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Clinicopathological characteristics and outcomes of squamous cell carcinoma of the tongue in different age groups

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Abstract

Background: The clinicopathological features and outcomes of squamous cell carcinoma (SCC) of the tongue in patients of different age groups remain debatable.

Methods: Medical records of 457 patients with tongue SCC were reviewed, grouped by age, followed up, and compared.

Results: Sex and TNM stage showed no intergroup differences. Tongue SCC in patients ≤30 years had the most advanced TNM classification and greatest proportion of poorly differentiation tumors. Both disease-free survival (DFS) and disease-specific survival (DSS) showed no statistically significant difference between the youngest and the oldest groups ($P = .605$ and $P = .520$). However, there was a tendency of higher death rate caused by recurrence or metastasis in the youngest group compared with the others (91.7% vs 75.4% and 77.4%).

Conclusion: Young patients had a tendency of higher death rate caused by recurrence or metastasis than middle-age and older patients; therefore, a larger case sample is needed for further confirmation.

KEYWORDS
oral cancer, squamous cell carcinoma, survival, tongue, young people

1 | INTRODUCTION

Squamous cell carcinoma (SCC) of the tongue is one of the most common cancers of the oral cavity and is considered to occur frequently after middle age.[1] However, a recent study has shown an increasing incidence among young patients[2] with inconsistent reports on differences in clinicopathological features and prognosis of tongue SCC between young and old patients. Some studies have shown a better outcome for the former patient group,[2,3] whereas others reported that tongue SCC in young patients was associated with a significant decrease in the survival rate.[4,5] Similar prognosis trends for the young and old patient groups have also been reported.[6–8] By reviewing literature on this topic, we found the limitation of patient's number was another problem (Table 1). Due to this limitation, there might be more difficulties to evaluate the prognosis and clinicopathological features.

Another issue has been the lack of an exact definition for "young age"; consequently, the grouping of young patients in previous studies was optional and, thus, inconsistent. A wide range of cutoff points from 30-45 years has been reported in previous studies.[9–14]

The purpose of the present study was to evaluate biological behaviors and outcomes of tongue SCC in 3 different age groups.

2 | MATERIALS AND METHODS

The institutional review board of Peking University School of Stomatology approved this study and waived the need for informed consent considering this was a retrospective study.

TABLE 1 Literature review on tongue squamous cell carcinoma of young patients

Author and reference	Country	Journal	Year	Age cutoff point (years)	No. of young patients
Sarkaria et al[38]	Mandison	Head Neck	1994	40	14
Pitman et al[39]	USA	Head Neck	2000	40	28 (94 from literature)
Mathew Iype et al[40]	India	Neoplasia	2001	35	115
Annertz et al[2]	Scandinavia	Int J Cancer	2002	40	276
Maneul et al[12]	India	Int J Oral Maxillofac Surg	2003	45	76
Popovter et al[7]	Israel	Laryngoscope	2004	45	16
Lee et al[41]	Taiwan	Acta Otolaryngol	2007	45	20
Garavello et al[5]	Italy	Oral Oncol	2007	40	46
Mallet et al[11]	France	Acta Otolaryngol	2009	35	52
Hilly et al[4]	Israel	Oral Oncol	2013	30	16
Fang et al[24]	China	Oncol Lett	2014	40	15
Sun et al[42]	China	Int J Clin Exp Med	2015	40	15

We included patients with tongue SCC who were diagnosed and treated at the Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, between January 2001 and January 2014. All patients were diagnosed with SCC based on histopathological examination of formalin-fixed paraffin blocks. The tumor site only involved the body of the tongue. Patients with tongue base tumors and incomplete information at diagnosis were excluded. Medical records were reviewed and the following data were collected: age, sex, tobacco and alcohol consumption, TNM classification, histological stage, and treatment (including both surgical procedure and postoperative treatment); the T and N classifications were based on pathological examinations.

The patients were followed up for 1-165 months (median 39 months). Disease-free survival (DFS) and disease-specific survival (DSS) were used to evaluate the prognosis.

Patients were divided into the following 5 age groups: ≤ 30 years old; 31-45 years old; 46-59 years old; 60-69 years old; and ≥ 70 years old. To avoid the influence of age overlap, we compared the 3 patient groups of ≤ 30 years (hereafter, the youngest group), 46-59 years (hereafter, the middle-age group), and ≥ 70 years (hereafter, the oldest group).

