

# Epidemiological and Histopathological Aspects of Tongue Squamous Cell Carcinomas- Retrospective Study

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**ABSTRACT:** Tongue squamous cell carcinoma is one of the most commonly diagnosed intraoral squamous cell carcinomas (25-40%), being considered an aggressive form of squamous cell carcinoma, as it is most commonly associated with lymph node metastases and the survival rate at five years is below 50%. In accordance with these data, we have proposed in this study to individualize an epidemiological and histopathological profile of the patients with such oral cancers, diagnosed and treated in the Oral and Maxillofacial Surgery Clinic and in the Otolaryngology Surgery Clinic of the Emergency Clinical County Hospital Craiova, between 2015-2017. The cases were histopathologically reassessed according to the latest WHO classification of head and neck tumors, the variables of interest being the age of the patients, the gender, the lesion topography, the histological subtype, the degree of tumor differentiation, the pTNM stage, the resection margin status and the Brandwein-Gensler prognostic score. Thus, we recorded an average age of 55.81±14.98 tongue cancer development, 65% of the casuistry being diagnosed during the 7th and 6th decades, with a slight prevalence in men, with development in two thirds of cases in the mobile portion of the tongue. Histopathologically, conventional forms of squamous cell carcinoma prevailed (53.7%), followed by varieties: acantholytic (26%), basaloid (13%), sarcomatoid (5.45%) and verrucous (1.85%). Moderate differentiated forms prevailed (44.44%), half of the cases falling within the moderate degree of Brandwein-Gensler's histological risk score and two thirds were diagnosed in pTNM stage II and III of the disease, and a quarter of the cases having the margins invaded.

**KEYWORDS:** Tongue, squamous cell carcinoma, epidemiology, histopathology

## Introduction

Tongue cancer appears to be among the most commonly diagnosed intraoral squamous cell carcinomas with an incidence varying between 25-40%, being responsible along with the carcinomas of the mouth floor for more than half of the intraoral carcinomas [1].

In 2017, in US, from 16.400 new cases of tongue cancer, 2.400 were predicted to die [2].

Traditionally, tongue squamous cell carcinoma (TSCC) was considered to affect predominantly 60-year-old and over 60-year-old men who consumed in excess alcohol and were heavy smokers [2,3,4].

However, over the past 20 years, the incidence of tongue cancer among these individuals has decreased, but with an increase in its incidence among young people, especially white women, without knowing the etiological significance of this increase [5,7].

From the point of view of its biological behavior, tongue cancer is considered an aggressive form of squamous cell carcinoma given that the tongue possesses a rich vascular lymphatic network and a well-represented musculature, which would explain the increased tendency to invasion and metastasis in this localization of oral squamous cell carcinoma [8].

In fact, tongue squamous cell carcinoma appears to be most commonly associated with lymph nodes metastases of all oral squamous cell carcinomas [9].

At the same time, tongue cancer seems to have a clinically unpredictable prognosis given the increased incidence of occult metastases at patients with small primary tumors and no clinical signs of metastatic disease [10].

Thus, a number of studies have shown that at the patients with tongue cancer developed at the base of the tongue, the survival rate at 5 years would be lower than 42.6% and in the rest of the

tongue localizations this percentage would vary between 40-49.9% [11,12].

Among the prognostic factors of TSCC are the presence of occult metastases, the depth of invasion, the presence of lympho-vascular invasion, perineural invasion, the histological subtype and the degree of tumor differentiation [13].

In this study, we aimed to investigate the epidemiological and histopathological profile of the patients diagnosed and treated for TSCC during the period 2015-2017, in the Oral and Maxillofacial Surgery Clinic and in the Otolaryngology Surgery Clinic of the Emergency Clinical County Hospital Craiova.

### Material and method

The study was retrospective and included 54 cases of tongue squamous cell carcinomas diagnosed and treated between 2015-2017 in the Oral and Maxillofacial Surgery Clinic and in the Otolaryngology Surgery Clinic at the Emergency Clinical County Hospital Craiova. Epidemiological data were collected from the Clinical Observation Form of these patients and for histopathological data were used the diagnostic registers from the Pathological Anatomy Laboratory archive of the same hospital. For reassessment of the histopathological diagnosis according to the latest WHO classification of head and neck tumors [14] were performed new serial sections from the archived paraffin blocks and these were stained with Hematoxylin Eosin (HE) and Masson's trichrome stain (kit from Bio-Optica, Code: 04-010802). For every patient included in the study group, the written informal consent was obtained and the working protocol meets the requirements of institutional ethics code. The variables of epidemiological interest were: the age of the patients, the gender, the lesion topography, the histological subtype, the degree of differentiation, the pTNM [14], the status of the resection margin and the Brandwein-Gensler prognostic score [15].

For the statistical analysis, t Student, ANOVA, Chi square and Pearson tests were used with the SPSS 10 software. To statistically test the probability of association between the different classes of descriptive categorical variables in this study, we compiled contingency tables with these data and subsequently we used the Chi square test. The results were considered statistically significant when  $P < 0.05$ . For comparisons on several variables of interest we used the ANOVA test.

### Results

The following table summarizes the main clinical and morphological characteristics of the investigated cases (Table 1).

