JULIANA CRISTINA FRARE

ANÁLISE DAS CARACTERÍSTICAS CLINICOPATOLÓGICAS DE CARCINOMAS ESPINOCELULARES ORAIS EM PACIENTES JOVENS PROVENIENTES DE CASCAVEL - PARANÁ

ANALYSIS OF CLINICOPATHOLOGICAL FEATURES OF ORAL SQUAMOUS CELL CARCINOMA IN YOUNG PATIENTS FROM CASCAVEL - PARANÁ.

Piracicaba

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Universidade Estadual De Campinas

Faculdade De Odontologia De Piracicaba

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Tese apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para obtenção do Título de Doutora em Estomatopatologia, na área de Patologia.

Thesis presented to the Piracicaba School of Dentistry of the University of Campinas in partial fulfillment of the requirements for the degree of Doctor in Estomatopathology, in the Patology area.

Orientador: Prof. Dr. Marcio Ajudarte Lopes
Coorientadora: Prof[a]. Dr[a]. Ana Lúcia Carrinho Ayrosa Rangel

Este exemplar corresponde à versão final da tese defendida pela aluna Juliana Cristina Frare orientada pelo Professor Dr. Marcio Ajudarte Lopes.

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RESUMO

O carcinoma espinocelular (CEC) é considerado uma doença relativamente incomum em pacientes com idade inferior a 40 anos e existem especulações que este tumor apresenta um comportamento biológico mais agressivo neste grupo. Sendo assim, o objetivo deste estudo foi analisar o perfil clinicopatológico de pacientes jovens (≤ 40 anos) com CEC oral e correlacioná-lo com o de um grupo controle (≥ 50 anos) através de quatro sistemas de gradação histopatológica – (1) Sistema da Organização Mundial de Saúde – Sistema OMS, (2) Sistema de Gradação de Malignidade de Margens Invasivas Profundas – Sistema MG, (3) Modelo de Risco Histológico – Sistema HR e (4) Escore de risco BD. Foram selecionados 14 pacientes jovens e 14 pacientes controle com similar estadiamento clínico e localização do tumor. Dados demográficos e clínicos foram obtidos de prontuários de pacientes e os cortes histológicos das peças cirúrgicas emblocadas em parafina foram avaliados de acordo com os quatro sistemas de gradação. As associações entre as categorias foram realizadas através do teste de Qui-quadrado ou teste Exato de Fischer. As análises de sobrevida foram realizadas de acordo com o método de Kaplan-Meier. A comparação entre os grupos mostrou maior associação de modalidades de tratamento em pacientes jovens (p=0.022) e que estes apresentaram maior taxa de recidiva local e metástase regional (p=0.018 / OR= 3.998). Pacientes jovens tiveram menor sobrevida livre de doença em 5 anos (p=0.069). Não houve diferença na sobrevida global em 5 anos entre grupos estudados (p=0.376). Não houve diferença na gradação histológica entre os grupos estudados de acordo com os quatro sistemas utilizados (OMS, MG, HR e BD). Nos sistemas HR e BD mais tumores foram classificados como de alto risco prognóstico que nos sistemas OMS e MG. Este estudo mostrou que, apesar de o grau de diferenciação histológica dos tumores ter sido semelhante entre os grupos e terem sido utilizadas mais modalidades terapêuticas (cirurgia, radioterapia e quimioterapia adjuvantes) no grupo jovem, maior incidência de recidivas e metástases foi

observado em pacientes jovens, mostrando uma tendência de um comportamento mais agressivo.

Palavras chaves: Carcinoma espinocelular. Pacientes jovens. Gradação de tumores.

ABSTRACT

Squamous cell carcinoma (SCC) is considered a relatively uncommon disease in patients younger than 40 years old and there are speculations that this tumor has a more aggressive biological behavior in this group. Thus, the aim of this study was to analyze the clinicopathologic profile of young patients (≤ 40 years) with oral squamous cell carcinoma and correlate with a control group (≥ 50 years) by means of four histopathological grading systems - (1) World Health Organization System - WHO System (2) Deep Invasive Margins Malignancy Grading System - MG System, (3) Histologic Risk Model - HR System, and (4) BD Risk Score. Fourteen young patients and 14 control patients with similar clinical stage and tumor location were selected. Demographic and clinical data were obtained from patient´s records and histological sections of the paraffin-embedded blocks of surgical specimens were evaluated according to four histopathological grading systems. Associations between categories were performed through Chi-square test and Exact Fisher test. The survival analyzes were performed according to Kaplan-Meier method. The comparison between groups showed that a greater association of treatment modalities in younger patients ($p = 0.022$) and these had a higher incidence of local recurrence and regional metastasis ($p = 0.018$ / OR=3.998). Younger patients had lower disease-free survival in 5 years ($p = 0.069$). There was no difference in overall 5-year survival between the studied groups ($p=0.376$). There was no difference in histological grading between groups according to the four used systems (WHO, MG, HR and BD). In HR and BD systems, more tumors were classified as high risk prognosis than in WHO and MG systems. This study showed that, despite tumors histologic grade was similar between groups and more therapeutic modalities (surgery, adjuvant radiotherapy and chemotherapy) were used in the young group, higher incidence of recurrence and metastasis were observed in young patients, showing a tendency to a more aggressive behavior.

Key words: Squamous cell carcinoma. Young patients. Tumors grading.

SUMÁRIO

DEDICATÓRIA

A Deus, que está acima de tudo.

À minha família, o bem mais precioso que tenho, sempre presente, incentivando e inspirando, mostrando que perseverança e sucesso andam juntos.

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LISTA DE ABREVIATURAS E SIGLAS

B	Buddings (Ninhos de células tumorais)
CEC	Carcinoma espinocelular
CEONC	Centro de Oncologia de Cascavel
CT	Chemotherapy
D	Deep of invasion (Profundidade de invasão tumoral)
DFS	Disease free survival
H	High risk
HE	Hematoxylin and Eosin (Hematoxilina e Eosina)
HR	Histological Risk (Risco Histológico)
INCA	Instituto Nacional do Câncer José de Alencar Gomes da Silva
L/I	Low/Intermediate risk
M	Metástase à distância (presença ou ausência)
MG	Deep Invasive Margins Malignancy (Gradação de Malignidade de Margens Invasivas Profundas)

N	Linfonodos regionais (Presença ou ausência e extensão de metástases)
OMS	Organização Mundial da Saúde
OR	Odds ratio
OS	Overall survival
P	Poorly differentiated
RT	Radiotherapy
SCC	Squamous cell carcinoma
T	Tumor primário (tamanho)
UOPECCAN	Hospital do Câncer Oeste Paranaense de Estudos e Combate ao Câncer
W/M	Well/Moderatelly differentiated
WHO	World Health Organization

INTRODUÇÃO

Estimativas mundiais sobre a incidência de câncer apresentadas pelo projeto GLOBOCAN 2012 da Agência Internacional para Pesquisa em Câncer, mostraram que no ano de 2012 ocorreram cerca de 14,1 milhões de novos casos de câncer e 8,2 milhões de mortes em todo o mundo (Ferlay, 2013). No Brasil, segundo a Estimativa de Incidência de Câncer do Instituto Nacional do Câncer José Alencar Gomes da Silva (INCA), esperam-se para o ano de 2014 aproximadamente 395 mil novos casos, excluindo os casos de câncer de pele não melanoma (Brasil, 2014).

O câncer de cavidade oral corresponde a cerca de 10% dos tumores malignos que ocorrem no corpo humano, sendo considerado um problema de saúde pública globalmente (Oliveira et al., 2006). No ano de 2012 foram estimados cerca de 300 mil novos casos deste tipo de câncer em todo o mundo, dos quais aproximadamente 80% ocorreram em países em desenvolvimento, sendo as maiores taxas observadas em populações asiáticas. No Brasil, encontra-se entre os 10 tipos mais incidentes de câncer, sendo estimados 11.280 novos casos em homens e 4.010 em mulheres para o ano de 2014. Excluindo os cânceres de pele não melanoma, este é o quarto mais frequente em homens nas regiões Sudeste e Nordeste e o sexto na região Sul. Para as mulheres é o nono mais frequente nas regiões Sudeste e Nordeste e o décimo quinto na região Sul (Brasil, 2014).

O carcinoma espinocelular (CEC), também chamado de carcinoma epidermóide ou de células escamosas é originário do epitélio pavimentoso estratificado e representa de 90 a 95% de todas as neoplasias malignas de cavidade oral (Beena et al., 2011; França et al., 2012; Monsjou et al., 2013) o que, segundo Rapoport (1997), é facilmente explicado quando se conhecem as causas desses tumores e se verifica que este epitélio é a estrutura mais exposta à ação dos agentes causadores.

Clinicamente o CEC oral pode apresentar-se como lesões brancas (leucoplasia) ou vermelhas (eritroplasia) em fases iniciais e proliferativas e/ou ulceradas em fases mais tardias e tem como localizações mais comuns a língua e o assoalho da boca. Em geral assintomático ou com mínimos achados clínicos nos estágios iniciais, podendo evoluir para dor local, dor referida auricular, halitose, disfonia, trismo, disfagia, sangramento, perda de peso e linfoadenopatia cervical nos estágios avançados (Johnson et al., 2005). A progressão e o prognóstico dos CECs orais são variáveis (Neville e Day, 2002; Venturi et al., 2004; Oliveira et al., 2006; Bello et al., 2010).

O CEC oral apresenta etiologia complexa e multifatorial e tanto fatores extrínsecos (tabaco, álcool, radiação, vírus oncogênicos, má higiene bucal) quanto intrínsecos (condição sistêmica) podem estar envolvidos (Neville e Day, 2002; Neville et al., 2004; Warnakulasuriya et al., 2005; Muwonge, 2008; Bachar et al., 2011; Johnson et al., 2011; Almeida et al., 2011).

