



UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"

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**Prognosis impact of perineural invasion in advanced stage oral
squamous cell carcinoma**

Araçatuba - SP
2022

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squamous cell carcinoma**

Dissertação apresentada à Faculdade de Odontologia de Araçatuba da Universidade Estadual Paulista “Júlio de Mesquita Filho” - UNESP, como parte dos requisitos para obtenção do título de Mestre em Odontologia - Área de concentração em Estomatologia.

Orientador: Professor Titular Glauco Issamu Miyahara

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Dissertação (Mestrado) – Universidade Estadual
Paulista, Faculdade de Odontologia de Araçatuba
Orientador: Prof. Glauco Issamu Miyahara

Black D6
CDD 617.63

Este trabalho é todo dedicado aos meus pais, Arildo e Marlei, pois é graças ao esforço deles em me proporcionar a oportunidade de estar em Araçatuba em meio à pandemia do COVID-19, que hoje posso concluir o meu curso de mestrado.

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“O câncer é uma doença que destrói o corpo de uma pessoa, mas não consegue destruir o sonho de quem luta pela vida.”

José Guimarães e Silva

ARAÚJO, W. A. F. **Impacto do prognóstico da invasão perineural no carcinoma espinocelular de boca em estágio avançado.** 2022. 34 f. Dissertação (Mestrado) – Faculdade de Odontologia, Universidade Estadual Paulista, Araçatuba, 2022.

RESUMO

Apesar de pesquisas recentes mostrarem baixa sobrevida em pacientes oncológicos que tiveram invasão perineural (IPN), pouco se sabe sobre a força do IPN relacionada à sobrevida do carcinoma espinocelular (CEC) de boca e em relação a suas variáveis clínico-patológicas. Os objetivos específicos do estudo foram medir o impacto do IPN na sobrevida do CEC de boca, bem como a correlação entre as características clínico-patológicas do paciente diagnosticado com CEC de boca com o IPN em pacientes tratados cirurgicamente. Foi realizado um estudo retrospectivo envolvendo 101 pacientes submetidos ao tratamento cirúrgico com ou sem associação de terapia adjuvante entre os anos de 1994 e 2016. Todas as variáveis foram inseridas simultaneamente no modelo de cox para cada modelo de sobrevida e na tabulação cruzada para avaliar a relação do IPN com as variáveis do CEC de boca. A significância estatística para o estudo foi estabelecida em um valor de P inferior a 0,05. A variável de interesse IPN provou ser preditora de sobrevida global (HR, 3,38; IC 95%, 0,139-0,624; $P = 0,004$) e sobrevida específica da doença (HR, 2,95; IC 95% 0,137-0,810; $P=0,019$). O IPN também mostrou relação com tratamento ($P = 0,011$) na análise de correlação. A invasão perineural foi considerada uma variável independente na sobrevida específica e global de pacientes com CEC de boca. Outros fatores relacionados à sensibilidade da avaliação do padrão de invasão perineural no CEC de boca ainda permanecem desconhecidos.

Palavras-chave: Câncer de boca. Tropismo celular. Prognóstico. Carcinoma de células escamosas. Análise de sobrevida.

ARAÚJO, W. A. F. **Prognosis impact of perineural invasion in advanced stage oral squamous cell carcinoma.** 2022. 34 f. Dissertação (Mestrado) – Faculdade de Odontologia, Universidade Estadual Paulista, Araçatuba, 2022.

