UNIVERSIDADE DE SÃO PAULO
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Confecção de dispositivo intraoral para proteção bucal durante a radioterapia

Fabrication of intraoral stent for oral protection during radiotherapy

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Orientador: Prof. Dr. Paulo Sérgio da Silva Santos

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Dedico este trabalho a todos os meus queridos pacientes.

Vocês me fazem querer ser melhor a cada dia.

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“Por vezes sentimos que aquilo que fazemos não é senão uma gota de água no mar. Mas o mar seria menor se lhe faltasse uma gota.”

Madre Teresa de Calcutá

RESUMO

Na necessidade de tratamento oncológico que envolva radioterapia, diversos efeitos colaterais são esperados pela terapia atingir, além de tecido neoplásico, tecido sadio. Os objetivos da pesquisa foram: a) confeccionar um dispositivo intraoral (“stent”) para separar mecanicamente palato, língua e assoalho bucal e manter a abertura bucal estável na tentativa de minimizar alguns dos efeitos colaterais como mucosite oral, disgeusia e trismo; b) avaliar o impacto da saúde bucal na qualidade de vida (QV); c) avaliar o conforto e estabilidade do dispositivo pela percepção do paciente; d) comparar os resultados de trismo, disgeusia e impacto da saúde bucal na qualidade de vida no momento pré e pós-radioterapia. O stent foi fabricado em resina acrílica, sendo utilizado para planejamento e durante todas as sessões de radioterapia. A mucosite oral foi avaliada através das escalas da Organização Mundial de Saúde (OMS) e Oral Mucositis Assessment Scale (OMAS); a disgeusia foi avaliada através de pergunta dicotômica (sim/não); o trismo foi avaliado por exame físico com auxílio de paquímetro universal; o impacto da saúde bucal na QV foi calculado através do questionário Oral Health Impact Profile (OHIP-14); foi elaborado questionário para avaliação do uso do dispositivo pela percepção do paciente. De um total de 26 pacientes recrutados, a amostra final foi composta por 20 participantes, 12 homens (60%) e 08 mulheres (40%) com idade variando entre 26 e 88 anos. O carcinoma espinocelular foi o tipo histológico mais prevalente (75%), sendo a língua o sítio mais acometido (50%). Metade da amostra foi diagnosticada com tumores de até 2 cm de extensão, sem comprometimento linfonodal em 45% dos casos ou metástase à distância (90%). O protocolo de tratamento mais realizado foi de cirurgia seguida de radioterapia. A maioria da amostra eram não fumantes (60%) e sem ingestão regular de bebida alcoólica (70%). Ao final da radioterapia, os participantes apresentavam mucosite oral Grau 2 (65%) pela OMS, com média de 2,64 ± 0,87 (OMAS). Pacientes submetidos às três modalidades de tratamento (cirurgia, seguida de quimioterapia e radioterapia) apresentaram maior score de OMAS que os que foram submetidos à radioterapia combinada apenas com quimioterapia ($p=0,01$) ou com cirurgia ($p=0,04$). Houve diminuição significativa de 6.6 mm (±7.58) de abertura de boca em comparação à inicial ($p<0,01$) e disgeusia em 80% da amostra, sem diferença estatística ($p>0,05$). Houve piora no impacto da saúde bucal na QL nos valores globais ($p=0,002$) e no

domínio 4 (p=0,014). Para a maioria dos participantes, o dispositivo não era incômodo (60%), seu uso não provocava dor (80%), sendo estável na boca durante as sessões de radioterapia (90%). Todos (100%) os pacientes avaliaram seu uso como importante para o tratamento. Apesar da variedade de efeitos colaterais apresentados, a maioria foi bem tolerado pelo paciente durante o tratamento. O uso do stent, assim como o tratamento integral e multidisciplinar do paciente, pode ter contribuído para estes resultados.

Palavras-chave: Radioterapia de Intensidade Modulada. Qualidade de Vida. Trismo.

ABSTRACT

Fabrication of intraoral stent for oral protection during radiotherapy

In the need for cancer treatment involving radiotherapy, several side effects are expected for the therapy to reach, in addition to neoplastic tissue, healthy tissue. The research objectives were: a) to make an intraoral device (“stent”) to mechanically separate the palate, tongue, and mouth floor and keep the mouth opening stable in an attempt to minimize some of the side effects such as oral mucositis, dysgeusia, and trismus; b) assess the impact of oral health on quality of life (QoL); c) assess the comfort and stability of the device according to the patient's perception; d) compare the results of trismus, dysgeusia and impact of oral health on QoL before and after radiotherapy. The device was fabricated of acrylic resin and used for planning and during all radiotherapy sessions. Oral mucositis was assessed using the World Health Organization (WHO) and Oral Mucositis Assessment Scale (OMAS) scales; dysgeusia was assessed using a dichotomous question (yes/no); trismus was assessed by physical examination with the aid of a universal caliper; the impact of oral health on QoL was calculated using the Oral Health Impact Profile (OHIP-14) questionnaire; a questionnaire was designed to assess the use of the device according to the patient's perception. From a total of 26 patients recruited, the final sample consisted of 20 participants, 12 men (60%) and 8 women (40%) aged between 26 and 88 years. Squamous cell carcinoma was the most prevalent histological type (75%), with the tongue being the most affected site (50%). Half of the sample was diagnosed with tumors up to 2 cm in length, without lymph node involvement in 45% of cases or distant metastasis (90%). The most common treatment protocol was surgery followed by radiotherapy. Most of the sample were non-smokers (60%) and without regular alcohol consumption (70%). At the end of radiotherapy, the participants presented WHO Grade 2 (65%) oral mucositis, with a mean of 2.64 ± 0.87 (OMAS). Patients who underwent all three treatment modalities (surgery, followed by chemotherapy and radiotherapy) had a higher OMAS score than those who underwent radiotherapy combined with chemotherapy alone ($p=0.01$) or with surgery ($p=0.04$). There was a significant decrease of 6.6 mm (±7.58) in mouth opening compared to before radiotherapy ($p<0.01$) and dysgeusia in 80% of the sample, without a statistical difference ($p>0.05$).

There was a worsening in the impact of oral health on QL in global values (p=0.002) and Domain 4 (p=0.014). For most participants, the device was comfortable (60%), its use did not cause pain (80%), and remained stable in the mouth during radiotherapy sessions (90%). All (100%) patients rated its use as important for treatment. Despite the variety of side effects presented, most were well tolerated by the patient during treatment. The use of stents, as well as the comprehensive and multidisciplinary treatment of the patient, may have contributed to these results.

Keywords: Intensity-Modulated Radiotherapy. Quality of Life. Trismus.

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LIST OF ABREVIATIONS

EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC-H&N-35	Quality of Life Questionnaire - Head and Neck Cancer Module (35 questões)
IMRT	Intensity-modulated radiation therapy
IOS	Intraoral device
LLLT	Low-Level Laser Therapy
LTDA	Sociedade de Responsabilidade Limitada
Max	Maximum
Med	Median
Min	Minimum
OHIP	Oral Health Impact Profile
OMAS	Oral mucositis assessment scale
OMS	Organização Mundial de Saúde
PMMA	Polymethyl methacrylate
QoL	Quality of life
QV	Qualidade de vida
RMO	Restricted mouth opening
sd	Standart deviation
UW-QoL	University of Washington Quality of Life

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1 INTRODUCTION

1 INTRODUCTION

Cancer is a worldwide known group of diseases that can be defined by the uncontrolled growth of cells, which have the capacity to invade neighboring and distant tissues (WHO, 2021).

Twenty million new cases of cancer were expected with 9.6 million related deaths in 2018 (Ferlay et al., 2019). Cancer is the second leading cause of death worldwide. Tumors in the oral and maxillofacial regions represent 7% of malignant neoplasms and, therefore, deserve the attention of health professionals (Siegel, Miller, Jemal, 2019).

The main lines of treatment are surgery, chemotherapy, and radiotherapy, which can be performed alone or in combination. Its indication depends on the histological type of tumor, extension, presence and metastasis, and systemic condition of the patient.

Radiotherapy is an important modality of antitumor treatment based on the emission of radiation beams in calculated doses, being an important ally against several diseases. However, when applied to the head and neck structures, it can trigger side effects such as oral mucositis, xerostomia, osteoradionecrosis, radiation caries, candidiasis, loss of taste, and trismus (Jaguar et al., 2017; Ganzer et al., 2015; Barkokeban et al., 2012; Bavahard et al., 2013; Ghelardi et al., 2008; Scully, Epstein, Sonis, 2004; Sonis et al., 1999).

To circumvent these side effects, intraoral devices (IOS) have been fabricated to mechanically separate the oral tissues, stabilize, and immobilize the patient during raid therapy sessions and maintain the mouth opening satisfactorily throughout the treatment (Inoue et al., 2020; Chen et al., 2020; Lee, Nguyen, Wu, 2019; Rocha et al., 2017; Agarwal, Shiva Kumar, Rai, 2016; Jain, Jananib, Suganya, 2016; Mall et al., 2016; Verrone et al., 2014; Hong et al., 2019). Johnson et al. (2013) declared the preservation of 51 m^3 of healthy tissue during radiotherapy. This result may indicate less pain, discomfort, less use of opioids, or discontinuation of treatment due to the

severity of side effects. The study that started our line of research revealed that the material indicated for the manufacture of IOS is acrylic resin (Martins et al., 2016).

Our objective was to fabricate a comfortable device, to assess radiotherapy-related side effects and the impact of oral health on quality of life.

