]. It has been clinically observed that extensive acute mucosal lesions associated with RT severely impact the patient's oral functioning and have consequent deleterious effects on general health status. Hence, an effective program of OPM that include incentives for greater patient adherence is critical to minimize acute oral symptoms [21,22,20,23-25], especially OM, in order to decrease the occurrence and duration of RT interruptions and the resulting detrimental effects on treatment outcomes, including tumor recurrence and lower patient survival.

Although OM was the main reason for RT interruption due to symptoms symptoms in all the study groups, the most common reason was non-compliance with the scheduled RT appointment due to unspecific causes, such as an inoperative RT device due to technical reasons, absenteeism due to difficult access since most patients were underprivileged people from other cities, and failure to complete cancer treatment due to overall health deterioration. Socioeconomic and organizational barriers associated with psychological factors are detrimental to access to medical treatment [28]. Corrigan et al [29] also observed that patients tend to associate cancer with general health, but not associate cancer with oral health, which can also make adherence to OPM more difficult.

Symptoms such as odynophagia/dysphagia, OM, and xerostomy were highly prevalent in all three groups and are common local causes that impact patient nutrition. Severe oral complications negatively affect daily nutrition, leading to malnutrition, increased hospitalization rates, and poor quality of life [30,31]. Kartin et al [31] observed a reduction in malnutrition and pain associated with OM through oral prevention protocols in patients irradiated in the head and neck. Kashiwazaki et al [32] found similar results regarding the positive effects of OPM on the control of oral complications in cancer patients. A reduction in oral complications also results in an improvement in quality of life [33,19], providing patients with better physical condition to confront the adverse effects of oncology treatment.

Other problematic aspect that affects the effectiveness of appropriate oral care in oncologic patients is the limited cooperation between the radiotherapist and the dental team, which results in poor consistency in the diagnosis of specific oral problems and inappropriate referral to oral health care. Patel et al [34] reported inadequate communication and collaboration among dentists and radiation oncologists regarding the dental management of patients treated with head and neck RT, and concluded that these obstacles hinder the results of prevention and the treatment of adverse effects of RT and chemotherapy. Many of these obstacles were related to a lack of time between the initial dental visit and the start of radiation therapy and inadequate communication between health care providers [34,35].

Survival rates were higher for patients with greater adherence to OPM.. Although the prognosis of SCC is directly related to the clinicopathological features of the tumor and the treatment protocol, the findings of this study suggest that better oral conditions may have a favorable impact on treatment outcomes. We believe that the lack of chemotherapy and/or surgery in groups 1 and 2 could influence survival rates in these groups, since surgical treatment combined with chemotherapy and/or adjuvant RT is associated with greater survival rates for head and neck cancer patients [36,3].

Group 2 (low to moderate adherence) showed overall survival rates similar to Group 1 (no adherence), although they had been supervised by a dental team and had nutritional support. This fact could probably be explained by the predominance of T4 tumors in groups 1 and 2 (lower adherence), since more severe tumors result in greater systemic and immune impairment and poorer prognosis [3,37,38] , requiring greater medical and general nutritional care [30].

However, there are limitations inherent to this retrospective study. Differences in the baseline characteristics of OPM groups (such as tumor size, therapeutic protocol and patient systemic conditions) may have influenced patient outcomes. In addition, inconsistencies in clinical criteria for the diagnosis of oral complications, poor standardization of OPM procedures, and inadequate completion of medical records are limitations that may negatively affect the validity of clinical data. Hence, future prospective studies are needed, including standardized criteria and instruments for the clinical assessment of patients in order to reduce inconsistencies, as well as more specific inclusion and exclusion criteria for controlling potential confounders.

Conclusion

These findings suggest that the implementation of oral preventive measures may contribute to improving the prognosis of SCC treatment by reducing the negative impact of oral complications.

Conflict of Interest

The authors declare that have no conflict of interest.

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Table 1. Frequency (percentage in parenthesis) of demographic and clinical characteristics of the sample (n=133).