ABSTRACT

Despite recent research showing low survival in cancer patients who had perineural invasion (PNI), little is known about the strength of the PNI related to oral squamous cell carcinoma (OSCC) survival and in relation to its clinicopathological variables. The specific objectives of the study were to measure the impact of the PNI on the survival of oral SCC, as well as the correlation between the clinicopathological characteristics of the patient diagnosed with OSCC of the mouth with the PNI in surgically treated patients. A retrospective study was carried out involving 101 patients who underwent surgical treatment with or without the association of adjuvant therapy between the years 1994 and 2016. All variables were entered simultaneously in the cox model for each survival model and in the cross-tabulation to evaluate the relationship between the PNI and the OSCC by mouth variables. Statistical significance for the study was established at a *P* value of less than 0.05. The PNI variable of interest proved to be a predictor of overall survival (HR, 3.38; 95% CI, 0.139-0.624; *P* = 0.004) and disease-specific survival (HR, 2.95; 95% CI 0.137-0.810; *P* = 0.019). The PNI also showed a relationship with treatment (*P* = 0.011) in the correlation analysis. Perineural invasion was considered an independent variable in the specific and overall survival of patients with OSCC. Other factors related to the sensitivity of the assessment of the perineural invasion pattern in OSCC of the mouth still remain unknown.

Keywords: Oral cancer. Cell tropism. Prognosis. Squamous cell carcinoma. Survival analysis.

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LISTA DE ABREVIATURAS E SIGLAS

AJCC	American joint committee on cancer
CT	chemotherapy
DSS	disease specific survival
OS	overall survival
OSCC	oral squamous cell carcinoma
PNI	perineural invasion
RCT	radiochemioteraphy
RT	radiotherapy
UNESP	São Paulo State University

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1 INTRODUCTION *

Perineural invasion (PNI) is defined as the dynamics of bidirectional attraction between neoplastic cells and nerve tissue cells, called cell tropism.¹ This cellular interaction seems to be more observed in solid tumors such as oral squamous cell carcinoma (OSCC).² Thus, there is great speculation about the survival of oral cancer related to PNI and the relationship between PNI and clinicopathological aspects of OSCC.³

Previous studies related PNI as a prognostic predictor of survival and an adjuvant therapy decision-making tool in neoplasms, especially in colorectal cancers and salivary gland neoplasms.⁴ Although the PNI and its clinical applicability have been widely discussed in different types of cancer, little is known about the influence strength of PNI related to clinicopathological features of patients diagnosed with OSCC, as well as the impact of PNI on OSCC survival.⁵ Therefore, there is still a need for further investigation of PNI related to survival in OSCC in specific groups of patients to understand the real clinical applicability of the PNI.

Thus, the objective of the study is to evaluate the predictive capacity of PNI in disease specific survival and overall survival in patients diagnosed with OSCC first surgically treated, as well as the correlation of PNI with patients clinicopathological characteristics.

* Normalizado de acordo com as normas da Journal of Oral and Maxillofacial Surgery (JOMS) (Anexo B)

2 PATIENTS AND METHODS

The Research Ethics Committee of São Paulo State University approved the study protocol (approval n ° 03876012.6.0000.5420). 101 medical records were selected from 1994 to 2016 in the Oral Oncology Center of the Araçatuba Dental School, São Paulo State University (UNESP). Which were reviewed in a cut-off of 5 years. The inclusion criteria were: (a) patients diagnosed with OSCC; (b) patients who underwent primarily tumor exegesis and neck dissection; (c) age above 18 years old; (d) follow-up for at least 5 years for alive patients. The exclusion criteria were: (a) patients who underwent preoperative chemotherapy (CT) or radiotherapy (RT).

The TNM stage was revised in all patients (AJCC 7th edition⁶). Patient data as clinical, demographic and histopathological details were obtained from the medical records.

2.1 Statistical analysis

Statistical analysis was performed using the software SPSS version 20.0 (version 20, SPSS, Inc., Chicago, IL). For each variable, according to PNI status, they were computed with a 95% confidence interval. The survival curves for overall survival (OS) and disease-specific survival (DSS) of the patients were done through Kaplan-Meier method and compared using the log-rank test. The period to establish DSS was the date of diagnosis until the date of the death by cancer. The event for OS was the period from the date of diagnosis until death for any circumstance. The strength of association between PNI and the categorical variables was estimated using Pearson's chi-square test. Multivariate analysis to evaluate the independent prognostic factor and survival impact was performed using the Cox proportional hazard model, forward stepwise selection. *P*-value < 0.05 was statistically significant.

