Original Article

# Clinicopathological Features and Survival Outcomes of 70 Tongue Squamous Cell Carcinoma Patients

# Yetmiş Dil Skuamöz Hücre Karsinomu Hastasının Klinikopatolojik Özellikleri ve Sağ Kalım Sonuçları

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**ABSTRACT**

**Introduction:** In this article, it is aimed to present the clinicopathological and demographic characteristics, treatment regimens and survival characteristics of locally advanced tongue squamous cell cancers (TSCC).

**Materials and methods:** This retrospective study included patients with histologically confirmed locally advanced TSCC followed up at the medical oncology clinic between January 2005 and June 2020. Clinicopathological features and treatment modalities of the patients were recorded from the hospital's patient registry database. The obtained data were compared statistically

**Results:** A total of 70 patients, 42 male and 28 female, were included in the study. The 5-year OS was found to be 59%. The median disease free survival (DFS) was 4.1 years. OS could not reach the median in the 2/3 anterior tumors of the tongue, while the median OS was 6.9 years in the 1/3 posterior tumors of the tongue (p=0.046). There was no statistically significant difference between age groups in terms of median OS and median DFS. But there was a remarkable point. The median DFS was numerically shorter in patients aged 45 years and younger than in patients over 45 years of age (2 years vs. 4.5 years). Also important here was that both the median OS and the median DFS were numerically worse in women (respectively, median OS: 4.1 years vs. not reached, p=0.075; median DFS: 2.2 years vs. 5.9 years, p=0.349).

**Discussion:** There are few studies that examine TSCC as a separate title under these headings of oral cavity cancers and oropharyngeal cancers. In this sense, this study will contribute to the literature.

**Keywords:** oral cavity cancers, oropharengeal cancers, tongue squamous cell cancers

**ÖZET**

**Giriş:** Bu yazıda, lokal ileri dil skuamöz hücreli kanserlerin (DSCC) klinikopatolojik ve demografik özellikleri, tedavi rejimleri ve sağkalım özelliklerinin sunulması amaçlanmaktadır.

**Gereç ve yöntemler:** Bu retrospektif çalışma, Ocak 2005 ile Haziran 2020 arasında medikal onkoloji kliniğinde takip edilen, patolojik olarak doğrulanmış lokal ileri DSCC'li hastaları içermektedir. Hastaların klinikopatolojik özellikleri ve tedavi yöntemleri hastanenin hasta kayıt veritabanından kaydedilmiştir. Elde edilen veriler istatistiksel olarak karşılaştırılmıştır.

**Bulgular:** Çalışmaya 42 erkek ve 28 kadın olmak üzere toplam 70 hasta dahil edildi. 5 yıllık gene sağ kalım (OS) %59 olarak bulundu. Medyan hastalıksız sağ kalım (DFS) 4.1 yıldı. Dil ön 2/3 tümörlerinde OS medyana ulaşamadı, dilin 1/3 arka tümörlerinde medyan OS 6.9 yıldı (p=0.046). Medyan OS ve medyan DFS açısından yaş grupları arasında istatistiksel anlamlı fark yoktu. Ancak dikkat çekici nokta, medyan DFS 45 yaş ve altındaki hastalarda, 45 yaşın üzerindeki hastalardan (2 yıla karşı 4,5 yıl) sayısal olarak daha kısaydı. Ayrıca hem medyan OS hem de medyan DFS kadınlarda numerik olarak daha

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kısaydı (sırasıyla, medyan OS: 4,1 yıla karşı 'ulaşılamadı', p=0,075; medyan DFS: 2,2 yıla karşı 5,9 yıl, p=0,349).
**Tartışma:** Oral kavite kanserleri ve orofaringeal kanserler başlıkları altında DSCC'yi ayrı bir başlık olarak inceleyen az sayıda çalışma bulunmaktadır. Bu anlamda bu çalışma literatüre katkı sağlayacaktır.

**Anahtar kelimeler:** oral kavite kanserleri, orofaringeal kanserler, dil squamoz hücreli kanseri

## Introduction

Squamous cell carcinoma of the tongue (TSCC) has increased significantly worldwide over the past decades and it is the second most common cancer of the oral cavity after lip cancer. TSCC was thought to primarily affect middle-aged men and has been associated with tobacco and alcohol use [1]. While men constitute more than 70% of the cases in the elderly, this rate decreases to 50-65% in patients under the age of 45 [2-4]. The incidence of TSCC is increasing, particularly in white women and younger white patients [5]. In the classification of head and neck tumors of the World Health Organization, oropharyngeal and base of the tongue tumors are classified separately from mobile tongue tumors due to their different characteristics [6].