Entre todos os fatores que contribuem para a etiologia do CEC oral, o tabaco, em todas as suas formas de consumo, é o mais importante. O contato crônico da mucosa com substâncias carcinogênicas liberadas durante a combustão do tabaco ou dissolvidas na saliva dos pacientes que mascam fumo, após um período de latência de vinte a trinta anos, faz com que as mutações induzidas nas células expostas comecem a se manifestar. A relação entre o tempo e a dose dos carcinógenos encontrados no tabaco é de extrema importância na etiologia do CEC (Johnson et al., 2005, Regezi et al., 2008).

O consumo de álcool também tem sido considerado um importante fator de risco para o CEC oral. Os efeitos do consumo de álcool ocorrem devido a uma sobreposição de fatores locais e sistêmicos e o dano por ele gerado na mucosa oral pode ser resultado de vários mecanismos. Pode-se considerar: a) a ação direta do álcool na mucosa oral com o aumento de sua permeabilidade e potencialização da penetração de outros carcinógenos; b) o álcool pode ser responsável por um aumento na proliferação epitelial, bem como pela modificação do seu processo de maturação, favorecendo a ocorrência de mutações e danos cumulativos e a redução

da capacidade de reparo do DNA frente aos mesmos; c) os distúrbios do sistema imune e do estado nutricional causados por seu consumo excessivo; e) o chamado estresse oxidativo resultante do aumento da produção de radicais livres e redução dos mecanismos antioxidantes do organismo causado pelo álcool (Pöschl e Seitz, 2004; Carrard et al., 2008; Zygogianni et al., 2011).

Estudos apontam que o hábito de fumar e beber estabelece um sinergismo entre estes dois fatores de risco, aumentando potencialmente o risco para o desenvolvimento do CEC oral (Melo et al., 2012; Brasil, 2014).

O CEC oral é uma doença que acomete principalmente indivíduos do gênero masculino, após a quinta década de vida e está fortemente associado ao consumo abusivo de álcool e tabaco. Observa-se, entretanto, que o número de casos no gênero feminino tem aumentado consideravelmente, possivelmente devido ao aumento do consumo destas substâncias (Iamaroon et al., 2004; Sassi et al., 2010; Johnson et al., 2011; Melo et al., 2012).

O CEC oral é considerado incomum em pacientes com idade inferior a 40 anos, tendo sua incidência variando entre 0,4 a 6% dos casos (Llewellyn et al., 2001; Neville e Day, 2002; Warnakulasuriya et al., 2005; Chiang et al., 2005; Muwonge et al., 2008; Hirota et al., 2008; Sassi et al., 2010; Santos-Silva et al., 2011).

Estudos apontam que a incidência global do CEC oral está diminuindo nos últimos anos, em contrapartida, observa-se uma tendência de aumento da sua ocorrência em pacientes jovens (Llewellyn et al., 2001; Iamaroon et al., 2004; Venturi et al., 2004; Shiboski et al., 2005; Harris et al., 2011; Patel et al., 2011; Santos-Silva, 2011; Hilly et al., 2013).

Segundo alguns autores, pacientes jovens com CEC apresentam um perfil clínico distinto e limitada associação com fatores de risco tradicionais (Llewellyn et al., 2001; Santos-Silva et al., 2011; Udeabor et al., 2012; Monsjou et al., 2013). Além disso, considera-se que o processo da oncogênese em adultos jovens possa ser diferente daquele que ocorre em pacientes idosos, como por exemplo, genes mutados herdados ou um defeito no reparo do DNA causando

propensão ao desenvolvimento de mutações (Koch et al., 1999; Pfeiffer et al., 2011). Segundo Santos-Silva et al. (2011), a alta incidência de anormalidades no DNA celular sugere que pacientes jovens com câncer de boca possam ter aumentada instabilidade genômica, indicando diferenças genéticas fundamentais entre a doença de pacientes jovens e pacientes idosos.

O câncer de boca em pacientes jovens tem sido considerado em alguns estudos como tendo um comportamento mais agressivo e um pior prognóstico do que em pacientes idosos (Andrade Sobrinho e Carvalho, 1994; Garavello et al., 2007; Sassi et al., 2010). Por outro lado, existem relatos conflitantes sobre o tema. Sendo assim, fatores etiológicos e prognósticos parecem ainda obscuros (Majchrzak et al., 2014).

Com a finalidade de padronização de informações foi desenvolvido o "Sistema TNM para Classificação de Tumores Malignos", o qual, ainda hoje, é o sistema de estadiamento clínico mais utilizado (Sobin et al., 2009; Almeida et al., 2011; Dissanayaka et al., 2012). Este sistema, baseia-se na extensão do tumor primário (T), na ausência ou presença e extensão de metástases em linfonodos regionais (N) e na ausência ou presença de metástase à distância (M) (Brasil, 2004) (Tabela 1). Entretanto, este sistema apresenta algumas limitações, principalmente em relação a previsão do prognóstico, visto que alguns pacientes com CEC oral inicial evoluem mal e outros com tumores avançados sobrevivem (Lindenblatt et al., 2012). Considera-se que sua maior desvantagem seja a incapacidade de se adaptar aos avanços na compreensão da biologia do câncer e incorporar novas variáveis de prognóstico conforme as mesmas se tornam disponíveis (Montero et al., 2014).

Tabela 1. Sistema TNM para Classificação de Tumores Malignos

Estágio	Descrição		
T – Tumor Primário			
TX	Tumor primário não pode ser avaliado		
T0	Não há evidência de tumor primário		
Tis	Carcinoma *in situ*		
T1	≤ 2 cm		
T2	> 2 até 4 cm		
T3	> 4 cm		
T4a	Invade cortical óssea, músculos profundos extrínsecos da língua, seios maxilares e pele		
T4b	Espaço mastigador, lâminas pterigoides, base do crânio e artéria carótida interna		
N – Linfonodos Regionais			
NX	Linfonodos regionais não podem ser avaliados		
N0	Ausência de metástase em linfonodos regionais		
N1	Homolateral, único, ≤ 3 cm		
N2	a) Homolateral, único, > 3 até 6 cm b) Homolateral, múltiplo, ≤ 6 cm c) Bilateral, contralateral, ≤ 6 cm		
N3	> 6 cm		
M – Metástase à Distância			
MX	Presença de metástase à distância não pode ser avaliada		
M0	Ausência de metástase à distância		
M1	Metástase à distância		
Estadiamento clínico			
Estadio 0	Tis	N0	M0
Estadio I	T1	N0	M0
Estadio II	T2	N0	M0
Estadio III	T1, T2	N1	M0
	T3	N0, N1	M0
Estadio IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
Estadio IVB	Qualquer T	N3	M0
	T4b	Qualquer N	M0
Estadio IVC	Qualquer T	Qualquer N	M1

Fonte: Brasil, 2004.

Com o objetivo de preencher esta lacuna, classificações histopatológicas para o CEC oral têm sido desenvolvidas, com o intuito de explicar o comportamento biológico divergente de tumores com características clínicas aparentemente similares. Muitos autores, em diferentes tempos, propuseram novos sistemas de gradação histológica para tumores na tentativa de prever seu comportamento clínico (Broders et al., 1920; Anneroth e Hansen, 1984; Bryne et al., 1989; Brandwein-Gensler et al., 2005; Barnes et al., 2005; Almangush et al., 2015).

O sistema de gradação recomendado pela Organização Mundial de Saúde (OMS), descrito inicialmente por Broders et al. (1920) e revisado por Barnes et al. (2005), classifica os CECs orais em três categorias com base no princípio da diferenciação celular, ou seja, considerando a semelhança do tecido tumoral com o de origem: (1) bem diferenciados, (2) moderadamente diferenciados e (3) pouco diferenciados (Tabela 2). Os CECs bem diferenciados são assim denominados quando sua arquitetura tecidual assemelha-se ao padrão normal do epitélio escamoso. Um tecido com predomínio de células imaturas, numerosas mitoses atípicas, excessivo pleomorfismo celular e nuclear e pouca ou nenhuma queratinização é classificado como pouco diferenciado ou anaplásico (Barnes et al., 2005; Johnson et al., 2005; Lourenço et al., 2007; Lindenblatt et al., 2012). Entretanto, o uso deste sistema de gradação na prática clínica é controverso e muitos autores afirmam que esta classificação histopatológica apresenta uma baixa correlação com a evolução e a resposta ao tratamento (Woolgar, 2006; Bhargava et al., 2010).

Bryne et al. (1992) propuseram o “Sistema de Gradação de Malignidade de Margens Invasivas Profundas” do CEC, o qual examina exclusivamente o fronte tumoral mais invasivo na interface tumor-hospedeiro. Os autores afirmaram que as células das áreas mais invasivas de um tumor mostram alterações parecidas com aquelas observadas em metástases, além de possuírem maior probabilidade de causar a disseminação do tumor. Neste sistema são atribuídos escores de 1 a 4 para as seguintes características morfológicas: grau de queratinização (1 – alto, 2 – moderado, 3 – mínimo e 4 – sem queratinização), pleomorfismo nuclear (1 –

discreto, 2 – moderado, 3 – abundante e 4 – extremo), padrão de invasão tumoral (1- bordas infiltrantes bem delineadas, 2 – forma de ilhas ou cordões infiltrantes, 3 – pequenos grupos ou cordões de células (n>15), 4 – células individuais ou pequenos grupos (n<15) e infiltrado linfoplasmocitário (1 – abundante, 2 – moderado, 3 – discreto e 4 – ausente) (Tabela 2). Ao final da avaliação os escores atribuídos a cada classificação são somados e classificados em grupos, sendo de 4 a 8 pontos considerados de baixo risco prognóstico, de 9 a 12 pontos risco intermediário e de 13 a 16 alto risco (Lourenço et al., 2007; Gueiros et al., 2011).