		Group 1 n= 58	Group 2 n=42	Group 3 n= 33	Total n= 133	*p*
Age in years	Mean (SD)	65 (12.9)	57.3 (11.2)	54.2 (11.1)	59.9 (12.8)	<0.01#
Gender	Male	39 (67.2)	36 (85.7)	25 (75.8)	100 (75.2)	0.10
Ethnic group	Leukoderma	28 (48.3)	20 (47.7)	17 (51.5)	65 (48.9)	0.99
	Feoderma	27 (46.6)	19 (45.2)	14 (42.4)	60 (45.1)	
	Melanoderma	3 (5.1)	3 (7.1)	2 (6.1)	8 (6.0)	
Tobacco	Yes	39 (67.2)	31 (73.8)	22 (66.6)	92 (69.2)	0.16
	Formed smoker	5 (8.6)	8 (19.0)	2 (6.1)	15 (11.3)	
	No	9 (15.6)	2 (4.8)	7 (21.2)	18 (13.5)	
	No information	5 (8.6)	1 (2.4)	2 (6.1)	8 (6.0)	
Alcohol	Yes	23 (39.7)	20 (47.6)	17 (51.5)	60 (45.1)	0.64
	Formed drinker	5 (8.6)	5 (11.9)	1 (3.0)	11 (8.3)	
	No	25 (43.1)	16 (38.1)	13 (39.4)	54 (40.6)	
	No information	5 (8.6)	1 (2.4)	2 (6.1)	8 (6.0)	
ECOG-PS*	0	22 (38.0)	21 (50.0)	18 (54.5)	61 (45.9)	0.21
	>1	8 (14.0)	1 (2.4)	3 (9.1)	12 (9.0)	
	No information	28 (48.0)	20 (47.6)	12 (36.4)	60 (45.1)	
Anatomical site of the tumor	Floor of the mouth	19 (32.8)	13 (31.0)	8 (24.2)	40 (30.1)	0.86
	Tongue	13 (22.4)	10 (23.8)	13 (39.4)	36 (27.1)	
	Oral mucosa	10 (17.2)	8 (19.0)	6 (18.2)	24 (18.0)	
	Alveolar ridge	8 (13.8)	7 (16.7)	3 (9.1)	18 (13.5)	
	Hard palate	7 (12.1)	4 (9.5)	3 (9.1)	14 (10.5)	
	Not specified	1 (1.7)	0 (0)	0 (0)	1 (0.8)	

Abbreviations: SD (Standard Deviation)
* ECOG-PS (Eastern Cooperative Oncology - Performance Status): scores were dichotomized into 0 (scores 0-1) and >1 (scores 2-3).
# = Statistically significant difference ($p<0.05$).

Table 2. Frequency (percentage in parenthesis) of clinical and pathological characteristics of the sample (n=133).

		Group 1 n= 58	Group 2 n=42	Group 3 n= 33	Total n= 133	*p*
T-stage	T1	5 (8.6)	0 (0)	1 (3.0)	6 (4.5)	0.05
	T2	9 (15.5)	5 (11.9)	10 (30.3)	24 (18.0)	
	T3	16 (27.6)	7 (16.7)	7 (21.2)	30 (22.6)	
	T4	28 (48.3)	30 (71.4)	15 (45.5)	73 (54.9)	
Histological grade of malignance	Grade I	11 (19.0)	8 (19.0)	5 (15.2)	24 (18.0)	0.96
	Grade II	35 (60.3)	27 (64.3)	19 (57.6)	81 (60.9)	
	Grade III	10 (17.2)	6 (14.3)	8 (24.2)	24 (18.0)	
	No information	2 (3.5)	1 (2.4)	1 (3.0)	4 (3.0)	
RT protocol	RT exclusive	8 (13.8)	3 (7.2)	2 (6.1)	13 (9.8)	<0.01[#]
	RT adjuvant	45 (77.6)	20 (47.6)	20 (60.6)	85 (63.9)	
	RT and chemotherapy	5 (8.6)	19 (45.2)	11 (33.3)	35 (26.3)	
Surgical treatment	Yes	44 (75.9)	23 (54.8)	25 (75.8)	92 (69.2)	0.05
Neck dissection	Yes	37 (63.8)	21 (50.0)	22 (66.7)	80 (60.2)	0.25
Chemotherapy	Yes	5 (8.6)	19 (45.2)	11 (33.3)	35 (26.3)	<0.01[#]
Completion of RT prescription	Yes	42 (72.4)	27 (64.3)	30 (90.0)	99 (74.4)	0.02[#]
BED – Gy_{10}	Mean (SD)	65.6 (16.7)	64.5 (22.2)	73.6 (9.1)	67.2 (17.6)	0.05
Nutritional support	Yes	26 (44.8)	26 (61.9)	18 (54.5)	70 (52.6)	0.23

Abbreviations: SD (Standard Deviation)
[#] = Statistically significant difference ($p<0.05$).

