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Oral Cancer – A descriptive analysis from a single institution
(Centro Hospitalar de São João, Porto, PORTUGAL)

Universidade Fernando Pessoa
Faculdade Ciências da Saúde
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Dissertação apresentada à Universidade Fernando Pessoa
como parte dos requisitos para obtenção do grau de Mestre em Medicina Dentária

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SUMÁRIO:

O cancro da cavidade oral é a sexta causa mais comum de cancro em todo o mundo e a forma mais comum de cancro da cabeça e pescoço. A sobrevida aos 5 anos pode ser bastante variável e é um fator da variabilidade do período de observação, caraterísticas dos doentes, experiência dos cirurgiões, percentagem de tumores iniciais comparada com mais avançados, qualidade da radioterapia e uso de tratamentos adjuvantes. Este estudo analisou os resultados de doentes submetidos a tratamento de tumores da cavidade oral para identificar o valor dos fatores de prognóstico.

Um total de 125 doentes submetidos a tratamento de carcinoma da cavidade oral foram estudados entre 2007 e 2011. Para cada doente, os dados pessoais, achados histológicos, tratamento e resultado foram registados e analisados estatisticamente. As curvas de sobrevida foram calculadas usando o algoritmo de Kaplan-Meier e a diferença de sobrevida entre grupos examinada.

A sobrevida global aos 5 anos nos 125 doentes foi de 52%. As diferenças na sobrevida global e na sobrevida específica aos 5 anos foi significativa ($p < 0,05$) para o género, o estadio tumoral, o envolvimento ganglionar a invasão perineural e a invasão óssea medular.

Palavras-chave: “cancro da cavidade oral”; “carcinoma da cabeça e pescoço”; “sobrevida”.

ABSTRACT:

Oral cancer is the sixth most common cancer worldwide and the most common form of head and neck cancer. The 5-year survival rate can be quite different as it is a factor of variability of observation period, patients' features, surgeons' expertise, percentage of starting tumors compared with advanced ones, quality of radiotherapy, and the use of adjuvant treatments. This report analyzed the outcomes of patients undergoing treatment for oral cancer to identify the value of prognostic factors.

A total of 125 patients were studied who had undergone treatment for oral cancer between 2007 and 2011. For each patient, personal data, histological findings, treatment and outcome were recorded and analyzed statistically. Survival curves were calculated using the Kaplan-Meier algorithm, and the difference in survival among subgroups was examined.

The overall 5-year survival rate in the 125 patients was 52%. The differences in the overall survival and disease-specific 5-year survival were significant ($p < 0.05$) for gender, tumor staging, lymph node involvement, perineural invasion, and bone medullary invasion.

Keywords: “oral cancer”; “head and neck cancer”; “survival”.

INDEX :

I. INTRODUCTION:

Oral cancer is the sixth most common cancer worldwide and the most common form of head and neck cancer (Shah and Gil, 2009, Lyons, 2006). Squamous cell carcinoma accounts for more than 90% of oral malignancies (Chi et al., 2015).

The etiology of oral cancer is well established in most instances with consumption of tobacco in any form and alcohol being the most common etiologic agents (Kumar et al., 2016).

Surgery is the most well established mode of initial definitive treatment for the majority of oral cancers. Indications for postoperative (adjuvant) radiation or chemoradiation therapy may include close or positive resection margins, high-grade histopathologic features, extracapsular spread, and perineural or angiolymphatic invasion. Very advanced disease or cases in which surgery would result in unacceptable functional outcomes may be treated with radiation therapy and/or chemotherapy (Day et al., 2003).

Cervical lymph node involvement is evident at presentation in approximately 30% of cases and occult (or subclinical) in about 10% to 40% of cases. In the past, radical neck dissection was standard treatment for clinically evident or suspected cervical lymph node metastasis. However, over the past several decades, modified radical neck dissection and selective neck dissection have gained favor (Nikolarakos and Bell, 2008).

The 5-year survival rate can be quite different, ranging from 58% to 94%. Variability in overall survival (OS) and in disease-specific survival (DSS) is a factor of the variability of observation period, patients' features, surgeons' expertise, percentage of starting tumors compared with advanced ones, quality of radiotherapy, and the use of adjuvant treatments (Geum et al., 2013, Le Campion et al., 2017, Amit et al., 2013, Garzino-Demo et al., 2016).

The aim of this study was to analyze how the clinicopathological parameters affected the OS and the DSS in a population of patients who were referred for primary treatment at our hospital center.

II. MATERIALS AND METHODS:

A retrospective analysis of patients who presented for treatment at Centro Hospitalar de São João, Porto, Portugal between January 2007 and December 2011 was performed.