Brandwein-Gensler et al. (2005) desenvolveram o chamado “Sistema de Avaliação Histopatológica de Risco” ou “Modelo de Risco Histológico” para CEC oral onde são avaliados o padrão de invasão, o infiltrado linfoplasmocitário e a invasão perineural. O método consiste em uma pontuação em três níveis (0, 1 e 3). O método utiliza os mesmos quatro padrões de invasão utilizados por Bryne et al. (1992), citados acima, somando um quinto padrão para um quadro de infiltração tumoral altamente disperso com, no mínimo, 1 milímetro (mm) de tecido normal interposto entre as células tumorais e o fronte de invasão tumoral. O infiltrado linfoplasmocitário na interface tumor/hospedeiro pode ser classificado em três padrões (1 - banda densa e contínua de infiltrado linfoplasmocitário, 2 - infiltrado moderado e descontínuo, 3 - infiltrado escasso ou ausente). A invasão perineural também é classificada em três padrões (ausente, presente em pequenos nervos (< 1mm) e presente em grandes nervos (≥ 1 mm). A atribuição de pesos é diferente para cada parâmetro histopatológico avaliado. Atribui-se escore 0 para padrões de invasão de 1 a 3, infiltrado tipo 1 e nenhuma invasão perineural; escore 1 para padrão de invasão 4, infiltrado tipo 2 e invasão perineural de pequenos nervos; escore 3 para padrão de invasão 5, infiltrado tipo 3 e invasão perineural de grandes nervos (Tabela 2). Os escores finais são somados e, então, classificados em três grupos de prognóstico sendo o zero considerado baixo risco prognóstico, 1 ou 2 risco intermediário e 3 a 9 alto risco. Alguns estudos apontam este método como uma boa ferramenta prognóstica para o CEC oral (Lourenço et al., 2007; Lindenblatt et al., 2012)

Recentemente, Almangush et al. (2015) propuseram um novo e simples sistema de gradação histopatológica para CECs em estágio inicial denominado “Escore de risco BD”, onde “B” representa um ninho de células tumorais (*tumor budding)* e “D” a profundidade de invasão tumoral (*depth of invasion).* Define-se como ninho de células tumorais a presença de células tumorais isoladas ou pequenos grupos com até cinco células no fronte de invasão, os quais refletem a atividade biológica do tumor. A profundidade de invasão representa a medida desde a superfície do tumor até seu ponto mais profundo de invasão e o ponto de corte foi estabelecido em 4 mm. Este sistema classifica os tumores em três grupos: (1) Escore 0 / baixo risco prognóstico: tumor com profundidade de invasão <4mm e ninhos de células tumorais ausente ou < 5 no fronte de invasão; (2) Escore 1 / risco prognóstico intermediário: o tumor deve ter uma das seguintes características: a - tumor com profundidade de invasão ≥ 4mm e < 5 ninhos de células no fronte de invasão ou b - tumor superficial (< 4mm), mas com alta atividade de ninhos de células no fronte de invasão (≥ 5buds) e (3) Escore 2 / alto risco prognóstico: tumor com profundidade de invasão ≥ 4mm e com alta atividade de ninhos de células no fronte de invasão (≥ 5 buds) (Broders et al., 1920; Barnes et al., 2005; Bryne et al., 1992; Brandwein-Gensler et al., 2005; Almangush et al., 2015) (Tabela 2).

Apesar dos esforços e investimentos na busca por marcadores biológicos, ainda há muito a ser descoberto sobre o CEC oral em pacientes jovens, e o que se tem de mais concreto e de fácil acesso aos clínicos e pesquisadores são os aspectos clínicos e histopatológicos das lesões. Assim, o conhecimento dos aspectos histopatológicos é essencial para prevenção e tratamento da doença (Almeida et al., 2011).

Sendo assim, o objetivo deste estudo foi identificar o perfil clinicopatológico de pacientes jovens (≤ 40 anos) com CEC oral provenientes de Cascavel - Paraná. Foram objetivos específicos: (a) identificar o perfil sociodemográfico e clinicopatológico de pacientes jovens (≤ 40 anos) e de um grupo controle (≥ 50 anos); (b) classificar os cortes histológicos da amostra através de quatro sistemas de gradação histopatológica: 1) Organização Mundial de Saúde –

OMS, 2) Sistema de Gradação das Margens Invasivas Profundas, 3) Modelo de Risco Histológico e 4) Escore de risco BD; (3) Comparar os dados histopatológicos de pacientes jovens (≤ 40 anos) com os de um grupo controle (≥ 50 anos)

Tabela 2. Sistemas de Gradação Histopatológicas

Sistema OMS

Parâmetro	Características
Pouco diferenciado	Predomínio de células imaturas Numerosas mitoses atípicas Mínima queratinização
Moderadamente diferenciado	Certo grau de pleomorfismo nuclear e atividade mitótica Pouca queratinização
Bem diferenciado	Arquitetura tecidual semelhante ao padrão normal do epitélio escamosos.

Sistema MG

Características	1	2	3	4
Grau de queratinização	Alta queratinização (> 50% das células)	Moderada queratinização (20-50%)	Queratinização mínima (5-20%)	Sem queratinização (0-5%)
Pleomorfismo nuclear	Discreto pleomorfismo (> 75% células maduras)	Moderado pleomorfismo (50-75%)	Abundante pleomorfismo (25-50%)	Extremo pleomorfismo (0-25%)
Padrão de invasão	Compressivo, bordas infiltrantes bem delineadas	Forma de ilhas ou cordões infiltrantes	Pequenos grupos ou cordões de células infiltrantes (n>15)	Células individuais e/ou pequenos grupos (n<15)
Infiltrado linfoplasmocitário	Abundante	Moderado	Discreto	Ausente

Sistema HR

Características	0	1	3
Invasão perineural	Ausente	Pequenos nervos	Grandes nervos
Infiltrado linfoplasmocitário	Contínuo	Moderado e descontínuo	Escasso ou ausente
Pior padrão de invasão	Padrão 1, 2 ou 3	4	5

Escore de risco BD

Escore	Descrição histológica
0	Tumor com <4mm de profundidade de invasão, e <5 ninhos tumorais (*buds*) no fronte de invasão
1	**a** – tumor com ≥4mm de profundidade de invasão, e <5 ninhos tumorais no fronte de invasão (ou) **b** – tumor superficial (<4mm), com alta atividade dos ninhos tumorais no fronte de invasão (≥5 ninhos tumorais)
2	Tumor com ≥4mm de profundidade de invasão, e com alta atividade dos ninhos tumorais (≥5 ninhos tumorais)

CAPÍTULO 1

Histopathological grading systems analysis of oral squamous cell carcinomas of young patients

Running title: oral SCC in young patients

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Abstract

Aim. To analyze the clinicopathological profile of young patients (≤ 40 years) with oral SCC and correlate with a control group (≥ 50 years) by means of histopathological grading systems. **Methods**. 14 young patients and 14 control patients were selected with similar clinical stage and tumor location. Demographic and clinical data were obtained from patient records and histological sections were evaluated according to four histopathological grading systems. Associations between categories of demographic and clinical data were performed through Chi-square test and Exact Fisher test. The survival analyzes were performed according to the Kaplan-Meier method. **Results**. The comparison between groups showed a greater association of treatment modalities in younger patients (p=0.022), they had a higher incidence of local recurrence and regional metastasis (p=0.018) and lower disease-free survival in 5 years (p=0.069). There was no difference in 5-year overall survival among the studied groups. There was no difference in histological grading between studied groups according to the four used systems. **Conclusion**. This study showed that, despite tumors had similar histological grade and more therapeutic modalities were used in the young group, tumors in young patients had a higher incidence of recurrence/metastasis, showing tendency to a more aggressive behavior.

Key words: squamous cell carcinoma, tumors histological grading, young.

INTRODUCTION

Squamous cell carcinoma (SCC) originates in the stratified squamous epithelium and represents 90-95% of all malignant neoplasms in the oral cavity (Barnes et al., 2005). This disease affects mostly males, after the fifth decade of life and is strongly associated with alcohol and tobacco abuse (Iamaroon et al., 2004; Sassi et al., 2010; Johnson et al., 2011; Melo et al., 2012).

The oral SCC is an uncommon disease in patients under the age of 40 years old, and its incidence ranges from 0.4 to 6% of cases. However, in recent years this number has been increasing gradually (Llewellyn et al., 2001; Neville and Day, 2002; Venturi et al., 2004; Warnakulasuriya et al., 2005; Muwonge et al., 2008; Hirota et al., 2008; Sassi et al., 2010; Santos-Silva et al., 2011). According to some authors, young patients with SCC have a distinct clinical profile and limited association with traditional risk factors (Llewellyn et al., 2001; Santos-Silva et al., 2011; Udeabor et al., 2012; Monsjou et al., 2013). Furthermore, it is considered that the process of oncogenesis in young adults may be different from that which occurs in elderly patients (Koch et al., 1999; Pfeiffer et al., 2011). According to Santos-Silva et al. (2011), the high incidence of abnormalities in cellular DNA suggests that young patients with oral cancer may have increased genomic instability, indicating genetic differences between the disease of these patients and the elderly.

In order to standardize information, it was developed the "TNM Classification of Malignant Tumors System", which, today, is still the most used clinical staging system (Sobin et al., 2009; Almeida et al., 2011; Dissanayaka et al., 2012). However, this system has some limitations, especially in relation to previewing a prognosis, as some patients with early oral SCC may die because of the tumor and others with advanced tumors survive (Lindenblatt et al., 2012). It is considered that its greatest disadvantage is the inability to adapt to advances in the understanding of cancer biology and incorporate new prognostic variables, as they become available (Montero et al., 2014).