Although the combined use of alcohol and cigarettes is blamed as the cause, the etiological factors are not fully known. It was shown that the incidence of TSCC is on the rise in countries with primary prevention campaigns to quit smoking and alcohol [1, 7, 8]. This suggests that other etiological, genetic and environmental factors are effective in the carcinogenesis of TSCC [9]. In addition, poor oral hygiene and trauma are among the conditions investigated. Epidemiological, studies and laboratory evidence have revealed the relationship between HPV and oro-pharyngeal cancer. However, data from the Surveillance, Epidemiology, and End Results (SEER) database showed that oral tongue tumors were not generally associated with human papillomavirus (HPV) infection and the incidence of HPV-related head and neck carcinomas is decreasing among women [8].

Significant advances have been identified in the locoregional treatment of TSCC due to modern and aggressive surgical resections and advances in adjuvant therapy [10, 11]. Despite all the recent advances in treatment, survival rates have remained stable in the last 5 decades, the 5-year survival rate of SCC cases 33-54% in patients with locally advanced disease [12, 13].

This article aimed to present the clinico-pathological and demographic characteristics, treatment regimens, survival characteristics and also independent prognostic factors of locally advanced TSCC (mobile tongue and base of tongue cancers).

## Patients and Methods

This study was approved by Ankara City Hospital Institutional Ethics Committee with decision number E1/1965/2021. The study was carried out in accordance with the Declaration of Helsinki. This retrospective study included patients with histologically confirmed locally advanced TSCC followed up at the medical oncology clinic between January 2005 and June 2021. Clinico-pathological features (smoking, gender, alcohol consumption, comorbidity, Eastern Cooperative Oncology Group Performance Status [ECOG PS], tumor location, pathological features) and treatment modalities of the patients were recorded from the hospital's patient registry database. Patients with oral cavity cancer other than mobile tongue cancer and patients with oropharyngeal cancer other than base of tongue cancer were excluded from the study. The obtained data were compared statistically.

 

In previous studies on tongue cancer and oral squamous cell cancer in the literature, patients were examined under different age groups. In this study, based on the previous studies in the literature, patients were examined in 3 different groups as ≥45 and >45 years old, <55 and ≥55 years old, <65 and ≥65 years old.

Overall survival (OS) was defined as the time from surgical resection until death due to any reason or last follow-up. Disease-free survival (DFS) was defined as the time from surgical resection to recurrence of the disease or death.

Statistical Analysis

Statistical analyzes were performed using SPSS Statistics version 24.0 (IBM Corp, Armonk NY", link: https: //www.ibm.com/ support/pages/how-cite-ibm-spss-statistics-or earlier-versions-spss). Continuous variables were presented as median (minimum-maximum). Categorical variables were presented as percentages. Normality of quantitative data was analyzed by Kolmogorov-Smirnov and Shapiro-Wilk tests. Pearson Chi-square test was used to compare the categorical variables of the two groups, and the independent sample T-test or Mann-Whitney U-test was used to compare the continuous variables of the two groups. Kaplan-Meier (Log rank) method was used for survival analysis. Univariate Cox regression analysis was used to identify independent predictors of OS and DFS. Variables with a p value of <0.05 in univariate analysis were included in multivariate analysis. P value <0.05 was considered statistically significant.