2 ARTICLES

2 ARTICLES

2.1 ARTIGO 1 - Clinical evaluation of semi-customized intraoral stents in head and neck radiotherapy

This article was presented in this Dissertation written according to the *Clinical Oral Investigations instructions and guidelines for article submission.*

Title: Clinical evaluation of semi-customized intraoral stents in head and neck radiotherapy

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Abstract

Objectives: To evaluate the clinical side effects of a custom intraoral stent (IOS) in patients under intensity-modulated radiation therapy (IMRT) treatment for head and neck cancer.

Materials and Methods: Oral mucositis was assessed using the World Health Organization (WHO) scale and Oral Mucositis Assessment Scale (OMAS); impact of oral health on quality of life was evaluated with OHIP-14 questionnaire; dysgeusia and comfort of using the IOS were assessed by a survey with a dichotomous question (yes/no).

Results: Twenty subjects (12 male and 08 female) with average age of 52.9 (± 17.31) years were submitted to radiation doses varying from 40 to 70 Gy. Squamous cell carcinoma represented 75% of the sample, while the tongue was the most affected site in 50% of the total. Individuals who underwent surgery, radiotherapy and chemotherapy had significantly higher scores of OMAS than those undergoing chemoradiotherapy ($p=0.01$) and those undergoing surgery followed by radiotherapy ($p=0.04$). There was a significant increase in oral health impact profile values in domain 4 ($p=0.014$) and in general ($p=0.002$).

Conclusions: There was a wide variation in the intensity of side effects, but most of them were well tolerated by the patient. The use of IOS along with the comprehensive treatment of the patient seems to contribute to alleviating the signs and symptoms.

Clinical Relevance: The use of IOS can be used as an adjunct to relieve the side effects of radiotherapy treatment in the head and neck region.

Introduction

Cancer is a worldwide known disease and a leading cause of death, resulting in nearly 10 million deaths in 2020 [1]. In its different forms and degrees of severity, cancer may cause pain and suffering for the patient and people in their social circle [2].

The main treatment modalities are surgery, chemotherapy, and radiation therapy, combined or isolated. Despite resulting in a good tissue response, several side effects are expected when radiotherapy is performed, which may affect the quality of life. Health professionals strive to find technologies capable of preventing or mitigating the complications caused by this disease [3].

Intraoral stents were developed aiming to limit radiotherapy toxicities in healthy tissue that receives unnecessary radiation. It also helps in the stability, reproducibility, and immobilization of the patient during radiotherapy sessions. Positive and considerable results have been obtained in patients who used the stent during the application of radiotherapy, however, there is still a need for improvement of the model and dissemination of a stent that is accessible to the entire community [4-10].

This study aimed to evaluate the use of IOS in patients undergoing radiotherapy with modulated intensity and their side effects.

Methodology

This research was approved by the Ethics Committee for Research in Human Beings of Bauru School of Dentistry (Brazil) with the Certificate of Presentation for Ethical Review 94436518.7.0000.5417.

The inclusion criteria were adult patients with cancer of the head and neck region, undergoing oral preparation before intensity-modulated radiotherapy, and with physical conditions to receive the IOS and mouth opening of at least 20 mm.

Exclusion criteria were patients undergoing other types of radiotherapy, with mouth opening that did not allow the insertion and maintenance of the IOS in the mouth during treatment, or who had extensive tumors inside the mouth that prevented them from receiving the IOS.

All participants signed a free, prior and informed consent document to participate in the study.

Study design

The sequence followed by all patients is shown in Table 1:

Table 1. Dental assistance workflow.

1. *Cancer diagnosis (by physician or dentist);*
2. *Referral to the Dental Service;*
3. *Oral preparation before radiotherapy;*
4. *Invitation to participate in the study;*
5. *Informed Consent to participate in the study;*
6. *OHIP-14 questionnaire application (1st);*
7. *Dysgeusia assessment (1st);*
8. *Fabrication of IOS;*
9. *Making the thermoplastic mask (IOS in position);*
10. *Computed tomography exam for planning (IOS in position);*
11. *Radiotherapy sessions (IOS in position);*
12. *Monitoring and treatment side effects of anticancer treatment with low-level laser therapy (LLLT) and drug prescriptions;*
13. *OHIP-14 questionnaire application (2nd);*
14. *Dysgeusia assessment (2nd);*
15. *Oral mucositis assessment;*
16. *Assessment of the IOS used by the patient.*

Oral care before and during radiotherapy

It is important to emphasize that all participants underwent removal of intraoral foci of infection before the fabrication of IOSs. All patients received specific oral care guidelines for each necessity.

The protocol for the prevention and treatment of oral mucositis involved the application of LLLT (Therapy XT, red laser, 100 mV, spot size 0.028 cm², 660 nm, DMC®, São Carlos, São Paulo, Brazil) to all participants. Laser prophylaxis (1J, 10s, 35.71 J/cm^2) started on day one of radiotherapy, while laser treatment (2 J, 20 s, 71.43 J/cm^2) began with the first sign of oral mucositis (erythema). Laser application was carried out 5 days per week from day one of radiotherapy until the complete remission of the lesions. The tumor area was not irradiated.

Pain, dry mouth and/or hyposalivation, and oral lesions such as opportunistic infections when diagnosed were treated.

IOS fabrication

The first step in fabricating the IOS was the material selection. It was established, in a previous study published by the authors [11] that polymethyl methacrylate (PMMA) might be the material of choice due to its density and structural integrity after the radiotherapeutic protocol.

PMMA is non-toxic, inert, non-irritating, and does not block radiation since it shows Hounsfield units (HU) close to water [8,9,11,12]. In addition, it is resistant, hygienic, low-cost, and an easy-to-handle material.

All devices were fabricated by experienced practitioners (Figure 1 A-H). First, acrylic resin (Jet - Artigos Odontológicos Clássico LTDA, São Paulo, SP., Brazil), plates were handcrafted for the mandible and maxilla, separately, in 2 sizes each (medium and large according to stock trays). The plates were measured in the patient's mouth, choosing the most suitable sizes. After that, the plates were joined in the mouth through a resin wall of 1.5 cm (minimum) to 2.5 cm (maximum) on each side, providing cheek support and keeping the mouth open, with enough room for accommodation of the tongue in the anterior region. The IOS was adjusted for dentate and edentulous patients. IOSs were stored in a 2% chlorhexidine solution, daily renewal, and rinsed in running water before use [13].

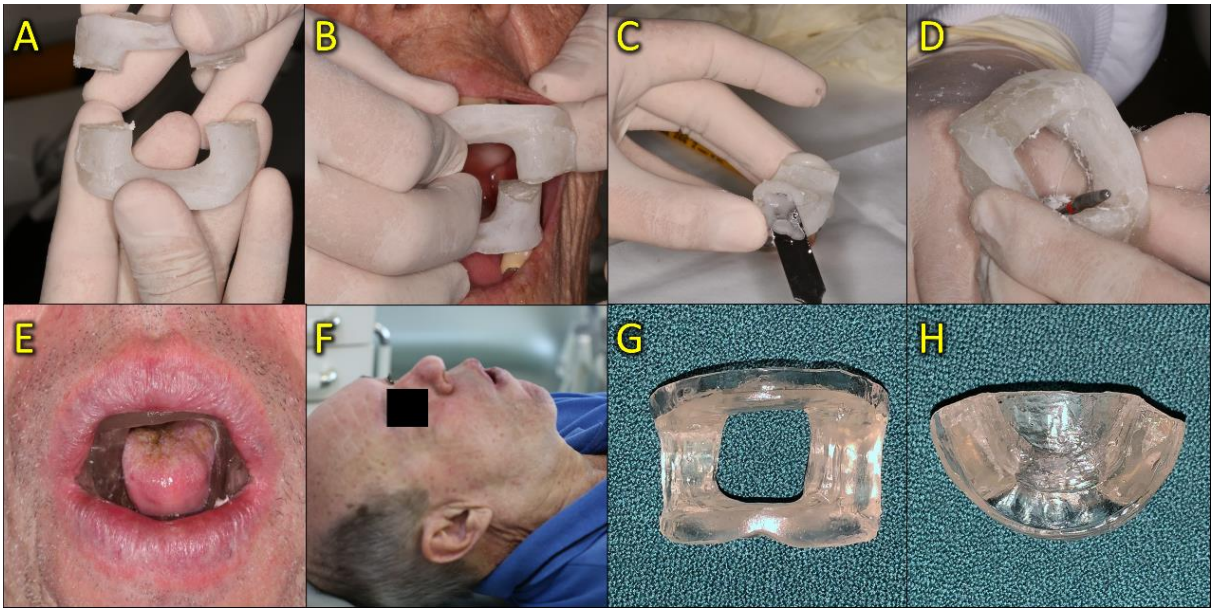

Figure 1. Process of fabrication of IOS for a male patient, diagnosed with a squamous cell carcinoma of the tongue (T2N1M0): A – Fabrication of the split IOS; B – Test and intraoral adaptation; C – Bonding the arches with acrylic resin; D – Finishing and polishing with tungsten maxi-cut bur. E – IOS in position. Note the placement of the tongue, which remains rested on an acrylic resin plateau, helping to maintain the IOS stable during the treatment session; F – Test in supine position; G – Front view of finished IOS; H – Upper view.