A total of 125 cases were analyzed. Of those, 104 were squamous cell carcinomas. Other histologic types were lymphoma (n=6), mucoepidermoid carcinoma (n=5), Kaposi sarcoma (n=3), verrucous carcinoma (n=3), sarcomatoid carcinoma (n=2) and adenocarcinoma (n=2). The patient population comprised 89 men (71.2%) and 36 women (28.8%). Their mean age was 58 years (range 15-97 years); in 114 patients age was greater than 40 years (90.5%) and in 12 the age was less than 40 years (9.5%).

Patients enrolled in the study underwent either primary surgical treatment or primary radiation therapy with or without chemotherapy.

The sites in the oral cavity were divided into subsites: the tongue was divided into anterior (2/3 anterior) and posterior (1/3 posterior) parts. The cheek was separated into the buccal mucosa, retromolar trigone and gingiva. In the floor of the mouth, the anterior and intermediate parts were considered, and the posterior part was considered as part of the tongue.

The tongue (55 cases, 44%), floor of the mouth (27 cases, 21.6%), and soft palate (15 cases, 12%) were the sites most commonly involved.

Seventy-one patients (58.2%) were submitted to surgery. Of those whose primary treatment was surgery, 20 were managed by local excision alone, while 51 cases (71.83%) were treated with ‘en bloc’ surgery of the primary tumor in combination with neck dissection (ND). Unilateral dissection was performed in 26 patients (21.3%). Simultaneous bilateral neck dissection in 25 patients (20.5%) when tumor invasion of the midline or near the midline structures was observed, or when positive nodes were found bilaterally preoperatively.

Supraomohyoid neck dissection (SOHND), including nodes at levels I, II, and III with preservation of the sternocleidomastoid muscle, internal jugular vein, and spinal accessory nerve, was performed 33 times, in patients who were clinically N0 and had primary tumors less than 3 cm in diameter. Modified neck dissection (MRND) was performed in 37 times, in N + patients with a single node less than 3 cm in diameter. When there was suspicion of invasion to more than two nodes, extranodal spread, or nodes greater than 3 cm in diameter, radical neck dissection (RND) or extended neck dissection (END) was performed (6 patients).

Surgical specimens were assessed with sections stained with hematoxylin and eosin (HE). Representative sections containing the full thickness of the tumor were used for histopathologic gradings and for other histopathological parameters. The distribution according to Broders' grading classification was 16 G1 (25.4%), 37 G2 (58.7%), and 10 G3 (15.9%).

In the histological analysis, distance from invasive carcinoma to surgical margins was measured with the use of a stage micrometer. The guidelines defined a histologic distance from invasive carcinoma to surgical margins of 5 mm as clear (24 patients, 35.3%), 1-5 mm as close (28 patients, 41.2%), and 1 mm as involved (16 patients, 23.5%).

Dysplasia at the resection margin was absent in 25 cases (64.1%), mild in 8 cases (20.5%), and severe in 6 cases (15.4%).

Bone invasion was categorized as absent, cortical, or medullary when extension into cancellous bone was present. Bone invasion was absent in 84 cases (80.8%), present with cortical bone invasion in 6 cases (5.8%), and present with medullary invasion in 14 cases (13.5%).

Perineural invasion (PNI), defined as tumors in close proximity to a nerve that involve one-third of its circumference and/or the presence of tumor cells within any of the three layers of the nerve sheath, was observed in 19 cases (28.4%) but was absent in 48 cases (71.6%).

Extra-nodal spread (ECS) was found microscopically in 6 patients (10.9%).

The distribution of patients according to tumor stage was 2 (2.9%) in stage 0, 15 (22.1%) in stage I, 20 (29.4%) in stage II, 10 (14.7%) in stage III, and 21 (30.9%) in stage IV.

External beam radiation therapy (EBRT), with or without chemotherapy, was used to enhance loco-regional control (LRC) for cases with unfavorable pathological features. PORT was given to 41 patients based on the following clinico-pathologic features: pT3 and pT4, positive or close surgical margins, poor cellular differentiation, perineural infiltration, involvement of multiple neck nodes, or ECS. In very high-risk cases (T3 tumor with close or positive surgical margins or multiple pathological positive lymph nodes with ECS or N3 neck) POCRT protocols were adopted (12 cases). Those with irresectable disease (51 cases) were submitted to RT (29 cases, 61.7%), QT (18 cases, 38.3%) or CRT (14 cases, 27.4%).

Patients submitted to surgery were generally monitored with the following: monthly clinical visits in the first year postoperatively and every 2 months from the second year onward; computed tomography (CT) or magnetic resonance imaging (MRI) of head and

neck every 6 months in the first and second years and once per year from the third year onward.

Survival curves were calculated using the Kaplan-Meier algorithm. Time zero was defined as the date of a patient's biopsy. Surviving patients were included in the total number at risk for death only up to the time of their last follow-up. Therefore, the survival rate changed only when death had occurred. The calculated survival curve was most likely estimated to be the true survival curve. A *log-rank* test was used to explore the differences between the survival curves stratified for the variable of interest.

