UNIVERSIDADE ESTADUAL DA PARAÍBA
PRO-REITORIA DE PÓS-GRADUAÇÃO E PESQUISA
PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA
DOUTORADO EM ODONTOLOGIA

MARIA BETÂNIA LINS DANTAS SIQUEIRA

IMPACTO DE FATORES CLÍNICOS DE PROGNÓSTICO E BIOMARCADORES SALIVARES NA QUALIDADE DE VIDA DE PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO: UM ESTUDO PROSPECTIVO

CAMPINA GRANDE/PB
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Orientadora: Profª. Drª. Pollianna Muniz Alves

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S618i Siqueira, Maria Betânia Lins Dantas.
Impacto de fatores clínicos de prognóstico e biomarcadores salivares na qualidade de vida de pacientes com câncer de cabeça e pescoço [manuscrito] : um estudo prospectivo / Maria Betânia Lins Dantas Siqueira. - 2018.
114 p.
Digitado.
Tese (Doutorado em Odontologia) - Universidade Estadual da Paraíba, Centro de Ciências Biológicas e da Saúde , 2018.
"Orientação : Profa. Dra. Pollianna Muniz Alves , Departamento de Odontologia - CCBS."
1. Câncer de Cabeça e Pescoço. 2. Qualidade de vida. 3. Saúde bucal. 4. Tratamento. I. Título
21. ed. CDD 616.994

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Aprovado em: 30/07/2018

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Dedico este trabalho aos meus pais, ***Marcelo*** *(in memorian) e* ***Lúcia****,*
ao meu esposo, ***Wellington****, aos meus filhos,* ***Mayara*** *e* ***Matheus****,*
e aos meus irmãos ***Laura****,* ***Gabriel****,* ***Marcelo*** *e* ***Marcos*** *,*
que sempre estiveram ao meu lado, me dando força,
apoio e incentivo para a realização deste sonho.
A vocês, minha eterna gratidão e todo meu amor.
Esta conquista é nossa!

AGRADECIMENTOS ESPECIAIS

À Deus, por sempre está comigo, me protegendo e dando coragem para alcançar meus objetivos e seguir em frente.

À minha Orientadora, Professora Dra. Pollianna Muniz Alves, pelos ensinamentos, pela compreensão, pela paciência e pela atenção, durante toda esta trajetória.

À minha mãe Lúcia, minha velha querida e minha companheira por toda vida, um exemplo de perseverança, coragem e disciplina, que sempre me guiou e me apoiou com muito amor, dedicação e confiança. Minha eterna gratidão.

À meu esposo Wellington e aos meus filhos, Mayara e Matheus, agradeço por todo companheirismo, força e apoio para chegar até aqui, assim como pela compreensão nos momentos de ausência. Com sabedoria, carinho e equilíbrio, vocês tornaram meus dias mais felizes e serenos.

.

AGRADECIMENTOS

Aos meus irmãos, Laura, Gabriel, Marcelo e Marcos, obrigada pelas inúmeras palavras de carinho, apoio, gestos e atitudes inesquecíveis, de cada um de vocês.

A minha cunhada France Anne, Oncologista que muito nos orgulha, por todo incentivo, carinho e apoio nesta caminhada.

A minha equipe de pesquisa, Yuri, Pâmela, Alana, Hítallo e Elizabeth, que com muita dedicação e responsabilidade, foram colaboradores para o êxito deste trabalho em todos os momentos. A união faz a força!

Aos meus amigos da turma de doutorado, pela convivência harmoniosa e amizade de cada um de vocês. Em especial a Monalisa e Marayza, amigas que conheci desde o mestrado e que se tornaram verdadeiras irmãs para mim. Companheiras de todas as horas. Muito obrigada por todo carinho, apoio e atenção, sempre dispensados. Nossa amizade vale ouro, perseverantes e unidas, sempre venceremos!

Aos meus amigos Ramon e Matheus, que desde o mestrado foram sempre muito atenciosos e prestativos, mesmo estando distantes nunca deixaram de me atender quando mais precisei, em especial a Ramon, pelas contribuições a este trabalho de maneira tão responsável e gentil.

Ao departamento de Odontologia da Universidade Estadual da Paraíba (UEPB), onde com muito orgulho fui graduada, fiz meu Mestrado, fui Professora Substituta do Componente Curricular Saúde Coletiva e hoje termino mais essa etapa da minha formação acadêmica.

Aos Professores Dra. Patrícia Meira Bento e Dr. Sérgio d'Ávila Lins Bezerra Cavalcanti, como coordenadores do Programa de Pós-Graduação em Odontologia/UEPB durante o período de meu doutorado, pelo incentivo e apoio sempre dispensados.

À Professora Dra. Ana Flávia Granville-Garcia, pela confiança, pelos ensinamentos, pelo carinho e pelo vínculo de amizade que construímos desde o Mestrado.

Às Professoras Dra. Rilva Suely, Dra. Renata Rocha e Dra. Edja Costa, por toda atenção e incentivo dispensados ao longo desta caminhada.

Aos demais professores e aos funcionários do Departamento de Odontologia da Universidade Estadual da Paraíba (UEPB), minha gratidão.

Ao Hospital da FAP e ao Hospital Napoleão Laureano, pela inestimável contribuição à esta pesquisa, assim como aos pacientes que aceitaram participar do nosso estudo.

As amigas Adriana, Suely e Marisa, grandes incentivadoras ao longo deste período, sempre com palavras de apoio e de carinho.

Aos professores Dr. Saul Martins de Paiva (UFMG), Dra. Ana Maria Gondim Valença (UFPB), Dr. Cassiano Francisco Weege Nonaka (UEPB) e Drª. Ana Flávia Granville-Garcia (UEPB) que gentilmente aceitaram participar da minha banca avaliadora.

*“*Ser feliz é encontrar força no perdão, esperança nas batalhas,
segurança no palco do medo, amor nos desencontros.
É agradecer a Deus a cada minuto pelo milagre da vida.”
Augusto Cury

IMPACTO DE FATORES CLÍNICOS DE PROGNÓSTICO E BIOMARCADORES SALIVARES NA QUALIDADE DE VIDA DE PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO: UM ESTUDO PROSPECTIVO

RESUMO

O câncer de cabeça e pescoço (CCP) exibe na população mundial alta incidência e aumento das taxas de mortalidade e morbidade. Grande parte dos casos são diagnosticados tardiamente, necessitando de tratamentos antineoplásicos combinados que resultam muitas vezes em impacto na qualidade de vida relacionada á saúde (QVRS) e apresentam efeitos adversos, dentre eles as alterações salivares. **Objetivo.** O objetivo desse estudo foi avaliar o impacto de fatores clínicos de prognóstico na QVRS de pacientes com CCP e mensurar a concentração salivar de proteínas totais (PT), ácido úrico (AU), e imunoglobulinas salivares (IgA e IgG), bem como associá-las com os parâmetros clínicos dos pacientes. **Material e Método**. Estudo longitudinal prospectivo, com amostra de 85 participantes, diagnosticados e tratados em hospitais oncológicos de referência, que responderam a versão validada para o Brasil do instrumento de QV da Universidade de Washington (UWQOL), em dois momentos: antes (F1) e durante o tratamento antineoplásico (F2). A análise salivar foi realizada com 45 participantes da amostra. Foram considerados e obtidos nos prontuários médicos, os parâmetros clínicos de prognóstico dos pacientes (sexo, faixa etária, hábitos nocivos) e da lesão (tipo de neoplasia, sítio anatômico, T- tamanho do tumor, N- metástase linfonodal, M- metástase à distância, estadiamento clínico e tipo de tratamento). A coleta da saliva foi realizada na F1 e F2. As amostras de saliva estimulada foram colocadas em tubos de polipropileno e mantidos a 4ºC. A análise salivar foi realizada em triplicata, usando microplacas de 96 poços e em cada poço foi colocado 4 µl de saliva. Kits de detecção enzimática (LABTEST®) foram utilizados para identificação e quantificação colorimétrica através de espectrofotometria. No primeiro plano de análise, os dados foram analisados por meio de estatística descritiva, Teste de Wilcoxon e por regressão logística múltipla ($p<0,05$). Para o segundo plano de análise, foram utilizados os testes de Mann-Whitney, de Kruskal-Wallis e de Wilcoxon, considerando o valor de $p<0,05$. **Resultados.** Os homens foram mais afetados (n=62/73%) e com média de idade +- dp de 63,22+-1.68 anos. O escore total, de QVRS na F1 770,41 (desvio padrão = 220,94) e na F2 568,98 (desvio padrão = 211,40), apresentaram diferença significativa entre as duas fases ($p < 0,001$). Os escores dos domínios do questionário UWQOL, aparência, atividade, recreação, deglutição, mastigação, paladar e saliva foram significativamente menores na F2, indicando uma piora na QVRS dos pacientes após o início do tratamento. As variáveis idade (OR=1.04; 95% IC:1.01-1.07); tabagismo e alcoolismo (OR=4.10; 95% IC:1.17-14.36), foram associadas com uma pior QVRS na F1. Tumores de tamanhos maiores (T3 e T4), foram associados com uma pior QVRS tanto na F1(OR=3.47; 95% IC:1.22-9.81), quanto na F2 (OR=4.04; 95% IC:1.41-11.60). No segundo plano de análise, referente a mensuração das concentrações salivares, não se observou redução significativa da concentração de PT entre F1 (9.88 mg/ml) e F2 (7.52 mg/ml), ($p=0.092$). Houve associação significativa da PT com o a presença de metástase linfonodal (N1-N3) na F2 ($p=0.048$). Quanto a concentração de AU,

verificou-se redução significativa entre F1 (56.53 µg/ml) e F2 (30.80 µg/ml) (p < 0,001). Não se observou redução significativa da concentração de IgA entre F1 (0.56 mg/ml) e F2 (0.56 mg/ml) p=(0.307), entretanto observou-se associação significativa da IgA com sexo do paciente na F1 (p=0,046), onde os maiores índices ocorreram no sexo feminino. Houve também associação significativa da IgA quanto ao tamanho do tumor na F2 (p=0,047). Em relação a IgG, não se observou redução significativa da concentração entre F1 (11.03mg/ml) e F2 (11.03 mg/ml) (p= 0,726), todavia verificou-se associação significativa da IgG com o sítio anatômico da lesão, na F1 (p=0,045). **Conclusão.** Observa-se que a idade, tabagismo e alcoolismo e tamanho de tumores maiores são os fatores clínicos de prognóstico que têm impacto negativo na QVRS de pacientes com CCP. Pode-se inferir que o tratamento antineoplásico para CCP, induz alterações salivares e diminui a atividade antioxidativa da saliva.

Palavras-chave: Câncer de Cabeça e Pescoço. Qualidade de vida. Saliva. Tratamento.

THE IMPACT OF CLINICAL PROGNOSTIC FACTORS AND SALIVARY BIOMARKERS ON THE QUALITY OF LIFE OF HEAD AND NECK CANCER PATIENTS: A PROSPECTIVE STUDY

ABSTRACT

Head and neck cancer (HNC) has high incidence rates and contributes significantly to an increase in the mortality and morbidity statistics worldwide. Most of the cases are diagnosed late, thus requiring combined antineoplastic treatments that often impact the patient's health related quality of life (HRQoL) for having adverse effects, including salivary changes. **Objective**: This study aimed to (i) evaluate the impact of clinical factors on the HRQoL of HNC patients; (ii) measure their salivary concentration of total proteins (TP), uric acid (UA), and salivary immunoglobulins (IgA and IgG); and further associate these outcomes with the clinical parameters of the patients. **Material and Methods**: This was a prospective longitudinal study with a sample of 85 individuals diagnosed with HNC and treated in reference cancer hospitals. The study subjects answered the validated Brazilian version of the University of Washington QoL questionnaire (UWQOL) before (phase 1 – P1) and during (phase 2- P2) antineoplastic treatment. Salivary analysis was performed with 45 participants from the sample. Clinical prognostic parameters of the patient (sex, age group, harmful habits) and of the lesion (type of neoplasia, anatomical site, T-tumor size, N-lymph node metastasis, M-distant metastasis, clinical staging and treatment modality) were obtained from medical records. Saliva samples were collected at P1 and P2. The stimulated saliva samples were placed in polypropylene tubes and kept at 4°C. Salivary analysis was performed in triplicate using 96-well microplates and four microliters of saliva were placed in each well. Enzymatic detection kits (LABTEST®) were used for colorimetric identification and quantification through spectrophotometry. In the first analysis, the data were analyzed using descriptive statistics, Wilcoxon test and multiple logistic regression ($p<0.05$), while in the second analysis, Mann-Whitney, Kruskal-Wallis and Wilcoxon tests were used, with $p<0.05$ considered significant. **Results:** Men were mostly affected by HNC (n=62; 73%), with a mean age of 63.22 ± 1.68 years. There was a significant difference in the total QoL score between P1 (770.41 ± 220.94) and P2 (568.98 ± 211.40) ($p<0.001$). The scores for the domains appearance, fitness, recreation, swallowing, chewing, taste and saliva were significantly lower at P2, indicating a worsening in the patients' QoL after the start of treatment. The variables age (OR=1.04; 95% CI: 1.01-1.07), smoking and alcoholism (OR=4.10; 95% CI: 1.17-14.36) were associated with a worse QoL at P1. Larger tumors (T3 and T4) were associated with a worse QoL at both P1 (OR=3.47, 95% CI: 1.22-9.81) and P2 (OR=4.04; 95% CI: 1.41-11.60). The second part of the study was carried out to determine the salivary concentrations of relevant biomarkers in HNC patients. While there was no significant reduction in TP concentration between P1 (9.88 mg/ml) and P2 (7.52 mg/ml), ($p=0.092$), a significant association of TP with the presence of lymph node metastasis (N1-N3) was found at P2 ($p=0.048$). A significant reduction in UA levels was observed between P1 (56.53 µg/ml) and P2 (30.80 µg/ml) ($p<0.001$). There was no significant reduction in IgA concentration between P1 (0.56 mg/ml) and P2 (0.56 mg/ml) ($p=0.307$). On the other hand, IgA levels were found to be

significantly associated with the patient's sex at P1 (p=0.046), with the highest concentrations observed among females. In addition, there was also a significant association of IgA with the tumor size at P2 (p=0.047). Lastly, no significant reduction in IgG concentration was detected between P1 (11.03 mg/ml) and P2 (11.03 mg/ml) (p=0.726); however, there was a significant association of IgG with the anatomical site of the lesion at P1 (p=0.045). **Conclusion:** Aging, smoking and alcoholism habits as well as larger tumors are clinical factors which significantly impact the HRQoL of HNC patients. It is concluded that the antineoplastic treatment for HNC induces salivary alterations and decreases the antioxidant activity of saliva.

Key-words: Head and Neck Cancer. Quality of life. Saliva. Treatment.