3 RESULTS

3.1 Patients 'and tumors' characteristics

table 1 summarizes the clinicopathologic characteristics of the 101 patients. In which 81 were men (80.2%) with the mean age of 56.7 years (range 21-88). Among the 101 patients, 82 reported having smoking habit (81.2%), and 73 patients had drinking alcohol habit (72.3%).

A great majority of tumors were diagnosed in the floor of the mouth and tongue, with 42 (41.6%) and 36 (35.6%) cases, respectively. At the time of diagnosis, clinically, T3 was the most frequent tumor size with 70 cases (69.3%), while 17 patients had T2 tumor size (16.8%), and the remaining patients had T4 (13.9%). Seventy-nine patients were node negative (78.2 %), 15 were N1 (14.9%), 6 were N2 (5.9%), and only one patient was N3 (1%). TNM Stage III was the most prevalent comprising 73 cases (72.3%), and the remaining tumors were TNM IV with 28 cases (27.7%).

PNI was present in 23 cases of 101 patients (22.8%), while pN positive was present in 46 cases (45.5%). A significant majority, comprising 80 cases (79.2%) had the histological grade defined as moderately differentiated. Recurrent disease occurred in 19 cases (18.8%). All patients underwent primary surgery, 68 patients received RT (67.3%) and 7 (6.9%) received radiochemioteraphy (RCT) as adjuvant therapy.

Table 1. Clinicopathological features of the sample

Age (mean $\pm$ SD)	56.5 $\pm$ 12.73
Range	21-88
Variables	N=101 (%)
Sex	
Male	81 (80.2)
Female	20 (19.8)
Smoking*	
Yes	82 (81.2)
No	18 (17.8)
Alcohol consumption*	
Yes	73 (72.3)
No	26 (25.7)
Tumor Site	
Floor of the mouth	42 (41.6)
Tongue	36 (35.6)
Retromolar	14 (13.9)
Alveolar ridge	7 (6.9)
Buccal Mucosa	2 (2)
Tumor Size	
2	17 (16.8)
3	70 (69.3)
4	14 (13.9)
Nodal status	
N0	79 (78.2)
N1	15 (14.9)
N2	6 (5.9)
N3	1 (1)

Table 1. Clinicopathological features of the sample

Variables	N=101 (%)
TNM stage	
III	73 (72.3)
IV	28 (27.7)
Histological Grade*	
Well differentiated	13 (12.9)
Moderately differentiated	80 (79.2)
Poorly differentiated	6 (5.9)
PNI	
Positive	23 (22.8)
Negative	78 (77.2)
pN*	
Positive	46 (45.5)
Negative	53 (52.5)
Recurrence*	
Yes	19 (18.8)
No	77 (76.2)
Treatment	
Surgery only	33 (32.7)
Surgery+RT	68 (67.3)
Surgery+RCT	7 (6.9)

*Variables with missing data; PNI, perineural invasion; RT, Radiotherapy; RCT, Radio-chemotherapy; OSCC, oral squamous cell carcinoma.

3.2 Survival analysis

The log-rank comparison test for survival was performed for both OS and DSS, as seen in Table 2. In which clinical nodal status ($P < 0.001$); TNM stage ($P = 0.001$); and PNI ($P = 0.009$) were statistically associated with 5-year OS, as seen in Figure 1. While Alcohol consumption and pN reached up to a p-value of $P = 0.087$ and $P = 0.156$ respectively. The univariate analysis for DSS showed only clinical nodal status ($P < 0.001$) interfered negatively in 5-year DSS as seen in figure2. Moreover, an analysis was performed to assess whether there was a relationship between PNI and the clinicopathological characteristics of the issue patients. Only treatment of the tumor was associated with PNI.