Survival probability was calculated using the product-limit method (Kaplan-Meier), with the 95% confidence interval (CI). The difference in survival among subgroups was tested using the *log-rank* statistic. The level of statistical significance was set at 0.05. Statistical analyses were performed using SPSS® v.24.0 (Statistical Package for the Social Sciences).

III. **RESULTS:**

The overall survival rate (OS) 5 years post diagnosis was 52% (Appendix 2). There was no recurrence in 97 patients (77.6%), whereas 28 (22.4%) of them developed a recurrence during the period of observation, consisting of a local recurrence in 22 patients and a neck recurrence in 6 patients. Of the latter patients with a neck recurrence, half developed neck metastases in the untreated neck, whereas the other patients developed a neck recurrence in the previously treated neck. The mean interval between surgery and loco-regional recurrence was 15.67 months (range 1-48 months).

The OS (Appendix 3) was plotted according to gender: the difference in survival between male and female was statistically significant ($p = 0.017$).

The OS percentage at 5 years since surgery in accordance with the age of the patients was respectively 75% (age < 40 years) and 47.6% (age > 40 years); the difference was not statistically significant ($p = 0.608$) (Appendix 1).

The OS percentages at 5 years since surgery according to stage I, II, III, and IV were 72.2%, 66.7%, 50%, and 29.6%, respectively. The difference in survival between stages was statistically significant ($p = 0.001$) (Appendix 1). The DSS percentage at 5 years since according to stage as follows: stage I 50%; stage II 47.4%; stage III 30%; and stage IV 11.5%. The difference between stages was statistically significant ($p < 0.001$)

(Appendix 1). The DSS curve (Appendix 4) was plotted according to the American Joint Committee on Cancer (AJCC) 2010 staging classification.

The OS rates stratified according to pN were as follows: Nx (without neck dissection, local excision alone), 86.7%; N0, 69%; N+, 36%. The difference in OS according to pN status was statistically significant (p = 0.003) (Appendix 1). The DSS rates stratified according to pN were: Nx 86.6%; N0 66.4% and N+ 44.5%. The difference in DSS according to pN status was statistically significant (p = 0.029). The DSS curve plotted according to pN status (recorded from histological reports) is depicted in (Appendix 5).

The probability of the patients surviving 5 years (OS) after the time of diagnosis according to Broder's tumor grades G1, G2, and G3 were 75%, 54.1%, and 50%, respectively (p = 0.309). The 5-year DDS rates in the groups stratified according to the grading were as follows: G1 = 70.6%; G2 = 55%; G3 = 65.2%.

The probability of patients with a positive resection margin surviving (OS) for 5 years was 56.3%, whereas the survival rate (OS) was 75% when the surgical margins were > to 5 mm and 57.1% when margins were < 5 mm (p = 0.325). The difference in DSS according to tumor resection margins status were also not statically significant (p = 0.958).

The difference in OS and DSS according to presence of dysplasia (absent: OS = 68%, DSS = 39.1%; mild: OS = 75%, DSS = 42.9%; severe: OS = 33.3%, DSS = 66.7%) at the resection margins was not statistically significant (OS, p = 0.270; DSS, p = 0.555).

The 5-year OS in the groups stratified according to osseous infiltration was 21.4% with presence of medullary invasion, 66.7% with only cortical invasion, and 50% without invasion (p = 0.096). The 5-year DDS in the groups stratified according to osseous infiltration

was 61.72% with presence of medullary invasion, 70.18% with only cortical invasion and 76.67% without invasion (p = 0.0144). The DSS survival curve plotted according to the osseous invasion is given in Appendix 6.

The 5-year OS in patients with perineural invasion was 36.8%, whereas the rate in patients without perineural invasion was 70.8% (p = 0.014). The 5-years DSS in patients with perineural invasion was 21.1%, whereas the rate in patients without perineural invasion was 53.5% (p = 0.018). The DSS curve plotted according PNI is depicted in Appendix 7.

IV. DISCUSSION:

A series of 125 patients who underwent OSCC treatment were retrospectively analyzed to identify the prognostic value of clinicopathological parameters.

Authors differ as to whether the prognosis in young patients is better or worse than in the older population. Some studies correlate age with a poor prognosis due to more aggressive features with poor overall treatment results despite relatively early stage disease presentation while others state that younger patients are in better physical condition and have better chances of curable treatment (Clarke and Stell, 1992, Sarkaria and Harari, 1994, McGregor and Rennie, 1987). Our study found no statistical differences between age groups.