**Results**

A total of 70 patients, 42 male and 28 female, were included in the study. 48 of the patients were under 65 years of age. The tumor localization was in the anterior 2/3 of the tongue in 19 (27.1%) patients, in the base of the tongue in 46 (65.7%) patients, and on both sides in 5 (7.1%) patients. Nine (12.9%) patients received neoadjuvant treatment (3 patients neoadjuvant chemotherapy [CT], 6 patients induction chemoradiotherapy [CRT]). All patients were operated. 53 patients received adjuvant therapy. Neo-adjuvant CT regimen was DCF (docetaxel 75 mg/m$^2$, cisplatine 75 mg/m$^2$, 5-fluorouracil 1000 mg/m$^2$/gün, 1-4 days). Patients receiving neoadjuvant/adjuvant CRT received RT concurrently with cisplatin 40 mg/m$^2$ weekly. Surgical pathology reports of 50 patients could be accessed. pTx was detected in 8 (16%) patients, pT1 in 11 (22%) patients, pT2 in 21 (42%) patients, pT3 in 9 (18%) patients, and pT4a in 1 (2%) patients. pNx was detected in 11 (22%) patients, pN0 in 14 (28%) patients, pN1 in 20 (40%) patients, pN2a in 4 (8%) patients, and pN2b in 1 (2%) patients. Grade 1 tumor was detected in 16 (22.9 %) patients, grade 2 tumor in 32 (45.7%) patients, and grade 3 tumor in 2 patients (2.9%). The clinical and pathological features of the patients are summarized in table 1 (Table-1).

The median follow-up period of the patients was 3.1 years. OS did not reach the median in the whole group and the 5-year OS was found to be 59%. The median DFS in the whole group was 4.1 (0.4-7.8) years.

Patients were divided into two age groups as ≤45 years and >45 years; <55 years and ≥55 years; <65 years and ≥65 years. OS did not reach the median in the first age group. 5-year median OS was 54% in patients aged 45 years and younger and 59% in patients over 45 years of age (p=0.872). The median OS was not reached in patients under 55 years of age, whereas it is 7 (2.1-12) years in patients aged 55 years and older (p=0.221). The median OS did not reach the median in patients under 65 years of age, and it was 4.4 years (0.9-8.2) in patients 65 years and older (p=0.140).

The median DFS was 2 (0.8-3.1) years in patients aged 45 years and younger and 4.5 (2.3-6.8) years in patients over 45 years of age (p=0.73). The median DFS was 5.9 (0.3-11.5)

 

Table 1. Demographic and clinicopathological characteristics of patients

| | | | Median (Minimum;Maximum) | N=70 (%) |
|---|---|---|---|---|
| Age of diagnosis (years) | | | 56 (22;92) | |
| Gender | Female | | | 28 (40%) |
| | Male | | | 42 (60%) |
| Age | <65 years | | | 48 (68.6%) |
| | ≥65 years | | | 22 (31.4%) |
| Smoking | Female | Yes | | 9 (32.1%) |
| | | No | | 19 (67.9%) |
| | Male | Yes | | 34 (80.9%) |
| | | No | | 8 (19,1%) |
| Alcohol | No | | | 55 (78.6%) |
| | Yes | | | 15 (21.4%) |
| Comorbidity | No | | | 36 (51.4%) |
| | Yes | | | 34 (48.6%) |
| ECOG-PS | 0 | | | 18 (25.7%) |
| | 1 | | | 40 (57.1%) |
| | 2 | | | 12 (17.2%) |
| Tumor location | 2/3 anterior of the tongue | | | 19 (27.1%) |
| | 1/3 posterior of the tongue | | | 46 (65.7%) |
| | Both sides | | | 5 (7.1%) |
| Pathological T | Tx | | | 8 (16%) |
| | T1 | | | 11 (22%) |
| | T2 | | | 21 (42%) |
| | T3 | | | 9 (18%) |
| | T4a | | | 1 (2%) |
| Pathological N | Nx | | | 11 (22%) |
| | N0 | | | 14 (28%) |
| | N1 | | | 20 (40%) |
| | N2a | | | 4 (8%) |
| | N2b | | | 1 (2%) |
| Extranodal extension | Negative | | | 20 (40%) |
| | Positive | | | 5 (10%) |
| | Unknown | | | 25 (50%) |
| Perineural invasion | No | | | 11 (22%) |
| | Yes | | | 18 (36%) |
| | Unknown | | | 21 (42%) |
| Lymphovascular invasion | No | | | 17 (34%) |
| | Yes | | | 10 (20%) |
| | Unknown | | | 23 (46%) |
| Grade | Grade1 | | | 16 (22.9%) |
| | Grade2 | | | 32 (45.7%) |
| | Grade3 | | | 2 (2.9%) |
| | Unknown | | | 20 (28.5%) |
| Neoadjuvant therapy | Yes | | | 9 (12.9%) |
| | No | | | 61 (87.1%) |
| Adjuvant therapy | No | | | 17 (24.3 %) |
| | RT | | | 9 (12.8%) |
| | CRT | | | 44 (62.9%) |