Table 3. Frequency (percentage in parenthesis) of reasons for discontinuation of RT adjunct therapy (n=81).

	Group 1 (n=37)	Group 2 (n=16)	Group 3 (n=28)	Total (n=81)
Cancelled appointment	26 (36.0)	10 (26.3)	19 (29.0)	55 (31.2)
Due to symptoms				
Oral mucositis (OM)	7 (10.0)	8 (21.0)	12 (18.0)	27 (15.3)
Dermatitis	1 (1.4)	4 (10.5)	4 (6.0)	9 (5.1)
Dysphagia	2 (2.7)	0 (0)	3 (4.5)	5 (3.0)
Odynophagia	0 (0)	0 (0)	3 (4.5)	3 (1.7)
Not specified symptom	1 (1.4)	1 (2.6)	1 (1.5)	3 (1.7)
Asthenia	1 (1.4)	0 (0)	0 (0)	1 (0.5)
Hemorrhage	0 (0)	1 (2.6)	0 (0)	1 (0.5)
Changes in treatment protocols	1 (1.4)	0 (0)	1 (1.5)	2 (1.1)
Technical problems	0 (0)	0 (0)	1 (1.5)	1 (0.5)
Absenteism	2 (2.7)	0 (0)	1 (1.5)	3 (1.7)
Not reported	31 (43.0)	14 (37.0)	21 (32.0)	66 (37.7)
Total	72 (100)	38 (100)	66 (100)	176 (100)

Table 4. Patients' complications in RT adjuvant therapy (n=81).

Symptoms	Group 1	Group 2	Group 3	Total
Odynophagia/ Dysphagia	22	15	20	57
Oral mucositis (OM)	17	10	22	49
Xerostomy	20	8	15	43
Dermatitis	16	7	12	35
Dysgeusia	5	1	4	10
Pain	5	1	1	7
Osteoradionecrosis	1	0	2	3
Dental caries irradiation	0	0	1	1