The TNM classification of AJCC relates well to the prognosis and overall survival: the earlier the tumor stage, the better the prognosis and the less complicated the treatment (Garzino-Demo et al., 2006). The findings of the present study for cancer staging were similar to other studies. According to Shah et al. (Shaha, 2008), oral cancer's TNM patient stage ratio was 37% (stage I), 36% (stage II), 18% (stage III), and 9% (stage IV). These findings confirm the early diagnosis of oral cancer as an important step in increasing survival rates. In addition, the early treatment of a primary neoplasm reduces the mortality, notably before its dissemination. Therefore, the prevention of oral cancer, earlier diagnosis, and active treatment of early stage disease may be the best means of improving 5-year survival rates and quality of life after treatment.

Several features of the primary tumor have a very significant bearing on outcome.

In the case of cervical lymph node metastasis, a significant difference was noted in the 5-year survival rate between patients with one or more lymph node metastases and N0 patients. Woolgar et al. (Woolgar et al., 1995) showed well-established relationship between cervical node metastasis and reduced rate of survival. The 5-year probability of survival in that study reduced from 86% among patients without cervical metastasis to 44% in patients with metastasis. Cervical metastases are more frequent in large tumours and in tumours with a histologically unfavourable pattern of invasion (Kapoor et al., 2015).

Tumor grading depends on the subjective pathological assessment of the degree of keratinization, cellular and nuclear pleomorphism, and mitotic activity (Woolgar, 2006). It has been significantly related to locoregional failure and tumor recurrence but most authorities consider this grading system as a poor indicator of outcome and response to treatment (Po Wing Yuen et al., 2002, P et al., 2003). The present analysis showed a trend towards a worst survival in tumors with higher grade but no statistical differences.

The impact of the surgical margins on the outcome of OSCC remains equivocal. Problems in assessing surgical margins have been correlated with tumor shrinkage and so, controversy exists regarding the quantity of normal tissue to be removed in OSCC and the impact of surgical margins on prognosis (Upile et al., 2007, Binahmed et al., 2007). This study also showed no significant impact in the OS and DSS, regarding the surgical margin status.

There are variations in the pathological interpretation and classification of dysplasia. It is widely accepted that dysplasia precedes OSCC (Lumerman et al., 1995) and that 11% of OSCC patients had cancer elsewhere (Slaughter et al., 1953). Field cancerisation concept and the presence of dysplastic epithelium in cancerous tissue have been reported in a number of studies (Thomson, 2002, Mohan and Jagannathan, 2014). Dysplasia at margin has been described as an excellent predictor of tumor spread (Jerjes et al., 2010). This study failed to demonstrate statistical differences between different grades of dysplasia.

In the literature, bone invasion is not an independent prognostic factor when confounding variables such as tumor size and involved surgical margins are taken into consideration (Dubner and Heller, 1993). Tumor size and medullary bone invasion are independent predictors of reduced survival; incontrast, tumors with bone invasion limited to the cortex have asimilar prognosis to those without bone invasion (Ebrahimi et al., 2011). The adverse effect of medullary involvement appears to result, at least in part, from an increased risk of distant metastatic failure (Garzino-Demo et al., 2016).

The results of this revision showed that PNI is related to poor OS and DSS. Several studies report that PNI is associated with disease recurrence, an increased probability of regional and distant metastasis, and an overall decrease in 5-year survival rate. Moreover, PNI has an impact in outcome in both early and late stage OSCC (Chinn et al., 2013) and is an indicator of the ability of OSCC to spread to cervical lymph nodes and therefore should

be weighed heavily when considering neck dissection or the use of adjunctive treatment (Fagan et al., 1998).

V. CONCLUSION:

This study identified gender, tumor staging, lymph node involvement, perineural invasion, and bone medullary invasion as predictive factors in patient prognosis. They were significantly associated with OS and DDS.

It is difficult to compare our outcomes directly with others because of variations in case mix, selection for treatment and presentation of outcome data. It is also interesting to note that the more up to date reports show better survival figures.