*ECOG PS: Eastern Cooperative Oncology Group Performance Status, RT: Radiotherapy, CRT: chemoradiotherapy*
*Surgical pathology reports of 50 patients could be accessed.*

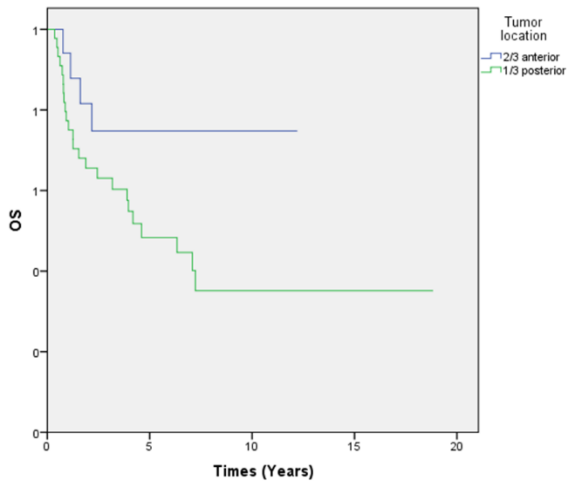


Figure 1. Kaplan-Meier Curve of Overall Survival by Tumor Location

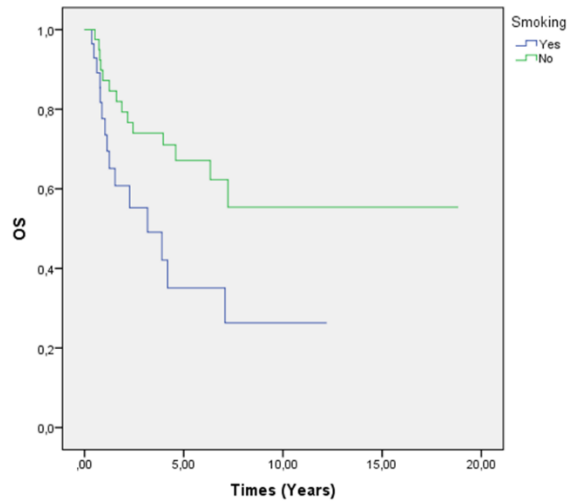


Figure 2. Kaplan-Meier Curve of Overall Survival by Smoking

years in patients <55 years of age, 4 (3.2-4.9) years in patients aged ≥55 years (p=0.450). The median DFS was 4.0 (0.1-7.9) years in patients <65 years of age, 4.5 (1.9-7.2) years in patients aged ≥65 years (p=0.951). There was no statistically significant difference between the groups in terms of median OS and DFS.

The median DFS was 5.9 (3.7-8.1) years in male patients and 2.2 (1.2-3.2) years in females (p=0.349). The median OS was 4.1

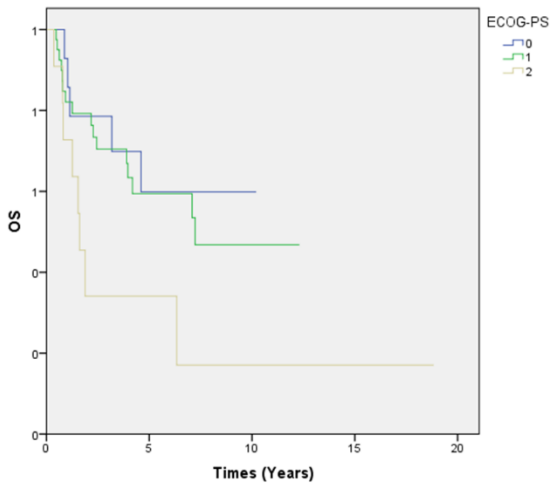


Figure 3. Kaplan-Meier Curve of Overall Survival by ECOG-PS

(1.1-8.2) years in female patients and was not reached in male patients (p=0.075).