2.1 | Statistical analysis

Variables were expressed as mean $\pm$ SD and percentages. Significance of differences among the 3 groups was analyzed by the Kruskal-Wallis test. The Mann-Whitney *U* test was used to analyze the significance of differences between each 2 groups. DFS, DSS, and overall survival were calculated by the Kaplan-Meier method and evaluated using the log-rank test. A P value of $< .05$ was considered statistically significant. All analyses were performed using SPSS version 20 (IBM, Chicago, IL).

3 | RESULTS

Among the 457 patients who were histologically diagnosed with SCC of the tongue, 5 patients were excluded because of incomplete information. Thirty-six patients (8.0%) were aged 30 years and younger at diagnosis; of these, 17 were men and 19 were women. The middle-age group included 159 patients (35.2%) with 84 men and 75 women. Sixty-eight patients (15.0%) were aged ≥ 70 years, with 33 men and 35 women. Patient characteristics are detailed in Table 2; sex predilection was not statistically significant among these 3 groups. However, significant differences were observed for tobacco and alcohol consumption among the 3 groups. The percentage of smokers and drinkers in the youngest and oldest groups were lower than that of the middle-age group (8.3% and 27.3% vs 42.9% and 5.6% and 20.9% vs 35.3%, respectively; $P = .014$ and $P = 0.011$, respectively).

Although the youngest group showed the most advanced T classification (28.6% vs 19.1% and 9.7%) and a more common N-positive classification (26.9% vs 22.9% and 20.0%) basing on histopathological examination, no statistical

TABLE 2 Patient demographics of the three age groups

	Patients aged ≤ 30 y (n = 36)	Patients aged 46-59 y (n = 159)	Patients aged ≥ 70 y (n = 68)	*P* value[a]
Age, year (range)	26.1 (21-30)	53.0 (46-59)	75.5 (70-95)	
Sex				
Male	17	84	33	.747
Female	19	75	35	
Lifestyle habits				
Tobacco	3/36 (8.3%)	67/156 (42.9%)	18/66 (27.3%)	.014
Alcohol	2/36 (5.6%)	55/156 (35.3%)	14/67 (20.9%)	.011

[a]Compared among three groups.

intergroup differences was found. On the other hand, the rates of advanced TNM classification of the youngest group (50.0%) and the middle-age group (40.6%) were significantly higher than that of the oldest group (19.4%; $P = .003$). Further, young patients had a significantly higher incidence of poor differentiation than the middle-age group ($P = .013$); this difference was not significant when compared with the oldest group ($P = .381$; Table 3).

Treatment modalities for the patients are presented in Table 4. Surgery with glossectomy and neck dissection was the basic treatment. One patient aged 47 years with a histopathological diagnosis of early carcinoma, opted for conservative therapy over invasive treatment. The oldest and middle-age groups had 1 and 3 patients, respectively, who had been diagnosed with early carcinoma receiving only radiotherapy without surgery for the primary tumor. Of the abovementioned 3 patients, local recurrence occurred only in an 86-year-old woman. Postoperative radiation and chemotherapy were advised to patients with advanced TNM classification or positive N classification. However, such treatment was opted for more often by the youngest group of patients (38.9%) than the middle-age and oldest groups (14.5% and 8.8%, respectively).

The Kaplan-Meier survival plots are presented in Figures 1 and 2. The respective 3-year and 5-year DFS rate of the youngest, middle-age, and oldest groups were 70.0%, 74.6%, and 68.0% and 33.1%, 64.8%, and 47.9%, respectively. Both DFS and DSS showed no statistically significant difference upon comparison of the youngest group with the oldest groups ($P = .605$ and $P = .520$), whereas DFS and DSS in the middle group were both significantly higher than that in patients older than 70 years ($P = .015$ and $P < .001$). Tumor recurrence occurred in 12 patients (33.3%) in the youngest group, 57 patients (35.8%) in the middle-age group, and 31 patients (45.6%) in the oldest group ($P = .209$; Table 5). Furthermore, a tendency of higher recurrence death rate (death caused by recurrence or metastasis) was found in the youngest group (11/12; 91.7%) compared with the other 2 groups (43/57; 75.4% and 24/31; 77.4%, respectively) although no statistically significant difference was shown ($P = .469$; Table 5).