In order to fill this gap, histopathological classifications for oral SCC have been developed in order to explain the divergent biological behavior of tumors with apparently similar clinical features. Many authors, at different times, proposed new histological grading systems for tumors in an attempt to predict their clinical behavior (Broders et al., 1920; Anneroth and Hansen, 1984; Bryne et al., 1992; Brandwein-Gensler et al., 2005; Barnes et al., 2005; Almangush et al., 2015).

Based on these data, this study aimed to identify the clinicopathological profile of young patients (≤ 40 years) with oral CEC and correlate it with a control group (patients ≥ 50 years) by histopathological grading systems.

MATERIALS AND METHODS

All patients aged under 40 years old with primary intra-oral SCC treated at the Parana Western Union Hospital for Studies and Cancer Combat - Uopeccan and Cascavel Oncology Center - Ceonc from 1998 to 2013 were retrieved.

Inclusion criteria were records with complete clinicopathological and demographic data, treatment based on surgery with or without adjuvant radiotherapy and/or chemotherapy and viability for analysis of tumor tissue embedded in paraffin blocks. The Research Ethics Committee of the Piracicaba Dental School, State University of Campinas, Protocol 100/2012 approved this study.

The demographic data (age and gender), social habits (tobacco and alcohol consumption), tumor location, TNM stage, surgical margins, lymph node involvement, recurrence, metastasis, treatment and the patient's current status were obtained from medical records. The results were compared with a control group (age ≥ 50 years) selected in a paired form of treated patients files in the period in the same institutions and with similar clinicopathological features (Tables 1 and 2).

Histopathological analysis

After the sample selection, new histological sections with 4 µm thick were obtained from the paraffin blocks corresponding to surgical specimens and stained by hematoxylin and eosin technique (HE). The slides were evaluated using an optical microscope according to four histopathologic grading systems: 1) World Health Organization System - WHO System (Broders, 1920; Barnes et al., 2005), 2) Malignancy Invasive Margins Deep Grading System - MG system (Bryne et al.,

1992), 3) Histological Risk Model - HR System (Brandwein-Gensler et al., 2005) and 4) BD Risk Score (Almangush et al., 2015).

The analysis and classification of slides were performed by two evaluators previously calibrated and independently and doubtful cases were reviewed by a third appraiser. All evaluators were blinded to the demographic and clinical data of the analyzed cases.

Statistical analysis

The associations between the categories of demographic and clinical data, as well as diagnostic of histopathological grading systems of the tumors were performed using the Chi-square test for independence and Fisher exact test. The age data was evaluated for standard distribution using the Shapiro-Wilk normality test and homogeneity of variance by F test. As these assumptions were not accepted, the two age groups were compared using the nonparametric Mann-Whitney. The analysis of overall survival and disease-free survival were performed according to the Kaplan-Meier method, comparing the two age classes through the Gehan's Wilcoxon test. The significance level was 0.05. Analyses were performed in the statistical package Statistica 7.0 (Statsoft, 2004).

Table 1. Distribution of patients according to age, gender, habits and location of the tumor.

VARIABLES	≤40 YEARS		≥50 YEARS		p
	N	%	N	%	
AGE*					
VARIATION	20 – 40		50 – 84		< 0,0001
MEAN±DP	36,21[b]±3,89		63,14[a]±8,62		
GENDER**					
MALE	12	85,71	11	78,57	0,622
FEMALE	2	14,28	3	21,43	
TOBACCO CONSUMPTION**					
YES	10	71,43	8	57,14	
NO	3	21,43	3	21,43	0,543
NOT AVAILABLE	1	7,14	3	21,43	
ÁLCOHOL CONSUMPTION**					
YES	7	50,00	6	42,87	
NO	5	35,71	5	35,71	0,871
NOT AVAILABLE	2	14,29	3	21,43	
LOCALIZATION**					
TONGUE	11	78,57	9	64,29	
FLOOR OF MOUTH	3	21,43	4	28,57	0,511
PALATE	0	0	1	7,14	

** Mann-Whitney-U Test ** Chi Square Test for independence *** different letter express statistical differences between the analyzed categories.*

Table 2. Distribution of patients according to clinical staging.

VARIABLES	≤40 YEARS		≥50 YEARS		P
	N	%	N	%	
T STAGE**					
T1	8	57,14	8	57,14	1,000
T2	2	14,29	2	14,29	
T3	2	14,29	2	14,29	
T4	2	14,29	2	14,29	
N STAGE**					
N0	10	71,43	10	71,43	0,766
N1	2	14,29	3	21,43	
N2	2	14,29	1	7,14	
M STAGE**					
M0	14	100	14	100	1,000
STAGING**					
STAGE I	8	57,14	8	57,14	0,924
STAGE II	1	7,14	1	7,14	
STAGE III	1	7,14	2	14,29	
STAGE IV	4	28,57	3	21,43	

** Mann-Whitney-U Test ** Chi Square Test for independence.*

RESULTS

During the period proposed in this study, from 1998 to 2013, there were 22 patients aged under 40 years with a diagnosis of oral SCC in the institutions surveyed. Of these 22 patients, 14 (63.64%) met the inclusion criteria. The mean age of these patients was 36.21 years (± 3.89), ranging from 20 years to 40 years. Most patients were male 12 (85.71%) and 2 (14.29%) were female. Regarding the social habits, 10 (71.43%) reported smoking and 7 (50%) of alcohol. In patients in the control group, the mean age was 63.14 years (± 8.62), ranging from 50 years to 84 years. Most were male 11 (78.57%) and 3 (21.43%) were female. According to the habits, 8 (57.14%) reported tobacco and 6 (42.87%) alcohol consumption.

Regarding the tumor location, 11 (78.57%) developed in the tongue and 3 (21.43%) in the floor of mouth in the group of young patients. In the control group, 9 (64.29%) occurred in the tongue, 4 (28.57%) in the floor of mouth and 1 (7.14%) on the palate. The comparison between groups of young patients and control patients showed no significant differences regarding gender ($p = 0.622$), smoking consumption ($p = 0.543$), alcohol consumption ($p = 0.871$) and tumor location ($p = 0.511$) (Table 1).

In both groups, young and control, 10 (71.42%) patients were classified as early stages T1-T2 and 4 (28.58%) as advanced stage T3-T4. Regarding the stage N, 10 (71.73%) patients in each group had non-metastatic regional lymph nodes (N0). In the youth group, 2 patients (14.29%) were N1 and 2 (14.29%) were N2. In the control group, 3 patients (21.43%) were N1 and 1 patient (7.14%) was N2. As for distant metastasis, in both groups 14 (100%) were M0. Clinical staging in both groups showed that 9 patients (64.28%) were classified as stage I and II, and 5 patients (35.72%) stages III and IV. The comparison between groups of young patients and control patients showed no difference in the T stage ($p = 1.000$), N stage ($p = 0.766$), M stage ($p = 1.000$) and clinical stage ($p = 0.924$) (Table 2).

As for treatment performed in young patients, 4 (28.57%) underwent only surgery, 4 (28.57%) surgery associated with adjuvant radiotherapy and 6 (42.86%) surgery associated with adjuvant radiotherapy and chemotherapy. In control patients group, 7 (50%) were only undergoing surgery and other 7 (50%) surgery associated with radiotherapy (Table 3).

The analysis of surgical margins showed that in 11 (78.57%) young patients the surgical margins were free and in 2 (14.29%) compromised. In one patient (7.14%), this information was not available. In all 14 (100%) control patients, the surgical margins were free (Table 3). Neck dissection was performed in 10 (71.42%) young patients and in 7 (50%) control patients. Histopathological confirmation of lymph node commitment was observed in 2 (14.29%) patients in each group (Table 3).

In the clinical follow-up after cancer treatment, 8 (57.14%) young patients presented recurrence/metastasis compared to only 2 (14.29%) control patients. Of

the young patients with recurrence/metastasis in 2 (25%) was local, in 2 (25%) lymph node and in 4 (50%) local and lymph node. In the control group, 1 (7.14%) patient had local recurrence and 1 (7.14%) lymph node (Table 3). Comparing both groups, young patients had almost 4 times more risk to develop recurrence/metastasis than the control group (OR=3.998). As for the current status of the patients, 7 (50%) in each group were alive and 7 (50%) dead. Of the dead patients, 5 (71.43%) in each group died due to tumor.

The comparison between young and control groups showed a greater association of treatment modalities used in younger patients ($p = 0.022$) and younger patients had higher rate of recurrence/metastasis ($p = 0.018$). On the other hand, regarding the surgical margins, lymph node commitment and current status did not differ between the groups, with p values respectively ($p = 0.186$) ($p = 0.254$) and ($p = 1.000$) (Table 3).

Table 3. Patients' distribution according to treatment and follow up.