**Table 1. Distribution of immunohistochemically investigated cases according to their main clinical and morphological variables**

Anatomical and clinical variables	No. of cases	(%)
Age		
<60	24	44,44
>60	30	55,56
Gender		
F	23	42,59
M	31	57,41
Topography		
Mobile part (including the margins)	36	66,66
Fixed part	18	33,33
Histopathological subtype		
Conventional	29	53,7
Verrucous	1	1,85
Acantholytic	14	26
Basaloid	7	13
Sarcomatoid	3	5,45
Degree of differentiation		
Well differentiated	18	33,33
Moderate differentiated	24	44,44
Poorly differentiated	12	22,22
Brandwein-Gensler score		
Low degree	8	14,8
Moderate degree	27	50
High degree	19	35,2
pTNM		
I	7	12,96
II	18	33,33
III	20	37,04
IV	9	16,67
Resection margins status		
Free	41	76
Invaded	13	24

### The results of the epidemiological study

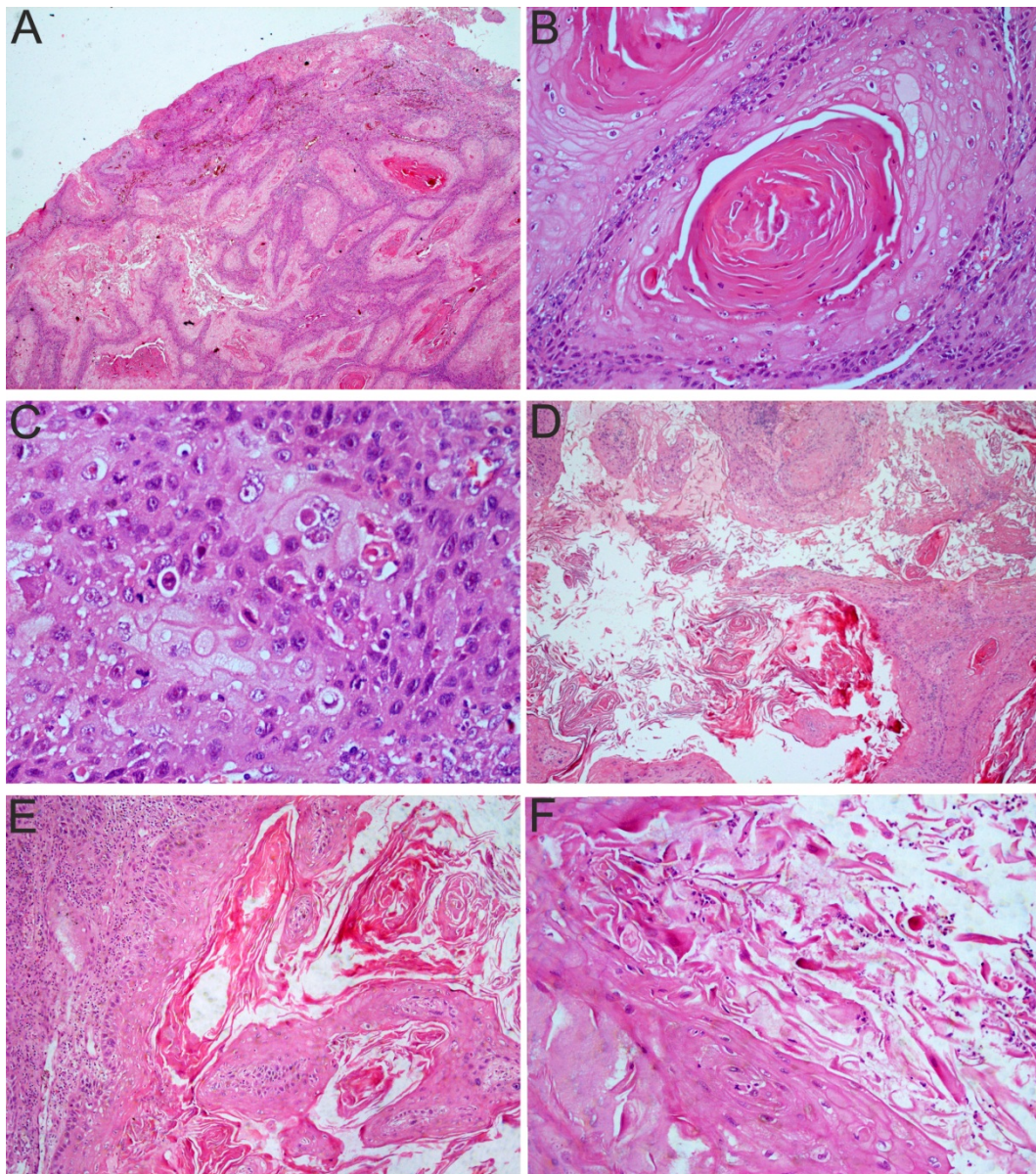
The analysis of the age distribution of cases showed that the range of the affected decades was between the second decade and the eighth decade, the youngest being diagnosed at age 17 and the oldest at 76 years. The most frequently affected age decade was the 7th decade with 50% of the investigated casuistry, followed by the 6th decade with 15% and the 5th decade with 13%. The average age for the entire study group was  $55.81 \pm 14.98$  and the median was 63 years. The gender distribution indicated the prevalence of male cases with 57.4%, compared to 42.59% that was the incidence among females. The gender ratio of our casuistry was 1: 1.34 in favor of male gender. In relation to the lesion topography, the highest frequency was recorded in the mobile

part of the tongue, namely 2/3 of the casuistry, the most affected being the margins of the tongue (73% of the localization of the mobile part of the tongue). The fixed part of the tongue was affected in one third of the investigated cases, with the basis as the most affected part within this location.

### The results of the histopathological study

Histopathologically the most common variant was the **conventional type** of squamous cell carcinoma with an incidence of 53.7% of the entire casuistry. This variety of tongue

squamous cell carcinoma was made out of neoplastic cells with varying degrees of squamous differentiation, in which the well-differentiated ones almost resembled malpighian cells of the normal epithelium, but they disrupt the basal membrane and invaded the underlying corium under various patterns (Fig.1A), disorderly growth, with the loss of polarity, with the development of dyskeratosis and the formation of "epithelial pearls" (Fig.1B), with an over unity of the nucleus/cytoplasm ratio and the constant presence of typical and atypical mitoses (Fig.1C).