Table 6 showed the tightest connection between TNM classification and DFS or DSS in the youngest group.

TABLE 3 TNM classifications and cell differentiation of tumors among the three age groups

	Patients aged ≤ 30 y (n = 36)	Patients aged 46-59 y (n = 159)	Patients aged ≥ 70 y (n = 68)	*P* value[a]
Advanced TNM classification (III-IV)	17/34 (50.0%)	63/155 (40.6%)	12/62 (19.4%)	.003
Advanced T classification				.060
T1 + T2	25/35 (71.4%)	123/152 (80.9%)	56/62 (90.3%)	
T3 + T4	10/35 (28.6%)	29/152 (19.1%)	6/62 (9.7%)	
Positive N classification	7/26 (26.9%)	22/96 (22.9%)	5/25 (20.0%)	.840
Positive M classification	0	0	0	NS
Poor differentiation	6/35 (17.1%)	7/143 (4.9%)	6/56 (10.7%)	.043

Abbreviation: NS, not significant.
[a]Compared among three groups.

TABLE 4 Treatment modalities of the three age groups

	Patients aged ≤ 30 y (n = 36)	Patients aged 46-59 y (n = 159)	Patients aged ≥ 70 y (n = 68)	*P* value[a]
Nonsurgery	0	3 (1.9%)	1 (1.5%)	NS
Interstitial brachytherapy		3		
Radiotherapy			1	
Surgery	22 (61.1%)	133 (83.6%)	61 (89.7%)	.001
Surgery + adjuvant treatment	14 (38.9%)	23 (14.5%)	6 (8.8%)	< .001
+ interstitial brachytherapy	2	3	1	
+ radiotherapy	8	18	2	
+ chemotherapy		1[b]	2	
+ radiotherapy + chemotherapy	4	1	1	

Abbreviation: NS, not significant.

[a]Compared among three groups.

[b]Patient did not receive radiotherapy because of post-operation infection.

4 | DISCUSSION

SCC of the tongue is a rare disease in patients younger than 45 years, with an incidence <3%.[1,15] However, recent studies showed an increasing incidence among young people. Garavello et al[5] reported that 16 of 113 patients (14.2%) were under the age of 30 years, whereas 11 of 85 patients (13%) in the Soudry et al[6] report belonged to the same age group. Our present study showed a slightly lower, but close, rate of 8.0% (36 of 452) patients aged < 30 years.

Previous studies had inconsistent and controversial findings regarding the differences in clinicopathological features and prognosis of tongue SCC between young and old patients. It is noteworthy that there are no exact/specific cut-off points of different age groups. Owing to the variability in the definitions of "young" and "old" age and the associated grouping methods, it is entirely likely that this lack of standardization influences the results.

Hilly et al[4] addressed this problem by eliminating all patients aged between 31 and 60 years, to avoid such interference. Regrettably, however, the patient groups were

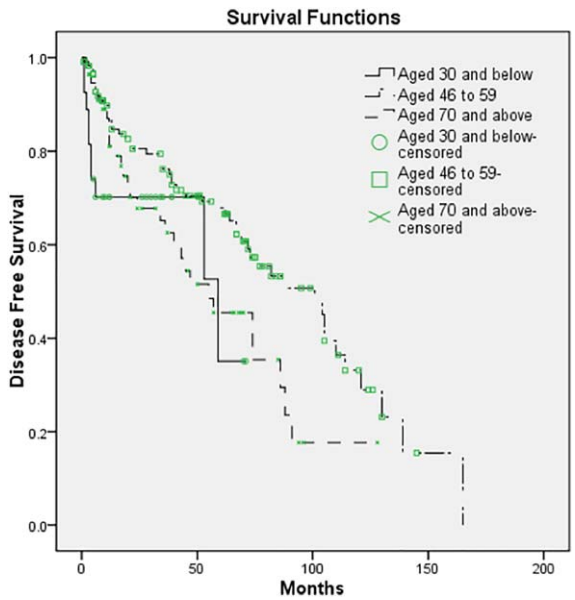

FIGURE 1 Kaplan-Meier disease-free survival curve of the youngest, middle-age, and oldest groups of patients. Log-rank test for patients ≤30 years old versus 46-59 years and ≥70 years old, $P = .052$ and $P = .605$, respectively [Color figure can be viewed at wileyonlinelibrary.com]