VARIABLES	≤40 YEARS		≥50 YEARS		P
	N	%	N	%	
TREATMENT**					
SURGERY	4	28,57	7	50,00	
SURGERY + RT	4	28,57	7	50,00	**0,022**
SURGERY + RT + CT	6[a]	42,86	0[b]	0	
SURGICAL MARGINS**					
FREE	11	78,57	14	100	
COMPROMISED	2	14,29	0	0	0,186
NOT AVAILABLE	1	7,14	0	0	
NECK DISSECTION**					
YES	10	71.42	7	50	0,246
NO	4	28.58	7	50	
LYMPH NODE INVOLVEMENT**					
YES	2	14,29	2	14,29	
NO	9	64,28	5	35,71	0,254
NOT AVAILABLE	3	21,43	7	50,00	
RECURRENCE/ METASTASIS**					
NO	6	42,86	12	85,71	**0,018**
YES	8[a]	57,14	2[b]	14,29	
Local	2	25,00	1	7,14	
Lymph node	2	25,00	1	7,14	0,435
Local + lymph node	4	50,00	0	0	
CURRENT STATUS**					
ALIVE	7	50,00	7	50,00	1,000
DEAD	7	50,00	7	50,00	

** Mann-Whitney-U Test ** Chi Square Test for independence *** different letter express statistical differences between the analyzed categories.*

In the young group overall survival rate (OS) the average was 47.93 (± 52.17) months and the disease free survival rate (DFS) of 30.29 (± 44.09), ranging from 4 to 144 months. In the control group the OS rate average was 50.14 (± 38.54) months

and the DFS rate of 49.21 (± 39.41), ranging from 8 to 127 months. When analyzing the rates of OS and DFS according to Kaplan-Meier method, comparing the two age classes through Gehan's Wilcoxon test, it was observed tendency to statistical difference from DFS variable (p = 0.069), younger patients had lower five years DFS (37.68%) compared to the control (77.78%). Young patients in 10 years DFS remained (37.68%) and the control group was reduced (18.84%) (Figure 1). There was no significant difference in overall survival rate between the groups (p = 0.376) (Figure 2).

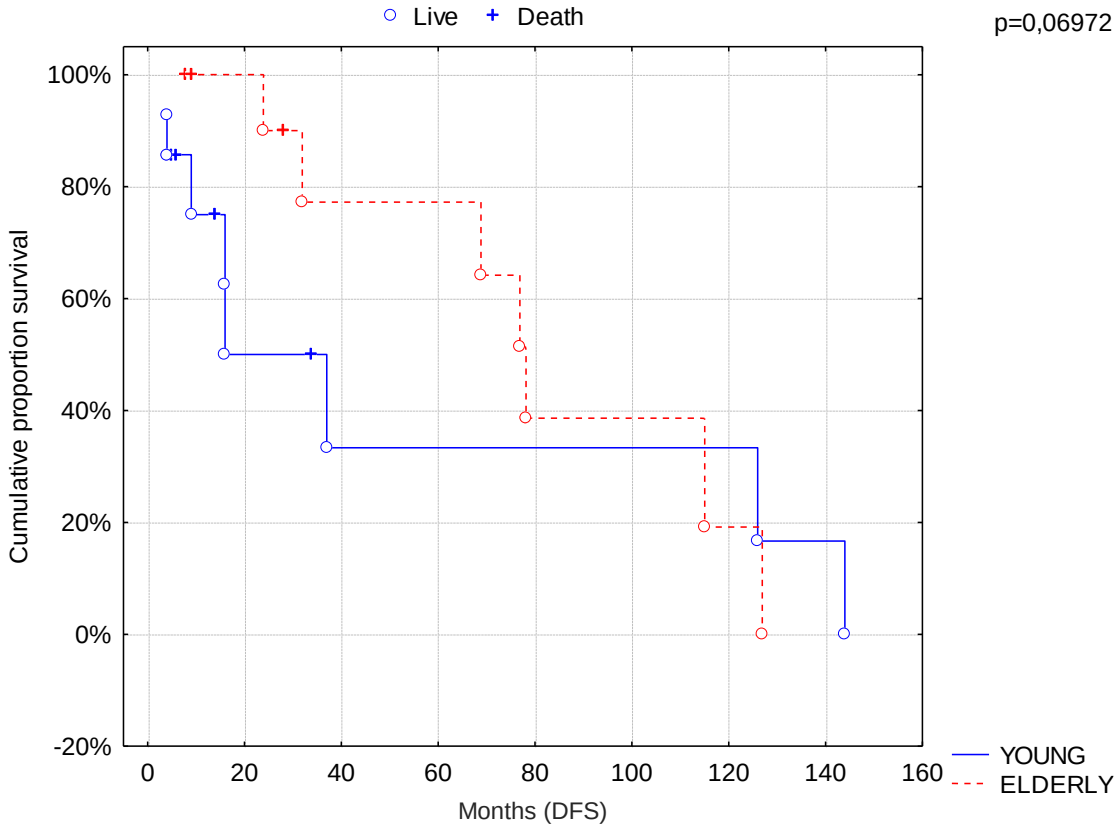

Figure 1. Comparative analysis of disease free survival rate among groups.

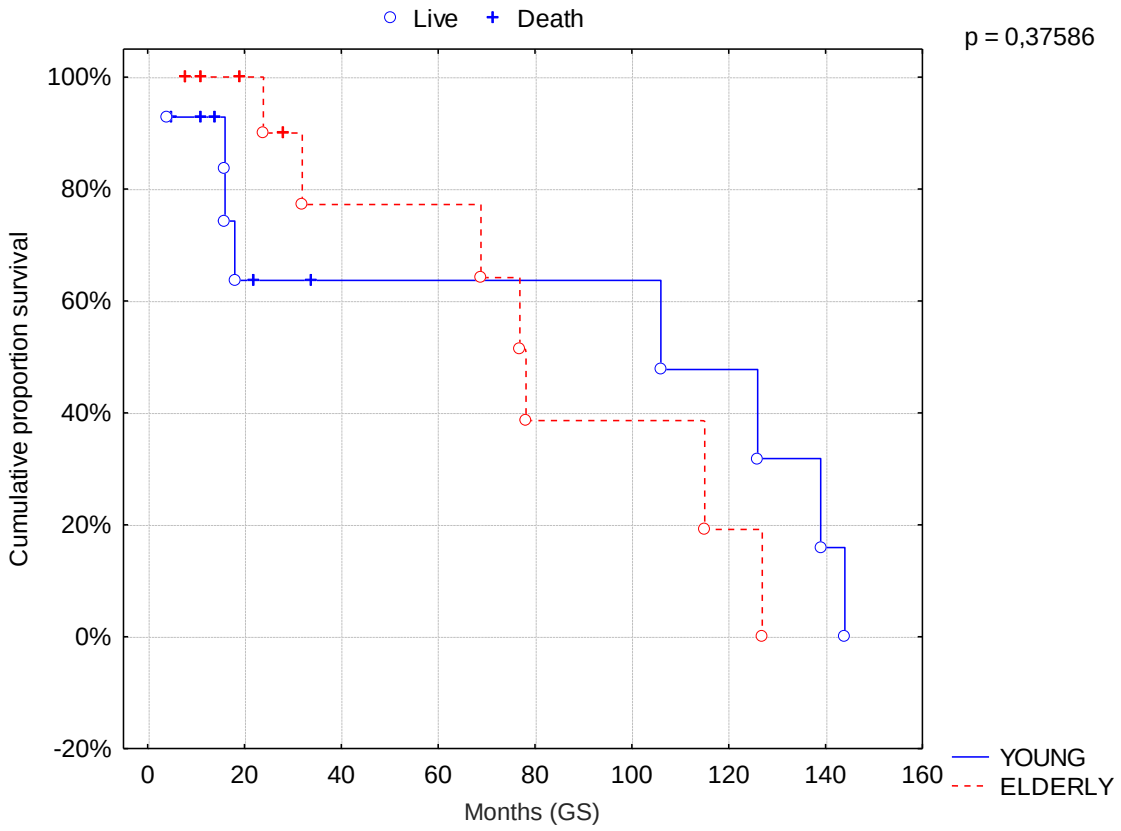

Figure 2. Comparative analysis of global survival rate among groups.

The WHO grading system classified in both groups, young and control, 13 (92.85%) tumors as well or moderately differentiated and 1 (7.15%) poorly differentiated. No significant associations were observed between the groups studied in the WHO grading system, except for the stage M0. In the young group 13 (92.86%) patients form classified as well or moderately differentiated and 1 (7.14%) poorly differentiated. In the control group 7 (50%) patients were classified as well or moderately differentiated and 7 (50%) poorly differentiated (p = 0.012) (Table 4).

Table 4. Association of clinical and demographic characteristics of the tumors of young patients (≤ 40 years) and control patients (≥ 50 years) with histopathological classification according to the WHO system.

		WHO grading system		
		≤ 40 years n (%)	≥ 50 years n (%)	p
Gender				
Male	W/M	11 (91,67)	10 (90,91)	0.949
	P	1 (8,33)	1 (9,09)	
Female	W/M	2 (100)	3 (100)	1
	P	0	0	
Tobacco consumption				
No	W/M	3 (100)	3 (100)	1
	P	0	0	
Yes	W/M	9 (90)	7 (87,50)	0.867
	P	1 (10)	1 (12,50)	
Alcohol consumption				
No	W/M	5 (100)	5 (100)	1
	P	0	0	
Yes	W/M	6 (85,71)	6 (100)	0.335
	P	1 (14,29)	0	
Localization				
Tongue	W/M	10 (90,91)	9 (100)	0.353
	P	1 (9,09)	0	
Floor of mouth	W/M	3 (100)	3 (75)	0.350
	P	0	1 (25)	
Palate	W/M	0	1 (100)	1
	P	0	0	
Stage T				
T1/T2	W/M	10 (100)	9 (90)	0.305
	P	0	1 (10)	
T3/T4	W/M	3 (75)	4 (100)	0.285
	P	1 (25)	0	
Stage N				
N0	W/M	10 (100)	9 (90)	0.305
	P	0	1 (10)	
N+	W/M	3 (75)	4 (100)	0.285
	P	1 (25)	0	
Stage M				
M0	W/M	13 (92,86)	7 (50)	**0.012**
	P	1 (7,14)	7 (50)	
Clinical stage				
I / II	W/M	9 (100)	8 (88,89)	0.303
	P	0	1 (11,11)	
III/IV	W/M	4 (80)	5 (100)	0.292
	P	1 (20)	0	