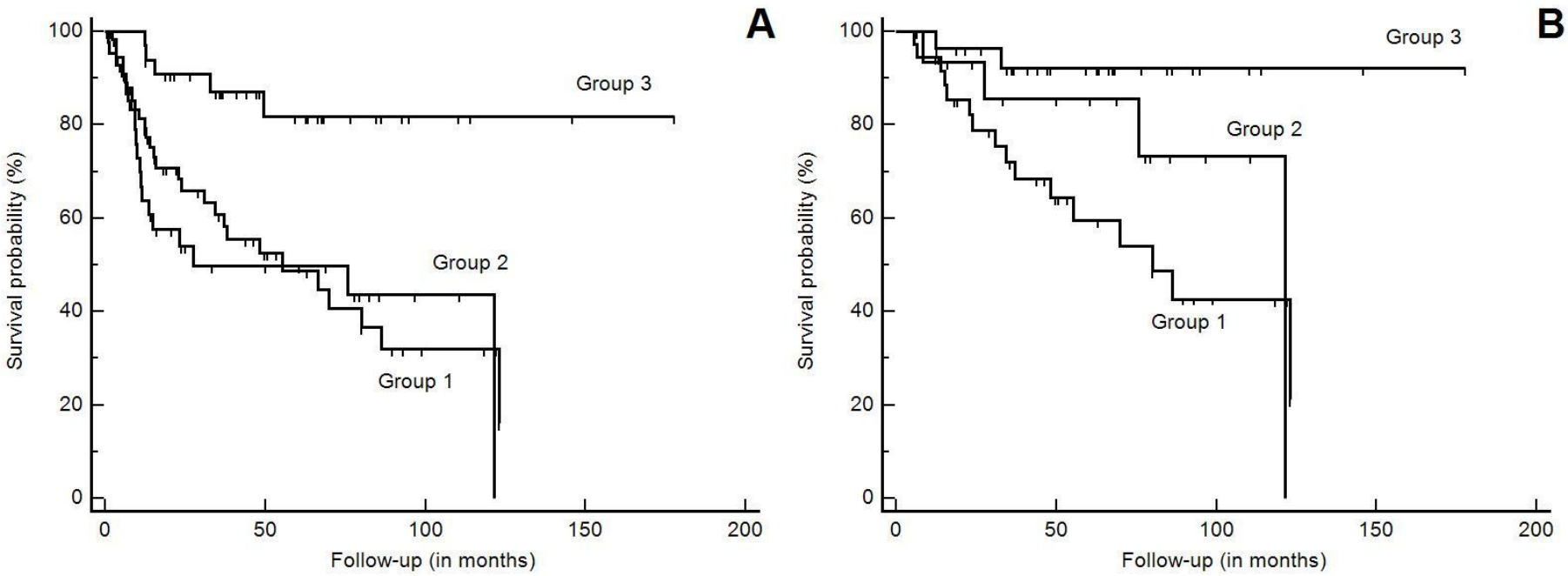

Fig. 1 Kaplan-Meier survival plots according to patient adherence to oral preventive measures (OPM) for the entire sample (A) and for the sample of patients with a favorable response to radiotherapy (B) in accordance with the defined time of the last visit performed (test of log-rank, p=0.01). Group 1 – no adherence to OPM; Group 2 – low to moderate adherence for less than six months of supervised OPM; Group 3 – high adherence for more than six months of supervised OPM.

6 CONSIDERAÇÕES FINAIS

Os resultados desse estudo trazem contribuições que fortalecerá a importância da odontologia no contexto das equipes transdisciplinares para o tratamento do câncer na região de cabeça e pescoço. Esse estudo indicou um aumento da sobrevida dos pacientes com câncer de cavidade oral que tiveram adesão ao PPO favorecendo a continuidade e conclusão do tratamento radioterápico, embora a adesão ao protocolo não tivesse impacto sobre a interrupção da RT. Outros fatores podem ter também influenciado neste processo.

O PPO não influenciou na interrupção da RT por sintomas no grupo com acompanhamento superior a 6 meses, mas pode ter reduzido as severidades das complicações orais decorrentes da RT, o que possivelmente favoreceu a finalização do tratamento oncológico. Neste estudo não foi avaliada as severidades das complicações orais em relação ao PPO, uma vez que nem sempre a severidade do efeito havia sido registrada no prontuário dos pacientes envolvidos. Acreditamos que um estudo prospectivo no qual o profissional seja orientado e preparado para registrar a severidade de acordo com os protocolos existentes, como a avaliação da mucosite e/ou xerostomia, os resultados poderão ser diferentes.

Por se tratar de um estudo retrospectivo de 20 anos, as dificuldades encontradas foram principalmente em relação ao acesso dos prontuários, pois a localização dos mesmos era permitida apenas a equipe do Arquivo Médico do HAJ, de acordo com a disponibilidade do serviço. Além disso, devido aos critérios de inclusão e exclusão, 692 prontuários de pacientes de câncer de cavidade oral foram excluídos da pesquisa, visto que alguns dados como metástase patológica e tratamento realizado (RT) não estavam dispostos no formulário eletrônico da Instituição e consequentemente estavam registrados apenas no prontuário do paciente, demandando ainda mais tempo para a execução da pesquisa.

Apesar disso, este trabalho viabilizará outras investigações nesta linha de pesquisa. A ampliação desse estudo em indivíduos portadores de câncer na região de cabeça e pescoço poderá ser conduzido e confrontado com esses achados específicos em cavidade oral. Um ensaio clínico randomizado poderá ser realizado para avaliação das severidades das reações adversas decorrentes da RT em relação ao PPO e confirmação em relação a interrupção da RT e sobrevida em

pacientes com câncer de cavidade oral. Em nível molecular, uma avaliação da atividade de proliferação celular e apoptótica em tumores recorrentes poderá ser investigado e até sua possível associação com a interrupção da RT .

Um fato que precisa ser considerado é que a adesão a um PPO do paciente portador de neoplasia maligna em cavidade oral e ou na região de cabeça e pescoço com indicação para tratamento cirúrgico e radioterápico, associado ou não a quimioterapia é fundamental. Embora neste estudo não tenha sido observado este impacto de maneira susbstancial na não interrupção da RT e na sobrevida podemos observar que os pacientes em geral apresentaram melhor sobrevida do que aqueles que não tiveram esse acompanhamento e com certeza melhor qualidade de vida. Acreditamos, portanto, que mais estudos nessa linha de investigação deverão ser continuadas em prol da cura e/ou controle da doença propiciando melhor sobrevida livre de doença e glogal do paciente.

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ANEXOS

Anexo A: Protocolo Preventivo Odontológico (PPO) do HAJ/ACCG – Tabelas I e II.

Tabela I: Estratégia de cuidados orais para pacientes antes, durante e após a RT e/ou QT.