**Fig.1A.** Tongue, conventional, well-differentiated, squamous cell carcinoma, lobular growth pattern, HE stain, x25; **B.** Epithelial parakeratotic pearl, HE stain, x200; **C.** Malignancy characters of neoplastic proliferations, nuclear atypia and atypical mitosis, HE stain, x400; **D.** E Tongue squamous cell carcinoma, acantholytic variant, pseudoluminal growth pattern, HE stain, x50/x100; **F.** Presence of acantholytic dyskeratotic cells in the neoplastic pseudolumens. HE stain, x200

The median age of conventional CSL was 57, with an average of  $54.72 \pm 15.26$  and the gender distribution of casuistry was almost balanced, with the gender ratio M/F being 1.07. Most casuistry developed in the mobile regions of the tongue (65.5%) and 55% of the cases were well differentiated. Related to the invasion pattern, 34.5% had invasion grade 2 in the form of large neoplastic cell lines and cords, followed by grade 3 (smaller neoplastic groups of cells and cords) and 4 (dissociated, isolated neoplastic cells and small groups of cells) with a frequency of 24.15% each. In more than two thirds of cases, a lymphoplasmacytic infiltrate and/or macrophagic infiltrate was associated at the stroma interface and the perineural invasion was revealed in 17.25% of the cases. Brandwein-Gensler scores for conventional TSCC cases were predominantly within the mid-range (58.6%), followed by higher grade (24.13%). Lymph node metastases was reported in 34.5% of the cases, most of them (80%) being type N1 (affecting a single lymph node from the same side with the tumor and having dimensions up to 3cm). In terms of pTNM stage, the vast majority of cases of conventional TSCC were in stage III (44.83%), followed by stage II (24.14%) and stage I (20.7%). We have revealed the presence of positive resection margins in only 6 cases, those cases belonging to large tumors that developed from the tongue base.

The second most common encountered histopathological subtype was acantholytic, diagnosed in 26% of the investigated patients. The growth pattern in this type is the lobular/insular one with the central presence of pseudoglandular/pseudoluminal spaces resulting from the acantholysis, delimited by polygonal neoplastic cells (Fig.1D-E). Often, in these lumens, discrete, acantholytic neoplastic cells can be observed (Fig.1F). Tumor cells from the periphery of the tumor lobules showed an obvious nuclear pleomorphism, nuclear anisochromia, dense eosinophilic cytoplasm and frequent mitosis. Also, focally can be highlighted keratotic pearls and areas of conventional squamous cell carcinoma.

This TSCC subtype appears to develop at a slightly older age compared to the conventional subtype, the median age for the acantholytic form was the age of 62, mainly affecting male gender, with a frequency of 2.5 times higher than for women. Topographically, most of these cases developed in the mobile parts of the tongue, respectively 71.43% of the acantholytic squamous cell carcinoma casuistry. Regarding

the degree of differentiation, the most frequently were the moderately differentiated forms (50%), followed by the poorly differentiated form of 35.72%. Regarding the invasion pattern, we observed a relatively uniform distribution with 28.6% of cases in each of grade 2, 3 and 4. The inflammatory stroma was present in 71.4% of the cases, while the perineural invasion in only 35.7% of cases. In relation with the Brandwein-Gensler score, the TSCC cases were equally divided (50%) between the high and moderate type. Lymph node metastases were revealed in 50% of cases, of which in 71.4% of the cases the N stage was N1 and in the rest of the cases was N2. Regarding the pTNM stage, 50% of cases were diagnosed in the third stage of the disease, followed by stage II patients (35.7%) and those diagnosed in stage IV of the disease (14.3%).

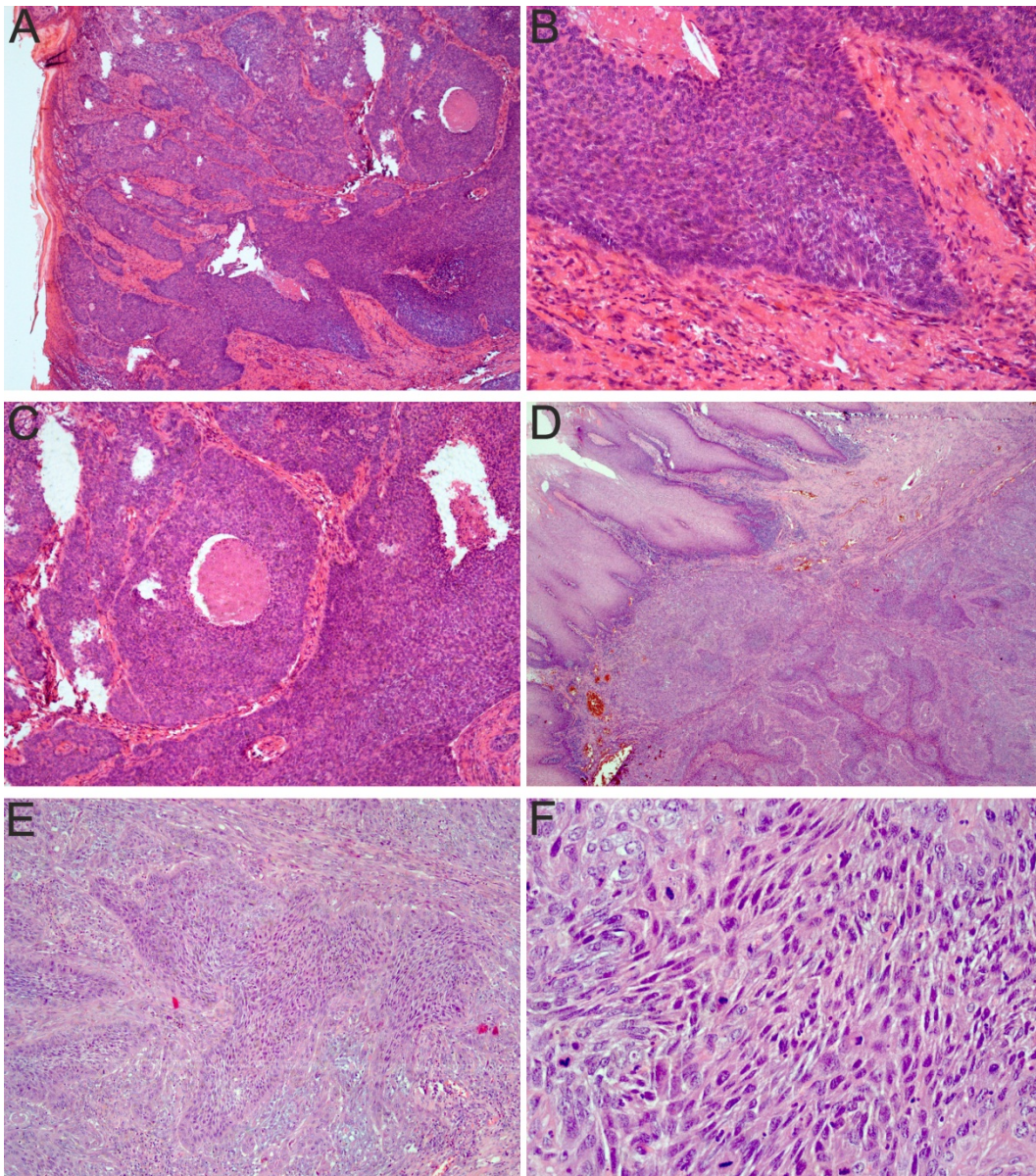
**The basaloid subtype** of TSCC has been diagnosed in 7 cases, representing approximately 13% of our casuistry. The growth pattern in such tumor subtype was variable with lobular/insular areas, trabecular areas, cribriform areas and nests of neoplastic cells (Fig.2A). The characteristics of this subtype were the neoplastic cells from periphery of the neoplastic proliferations, that presented a basaloid morphology (cubico-cylindrical with a little cytoplasm and tachychromatic nuclei) (Fig.2B). Often, in the central area of tumor proliferations, comedonecrosis has been shown (Fig.2C). Focally were also observed conventional TSCC areas in close contact with basaloid proliferations.