		WHO grading system		
		≤ 40 years n (%)	≥ 50 years n (%)	p
Treatment				
Surgery	W/M	4 (100)	7 (100)	1
	P	0	0	
Surgery +RT	W/M	4 (100)	6 (85,71)	0.428
	P	0	1 (14,29)	
Surgery +RT+CT	W/M	5 (83,33)	0	1
	P	1 (16,67)	0	
Surgical margins				
Free	W/M	10 (90,91)	13 (92,86)	0.859
	P	1 (9,09)	1 (7,14)	
Compromised	W/M	2 (100)	0	1
	P	0	0	
Not available	W/M	1 (100)	0	1
	P	0	0	
Recurrence				
No	W/M	6 (100)	11 (91,67)	0.467
	P	0	1 (8,33)	
Yes	W/M	7 (87,50)	2 (100)	0.598
	P	1 (12,50)	0	
Local recurrence				
No	W/M	8 (100)	12 (92,31)	0.421
	P	0	1 (7,69)	
Yes	W/M	5 (83,33)	1 (100)	0.659
	P	1 (16,67)	0	
Regional recurrence				
No	W/M	8 (100)	12 (92,31)	0.421
	P	0	1 (7,69)	
Yes	W/M	5 (83,33)	1 (100)	0.659
	P	1 (16,67)	0	
Distant metastasis				
No	W/M	13 (92,86)	13 (92,86)	1
	P	1 (7,14)	1 (7,14)	
Yes	W/M	0	0	1
	P	0	0	
Status				
Alive	W/M	7 (100)	7 (100)	1
	P	0	0	
Dead	W/M	6 (85,71)	6 (85,71)	1
	P	1 (14,29)	1 (14,29)	

W/M: Well/Moderately differentiated, P: Poorly differentiated, RT: Radiotherapy, CT: Chemotherapy

The MG grading system ranked in the young group 1 (7.14%) tumor as low prognosis risk and 13 (92.86%) as intermediate risk. In the control group 3 (21.43%) tumors were classified as low prognosis risk and 11 (78.57%) as intermediate risk.

There were no significant associations between this classification and the comparative analysis between the groups (Table 5).

Table 5. Association of clinical and demographic characteristics of the patients tumor young (≤ 40 years old) and control patients (≥ 50 years) the histopathological classification MG according to the grading system.

		MG grading system		
		≤ 40 years n (%)	≥ 50 years n (%)	p
Gender				
Male	L/I	12 (100)	11 (100)	1
	H	0	0	
Female	L/I	2 (100)	3 (100)	1
	H	0	0	
Tobacco consumption				
No	L/I	3 (100)	3 (100)	1
	H	0	0	
Yes	L/I	10 (100)	8 (100)	1
	H	0	0	
Alcohol consumption				
No	L/I	5 (100)	5 (100)	1
	H	0	0	
Yes	L/I	7 (100)	6 (100)	1
	H	0	0	
Localization				
Tongue	L/I	11 (100)	9 (100)	1
		0	0	
Floor of mouth	L/I	3 (100)	4 (100)	1
	H	0	0	
Palate	L/I	0	1 (100)	1
	H	0	0	
Stage T				
T1/T2	L/I	10 (100)	10 (100)	1
	H	0	0	
T3/T4	L/I	4 (100)	4 (100)	1
	H	0	0	
Stage N				
N0	L/I	10 (100)	10 (100)	1
	H	0	0	
N+	L/I	4 (100)	4 (100)	1
	H	0	0	
Stage M				
M0	L/I	14 (100)	14 (100)	1
	H	0	0	
Clinical stage				
I / II	L/I	9 (100)	9 (100)	
	H	0	0	1
III/IV	L/I	5 (100)	5 (100)	
	H	0	0	1

		MG grading system		
		≤ 40 years n (%)	≥ 50 years n (%)	p
Treatment				
Surgery	L/I	4 (100)	7 (100)	
	H	0	0	1
Surgery +RT	L/I	4 (100)	7 (100)	
	H	0	0	1
Surgery +RT+CT	L/I	6 (100)	0	1
	H	0	0	
Surgical margins				
Free	L/I	11 (100)	14 (100)	1
	H	0	0	
Compromised	L/I	2 (100)	0	1
	H	0	0	
Not available	L/I	1 (100)	0	1
	H	0	0	
Recurrence				
No	L/I	6 (100)	12 (100)	
	H	0	0	1
Yes	L/I	8 (100)	2 (100)	
	H	0	0	1
Local recurrence				
No	L/I	8 (100)	13 (100)	
	H	0	0	1
Yes	L/I	6 (100)	1 (100)	
	H	0	0	1
Regional Recurrence				
No	L/I	8 (100)	13 (100)	
	H	0	0	1
Yes	L/I	6 (100)	1 (100)	
	H	0	0	1
Distant metastasis				
No	L/I	14 (100)	14 (100)	
	H	0	0	1
Yes	L/I	0	0	
	H	0	0	1
Status				
Alive	L/I	7 (100)	7 (100)	1
	H	0	0	
Dead	L/I	7 (100)	7 (100)	
	H	0	0	1

L/I: Low/Intermediate risk, H: High risk, RT: Radiotherapy, CT: Chemotherapy.

In HR grading system, 7 (50%) tumors in the young group were classified as intermediate prognosis risk and 7 (50%) as high risk. In the control group 1 (7.14%) tumor was classified as low risk, 5 (35.72%) as intermediate risk and 8 (57.14) as high prognosis risk. When evaluating the relationship between the young and control

groups, there were statistical differences in the variables clinical stage III/IV (p = 0.002), free surgical margins (p = 0.002) and no regional recurrence (p = 0.017) (Table 6).

Table 6. Association of clinical and demographic characteristics of the tumors of young patients (≤ 40 years) and control patients (≥ 50 years) with histopathological classification according to the HR grading system.

		HR grading system		
		≤ 40 years n (%)	≥ 50 years n (%)	p
Gender				
Male	L/I	6 (50)	3 (27,27)	0.265
	H	6 (50)	8 (72,73)	
Female	L/I	1 (50)	3 (100)	0.171
	H	1 (50)	0	
Tobacco consumption				
No	L/I	3 (100)	3 (100)	1
	H	0	0	
Yes	L/I	3 (30)	2 (25)	0.814
	H	7 (70)	6 (75)	
Alcohol consumption				
No	L/I	4 (80)	4 (80)	1
	H	1 (20)	1 (20)	
Yes	L/I	1 (14,29)	2 (33,33)	0.416
	H	6 (85,71)	4 (66,67)	
Localization				
Tongue	L/I	5 (45,45)	4 (44,44)	0.964
	H	6 (54,55)	5 (55,56)	
Floor of mouth	L/I	2 (66,67)	4 (100)	0.212
	H	1 (33,33)	0	
Palate	L/I	0	1 (100)	1
	H	0	0	
Stage T				
T1/T2	L/I	6 (60)	5 (50)	0.653
	H	4 (40)	5 (50)	
T3/T4	L/I	1 (25)	1 (25)	1
	H	3 (75)	3 (75)	
Stage N				
N0	L/I	6 (60)	6 (60)	1
	H	4 (40)	4 (40)	
N+	L/I	1 (25)	0	0.285
	H	3 (75)	4 (100)	
Stage M				
M0	L/I	7 (50)	6 (42,86)	
	H	7 (50)	8 (57,14)	0.704

		HR grading system		
		≤ 40 years	≥ 50 years	p
		n (%)	n (%)	
Clinical stage				
I / II	L/I	9 (100)	6 (66,67)	
	H	0	3 (33,33)	0.058
III/IV	L/I	5 (100)	0	
	H	0	5 (100)	**0.002**
Treatment				
Surgery	L/I	3 (75)	7 (100)	
	H	1 (25)	0	0.165
Surgery +RT	L/I	2 (50)	6 (85,71)	
	H	2 (50)	1 (14,29)	0.201
Surgery +RT+CT	L/I	2 (33,33)	0	
	H	4 (66,67)	0	1
Surgical margins				
Free	L/I	11 (100)	6 (42,86)	
	H	0	8 (57,14)	**0.002**
Compromised	L/I	2 (100)	0	
	H	0	0	1
Not available	L/I	0	0	
	H	1 (100)	0	1
Recurrence				
No	L/I	3 (50)	6 (50)	
	H	3 (50)	6 (50)	1
Yes	L/I	4 (50)	0	
	H	4 (50)	2 (100)	0.197
Local recurrence				
No	L/I	4 (50)	6 (46,15)	
	H	4 (50)	7 (53,85)	0.864
Yes	L/I	3 (50)	1 (100)	
	H	3 (50)	0	0.350
Regional recurrence				
No	L/I	5 (62,50)	13 (100)	
	H	3 (37,50)	0	**0.017**
Yes	L/I	2 (33,33)	1 (100)	
	H	4 (66,67)	0	0.212
Distant metastasis				
No	L/I	7 (50)	6 (42,86)	
	H	7 (50)	8 (57,14)	0.705
Yes	L/I	0	0	
	H	0	0	1
Status				
Alive	L/I	4 (57,14)	4 (57,14)	
	H	3 (42,86)	3 (42,86)	1
Dead	L/I	3 (42,86)	2 (28,57)	0.577
	H	4 (57,14)	5 (71,43)	

L/I: Low/Intermediate risk, H: High risk, RT: Radiotherapy, CT: Chemotherapy.

One case was not possible to evaluate according to the BD risk score in the young group. The BD risk score ranked 2 (15.38) tumors as low prognosis risk, 4 (30.77%) as intermediate risk and 7 (53.85) as high risk in the young group. In the control group 3 (21.43%) tumors were classified as low risk, 5 (35.71%) as intermediate risk and 6 (42.86%) as high risk. No significant correlation was observed between clinical parameters and the BD risk score in the comparison between groups (Table 7).

Table 7. Association of clinical and demographic characteristics of the tumors of young patients (≤ 40 years) and control patients (≥ 50 years) with histopathological classification according to the BD risk score.