LISTA DE TABELAS

ARTIGO 1

ARTIGO 2

LISTAS DE ABREVIATURAS, SIGLAS E SÍMBOLOS

AU	Ácido Úrico
CCE	Carcinoma de células escamosas
CCP	Câncer de Cabeça e Pescoço
CEP	Comitê de ética em pesquisa
FAP	Fundação Assistencial da Paraíba.
IgA	Imunoglobulina A
IgG	Imunoglobulina G
IBGE	Instituto Brasileiro de Geografia e Estatística
INCA	Instituto Nacional do Câncer
N	Metástase Linfonodal
M	Metástase á distância
OMS	Organização Mundial da Saúde
PT	Proteínas Totais
QT	Quimioterapia
QV	Qualidade de vida
QVRS	Qualidade de vida relacionada à saúde
RT	Radioterapia
T	Tamanho do tumor
TCLE	Termo de consentimento livre e esclarecido
TNM	Sistema de estadiamento clínico
UEPB	Universidade Estadual da Paraíba
UW-QOL	Questionário de qualidade de vida da Universidade de Washington

SUMÁRIO

Considerações iniciais

1 CONSIDERAÇÕES INICIAIS

O câncer de cabeça e pescoço (CCP) representa o sétimo tipo de neoplasia mais comum no mundo, com alta incidência e diagnósticos tardios, considerado um problema de saúde pública mundial, que envolve uma diversidade de neoplasias malignas com diferentes características, sendo 95% dos casos correspondentes ao carcinoma de células escamosas (CCE), que exibe pior prognóstico (RETHMAN et al., 2010; GIEBULTOWICZ et al., 2011; GALBIATTI et al., 2012; YOUNG et al., 2013; NOSRATZEHI, 2017).

Essas neoplasias constituem um grupo de regiões anatômicas heterogêneas com alto índice de incidência e mortalidade, incluindo tumores malignos de uma variedade de sítios não só no trato aerodigestivo superior, podendo acometer as fossas nasais, seios paranasais, cavidade oral, nasofaringe, orofaringe, hipofaringe, laringe e esôfago cervical, glândulas salivares, tireoide, paratireoide, órbita, base do crânio, ossos e partes moles (PAKIN et al., 2005; MOSJOU et al., 2013; ZANDBERG et al., 2015; PETERSON et al., 2016). A cavidade oral é o sítio anatômico mais prevalente, seguido pela faringe e laringe, respectivamente (ALMADORI et al., 2007; CHENG et al., 2014). Em 2018, segundo as estimativas do Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA, 2017), estão previstos aproximadamente 31.980 casos novos no Brasil, incluindo cavidade oral, laringe e glândula tireoide.

Dentre os principais fatores causais associados ao desenvolvimento das neoplasias malignas de cabeça e pescoço estão a exposição ao tabaco e ao álcool, embora outros fatores etiológicos, incluindo fatores genéticos, terapia imunossupressora, exposição e inalação de produtos químicos, infecção viral (Papiloma Vírus Humano e Epstein Bar) e exposição à radiação ultravioleta também estão associados a carcinogênese (MANNARINI et al., 2009; PINTO et al., 2011; NIKAKHLAGH et al., 2012; FERREIRA et al., 2012; VELDHUIS et al., 2015).

Para o CCP, a cirurgia, a radioterapia (RT) e quimioterapia (QT), isoladas ou em associação, a depender do estágio ou risco do paciente, correspondem as principais modalidades de tratamento (BERNIER et al., 2004; BEENA et al., 2011; AMAR et al., 2013; GALBIATTI et al., 2013; IQBAL; PAN, 2016). A cirurgia muitas vezes consiste em amplas ressecções que promovem a desfiguração do paciente e aumentam a morbidade (FURNESS et al., 2010). A RT e a QT podem ser utilizadas

como terapias adjuvantes (PIGNON et al., 2009; GLENNY et al., 2010; KESSEL; BLANCO, 2014) e são modalidades que induzem uma série de efeitos adversos locais e sistêmicos que comprometem a qualidade de vida (QV) do paciente (CHANG et al., 2012; GAUTAM et al., 2013; RATHOD et al., 2015). A RT é uma modalidade comum para pacientes com CCP, que provoca danos principalmente nas células com alta taxa de divisão celular, devido à grande liberação de radicais livres (SOUZA et al., 2005; SROUSSI et al., 2017) e dentre os efeitos deletérios causados e considerados nesta região, estão aqueles que ocorrem principalmente nas glândulas salivares (BEKIROGLU et al., 2011). A RT é conhecida por causar uma série de complicações orais, incluindo a mucosite, aumento do risco de cárie dentária, redução da abertura da boca, osteorradionecrose e hipossalivação (BUGLIONE, CAVAGNINI, DI ROSARIO, MADDALO et al., 2016; LALLA et al., 2017, SROUSSI et al., 2017). A hipossalivação é uma das sequelas mais frequentes e é definida como uma condição clínica caracterizada pela redução qualitativa e quantitativa do fluxo salivar ocasionando danos na fisiologia bucal, tais como: dificuldade na mastigação, deglutição, fonação e um aumento na prevalência de infecções como a mucosite, candidose, cárie e doença periodontal (VELDHUIS et al., 2015).

A saliva reveste a mucosa bucal e é responsável pela lubrificação facilitando a movimentação da língua e dos lábios no momento da fonação, mastigação e deglutição, tem proteção antifúngica, antibacteriana, antiviral, lubrificante e agente de tamponamento, constituindo-se em um importante componente de defesa da cavidade oral (PINNA et al., 2015). O sistema antioxidante inclui várias enzimas salivares e compostos não-enzimáticos, entre eles o ácido úrico, originado a partir de plasma, que é o antioxidante salivar mais importante e assegura aproximadamente 70% da capacidade antioxidante total da saliva (M. GREABU et al., 2008; LAWAL et al., 2012).

Estudos mostram que a análise da composição salivar de pacientes com CCP, representa uma abordagem potencialmente promissora para localizar biomarcadores salivares, uma vez que, a saliva é um líquido facilmente acessível em comparação com biópsias de tecidos, pode ser utilizada em diagnósticos de condições fisiológicas e patológicas do corpo humano, sua composição é complexa, dinâmica além de ser um método de amostragem não invasivo e de fácil manuseio quando comparado ao sangue (SOARES et al., 2007; HU et al., 2008; CROHNS et

al., 2009; LEE et al., 2009; MOLLASHAHI et al., 2016; NORMANDO et al., 2017; KAUR et al., 2018).

Estudo de Lawal et al. (2012) mostrou que o ácido úrico era menor em pacientes com câncer na cavidade oral quando comparados com indivíduos saudáveis e que níveis mais baixos do ácido úrico foram associados com risco aumentado de desenvolvimento de câncer oral. De acordo com Nosratzehi et al, (2017), mudanças nas concentrações salivares incluindo antioxidantes, antioxidantes totais e ácido úrico, foram relacionadas ao CCE e poderiam ser utilizadosdos como potenciais biomarcadores para o prognóstico do câncer. Estes autores sugerem ainda, que o aumento do nível de antioxidantes pode ser um tratamento potencial para prever e/ou tratar complicações com câncer em indivíduos fumantes e não fumantes. Para Pontes et al. (2004), pacientes submetidos à RT para tratamento de CCP apresentam redução significativa no fluxo salivar, capacidade tamponante e padrão eletroforético de proteínas em relação a indivíduos saudáveis.

No que se refere às imunoglobulinas, a IgA é considerada a principal encontrada nas secreções exócrinas, como a saliva, e atua como um sistema de defesa de primeira linha, contra a invasão microbiana desempenhando um papel importante na neutralização e eliminação de antígenos locais e na modulação de fatores imunológicos teciduais ou humorais (SOUZA et al., 2003; DIVYA et al., 2014), enquanto que a IgG é a imunoglobulina predominante em soro, sendo considerada o anticorpo mais importante da resposta imune secundária (SOUZA, et al., 2003; DIVYA et al., 2014**;** ARBABI-KALATI, et al., 2017).

O estudo de Shpitzer et al. (2007), através de uma análise salivar abrangente para avaliar parâmetros bioquímicos e imunológicos em pacientes com carcinoma de células escamosas (CCE) mostrou que a concentração salivar de IgA no grupo de pacientes com câncer oral, foi significativamente menor em 45%, quando comparados com o grupo de indivíduos saudáveis. Em relação a IgG, estes mesmo autores observaram que no grupo de pacientes com câncer oral a concentração salivar teve um valor foi significativamente maior em 125%, quando comparados com indivíduos saudáveis. Arbabi-Kalati et al. (2017) avaliaram alterações salivares em pacientes fumantes e concluíram que o uso do tabaco diminui a atividade antioxidante da saliva e aumenta os níveis de IgA salivar.

Diante desse contexto, é notória a importância da saliva para a avaliação de alterações locais e sistêmicas nos pacientes com CCP. Os componentes bioquímicos salivares vêm sendo alvos de estudos e tornando-se evidente a sua contribuição nos mecanismos de defesa, diagnóstico e monitorização dos efeitos da RT na cavidade oral, que comprometem a QV do paciente (RATHOD et al., 2015). Os efeitos adversos do tratamento antineoplásico, podem causar diversos transtornos a atividade antioxidante e baixa imunidade, que levam o paciente a paralisar ou prolongar o tempo do tratamento, gerando interrupções não programadas e graves consequências negativas no seu prognóstico (RUSSO et al., 2008; CUNHA-CRUZ et al., 2013; PINNA et al., 2015; LALLA et al., 2014; GONZÁLEZ FERREIRA et al., 2015).

O prognóstico por sua vez, assim como a tomada de decisão terapêutica, geralmente são baseados no sistema de estadiamento clínico (TNM) (ARAÚJO JÚNIOR et al., 2006; TIRELLI et al., 2018), para classificar as neoplasias malignas em estágios e estimar tanto a resposta clínica à terapia quanto a sobrevida dos pacientes (LOURENÇO et al., 2007; LINDENBLAT et al., 2012; GONZÁLEZ FERREIRA et al., 2015). O tratamento pode resultar em grave comprometimento da função física e social, de modo que a sofisticada análise dos efeitos de tratamento na QV é importante (REGO et al., 2015; VELDHUIS et al., 2015). Desta forma, tão importante quanto o tratamento antineoplásico, é a atenção dada aos aspectos sociais da doença. O impacto na QV por sua vez, torna-se relevante indicador de saúde e para mensurá-lo, a utilização de instrumentos desenvolvidos e validados torna-se cada vez mais necessária.

Há dois questionários de QV especificamente direcionados para pacientes com CCP, os quais já foram traduzidos e validados para o idioma português: o EORTC QLQ H&N C-35 (totalizando 65 questões), desenvolvido pela Organização Europeia para Pesquisa e Tratamento de Câncer e o UW-QOL (12 questões), desenvolvido pela Universidade de Washington. Para estudos realizados no Brasil, o UW-QOL pode ser vantajoso do ponto de vista operacional, em função do menor número de questões, e em função de sua tradução e validação terem considerado o português falado no país, sendo assim, uma ferramenta importante para avaliar a progressão desta doença e a eficácia do tratamento (ANDRADE et al., 2012).

Estudos têm revelado que um diagnóstico de CCP, assim como os efeitos colaterais do tratamento antineoplásico, podem resultar em problemas psicossociais

e comprometimento do paciente, afetando a QV e que a sua mensuração desempenha um papel cada vez mais importante (MELO et al., 2013; BOYAPATI et al., 2013; ARGAWL et al., 2014; OLIVEIRA et al., 2017; BECKER et al., 2018).

Em estudo prospectivo e analítico, Agarwal et al. (2014) avaliaram as mudanças relacionadas na QV de 72 pacientes com CCP após 12 meses de tratamento. Todos os pacientes apresentaram a lesão com sítio de localização na língua e com estadiamento clínico inicial (T1-2N0M0). Os autores recomendam que os tumores com a referida localização quando diagnosticados precocemente e sem metástase linfonodal, podem ser facilmente gerenciados sem o comprometimento significativo da QV. Para Efunkoya et al. (2015), em um estudo prospectivo com 68 pacientes com câncer oral, que avaliou a QV utilizando o UW-QOL, um dia antes da cirurgia e no pós-operatório (7 dias, 1 mês, 3 meses e 6 meses), os domínios aparência, recreação e mastigação foram identificados como os mais importantes determinantes da QV no pós-operatório. Ghazali et al. (2017), também utilizaram o UWQOL para avaliar o humor de pacientes que já tinham realizado um tratamento prévio para o CCP e que estavam em acompanhamento ambulatorial de rotina. O estudo teve 261 participantes, e os autores concluíram que uma aflição significativa está associada com uma pior QV, para aqueles pacientes que fizeram RT, assim como para aqueles que precisaram de consultas mais longas para acompanhamento clínico.

Avaliar a QV em pacientes oncológicos é complexo, considerando-se o grande número de variáveis que interferem na autopercepção do paciente, desde suas condições sociais até as particularidades da sua doença. Por estas mesmas razões, é uma ferramenta fundamental para avaliar o impacto da doença e de seu tratamento, obtendo-se evidências epidemiológicas que sustentem mudanças nos protocolos de suporte multiprofissional mais efetivo aos pacientes (MELO et al., 2013; BOYAPATI et al., 2013; ARGAWL et al., 2014; OLIVEIRA et al., 2017 ; EFUNKOYA, 2015).

Diante do exposto, pode-se dizer que há uma lacuna de estudos prospectivos com a avaliação do impacto de fatores clínicos de prognóstico e biomarcadores salivares na QV de pacientes com CCP, antes e durante o tratamento antineoplásico. Através de evidências científicas mais fortes, como as investigações epidemiológicas prospectivas, os resultados podem fomentar a implementação de politicas públicas de prevenção e atenção aos pacientes com CCP, afim de que a

resposta à terapêutica seja mais adequada e desta forma diminuir os agravos à saúde.

Nesta perspectiva, o objetivo desse estudo foi avaliar o impacto de fatores clínicos de prognóstico na QV de pacientes com CCP e mensurar a concentração salivar de proteínas totais (PT), ácido úrico (AU), e imunoglobulinas salivares (IgA e IgG), bem como associá-las com os parâmetros clínicos dos pacientes.

Objetivos

2 OBJETIVOS

2.1 OBJETIVO GERAL

Avaliar o impacto de fatores clínicos de prognóstico e biomarcadores salivares, na QVRS de pacientes com CCP, no estado da Paraíba.

2.2 OBJETIVOS ESPECÍFICOS

Plano de análise I (Artigo 1)

- Avaliar o perfil epidemiológico (sexo, faixa etária, hábitos nocivos, tipo de neoplasia, sítio anatômico, tamanho do tumor (T), metástase linfonodal (N), metástase à distância (M), estadiamento clínico e tipo de tratamento) dos pacientes com CCP;

- Associar os parâmetros clínicos de prognóstico do paciente (sexo, faixa etária, hábitos nocivos) e da lesão (tipo de neoplasia, sítio anatômico, tamanho do tumor (T), metástase linfonodal (N), metástase à distância (M), estadiamento clínico e tipo de tratamento), com a qualidade de vida dos pacientes (antes durante o tratamento antineoplásico).

Plano de análise II (Artigo 2)

- Avaliar o perfil epidemiológico (sexo, faixa etária, hábitos nocivos, tipo de neoplasia, sítio anatômico, tamanho do tumor (T), metástase linfonodal cervical(N), metástase à distância (T), estadiamento clínico e tipo de tratamento) dos pacientes com CCP;

- Mensurar a concentração salivar de ácido úrico (AU), proteínas totais (PT), e imunoglobulinas salivares (IgA e IgG) e associá-las com os parâmetros clínicos dos pacientes.

Metodologia

3 METODOLOGIA

3.1 CARACTERIZAÇÃO DA ÁREA DE ESTUDO

O estudo foi desenvolvido no estado da Paraíba, uma das 27 unidades federativas do Brasil. Situada no leste da região nordeste, limita-se com outros três estados: Rio Grande do Norte (norte), Pernambuco (sul) e Ceará (oeste). A Paraíba apresenta uma área territorial de 56 469,778 km². Possui 223 municípios e 3.766.528 habitantes, com a densidade demográfica de 66,70 habitantes por km² (IBGE, 2010).