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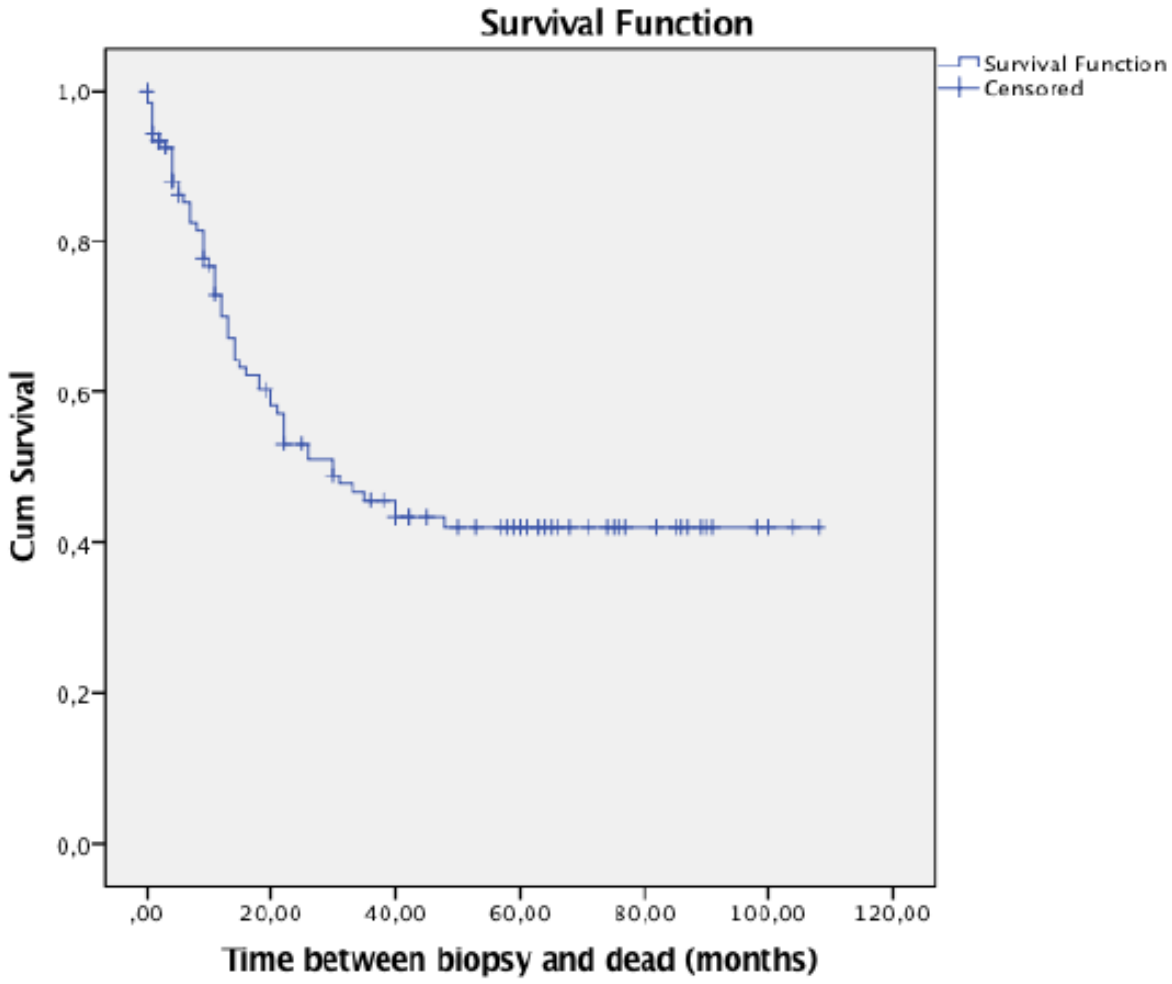
VII. APPENDIX

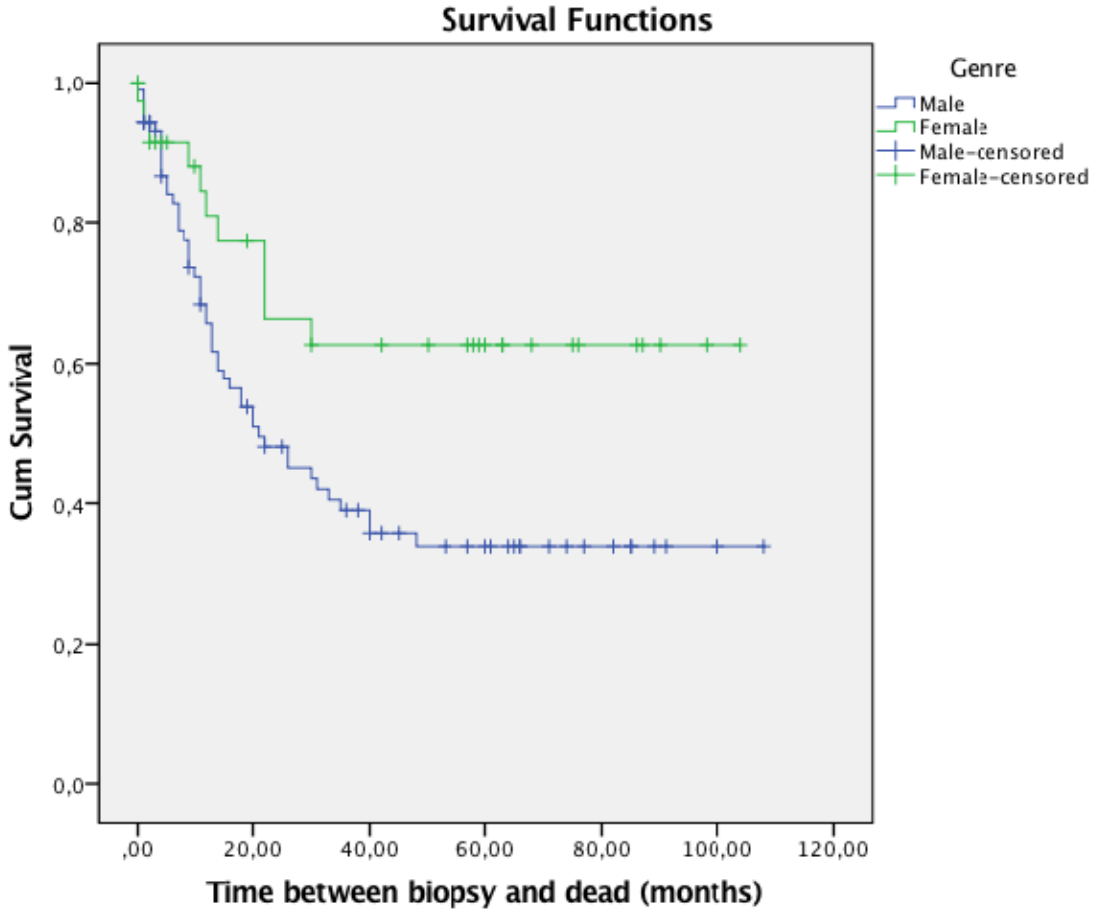
Appendix 1. Clinicopathological parameters and disease-specific survival (DSS)/overall survival (OS) at 5 years in cases of oral squamous cell carcinoma.