Oral Health Impact Profile (OHIP-14)

In the first appointment and after the end of cancer treatment (2 phases), the patients answered the OHIP-14 questionnaire to assess the impact of the oral condition on their quality of life. It englobed 14 questions, divided into 7 domains: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap. The answers were coded in ordinal values from 0 to 4, never, rarely, sometimes, usually, and always, respectively, [14].

The scale of responses is multiplied by the weight of each domain, resulting in the impact of the dimension. Values lower than 9.33 were considered as having a weak impact, moderate impact when between 9.33 and 18.66 and, strong between 18.66 and 28 [14]. A Brazilian validated questionnaire was used [15].

Oral mucositis assessment

Oral mucositis was assessed according to the World Health Organization (WHO) scale [16] and the Oral Mucositis Assessment Scale (OMAS) [17]. Results were tabulated between 7 and 14 days after completion of radiotherapy.

According to the WHO scale, mucositis is classified into 5 degrees: Grade 0 (Normal), Grade 1 (Erythema, irritation, pain), Grade 2 (Erythema, ulcers, the patient can eat solids), Grade 3 (Ulcers, the patient can only eat liquid) and Grade 4 (Oral alimentation impossible).

For the OMAS scale, the evaluation of the severity and degree of oral mucositis was obtained using the standard OMAS score: $(\sum ui/nu) + (\sum ei/ne)$, with $\sum ui$ being the sum of the ulcerated areas; nu: number of ulcerated areas and $\sum ei$ the sum of the intensity of erythema; ne: number of areas with erythema. The score ranges from 0 to 5.

Patients' perception

Patients were asked about any changes in the taste of food in two different periods: before the start of radiation treatment and from 7 to 14 days after the last radiotherapy session. It was a dichotomic question (yes/no). The evaluation of the IOS was achieved using the questionnaire shown in Table 2. The questionnaire was applied between 7 and 14 days after the end of treatment.

Table 2. Questionnaire developed to assess the patient's perception of the use of IOSs in radiotherapy treatment.

Questions:
1. Was using the stent bothersome?
2. Did you feel pain while using the stent?
3. Was the stent stable in the mouth during use?
4. Did you have difficulties maintaining the use of the stent during treatment?
5. Did you move your tongue while using the stent?
6. Was the use of the stent important to you during the period of radiotherapy?

Radiotherapy application

All patients required IMRT planning. To perform the computed tomography, aiming to determine the target volume for planning, the IOS was positioned by the patient with the assistance of the nursing staff, when necessary, followed by the fabrication of individual thermoplastic masks, then by computed tomography.

The radiotherapy protocol used for all patients was 6 MV (megavoltage) with a 1.8 to 2.12 Gy fraction, once a day, 5 days a week.

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 20.0 for Windows (IBM, USA). Quantitative data were presented as mean and standard deviation, and qualitative data were presented as the number of patients and percentage of the sample. The association between the degree of oral mucositis (OMAS) and clinical variables was investigated using the One-Way ANOVA or Student's T-test, while oral mucositis (WHO) used the Mann-Whitney U test or Kruskal-Wallis. The correlation between radiotherapy doses and the intensity of oral mucositis, OMAS and WHO scales, was evaluated using Spearman's and Pearson's correlation test, respectively. The

correlation between the two tools used to assess the intensity of mucositis (WHO and OMAS) was evaluated using Spearman's correlation.

The association between dysgeusia and clinical variables was evaluated using the Chi-square test. The influence of neoplasm size (T), type of cancer treatment, and dysgeusia on patients' quality of life (OHIP-14) was evaluated using the One-Way ANOVA and Student's T-test.

The correlation between the intensity of oral mucositis and treatment prescribed dose and domains 2 (Physical pain) and 4 (Physical disability) and total OHIP-14 value was evaluated using Pearson's correlation (OMAS) and Spearman's correlation (WHO).

The level of significance for all variables was established at 5%.

Results

This is a cross-sectional study, in which a convenience sample of 26 patients who were diagnosed with cancer in the head and neck region with the indication for radiotherapy treatment (IMRT type) were invited to participate. From 26, 02 patients dropped out of the study, 02 died before the final data were collected, 01 had insufficient mouth opening for IOS accommodation and 01 had an extensive tumor in the mouth that prevented placement of the IOS. They were excluded from the final sample.

The sample consisted of 12 men (60%) and 8 women (40%), aged between 26 and 88 years. The patient profile results are presented in Table 3 and side effects in Table 4 and Table 5.

Table 3. Clinical characteristics of patients with cancer in the head and neck region undergoing intensity-modulated radiation therapy (n = 20).

Variant	Grade	n (%)
Sex	Female	8 (40%)
	Male	12 (60%)
Age	Mean ± sd	52.9 ± 17.31
	Median	55.5
	Variation	26-88
Tumor site	Buccal mucosa	2 (10%)
	FOM	1 (5%)
	Gingiva	1 (5%)
	Lip	2 (10%)
	Nasopharynx	2 (10%)
	Oropharynx	1 (5%)
	Soft palate	1 (5%)
	Tongue	10 (50%)
Histological subtype	Adenoid cystic carcinoma	1 (5%)
	Adenocarcinoma	1 (5%)
	Microcystic adnexal carcinoma	1 (5%)
	Squamous cell carcinoma	15 (75%)
	Unspecified malignant neoplasm	1 (5%)
	Unspecified malignant salivary gland tumor	1 (5%)
T stage	Tx	0 (0%)
	T0	0 (0%)

	Tis	0 (0%)
	T1	2 (10%)
	T2	8 (40%)
	T3	6 (30%)
	T4	4 (20%)
N stage	N0	9 (45%)
	N1	3 (15%)
	N2	7 (35%)
	Nx	1 (5%)
M stage	Mx	2 (10%)
	M0	18 (90%)
	M1	0 (0%)
Treatment	RT	1 (5%)
	RT + Surg	10 (50%)
	RT + CTx	4 (20%)
	RT + Surg + CTx	5 (25%)
Prescribed radiation dose (Gray)	Mean ± sd	63.57 ± 6.59
	Median	65
	Variation	40-70
Tobacco smoking	Yes	8 (40%)
	No	12 (60%)
Alcohol consumption	Yes	6 (30%)
	No	14 (70%)

CTx = Chemotherapy; RT = Radiotherapy; sd = Standard deviation; Surg = Surgery.

Table 4. Oral mucositis and dysgeusia results of patients with cancer in the head and neck region undergoing intensity-modulated radiation therapy (n = 20).

Side effect	Grade	Values
Oral mucositis (WHO)	Median	Grade 2
	25%	Grade 2
	75%	Grade 2
	Minimum	Grade 1
	Maximum	Grade 3
Oral mucositis (OMAS)	Mean ± sd	2.64 ± 0.85
	Median	2.71
	Minimum	1
	Maximum	4.14
Dysgeusia	Yes	16 (80%)
	No	4 (20%)

sd = Standard deviation.

Table 5. Oral mucositis assessment scales of patients with cancer in the head and neck region undergoing intensity-modulated radiation therapy (n = 20).

Oral mucositis	Grade	n (%)
Oral mucositis (WHO)	Grade 0	0 (0%)
	Grade 1	3 (15%)
	Grade 2	13 (65%)
	Grade 3	4 (20%)
	Grade 4	0 (0%)

Oral mucositis (OMAS)	0.00 – 1.00	0 (0%)
	1.00 – 1.99	3 (15%)
	2.00 – 2.99	10 (50%)
	3.00 – 3.99	3 (15%)
	4.00 – 5.00	2 (10%)

A moderate positive correlation between WHO and OMAS oral mucositis assessment tools used was observed (r=0.642; p=0.002). There was no association between the intensity of mucositis (WHO and OMAS) and sex, history of smoking or alcohol consumption, location, tumor size, and presence of metastasis or dysgeusia (p>0.05). The presence of pain or discomfort with the use of the IOS was not associated with the degree of oral mucositis (p>0.05).

The type of treatment proposed had a significant effect on the intensity of oral mucositis. Regarding OMAS, only one patient was submitted to isolated treatment with radiotherapy. Thus, the statistical comparison was performed only between combined treatments. Patients undergoing treatment with a combination of all three modalities (radiotherapy, surgery, and chemotherapy) had significantly higher OMAS scores than those undergoing radiotherapy combined with chemotherapy (p=0.01) and with surgery radiotherapy (p=0.04).

The distribution of the impact of oral health on quality of life was assessed using the OHIP-14 questionnaire, applied before and after completion of radiotherapy treatment (Table 6). The results, by domain, are described in Table 7.

Interestingly, 11 (55) of the participants remained with the same impact before and after radiotherapy, while 08 (40%) had a worsened impact after treatment and 01 (5%) had a better impact.

Table 6. Distribution of the impact of oral health on quality of life, before and after radiotherapy (n=20).

Impact	**Pre-radiotherapy** n (%)	**Post-radiotherapy** n (%)
Weak	6 (30%	4 (20%)
Moderate	13 (65%)	11 (55%)
Strong	1 (5%)	5 (25%)

p = significance level (<0.05). Paired t-test

Table 7. Oral Health Impact Profile Instrument (OHIP-14), by domain (n = 20).