3.2 DESENHO DO ESTUDO

Este estudo foi do tipo coorte, analítico, de caráter observacional prospectivo, para mensurar o impacto de fatores clínicos de prognóstico e biomarcadores salivares, na QVRS de pacientes com CCP, no estado da Paraíba.

3.3 POPULAÇÃO DO ESTUDO

Pacientes com diagnóstico de CCP, atendidos nos hospitais oncológicos de referência do estado da Paraíba e que ainda não tinham iniciado o tratamento antineoplásico. O estado da Paraíba possui como hospitais oncológicos de referência, o Hospital da FAP (Fundação Assistencial da Paraíba), no município de Campina Grande e o Hospital Napoleão Laureano, em João Pessoa, capital do estado, perfazendo um total de dois centros de referência para atendimento ao paciente com neoplasias malignas.

3.4 CARACTERÍSTICAS DA AMOSTRA

O tamanho da amostra foi calculado de acordo com o estudo de Agarwal et al. (2014), levando a uma amostra mínima estimada de 82 pacientes, aos quais foram adicionados mais 20% para compensar possíveis perdas, resultando em uma amostra total de 103 pacientes.

3.5 CALIBRAÇÃO

Primeira Etapa: consistiu em um momento teórico no qual foram apresentados os instrumentos a serem utilizados. Foi, então, realizado o estudo da ficha clínica e do instrumento de QV da Universidade de Washington, (UW-QOL).
Segunda Etapa: foram conduzidas as orientações para padronização da técnica de coleta da saliva, assim como da técnica da análise salivar, de acordo com os parâmetros dos fabricantes de cada reagente.

3.6 CRITÉRIOS DE ELEGEBILIDADE

Foram incluídos no estudo, pacientes com diagnóstico de CCP que ainda não tinham iniciado o tratamento antineoplásico e que aceitaram participar do estudo preenchendo e assinando o termo de consentimento livre e esclarecido (TCLE) sendo excluídos os pacientes que já tinham iniciado o referido tratamento. Para a coleta da saliva, foram excluídos também os pacientes traqueostomisados.

3.7 ESTUDO PILOTO

Previamente ao estudo principal foi realizado um estudo piloto para testar e avaliar a metodologia proposta para o estudo.

3.8 COLETA DE DADOS

A coleta dos dados foi realizada nos Hospitais Oncológicos de Referência, no estado da Paraíba, no período de maio de 2016 a dezembro de 2017.

3.8.1 Instrumentos para coleta de dados

Para coleta dos dados foram necessários os seguintes instrumentos de pesquisa:

- Ficha clínica para anotação dos dados clínicos e sociodemográficos (APÊNDICE A).

- Ficha clínica para anotação dos dados referentes a coleta e análise salivar (APÊNDICE B).
- Questionário UW-QOL (ANEXO A).

3.8.2 Estudo Clínico

- Preenchimento de Ficha Clínica de acordo com os prontuários médicos dos pacientes, onde foram anotados os dados dos pacientes e da lesão; (dados sociodemográficos e clínicos).

3.8.3 Mensuração da Qualidade de Vida

- Os dados foram avaliados de acordo com os escores preconizados para cada resposta individual do paciente.

UW-QOL

Os pacientes responderam o instrumento de QV da Universidade de Washington, UW-QOL (*University of Washigton Quality of Life*), versão 4, validado para a língua portuguesa no Brasil (VARTANIAN et al,2006), em dois momentos: antes (F1) e durante (F2) o tratamento antineoplásico. O UW-QOL avalia a qualidade de vida de pacientes com CCP, através de 16 questões, sendo 12 questões objetivas que abordam a QV ao longo dos últimos 7 dias, em relação aos domínios: dor, aparência, atividade, recreação, deglutição, mastigação, fala, função do ombro, gosto, saliva, humor e ansiedade. Cada questão tem entre três e seis possíveis respostas e é pontuada de 0 a 100. A pontuação é dimensionada igualmente, dependendo do número de respostas para cada aspecto, de modo que uma pontuação "0" representa a pior resposta possível (maior impacto na QV), enquanto "100" representa a melhor resposta possível (menor impacto na QV). A escala obtida permite a avaliação de cada domínio de qualidade de vida através de escores específicos. Isso também permite a integração de todas as medidas em um escore sintético geral para cada paciente, que pode variar de 0, a pontuação total mais baixa, à 1200, a pontuação total mais alta (melhor resposta possível). O instrumento ainda possui 1 questão sobre os problemas mais importantes para o paciente durante os últimos 7 dias, onde as alternativas de resposta são os 12

domínios do questionário, que podem ser marcadas em até três opções e mais 3 questões gerais relacionadas a QV, comparando com um mês antes do desenvolvimento do câncer, QV relacionada à saúde nos últimos 7 dias e qualidade de vida em geral durante os últimos 7 dias. O questionário também contém uma questão subjetiva, onde o paciente pode descrever quaisquer outros problemas (médicos ou não médicos) que foram importantes para sua QV e que não tenham sido adequadamente mencionados nas outras questões do instrumento.

3.8.4. Coleta da Saliva

A coleta da saliva foi realizada sempre no mesmo momento do dia, uma hora após o paciente ter se alimentado, fumado ou ingerido qualquer tipo de líquido. No momento da coleta o paciente foi orientado para sentar-se com a cabeça ligeiramente curvada para baixo e procurar não deglutir ou movimentar a língua e lábios. Para a coleta de saliva estimulada foi utilizado o Parafilm (Prolab®) a fim de estimular o fluxo salivar durante 1 minuto. Para a coleta de saliva foi estipulado o tempo de 2 minutos para cada paciente expelir no tubo de polipropileno. A taxa do fluxo salivar foi determinada pela razão entre o volume de saliva coletada e o tempo utilizado para coleta, expressa em ml por minuto. Foi considerado portador de hipossalivação o indivíduo que apresentou taxas de fluxo salivar estimulada ≤ 1 ml/min (FALCÃO et al., 2013).

3.8.5 Análise Salivar

As amostras de saliva estimulada foram colocadas em tubos de polipropileno e mantidos a 4ºC. A análise salivar foi realizada em triplicata, usando microplacas de 96 poços, onde em cada poço foi colocado 4 µl de saliva. Para análise sialoquímica, kits para determinação da concentração salivar e de detecção enzimática (LABTEST®) foram utilizados para identificação e quantificação colorimétrica através de espectrofotometria, em leitor de placa EZ Reader®. Posteriormente, as microplacas foram levadas a estufa a 37°/5min de acordo com os parâmetros estabelecidos pelo fabricante e em seguida analisadas de acordo com o nível de absorbância: AU (492nm), PT (562nm), IgA e IgG (600nm).

3.9 ELENCO DE VARIÁVEIS

O estudo apresenta dois planos de análise. Foi avaliado inicialmente o impacto dos fatores clínicos de prognóstico na qualidade de vida dos pacientes com CCP, antes e durante o tratamento. Num segundo plano de análise, foi avaliado a associação da concentração salivar de AU, PT, e imunoglobulinas salivares (IgA e IgG) com os parâmetros clínicos dos pacientes com CCP, antes e durante o tratamento. Neste sentido, as variáveis foram classificadas em duas etapas distintas, de acordo com os planos de análise descritos a seguir:

3.9.1 Plano de análise I

Variável dependente

- A variável dependente desse plano de análise da pesquisa foi relativa ao impacto na QVRS.

- **Variáveis independentes**

As variáveis independentes desse plano de análise foram relativas aos parâmetros clínicos de prognóstico dos pacientes (sexo, faixa etária, hábitos nocivos) e da lesão (tipo de neoplasia, sítio anatômico, tamanho do tumor [T], metástase linfonodal [N], metástase à distância [M], estadiamento clínico e tipo de tratamento).

3.9.2 Plano de análise II

Variável dependente

A variável dependente analisada nesta parte da pesquisa foi a concentração salivar de AU, PT e imunoglobulinas salivares (IgA e IgG).

Variáveis independentes

As variáveis independentes desse plano de análise foram relativas aos parâmetros clínicos dos pacientes (sexo, faixa etária, hábitos nocivos) e da lesão (tipo de neoplasia, sítio anatômico, tamanho do tumor [T], metástase linfonodal [N], metástase à distância [M], estadiamento clínico e tipo de tratamento).

3.10 PROCESSAMENTO E ANÁLISE DOS DADOS

A análise estatística foi realizada por meio do software Statistical Package for the Social Sciences (SPSS, para Windows, versão 23.0, SPSS Inc., Chicago, EUA). No primeiro plano de análise, estatística descritiva foi realizada para caracterizar a amostra e avaliar a distribuição dos itens do UW-QOL. O escore total, bem como os escores do UW-QOL em cada domínio, foram comparados entre os tempos por meio dos testes t pareado e do Teste de Wilcoxon, respectivamente. Foram construídos dois modelos de regressão logística múltipla (um para F1 e outro para F2). As variáveis com p-valor <0,20 na análise bivariada, bem como aquelas com relevância teórica, foram testadas no modelo múltiplo. O nível de significância foi de 5%. Para o segundo plano de análise, foi realizada uma descrição absoluta e frequências relativas das variáveis estudadas e posteriormente foram utilizados os testes de Mann-Whitney, Kruskal-Wallis e Wilcoxon, considerando o valor de p <0,05.

3.11 PRINCÍPIOS ÉTICOS

Este estudo recebeu aprovação do Comitê de Ética em Pesquisa da Universidade Estadual da Paraíba - UEPB sob número de processo CAAE: (51209515.6.0000.5187), de acordo com a resolução CNS Nº 466/2012 (ANEXO B). Os procedimentos foram conduzidos de acordo com os padrões para experimentos envolvendo seres humanos e a Declaração de Helsinki. Cartas de Anuência dos hospitais oncológicos de referência no estado da Paraíba, FAP e Hospital Napoleão Laureano, foram emitidas, autorizando a execução do estudo (ANEXOS C e D). Os pacientes que concordaram em participar do estudo assinaram um termo de consentimento livre e esclarecido (TCLE) (APÊNDICE C)**.**

Resultados

4 RESULTADOS

O presente trabalho foi dividido em dois artigos. Desse modo, os resultados serão apresentados conforme a apresentação de cada artigo.

Artigo 1

Impact of clinical factors on the health related quality of life of patients with head and neck cancer

Periódico: Brazilian Oral Research – BOR

Fator de impacto: 0,937– Qualis A2

Formato segundo as normas de publicação do periódico (ANEXO E)

Artigo 2

Salivary expression of antioxidants and immunoglobulins in patients with heand and neck cancer

Periódico: Oral Oncology

Fator de impacto: 4,794– Qualis A1

Formato segundo as normas de publicação do periódico (ANEXO F)

Artigo 1

IMPACT OF CLINICAL FACTORS ON THE HEALTH RELATED QUALITY OF LIFE OF PATIENTS WITH HEAD AND NECK CANCER

IMPACTO DOS FATORES CLÍNICOS NA QUALIDADE DE VIDA RELACIONADA À SAÚDE DE PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO

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ABSTRACT

This study evaluated the impact of clinical factors on the health related quality of life (HRQoL) of head and neck cancer (HNC) patients. This was a longitudinal study with a sample of eighty-five patients diagnosed and treated in reference oncological hospitals. The study subjects answered the validated version for the Brazilian population of the QoL instrument of the University of Washington (UWQOL) before (Phase 1 – P1) and during (Phase 2 – P2) antineoplastic treatment. Clinical prognostic parameters of the patients (sex, age group, harmful habits) and of the lesion (type of neoplasia, anatomical site, T - tumor size, N - metastasis, M - distant metastasis, clinical staging and treatment modality) were obtained from medical records. The data were analyzed using descriptive statistics, Wilcoxon test, paired t-test and multiple logistic regression ($p<0.05$). There was a predominance of men with HNC (n=62; 73%), with a mean age of 63.22 years (±1.68). The overall QoL score at P1 (770.41±220.94) was found to be significantly different from that at P2 (568.98 ±211.40) ($p<0.001$). The UWQOL scores for the domains appearance, fitness, recreation, swallowing, chewing, taste and saliva were significantly lower at P2, which indicates a decline in the QoL of patients after the start of treatment. The variables age (OR=1.04; 95% CI:1.01-1.07),

smoking and alcoholism (OR=4.10; 95% CI:1.17-14.36) were associated with a lower QoL at P1. In addition, larger tumors (T3 and T4) were associated with a lower QoL both at P1 (OR=3.47; 95% CI:1.22-9.81) and P2 (OR=4.04; 95% CI:1.41-11.60). We can conclude that aging, smoking and alcoholism habits as well as larger tumors are clinical factors which impact the QoL of HNC patients.

Keywords: Head and Neck Cancer; Quality of life; Treatment.

RESUMO

Objetivo: Este estudo avaliou o impacto de fatores clínicos na qualidade de vida relacionada à saúde (QVRS) de pacientes com câncer de cabeça e pescoço (CCP). **Metodologia**: Foi um estudo longitudinal, com amostra de oitenta e cinco pacientes, diagnosticados e tratados em hospitais oncológicos de referência que responderam a versão validada para o Brasil do instrumento de QV da Universidade de Washington (UWQOL), em dois momentos: antes (F1) e durante (F2) o tratamento antineoplásico. Foram considerados e obtidos nos prontuários médicos, os parâmetros clínicos de prognóstico dos pacientes (sexo, faixa etária, hábitos nocivos) e da lesão (tipo de neoplasia, sítio anatômico, T- tamanho do tumor, N-metástase linfonodal, M-metástase à distância, estadiamento clínico e tipo de tratamento). Os dados foram analisados por meio de estatística descritiva, Teste de Wilcoxon, Teste t pareado e por regressão logística múltipla ($p<0,05$). **Resultados**: Os homens foram mais afetados (n=62;73%) e com média de idade de 63,22 anos (+-1.68). O escore total de QV na F1 (770,41 ± 220,94) e na F2 (568,98 ±211,40), apresentaram diferença significativa entre as duas fases ($p<0,001$). Os escores dos domínios aparência, atividade, recreação, deglutição, mastigação, paladar e saliva do UWQOL foram significativamente menores na F2, indicando uma piora na QV dos pacientes após o início do tratamento. As variáveis idade (OR=1.04; 95% IC:1.01-1.07); tabagismo e alcoolismo (OR=4.10; 95% IC:1.17-14.36), foram associadas com uma pior QV na F1. Tumores de tamanhos maiores (T3 e T4), foram associados com uma pior QV tanto na F1(OR=3.47; 95% IC:1.22-9.81), quanto na F2 (OR=4.04; 95% IC:1.41-11.60). **Conclusão**: Diante dos resultados encontrados, pode se inferir que pacientes mais velhos, que exibem hábitos de tabagismo e alcoolismo e lesões de tamanhos maiores são fatores clínicos que apresentam impacto na QVRS de indivíduos com CCP.

Descritores: Câncer de Cabeça e Pescoço; Qualidade de Vida; Tratamento.