When the patients were divided into two groups according to tumor location, median OS could not be reached in the 2/3 anterior tumors of the tongue, while the median OS was 6.9 (2.7-9.8) years in the 1/3 posterior tumors of the tongue (p=0.046) (Figure-1). While the median DFS could not be reached in the anterior 2/3 anterior tumors of the tongue, the median DFS was 3.8 (1.0-6.7) years in the 1/3 posterior tumors of the tongue (p=0.073). While the median OS was 7.2 (6.8-7.6) years in those who did not receive adjuvant therapy, it did not reach the median in those who received adjuvant therapy (RT or CRT) (p=0.877). While the median DFS was 6.5 (0.2-13.2) years in those who did not receive adjuvant therapy, it was 3.9 (1.7-6.1) years in those who received adjuvant therapy (RT or CRT) (p=0.317).

While the median OS was 3.1 (0.5-5.8) years in smokers, the median OS could not be reached in non-smokers (p=0.019) (Figure-2). While the median OS was 1.6 (0.9-2.2) years in the group of patients with ECOG PS of 2, the median OS could not be reached in

Table 2. Univariate and multivariate analysis for overall survival

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Male (reference=female) | 0.52 (0.24-1.12) | 0.098 | | |
| Age at diagnosis | 1.01 (0.98-1.04) | 0.237 | | |
| Smoking-<br>No (reference=yes) | 0.43 (0.20-0.92) | **0.031*** | 0.37 (0.17-0.81) | **0.011*** |
| ECOG-PS | 1 | **0.032*** | 1 | |
| 1 (reference=0) | 1.1 (0.41-3.22) | | 1.13 (0.4-3.15) | **0.025*** |
| 2 (reference=0) | 3.3 (1.1-10.4) | | 3.93 (1.26-12.23) | |
| Neoadjuvant therapy | | 0.323 | | |
| Yes (reference=no) | 1.7 (0.59-4.96) | | | |
| Adjuvant therapy | 1 | 0.952 | | |
| RT (reference=no) | 0.85 (0.25-2.92) | | | |
| CRT (reference=no) | 1.02 (0.41-2.49) | | | |

*ECOG PS: Eastern Cooperative Oncology Group Performance Status, RT: Radiotherapy, CRT: chemoradiotherapy*

patients with ECOG PS of 0 and 1 (Figure-3) (p=0.054).

Smoking and ECOG PS were found to be prognostically significant factors in univariate and multivariate analysis for OS (Table 2).

## Discussion

Most of the studies in the literature examined tongue cancers together with other cancers under the headings of oral cavity cancers or oropharyngeal cancers. Therefore, very few studies have been found examining tongue cancer (mobile tongue and base of tongue) under a separate heading. Therefore, we believe that this study will be a guide for future studies.

Physician's give more aggressive therapies to young patients to achive longer survival. Another important condition is that tongue cancer presenting at a young age is thought to be a poor prognostic factor [14, 15]. Besides, some recent studies [16, 17] that did not find a significant difference in OS between different age groups, there are also studies [7, 18-20] claiming that younger TSCC patients have better survival than older patients. Memorial Sloan-Kettering CancerCenter reported that there was no difference between age groups in terms of OS in patients with TSCC, but a higher rate of locoregional recurrence in younger patients (<40 years) [21]. In addition to these conflicting results reported in the literature, in this study, there was no statistically significant difference between age groups in terms of median OS and median DFS. But there was a remarkable point. The median DFS was numerically shorter in patients aged 45 years and younger than in patients over 45 years of age (2 years vs. 4.5 years). In two different studies comparing patients under 40 years of age and over 40 years of age, OS was similar between age groups, while recurrence rates were higher in the group below 40 years of age [22, 23].

In this study, the median OS was 7 years in patients over 55 years of age, it could not

 

reach the median in patients 55 years and younger; similarly, while it was 4.4 years in patients over 65 years of age, it could not reach the median in patients 65 years and younger. Although it does not reach statistical significance, these results may be a precursor to a better OS outcome at a younger age, with the prolongation of the follow-up period. But this remains only a hypothesis for now. Many studies have reported that there is no difference in biological behavior, genomic profiles, and frequencies of mutations, tumorigenesis mechanisms, gene-specific mutations and copy number changes between young and elderly patients with TSCC [24-28]. In this study, 52.2% of patients aged 65 and over had comorbidities such as diabetes mellitus, coronary artery disease, hypertension, and chronic obstructive pulmonary disease. Perhaps the reason why the OS rates in elderly patients, albeit numerically, are poor may be due to the existing comorbidities of these patients and their poor tolerance to CT or CRT.