Domain	**Pre-radiotherapy**				**Post-radiotherapy**				**p***
	Med	**Mean±sd**	**Min**	**Max**	**Med**	**Mean±sd**	**Min**	**Max**	
1	1.00	1.06±0.86	0.00	2.98	2.47	2.41±0.89	0.98	4.00	>0.05
2	1.50	1.78±1.26	0.00	4.00	2.34	2.41±1.09	0.00	4.00	>0.05
3	2.18	2.30±1.03	0.00	4.00	2.73	2.54±1.07	0.45	4.00	>0.05
4	1.52	1.49±1.21	0.00	4.00	2.52	2.34±1.19	0.48	4.00	*0.014*
5	0.80	1.00±0.91	0.00	3.40	1.30	1.26±1.11	0.00	3.40	>0.05
6	1.24	1.55±1.14	0.00	3.62	2.19	1.93±1.16	0.00	4.00	>0.05
7	1.00	1.36±1.36	0.00	3.82	1.64	1.83±1.13	0.00	4.00	>0.05
Overall	10.49	10.55±4.94	1.70	22.24	15.98	14.72±5.10	4.94	22.38	*0,002*

Med = Median; Min = Minimum; Max = Maximum; sd = Standard deviation

p = significance level (<0.05). Paired t-test

A significant increase in OHIP-14 values in domain 4 (physical disability) ($p=0.014$), in gross values ($p=0.002$), and OHIP grade ($p<0.001$) was observed after treatment. The other domains did not show significant changes ($p>0.05$). There was no influence of neoplasm size (T), treatment modality, and dysgeusia on OHIP values ($p>0.05$). There was no significant correlation between oral mucositis (WHO and OMAS) and prescribed treatment dose with OHIP-14 and Domains 1-7 ($p>0.05$).

Regarding the use of the IOS, 12 (60%) participants reported comfort during treatment, and 18 (90%) of them did not feel any pain. Only 2 (10%) participants reported instability of the IOS in their mouths, also reporting difficulty in keeping it. Eleven (55%) of the individuals were able to move their tongues during its use and all participants considered the IOS important for radiotherapy treatment.

Discussion

Treatment planning for patients with cancer in the head and neck region remains challenging, despite the technological advances in medicine in recent decades. The difficulty is mainly due to the proximity of the tumor to important anatomical regions for oral functions, such as speech, chewing, and swallowing [18]. In addition to the lack of self-care, the oral condition, and the profile of the most affected patients, the main goals of an acting multidisciplinary team of cancer patients include managing the toxicity of cancer therapy to minimize the negative impact of oral health conditions on the quality of life [18-21].

Radiotherapy is commonly chosen for head and neck cancer due to the good tissue response to radiation, but it is associated with several side effects that can affect short and long-term esthetics, function, and quality of life. Oral mucositis, dysgeusia, salivary changes, trismus, and bone necrosis are some of the complications that most affect the patient, which justifies the number of studies focusing on both their prevention and treatment [8,17-19,22]. Thus, it becomes implausible to dissociate the use of IOSs from comprehensive patient care.

Stents that help the radiotherapy technique have been created and used for decades, but without standardization regarding indications, form, material, and function. There are two types of IOS, the shielding stent, made with materials that block radiation, and a positioning stent, which helps in reproducibility and separation of oral tissues, which is the target of the current study [23].

Aware of the existence of late side effects of radiotherapy, like radiation decay, reduced mouth opening, and osteoradionecrosis, patients should be continuously monitored by the dental team according to their individual needs.

The results obtained in this study reinforce the importance of the interaction between the radiotherapist and the dentist, as well as other health professionals such as oncologists, nutritionists, physiotherapists, psychologists, requiring further studies for its standardization and accessibility of IOS for those undergoing radiotherapy.

Oral mucositis

Unfortunately, oral complications are common in patients after head and neck radiotherapy. In this context, oral mucositis is one of the main complications of patients undergoing this treatment modality, combined or not with chemotherapy. With variable incidence, the factors that are related to its clinical course are the degree of toxicity of the therapy, the individual patient's response to the treatment protocol, oral condition, and harmful habits such as smoking and drinking. In addition to pain and greater susceptibility to opportunistic infections, it can result in weight loss, treatment interruption, hospitalization, increased use of opioids, and gastrostomy feeding.

The assessment of the severity of oral mucositis and the patient's ability to feed are important factors in this regard [20,24,25].

All participants in this study completed treatment with some degree of mucositis. Three of them ended up with no ulcers present in the mouth and OMAS below 2.00, all-male, 02 with tumors in the nasopharynx, and 01 in the tongue, with no common characteristics regarding the underlying disease, staging, or treatment performed. In contrast, 4 patients reached grade 3 (WHO) between 7 and 14 days after completion of radiotherapy, 02 with tongue, 01 lip, and 01 oropharynx tumor, without unanimity regarding the disease, treatment performed, and presence of risk factors such as smoking and regular drinking.

Two participants reached an OMAS value above 4.00, indicating the presence of intense erythema and ulcers, but both were able to feed on solids (Grade 2 - WHO). The tumor location in these 02 cases was in the soft palate and cheek mucosa and the patients underwent multiple surgical treatments followed by chemoradiotherapy, without the habit of smoking or drinking. The disparity between the oral mucositis scales could be observed, despite the moderate positive correlation between them ($r=0.642$; $p=0.002$)

Only one participant required enteral nutrition (Grade 4 - WHO) and three suspended radiotherapy for a week due to oral lesions, but before the end of radiotherapy, they were able to eat orally again (Grade 1 - WHO).

These findings corroborate the literature. It is not possible to prevent the appearance of oral mucositis, with a predominance of moderate presentation with erythema and ulcers, but with the maintenance of solid food intake [8,9,24,26,27]. Rocha et al. (2017) reported that the suspension of treatment temporarily due to oral mucositis reached 33% of the sample composed of patients using IOS in the treatment of cancer of the lower lip [24].

Studies have already shown that besides decreasing the intensity and volume of oral mucositis lesions, the use of IOSs can delay the onset of severe oral mucositis [8,9,23,28]. Our study points to a similar result since moderate mucositis was observed in most of the cases.

Inoue et al. (2020) performed a retrospective cohort study of patients treated with radiotherapy for cancer of the maxilla and nasal cavity divided into Group IOS and Control Group. They obtained a lower degree of oral mucositis ($p=0.028$) and less need for opioids during treatment ($p=0.009$) in the IOS Group. However, only 8.82% of participants underwent IMRT, different from the current study with 100% of IMRT [28].

In contrast, Verrone et al. (2014) compared 33 patients undergoing IMRT for the treatment of tongue and floor of mouth cancer. Group 1 (with IOS) consisted of 19 patients and the Control Group (without IOS) of 14. There was no significant difference in the severity of oral mucositis between the groups (p-0.082), but Grade 3 (WHO) was observed a week before in the Control Group. [9]. Our study corroborates the worsening of mucositis between the 3rd and 4th weeks after starting radiotherapy.

Patients undergoing treatment with a combination of surgery, radiotherapy, and chemotherapy in our study had significantly higher OMAS scores (more erythema and ulcers) than those undergoing radiotherapy associated with chemotherapy ($p=0.01$) and surgery ($p= 0.04$). This result indicates that the more treatments the patient undergoes in a short period, the greater the side effects may be present and, consequently, greater attention should be paid to their prevention.

The impact of oral health on quality of life

Before cancer treatment, most of the patients with cancer in the head and neck region already have conditions in oral health such as periodontal disease, residual roots, opportunistic infections, need for extractions

and restorations, and salivary changes. [21]. In this scenario, it might be considered that the oral condition implies, as well as the oral complications of cancer treatment, in the quality of life and that the evaluation of it must be based on a personal perception of well-being [29].

The Oral Health Impact Profile-14 was designed to assess patients' perception of the impact of oral health on quality of life, originally used in patients without head and neck cancer [14]. For this population, the literature still lacks studies, and as a patient-dependent scale, the results are subjective.

Melo et al. (2019) conducted a cross-sectional study carried out with 130 patients with head and neck cancer in the Brazilian population before or during anti-neoplastic treatment [30]. The average score obtained was 19.52 (±11.79), characterizing it as a strong impact, similar to 21.40 (±10.11) found by Torabi et al. (2012) of the Iranian population [31]. A study that applied the questionnaire to 345 patients in Serbia before treatment resulted in a strong impact (24.30±14.15) in this population [32].

In the present study, patients started (10.55±4.94) and finished (14.72±5.10) treatment with a medium impact, but with worsening between the two periods (p=0.002), more positive results than those found in previous studies [30-32] where the main factors that affected the quality of life were physical pain, physical disability, and functional limitation.

On the other hand, the results observed in this study pointed to psychological discomfort, physical pain, and social disability pre-radiotherapy. After radiotherapy, there was a shift to functional limitation rather than social disability, physical pain and physical disability amongst OHIP-14 domains were greatly affected. In another study, the most affected domains were physical pain and physical disability [33].

Santos et al. (2017) assessed the impact of oral health on quality of life using the OHIP-14 questionnaire in 30 patients with head and neck cancer (Study group) and 45 without a history of cancer (Control group). The values obtained were (4.67 to 12.94, median 9.62), lower than those found in this study, but also indicating a medium impact. In contrast, in the Control Group, values were lower ($p < 0.001$) and ranged from 0 to 6.42 (median of 1.48), indicating a weak impact on quality of life and indicating how the effects of cancer treatment can harm the quality of life of patients [18].

When the most affected domains of the patient are identified, they might be related to clinical findings, but also to complaints that may not be clearly expressed during dental follow-up. To this extent, = treatments aiming to improve quality of life might be established.

One patient (female, 57 years old, T4N2M0 tongue squamous cell carcinoma treated concomitantly with chemotherapy and radiotherapy, non-smoker and non-alcoholic) showed a decrease in OHIP-14 after treatment from 22.24 (strong impact) to 7.92 (low impact). The patient reported severe pain due to the extensive tumor in the mouth, which improved with the treatment.