Antes da RT / QT	**Nota**
Diagnóstico definitivo	Localização e tamanho do tumor.
História Médica	Fatores de riscos – tabagismo, etilismo, entre outros.
Exame clínico	Identificação dos focos de infecção; avaliação do periodonto, dentes e mucosa oral.
Orientação de Higiene Oral	
Orientação de cuidados com a prótese	Higiene e remoção da prótese ao dormir.
Avaliação de exames radiográficos	Radiografia panorâmica, radiografias periapicais e bite-wing, quando indicado.
Prognóstico	Cura ou paliativo.
Proposta terapêutica	QT, RT (dose, campos e duração).
Orientação nutricional	Redução de alimentos cariogênicos.
Durante a RT / QT	
Orientação de uso de fator de proteção solar (FPS)	
Hidratação	Ingestão frequente de água, no mínimo 1,5 litros / dia. Saliva artificial: Carmelose sódica.
Fluorterapia	Fluoreto de Sódio 0,05%.
Eliminação de infecção	Antimicrobianos, anti-fúngicos e anti-virais, solução salina.
Laserterapia	Laser de baixa potência. Aplicações semanais.
Exercícios passivos de abertura de mandíbula para redução do trismo	
Orientação nutricional	Redução de alimentos cariogênicos e derivados de ácidos cítricos.
Após a RT / QT	
Finalização de tratamentos odontológicos adiados durante a RT.	Reabilitação oral.
Seguimentos frequentes - proservação	Retornos: mensal, trimestral, semestral e anual. Avaliação da higiene oral, descalcificação dentária, xerostomia, osterradionecrose, doença em atividade (recidiva, metástase, presença de novos tumores primários).
Orientação nutricional	Redução de alimentos cariogênicos e derivados de ácidos cítricos.

Anexo A: Protocolo Preventivo Odontológico (PPO) do HAJ/ACCG – Tabelas I e II.

Tabela II: Terapias para as complicações orais decorrentes das RT e QT.

Terapêutica	Posologia
Laserterapia	Laser de baixa potência. Aplicações semanais.
Saliva artificial	
Carmelose sódica	Até 8 vaporizações diárias.
Agentes antimicrobianos	
Tetraciclina	1 cápsula/meia xícara de água. 3 vezes/dia.
Agentes anti-fúngicos	
Tópico Nistatina 100.000UI	12 gotas/xícara de água; 3 a 4 vezes/dia.
Sistêmico Fluconazol 150 mg	150 mg/semana;1 vez/semana.
Agentes anti-virais	
Aciclovir	200mg/5 vezes/dia; 10 dias.
Agentes corticosteroides tópicos	
Triamcinolona em orabase	1 vez/dia antes de dormir.
Enxaguatórios	
Fluoreto de Sódio 0,05%	3 vezes/dia/1 minuto.
Enxague com água bicarbonatada	3 a 4 vezes/dia.
Gluconato de Clorexidina a 0,12%	3 colheres/meia xícara de água; 3 vezes/dia.

Anexo B: Pareceres do Comitê de Ética em Pesquisa da Universidade Federal de Goiás e Hospital Araújo Jorge – Associação de Combate ao Câncer (HAJ/ACCG).

SERVIÇO PÚBLICO FEDERAL
UNIVERSIDADE FEDERAL DE GOIÁS
PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO

COMITÊ DE ÉTICA EM PESQUISA

UFG

Goiânia, 23 de abril de 2012.

PARECER CONSUBSTANCIADO REFERENTE AO PROJETO DE PESQUISA, PROTOCOLADO NESTE COMITÊ SOB O Nº: 415/11

I – Identificação
– Título do projeto: Índice de adesão ao programa de preparo e controle odontológico de pacientes com câncer de boca submetidos a tratamentos adjuvantes de radioterapia e/ou quimioterapia e avaliação dos efeitos adversos
– Pesquisador Responsável: Marília Oliveira Morais
– Orientador (quando necessário): Elismauro Francisco de Mendonça
– Pesquisadores participantes: Cláudio Rodrigues Leles
– Instituição onde será realizado o estudo: Faculdade de Odontologia - UFG
– Data de apresentação ao CEP/UFG: 08 de dezembro de 2011.
– Área Temática: Grupo III

II– Parecer do CEP

- Após análise dos documentos anexados pelos pesquisadores, em atenção aos itens pendentes (abaixo descritos), constata-se o atendimento aos requisitos solicitados e por sua vez à resolução CNS 196/96.

Portanto, o parecer, S.M.J. deste comitê, é pela **APROVAÇÃO**.

A seguir listam-se as pendências identificadas (atendidas conforme solicitado).