	5 years from diagnosis		P value	5 years from diagnosis		P value
	OS (%)	95 CI (%)		DSS (%)	95 CI (%)	
Gender			**0,017**			0,294
Male	44,9	34,9-55,3		26,5	17,9-36,7	
Female	69,4	53,3-82,6		36,7	21,3-54,5	
Staging			**0,001**			**<0,001**
I	72,2	49,4-88,5		50,0	27,2-72,8	
II	66,7	45,4-83,7		47,4	26,6-68,8	
III	50,0	22,4-77,6		30,0	9,3-60,6	
IV	29,6	18,7-42,6		11,5	5,0-22,2	
pN status			**0,003**			**0,029**
pNx	86,7	63,7-97,1		69,2	42,3-88,6	
pN0	69,0	51,0-83,4		48,1	30,3-66,4	
N+	36,0	19,5-55,5		25,0	11,2-44,5	
Grading			0,309			0,784
G1	75,0	50,9-90,9		46,7	23,9-70,6	
G2	54,1	38,2-69,3		38,2	23,4-55,0	
G3	50,0	22,4-77,6		33,3	10,4-65,2	
Margins			0,325			0,958
Clear	75,0	55,5-88,8		60,9	40,6-78,6	
Close	57,1	38,9-74,0		57,1	23,5-86,1	
Involved	56,3	32,6-77,8		33,3	7,7-71,4	
Dysplasia			0,270			0,555
Absent	68,0	48,5-83,6		39,1	21,4-59,4	
Mild	75,0	40,8-94,4		42,9	13,9-76,5	
Severe	33,3	7,7-71,4		66,7	28,6-92,3	
Bone Invasion			0,096			**0,031**
Absent	50,0	39,5% 60,5		35,4	25,6% 46,4	
Cortical	66,7	28,6% 92,3		33,3	7,7% 71,4	
Medulary	21,4	6,4% 46,9		0,0	-	
Perineural Invasion			**0,014**			**0,018**
Yes	36,8	18,2% 59,1		21,1	7,6% 42,6	
No	70,8	57,0% 82,2		53,5	38,8% 67,8	