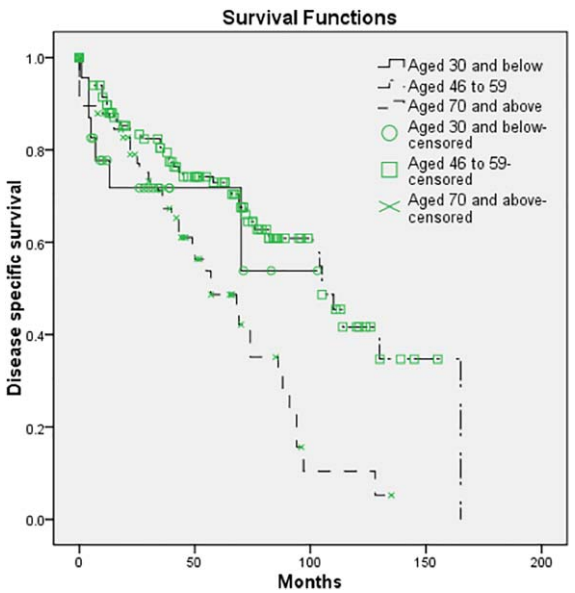

FIGURE 2 Kaplan-Meier disease-specific survival curve of the youngest, middle-age, and oldest groups of patients. Log-rank test for patients ≤30 years old versus 46-59 years and ≥70 years old, $P = .270$ and $P = .520$, respectively [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 5 Regions of recurrence or metastasis among the three age groups

	Patients aged ≤ 30 y (n = 36)	Patients aged 46-59 y (n = 159)	Patients aged ≥ 70 y (n = 68)	*P* value[a]
All	12 (33.3%)	57 (35.8%)	31 (45.6%)	.209
Local recurrence	7 (19.4%)	46 (28.9%)	24 (35.3%)	.238
Regional metastasis	4 (11.1%)	11 (6.9%)	6 (8.8%)	.675
Distant metastasis	1 (2.8%)	0	1 (1.5%)	.165
Recurrence death	11/12 (91.7%)	43/57 (75.4%)	24/31 (77.4%)	.469

[a]Compared among three groups.

incomplete and comparison of the middle-age subjects was not possible.

Our study showed clinicopathological characteristics and outcomes of tongue SCC among young, middle-age, and old patients and might have presented the largest series of patients with tongue SCC under the age of 30. To avoid age overlapping, we eliminated the patient groups aged 31-45 years and 60-69 years.

Consistent with previous reports, sex predisposition was not a significant factor among these 3 groups in our study.[5,6,13] Middle-age patients tended to form the majority of the patients with tongue SCC.

It is well known that tobacco and alcohol consumption are important causes of oral SCC.[16–20] Ma et al[21] reported that there was little difference in the rate of smoking among diverse age groups in China. Our study showed that the percentages of smokers and drinkers were highest in the middle-age group and very low in the youngest patient group, indicating that tongue SCC had a higher risk of nonsmoking and nondrinking people involvement in the young; these results are concordant with previous studies.[22,23] To explain the absence of tobacco risk in young patients, Llewellyn et al[10] suggested that only smoking history >21 years would increase the risk of prevalence largely, and this was more likely to occur in older patients.

Tobacco and alcohol abuse were also important influencing factors of disease prognosis. In our study, the DFS and DSS in the middle-age group were low, which was possibly related to higher percentages of smokers and drinkers.

There was no statistically significant difference of advanced T classification or positive N classification among the 3 groups in our study. There are contrary opinions on the difference of pTNM percentages in various age groups. Park et al[13] and Fang et al[24] found no significant differences between the young and old patient groups in terms of T or N classification, whereas Hilly et al[4] and Soudry et al[6] reported significantly higher percentages of advanced N or TNM classification among the younger patients. In our study, the youngest (50.0%) and middle-age groups (40.6%) had a significantly higher percentage of advanced pTNM classification than the oldest patients (19.4%). When we further analyzed the percentage of poor differentiation among the various age groups, the results showed that patients <30 years of age had a significantly higher percentage of poorly differentiated tumors (17.1%) than those in the middle-age group (4.9%).