Both the median OS and the median DFS were numerically lower in women than men (respectively, median OS: 4.1 years vs. not reached, median DFS: 2.2 years vs. 5.9 years).The fact that this difference did not reach statistical significance was attributed to the low number of patients. Similarly, in another study examining younger patients with TSCC, women have been shown to have higher recurrence rates than men [29]. Results from the SEER database support an increased incidence of TSCC, particularly in young white women. The increase in the incidence of TSCC with increasing smoking in women may have revealed more clearly that TSCC has a poor prognosis in women.

In this study, in the analysis by tumor location, median OS was found to be significantly higher in tumors located in the anterior 2/3 of the tongue (oral tongue cancer). Although median DFS was numerically better detected in tumors located in the anterior 2/3 of the tongue, statistical significance was not be obtained. According to the results of SEER database, which evaluated 74680 head and neck cancer patients between 1976 and 2015, it was revealed that oral TSCC showed a greater improvement in survival than other oral cavity cancers (37.0% in 1976-1985, 61.7% in 2006–2015). During 2006–2015, the 5-year conditional survival exceeded 90% only for oral TSCC and oropharyngeal SCC. It can be thought that early detection of the disease and the contribution of modern surgical methods to this survival are very important factors.

In this study, overall survival in smokers was shorter than in non-smokers. In a study, no association was found between smoking and DFS/OS in young oral TSCC patients [30]. However, there are also studies with similar results to our study. Previous studies showed that tongue neoplasia (tongue + tongue base) had a high prevalence of advanced disease in smokers, also showed that cancers of the tongue base were more aggressive in smokers [31, 32]. Several large studies reported that current smoking increases overall mortality in patients with head and neck cancer [33, 34]. Cigarette components increase tumor aggressiveness by increasing proliferation, angiogenesis, migration of cancer cells and decrease the response to cytotoxic cancer agents such as chemotherapy/radiotherapy [35, 36]. OS may be shorter in the smokers group due to these effects.

ECOG PS was found to be significant for OS in univariate and multivariate analysis in this study. When ECOG PS was divided into 0, 1, and 2 in the Kaplan-Meier analysis, no statistical difference was found between the groups, but OS was shorter in the group with ECOG PS of 2. This was attributed to the small number of patients in the groups separated according to ECOG PS. There are several studies showing poor ECOG PS were associated with a shorter OS. In a study of patients receiving palliative chemotherapy for

 

advanced bile duct cancer, poor ECOG PS was associated with shorter OS [37]. Similar results were obtained in patients with advanced melanoma [38].

Treatment strategies such as CRT or surgery following neoadjuvant treatment for TSCC have been shown without significant improvement in survival in many studies. In this study, when the patients were divided into two groups as those who received adjuvant treatment and those who did not, no difference was found between the groups in terms of OS and DFS. Considering that the patients who did not receive adjuvant therapy consisted of patients with T1-2/N0 and without poor risk factors (extranodal extension, positive or close margin, perinoral invasion, vascular invasion, etc.), the fact that patients have poor risk factors, have T3 disease and above, and/or node positivity worsens the prognosis. It suggests that the contribution of adjuvant therapy is limited at this stage. Furthermore, this result demonstrates the importance of an effective surgery ± neck dissection in locally/locally advanced disease.

Limitations

This study had some limitations. The first limitation was that it was a retrospective study. We could not obtain information from the patient files about the surgical method and whether neck dissection was added or not. In this study, nine patients were given neo-adjuvant therapy. However, the neoadjuvant treatment indications of these patients could not be obtained from the patient files. This was another limitation of our study. Although the National Comprehensive Cancer Network stated that HPV positivity or HPV negativity did not make a difference when starting adjuvant treatment for locally advanced oropharyngeal cancer patients, we could not evaluate the effect of HPV on survival.

## Conclusion

In conclusion, in TSCC patients, OS was found to be longer in oral cavity TSCC patients than in base of tongue cancers. OS was found to be significantly longer in non-smokers. There was no difference in OS or DFS, especially in patients who received and did not receive adjuvant therapy, may indicate the importance of effective surgery ± neck dissection in patients with locally advanced TSCC. Base of tongue and oral tongue cancers should be considered as a specific title, without being under the headings of oropharyngeal cancers or oral cavity tumors. So, it will be guiding in terms of showing the differences between the two groups.

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