The median age at which these TSCC cases were developed was 67 years, men being found 2.5 times more likely to be affected than women. In 71.4% of the cases developed at the level of the mobile parts of the tongue and the vast majority (57.14%) were in the third degree of differentiation. The invasion pattern was extremely heterogeneous in this TSCC subtype, recording all types of invasion in almost equal proportions. In half of the cases, an inflammatory stroma was revealed and only in 2 cases we noticed the perineural invasion. The Brandwein-Gensler scores recorded in these cases were evenly distributed between the three grades, namely 2 cases in the low and moderate grades and 3 cases were ranked high grade. Lymph node metastases was revealed in 42,85% of the cases, two thirds of which were in N1 stage and one third in N2 stage.

Regarding staging of pTNM, 57.14% were diagnosed in stage II and the remaining cases were in stage IV.

In 3 of the cases (5.45%), the histopathological aspect was **the sarcomatoid subtype**. In this subtype we have observed mixed areas of conventional squamous cell carcinoma with malignant fusiform cell proliferation (Fig.2D). The sarcomatoid

proliferation pattern was predominantly fascicular and rarely storiform (Fig.2E), neoplastic cells being mixed with inflammatory cells and rarely the neoplastic cells presented epithelioid morphology (Fig.2F).



**Fig.2A.** Tongue squamous cell carcinoma, basaloid variant, insular and trabecular growth patterns, HE stain, x50; **B.** The presence of peripheral palisades in this neoplastic proliferations, HE stain, x200; **C.** Neoplastic lobules with central necrosis (comedonecrosis), HE stain, x100; **D.** Tongue squamous cell carcinoma, sarcomatoid variant, insular and trabecular growth patterns HE, x25; **E.** Storiform layout of neoplastic cells with fusiform morphology, HE stain, x50; **F.** Fusiform morphology of neoplastic cells in sarcomatoid proliferation, HE stain, x400

One of the 3 cases developed at the age of 53 and the other two cases were diagnosed at age of 65 and 66. Two of the 3 cases were found in females at the fixed part of the tongue and the third developed in a male in the mobile part of the tongue. All three cases were classified as low grade G3 and the predominant invasion

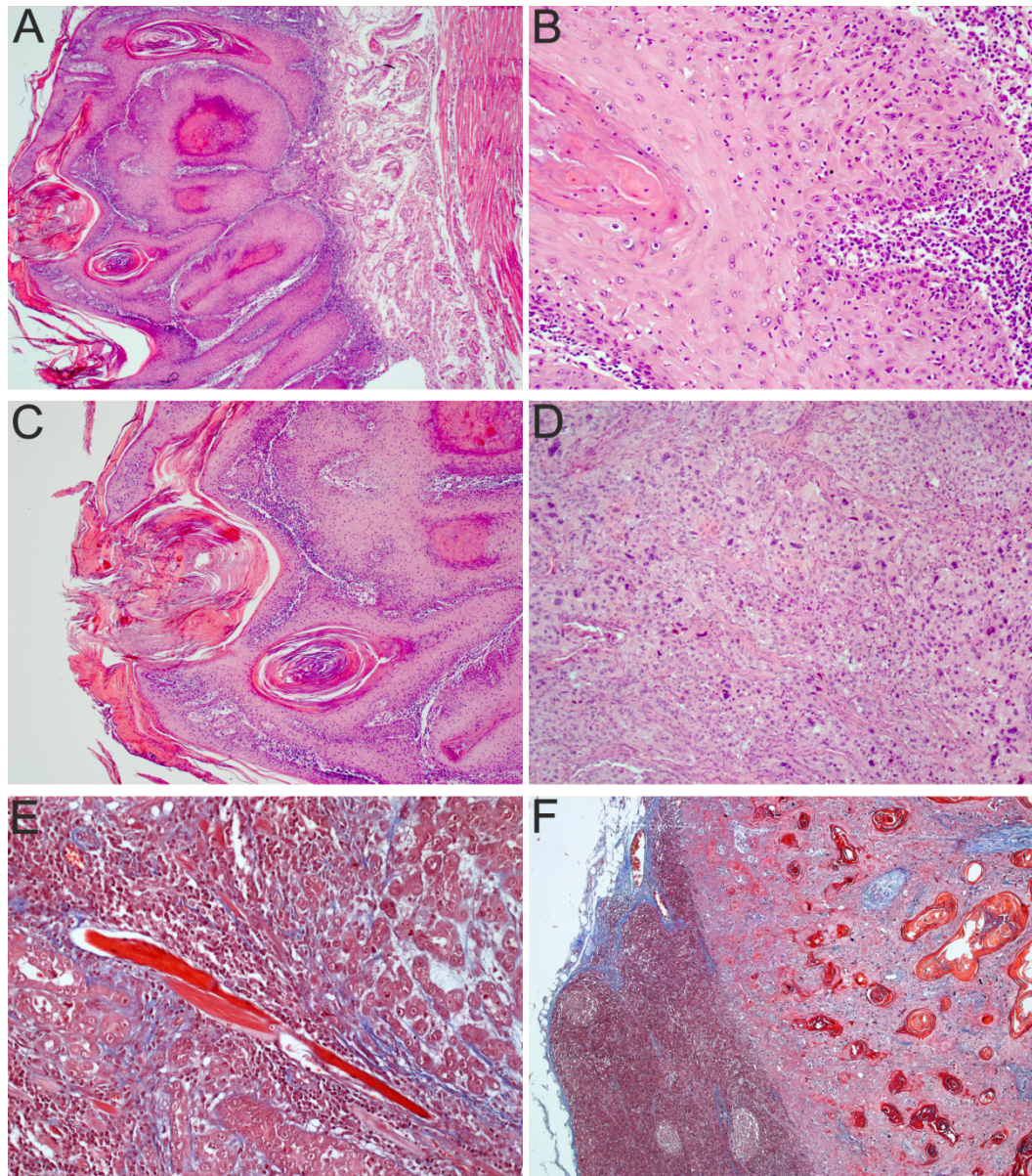
pattern was subtype 2 noticed in two cases and subtype 3 in the third one. In all three cases we found an inflammatory stroma and also in two cases was noticed a perineural invasion. Brandwein-Gensler score values were moderate in two cases and high in the third case. Lymph node metastases were diagnosed in only one