Table 2. Univariate survival analysis with Kaplan–Meier method for overall survival and disease-specific survival

Variables	5-year OS (%)	p-value	5-year DSS (%)	p-value
Clinical nodal status		< 0.001*		< 0.001*
N0	60.9		68	
N1	70		70	
N2	25		25	
N3	0		0	
TNM stage		.043*		
III	63.4			
IV	50			
PNI		.010*		
Negative	62.3			
Positive	46.2			

* Statistically significant. OS, Overall survival; DSS, Disease specific survival; PNI, perineural invasion.

Table 3. Correlation between perineural invasion (PNI) and clinicopathological parameter

Parameters	Categories	PNI negative	PNI positive	P-value
Treatment				.011*
	Surgery only	31	2	
	Surgery+RT	41	20	
	Surgery+RCT	6	1	

* Statistically significant. RT, Radiotherapy; RCT, Radio-chemotherapy PNI, perineural invasion.

All variables that had p-value <0.2 in the univariate analysis by Kaplan Meier were included in the cox regression model by the stepwise method. For the multivariate analysis in OS, as shown in Table4, PNI proved to be an independent predictor (HR, 3.38; 95% CI, .139-.624; $P=0.004$), as alcohol consumption (HR, 2.59; 95% CI, 1.212-5.567; $P=0.014$). Additionally, PNI was also shown to be a predictor for DSS (HR, 2.95; 95% CI, .137-.810; $P=0.019$), along with TNM stage (HR, 3.70; 95% CI.120-.608; $P=0.002$), recurrence (HR, 2.97; 95% CI, .140-.810; $P=0.015$) and alcohol consumption (HR, 2.60; 95% CI, 1.053-6.417; $P=0.038$).

Table 4. Multivariate analysis for the factors influencing overall survival and disease-specific survival

Factor	OS			DSS		
	HR	95% CI	p-value	HR	95% CI	p-value
Clinical nodal status	6.13	.015-1.740	.133	-	-	-
TNM stage	-	-	-	3.70	.120-.608	.002
PNI	3.38	.139-.624	.004	2.95	.137-.810	.019
Recurrence	-	-	-	2.97	.140-.810	.015
Alcohol consumption	2.59	1.212-5.567	.014	2.60	1.053-6.417	.038