INTRODUCTION

Cancer has been long considered one of the main causes of morbidity and mortality worldwide, resulting in an extensive social impact. Head and neck cancer patients are prone to develop psychological disorders, as social interaction and emotional expression depend heavily upon the functional and structural integrity of the head and neck elements. Anatomically and functionally, they are responsible for essential functions, including speech, breathing, chewing and swallowing.[1-3] Head and neck cancer (HNC) may severely affect one's daily routine, interfering with their quality of life (QoL) in terms of diagnosis and treatment, and generating emotional, physical and social distress. [2,3]

Considered as a global health burden, HNC has been shown to have high prevalence rates and late diagnosis. It encompasses a variety of malignant neoplasms with different characteristic, 95% of the cases corresponding to squamous cell carcinoma – which has the worst prognosis among the HNC types [4-8] and the oral cavity as the most frequently affected site. [9,10]

Conventional treatment modalities include surgery, radiotherapy (RT) and chemotherapy (CT), individually or in combination. [11-15] These approaches are known to have aesthetic and emotional consequences that impact the QoL of cancer patients. [16,17] Therapeutic decision-making is usually based on tumor staging in addition to histopathological classification.[18] Nevertheless, it turns out to be an inaccurate prognostic indicator which requires the use of other diagnostic tools to manage individual patient needs.[19] Health-related QoL is an important indicator of treatment outcome which has gained increasingly importance in oncology. Such a construct measures individual sense, as well as cultural and intellectual conditions, taking into account expectations and concerns and defining what is most important for each individual. [1]

In the literature, different instruments were designed to assess patients' subjective QoL and allow for a better estimation of treatment outcomes.[18] For instance, the University of Washington Quality of Life Questionnaire (UW-QOL), developed in the United States for HNC patients, is an important tool to evaluate the progression of HNC and the efficacy of treatment. [20]. A few studies with longitudinal prospective design have evaluated the impact of HNC on the quality of life of affected patients. [1,21,22] In addition, little is known about the impact of clinical prognostic factors on the QoL of HNC patients during antineoplastic treatment.

There is an obvious need for prospective epidemiological investigations in this field. In addition to providing stronger scientific evidence, the outcomes of these types of studies may foster the implementation of public policies for the prevention and care of HNC patients, in a way that a more responsive therapy may reduce health issues. In light of this, this study aims to prospectively evaluate the impact of clinical on the HRQoL of HNC patients before and during the antineoplastic treatment.

METHODOLOGY

Ethical issues

This study was approved by the Research Ethics Committee of the State University of Paraíba - UEPB (Brazil) under protocol CAAE: 51209515.6.0000.5187. The procedures were performed in accordance with the standards for experiments involving humans and the Declaration of Helsinki of 1975 (revised by the World Medical Association, 2013). Patients who agreed to participate in the study were asked to sign an informed consent form (ICF).

Sample characterization

A longitudinal study was carried out with 85 patients (62 men and 23 women) diagnosed with HNC and with indication for antineoplastic treatment, treated in reference hospitals in the state of Paraíba, Brazil. The sample size was calculated as described elsewhere,[1] with an estimated minimum sample of 82 patients plus 20% to compensate for possible losses, resulting in a total sample of 103 patients. The data were collected from May 2016 to December 2017.

Eligibility criteria

The study included patients with a diagnosis of HNC who had not yet started the antineoplastic treatment and had agreed to participate in the study by filling out and signing an ICF. Patients who had already started the treatment were excluded from analysis.

Data collection

The patients responded to the QoL instrument of the University of Washington, UW-QOL (University of Washington Quality of Life) version 4.0, validated for the Portuguese language in Brazil,[23] before (Phase 1 – P1) and during (Phase 2- P2) the antineoplastic treatment. The UW-QOL evaluates the quality of life of HNC patients through 16 questions,

with 12 objective questions addressing their QoL over the previous 7 days in relation to the domains: pain, appearance, fitness, recreation, swallowing, chewing, speech, shoulder function, taste, saliva, mood and anxiety. Each question has between three and six possible responses and is scored from 0 to 100. The score is scaled equally, depending on the number of responses for each aspect, so that a "0" score represents the worst possible answer (highest impact on quality of life), while "100" represents the best possible response (less impact on quality of life). The scale obtained allows the evaluation of each QoL domain through specific scores. This also makes possible the integration of all measures into a general summarized score for each patient, which can range from 0 (the lowest total score) to 1200 (the highest total score) – best answer possible. The questionnaire includes one question about the most important problems for the patient during the previous 7 days, whose response alternatives fall into the 12 domains of the questionnaire, and up to three options could be checked. In addition, it also includes three general questions related to QoL, comparing the current QoL with that of one month before cancer onset; health-related QoL in the previous 7 days; and overall QoL during the previous 7 days. The questionnaire also contains a subjective question, where the patient can describe any other problems (medical or non-medical) that were important to their QoL and that have not been adequately addressed in the other questions of the questionnaire. The data were evaluated according to the recommended scores for each individual response.

The clinical prognostic parameters of the patients (sex, age group, harmful habits) and of the lesion (type of neoplasia, anatomical site, T - tumor size, N - lymph node metastasis, M - distant metastasis, clinical staging and treatment modality) were obtained from medical records.

Statistical analysis

The data were analyzed on SPSS (Statistical Package for the Social Sciences) for Windows, version 23.0 (SPSS Inc., Chicago, EUA). Descriptive statistics were used to characterize the sample and to evaluate the distribution of UW-QOL items. The total score, as well as the UW-QOL scores in each domain, were compared between the time points using the paired t-test and Wilcoxon's test, respectively. Two multiple logistic regression models (one for P1 and one for P2) were built. The variables with p-value <0.20 in the bivariate analysis, as well as those with theoretical relevance, were tested in the multiple model, with a 5% significance level.

RESULTS

Among the 103 patients selected, 85 participated in the present study, corresponding to a response rate of 82.5%. The loss of 18 participants occurred due to deaths during treatment (n=13) and treatment withdrawal (n=5). Table 1 shows the sociodemographic and clinical data of the sample. Men were most frequently affected by HNC (n=62; 73%), with a mean age of 63.22 years (±1.68). The intraoral region (n=42, 49.4%) was the most affected anatomical site, and other sites (n=43, 50.6%) included pharynx, larynx, esophagus, skull and lip. The most prevalent clinical staging corresponded to stage IV (n = 30, 35.3%), whereas the combined therapy, represented by surgery associated with RT and CT, was the most common treatment modality (n=29, 34.0%).

The total QoL score was 770.41 (±220.94) at P1 and 568.98 (±211.40) at P2, with a significant difference between them ($p<0.001$). The total score as well as the scores of most domains of the UWQOL questionnaire were significantly lower at P2, indicating a worsening in the QoL of patients after the start of treatment. Table 2 shows that the appearance, fitness, recreation, swallowing, chewing, taste and saliva domains had significantly lower scores at P2, indicating a worsening in these domains after the start of treatment.

As seen in Table 3, the logistic regression model revealed that before the antineoplastic treatment, the following variables were associated with a worse impact on the QoL of HNC patients: age (OR=1.04; 95% CI: 1.01-1.07); smoking and alcoholism (OR=4.10; 95% CI: 1.17-14.36) and large tumors (T3 and T4), (OR=3.47; 95% CI: 1.22-9.81). Logistic regression also showed that only the variable large tumor size (T3 and T4) (OR=4.04; 95% CI:1.41-11.60) remained in the final model associated with a worse QoL of HNC patients (Table 4).

DISCUSSION

A higher prevalence of head and neck malignancies was observed in male patients, and in the group aged over 41 years. These results corroborate with the literature, since epidemiological studies of head and neck neoplasms show the predominance of this gender within an age range between the 5th and 6th decades of life.[1,24-26]

With regard to harmful habits, the majority of patients presented the habit of smoking associated with alcoholism, which is in agreement with the studies that consider these practices as the main risk factors for HNC.[9,27-30] Other etiological factors, including genetic

factors, immunosuppressive therapy, exposure to and inhalation of chemicals, viral infection (Human Papilloma Virus and Epstein Bar) and exposure to ultraviolet radiation, are also associated with carcinogenesis.[31,32]

In our study, the most frequent anatomical site of HNC was the oral cavity, which is in line with the literature in the field.[9,10,26,33]. Oral cancer can lead to greater difficulties in breathing, swallowing and aesthetics as compared to other anatomical sites of the head and neck region. In addition, among the histological types HNC is the most common one in the oral cavity,[4,-8] which is consistent with our findings. It is also worth noting that during the antineoplastic treatment for HNC, RT towards the oral cavity leads to adverse effects such as oral mucositis (OM), loss of taste, hyposalivation and xerostomia,[34-37], in addition to opportunistic infections that may also evolve during cancer treatment, such as candidiasis and herpes virus.[38]

In our study, the majority of patients were diagnosed in advanced clinical stages of the disease and, because of this, the type of treatment recommended in the majority of cases was RT combined with CT, and surgery. This finding corroborates with other authors, who argue that combined treatment continues to be widely used and indicated in cases of neoplasia with advanced staging.[15,30,39] Here, the type of treatment had no impact on the patients' QoL, although in the literature other authors point out that the combined antineoplastic therapy can induce a series of local and systemic adverse effects that compromise the patient's QoL.[15,30,39]

The total UW-QOL score, as well as the scores of most domains were significantly lower at P2, indicating a worsening in the QoL of the patients after the start of treatment. Although anxiety and pain may potentially have an impact on the QoL of HNC patients, either because of their duration or adverse effects that may develop during treatment, we observed that these domains had no impact on the QoL of the study participants. On the other hand, the domains appearance, fitness, recreation, swallowing, chewing, taste and saliva were significantly more affected at P2, indicating a worsening in the QoL of the patients after the start of treatment.

Facial disfigurement is frequent in HNC patients after surgery and has a significant impact on their HRQoL. [40] This is confirmed by our study, since the domain appearance was significantly impaired during antineoplastic treatment. For Efunkoya et al.,[21] appearance, recreation and chewing were the domains identified as the most important determinants of postoperative HrQoL in oral cancer patients. This result is also consistent with the present study, in that these domains showed significantly lower scores at P2. Therefore, it is inferred

that the antineoplastic treatment for HNC has adverse effects mainly in the oral cavity, in accordance with other reports in the literature.[35-37]

Patients reported significant worsening of swallowing and chewing functions at P2. In a recent study, Oliveira et al. [26] concluded that mood, anxiety and pain were the domains mostly affected at the time of diagnosis and that chewing and swallowing were the mostly affected ones three months following diagnosis. While the domains affected three months after diagnosis are similar to our results at P2, we cannot affirm that our results corroborate with the authors, given that the description of the HRQoL assessment performed by them is not clear on whether patients were undergoing treatment, awaiting the start of treatment or whether they had already completed the protocol.

The variables, age, smoking and alcoholism, as well as large tumor size (T3-T4), were associated with a worse HRQoL at P1. These results corroborate with findings in the literature suggesting that the consequences of a late diagnosis of HNC have a clear and direct influence on the patients' well-being and HRQoL.[26,30,41] We can reason that at late diagnosis HNC tumors are probably larger, thus requiring more complex procedures with a worse prognosis.

The variable large tumor size (T3-T4) was the only one associated with a worse HRQoL at P2. This is in contrast with the study by Tirelli et al. [18] who reported that larger tumors were not correlated with HRQoL. It is known that the prognosis of HNC patients is directly related to the affected area and that late-diagnosed tumors are generally larger, have a worse prognosis, lead to a shorter survival and a high HRQoL impairment. It is believed that larger tumors (T3-T4) are clinical prognostic factors that affect functional aspects, thus leading the patient to oncologic fatigue and impaired HRQoL. Therefore, it is important to develop programs and public policies for health promotion aimed at tracking HNC, with the aim of preventing, diagnosing and treating patients at an earlier stage.

The present study presents limitations inherent to the clinical protocols of the antineoplastic treatment for HNC. Interruptions in treatment by clinical complications may have resulted in a certain heterogeneity within the time period established for application of the QoL instrument at P2. Despite of that, the prospective identification of clinical prognostic factors influencing the HRQoL of patients, before and during the antineoplastic treatment, in different stages and treatment protocols, is a strong point of this study.

CONCLUSION

HNC is a clinical condition which affects the patient's HRQoL before and during treatment. Among the clinical prognostic factors studied, aging, smoking and alcoholism habits as well as large tumor size were the ones with higher impact on the patient's HRQoL.

Declaration of Interest

The authors certify that they have no commercial or associative interest that represents a conflict of interest in connection with the manuscript.

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Table 1. Absolute and relative distribution of the independent variables of the study. Campina Grande, 2018 (n = 85).

Variable	Frequency	
	n	%
Sex		
Female	23	27.0%
Male	62	73.0%
Harmful habits		
None	21	24.7%
Smoking	25	29.4%
Alcoholism	5	5.9%
Smoking + Alcoholism	34	40.0%
Anatomical site of the lesion		
Intraoral region	42	49.4%
Others	43	50.6%
Tumor size (T)		
T1	16	18.8%
T2	27	31.8%
T3	26	30.6%
T4	16	18.8%
Lymph Node Metastasis (N)		
N0	49	57.7%
N1	15	17.6%
N2	16	18.8%
N3	5	5.9%
Distant metastasis (M)		
M0	82	96.5%
M1	3	3.5%
Clinical staging		
I	14	16.5%
II	19	22.3%
III	22	25.9%
IV	30	35.3%
Treatment modalities		
Surgery		
Radiotherapy	2	2.4%
Surgery + Radiotherapy	10	11.8%
Radiotherapy + Chemotherapy	16	18.8%
Surgery + Radiotherapy + Chemotherapy	28	33.0%
	29	34.0%
	Mean (Std)	**Median**
Age	63.22(1.68)	64(73)

Table 2. Distribution of the UW-QOL 12 domains scores before and during antineoplastic treatment – P1 and P2, respectively. Campina Grande, 2018 (n = 85).

			p-value*
Domain	P1	P2	
	Median (Q_{25}-Q_{75})	Median (Q_{25}-Q_{75})	
Pain	75 (50 - 100)	75 (50 - 100)	0.324
Appearance	75 (50 - 100)	50 (25 - 75)	**<0.001**
Fitness	75 (50 - 75)	50 (12.50 - 50)	**<0.001**
Recreation	50 (25 - 75)	25 (25 - 50)	**<0.001**
Swallowing	67 (33 - 100)	33 (16.5 - 67)	**<0.001**
Chewing	50 (0 - 100)	0 (0 - 50)	**<0.001**
Speech	67 (67 - 100)	67 (33 - 67)	**0.019**
Shoulder	100 (100 - 100)	100 (67 - 100)	0.316
Taste	67 (33 - 100)	0 (0 - 67)	**<0.001**
Saliva	100 (67 - 100)	33 (33 - 67)	**<0.001**
Mood	50 (25 - 100)	50 (25-75)	**0.033**
Anxiety	67 (16.5 - 67)	33 (0-67)	0.134

* Wilcoxon test. Results at 5% significance level are highlighted in bold.

Table 3. Logistic regression of the independent variables associated with the impact on the quality of life of head and neck cancer patients before antineoplastic treatment.