1) Na folha de rosto do CONEP: preencher o item 9, colocando o número médio ou no centro de prontuários (sujeitos) a serem avaliados
2) Na folha de rosto do CEP: adequar a data da coleta de dados de acordo com o cronograma do projeto (após a apreciação do Comitê de Ética)
2) No projeto:
- Mencionar o número (médio) de prontuários que serão avaliados, de acordo com os critérios de
inclusão da pesquisa
- Mencionar os critérios de exclusão da pesquisa
- Mencionar os critérios de interrupção da pesquisa, caso necessário
- Mencionar os riscos e benefícios aos sujeitos com a realização da pesquisa

III – Data da reunião: 23 de abril de 2012.

Assinatura do(a) relator(a):

Assinatura do(a) Coordenador(a)/ CEP/UFG: Prof. João Batista de Souza
Coordenador do Comitê de Ética em Pesquisa
Pró-Reitoria de Pesquisa e Pós-Graduação/UFG

PROTOCOLO CEP/ACCG Nº 012/2012 **Goiânia, 05 de junho de 2012**

INVESTIGADOR RESPONSÁVEL: Odontóloga Marília Oliveira Morais
ORIENTADOR: Prof. Dr. Elismauro Francisco de Mendonça
PESQUISADORES PARTICIPANTES: Drª Juliana Castro Dourado Pinezi, Prof. Dr. Cláudio Rodrigues Leles

TÍTULO: "Índice de adesão ao programa de preparo e controle odontológico de pacientes com câncer de boca submetidos a tratamentos adjuvante de radioterapia e/ou quimioterapia e avaliação dos efeitos adversos".

Área Temática: Grupo III
Área de Conhecimento: Ciências da Saúde/Odontologia
Instituição Proponente: Faculdade de Odontologia/UFG
Local de Realização: Hospital Araújo Jorge/ACCG

Informamos que o Comitê de Ética em Pesquisa da ACCG **analisou e aprovou** o projeto de Pesquisa acima referido, juntamente com os documentos apresentados e os mesmos foram considerados em acordo com os princípios éticos vigentes.

Não há necessidade de aguardar o parecer da CONEP – Comissão Nacional de Ética em Pesquisa para iniciar a pesquisa.

O Pesquisador responsável deverá encaminhar ao CEPACCG, **relatórios semestrais** do andamento da pesquisa, encerramento, conclusão, resultados e publicação. Os relatórios deverão ser entregues em CD e devidamente assinados.

O CEP/ACCG pode, a qualquer momento, fazer escolha aleatória de estudo em desenvolvimento para avaliação e verificação do cumprimento das normas da Resolução 196/96 (*Manual Operacional Para Comitês de Ética em pesquisa – Item 13).*

Comitê de Ética em Pesquisa
Associação de Combate ao Câncer em Goiás

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F - 20.15

Anexo C: Classificação clínica TNM e graduação histológica para carcinoma de cavidade oral (C02-C06), segundo UICC (SOBIN e WITTEKIND, 2002).

Regras para Classificação

A avaliação das categorias T,N e M é obtida por exame físico e diagnóstico por imagem.

Localizações e sub-localizações anatômicas

Cavidade oral (C02-06)

1. Mucosa oral
   i) Mucosa do lábio superior e inferior
   ii) Mucosa da bochecha (mucosa jugal)
   iii) Áreas retromolares
   iv) Sulcos buco-alveolares
2. Gengiva, alvéolos superiores (rebordo alveolar superior)
3. Gengiva, alvéolos inferiores (rebordo alveolar inferior)
4. Palato duro
5. Língua
   i) Superfície dorsal e bordas lateral anterior às papilas valadas (dois terços anteriores)
   ii) Superfície ventral da boca
6. Assoalho da boca

Linfonodos Regionais

Os linfonodos regionais são os linfonodos cervicais

TNM – Classificação Clínica

T – Tumor primário

TX Tumor primário não pode ser avaliado

T0 Não há evidência de tumor primário

Tis Carcinoma *in situ*

T1 Tumor de até 2 cm em sua maior dimensão

T2 Tumor maior que 2 cm e até 4 cm em sua maior dimensão

T3 Tumor maior que 4 cm em sua maior dimensão

T4 Tumor invade estruturas adjacentes: cortical óssea, músculos profundos/extrínsecos da língua (genioglosso, hioglosso, palatoglosso e estiloglosso), seios maxilares ou pele da face.