Figure 1

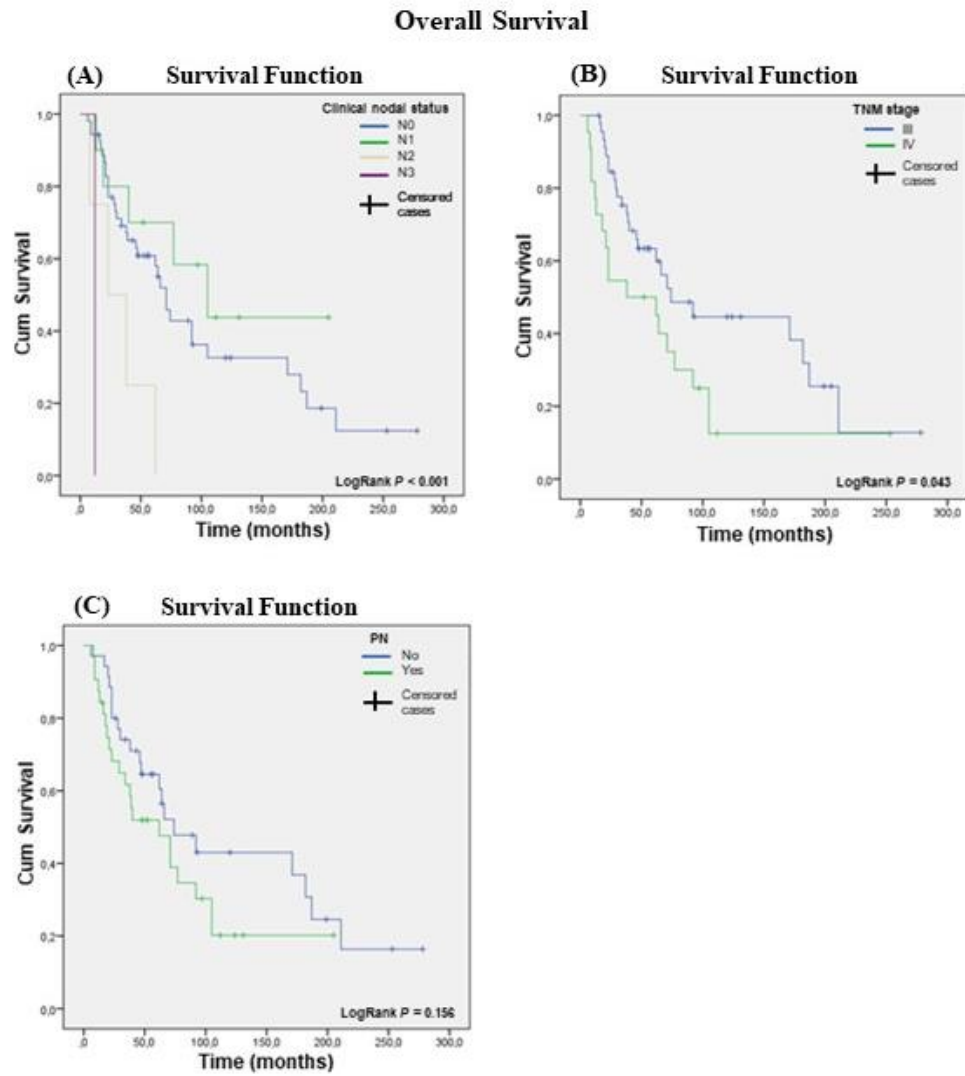


Figure 1. Kaplan–Meier survival curves for overall survival according to (A) Clinical nodal status, (B) TNM stage, and (C) Perineural invasion (PNI).

Figure 2

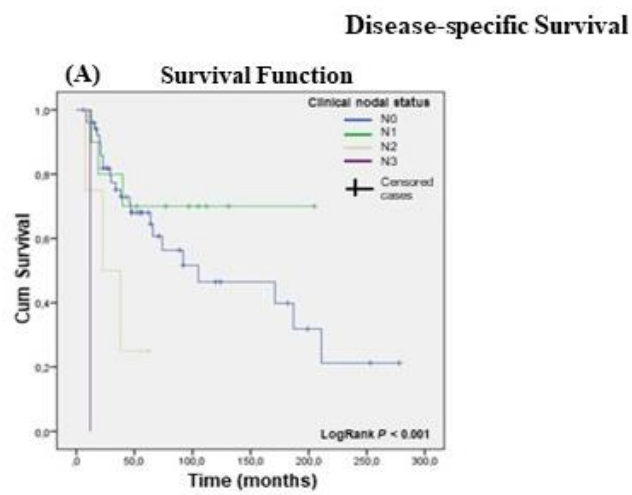


Figure 2. Kaplan–Meier survival curves for disease-free survival according to (A) Clinical nodal status.

5 DISCUSSION

PNI is the invasion of perineural space or the nerve bundles by tumor cells, known as cell tropism.¹ The diagnosis of PNI is determined by evaluation of microscopic image, in which the analyzed nervous structure needs to be more than 33% surrounded by neoplastic cells.⁷ The occurrence of PNI in the present analysis was 22.8% of all patients, in agreement with earlier investigations of some authors, who clarified that the occurrence of PNI in groups of patients diagnosed with OSCC can vary from 2.5% to 71%.^{2,8} In the current study, both clinicopathological characteristics and proportion of patients diagnosed with PNI were consistent with previous studies analyzing the relationship between PNI in OSCC.^{9–11}

PNI has been increasingly recognized as an independent prognostic factor in colorectal carcinoma and salivary gland malignancies, related to poor survival rate,^{10,12} of which such effectiveness of PNI can be observed in OSCC in our study, since PNI was shown to be an independent predictor in both 5-years OS (HR, 3.38; CI, .139-.624), and in the 5-years DSS (HR, 2.95; CI, .137-.810). Additionally, in the study carried out by Jardim et al.¹⁰ also evaluated the influence of PNI in the advanced OSCC stage (III and IV, AJCC 7th edition⁶), it was found that PNI has a predictive impact on OS, as well as having a negative influence on disease-free survival for 5 years. In addition, even in the early stage of OSCC, T1N0, PNI also showed a worse evolution in survival, and increasing the risk of regional recurrence.¹³