Independent variable	Impact on QoL High (n=43) n(%)	Low (n=42) N(%)	p-value*	Unadjusted OR (95% CI)	p-value**	Adjusted OR (95% CI)
Sex						
Female	10(43.5)	13(56.5)	0.426	1	-	-
Male	33(53.2)	29(46.8)		1.479(0.564-3.877)	-	-
Age [mean(SD)]	66.8(±17)	59.6(±17)	0.035	1.032(1.002-1.063)	**0.028**	1.040(1.004-1.077)
Harmful habits						
None	6(28.6)	15(71.4)		1		1
Smoking	13(52.0)	12(48.0)	0.112	2.708(0.792-9.262)	0.403	1.807(0.451-7.237)
Alcoholism	3(60.0)	2(40.0)	0.201	3.750(0.495-28.389)	0.229	4.111(0.412-41.055)
Smoking and alcoholism	21(61.8)	13(38.2)	0.020	4.038(1.250-13.045)	**0.027**	4.105(1.173-14.361
Anatomical site						
Intraoral region	24(57.1)	18(42.9)	0.234	1.684(0.714-3.971_	-	-
Others	19(44.2)	24(55.8)		1	-	-
Tumor size (T)						
T1 and T2	17(39.5)	26(60.5)		1		1
T3 and T4	26(61.9)	16(38.1)	0.041	2.485(1.038-5.958)	0.019	3.474(1.229-9.815)
Lymph node metastasis						
N0	25(51.0)	24(49.0)		1	-	-
N1-N3	18(50.0)	18(50.0)	0.926	0.960(0.406-2.270)	-	-
Distant metastasis (M)						
M0	41(50.0)	41(50.0)		1	-	-
M1	2(66.7)	1(33.3)	0.578	2.000(0.174-22.927)	-	-
Clinical staging						
I and II	14(42.4)	19(57.6)		1	-	-
III and IV	29(55.8)	23(44.2)	0.232	1.711(0.709-4.129)	-	-

* Unadjusted conditional logistic regression analysis

** Variables incorporated into the multivariate model: age, harmful habits, categorized T, and categorized N.

Table 4. Logistic regression of the independent variables associated with the impact on the quality of life of head and neck câncer patients during antineoplastic treatment.

	Impact on QoL					
Independent variable	**High (n=44) n(%)**	**Low (n=41) N(%)**	**p-value***	**Unadjusted OR (95% CI)**	**p-value****	**Adjusted OR (95% CI)**
Sex						
Female	10(43.5)	13(56.5)	0.353	1	-	-
Male	34(54.8)	28(45.2)		1.579(0.602-4.140)	-	-
Age [mean(±SD)]	66.8(±13)	59.6(±17)	0.612	1.007(0.980-1.035)	-	-
Harmful habits						
None	13(61.9)	8(38.1)		1	-	-
Smoking	12(48.0)	13(52.0)	0.347	0.568(0.175-1.848)	-	-
Alcoholism	2(40.0)	3.(60.0)	0.381	0.410(0.056-3.014)	-	-
Smoking and alcoholism	17(50.0)	17(50.0)	0.390	0.615(0.203-1.864)	-	-
Anatomical site						
Intraoral region	23(54.8)	19(45.2)	0.585	1.268(0.541-2974)	-	-
Others	21(48.8)	22(51.2)		1	-	-
Tumor size (T)						
T1 and T2	17(39.5)	26(60.5)		1		**1**
T3 and T4	27(64.3)	15(35.7)	0.024	2.753(1.143-6.628)	**0.009**	**4.046(1.411-11.601)**
Lymph node metastasis						
N0	26(53.1)	23(46.9)		1	-	-
N1-N3	18(50.0)	18(50.0)	0.780	0.885(0.374-2.093)	-	-
Distant metastasis						
M0	42(51.2)	40(48.8)		1	-	-
M1	2(66.7)	1(33.3)	0.605	1.905(0.166-21.836)	-	-
Clinical staging						
I and II	14(42.4)	19(57.6)		1	-	-
III and IV	30(57.7)	22(42.3)	0.172	1.851(0.766-4.474)	-	-
Treatment modality						
Surgery and/or radiotherapy	13(46.4)	15(53.6)		1	-	-
Sugery, radiotherapy	15(51.7)	14(48.3)	0.889	1.077(0.381-3.048)	-	-

and chemotherapy						
Radiotherapy and Chemotherapy	11(39.3)	17(60.7)	0.286	1.783(0.617-5.155)	-	-

* Unadjusted logistic regression analysis

** Variables incorporated into the multivariate model: sex, age, harmful habits, categorized T, categorized N, M, and treatment modality.

Artigo 2

EXPRESSION OF ANTIOXIDANTS AND IMMUNOGLOBULINS IN THE SALIVA OF PATIENTS WITH HEAD AND NECK CANCER

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Word count: 2,889

ABSTRACT

Objective: To measure the salivary concentration of total proteins (TP), uric acid (UA), and immunoglobulins (IgA and IgG) in HNC patients and associate these variables with clinical parameters. **Methods:** This was a longitudinal study with a sample of 45 patients. Clinical and sociodemographic data were obtained from medical records and saliva samples were collected before (Phase 1 - P1) and during treatment (Phase 2 – P2). Stimulated saliva samples were placed in polypropylene tubes and kept at 4°C. The analyses were performed in triplicate and enzymatic detection kits were used for colorimetric identification and quantification through spectrophotometry. Mann-Whitney, Kruskal-Wallis and Wilcoxon tests were used, with p-value<0.05. **Results:** No significant reduction in TP concentration was found between P1 (9.88 mg/ml) and P2 (7.52 mg/ml), (p=0.092). However, there was a significant association of TP with lymph node metastasis (N1-N3) at P2 (p=0.048). A significant reduction in UA concentration was observed between P1 (56.53 μg/ml) and P2 (30.80 μg/ml) (p<0.001). While there was no significant reduction in IgA concentration between P1 (0.56 mg/ml) and P2 (0.56 mg/ml) (p=0.307), a significant association of IgA was found with the patient's sex at P1 (p=0.046) and tumor size at P2 (p=0.047). Lastly, no significant reduction in IgG concentration was detected between P1 (11.03 mg/ml) and P2 (11.03 mg/ml) (p=0.726); however, there was a significant association of IgG with the anatomic site of the lesion at P1 (p=0.045). **Conclusion:** The antineoplastic treatment for HNC induces salivary alterations and decreases the antioxidative activity of saliva.

Key-words: Head and Neck Cancer; Saliva; Treatment.

INTRODUCTION

Head and neck cancer (HNC) is considered a public health issue with high incidence rates worldwide and, commonly, of late diagnosis. This condition involves a variety of malignancies with different characteristics, 95% of which being squamous cell carcinoma (SCC) – a type of tumor which exhibits poor prognosis [1-5]. Overall, HNC comprises malignant tumors located not only in the upper aerodigestive tract, but may also in the nasal cavities, paranasal sinuses, oral cavity, nasopharynx, oropharynx, hypopharynx, larynx and cervical esophagus, salivary glands, thyroid, parathyroid, orbit, skull base, bones and soft tissues [6-8]. In 2018, according to estimates by the José Alencar Gomes da Silva National Cancer Institute [9], approximately 31,980 new cases are anticipated in Brazil, including oral cavity, larynx and thyroid gland cancer. The oral cavity is the most prevalent anatomical site, followed by the pharynx and larynx, respectively [10,11].

Surgery, radiotherapy (RT) and chemotherapy (CT), individually or in combination, are the conventional treatment modalities indicated depending on the stage of the disease and patient's risk [12-16]. Although radiotherapy is a common treatment administered to patients with HNC, it may cause damage to cells, in particular to cells with high division activity, due to the pronounced free-radical release [17,18]. Such a treatment modality is known to cause a number of oral complications, including mucositis, increased risk of dental caries, reduced mouth opening, osteoradionecrosis and hyposalivation [18-20]. Hyposalivation is associated with a low buffering capacity, which may impact the antioxidant activity of the host and lead to a low immunity response [20-22].

In addition to physiological functions, saliva has been shown to be a measurable fluid which may aid in the diagnosis of diseases as well as to be a source of DNA and RNA, proteins and several parameters of oxidative stress [23,24]. The antioxidant system includes several salivary enzymes and non-enzymatic compounds, for instance, uric acid. Originating from plasma, it is the most important salivary antioxidant which accounts for approximately 70% of the total antioxidant capacity of saliva [25,26].

Immunoglobulins belonging to the class of gammaglobulins are plasma proteins that exhibit immunological properties. Among them, IgA is the main immunoglobulin found in exocrine secretions such as saliva, tear and mucus of the respiratory, genitourinary and digestive tracts. It acts as a first-line defense system against microbial invasion, playing an important role in the neutralization and elimination of local antigens and in the modulation of

immunological or tissue-related immune factors [27,28]. IgG is the predominant immunoglobulin in serum, most abundant in blood and extravascular spaces, being considered the most important antibody of the secondary immune response [27-29].

Hence, the analysis of saliva allows for the evaluation of local and systemic alterations in the host. Salivary biochemical components have been studied for their contribution to defense mechanisms, diagnosis and monitoring of the deleterious effects of radiotherapy on the oral cavity, which can potentially compromise the patient's quality of life [30]. Here we carried out a prospective study to measure the concentration of total proteins (TP), uric acid (UA) and salivary immunoglobulins (IgA and IgG) in patients with HNC, as well as to associate these variables with the patient's clinical parameters before and during antineoplastic treatment.

METHODS

This study was approved by the Research Ethics Committee of the State University of Paraíba, Brazil, under protocol CAAE: 51209515.6.0000.5187. The procedures were conducted in accordance with the standards for experiments involving humans and the Declaration of Helsinki of 1975 (revised by the World Medical Association in 2013). The patients who agreed to participate in the study were asked to sign an informed consent form.

This was a longitudinal study with a sample of 45 patients diagnosed with HNC undergoing treatment at reference cancer hospitals in the state of Paraíba, Brazil, carried out in accordance with established consent and authorization. The study included patients with a diagnosis of head and neck cancer, who had not yet started the antineoplastic treatment and agreed to participate in the study by completing and signing an informed consent form. Tracheostomized patients as well as those who had already initiated treatment were excluded from the sample.

Clinical and sociodemographic data (sex, age, harmful habits, anatomical site of the lesion, type of neoplasia, tumor size, cervical lymph node metastasis, distant metastasis, TNM clinical staging and treatment modality) were obtained from the medical records. Saliva samples were collected at two timepoints, before (Phase 1 - P1) and during treatment (Phase 2 - P2). The collection of saliva was performed at the same time of day, one hour after the patient had fed, smoked or ingested any type of liquid. At the time of collection, the patient was instructed to sit with the head slightly curved down and not to swallow or move the tongue and lips. To collect stimulated saliva, parafilm (Prolab®) was used in order to

stimulate salivary flow for 1 minute. A total of 2 minutes was determined for each patient to expel the saliva into the polypropylene tube. The salivary flow rate was determined by the ratio between the volume of saliva collected and the time used for collection, expressed in ml per minute. Individuals presenting stimulated salivary flow rates ≤ 1 ml/min were considered as having hyposalivation. Stimulated saliva samples were placed in polypropylene tubes and kept at 4°C. The analysis of the samples was performed in triplicate using 96-well microplates, with four microliters of saliva placed in each well. Kits for enzymatic detection and salivary concentration (LABTEST®) were used for identification and colorimetric quantification using spectrophotometry in an EZ Reader® microplate reader. Subsequently, the microplates were incubated at 37°C for 5 minutes according to the manufacturer's parameters and then read at specific wavelengths, namely: uric acid (492nm), total proteins (562nm), immunoglobulin A and immunoglobulin G (600nm).

The data were treated and analyzed on SPSS (Statistical Package for Social Sciences) version 23.0. Absolute and relative frequencies of the studied variables were calculated, and the Mann-Whitney, Kruskal-Wallis and Wilcoxon tests were employed, with $p < 0.05$ considered significant.

RESULTS

Of the 45 study subjects, 64.4% (n=29) were males while 16 (35.6%) were females. The majority of patients were aged 41 years or older (88.9%, n=40) and epithelial neoplasia was the most prevalent condition (95.5%, n=43). As seen in Table 1, the intraoral region was the most frequently affected anatomical site (44.4%; n=20); sixteen subjects (35.5%) made no concomitant use of tobacco and alcohol; and the most prevalent clinical staging was stage IV (35.6%, n=16). With regard to the combination of treatment modalities, there was a predominance of radiotherapy and chemotherapy (73.3%, n=33), as seen in Table 1.

Table 1. Distribution of patients according to sociodemographic, clinical and prognostic characteristics. Campina Grande, 2018 (n=45).

Variable	N	%
Sex		
Male	29	64.4
Female	16	35.6
Age range		
≤ 40 years	5	11.1
≥ 41 years	40	88.9
Type of neoplasia		
Epithelial	43	95.5

Mesenchymal	02	4.5
Anatomical site of the lesion		
Intra-oral region	20	44.4
Lip	01	2.3
Others	24	53.3
Harmful habits		
Smoking	13	28.9
Alcoholism	02	4.5
Smoking and alcoholism	16	35.6
None	14	31.0
Tumor size (T)		
T1	11	24.4
T2	15	33.3
T3	12	26.7
T4	07	15.6
Cervical lymph node metastasis (N)		
N0	28	62.2
N1	4	8.9
N2	11	24.4
N3	2	4.5
Distant metastasis (M)		
M0	43	95.5
M1	02	4.5
Clinical staging		
I	09	20.0
II	11	24.4
III	09	20.0
IV	16	35.6
Treatment modality		
Surgery	02	4.5
Radiotherapy	10	22.2
Combined therapy	33	73.3
Total	**45**	**100.0**

Table 2 shows the results of the stimulated salivary flow (SSF) and the concentrations of all salivary biomarkers evaluated. It can be seen that there was a decrease in the medians of SSF, UA and TP levels during treatment, however, with statistical significance only for SSF ($p < 0.001$) and UA ($p < 0.001$).

Table 2. Median and quartiles of the dependent variables analyzed before and during the antineoplastic treatment. Campina Grande, 2018 (n=45).

Variable	P1 – Before treatment Median (Q25-Q75)	P2 – During treatment Median (Q25-Q75)	p-value*
SSF	1.00(0.64-1.66)	0.88(0.53-1.40)	**<0.001**
TP (mg/ml)	9.88(5.82-27.92)	7.52(2.33-14.73)	0.092
UA (µg/ml)	56.53(32.3-88.72)	30.80(14.15-52.98)	**<0.001**
IgA (mg/ml)	0.56(0.09-5.39)	0.56(0.03-4.17)	0.307
IgG (mg/ml)	11.03(10.55-11.44)	11.03(10.58-11.66)	0.726

* Wilcoxon's test. Significant results at 5% level are highlighted in bold.

Table 3 shows the association of the salivary concentrations of UA and TP with all the independent variables of the study at P1 and P2. The TP concentration showed a significant association with the patient's sex at P1 (p=0.048), with higher concentrations observed in women. In addition, TP concentration was also significantly associated with the presence of metastasis in regional lymph nodes (N1-N3) at P2 (p=0.048).

Table 4 shows the results of the associations of IgA and IgG concentrations with all the independent variables of the study at P1 and P2. There was a significant association of IgA with the patient's sex at P1 (p=0.046), with the highest concentrations observed in women. There was also a significant association of IgA with the tumor size T3-T4 at P2 (p=0.047). Lastly, a significant association was found between the IgG salivary concentrations and the anatomic site of the lesion at P1 (p=0.045), with the highest concentrations observed in intra-oral lesions.

DISCUSSION

While several studies have looked into the oral conditions of HNC patients as a serious global health issue [2-5,31-34], there is little research focused on longitudinal follow-up of these patients. Here we aimed to measure the expression of antioxidants and immunoglobulins in the saliva of HNC patients and associate these variables with the patient’s clinical parameter before and during antineoplastic therapy.

The results showed a higher prevalence of HNC among males aged 41 years and older, with the intraoral region the most frequently affected site. These findings are in agreement with those previously reported in the literature [1,3,4,8,20,35-38].

With regard to harmful habits, tobacco and alcohol have been known to be the major risk factors for HNC, especially when they are used frequently and for prolonged periods of time [10,39-42]. The higher frequency of alcoholics and smokers in our study reinforces the observation of a risk behavior.