There was a statistical difference in Domain 4 (physical disability) between the two periods evaluated ($p = 0.014$). This domain contains questions about eating in terms of satisfaction with eating and the need to interrupt meals. Although there is no correlation between this domain and the two oral mucositis assessment scales ($p>0.05$), it could be observed the need that health professionals to focus on this complaint. In this study, not all patients received nutritional monitoring during radiotherapy.

Use of IOS

The IOS needs to be well-fitted and stable in the patient's mouth, causing minimal discomfort. It should be usable in both edentulous and dentate patients. Single-piece IOSs for the maxilla and mandible can be difficult to insert depending on the degree of oral mucositis and trismus, and therefore must be delicate and well-polished, not causing further trauma to already-sensitive mucosa during radiotherapy [8,24,34].

There is still no consensus on the ideal shape, height, and thickness for the IOS. The IOS used in this study was made to accommodate teeth or alveolar ridges and to have support for tongue stabilization, similar to studies found in the literature [11,28,34]. As for height, a distance between the incisors of 1.5 to 2.5 cm was chosen, depending on the initial mouth opening, without the patient feeling pain when keeping the IOS in position. Similar measurements were found in the literature as 1.0-2.0 cm [9], 1.0-3.0 cm [7,35], 1.5 cm [8,27], 1.5-2.0 cm [36] and 2 cm [37]. Hong et al. considered a height ranging from 2.1 to 6.8 cm, superior to all other studies that provided this measure [38]. The lack of standardization is due to the variation in mouth opening in the general population and may also be related to the location and extension of the tumor, often resulting in pre-radiotherapy trismus. Other studies have considered other methods to define this height: 1.5 to 2 cm less than the mouth opening [36] or between 50 to 75% of it [10,28,39,40].

The chosen thickness of the upper and lower walls was approximately 3 mm and the sides, 1.5 cm. Bø et al. and Rocha et al. established, respectively, 2 and 5 mm for upper and lower walls [24,41]. Most studies do not specify IOS thickness.

IOS stability is still a limitation of studies, due to the variety of oral conditions. such as missing teeth with severe bone resorption [28,41], edentulism [26,28], and absence of incisors and canines [43]. Furthermore, the extension and location of the tumor, especially extensive tumors in the tongue and alveolar ridge and pre-radiotherapy trismus [28,40]. In the initial sample, the stent was contraindicated in two situations: a) A male patient with lip cancer initially treated with surgery, developed severe fibrosis, and limited mouth opening (<1 cm), making it impossible to insert the device; b) A male patient with extensive cancer on the floor of the mouth (>4 cm) extending to the alveolar ridge, making it impossible to manufacture the device.

Only 01 patient required minor stent readjustment during treatment because there was an oral mucositis ulcer in the lip. If a significant change in the size or shape of the IOS is required, the repetition and re-planning of radiotherapy must be evaluated. It is important to emphasize that none of the patients' treatments needed to be aborted, but three participants needed one-week radiotherapy suspension to recover from oral mucositis during the study.

Its indication, for many years, was restricted to tongue tumors [9, 44], but the treatment of lesions in other locations in the head and neck region can also benefit from the use of the IOS [6,8,10,24,45]. In this case, in addition to the tongue (50%), the sample consisted of lesions in the buccal mucosa, floor of the mouth, gums, lower lip, nasopharynx, oropharynx, and soft palate.

Patient's perception about the IOS

This is the first study that reports the patient's perception regarding the use of the IOS. Most of the sample did not report any discomfort with its use (60%) in general and 90% of them did not feel any pain during treatment, an extremely positive result. Despite adjustments and tests, 02 patients (10%) reported instability during the sessions.

In one of the cases, a male patient was diagnosed with extensive squamous cell carcinoma on the floor of the mouth, decreasing its clinical size during chemoradiotherapy, which may explain the reported instability. In the second case, another male patient was diagnosed with squamous cell carcinoma in the nasopharynx and lost approximately 25 kg during chemoradiotherapy treatment, which may also be the reason for the instability. All participants, at the end of the treatment, considered the use of the IOS important, even with the side effects presented.

The findings of this study align with those of previous studies, showing that the stent must be comfortable for the patient [7,24]. Differently, the IOS can be fabricated through the impression of the upper and lower arches of each patient [7-9,24,27,28,36,42,46,47]. The probability of discomfort and adjustments is reduced but taking an impression may be difficult depending on the extension, location of the tumor, and gag reflex. The handcrafted, prefabricated resin plates used fit satisfactorily for all patients after minor adjustments.

Patient's perception about taste alteration

In the present investigation, attention should be paid to the high incidence (80%) of patients who, within two weeks after the end of treatment, already had some degree of taste alteration.

Radiotherapy-related dysgeusia in the head and neck region maintains a more discreet interest in the scientific community compared to oral mucositis, although almost 100% of patients have short- or long-term taste disorders [48,49].

This alteration can result in the reduction, absence, or distortion of normal taste and its persistence and worsening can lead to inability to eat, nutritional deficiency, weight loss, malnutrition, and dietary changes, in addition to negatively impacting the quality of life [50-52].

Although there was no influence of dysgeusia on the impact of oral health on quality of life ($p>0.05$) in the current study, it is an important variable for the comprehensive treatment of the patient.

Limitations of the study

- Given the benefits of the IOS in reducing the side effects of radiotherapy in the head and neck region, it was determined not to use a control group for data comparison and use the literature already available.
- The sample was heterogeneous in terms of tumor location and staging, in addition to smoking and regular alcohol consumption.
- Despite the subjective method used, other methods are recommended for better diagnosis and treatment in research, such as solution-based [53], filter paper strips [54], electrogustometry, contact endoscopy [55], and filter paper discs [56].
- The relatively small sample can be explained by the fact that part of the study took place during the Covid-19 pandemic, which prevented, for one year, patients' access to the research location.

Conclusion

- All patients had oral mucositis at the end of radiotherapy treatment, but most of them (65%) were able to eat solids. The comprehensive treatment of the patient, considering the use of stents and oral care, may have contributed to this good result.

● There was a worsening of the impact of the oral condition on quality of life regardless of the oral care provided.

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2.2 ARTIGO 2 - Restricted mouth opening in intensity-modulated radiation therapy for head and neck cancer

This article was presented in this Dissertation written according to the *Acta stomatologica Croatica instructions and guidelines for article submission.*

Title: Restricted mouth opening in intensity-modulated radiation therapy for head and neck cancer

Running title: Limited mouth opening in IMRT

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Abstract

This case series aims to report the evolution of trismus in patients undergoing intensity-modulated radiotherapy (IMRT) for the treatment of head and neck cancer and correlates it with gender, cancer treatment, tumor size (T - staging), and the prescribed total radiation dose, and the dose to the mandible. Spontaneous mouth opening was measured with the aid of an analog caliper before cancer treatment and between 7 and 14 days after completion of radiotherapy. From a total of 20 patients, three had an initial mouth opening smaller than 30 mm before radiotherapy. After treatment, six participants developed trismus. The difference in the opening capacity between the two periods ranged from +7 mm to -23 mm with a significant reduction of 6.6 mm (±7.58) ($p<0.01$). There was no correlation between mouth opening reduction and the prescribed dose of radiotherapy or the dose to the mandible ($p>0.05$). The patient with head and neck cancer must be monitored by a qualified multidisciplinary team, given the incidence and severity of this side effect.

MESH terms: Head and Neck Neoplasms, Radiotherapy. Trismus

Author keywords: Oral cancer, Intensity-modulated radiation therapy, Stent

Introduction

During the last decades, the number of studies on the multiple oral complications arising from head and neck anticancer treatments has increased (1). Regarding radiotherapy modality, some of its side effects are oral mucositis (1), salivary changes (2), bone necrosis (3), dysgeusia (4), dysphagia (5), and trismus (6).

Trismus or restricted mouth opening (RMO) is defined as a contraction involving dysfunction of the masticatory muscles of any etiology (7,8), restricting the maximum mouth opening by up to 30 mm (9).

It is a common complication of anticancer treatment, but it is still considered a problem neglected by professionals despite being predictable in most cases (10-13).

This study aims is to discuss, through a series of cases, the comparison between mouth opening before and after radiotherapy treatment in patients undergoing intensity-modulated radiotherapy using an intraoral stent.

Patients and Methods

Firstly, this study was approved by the Ethics Committee for Research in Human Beings of the Bauru School of Dentistry under certificate of presentation for ethical review #94436518.7.0000.5417.

This case series comprises the dental care of 20 patients diagnosed with head and neck cancer with an indication for IMRT. The patients were followed by the Dental Team before, during, and after (14 days) the radiotherapy treatment.

All patients received dental treatment before radiotherapy to eliminate possible foci of infection that could worsen during anticancer therapy. Then, IOS was fabricated with acrylic resin to separate healthy tissue from the primary focus of radiation and keep the mouth open in a stable and reproducible position during all radiotherapy sessions (Figure 1 A-C).

(*Figure 1 A-C*)

The IOSs were manufactured with a height of 1.5 to 2.5 cm to help maintain mouth opening during and after irradiation (14-17). Data obtained through anamnesis and physical examination are shown in Table 1.

(*Table 1*)

The correlation between mouth opening reduction and total and mandibular doses were evaluated using Pearson's correlation but without significant correlation ($p>0.05$)

Lee et al. (2012) proposed a classification of mouth opening in degrees 1-4, also considering the patient's feeding capacity (9). Our results for the mouth opening capacity are shown in Table 2 and Table 3.