There is a challenge in the literature to identify and establish clinical-pathological variables of OSCC that have a statistically significant relationship with PNI. In the study carried out by Kim et al.¹⁴, significant relationship was observed in PNI with advanced TNM stage and T2 tumor size in OSCC. Although PNI was statistically associated in other studies to advanced and early TNM stage, local recurrence and tumor size, in our study, on the other hand, there was no such relationship between PNI and those variable.^{5,14–16} In the present study, PNI was correlated with treatment. In a review performed by Silva and Kowalski¹⁷ sought that in the literature there is a relationship between PNI and the tumor site. Also in the study performed by Kim et al.¹⁴ the association between PNI and primary tumor site was evidenced, from which tongue and floor tumors were more likely to occur PNI.

Despite the relationship between PNI and postoperative neoadjuvant therapy, in our study 21 of the 23 patients diagnosed with PNI underwent adjuvant therapy, in agreement with the

literature when referring the recommendation of adjuvant treatment in PNI-positive patients.¹⁹ Although some authors indicate adjuvant therapy in doubly positive pathological risk variables in patients with OSCC, Nair et al.⁷ elucidate the indication of adjuvant therapy in PNI positive patients even in patients without nodal involvement, as some publications have correlated the presence of PNI with the development of metastases and poor survival.^{10,20}

The unfavorable pathological features as lymph node metastasis, margin positivity, lymphovascular invasion and PNI are findings capable of dramatically reducing survival, from 74.5 to 39.9 months.^{21,22} The difference of PNI in survival, suit even more when analyzes the depth and the patterns of neoplastic cells invasion through the nerves⁵ what led to the thought of categorizing the pattern of depth of PNI.²³ Despite the depth of PNI showing promising results, such evaluation was not possible in the present study. This is a retrospective study and some analysis as the number of nerves involved per section (PNI density), PNI location and patterns of invasion could not be assessed in relation to tumor mass.

Multivariate analysis also shows the association of nodal status, TNM stage and drinking to poor prognosis. There is the consensus that nodal metastasis and increasing TNM stage are one of the most important predictors in OSCC survival.¹⁰ Alcohol consumption is understood as a risk factor to development of cancer and the present study was correlated to poor prognosis in DSS and OS, which was also seen in the study performed by Zanoni et al.²⁴ The presence of PNI in the advanced TNM stage is high. Some authors have also reported the association of PNI and lymph node metastasis.¹⁰

The clinical implication of PNI is still obscured. Although PNI may present some symptoms, such as pain, dysesthesia or motor deficits, about 40% of patients are asymptomatic.²⁵ The diagnosis by magnetic resonance imaging (MRI) is recommended for detection of perineural invasion in the preoperative approach. The sensitivity and specificity of MRI in PNI diagnosis reaches up to 85%.²⁵ PNI falls into the intermediate risk category, which RT is indicated.^{22,25} On the other hand, some studies have shown that there is no significant benefit of RT after surgery in patients PNI positive, without other risk indicators, at an early stage of the disease, compared whose underwent only surgery.²⁵

In conclusion, this study demonstrates the PNI is an independent predictor in DSS and OS after surgical treatment in OSCC advanced TNM stage. We encourage the indication of adjuvant

therapy in PNI-positive-patients, as well as encouraging future research to better understand the implications and pattern of invasion of the PNI relating to OSCC variables and survival in both early and advanced stage, which remains understood.

Conflict of interest

There is no conflict of interest involved in this work.