Advanced TNM classification is usually considered an influencing factor of survival rate.[6,13,24,25] In the present study, by using the Cox proportional hazards regression model, we found that TNM classification was the only factor other than smoking and drinking that influenced DSS rate ($P = .045$). In addition, the influence was more obvious in the youngest group. The DFS and DSS rates showed no difference between patients aged ≤30 years and ≥70 years. Nevertheless, our results showed the recurrence death rate in the youngest group as higher than the other 2 groups (91.7% vs 75.4% and 77.4%) although no statistically significant difference was shown due to the relatively small sample of young patients. Hilly et al[4] reported that young patients had higher rates of regional metastases and distal failure, and recurrent disease was more aggressive with a fatality rate of 100%. These results indicate that more attention should be paid to SCCs of the tongue in young patients.

Veness et al[26] reported a higher incidence of poorly differentiated tumors in patients younger than 40 years, whereas Manuel et al[12] reported contradicting results of a greater

TABLE 6 Results from fitting the Cox models on all patients with complete data for disease-specific survival and disease-free survival: estimated hazard ratios with 95% confidence intervals associated with selected prognostic factors

	DFS		DSS	
	HR	95% CI	HR	95% CI
Age				
≤30	0.7393	0.559-0.9776	1.1064	0.9145-1.339
46-59	0.9641	0.8911-1.043	1.041	0.9803-1.106
≥70	1.017	0.8499-1.216	1.139	0.9347-1.388
TNM classification				
≤30	2.1086	1.153-3.8555	0.8706	0.5927-1.279
46-59	1.5925	1.2045-2.105	1.002	0.8126-1.237
≥70	1.55	0.8457-2.840	1.29	0.7283-2.284

Abbreviations: CI, confidence interval; DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio.

proportion of well-differentiated tumors in the same age group. However, further reports have confirmed our study results.[4,13,24] No relation between tumor differentiation and DSS rate was found in our study ($P = .326$), similar to the reports from Soudry et al[6] and Hilly et al.[4]

Treatment modalities were essentially surgery by glossectomy and neck dissection with or without defect reconstruction. The main differentiating factor is whether patients opted for postoperative radiation and chemotherapy. In clinical practice, adjuvant therapy is advised to patients with advanced TNM classification or positive N classification. However, the youngest group patients (38.9%) more often opted for such treatment than the other groups (13.9% and 7.2%, respectively). The application of postoperative adjuvant therapy was not a determining factor for either DFS or DSS. However, despite the vigorous postsurgical treatment, the youngest group was associated with an increased rate of recurrence, especially regional and distant metastasis. Although the difference was not statistically significant, it should be noted that distant failure among young patients could, to some extent, influence the DSS ($P < .001$). Increased incidence of distant failure in young patient groups has been reported in several other studies.[4,8,10,27,28] However, Almangush et al[29] reported no statistical difference of recurrence of early-stage tongue SCC in different age groups. In their study, only patients in T1 and T2 classifications were included. In addition, in our study, 2 of 4 patients who had regional metastasis and the 1 patient who had distant metastasis were at T4 classification. According to our study, 91.7% of the youngest group patients who experienced recurrence died because of the disease; this extremely high recurrence death rate has also been reported by previous researchers.[4,11] Younger patients usually already opt for a comparatively comprehensive therapy, but still tend to have higher recurrence rates and the highest recurrence death rate. Therefore, such results and trends are of clinical importance and, thus, both clinicians and patients themselves should exercise more caution.

The biological factors that determine or influence the various features of tongue SCC between young and old patients are still largely unknown. Several researchers had made efforts to study the underlying molecular and genomic causes. Although some believe that disease development and progression could be attributed to the role of a virus,[5,30–32] others suggest some specific gene overexpression in patients with tongue SCC; however, the difference among diverse age groups was not significant.[33–36] Although the exact biological cause and mechanism remain poorly understood, a remarkably high rate of tumor aneuploidy and tetraploidy in patients with tongue SCC aged <40 years has been observed, as compared to patients older than 50 years.[37] Therefore, it is within reason to infer that SCC of the tongue in young people might differ from that among the elderly at the genetic level.

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