(*Table 2*)

(*Table 3*)

The present study showed that 75% (n=15) of the sample underwent surgery before radiotherapy. Of these, 20% (n=3) had an initial mouth opening less than 30 mm (Table 1 - Participants 2, 14, and 18). After completion of radiotherapy, this value rose to 46.67% (n=7).

When performing Spearman's correlation of tumor extension (T - staging) with initial mouth opening, we obtained a moderate negative correlation ($r=-0.3571$, $p=0.1222$). By correlating the tumor size with the difference in measurements in the pre and post-radiotherapy periods, a moderate positive correlation was found ($r=0.5186$, $p=0.1915$).

Spearman's correlation between cancer treatment performed (radiotherapy alone or combined with surgery and/or chemotherapy) and mouth opening after treatment completion revealed a weak positive correlation ($r=0.0914$, $p=0.7017$).

Discussion

The consequences of trismus can range from mild to severe. Studies show that, in addition to difficulties in talking, eating, chewing, and swallowing, RMO can cause breathing difficulties, severe pain accompanied by weight loss, difficulty in oral hygiene, and a negative

impact on the patient's quality of life (8,10, 18, 19). Thus, it is essential to study and better understand the development of this dysfunction.

The maximum interincisal opening was measured in dentate patients or the distance between the upper and lower edges in the midline region of edentulous patients, without causing pain. With the aid of an analog steel caliper (FORTGPRO-FG8330, Gurgelmix Máquinas e Ferramentas S/A, Franca, SP, Brazil.), all patients were evaluated before and after radiotherapy. The evaluation method corroborates those found in the literature (7, 8, 20).

Our study indicates that only 15% of patients had RMO (<30 mm) before radiotherapy and 20% after treatment, with a statistically significant difference between the periods ($p<0.01$) and a mean reduction of 6.60 ± 7.58 cm. Other studies have also pointed out the difference between measurements before and after radiotherapy (8, 11, 21-25). We consider this result to be positive, given the incidence of trismus in 8 to 62% of patients undergoing radiotherapy (12).

Our results are similar to those found by Steiner et al. (2015), which of 120 patients evaluated 6 months after radiotherapy, had a mouth opening of 40.1 mm (ranging from 11 to 65 mm), with 28.3% of trismus. The authors emphasized the negative impact of RMO (23).

Regarding the difference between genders, women had a higher incidence of trismus than men ($p<0.01$), representing 100% of the sample of trismus pre-radiotherapy and two-thirds post-radiotherapy, unlike Watters et al. (2019) (11). Caetano et al. (2016) (26) found no difference between genders when evaluating 32 patients 6 months post-radiotherapy with 21.9% of RMO (26).

This study points that the more extensive the tumor (T - staging), the smaller the pre-cancer treatment mouth opening ($r=-0.3571$, $p=0.1222$) and the greater the difference between initial and final measurements ($r=0.5186$, $p=0.1915$), corroborating findings in the literature (27,28).

For patients previously submitted to surgery, the initial RMO was 20%, a value lower than those found in Cohen et al. (2015) (13) (55.6%), Aggarwal et al. (2016) (22) (53.3%), Lee et al. (2012) (9) (47%) and Scott et al. (2011) (29) (30%). The heterogeneous sample may be a limitation of the study.

Cohen Et al. (2005) (13) concluded that 80.2% of patients with oral mucosal cancer had trismus after surgery. In this study, the 2 patients with this diagnosis also had trismus before and after surgery, but the small sample makes it difficult to extrapolate the interpretation of the data.

The literature suggests that the risk of developing RMO is greater with radiation doses to oral tissues above 60 Gy (27, 30). Our study had 70 Gy as the maximum prescribed dose, but there was no relationship between the total dose or dose applied to the mandible with a decrease in mouth opening. Interestingly, Teguh et al. (2008) (31) stated that for every 10 Gy irradiated in the pterygoid muscle, the chance of developing trismus is increased by 24%.

Studies, with up to 5 years of post-radiotherapy follow-up, revealed that there is a gradual decrease in mouth opening over the months (6, 11, 21, 22). Our data collection was restricted to 7-14 days post-completion of radiotherapy; however, patients remain in follow-up to monitor late side effects.

The differential of our work was the use of IOS to help maintain the mouth opening during radiotherapy treatment. The literature is scarce in this regard, being restricted to four studies: 01 systematic review (32), 01 randomized controlled trial (33), 01 retrospective cohort study (34), and 01 prospective study (35).

Yangchen et al. (2020) (33) compared two groups regarding the development of oral complications in a patient with oral mucosal cancer. Study Group (n=14) used a cerrobend shielding stent during radiotherapy, while the Control Group (n=14) did not. There was no statistical difference in the measure of mouth opening between the groups up to 3 months after

radiotherapy ($p>0.05$). In contrast, our stent was built as a deployment stent, not a shielding stent.

Nayar et al. (2016) (34) studied the influence of position stent use in patients with head and neck cancer. It was concluded that a better mouth opening occurred in the study group ($p<0.01$), maintaining the mouth opening after treatment. This information points to the need for more studies to standardize stent use

It is important to emphasize that all patients were followed up by the Physiotherapy team before, during, and after completion of radiotherapy. Exercise therapy is a method that effectively prevents and lessens the severity of trismus (36).

Conclusion

Patients undergoing IMRT in the head and neck region tend to reduce their mouth opening capacity in the short and long term, reinforcing the importance of multidisciplinary care.

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Figures

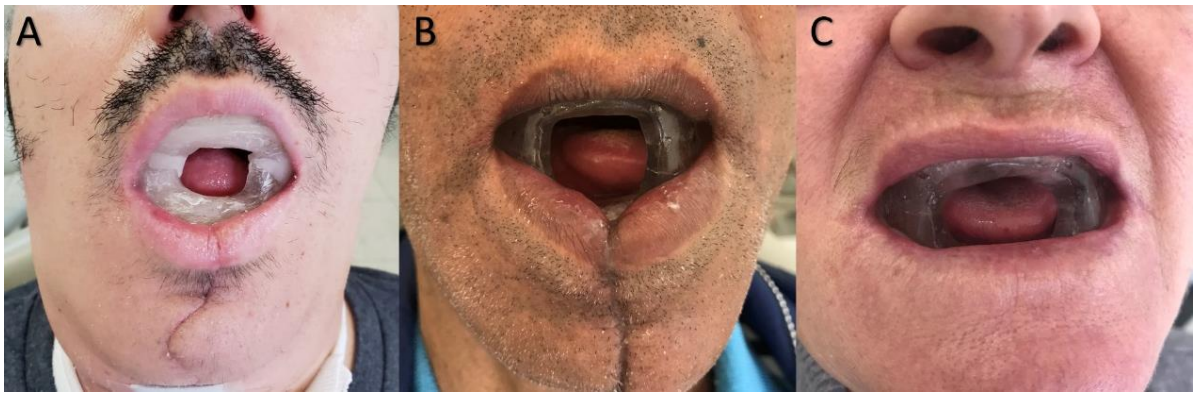

Figure 1. Patient with tongue squamous cell carcinoma in the mouth with IOS in position: A - T3N0M0 treated with surgery before chemotherapy and radiotherapy; B - T3N0MO treated with surgery prior to radiotherapy; and C - T4N2MO treated with chemotherapy plus radiotherapy.

Tables

Table 1. Clinical characteristics of patients with cancer in the head and neck region undergoing intensity-modulated radiation therapy (n = 20).

Participant	Sex and age (y)	Tumor site	Histological subtype	T stage	N stage	Prescribed radiation dose (Gray)	Dose in mandible (Gray)	Treatment	Tobacco smoking	Alcohol consumption	Mouth opening measure (mm)		
											Pre-radiotherapy (a)	Post-radiotherapy (b)	Difference (a-b)
P1	M, 66	Tongue	SCC	T4	N2	64	69.5	Sx + CTx + RT	Yes	Yes	60	49	-11
P2	F, 45	Lip	MAC	T3	N0	66	0	Sx + RT	No	No	29	29	0
P3	F, 88	Oropharynx	UMN	T3	N2	40	43.9	RT	No	No	53	60	7
P4	M, 34	Tongue	SCC	T3	N0	66	70.8	Sx + CTx + RT	Yes	No	45	46	1
P5	F, 20	Tongue	SCC	T2	N0	60	64.0	Sx + RT	No	No	52	39	-13
P5	M, 74	FOM	SCC	T4	N0	70	73.8	CTx + RT	Yes	Yes	40	37	-3
P6	M, 52	Tongue	SCC	T2	N0	60	63.8	Sx + RT	No	Yes	52	48	-4
P7	F, 57	Tongue	SCC	T4	N2	70	72.5	CTx + RT	No	No	55	45	-10
P8	M, 55	Tongue	SCC	T3	N2	66	71.7	Sx + RT	Yes	Yes	45	35	-10
P9	M, 52	Tongue	ACC (CP)	T2	N0	66	70.2	Sx + RT	Yes	No	57	49	-8
P10	F, 26	Tongue	SCC	T1	N0	70	71.7	Sx + CTx + RT	No	No	53	30	-23
P11	M, 56	Lip	SCC	T1	N1	60	65.2	Sx + RT	Yes	Yes	49	34	-15
P12	F, 66	Gingiva	SCC	T2	N2	64	68.5	Sx + RT	No	No	40	36	-4
P13	F, 56	Buccal mucosa	SCC	T4	N2	60	62.7	Sx + CTx + RT	No	No	27	30	3
P14	M, 76	Nasopharynx	UMSGT	T2	N1	64	80.2	CTx + RT	Yes	Yes	52	45	-7
P15	M, 32	Tongue	SCC	T2	Nx	60	65.1	Sx + RT	No	No	60	42	-18
P16	M, 62	Nasopharynx	SCC	T2	N2	70	76.0	CTx + RT	No	No	56	52	-4
P17	F, 48	Buccal mucosa	SCC	T3	N0	60	67.2	Sx + RT	No	No	20	24	4
P18	M, 30	Soft palate	AdenoCa	T3	N0	66	70.0	Sx + CTx + RT	No	No	38	31	-7
P19	M, 63	Tongue	SCC	T2	N1	70	70.9	Sx + RT	Yes	No	60	50	-10
P20	M, 66	Tongue	SCC	T4	N2	64	69.5	Sx + CTx + RT	Yes	Yes	60	49	-11

Table 2. Mouth opening classification adapted from LENT SOMA table (1995) (n=20).