		BD risk score		
		≤ 40 years n (%)	≥ 50 years n (%)	p
Gender				
Male	L/I	5 (45,45)	6 (54,55)	0.670
	H	6 (54,55)	5 (45,45)	
Female	L/I	1 (50)	2 (66,67)	0.710
	H	1 (50)	1 (33,33)	
Tobacco consumption				
No	L/I	2 (66,67)	2 (66,67)	1
	H	1 (33,33)	1 (33,33)	
Yes	L/I	3 (33,33)	5 (62,50)	0.229
	H	6 (66,67)	3 (37,50)	
Alcohol consumption				
No	L/I	3 (60)	3 (60)	1
	H	2 (40)	2 (40)	
Yes	L/I	2 (33,33)	4 (66,67)	0.248
	H	4 (66,67)	2 (33,33)	
Localization				
Tongue	L/I	5 (50)	6 (66,67)	0.462
	H	5 (50)	3 (33,33)	
Floor of mouth	L/I	1 (33,33)	1 (25)	0.180
	H	2 (66,67)	3 (75)	
Palate	L/I	0	1 (100)	1
	H	0	0	
Stage T				
T1/T2	L/I	5 (50)	5 (50)	1
	H	5 (50)	5 (50)	
T3/T4	L/I	1 (33,33)	3 (75)	0.270
	H	2 (66,67)	1 (25)	

		BD risk score		
		≤ 40 years	≥ 50 years	p
		n (%)	n (%)	
Stage N				
N0	L/I	5 (50)	6 (60)	0.653
	H	5 (50)	4 (40)	
N+	L/I	1 (33,33)	2 (50)	0.659
	H	2 (66,67)	2 (50)	
Stage M				
M0	L/I	6 (46,15)	8 (57,14)	
	H	7 (53,85)	6 (42,86)	0.568
Clinical stage				
I / II	L/I	5 (55,56)	5 (55,56)	
	H	4 (44,44)	4 (44,44)	1
III/IV	L/I	1 (25)	3 (60)	
	H	3 (75)	2 (40)	0.294
Treatment				
Surgery	L/I	3 (75)	4 (57,14)	
	H	1 (25)	3 (42,86)	0.554
Surgery +RT	L/I	2 (50)	4 (57,14)	
	H	2 (50)	3 (42,86)	0.819
Surgery +RT+CT	L/I	1 (20)	0	
	H	4 (80)	0	1
Surgical margins				
Free	L/I	5 (50)	8 (57,14)	
	H	5 (50)	6 (42,86)	0.729
Compromised	L/I	0	0	
	H	2 (100)	0	1
Not available	L/I	1 (100)	0	
	H	0	0	1
Recurrence				
No	L/I	4 (66,67)	7 (58,33)	
	H	2 (33,33)	5 (41,67)	0.732
Yes	L/I	2 (28,57)	1 (50)	
	H	5 (71,43)	1 (50)	0.571
Local recurrence				
No	L/I	4 (50)	8 (61,54)	
	H	4 (50)	5 (38,46)	0.604
Yes	L/I	2 (40)	1 (100)	
	H	3 (60)	0	0.273
Regional recurrence				
No	L/I	5 (62,50)	8 (61,54)	
	H	3 (37,50)	5 (38,46)	0.964
Yes	L/I	1 (20)	0	
	H	4 (60)	1 (100)	0.624
Distant metastasis				
No	L/I	6 (46,15)	8 (57,14)	
	H	7 (53,85)	6 (42,86)	0.568
Yes	L/I	0	0	
	H	0	0	1

		BD risk score		
		≤ 40 years n (%)	≥ 50 years n (%)	p
Status				
Alive	L/I	3 (42,86)	3 (42,86)	
	H	4 (57,14)	4 (57,14)	1
Dead	B/I	3 (50)	5 (71,43)	0.428
	H	3 (50)	2 (28,57)	

L/I: Low/Intermediate risk, H: High risk, RT: Radiotherapy, CT: Chemotherapy.

Table 8 shows a summary of the four classifications used in the study.

Table 8. Distribution of tumors according to the clinical stage and degree of differentiation in the four systems (WHO, MG, HR and BD).

		WHO system		MG system		HR system		BD score	
TNM		≤ 40 n (%)	≥ 50 n (%)	≤ 40 n (%)	≥ 50 n (%)	≤ 40 n (%)	≥ 50 n (%)	≤ 40 n (%)	≥ 50 n (%)
I/II									
	W/L	3 (33,33)	1 (11,11)	1 (11,11)	1 (11,11)	0	1 (11,11)	2 (22,22)	2 (22,22)
	M/I	6 (66,67)	7 (77,78)	8 (88,89)	8 (88,89)	6 (66,67)	4 (44,44)	3 (33,33)	3 (22,22)
	P/H	0	1 (11,11)	0	0	3 (33,33)	4 (44,45)	4 (44,45)	4 (44,45)
III/IV									
	W/L	0	1 (20)	0	2 (40)	0	0	0	1 (20)
	M/I	4 (80)	4 (80)	5 (100)	3 (60)	1 (20)	1 (20)	1 (25)	2 (40)
	P/H	1 (20)	0	0	0	4 (80)	4 (80)	3 (75)	2 (40)

W/L: Well differentiated/Low risk, M/I: Moderately differentiated/Intermediate risk, P/H: Poorly differentiated/High risk.

DISCUSSION

In Brazil, oral carcinoma is among the 10 most incidents cancers and it is estimated approximately 15,000 new cases for the year 2014 (Brazil, 2014). Among young patients, the incidence is considered low and retrospective analyzes are rarely higher rates to 6% of this tumor in this population (Santos-Silva et al., 2011; Udeabor

et al., 2012). However, in recent years, it has been seen an increased incidence of oral carcinoma among patients younger than 40 years old (Soundry et al., 2010; Patel et al., 2011; Santos-Silva et al., 2011; Hilly et al., 2013). Hirota et al. (2008) in a retrospective study conducted in Brazil between 1994 and 2004, it was observed incidence of SCC in young patients of 10.7%.

In literature, the prevalence of oral carcinoma in male patients is observed. The ratio of men to women was 3.8: 1 in the study of Udeabor et al. (2012), and 1.6: 1 in the studies of Hirota et al. (2008) and Santos-Silva et al. (2011). In this study, the ratio was 6: 1, which is higher than in other studies. There is no consensus in the literature on demographic characteristics, lifestyle, etiology, prognosis and results in young patients with oral carcinoma. In this study, it was found that the majority of patients were male (85.71%), consumed tobacco (71.43%) and alcohol (50%) and often the predominant location of the tumors was tongue (78.57%), similar data to the control group.

The fact that even when young patients have the risk factors of tobacco and alcohol, it is due to a shorter period to induce carcinogenesis when compared to older patients; allowing new research about other etiologic factors responsible for the development of SCC in young individuals, such as genetic and viral infections (O'Regan et al., 2006; Hirota et al., 2008; Bachar et al., 2011; Pfeiffer et al., 2011; Santos-Silva et al., 2011; Udeabor et al., 2012; Benevenuto et al., 2012; Kaminagakura et al., 2012; Mesquita et al., 2014).

Furthermore, it is suggested that the increased effect of oral carcinoma in young individuals is related to the possibility of this being a different type of cancer with apparently more aggressive biological behavior (Siriwardena et al., 2006; Soudry et al., 2010; Beena et al., 2011). However, there is no consensus in the literature on the subject. Some studies found no significant differences between groups with different age groups showing that the profile of young patients is not well defined in the biological behavior of tumors (Sasaki et al., 2005; Kaminagakura et al., 2011; Benevenuto et al., 2012). O´Regan et al. (2006) reported in their study that a significant proportion of young patients with oral cancer had absence of traditional

risck factors which is in contrast to the conventional patients with oral cancer. These data indicate that oral cancer in young patients may possibly have a different etiology and disease progression.

In this study, the majority (64.28%) of young patients were diagnosed at an early stage (I and II) of disease, other than the study Benvenuto et al. (2012) in which 67% of oral SCC in young patients were diagnosed in stages III and IV. This high proportion of young patients can be explained by delayed diagnosis, as also occurs in older patients (Patel et al., 2011) or by a more aggressive tumor behavior associated with age (Santos-Silva et al., 2011) .

Neck dissection was performed in 10 (71.42%) young patients and in 7 (50%) control patients and histopathological confirmation of lymph node involvement was seen in only 14.29% of each group. One of the major clinical prognostic indicators is the nodal status, so that survival can decrease by 20% when regional metastases are present (Kligerman et al., 1994; Gueiros et al., 2011).

The parameters used to plan the treatment of patients with SCC are mainly based on clinical staging of the disease, which can often contribute to lower survival rates. The main form of treatment of oral carcinoma is surgery, usually in more advanced cases, combined with other modalities such as radiotherapy and chemotherapy (Deng et al., 2011).

Montero et al. (2014), in a systematic review, from 2007 to 2012 on CEC features in young patients, noted that the evaluated studies showed a predominance of surgery as a treatment of young patients, followed by combination surgery + radiotherapy. According to the authors, the association of chemotherapy would be a suitable option for more advanced tumors, with margins showing neoplastic infiltration. They also noted that the treatment used to pump in young patients is similar to that used in older individuals. However, according to the analyzed studies, the young patients are often subjected to combination treatments, regardless of the stage of the disease, because a large number of authors reports that the CEC's behavior is more aggressive in this group. In this study, there was statistical difference between the groups regarding the type of treatment used, with a higher

association of treatment modalities in younger patients (p = 0.022) for both tumors diagnosed in the early stages as later.