The diagnosis and treatment of HNC are based on clinical and histopathological characteristics, and its prognosis is generally determined according to the clinical staging system (TNM). This system serves to classify stage malignant neoplasms and also to estimate both the clinical response to therapy and patient survival [43,44]. In our study, stage IV was the most prevalent clinical staging and the majority of patients were submitted to combined radiotherapy and chemotherapy. The combination of treatment makes it more aggressive and debilitating, but on the other hand renders it more effective [45]. Accordingly, the late

diagnosis of HNC implicates in the need for more complex treatments, therefore resulting in a worse prognosis.

A number of studies in the literature have shown that biochemical alterations of the saliva may take place when patients are exposed to radiotherapy, which triggers adverse effects in the oral cavity [30,46-47]. In light of this, our study determined the concentrations of salivary biomarkers in HCN patients. We showed that the antineoplastic treatment significantly decreased the UA levels in the saliva of these patients. These findings corroborate with other studies in the literature showing modifications in the mechanisms of free radicals associated with a reduction in salivary antioxidants, in particular a decreased concentration of uric acid [2,10,48-50]. Although not evaluating HNC patients undergoing anti-neoplastic treatment, the authors of a previous study also observed reduced levels of salivary UA (5.18 mg/dl, SD ± 1.96) in patients with oral cancer as compared to healthy individuals (7.09 mg/dl, SD ± 1.84) [26]. Contrarily, Almadori et al. [10] did not find any significant difference in the salivary concentration of UA comparing HNC and healthy individuals ($p=0.228$ and $p=0.122$, respectively).

In our study, HNC patients were found to have harmful habits, with tobacco being known as the main responsible for the reduction of salivary antioxidants, especially when associated with alcohol [10,51-53]. The reduction of salivary antioxidants and especially of uric acid makes the oral cavity more susceptible to oxidative stress [54]. In a previous study, Nosratzehi et al. [5] concluded that changes in the salivary concentrations of antioxidants, total antioxidants and uric acid were related to SCC and could be used as potential biomarkers for cancer prognosis. Moreover, the increase in the level of antioxidants may be a potential therapy to predict and/or treat cancer complications in smokers and nonsmokers.

The salivary concentrations of UA during the antineoplastic treatment, although not significant, were found to be lower in intra-oral lesions, larger tumors (T3-T4), with metastasis in cervical lymph nodes (N1-N3), and in cases treated with radiotherapy. This suggests a possible interference of these types of lesion and treatment with a diminished antioxidant action of saliva.

There was a reduction in TP levels between P1 and P2, although it was not statistically significant. These findings are in agreement with the study by Pontes et al. [47], who concluded that there was no statistically significant difference in the salivary concentration of total proteins, both before and after antineoplastic treatment ($p>0.05$). In the study by Shpitzer et al. [55], the salivary concentration of TP in the group of healthy patients was 68 mg/dl, whereas in patients with oral cancer it was significantly higher (26%, $p=0.01$). In our study, a

significant difference was observed between the TP levels and the patient's sex at P1, with higher concentrations in women. During the antineoplastic treatment there was a significant difference for metastasis in cervical lymph nodes (N1-N3), with a lower TP concentration. Although no significant association was found, the salivary concentration of TP during the antineoplastic treatment was lower in lesions located in the intra-oral region. We can infer that these results contribute to the increase of nutritional risk, improper food intake and, consequently, reduction of protein levels in the saliva. The evaluation of total protein allows measuring the number of healthy functional cells together with the secretory capacity of the salivary gland [56].

Immunoglobulins belong to the class of gammaglobulins, which are plasma proteins that exhibit immunological properties [27]. In our study, we found that the antineoplastic treatment did not affect the salivary concentrations of IgA and IgG. It can also be noted that salivary IgA concentrations during antineoplastic treatment were found to be lower among tobacco users, although it was not statistically significant. The findings reported by Shpitzer et al. [55] show that the salivary IgA concentrations in the group of healthy patients was 599 mg/dl, whereas in the group of patients with oral cancer it was significantly lower (45%, p=0.001). Possible causes associated with the decrease of salivary IgA observed in our study may include malnutrition, stress and tobacco use. No correlation was found between age, clinical staging and salivary IgA levels, a result corroborated by the study of Souza et al. [27], in which the salivary IgA concentration was 7.2±5.0 mg/dl in HNC patients.

The salivary concentration of IgA showed a significant difference at P1 according to the patient’s sex, with the highest concentrations observed in women. A significant difference was also observed at P2 in relation to the tumor size (T3-T4), with higher IgA levels found in larger tumors. The salivary IgA concentrations during antineoplastic treatment were higher in lesions with cervical lymph node metastasis (N1-N3), although with no significant difference. Guerra et al. [57] carried out a study to investigate salivary parameters of pediatric cancer patients. The authors concluded that the total IgA salivary concentration was lower in children with cancer regardless of antineoplastic treatment when compared to healthy subjects.

Arbabi-Kalati et al. [29] evaluated salivary changes in smoking patients and concluded that tobacco use decreases the antioxidant activity of saliva and increases salivary IgA levels. Likewise, Mollashahi et al. [58] observed salivary changes in smokers, with a decrease in total protein concentration as compared to healthy individuals. In our study, most of the participants were smokers, and with this, it can be inferred that the results found corroborate with those studies previously mentioned.

IgG is a molecule expressed on carcinoma cells which is significantly correlated with differentiation, metastasis, local invasion and poor prognosis of many types of cancer [59]. No correlations were found between the patient's sex, tumor size and salivary IgG concentrations. On the other hand, there was a significant association between salivary IgG concentration and the anatomical site of the lesion at P1, with the highest concentrations observed in intra-oral lesions. These findings are in line with the study by **S**hpitzer et al. [55] reporting a salivary IgG concentration of 12.4 mg/dl in the group of healthy patients as compared to levels significantly higher in patients with oral cancer (125%, p=0.01).

Taken altogether, it is suggested that the antineoplastic treatment for HNC makes the oral milieu conducive to the development of inflammation and infection and that the salivary analysis is relevant, since it allows for the evaluation of local and systemic alterations.

CONCLUSION

We conclude that the antineoplastic treatment for head and neck cancer contributes to a reduction in UA levels and may affect the availability of salivary IgA and IgG – in women and in tumors located in the oral region – which can ultimately impact local immunity.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

None declared.

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Table 3. Association of salivary Uric Acid (UA) and Total Protein (TP) concentrations with the independent variables of the study (Phase 1 – P1, and Phase 2- P2).

		n	**UA** µg/ml **(P1)** Median (Q25-Q75)	**UA** µg/ml **(P2)** Median (Q25-Q75)	p-value	**TP** mg/ml **(P1)** Median (Q25-Q75)	**TP** mg/ml **(P2)** Median (Q25-Q75)	p-value
Sex	Male	29	45.38 (36.88-77.03)	31.85 (20.73-45.58)	0.507†	7.45 (5.45-16.11)	5.44 (2.43-14.41)	**0.048**†
	Female	16	61.94 (29.95-112.01)	27.57 (11.64-56.44)	0.740§	15.85 (8.92-40.28)	7.61 (-0.70-14.06)	0.943§
Age	Up to 40 years	5	42.51 (36.88-50.33)	50.62 (30.80-67.88)	0.264†	9.26 (8.90-20.28)	9.07 (5.44-16.36)	0.903†
	≥41 years	40	62.49 (32.04-96.66)	29.21 (14.16-47.32)	0.220§	9.90 (5.83-27.78)	6.54 (1.68-14.13)	0.234§
Harmful habits	Smoking	13	38.10 (28.26-128.75)	37.90 (27.87-72.77)		9.26 (5.45-16.11)	7.85 (5.44-10.79)	
	Alcoholism	2	68.28 (41.24-95.31)	77.43 (44.67-110.18)	0.966†	6.49 (5.87-7.11)	26.68 (25.17-28.18)	0.303†
	Smoking and alcoholism	16	60.21 (40.01-81.57)	26.21 (11.84-52.05)	0.086§	8.36 (5.11-19.39)	6.83 (2.38-20.55)	0.127§
	None	14	60.56 (42.02-77.81)	24.31 (10.69-34.06)		17.09 (8.94-38.89)	3.92 (-2.75-10.04)	
Anatomical site of the lesion	Intraoral region	20	53.43 (31.19-82.63)	22.98 (12.64-35.86)		12.50 (4.85-28.21)	4.83 (2.34-10.42)	
	Lip	1	165.44 (165.44-165.44)	107.61 (107.61-107.61)	0.281† 0.064§	11.24 (11.24-11.24)	5.56 (5.56-5.56)	0.966† 0.687§
	Others	24	57.87 (34.48-90.71)	35.23 (23.31-52.99)		9.08 (5.93-27.92)	8.22 (1.82-17.07)	
Type of neoplasia	Epithelial	43	60.00 (33.22-90.00)	30.80 (15.48-50.62)	0.396†	9.88 (5.78-20.28)	7.53 (2.24-14.1)	0.549†
	Mesenchymal	2	38.50 (26.67-50.32)	115.05 (12.44-217.66)	0.655§	23.90 (8.90-38.89)	19.38 (4.90-33.85)	0.396§

Tumor size (T)	T1 or T2	26	63.85 (41.24-101.16)	35.11 (15.48-62.25)	0.241†	9.10 (6.29-35.56)	5.50 (1.11-20.70)	0.845†
	T3 or T4	19	50.32 (29.15-68.02)	26.62 (12.44-37.90)	0.414§	9.92 (3.15-20.00)	7.69 (2.43-11.75)	0.260§
Cervical lymph node metastasis (N)	N0	28	60.56 (41.63-86.78)	35.23 (14.16-52.99)	0.527†	9.10 (6.60-20.14)	8.74 (3.99-17.07)	0.870†
	N1-3	17	50.32 (28.26-101.16)	24.09 (19.35-34.06)	0.228§	13.12 (3.15-37.65)	2.83 (0.00-8.81)	**0.048**§
Distant metastasis (M)	M0	43	55.74 (30.85-87.45)	30.80 (12.83-50.62)	0.244†	9.88 (5.78-35.56)	5.56 (2.24-13.84)	0.978†
	M1	2	109.90 (63.89-155.91)	47.14 (21.50-72.77)	0.691§	12.38 (5.99-18.77)	65.31 (15.05-115.56)	0.061§
Clinical staging	I and II	20	61.11 (42.02-77.81)	36.39 (30.55-58.04)	0.725†	8.94 (6.29-20.28)	5.56 (3.22-16.36)	0.861†
	III and IV	25	53.03 (28.71-98.24)	25.58 (14.16-46.61)	0.215§	11.52 (4.69-27.78)	7.61 (0.56-13.08)	0.413§
Treatment modality	Surgery	2	36.68 (30.85-42.51)	43.08 (30.80-55.35)		8.17 (7.08-9.26)	6.65 (5.44-7.85)	
	Radiotherapy	10	70.85 (42.02-135.77)	24.06 (6.42-34.06)	0.326† 0.378§	16.33 (5.99-49.23)	10.77 (0.00-20.70)	0.365† 0.866§
	Radiotherapy and Chemotherapy	33	55.74 (32.22-86.11)	31.85 (19.35-50.62)		9.88 (5.45-20.00)	5.56 (2.43-11.75)	

† Mann-Whitney test for P1

§ Mann-Whitney test for P2

¶ Wilcoxon test

Significant p values are highlighted in bold.

5% significance level

Table 4. Association of IgA and IgG Salivary Concentrations with the independent variables of the study (Phase 1 – P1, and Phase 2 – P2).

		n	**IgA** mg/ml **(P1)** Median (Q25-Q75)	**IgA** mg/ml **(P2)** Median (Q25-Q75)	p-value	**IgG** mg/ml **(P1)** Median (Q25-Q75)	**IgG** mg/ml **(P2)** Median (Q25-Q75)	p-value
Sex	Male	29	0.27 (-0.030.85)	0.50 (-0.08-1.57)	**0.046**†	10.80 (10.58-11.19)	10.91 (10.64-11.58)	0.240†
	Female	16	0.72 (0.52-9.90)	0.69 (0.30-8.12)	0.265§	11.33 (10.56-11.53)	11.17 (10.61-11.83)	0.585§
Age	Up to 40 years	5	0.68 (0.56-0.71)	0.56 (0.27-1.09)	0.903†	11.25 (10.14-11.58)	10.75 (10.47-11.47)	0.875†
	≥ 41 years	40	0.50 (0.09-5.39)	0.55 (0.03-4.18)	0.930§	11.00 (10.61-11.39)	11.06 (10.64-11.66)	0.586§
Harmful habits	Smoking	13	0.74 (0.12-9.55)	0.12 (-0.08-1.57)		10.64 (10.47-11.30)	10.80 (10.64-11.25)	
	Alcoholism	2	0.00 (-0.06-0.06)	1.22 (0.53-1.91)	0.422†	11.36 (10.75-11.96)	11.14 (10.25-12.02)	0.327†
	Smoking and alcoholism	16	0.53 (0.03-10.86)	0.71 (0.27-8.06)	0.628§	10.94 (10.45-11.17)	11.25 (10.72-11.72)	0.849§
	None	14	0.53 (0.27-0.76)	0.56 (-0.08-1.09)		11.31 (10.75-11.58)	11.03 (10.47-11.58)	
Anatomical site of the lesion	Intraoral region	20	0.53 (0.09-5.87)	0.74 (0.31-8.12)		11.28 (10.92-11.66)	11.33 (10.61-11.85)	
	Lip	1	1.23 (1.23-1.23)	0.03 (0.03-0.03)	0.682† 0.295§	11.08 (11.08-11.08)	10.80 (10.80-10.80)	**0.045**† 0.400§
	Others	24	0.58 (0.08-5.29)	0.43 (-0.08-1.74)		10.75 (10.48-11.17)	10.89 (10.59-11.47)	
Type of neoplasia	Epithelial	43	0.50 (0.09-1.23)	0.53 (0.03-1.91)	0.396†	11.03 (10.58-11.41)	11.03 (10.64-11.69)	0.989†
	Mesenchymal	2	5.78 (0.56-11.00)	4.31 (056-8.06)	0.455§	11.27 (9.47-13.07)	10.78 (10.09-11.47)	0.485§
Tumor size (T)	T1 or T2	26	0.41 (0.09-1.23)	0.40 (-0.08-1.12)	0.414† **0.047**§	11.06 (10.64-11.36)	10.83 (10.47-11.41)	0.954† 0.121§

	T3 or T4	19	0.65 (0.09-10.25)	1.44 (0.27-8.17)		10.75 (10.47-11.66)	11.25 (10.75-12.02)		
Cervical lymph node metastasis (N)	N0	28	0.55 (0.08-0.90)	0.47 (0.08-1.74)	0.355†	10.94 (10.59-11.31)	10.89 (10.50-11.50)	0.504†	
	N1-3	17	0.56 (0.27-10.25)	1.12 (0.03-8.06)	0.447§	11.08 (10.58-11.65)	11.25 (10.75-11.74)	0.146§	
Distant metastasis (M)	M0	43	0.50 (0.09-1.03)	0.53 (0.03-1.91)	0.145†	11.08 (10.64-11.47)	10.91 (10.53-11.58)	0.061†	
	M1	2	10.13 (9.55-10.71)	8.79 (1.12-16.40)	0.164§	10.05 (9.73-10.36)	14.01 (11.63-16.38)	0.073§	
Clinical staging	I and II	20	0.68 (0.12-1.23)	0.35 (-0.08-1.09)	0.806†	10.97 (10.75-11.25)	10.86 (10.47-11.36)	0.682†	
	III and IV	25	0.53 (0.09-5.29)	0.87 (0.20-4.99)	0.194§	11.06 (10.56-11.65)	11.14 (10.70-11.72)	0.292§	
Treatment modalities	Surgery	2	0.42 (0.12-0.71)	-0.11 (-0.14-(-0.08))		12.74 (11.25-14.23)	10.56 (10.47-10.64)		
	Radiotherapy	10	0.81 (0.47-10.37)	0.92 (0.35-9.24)	0.408†	10.69 (9.73-11.30)	10.86 (10.42-11.63)	0.169†	
	Combined therapy (radiotherapy and chemotherapy)	33	0.50 (0.06-1.03)	0.53 (0.12-1.57)	0.177§	11.03 (10.64-11.47)	11.14 (10.75-11.69)	0.283§	

† Mann-Whitney test for P1

§ Mann-Whitney test for P2

¶ Wilcoxon test

Statistically significant values are highlighted in bold.