case, with stage N1 and regarding the pTNM stage, two of the cases were diagnosed in stage II and the third in stage IV. The resection margins were invaded in only one of the cases.

**The verrucous subtype** was diagnosed in only one case, and its peculiar microscopic aspect consist in the broad invasion front in the underlying corium, that take the form of plump papillary invaginations of thickened epithelium (Fig.3A), with minimal atypia (Fig.3B). The epithelium of the surface showed hyperparakeratosis, more evident especially at

the level of the sites of invaginations (Fig.3C). At the level of the broad neoplastic epithelial ridges that invade the corium, we noticed some cystic structure with keratin in the lumen.

The tumor developed in a 66-year-old man at the mobile part of the tongue, being classified as a G1 differentiation tumor degree without perineural invasion or lymph node metastases, with a low Brandwein-Gensler index, being diagnosed in stage I pTNM and with free resection margins.

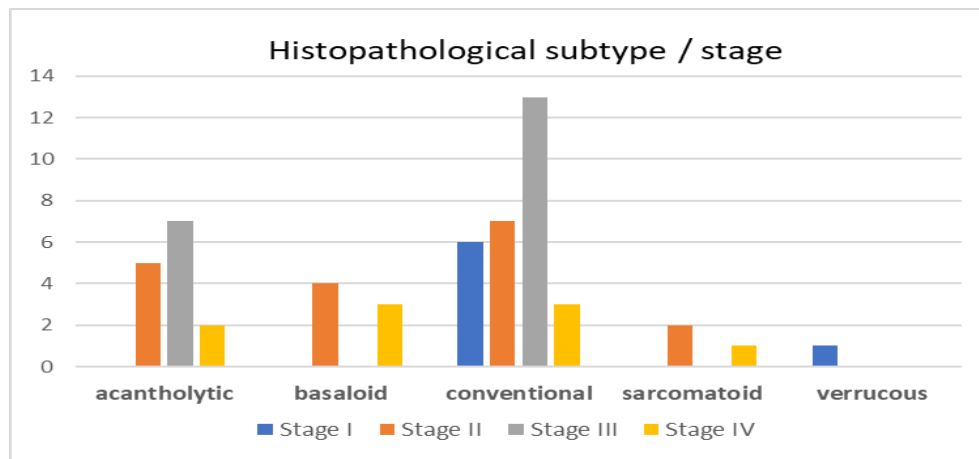


**Fig.3A. Tongue squamous cell carcinoma, verrucous variant, pattern of invasion in the broad front of the underlying corium, HE stain, x25; B. Minimal atypia of neoplastic cells from the invasive front, HE stain, x200; C. Hyperparakeratosis at the level of neoplastic epithelial invaginations, HE stain, x50; D. Poorly differentiated conventional tongue squamous cell carcinoma, neoplastic cells presenting marked atypia, frequently and atypical mitosis, HE stain, x100; E. Classical tongue squamous cell carcinoma with moderate Brandwein-Gensler score (with grade 2 invasion pattern, lymphoid stroma, deeply invasive in the tongue's own musculature), Masson's trichrome stain, x200; F. Conventional tongue squamous cell carcinoma, metastases in loco-regional lymph nodes (stage III-T2 / N1 / M0), Masson's trichrome stain, x50**

Generally, the investigated casuistry was represented by the moderately differentiated G2 forms (44.44%), followed by well-differentiated G1 forms (33.33%) and lastly by the poorly differentiated G3 forms with 22,22% (Fig.3D). Brandwein-Gensler scores included most of the moderate grades (50%) (Fig.3E), followed by the high grade (35.2%) and the low grade (14.8%). Regarding the pTNM stage, the most commonly diagnosed stage was stage III with 37.04%, (Fig.3F) closely followed by stage II with 33.33% and at a distance by stage IV with 16.67% and stage I with 12.96%. Invaded resection margins were recorded in about 24% of the investigated cases.