Grade	**Pre-radiotherapy n (%)**	**Post-radiotherapy n (%)**
Absence of RMO	17 (85%)	16 (80%)
Grade 1 *(RMO of 21-30 mm)*		4 (20%)
Grade 2 *(RMO of 11-20 mm; difficulty in feeding)*	2 (10%)	0 (0%)
	1 (5%)	0 (0%)
Grade 3 *(RMO of 5-10 mm; difficulty in feeding soft food)*	0 (0%)	0 (0%)
	0 (0%)	
Grade 4 *(RMO < 5 mm; nasal feeding)*		
Total	20 (100%)	20 (100%)

RMO = Restricted mouth opening

Table 3. Description of mouth opening measure before and after radiotherapy, by gender (n=20).

Sample	Period	Median (mm)	Mean ± sd (mm)	Minimum (mm)	Maximum (mm)	*p*
Male	*Pré-RT*	52.00	51.17 ± 7.81	38.00	60.00	<0.01
	Post-RT	45.50	43.17 ± 7.17	31.00	50.00	
	Difference	-7.50	-8.00 ± 5.27	-18.00	1.00	
Female	*Pré-RT*	46.00	41.12 ± 14.08	20.00	55.00	
	Post-RT	33.00	36.62 ± 11.51	24.00	45.00	
	Difference	-2.00	-4.5 ± 10.18	-23.00	7.00	
Total	*Pré-RT*	52.00	47.15 ± 11.57	20.00	60.00	<0.01
	Post-RT	40.50	40.55 ± 9.46	24.00	60.00	
	Difference	-7.00	-6.60 ± 7.58	-23.00	7.00	

sd = Standard deviation

p = significance level (<0.05). Paired t-test

3 DISCUSSION

3 DISCUSSION

Our study included a sample of 20 participants. Despite considering the sample relatively small, when compared to the 19 studies included in the last systematic review published on stents (Alves et al., 2021), we observed that 13 (Bruno et al., 2020; Huang et al., 2020; Lee, Nguyen, Wu, 2019; Appendino et al., 2019; Hong et al., 2019; Ikawa et al., 2018; Rocha et al., 2017; da Costa Filho et al., 2017; Verrone et al., 2013; Johnson et al., 2013; Bodard et al., 2009; Kaanders et al., 1992; Epstein, Stevenson-Moore, 1985) of them included less than 20 participants in the study and 12 (Bruno et al., 2020; Huang et al., 2020; Appendino et al., 2019; Hong et al., 2019; Ikawa et al., 2018; Rocha et al., 2017; da Costa Filho et al., 2017; Verrone et al., 2013; Johnson et al., 2013; Bodard et al., 2009; Kaanders et al., 1992; Epstein, Stevenson-Moore, 1985) of them were case reports or series of cases.

To assess the impact of oral health on quality of life, we used the OHIP-14, a questionnaire adapted by Slade (1997) with 14 questions divided into 7 domains non-specific for cancer patients. For future studies, we suggest the evaluation of other questionnaires aimed at patients with head and neck cancer, such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (Paiva et al., 2017) and those that indicate the impact on head and neck cancer as the University of Washington Quality-of-Life Questionnaire (UW-QoL) (Vartanian et al., 2006), and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Head and neck cancer (EORTC–H&N-35) (Melo Filho et al., 2013). Perhaps turning our attention to more specific questionnaires for the head and neck region will contribute to the understanding of the impact of oral conditions on quality of life.

With the evolution of new radiotherapeutic techniques increasingly present in the treatment of head and neck, such as intensity-modulated radiation therapy (Fregnani et al., 2016), image-guided radiation therapy (Hsieh et al., 2016), volumetric-modulated arc therapy with RapidArc (Mashhour, Kamaleldin, Hashem, 2018) and proton beam therapy (Karube, Nakayama, 2021), we need to pay attention to a change in the profile of the patient's oral complications. However, these techniques are not yet

available for a large portion of the population that depends on public-private partnerships between public health systems and private treatment.

In a future perspective, we can consider the making of devices through 3D printers through digital flow. Thus, we can consider that adjustments tend to decrease, but evaluate cost-benefit, operator practice, and available laboratory. Studies already carried out with this technology seem promising (Ju et al., 2021; Bruno et al. 2020; Hong et al., 2019).

The results obtained in this research should encourage future studies aiming at the standardization and accessibility of the device. After all, it is easy to handle, has a low cost, and has good patient acceptance.

4 CONCLUSION

4 CONCLUSION

- Antineoplastic treatment influences the impact of oral conditions on quality of life.
- There is a worsening in mouth opening at the end of treatment, emphasizing the importance of trained professionals to monitor the patient during all phases of treatment.
- The use of stents, along with pre and during radiotherapy follow-up, may have alleviated the adverse effects of treatment.
- There must be a multidisciplinary team centered on the patient and capable of caring for, diagnosing, and treating oral alterations.

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ANNEX

USP - FACULDADE DE ODONTOLOGIA DE BAURU DA USP

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: CONFECÇÃO DE DISPOSITIVO INTRAORAL PARA PROTEÇÃO BUCAL DURANTE A RADIOTERAPIA

Pesquisador: PAULO SÉRGIO DA SILVA SANTOS

Área Temática:

Versão: 1

CAAE: 94436518.7.0000.5417

Instituição Proponente: Universidade de Sao Paulo

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.820.945

Apresentação do Projeto:

O câncer em região de cabeça e pescoço (CRCP) é considerado uma doença muito comum, principalmente em países pobres. Quando há a necessidade de tratamento que envolva radioterapia, os efeitos colaterais desta técnica prejudicam muito a qualidade de vida do paciente, atingindo além de tecido neoplásico, tecido sadio.Os principais tratamentos da doença são a cirurgia, quimioterapia e radioterapia. Esses podem gerar diversos efeitos colaterais que prejudicam a qualidade de vida do paciente durante e depois de cessado o tratamento oncológico. (INCA, 2014)

A pesquisa será realizada no "Centro de Radioterapia – Regional Bauru e no Centro de Pesquisas Clínicas da Faculdade de Odontologia de Bauru".

Objetivo da Pesquisa:

utizar um dispositivo intraoral terá como função diminuir os efeitos colaterais como: mucosite oral, xerostomia, osteorradionecrose, e cárie por radiação em

pacientes em fase de tratamento oncológico em regiões de cavidade bucal e lábios que necessitam receber radiação oriunda da radioterapia.

Inicialmente é necessário conhecer características anatômicas da região de cabeça e pescoço do paciente, o qual receberá o tratamento

radioterápico, definindo posicionamento e forma do modelo confeccionado. Os dispositivos serão

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Continuação do Parecer: 2.820.945

confeccionados com material resinoso, inerte e
resistente, em quatro tamanhos diferentes, abrangendo de forma geral a anatomia diversificada da população que necessitará utilizar o dispositivo

Avaliação dos Riscos e Benefícios:

Riscos:

O protótipo necessita estar bem adaptado na boca do paciente que receberá a radiação, evitando assim, úlceras traumáticas no momento das
sessões de radioterapia em região de contato do stent com mucosa bucal. Caso o paciente necessite, será fornecida medicação que diminua dor
local. O Dispositivo pode ser incômodo durante uso, devido debilitação do paciente, causada pelo tratamento radioterápico.

Benefícios:

O uso do stent em pacientes em fase de tratamento radioterápico em região de cavidade bucal e lábios pode gerar benefícios significativos para a
qualidade de vida do mesmo. Devido à proteção do tecido sadio (através de afastamento mecânico do tecido sadio da região neoplásica que
receberá radiação), ocorrerá diminuição dos efeitos colaterais: mucosite oral, xerostomia, osteorradionecrose, cárie por radiação, candidíase, perda
de paladar e trismo. Além do benefício direto para o paciente com diminuição dos efeitos colaterais oriundos da radioterapia em região de cabeça e
pescoço, ocorre também benefício social, devido aos resultados positivos no tratamento com uso do stent e ampliação do uso para uma parcela
maior da população que necessita do tratamento.