5% significance level

Considerações Finais

5 CONSIDERAÇÕES FINAIS

Os resultados encontrados revelam que o CCP é uma condição clínica que acomete a QVRS do paciente, antes e durante o tratamento e que dentre os fatores clínicos de prognóstico estudados, a idade, tabagismo e alcoolismo e tamanho de tumores maiores, apresentaram maior impacto na QVRS. Pode-se inferir também, que o tratamento antineoplásico induz a redução dos níveis de AU e é capaz de alterar a mensuração da IgA e IgG salivar, induzindo assim, uma alteração da imunidade local.

Com base nisso, ressaltamos a importância do rastreamento do CCP, com o objetivo de prevenir e diagnosticá-lo de forma mais precoce possível. Destaca-se também a importância de uma equipe multiprofissional para acompanhar os pacientes em tratamento, com a inserção do cirurgião dentista, afim de que se possa reduzir e controlar os efeitos adversos na cavidade oral, colaborando assim com uma melhoria no prognóstico e na QVRS do paciente. A QVRS deve ser sempre considerada na prática clínica de cada profissional envolvido no cuidado integral do paciente, através do atendimento humanizado, buscando apreender suas necessidades em tempo oportuno e da melhor maneira possível.

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Apêndices

APÊNDICE A

UNIVERSIDADE ESTADUAL DA PARAÍBA
CENTRO DE CIÊNCIAS BIOLÓGICAS E DA SAÚDE
DEPARTAMENTO DE ODONTOLOGIA

FICHA CLÍNICA

IDENTIFICAÇÃO DO PACIENTE

1. Nome:_____
2. Idade: _____anos - DN (___/___/____) Sexo ( ) M ( ) F
3. Cor: ( ) Melanoderma ( ) Feoderma ( ) Leucoderma
4. Estado civil: ( ) Solteiro ( ) Casado ( ) Outro
5. Ocupação Profissional: _____
6. Naturalidade:_____Nacionalidade:_____
7. Endereço:_____ Telefone para contato:_____
8. Tipo de Neoplasia: Epitelial ( ) Mesenquimal ( )
9. Sítio Anatômico da Lesão: _____
10. Metástase: Sim ( ) Não ( )
11. Tipo de Tratamento: Cirurgia ( ) Radioterapia ( ) Quimioterapia ( )
12. Estadiamento Clínico - TNM: _____
13. Hábitos Nocivos:

    Sim ( ) Qual? ( ) tabagismo ( ) alcoolismo

    Há quanto tempo? _____

    Não ( )
14. Recebeu orientações de Saúde Bucal antes do tratamento? Sim ( ) Não ( )
15. Apresentou complicações bucais durante o tratamento? Sim ( ) Não ( )

APÊNDICE B

UEPB

FICHA PARA REGISTRO DA ANÁLISE SALIVAR

IDENTIFICAÇÃO DO PACIENTE:_____

TEMPO DE COLETA FSE (Pré-tratamento)**:**_____

TEMPO DE COLETA FSE (Intermediária)**:**_____

SIALOMETRIA

Período da avaliação	**Volume de saliva estimulada (ml)**	**Fluxo salivar estimulado (ml/min)**
Pré-tratamento **(F1):**		
Intermediária: **(F2)**		

SIALOQUÍMICA

Data da avaliação	**Ácido Úrico(AU)** µg/ml	**Proteínas Totais(PT)** mg/ml	**IgA** mg/ml	**IgG** mg/ml
Pré-tratamento: **(F1)**				
Intermediária: **(F2)**				

APÊNDICE C

UNIVERSIDADE ESTADUAL DA PARAÍBA
CENTRO DE CIÊNCIAS BIOLÓGICAS E DA SAÚDE
DEPARTAMENTO DE ODONTOLOGIA

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Você está sendo convidado para participar da pesquisa **"Impacto de fatores de prognóstico e biomarcadores salivares na qualidade de vida de pacientes com neoplasia maligna de cabeça e pescoço: um estudo prospectivo".**

No entanto, sua participação não é obrigatória. A qualquer momento você pode desistir de participar e retirar seu consentimento. Sua recusa não trará nenhum prejuízo em sua relação com o pesquisador ou com a instituição em questão. O objetivo principal deste estudo é saber como o paciente se sente durante a realização do seu tratamento, bem como conhecer os problemas que o tratamento pode causar no seu estado psicológico e conhecer as alterações da saliva que ocorrem no paciente com neoplasia maligna de cabeça e pescoço.
Não haverá nenhum risco previsível que possa prejudicá-lo(a), quando da sua participação nesta pesquisa. A sua participação contribuirá com a comunidade científica quanto ao grau de conhecimento sobre o câncer bucal, induzindo, assim, a uma posterior implantação de programas de prevenção a esta doença. As informações obtidas através dessa pesquisa serão confidenciais e asseguramos o sigilo sobre sua participação. Os dados não serão divulgados de forma a possibilitar sua identificação. Você receberá uma cópia deste termo onde consta o telefone e o endereço institucional do pesquisador principal, podendo tirar suas dúvidas sobre o projeto e sua participação, agora ou a qualquer momento.

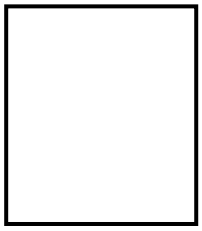
Pesquisadora responsável: Maria Betânia Lins Dantas Siqueira
Telefone para contato: (83) 91990576

Orientadora Responsável: Pollianna Muniz Alves
Telefone para contato: (83) 33153471

Endereço: Universidade Estadual da Paraíba – UEPB
Departamento de Odontologia , Campina Grande-PB
Declaro que entendi os objetivos, riscos e benefícios de minha participação na pesquisa e concordo em participar da pesquisa.

Campina Grande,___ de _____

_____
Nome por extenso



Anexos

ANEXO A

Questionário UW-QOL

Questionário de qualidade de vida da Universidade de Washington

Este questionário pergunta sobre sua saúde e qualidade de vida **durante os últimos sete dias**. Por favor, responda a todas as questões marcando uma alternativa para cada questão.

1. Dor (marque uma alternativa [ ])

100 [ ] Eu não tenho dor

75 [ ] Há dor leve não necessitando de medicação

50 [ ] Eu tenho dor moderada, requerendo uso de medicação regularmente

25 [ ] Eu tenho dor severa controlada somente com medicamentos controlados

0 [ ] Eu tenho dor severa, não controlada por medicação

2. Aparência (marque uma alternativa [ ])

100 [ ] Não há mudança na minha aparência

75 [ ] A mudança na minha aparência é mínima

50 [ ] Minha aparência me incomoda, mas eu permaneço ativo

25 [ ] Eu me sinto desfigurado significativamente e limito minhas atividades devido a minha aparência

0 [ ] Eu não posso estar com outras pessoas devido a minha aparência

3. Atividade (marque uma alternativa [ ])

100 [ ] Eu estou tão ativo quanto sempre estive

75 [ ] Existem vezes em que não posso manter meu ritmo antigo, mas não frequentemente

50 [ ] Eu estou frequentemente cansado e tenho diminuído minhas atividades embora eu ainda saia de casa

25 [ ] Eu não saio de casa porque eu não tenho força

0 [ ] Eu geralmente fico na cama ou na cadeira e não saio de casa

4. Recreação (marque uma alternativa [ ])

100 [ ] Não há limitações para recreação em casa ou fora de casa

75 [ ] Há poucas coisas que eu não posso fazer, mas eu ainda saio de casa para me divertir

50 [ ] Há muitas vezes que eu gostaria de sair mais de casa, mas eu não estou bem para isso

25 [ ] Há limitação severa para o que eu posso fazer, geralmente eu fico em casa e assisto TV

0 [ ] Eu não posso fazer nada agradável

5. Deglutição (marque uma alternativa [ ])

100 [ ] Eu posso engolir tão bem como sempre

67 [ ] Eu não posso engolir algumas comidas sólidas

33 [ ] Eu posso engolir somente comidas líquidas

0 [ ] Eu não posso engolir porque desce errado e me sufoca

6. Mastigação (marque uma alternativa [ ])

100 [ ] Eu posso mastigar tão bem como sempre

50 [ ] Eu posso comer alimentos sólidos leves mas não consigo mastigar algumas comidas

0 [ ] Eu não posso mastigar nem mesmo alimentos leves

7. Fala (marque uma alternativa [ ])

100 [ ] Minha fala é a mesma de sempre

67 [ ] Eu tenho dificuldade para dizer algumas palavras mas eu posso ser entendido mesmo ao telefone

33 [ ] Somente minha família e amigos podem me entender

0 [ ] Eu não sou entendido pelos outros

8. Ombro (marque uma alternativa [ ])

100 [ ] Eu não tenho problemas com meu ombro

67 [ ] Meu ombro é endurecido mas isto não afeta minha atividade ou força

33 [ ] Dor ou fraqueza em meu ombro me fizeram mudar meu trabalho

0 [ ] Eu não posso trabalhar devido problemas com meu ombro

9. Paladar (marque uma alternativa [ ])

100 [ ] Eu sinto sabor da comida normalmente

67 [ ] Eu sinto o sabor da maioria das comidas normalmente

33 [ ] Eu posso sentir o sabor de algumas comidas

0 [ ] Eu não sinto o sabor de nenhuma comida

10. Saliva (marque uma alternativa [ ])

100 [ ] Minha saliva é de consistência normal

67 [ ] Eu tenho menos saliva que o normal, mas ainda é o suficiente

33 [ ] Eu tenho muito pouca saliva

0 [ ] Eu não tenho saliva

11. Humor (marque uma alternativa [ ])

100 [ ] Meu humor é excelente e não foi afetado por causa do meucâncer

75 [ ] Meu humor é geralmente bom e é somente afetado por causa do meu câncer ocasionalmente

50 [ ] Eu não estou nem com bom humor nem deprimido por causa do meu câncer

25 [ ] Eu estou um pouco deprimido por causa do meu câncer

0 [ ] Eu estou extremamente deprimido por causa do meu câncer

12. Ansiedade (marque uma alternativa [ ])

100 [ ] Eu não estou ansioso por causa do meu câncer

67 [ ] Eu estou um pouco ansioso por causa do meu câncer

33 [ ] Eu estou ansioso por causa do meu câncer

0 [ ] Eu estou muito ansioso por causa do meu câncer

Quais problemas tem sido os mais importantes para você durante os últimos 7 dias? Marque [ ] em até 3 alternativas

[ ] Dor [ ]Deglutição [ ] Paladar [ ] Aparência [ ] Mastigação [ ] Saliva [ ] Atividade

[ ]Fala [ ] Humor [ ] Recreação [ ] Ombro [ ] Ansiedade

Questões gerais

Comparado com o mês antes de você desenvolver o câncer, como você classificaria sua qualidade de vida relacionada à saúde (marque uma alternativa: [ ])

[ ] Muito melhor

[ ] Um pouco melhor

[ ] Mais ou menos o mesmo

[ ] Um pouco pior

[ ] Muito pior

Em geral, você poderia dizer que sua qualidade de vida relacionada à saúde nos últimos 7 dias tem sido: (marque uma alternativa [ ])

[ ] Excelente

[ ] Muito boa

[ ] Boa

[ ] Média

[ ] Ruim

[ ] Muito ruim

De um modo geral a qualidade de vida inclui não somente saúde física e mental, mas também muitos outros fatores, tais como família, amigos, espiritualidade, atividades de lazer pessoal que são importantes para sua satisfação com a vida. Considerando tudo em sua vida que contribui para seu bem-estar pessoal, classifique a sua qualidade de

vida em geral durante os últimos 7 dias. (Marque uma alternativa: [ ])

[ ] Excelente

[ ] Muito boa

[ ] Boa

[ ] Média

[ ] Ruim

[ ] Muito ruim

Por favor, descreva quaisquer outros problemas (médicos ou não médicos) que são importantes para sua qualidade de vida e que não tenham sido adequadamente mencionados pelas nossas perguntas (você pode anexar folhas adicionais, se necessário).

ANEXO B

Parecer do Comitê de Ética em Pesquisa

MINISTÉRIO DA SAÚDE - Conselho Nacional de Saúde - Comissão Nacional de Ética em Pesquisa – CONEP

PROJETO DE PESQUISA ENVOLVENDO SERES HUMANOS

UNIVERSIDADE ESTADUAL DA PARAÍBA
PRÓ-REITORIA DE PÓS-GRADUAÇÃO E PESQUISA
COMITÊ DE ÉTICA EM PESQUISA

Título da Pesquisa: Impacto de fatores clínicos de prognóstico e biomarcadores salivares na qualidade de vida de pacientes com neoplasia maligna de cabeça e pescoço: um estudo prospectivo.
Pesquisador: Maria Betânia Lins Dantas Siqueira
CAAE: 51209515.6.0000.5187
Data da 1ª relatoria: 25/11/2015

Apresentação do Projeto: Trata-se de projeto de pesquisa destinado a elaboração e desenvolvimento da tese de Conclusão do Curso de Doutorado, da Pós-Graduação em Odontologia, da Universidade Estadual da Paraíba, da Doutoranda Maria Betânia Lins Dantas Siqueira, sob a orientação da Professora Dra. Polliana Muniz Alves. Será realizado um estudo de abordagem indutiva, com desenho longitudinal (prospectivo), procedimento comparativo-estatístico e com utilização de técnicas de observação direta extensiva e documentação direta em laboratório (Lakatos; Marconi, 2007).Para este estudo clínico, prospectivo e exploratório, os períodos relacionados ao tratamento antineoplásico (prévio; inicial; intermediário e pós-tratatamento) serão considerados como fatorde estudo (variáveis dependentes). As variáveis resposta (variáveis independentes) consistirão na qualidade de vida, determinada segundo o questionário da qualidade de vida da universidade de Washington (UW-QoL); na mensuração dos biomarcadores salivares (amilase, ácido úrico,imunoglobulinas e PCR); bem como na quantificação das espécies microbianas (Candida sp., Streptococcus sp; Staphylococcus sp) presentes no biofilme oral.