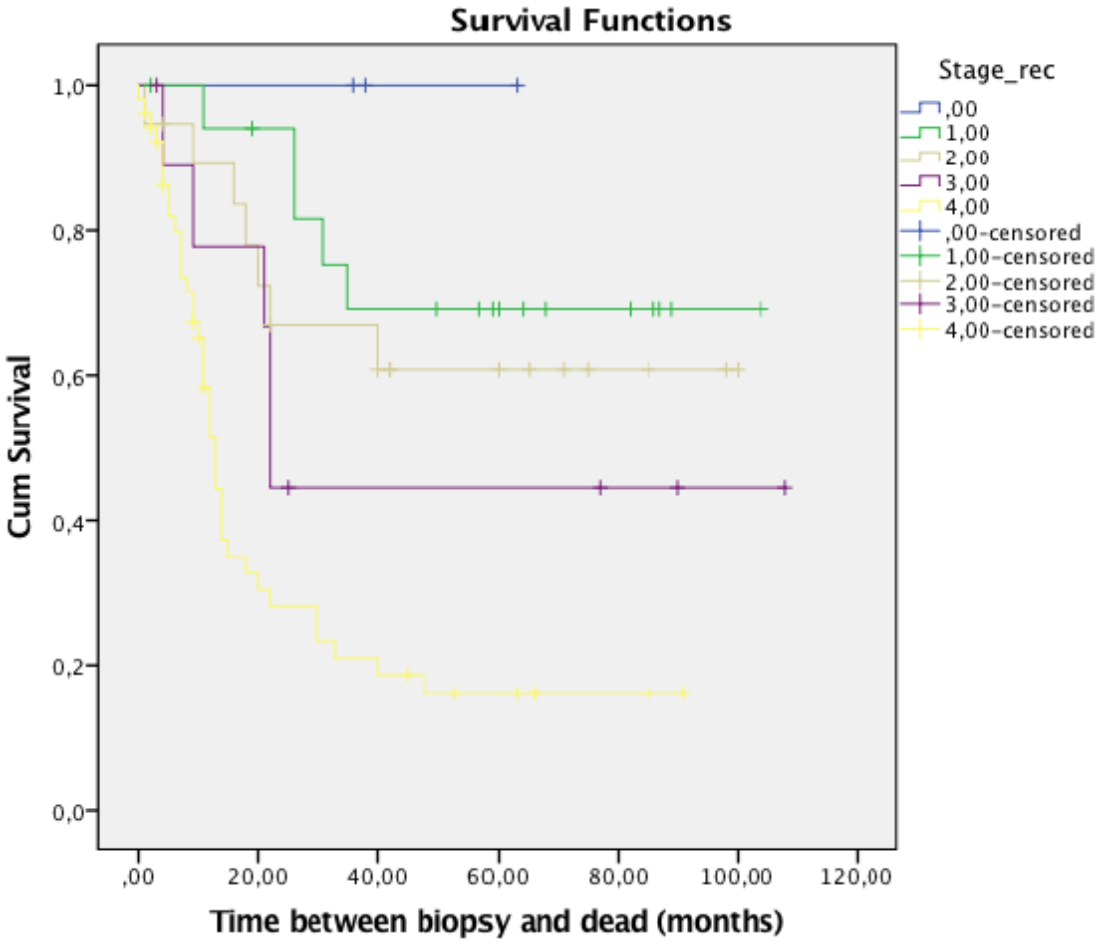
Appendix 2. Overall survival curve (125 oral squamous cell carcinoma patients).



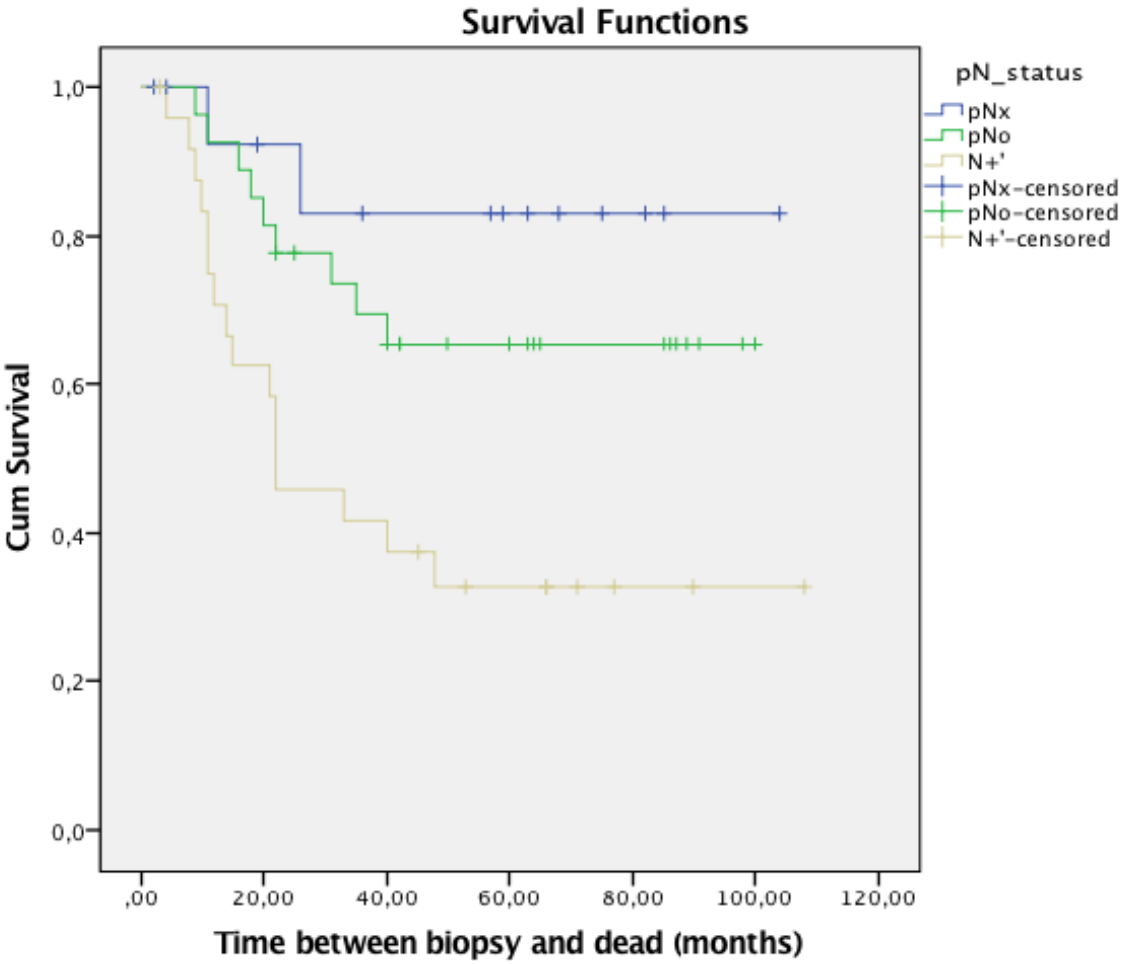
Appendix 3. Survival estimates by gender