Affected surgical margins, according Binahmed et al. (2007) may be associated with local recurrence and poorer survival rates. Had Brandwein-Gensler et al. (2005) in their study, found that the histological grading is more important that the assessment of surgical margins in determining the prognosis. In the present study, it was observed a small percentage of young patients (14.29%) with compromised surgical margins in the control group, all margins were free.

In the clinical follow-up after cancer treatment, when comparing the groups, there was a higher rate of local recurrence and regional metastasis among young people (p = 0.018). The study of Siriwardena et al. (2006) observed a higher recurrence rate in young (39%) than in older (30%). In review by Montero et al. (2014) it was observed a controversy between studies analyzed with regard recurrence rates of oral carcinoma in young. However, the authors stated that the overall survival rates seem to be more favorable to patients with no history of risk factors compared to who use tobacco and alcohol, regardless of age.

It was observed in this study that young patients had DFS rate in 5 years significantly lower (37.68%) than the control group (77.78%), suggesting greater aggressiveness of tumors in the first group. Already, in 10 years, this rate has remained in the young group and decreased in the control (18.84%). The OS rate was not significantly different between groups at 5 and 10 years. The no difference in OS may, in part, be explained by the fact that older patients are more prone to other diseases and other causes of deaths.

An important feature about causal effects of age on survival are the comorbidities in other systems that are common in this population and demonstrate a significant impact on the prognosis of oral cancer (Datema et al., 2010). That is, a longer period associated with these diseases could lead to reduced patient survival. The study of Monsjou et al. (2013) found no significant difference in DFS rates among the young and elderly patients, however, noted that younger patients had

better OS rate, possibly due to the influence of comorbidities associated with old age.

In this study, the dead patients, the majority (71.43%) in both groups died due to tumor. According Warnakulasuriya (2010), despite the modern surgical techniques and new therapeutic strategies mortality rates by oral carcinoma remain high in most countries, with an overall survival rate at 5 years less than 50%

The evaluation of prognostic factors of oral SCC has been widely studied in order to more effective therapeutic strategies. Considering the poor prognosis of oral SCCs, as well as clinical studies, several histopathological grading systems have been developed trying to explain the differences in biological behavior of tumors with similar clinical characteristics (Lindenblatt et al., 2012). However, none of these systems is universally accepted (Rodrigues et al., 2014). This study used the systems developed by Broders et al. (1920), Bryne et al. (1992), Brandwein-Gensler et al. (2005) and Almangush et al. (2015).

Regarding the histopathological grading of tumors, degree distribution of malignancy, several authors found a similarity between groups of young and elderly patients (Soudry et al., 2010; Bachar et al., 2011; Benevenuto et al., 2012; Udeabor et al., 2012; Hilly et al., 2013). Since Kaminagakura et al. (2011) found a higher frequency of poorly differentiated tumors in young patients compared to older.

WHO still recommends the Broders et al. (1920) system, reviewed by Barnes et al. (2005), for histopathological classification of SCC, but their use as prognostic tool has been criticized in recent years (Weijers et al., 2009). The main criticism of this system refers to their subjectivity, in the absence of important features related to tumorigenesis, such as invasion pattern and, more importantly, the poor correlation with the results and responses to treatment (Bryne et al., 1992; Woolgar, 2006). In this study the WHO grading system in both groups ranked 13 (92.85%) tumors as well or moderately differentiated and 1 (7.15%) poorly differentiated. In relating the young and control groups with the WHO grading system were found statistically significant associations in stage M0 ($p = 0.012$).

Systematic review by Montero et al. (2014) noted that the pathophysiological point of view, the majority (72%) of the injuries were classified as moderately differentiated, that is, associated with a more favorable prognosis.

Since it was described as an applicable grading system in biopsies, the MG system (Bryne et al., 1992) has been used for prognostic analysis, but the results of the studies are controversial, (Costa et al., 2005; Gueiros et al., 2011; Lindenblatt et al., 2012) which can be explained by the subjectivity attributed to some of their parameters resulting in high variability among examiners (Sawair et al, 2003). In this study, the majority of tumors in both groups was classified as intermediate risk associations were not found in the comparative analysis between the groups.

The HR system (Brandwein-Gensler et al., 2005) was proposed as a multiparameter system modified and updated with an important role in making decisions about the need for post-operative therapy and prognosis of patients with oral carcinoma. Although some studies, such as Lourenço et al. (2007), Brandwein-Gensler et al. (2010) and Lindenblatt et al. (2012) have confirmed their predictive value, other, more recent, such as Almangush et al. (2015) and Rodrigues et al. (2014) showed no correlation between this system and the epidemiological and clinical characteristics. According to Rodrigues et al. (2014) none of the three parameters individually considered in the HR system as prognostic predictors for patients with CPB has shown high reproducibility. In this study, the HR grading system ranked 7 (50%) tumors of the youth group as intermediate risk and 7 (50%) high prognostic risk. In the control group 1 (7.14%) tumor was classified as low risk, 5 (35.72%) as intermediate risk and 8 (57.14) as high prognostic risk. When evaluating the relationship between the young and control groups, no statistical differences were found in significant clinical staging variables III / IV, free margins and the absence of regional recurrence.

The BD risk score (Almangush et al., 2015) is the latest proposal for histopathologic grading system of oral tumors. Its two evaluation items, the depth of tumor invasion and tumor cell nests have been individually described as prognostic predictors for patients with oral carcinoma (O-Charoenrat et al., 2003; Wang et al.,

2011; Ganly et al., 2013). The depth of invasion, related to cervical lymph node metastasis (O-Charoenrat et al., 2003; Ganly et al., 2013), reflecting the aggressiveness of tumor growth. The nests of tumor cells, defined as isolated tumor cells or cell group of compounds within five cancer cells in the tumor invasion front, which reflects the biological activity of the tumor (Wang et al., 2011). In this study, there was no difference between the group of young patients and the control group patients compared to histological grading system for BD.

Interestingly, in the HR and BD systems more tumors were classified as high risk prognosis than in the WHO and MG systems, suggesting that these systems can more accurately identify undifferentiated tumors than WHO and MG systems.

To sum up, in this study statistically significant differences were observed in histological grading of the tumors of young patients and control patients in the four used systems (WHO, MG, HR and BD). However, even considering the limitation of the sample, it was observed that younger patients had a higher rate of local and regional metastases recurrence, despite the use of more therapeutic modalities.

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CONCLUSÃO

1- Pacientes jovens foram tratados com mais modalidades terapêuticas que os pacientes do grupo controle.

2- Pacientes jovens tiveram mais recidivas e metástases regionais que os pacientes do grupo controle.

3- Pacientes jovens apresentaram menor sobrevida livre de doença em 5 anos que pacientes do grupo controle.

4- Não houve diferença na sobrevida global em 5 anos entre os pacientes jovens e pacientes do grupo controle.

5- Não houve diferença na gradação histológica entre os pacientes jovens e pacientes do grupo controle nos quatro sistemas utilizados (OMS, MG, HR e BD).

6- Nos sistemas HR e BD mais tumores foram classificados como alto risco prognóstico que nos sistemas OMS e MG.

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ANEXO 1 – Parecer Comitê de Ética em Pesquisa

COMITÊ DE ÉTICA EM PESQUISA
FACULDADE DE ODONTOLOGIA DE PIRACICABA
UNIVERSIDADE ESTADUAL DE CAMPINAS

CERTIFICADO

O Comitê de Ética em Pesquisa da FOP-UNICAMP certifica que o projeto de pesquisa **"Caracterização histopatológica do estroma do carcinoma espinocelular de cavidade oral e sua correlação clinicopatológica"**, protocolo nº 100/2012, dos pesquisadores Iris Sawazaki Calone, Ana Lúcia Carrinho Ayroza Rangel, Juliana Cristina Frare, Marcio Ajudarte Lopes, Ricardo Della Coletta e Roberto Longoni de Souza, satisfaz as exigências do Conselho Nacional de Saúde - Ministério da Saúde para as pesquisas em seres humanos e foi aprovado por este comitê em 10/10/2012, com alterações em 15/08/2013.

The Ethics Committee in Research of the Piracicaba Dental School - University of Campinas, certify that the project **"Oral squamous cell carcinoma stromal histopathological characterization and clinical pathological correlation"**, register number 100/2012, of Iris Sawazaki Calone, Ana Lúcia Carrinho Ayroza Rangel, Juliana Cristina Frare, Marcio Ajudarte Lopes, Ricardo Della Coletta and Roberto Longoni de Souza, comply with the recommendations of the National Health Council - Ministry of Health of Brazil for research in human subjects and therefore was approved by this committee on Oct 10, 2012; with alterations on Aug 15, 2013.

Prof. Dr. Felippe Bevilacqua Prado
Secretário
CEP/FOP/UNICAMP

Profa. Dra. Lívia Maria Andaló Tenuta
Coordenadora
CEP/FOP/UNICAMP

Nota: O título do protocolo aparece como fornecido pelos pesquisadores, sem qualquer edição.
Notice: The title of the project appears as provided by the authors, without editing.

ANEXO 2 – Confirmação de submissão do artigo

Em Segunda-feira, 9 de Fevereiro de 2015 14:43, International Journal of Oral & Maxillofacial Surgery <IJOMS@elsevier.com> escreveu:

Dear Dr. Juliana Frare,

You have been listed as a Co-Author of the following submission:

Journal: International Journal of Oral & Maxillofacial Surgery
Corresponding Author: Marcio Lopes
Co-Authors: Juliana Frare; Iris Sawazaki-Calone; Ana Lucia C Rangel; Alexandre G Bueno; Carlos F de Morais; Reno P Kunz; Hildebrando M Nagai;
Title: Histopathological grading systems analysis of oral squamous cell carcinomas of young patients

If you did not co-author this submission, please contact the Corresponding Author of this submission atmalopes@fop.unicamp.br; do not follow the link below.

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