Objetivo da Pesquisa: Avaliar a qualidade de vida, a mensuração de biomarcadores salivares (antioxidantes, enzimas e imunoglobulinas) e a composição do biofilme oral em pacientes diagnosticados com neoplasias de cabeça e pescoço, nas diferentes etapas do tratamento antineoplásico.
Avaliação dos Riscos e Benefícios: Segundo a pesquisadora "Não existe nenhum tipo de risco previsível durante o exame clínico, anamnese, preenchimento do questionário e coleta da saliva. Desse modo, sua participação neste estudo não oferece nenhum tipo de risco para a sua saúde. Além do mais, o tratamento odontológico que você irá receber é semelhante ao que você estaria recebendo se não fizesse parte desta pesquisa. Os pesquisadores responsáveis se comprometem a resguardar todas as informações da pesquisa, não revelando a identidade do voluntário que as originou. Enquanto benefícios: Receber além do diagnóstico de alguma necessidade de tratamento odontológico, antes e durante o tratamento oncológico nos hospitais,a assistência odontológica fornecida pela equipe de odontologia do hospital, em articulação com o pesquisador responsável por esta pesquisa.

Comentários e Considerações sobre a Pesquisa: A pesquisa tem relevância.

Considerações sobre os Termos de apresentação obrigatória: Os termos necessários e obrigatórios encontram-se presentes.

Recomendações: Sem recomendações.

Conclusões ou Pendências e Lista de Inadequações: Sem pendências.

ANEXO C

Cartas de Anuência da Fundação Assistencial da Paraíba (FAP)

Fundação Assistencial da Paraíba - FAP

C.G.C.: 08.841.421/0001-57 Inscrição Estadual: Isento
Av. Dr. Francisco Pinto, s/n - Bodocongó - Cx. Postal 405
CEP 58.429-350 - Campina Grande - PB
Telefone/fax: (83) 2102-0300 – E-mail: fapcg@uol.com.br

DECLARAÇÃO

Declaramos para os devidos fins e a quem interessar que estamos cientes da intenção da realização da Pesquisa intitulada: "IMPACTO DE FATORES CLÍNICOS DE PROGNÓSTICO E BIOMARCADORES SALIVARES NA QUALIDADE DE VIDA DE PACIENTES COM NEOPLASIA MALIGNA DE CABEÇA E PESCOÇO: UM ESTUDO PROSPECTIVO". Sob orientação da Profª Dra. Pollianna Muniz Alves, desenvolvida pela orientanda Maria Betânia Lins Dantas Siqueira, ambas da Universidade Estadual da Paraíba - UEPB – a orientadora será responsável pela orientanda, caso contrário a primeira não poderá desenvolver e/ou orientar projetos na Instituição FAP. Após aprovação do Comitê de Ética. Toda documentação relativa a esta Pesquisa deverá ser entregue em uma via (CD) ao Núcleo de Estudo, Pesquisa e Extensão (NEPE) da FAP e arquivado por cinco anos de acordo com a Res 466/2012 do Ministério da Saúde.

Campina Grande, 04 de agosto de 2015.

PROFª RAILDA SHELSEA TAVEIRA R. NASCIMENTO
Coordenadora do NEPE/FAP

Profª Railda Shelsea T. R. Nascimento
Coordenadora do Núcleo de Estudo, Pesquisa e Extensão
NEPE/FAP

Anexo D

Cartas de Anuência do Hospital Napoleão Laureano,

Hospital Napoleão Laureano

Centro de Estudos Mário Kröeff

AUTORIZAÇÃO INSTITUCIONAL/CARTA DE ANUÊNCIA

Avaliamos o Projeto de Pesquisa "**IMPACTO DE FATORES CLÍNICOS DE PROGNÓSTICO E BIOMARCADORES SALIVARES NA QUALIDADE DE VIDA DE PACIENTES COM NEOPLASIA MALIGNA DE CABEÇA E PESCOÇO: UM ESTUDO PROSPECTIVO**", e, em nossa avaliação, o Hospital Napoleão Laureano poderá participar como instituição colaboradora do referido projeto. Ressaltamos ainda, que é da responsabilidade do pesquisador todo e qualquer procedimento metodológico, bem como o cumprimento da **Resolução 466/12**, sendo necessário após a conclusão da pesquisa o encaminhamento de urna cópia para a instituição.

João Pessoa, 09 de julho de 2015.

Dr. Igor Lemos Duarte
Pres. do CEMAK
Pres. da Comissão de Ética Médica do HNL

Autorizo

21.07.15

Hospital Napoleão Laureano
Dr. Paulo Vitório Serpa Filho
Diretor Geral

Anexo E

Normas de publicação do periódico Brazilian Oral Research – BOR

Brazilian Oral Research

ISSN 1807-3107 *online version*

INSTRUCTIONS TO AUTHORS

Mission, scope, and submission policy

Brazilian Oral Research - BOR (online version ISSN 1807-3107) is the official publication of the *Sociedade Brasileira de Pesquisa Odontológica* - SBPqO (the Brazilian division of the International Association for Dental Research - IADR). The journal has an Impact Factor™ of 0.937 (Institute for Scientific Information - ISI), is peer-reviewed (double-blind system), and its mission is to disseminate and promote an information interchange concerning the several fields in dentistry research and/or related areas with gold open access.

BOR invites the submission of original and review manuscripts and papers in the following typology: Original Research (complete manuscript or Short Communication), Critical Review of Literature, Systematic Review (and Meta-Analysis) and Letters to the Editor. All submissions must be exclusive to.

Manuscripts and all corresponding documentation should be exclusively submitted through ScholarOne Manuscripts™ via the online submission link (http://mc04.manuscriptcentral.com/bor-scielo).

The evaluation process of manuscript's scientific content will only be initiated after meeting of all the requirements described in the present Instructions for Authors. Any manuscript that does not meet these requirements will be returned to the corresponding author for adaptations.

Important: Once having been accepted on their scientific merit, all manuscripts will be submitted for grammar and style revision as per the English language. Contact BOR by bor@sbpqo.org.br to get information about the recommended translation companies.The authors should forward the revised text with the enclosed revision certificate provided by the chosen editing company. **Linguistic revisions performed by companies that do not provide the mentioned certificate will not be accepted.** As an exception, this rule does not apply when one of the authors is a native English speaker.

Presentation of the manuscript

The manuscript text should be written in English and provided in a digital file compatible with "Microsoft Word" (in DOC, DOCX, or RTF format).

All figures (including those in layouts/combinations) must be provided in individual and separate files, according to recommendations described under the specific topic.
Photographs, micrographs, and radiographs should be provided in TIFF format, according to the recommendations described under the specific topic.

Charts, drawings, layouts, and other vector illustrations must be provided in a PDF format individually in separate files, according to the recommendations described under the specific topic.

Video files may be submitted as per the specifications, including the author's anonymity (for purposes of evaluation) and respect for the patient's rights.

Important: ScholarOne™ allows upload of a set of files up to 10 MB. In case the video file exceeds this size, it is possible to leave information about the link to access the video. The use of patients' initials, names, and/or registry numbers is prohibited in the reproduction of clinical documentation. The identification of patients is prohibited. An informed consent statement, signed by the patient, concerning the use of his/her image should be provided by the author(s) when requested by **BOR**. The Copyright legislation in force must be respected and the source cited when the manuscript reproduces any previously published material (including texts, charts, tables, figures, or any other materials).

Title page (compulsory data)

- This must indicate the specialty* or research field focused on in the manuscript.

*Anatomy; Basic Implantodontology and Biomaterials; Behavioral Sciences; Biochemistry; Cariology; Community Dental Health; Craniofacial Biology; Dental Materials; Dentistry; Endodontic Therapy; Forensic Dentistry; Geriatric Dentistry; Imaginology; Immunology; Implantodontology – Prosthetics; Implantodontology – Surgical; Infection Control; Microbiology; Mouth and Jaw Surgery; Occlusion; Oral Pathology; Orthodontics; Orthopedics; Pediatric Dentistry; Periodontics; Pharmacology; Physiology; Prosthesis; Pulp Biology; Social/Community Dentistry; Stomatology; Temporomandibular Joint Dysfunction.

- Informative and concise title, limited to a maximum of 110 characters, including spaces.
- Names of all authors written out in full, including respective telephone numbers and email addresses for correspondence. We recommend that authors collate the names present in the Cover Letter with the profile created in ScholarOne™, to avoid discrepancies.
- The participation of each author must be justified on a separate page, which should meet the authorship and co-authorship criteria adopted by the International Committee of Medical Journal Editors, available at http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html
- Data of institutional/professional affiliation of all authors, including university (or other institution), college/program, department, city, state, and country, presented according to internal citation norms established by each author's institution. Verify that such affiliations are correctly entered in ScholarOne™.

Abstract: This should be presented as a single structured paragraph (but with no subdivisions into sections) containing the objective of the work, methodology, results, and conclusions. In the System if applicable, use the Special characters tool for special characters.

Keywords: Ranging from 3 (three) to 5 (five) main descriptors should be provided, chosen from the keywords registered at http://decs.bvs.br/ or http://www.nlm.nih.gov/mesh/MBrowser.html (no synonyms will be accepted).

Main Text

Introduction: This should present the relevance of the study, and its connection with other published works in the same line of research or field, identifying its limitations and possible biases. The objective of the study should be concisely presented at the end of this section.

Methodology: All the features of the material pertinent to the research subject should be provided (*e.g.*, tissue samples or research subjects). The experimental, analytical, and statistical methods should be described in a concise manner, although in detail, sufficient to allow others to recreate the work. Data from manufacturers or suppliers of products, equipment, or software must be explicit when first mentioned in this section, as follows: manufacturer's name, city, and country. The computer programs and statistical methods must also be specified. Unless the objective of the work is to compare products or specific systems, the trade names of techniques, as well as products, or scientific and clinical equipment should only be cited in the "Methodology" and "Acknowledgments" sections, according to each case. Generic names should be used in the remainder of the manuscript, including the title. Manuscripts containing radiographs, microradiographs, or SEM images, the following information must be included: radiation source, filters, and kV levels used. Manuscripts reporting studies on humans should include proof that the research was ethically conducted according to the Helsinki Declaration (*World Medical Association,* http://www.wma.net/en/30publications/10policies/b3/). The approval protocol number issued by an Institutional Ethics Committee must be cited. Observational studies should follow the STROBE guidelines (http://strobe-statement.org/), and the check list must be submitted. Clinical Trials must be reported according to the CONSORT Statement standard protocol (http://www.consort-statement.org/); systematic reviews and meta-analysis must follow the PRISMA (http://www.prisma-statement.org/), or Cochrane protocol (http://www.cochrane.org/).

Clinical Trials

Clinical Trials according to the CONSORT guidelines, available at www.consort-statement.org. The clinical trial registration number and the research registration name will be published along with the article.

Manuscripts reporting studies performed on animals must also include proof that the research was conducted in an ethical manner, and the approval protocol number issued by an Institutional Ethics Committee should be cited. In case the research contains a gene registration, before submission, the new gene sequences must be included in a public database, and the access number should be provided to BOR. The authors may use the following databases:

- GenBank: http://www.ncbi.nlm.nih.gov/Genbank/submit
- EMBL: http://www.ebi.ac.uk/embl/Submission/index.html
- DDBJ: http://www.ddbj.nig.ac.jp

Manuscript submissions including microarray data must include the information recommended by the MIAME guidelines (Minimum Information About a Microarray Experiment: http://www.mged.org/index.html) and/or itemize how the experimental details were submitted to a publicly available database, such as:

- ArrayExpress: http://www.ebi.ac.uk/arrayexpress/
- GEO: http://www.ncbi.nlm.nih.gov/geo/

Results: These should be presented in the same order as the experiment was performed, as described under the "Methodology" section. The most significant results should be described. Text, tables,

and figures should not be repetitive. Statistically relevant results should be presented with enclosed corresponding p values.

Tables: These must be numbered and cited consecutively in the main text, in Arabic numerals. Tables must be submitted separately from the text in DOC, DOCX, or RTF format.

Discussion: This must discuss the study results in relation to the work hypothesis and relevant literature. It should describe the similarities and differences of the study in relation to similar studies found in literature, and provide explanations for the possible differences found. It must also identify the study's limitations and make suggestions for future research.

Conclusions: These must be presented in a concise manner and be strictly based on the results obtained in the research. Detailing of results, including numerical values, etc., must not be repeated.

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- Methodology
- Results
- Discussion
- Conclusion
- Acknowledgments
- Tables
- References: maximum of 40 references
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- Conclusion
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- Results
- Discussion
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EXAMPLES OF REFERENCES

Journals

Goracci C, Tavares AU, Fabianelli A, Monticelli F, Raffaelli O, Cardoso PC, et al. The adhesion between fiber posts and root canal walls: comparison between microtensile and push-out bond strength measurements. Eur J Oral Sci. 2004 Aug;112(4):353-61.

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Websites
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Instituto Brasileiro de Geografia e Estatística [homepage]. Brasília (DF): Instituto Brasileiro de Geografia e Estatística; 2010 [cited 2010 Nov 27]. Available from: http://www.ibge.gov.br/home/default.php.

World Health Organization [homepage]. Geneva: World Health Organization; 2011 [cited 2011 Jan 17]. Available from: http://www.who.int/en/

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Anexo F

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A Journal Related to Head & Neck Oncology

AUTHOR INFORMATION PACK

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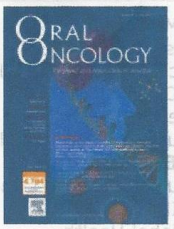

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DESCRIPTION

Oral Oncology is an international interdisciplinary journal which publishes high quality original research, clinical trials and review articles, editorials, and commentaries relating to the etiopathogenesis, epidemiology, prevention, clinical features, diagnosis, treatment and management of patients with **neoplasms** in the **head** and **neck**.

Oral Oncology is of interest to head and neck surgeons, radiation and medical oncologists, maxillo-facial surgeons, oto-rhino-laryngologists, plastic surgeons, pathologists, scientists, oral medical specialists, special care dentists, dental care professionals, general dental practitioners, public health physicians, palliative care physicians, nurses, radiologists, radiographers, dieticians, occupational therapists, speech and language therapists, nutritionists, clinical and health psychologists and counselors, professionals in end of life care, as well as others interested in these fields.

Basic, translational, or clinical Research or Review papers of high quality and that make a contribution to new knowledge are invited on the following aspects of neoplasms arising in the head and neck (including lip, tongue, oral cavity, oropharynx, salivary glands, sinuses, nose, nasopharynx, larynx, skull base, thyroid, and craniofacial region, and the related hard and soft tissues and lymph nodes):

- **Etiopathogenesis**: natural history of cancer and pre-cancer; basic pathology, metastatic mechanisms; genetic changes; cellular and molecular changes; microorganisms; growth factors, adhesion and other molecules
- **Epidemiology**; risk factors; biomarkers; protective factors; geographic factors; prevention; screening and intervention
- Clinical features; **orofacial** effects of neoplasms at both local and distant sites; tumor staging and grading
- Diagnosis; **detection** of **cancer** and pre-cancer; cellular and molecular markers for diagnosis; advances in **imaging** and other functional diagnostic modalities for cancer and pre-cancer
- **Management** and **Prognosis**; clinical, cellular and molecular markers for prognosis; **treatment** options including surgical, lasers, photodynamic therapy, cryosurgery, micro- vascular and other forms of surgery, medical, radiotherapy, chemotherapy, immunotherapy, biological and gene therapy advances; molecular targets and new therapeutics (new cytotonics and molecular-targeted therapies); multimodality treatment; advances in reconstruction and rehabilitation, including flaps and grafts, alloplasty, bone and connective tissue biology; multidisciplinary teamwork in cancer care and **oral health care**.
- Quality of life issues; issues of consent; psychosocial aspects; patient and health professional information; patient involvement; psychological interventions, improving outcomes; the prevention,

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INTRODUCTION

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