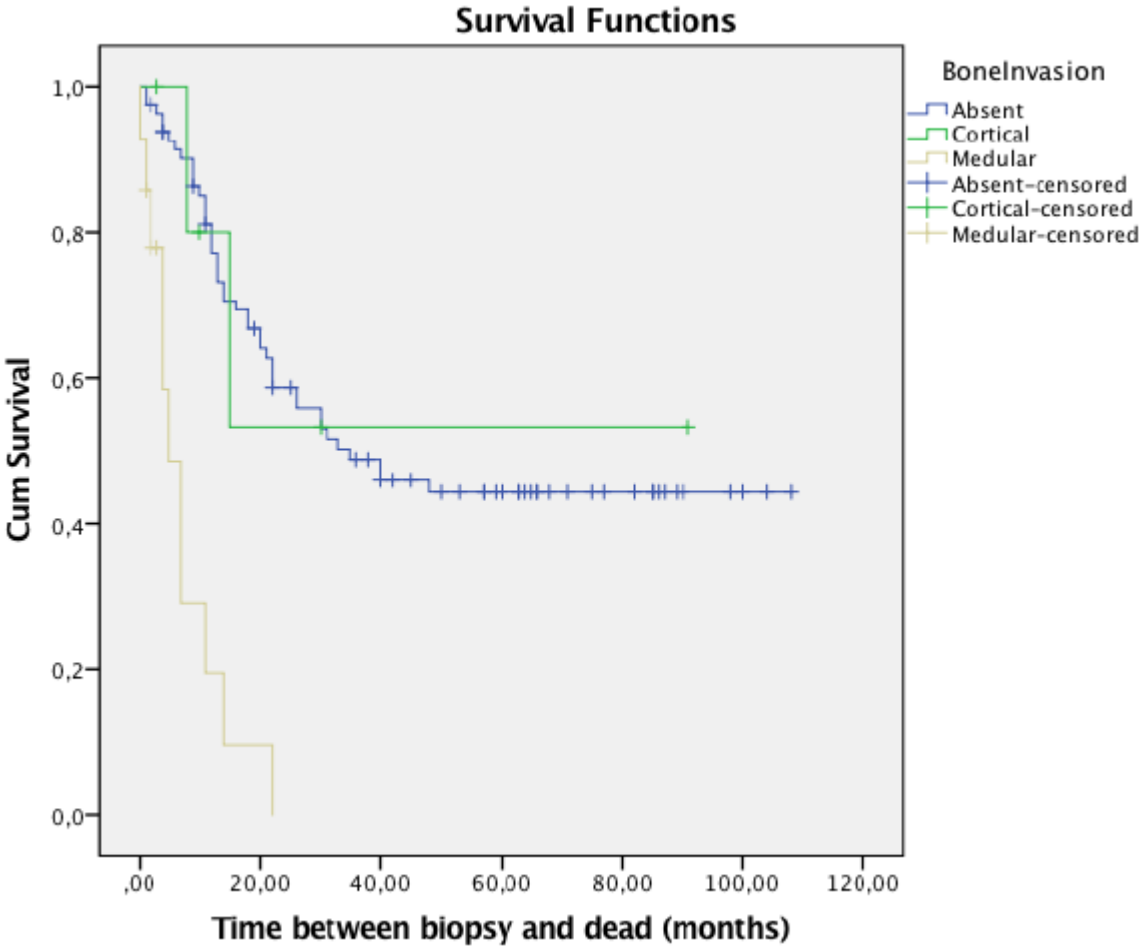
Appendix 4. Survival estimates by stage



Appendix 5. Survival estimates by status.



Appendix 6. Survival estimates by osseous invasion



Appendix 7. Survival estimates by perineural invasion