**The results of the statistical survey**

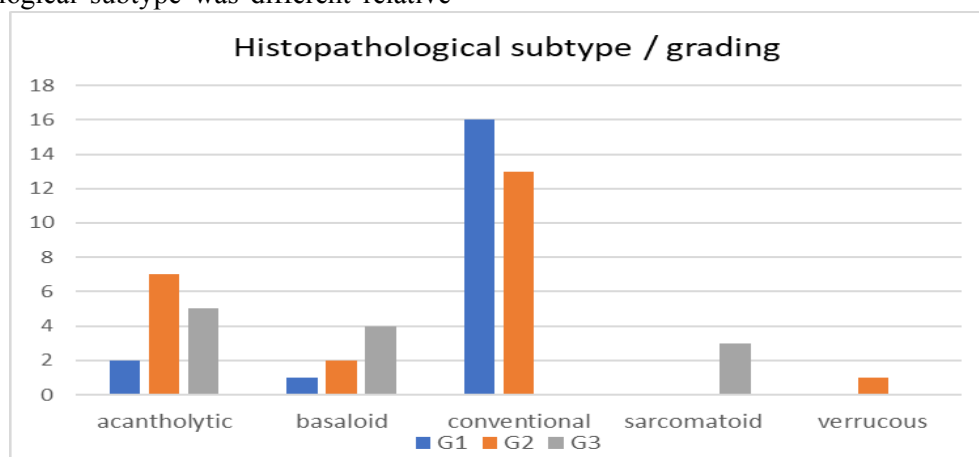
The statistic study highlighted the fact that most of the t3-t4 cases were over 60 years old, while most of the t2 cases were below 60 years old [x2 (3, N=54)=0.505, p=0.048]. Also, most of the cases with invaded resection margins were patients over 60 years old [x2 (1, N=54)=0.0008, p=0.022]. Regarding the correlation of the histopathological variants with other morphological parameters, we noticed that the distribution was different relative to the tumor stage, [x2 (12, N=54)=4.497, p=0.027] (Fig.4A).



**Fig.4A. Histopathology distribution of tongue squamous cell carcinomas was different relative to the tumor stage**

Therefore, we noticed that for the conventional and acantholytic variants, the most diagnosed stage was stage III, while for basaloid and sarcomatoid variants stage II it was more commonly diagnosed. In addition, the histopathological subtype was different relative

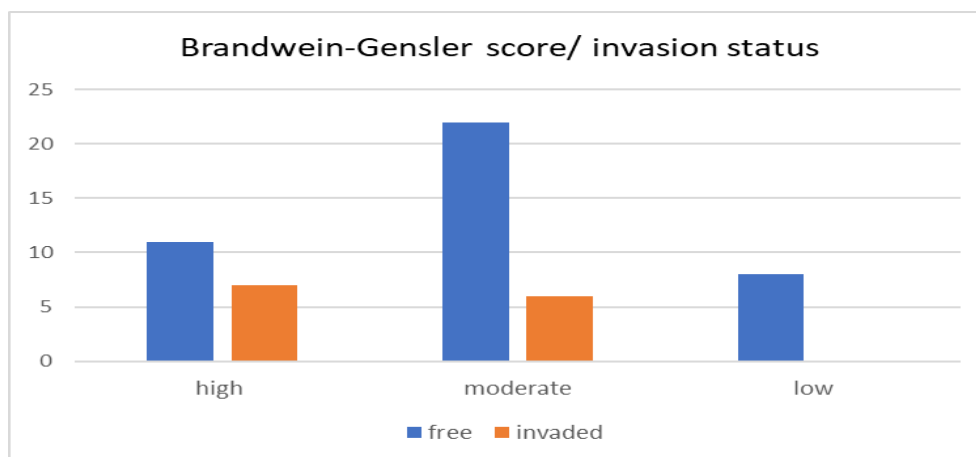
to the tumor grading, most G1-G2 cases being of the conventional subtype, while G3 cases were relatively fair distributed between acantholytic, basaloid and sarcomatoid types, [x2 (8, N=54)=0.582, p<0.001] (Fig.4B).



**Fig.4B. Most G1-G2 tumor grading cases being of conventional subtype, while G3 cases were relatively fair distributed between acantholytic, basaloid and sarcomatoid types**

Regarding resection margins we noticed that all stage IV cases had been invaded, while for stage II and III they were free, [ $\chi^2(3, N=54)=34.882, p<0.001$ ]. The percentages ratio between free and invaded margins increased

from high to moderate Brandwein-Gensler scores, with no invading margins being described for low Brandwein-Gensler scores, [ $\chi^2(2, N=54)=4.805, p=0.0487$ ] (Fig.4C).



**Fig.4C. The percentages ratio between free and invaded margins increased from high to moderate Brandwein-Gensler scores, with no invading margins for the low scores**

## Discussions

In 2012, the standardized age-related rate of oral cancer incidence was estimated at 2.7 new cases per 100,000 inhabitants with notable differences in gender, age and geographic region [16]. Thus, for the US, an annual incidence of about 11 new cases per 100,000 inhabitants was estimated. Tongue localization appears to be one of the most frequent and lethal forms of oral cancer that would traditionally affect men over 60, heavy smokers and chronic alcoholics [2,3,4]. For 2018, an incidence of 17.110 new TSCC cases was estimated in the US, of which 12.490 would develop in men and the remaining 4.620 would develop in women. However, over the past 20 years, there has been a tendency to decrease the incidence of tongue cancer among the elderly as a result of reduced exposure to smoking and chronic alcohol consumption. What is worrying is that in recent years there has been an alarming increase in the incidence of tongue cancer among young people and especially among white women [5,6,7]. Thus, between 1975 and 2007, CSL incidence increased among white men by 44%, while among white women this increase was about 111% [6]. With regard to the rate of fatal cancer deaths, according to the data projected by the Surveillance, Epidemiology, and End Results (SEER) program for 2018, would be recorded 2.510 deaths (1,750 men and 760 women) [Noone AM, 2018]. The trend over the past

3 decades in terms of death rate for the tongue cancer it was decreasing, respectively for the male gender, was noticed a decrease of 1.2% per year, while in women this was about 2.1% per year.