N – Linfonodos regionais

NX Os linfonodos regionais não podem ser avaliados

N0 Ausência de metástase em linfonodos regionais

N1 Metástase em um único linfonodo homolateral, com 3 cm ou menos em sua maior dimensão

N2 Metástase em um único linfonodo homolateral, com mais de 3 cm e até 6 cm em sua maior dimensão, ou linfonodos homolaterais múltiplos, nenhum deles com mais de 6 cm em sua maior dimensão; ou linfonodos bilaterais ou contralaterais, nenhum deles com mais de 6 cm em sua maior dimensão.

N3 Metástase em linfonodo com mais de 6 cm em sua maior dimensão.

M – Metástase à Distância

MX A presença de metástase à distância não pode ser avaliada

M0 Ausência de metástase à distância

M1 Metástase à distância

As categorias M1 podem ser mais especificadas de acordo com as seguintes notações: pulmonar, medula óssea, óssea, pleural, hepática, peritoneal, cerebral, supra-renal e linfonodal.

Anexo D: Escala da escala de capacidade funcional *performance status* Eastern Cooperative Oncology Group (ECOG – PS)

Grau	ECOG
0	Capacidade de executar as atividades normalmente sem restrições
1	Capacidade de executar o trabalho de forma leve ou sedentária
2	Capacidade de auto cuidado, mas incapaz de executar qualquer atividade de trabalho. Fora do leito mais de 50% das horas.
3	Capacidade de auto cuidado limitado. Mais de 50% das horas no leito.
4	Incapacidade total de autocuidado. Totalmente confinado ao leito
5	Óbito

Anexo E: Normas do periódico *Supportive Care in Cancer*.

SUPPORTIVE CARE IN CANCER

EditorinChief: Fred Ashbury
EditorinChief Emeritus: HansJörg Senn
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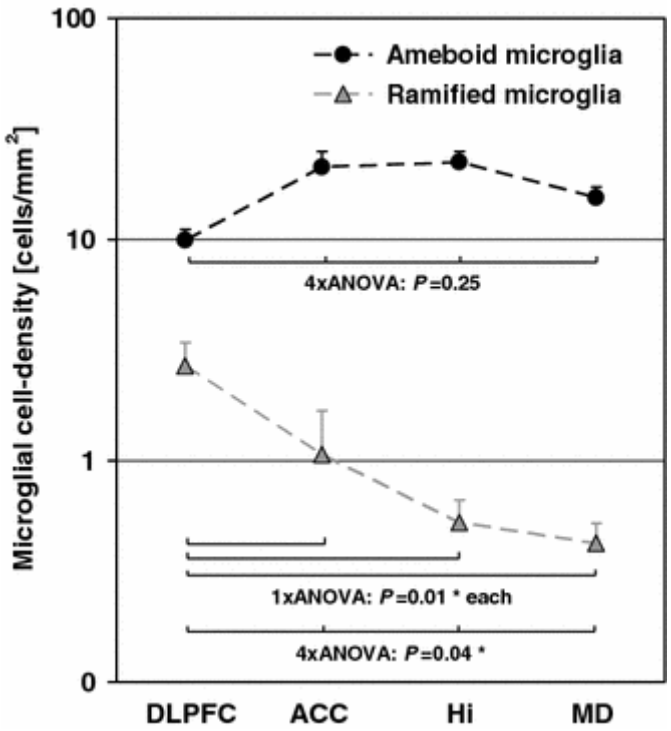

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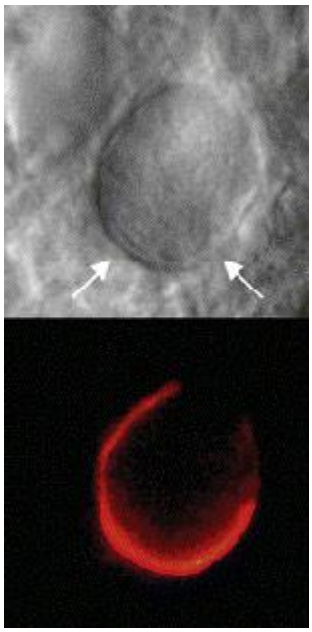