Comentários e Considerações sobre a Pesquisa:

Os pacientes que recebem tratamento radioterápico para câncer em região de cabeça e pescoço sofrem os efeitos colaterais da radioterapia incluindo os que afetam estruturas bucais. Com a adaptação de um dispositivo intraoral (Stent), ocorrerá separação mecânica dos tecidos: palato, língua e assoalho de boca; sendo possível diminuir os efeitos colaterais protegendo regiões da boca que não necessitam receber a radiação. Consequentemente diminuindo os efeitos colaterais (principalmente a mucosite oral) e melhorando a qualidade de vida do paciente durante e após o tratamento radioterápico.
sendo assim, esta pesquisa contribuirá para a qualidade de vida dos pacientes com câncer de

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cabeça e pescoço.

Considerações sobre os Termos de apresentação obrigatória:

Após análise, o CEP do Hospital Pró-Cardíaco APROVOU a presente pesquisa e seus documentos anexados na Plataforma Brasil, o qual foi responsável pela confecção do dispositivo (stent)
Os termos de aquiescência do Centro de Radioterapia – Regional Bauru e no Centro de Pesquisas Clínicas da Faculdade de Odontologia de Bauru, foram apresentados e estão de acordo com a Recomendação do CEP.

Recomendações:

Enviar o relatório final ao CEP

Conclusões ou Pendências e Lista de Inadequações:

Não há pendências ou inadequações na documentação apresentada.

Considerações Finais a critério do CEP:

Esse projeto foi considerado APROVADO na reunião ordinária do CEP de 08/08/2018, com base nas normas éticas da Resolução CNS 466/12. Ao término da pesquisa o CEP-FOB/USP exige a apresentação de relatório final. Os relatórios parciais deverão estar de acordo com o cronograma e/ou parecer emitido pelo CEP. Alterações na metodologia, título, inclusão ou exclusão de autores, cronograma e quaisquer outras mudanças que sejam significativas deverão ser previamente comunicadas a este CEP sob risco de não aprovação do relatório final. Quando da apresentação deste, deverão ser incluídos todos os TCLEs e/ou termos de doação assinados e rubricados, se pertinentes.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1137743.pdf	20/07/2018 09:49:25		Aceito
Parecer Anterior	PB_PARECER_CONSUBSTANCIADO_CEP_ANTERIOR.pdf	20/07/2018 09:48:37	Gabriela Moura Chicrala	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_Pesquisa_Confeccao_Dispositivo_Intraoral_2018.docx	20/07/2018 00:24:52	Gabriela Moura Chicrala	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_Pesquisa_Confeccao_Dispositivo_Intraoral_2018.docx	20/07/2018 00:02:17	Gabriela Moura Chicrala	Aceito

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Continuação do Parecer: 2.820.945

Outros	Termo_Aquiescencia_Depto.pdf	19/07/2018 23:33:50	Gabriela Moura Chicrala	Aceito
Outros	Questionario_Tecnico_Pesquisador_Responsavel.pdf	19/07/2018 23:12:30	Gabriela Moura Chicrala	Aceito
Declaração de Pesquisadores	Declaracao_Compromisso_Pesquisador.pdf	19/07/2018 23:10:43	Gabriela Moura Chicrala	Aceito
Outros	Carta_Aceite_Centro_de_Radioterapia.pdf	19/07/2018 17:34:18	Gabriela Moura Chicrala	Aceito
Outros	Termo_Aquiescencia_Centro_de_Radioterapia.pdf	19/07/2018 17:33:12	Gabriela Moura Chicrala	Aceito
Outros	Termo_Aquiescencia_CPC.pdf	19/07/2018 17:32:16	Gabriela Moura Chicrala	Aceito
Folha de Rosto	FR.pdf	19/07/2018 16:44:32	Gabriela Moura Chicrala	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

BAURU, 14 de Agosto de 2018

Assinado por:
Ana Lúcia Pompéia Fraga de Almeida
(Coordenador)

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Universidade de São Paulo
Faculdade de Odontologia de Bauru

Departamento de Cirurgia, Estomatologia,
Patologia e Radiologia

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Gostaríamos de convidá-lo (a) a participar da pesquisa "**CONFECÇÃO DE DISPOSITIVO INTRAORAL PARA PROTEÇÃO BUCAL DURANTE A RADIOTERAPIA**" sob a responsabilidade de **Paulo Sérgio da Silva Santos** realizada no "Centro de Radioterapia – Regional Bauru e no Centro de Pesquisas Clínicas da Faculdade de Odontologia de Bauru". O objetivo da pesquisa é utilizar um dispositivo intraoral feito de uma resina, chamado de "Stent", que separa mecanicamente as estruturas da boca (palato, língua e assoalho bucal) durante o planejamento para a radioterapia, através de exame de Tomografia Computadorizada e o próprio tratamento radioterápico de câncer em região de cabeça e pescoço, para diminuição dos efeitos colaterais na boca, como dor, ardência, feridas na boca, dificuldade para engolir os alimentos e para falar.

Rubrica do Pesquisador Responsável:

Aceitando ou não participar desta pesquisa, o(a) Sr(a) receberá tratamento odontológico fornecido pelo Centro de Pesquisas Clínicas da Faculdade de Odontologia de Bauru incluindo sessões de laserterapia conforme necessidades apresentadas pelo paciente. Mesmo após finalizado tratamento radioterápico do paciente, o mesmo continuará recebendo atendimento odontológico especializado conforme suas necessidades. Esta pesquisa não prejudica a qualidade do planejamento e tratamento radioterápico do paciente. A participação nesta pesquisa é totalmente voluntária e o(a) Sr(a) poderá recusar-se a participar ou desistir da pesquisa a qualquer momento, sem ocorrer prejuízos. Não haverá benefício financeiro aos participantes da pesquisa e os custos de ida e vinda ao Centro de Radioterapia – Regional Bauru e ao Centro de Pesquisas Clínicas da Faculdade de Odontologia de Bauru para atendimento médico e odontológico respectivamente, serão de total responsabilidade do paciente e responsável. O uso do dispositivo pode causar pequenas feridas na boca durante o uso caso não esteja bem adaptado, além de ser desconfortável de acordo com a debilitação do paciente como dificuldade de abertura de boca. Se houver qualquer ferida, o(a) Sr(a) terá o stent ajustado no Centro de Pesquisas Clínicas (FOB/USP). Ao aceitar participar desta pesquisa, será entregue ao paciente uma via deste Termo de Consentimento Livre e Esclarecido. Diante de qualquer dano recorrente da pesquisa o paciente terá a garantia de indenização. (Lei 466/12, item IV.3, alínea "b", "c", "d", "e", "f", "g", "h").

A sua participação é muito importante, pois além dos benefícios diretos pelo uso do Stent reduzindo a possibilidade de efeitos da radioterapia na boca, contribuirá para ajudar outros futuros pacientes que também necessitarão deste mesmo tratamento radioterápico.

Rubrica do Participante da Pesquisa :

Pelo presente instrumento que atende às exigências legais, o Sr. (a) _____,portador da cédula de identidade _____, após leitura minuciosa das informações constantes neste TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO, devidamente explicada pelos profissionais em seus mínimos detalhes, ciente dos serviços e procedimentos aos quais será submetido, não restando quaisquer dúvidas a respeito do lido e explicado, DECLARA e FIRMA seu CONSENTIMENTO LIVRE E ESCLARECIDO concordando em participar da pesquisa proposta. Fica claro que o participante da pesquisa, pode a qualquer momento retirar seu CONSENTIMENTO LIVRE E ESCLARECIDO e deixar de participar desta pesquisa e ciente de que todas as informações prestadas tornar-se-ão confidenciais e guardadas por força de sigilo profissional (Cap. III, Art. 9º do Código de Ética Odontológica (Res. CFO-118/2012).

Por fim, como pesquisador(a) responsável pela pesquisa, DECLARO o cumprimento do disposto na Resolução CNS nº 466 de 2012, contidos nos itens IV.3, item IV.5.a e na íntegra com a resolução CNS nº 466 de dezembro de 2012.

Al. Dr. Octávio Pinheiro Brisolla, 9-75 – Bauru-SP – CEP 17012-901 – C.P. 73
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Universidade de São Paulo
Faculdade de Odontologia de Bauru

Departamento de Cirurgia, Estomatologia,
Patologia e Radiologia

Por estarmos de acordo com o presente termo o firmamos em duas vias igualmente válidas (uma via para o participante da pesquisa e outra para o pesquisador) que serão rubricadas em todas as suas páginas e assinadas ao seu término, conforme o disposto pela Resolução CNS nº 466 de 2012, itens IV.3.f e IV.5.d.

Bauru, SP, _____ de _____ de _____.

_____ _____
Assinatura do Participante da Pesquisa Nome/Assinatura do Responsável Principal

Rubrica do Pesquisador Responsável:

O **Comitê de Ética em Pesquisa – CEP**, organizado e criado pela **FOB-USP**, em 29/06/98 (**Portaria GD/0698/FOB**), previsto no item VII da Resolução CNS nº 466/12 do Conselho Nacional de Saúde do Ministério da Saúde (publicada no DOU de 13/06/2013), é um Colegiado interdisciplinar e independente, de relevância pública, de caráter consultivo, deliberativo e educativo, criado para defender os interesses dos participantes da pesquisa em sua integridade e dignidade e para contribuir no desenvolvimento da pesquisa dentro de padrões éticos.

Qualquer denúncia e/ou reclamação sobre sua participação na pesquisa poderá ser reportada a este CEP:

Horário e local de funcionamento:
Comitê de Ética em Pesquisa
Faculdade de Odontologia de Bauru-USP - Prédio da Pós-Graduação (bloco E - pavimento superior), de segunda à sexta-feira (em dias úteis), no horário das **14hs às 17h30**.
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Rubrica do Participante da Pesquisa :