The tongue localization, especially at its mobile part, seems to be the most deadly of the topographic locations of oral squamous cell carcinoma and this is due to the much higher frequency of lymph node metastases in this topography [13,17]. In fact, the presence of these metastases is one of the most important prognostic factors for TSCC survival [18]. However, despite modern acquisitions in surgical techniques and the development of new therapeutic strategies, the TSCC mortality rate continues to be high in the vast majority of countries with a five-year survival rate at less than 50% [19]. All of these data encouraged studies to identify new parameters with prognostic and therapeutic value. In this respect, efforts have been also made up to develop a new system of histological grading of malignancy for this type of cancer [20,21]. Thus, the score proposed by Brandwein-Gensler M et al. seems to have a significant predictive power on the recurrences and the overall survival rate for patients with oral squamous cell carcinomas [15,22]. In this regard, more recently, the same group of authors validated this predictive score especially in the cases with early oral squamous carcinoma, where the Brandwein-Gensler score is able to identify patients with the highest risk



of loco-regional recurrences and with the most severe prognosis [23].

In the light of the data presented above, our study aimed to individualize an epidemiological and histopathological profile of TSCC patients diagnosed and operated in the Oral and Maxillofacial Surgery Clinic and Otolaryngology Surgery Clinic at the Emergency Clinical County Hospital Craiova during 2015-2017.

Our epidemiological study showed that the average age for the tongue cancer development was  $55.81 \pm 14.98$ , with the median at 63, and the decades VII and VI as being the most frequently interested, summing together 65%. Gender distribution showed a slight prevalence of male gender, with a male / female ratio of 1: 1.34. In relation to the lesion topography, the highest frequency of cases was recorded in the mobile part of the tongue, namely 2/3 of the casuistry, the most affected being the margins of the tongue (73% of the localization of the mobile part of the tongue). The fixed part of the tongue was affected in one third of the investigated cases, with the tongue base as the most prevalent involved site for this topography.

The histopathological study revealed the prevalence of **conventional** squamous cell carcinoma cases with 53.7% of the entire casuistry. Cases have developed especially among people over the age of 55, with a balanced gender ratio and having the preferential origin at the level of the tongue mobile part. Most cases were moderately differentiated forms, with type 2 and 3 as the prevailing invasion patterns. About two thirds of the cases were associated with an inflammatory stroma and less than 18% had perineural invasion. More than half of these cases were classified within the moderate degree of the Brandwein-Gensler risk score, and one third of the cases presented lymph node metastases at the time of diagnosis. Regarding the pTNM staging, about two thirds of the cases were diagnosed into stages III and II of the disease, with 1/5 of the cases with positive resection margins.

The most of the studies indicate conventional squamous cell carcinoma as being the most common neoplasm developed from the oral epithelium, with etiological factors as smoking and chronic alcoholism [14,24]. According to the latest classification of oral tumors [14], beside the conventional type, six other histopathological varieties of squamous cell carcinoma were also described such as: verrucous carcinoma, basaloid carcinoma,

fusiform cell carcinoma (sarcomatoid), papillary carcinoma, acantholytic carcinoma and adenosquamous carcinoma.

In our study, beside the conventional subtype, we also noted the following histopathological subtypes: verrucous (1.85%), acantholytic (26%), basaloid (13%) and sarcomatoid (5.45%). Thus, the second most common histopathological subtype encountered was the acantholytic, with an average age of development at 62 years, men being 2.5 times more likely to be affected than women and in 2/3 of the cases tumors developed in the tongue mobile part. Half of the cases were classified in moderate differentiated form and one third in the poorly differentiated, the invasion patterns being evenly distributed between grade 2, 3 and 4, and with the Brandwein-Gensler risk scores predominantly framed in the moderate and high degree type. In half of the cases, the histopathological appearance was a mixed one, containing areas of conventional squamous cell carcinoma and areas of acantholytic carcinoma. At the time of diagnosis, lymph node metastases were reported in half of the cases and as a pTNM stage, 50% of cases were diagnosed in the third stage of the disease and one third in the second stage.

Literature data indicate acantholytic squamous cell carcinoma as a distinct entity of squamous cell carcinoma, characterized by a pronounced acantholysis in the tumor proliferating isles leading to the appearance of pseudoglandular or pseudoluminal spaces. Most commonly, this subtype of carcinoma develops on the sun exposed skin [25] and more rarely in the mucous membranes [26,27]. In the oral mucosa, the literature data indicates an increased incidence of this histopathological variant, especially in the sixth and seventh decades of life [28]. Due to its growth pattern quite often the pathologist is forced to make a differential diagnosis with other variety of carcinomas that could develop at this site, respectively with adenosquamous carcinoma, mucoepidermoid carcinoma of minor salivary glands or with an angiosarcoma. Most authors agree that this subtype would be more aggressive than conventional carcinoma [29,30], however, there have been studies that have identified inconsistencies in reporting relapses and metastases in this squamous subtype [31].

The **basaloid variant** of squamous cell carcinoma in our casuistry was at the third place, with 13% of the cases. The average age of these patients was 67 years, men found 2.5 times more

likely to be affected than women. Two thirds of cases have developed at the mobile part and more than half have been assigned to the group of poorly differentiated forms. The invasion patterns were extremely heterogeneous, with no prevalence for any of the 4 degrees and the Brandwein-Gensler histological risk scores were also uniformly distributed between the three degrees. Approximately 43% of the cases had lymph node metastasis and 57.14% were diagnosed in stage II pTNM while the rest of them were in stage IV.