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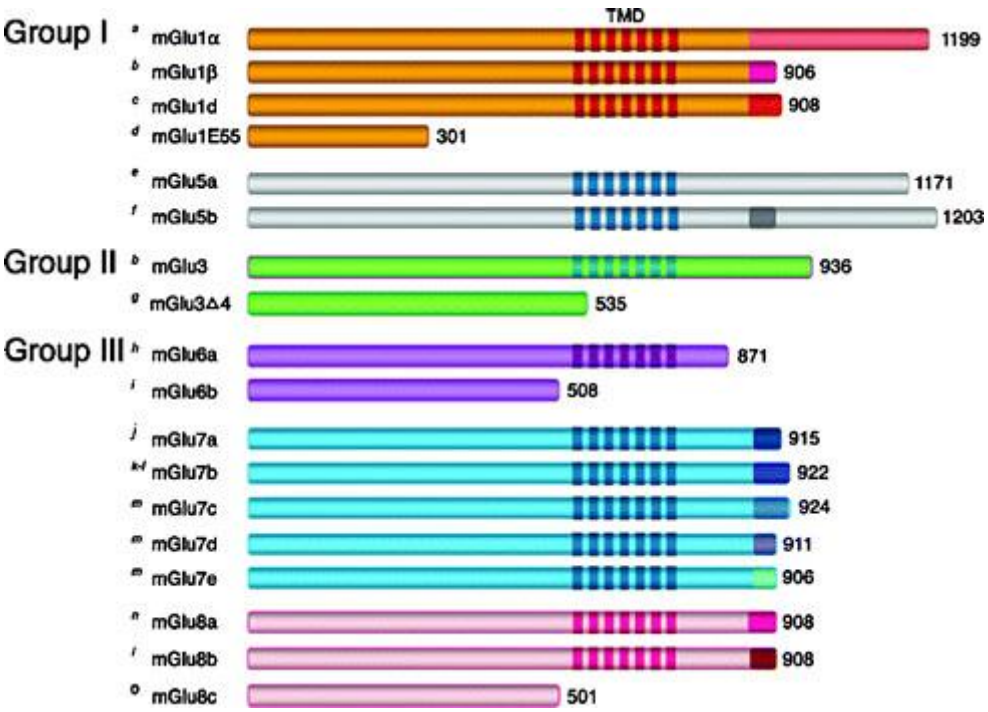

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Supportive Care in Cancer

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ORIGINAL ARTICLE

The effect of preventive oral care on treatment outcomes of a cohort of oral cancer patients

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Abstract

Purpose The purpose of this study was to assess patient adherence to an oral preventive measures (OPM) protocol and its impact on cancer treatment outcomes.

Methods A retrospective cohort of oral cancer of 133 patients submitted to radiotherapy (RT) was selected, excluding those with metastasis. Patients were grouped according to their local tumor response after finishing RT (favorable or unfavorable) and adherence to an OPM (none, ≤6 months, and >6 months). OPM included education and counseling about adverse effects, elimination of infection foci, restorative procedures, fluoride therapy, oral rehydration, and maintenance and supervision of oral hygiene throughout treatment. Clinical and path-ological characteristics were recorded, and patient outcomes (frequency of adverse effects, RT interruption, and overall survival) were analyzed.

Results Patients with higher adherence to the OPM had greater occurrence of RT interruption as a consequence of symptoms (p=0.01); however, these patients were more likely to complete the established RT protocol (p=0.02). Overall survival (p=0.01) was higher in the group with higher adherence.

Conclusions This study suggests that the implementation of oral preventive measures may contribute to improving the prognosis of squamous cell carcinoma (SCC) treatment by reducing the negative impact of oral complications.

Keywords Oral cancer · Preventive dentistry · Radiotherapy · Survival

Introduction

Radiotherapy (RT) is one of the therapies used for oral cancer, used as an exclusive, adjuvant, or palliative treatment, depending on the patient's clinical and histopathological features [1–3]. However, RT results in local and systemic side effects which affect the patient's quality of life, especially when major salivary glands are included in the area to be irradiated [4, 5].

Adverse effects such as acute mucositis (OM), dysphagia, odynophagia, pain, and dermatitis have been reported as causes of interruption of the RT in head and neck cancer patients [6–8]. OM is the main adverse effect of RT in oral cancer patients (squamous cell carcinoma (SCC)) [9]. Depending on its severity, OM can make food intake extremely difficult, compromising the patient's general health and, in many cases, leading to interruption of RT adjuvant therapy [7, 9, 10]. RT interruption, even for a few days, is enough for the remaining cancer cells to begin the processes of differentiation, proliferation, migration, and tumor growth [11], thereby increasing the risk of local recurrence and reducing the likelihood of disease and patient survival [8, 12–14].

For patients undergoing oral cancer treatment, early oral preventive measures (OPM) are recommended as a standard

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