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ANEXOS

ANEXO A- Comitê de Ética em Pesquisa

Plataforma Brasil - Ministério da Saúde

Faculdade de Odontologia - Câmpus de Araçatuba - Júlio de Mesquita Filho/ UNESP

PROJETO DE PESQUISA

Título: Efeito das oncoproteínas virais na resposta de células T de pacientes com carcinoma espinocelular

Área Temática:

Pesquisador: Glaucio Issamu Miyahara

Versão: 1

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PARECER CONSUBSTANCIADO DO CEP

Número do Parecer: 72921

Data da Relatoria: 13/08/2012

Apresentação do Projeto:

O papilomavírus humano (HPV) vem sendo associado ao carcinoma espinocelular (CEC) de orofaringe, como um possível fator etiológico. As oncoproteínas virais E6 e E7 são capazes de inibir a produção de algumas citocinas e iniciar a produção de outras, tornando a resposta celular frente à infecção deficiente. O propósito deste trabalho é avaliar a influência das oncoproteínas virais E6 e E7 do HPV-16 sobre a resposta de linfócitos T (CD4+ e CD8+) de pacientes com CEC de orofaringe. Apesar do HPV ser encontrado em carcinomas de boca e estudos indicarem uma possível influência da infecção sobre o prognóstico do paciente, a exata participação desse vírus nas alterações imunológicas locais e sistêmicas não está esclarecida. Assim, na tentativa de melhor compreender como o vírus atua no sistema imune, será investigado os efeitos das oncoproteínas virais mais associadas à oncogênese (E6 e E7) sobre a resposta de linfócitos obtidos de sangue periférico de pacientes com CEC de orofaringe, acreditando que estas proteínas desregulem a resposta imune celular.

Objetivo da Pesquisa:

O propósito deste projeto é avaliar a influência das oncoproteínas virais E6 e E7 do HPV-16 sobre a resposta imunológica das células T (CD4+ e CD8+) de pacientes com carcinoma espinocelular de orofaringe.

Avaliação dos Riscos e Benefícios:

Riscos: O pesquisador esclarece que estes procedimentos (coleta de sangue e biópsias) serão realizados independentemente da realização desta pesquisa, pois fazem parte do processo de diagnóstico e tratamento. - Nos casos de coleta de sangue poderá haver desconforto mínimo, inerente ao procedimento, porém necessário como exame pré-operatório do paciente. Nos casos de biópsias de pacientes e cirurgias estéticas do grupo voluntário saudável os riscos são de dor pós-operatória e possível processo inflamatório, inerentes a qualquer procedimento cirúrgico com finalidade curativa ou estética. Estes procedimentos são necessários para diagnóstico (casos de carcinoma) ou tratamento oral estético (plástica gengival e frenectomia de freio lingual e labial) dos participantes.

Benefícios: Através dos resultados obtidos com este projeto, será possível hortear novas pesquisas com a finalidade de descobrir a real influência do vírus no desenvolvimento do câncer, para que medidas preventivas, como a inserção da vacina possa ser uma iniciativa de saúde pública.

Comentários e Considerações sobre a Pesquisa:

Trata-se de uma pesquisa séria e de extrema importância, pois motivará novas pesquisas para se descobrir a real influência deste vírus (HPV) no desenvolvimento do câncer, para que medidas preventivas, como a inserção da vacina possa ser uma iniciativa de saúde pública.

Considerações sobre os Termos de apresentação obrigatória:

Parece estar dentro das normas.

Recomendações:

Nenhuma

Conclusões ou Pendências e Lista de Inadequações:

Analisando-se a proposta deste projeto, podemos observar que se trata uma pesquisa séria e de extrema importância, que no futuro beneficiará e muito a população como um todo, tanto com tratamentos curativos quanto com preventivos. Portanto, sou FAVORÁVEL À APROVAÇÃO deste projeto.

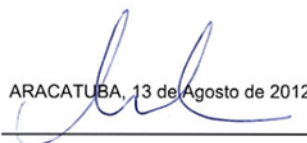
Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

ARACATUBA, 13 de Agosto de 2012



Assinado por:
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