The basaloid subtype is considered a rare but aggressive variant of oral squamous cell carcinoma, identified as a distinct histopathological entity [32]. The basic histological characteristic of this variant is the biphasic aspect, with the presence of a basaloid component associated with a conventional squamous component, which was included since 1991 as a separate entity in the WHO classification of head and neck tumors [33]. It seems to develop predominantly in the head and neck and in the oral cavity, with the tongue as the most often affected (61%) [34,35]. Usually men with an average age of 63 years are more commonly affected. In the oral cavity, when we need to diagnose such entity we should also consider the possibility of developing tumors with similar morphology, and thus imposing a differential diagnosis with entities such as: cystic adenoid carcinoma, adenosquamous carcinoma, low grade polymorphic adenocarcinoma, basal cell carcinoma and ductal salivary carcinoma [36,37]. In terms of clinical evolution and prognosis, the vast majority of authors considered this variant to be much more aggressive compared to the conventional variant of squamous cell carcinoma [38]. The 5-year survival rate for tongue topography seems to be below 40%, especially as a result of the rich blood and lymphatic vasculature that exist at this level [35,39]. Thus, data from the literature cites that about 64% of patients with basaloid squamous cell carcinoma would develop lymph node metastases [40], while distance metastasis rate would be 44%, respectively six times higher than the conventional variant of squamous cell carcinoma [41].

**Sarcomatoid** subtype was diagnosed in our group in only 3 of the cases (5.45%), affecting the persons aged 53, 65 and 66 of both genders. All cases were classified as G3 differentiation grade and had 2 and 3 tumor invasion patterns. In relation to the histological risk score, the Brandwein-Gensler score recorded in two cases

was the moderate degree and the third case was classified as high degree. Lymph node metastasis was revealed in one case and as a pTNM stage, two cases were classified in the second stage of the disease and the third in the fourth stage.

Sarcomatoid squamous cell carcinoma is considered to be an unusual variant of squamous cell carcinoma developed especially in the upper digestive tract [42,43], which consists of a conventional carcinomatous proliferation associated with a malignant fusocellular epithelial component [44]. In the oral cavity, this variant accounts for less than 2% of all the tumors with this localization and in the English literature only a small number of cases have been described [44,45,46,47]. It appears to affect elderly men, especially decades VI and VII of life [43,48,49] and exceptionally young ages [50]. Potential risk factors in oral site include: smoking, poor oral hygiene, alcoholism and local irradiation [43,48,49,50]. Particularly for tongue localization, the possible pathogenic role of the accumulation of gene mutations in the cyclin-D1 cell cycle has been described [51]. The existence of the sarcoma component often requires a differential diagnosis with fusocellular mucosal melanoma, leiomyosarcoma, myoepithelial carcinoma or mucosal extension of a maxillary osteosarcoma [43,52]. Literature data indicates a more aggressive behavior of this variant than the conventional subtype of squamous cell carcinoma, with a relapse rate ranging between 16-32% [43] and a metastatic rate of 7,5-26% [43,53]. Similarly, the survival rate is lower compared to conventional squamous cell carcinoma [43,44].

The **verrucous** subtype of squamous cell carcinoma in our casuistry was diagnosed only in one case, developed in 66 aged man, being a well-differentiated form of squamous cell carcinoma without perineural invasion or lymph node metastasis, with a low grade Brandwein-Gensler score and in the first pTNM stage of the disease.

This type of squamous cell carcinoma was first described by Ackerman in 1948 as a variant of carcinoma with limited capacity for local invasion and a metastatic potential [54]. One of the most common localizations of this tumor is the head and the neck, with the oral cavity at the most frequently involved site (75%), followed by laryngeal localization (15%) [55]. However, the tumor itself has a rare incidence in the oral cavity, between 2 and 12% of all the carcinomas with this topography [56,57,58], most of all

interesting the jugal and gingival mucosa [59,60]. The number of cases with tongue localization reported in the literature is very low [61,62]. The differential diagnosis of this entity should include: typical papilloma, inverted papilloma, verrucous hyperplasia, proliferative verrucous leukoplakia, well differentiated conventional carcinoma and papillary squamous cell carcinoma. Men over the age of 50 are usually affected [63], heavy smokers and betel consumers [64]. The tumor grows slowly, rarely metastasizing [65,66], but although a 30-50% recurrence rate is reported in the oral localization [66,67,68]. Overall the prognosis of these lesions after surgical excision is very good.

In our study, the vast majority of cases were moderately differentiated forms, followed by well differentiated forms. Although, literature data indicates that poorly differentiated tumors are the most aggressive and have the worst prognosis [69], this Broders grading system for TSCC, especially for early forms, seems to have prognostic value [70]. Considering the Brandwein-Gensler histological risk score, we noticed that the majority of our casuistry was ranked moderate, followed by the cases of high grade. Although, some studies have found prognostic correlations for such a TSCC histologic risk score, others have not reported such correlations [71]. Regarding the pTNM staging, the vast majority of investigated cases were framed in stages III and II. The management of TSCC patients continues to be primarily based on the staging of TNM despite numerous histological, immunohistochemical and molecular prognostic parameters reported in literature [72].

However, its major role, both for prognosis and therapy management, is significantly more important for the advanced stages of TSCC, while its utility for early forms T1/T2N0M0 is low [73,74,75]. Some authors, just to increase the prognostic value of the TNM system, have proposed to incorporate the tumor invasion depth into the system [74,76].

In our study, about a quarter of the casuistry presented invaded margins and they had a poor prognosis. The surgical margin status has been shown to have predictive value for early TSCC cases [78], most of the authors insisting on such cases for wider surgical excision in all directions [79].

Although, there is a whole series of discussions on the use of such a parameter as a prognostic factor [80], however in clinical practice it is recommended that those cases with

positive surgical margins to be included in the group of high-risk cases and to be eligible for chemotherapy and radiotherapy [81].

## Conclusions

The epidemiological profile of our TSCC casuistry indicates their development predominantly in men with an average age of approximately 56 years, especially in the mobile parts of the tongue. Histopathologically, the encountered variants were conventional, acantholytic, basaloid, sarcomatoid and verrucous, with the conventional subtype predominating in more than half of the cases. Most cases were moderate differentiated forms, with poorly differentiated forms being evenly distributed among acantholytic, basaloid and sarcomatoid variants. Two thirds of the cases were diagnosed in pTNM stages II and III of the disease, the third stage prevailing in the acantholytic variant and the second stage in the basaloid variant. In a quarter of the cases, the resection margins were invaded, and the patients being particularly in the fourth stage and with high Brandwein-Gensler scores.

## Acknowledgment

\*These authors had equal contributions to the study

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