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Survival of oral tongue squamous cell carcinoma in young adults

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Abstract

Background: Small cohort studies have suggested oral tongue squamous cell carcinoma (OTSCC) could be associated with worse prognosis in individuals younger than 40.

Methods: We compared the survival of all OTSCC cases in the National Cancer Database under 40 years old with those older than 40, excluding patients over 70. Cox regression and propensity score matched (PSM) survival analyses were performed.

Results: A total of 22 930 OTSCC patients were identified. The under 40 group consisted of 2566 (9.9%) cases; 20664 were 40 to 70 (90.1%). Most were male (13 713, 59.8%), stage I-II (12 754, 72.4%), and treated by surgery alone (13 973, 63.2%). Survival in patients under 40 was higher (79.6% vs 69.5%, $P < .001$). In PSM analysis (n = 2928) controlling for all 10 significant factors in multivariate regression, patients under 40 had a 9% higher 5-year survival (77.1% vs 68.2%, $P < .001$).

Conclusion: Contrary to the prior reports, younger patients with OTSCC did not have worse survival in the National Cancer Database.

KEYWORDS

age, oral cancer, squamous cell carcinoma, tongue, young

1 | INTRODUCTION

Squamous cell carcinoma of the tongue is the most common malignancy of the oral cavity, with approximately 16 000 cases projected to be diagnosed in the United States in 2018.[1,2] Oral tongue squamous cell carcinoma (OTSCC) is less common in young adults,[3] but has been reported to be increasing in incidence in younger populations both in the United States and other nations.[3-6] Previous studies have analyzed the clinicopathologic features and prognosis of OTSCC in young adults and drawn a range of conclusions. Some studies have found young adults present with more aggressive disease, have worse survival, and have recommended more aggressive treatment in young patients.[7-12] In contrast, other studies have observed better outcomes in young patients and argued "it is essential to avoid unjustified overtreatments on the basis of patient's age alone."[3,13-15]

Many of the studies that have reported OTSCC is more aggressive in young adults have analyzed small cohorts of patients whereas others have compared survival between populations that vary both by age and disease severity.[8-13] This limits their ability to attribute differences in outcomes to age itself, and may contribute to their conflicting conclusions.

We set out to examine the National Cancer Database (NCDB) and conduct an analysis of OTSCC in young adults. We analyzed trends in incidence, clinicopathologic features, practice patterns, and survival outcomes stratified by age. Our primary aim was to determine the influence of age on survival using propensity score matched analysis controlling for all available prognostic factors. Our secondary aim was to analyze patterns of care and determine if management strategies currently differ by patient age.

This manuscript was presented on 10/7/18 at the AAO-HNSF Annual Meeting in Atlanta, GA. (Abstract number 1119.)

2 | METHODS

The data of this study were obtained from the NCDB, a hospital-based database, jointly sponsored by the American College of Surgeons and American Cancer Society. Its data are gathered from more than 1500 Commission on Cancer-accredited facilities, which represent more than 70% of newly diagnosed cancer cases in the United States.[16] However, they have not verified and are not responsible for the statistical validity or conclusions derived by the authors of this study. As the NCDB is a de-identified database, the New York University School of Medicine Institutional Review Board determined this study was exempt from review.

We queried the NCDB from the years 2004 to 2015 for all patients diagnosed with squamous cell carcinoma of the oral tongue. Squamous cell malignancies were identified using 15 International Classification of Diseases for Oncology (ICD-O-3.1) histology codes: 8050/3, 8051/3, 8052/3, 8070/3, 8070/6, 8071/3, 8072/3, 8073/3, 8074/3, 8075/3, 8076/3, 8078/3, 8082/3, 8083/3, and 8084/3.[17] These codes refer to all the World Health Organization-recognized subtypes of squamous cell carcinoma. Tumors attributed to the oral tongue were identified using the six ICD-O-3.1 topography codes: C02.0, C02.1, C02.2, C02.3, C02.8, and C02.9.[18] Tumors attributed to the posterior third of tongue, base of tongue, and lingual tonsils were not included.

Patients were divided into two populations based on age. Patients 18 to 39 years of age were considered young adults, whereas those 40 to 70 years old were considered middle-aged adults. Forty years was used as a cutoff because it has been the age most frequently used to define young adulthood in previous studies of OTSCC.[9,18] Demographics, clinicopathologic factors, treatments, and survival were analyzed and compared between these two populations. Patients were excluded if they were over 70 years of age, had unknown outcomes, died or had last follow-up within 6 months of diagnosis, or did not receive surgery as part of their treatment. Since definitive surgical treatment is the preferred method of treatment for OTSCC, definitive radiotherapy is rarely employed. Only 0.4% (10) of young adults and 1.5% (349) of middle-aged adults in the NCDB were treated with definitive radiotherapy. Given the rarity of definitive radiotherapy and agreed upon guidelines in preferring primary surgical treatments, all patients treated with definitive radiotherapy alone were excluded.[19] Patients with last follow-up or death within 6 months of diagnosis were excluded to limit the influence of mortality related to treatments (ie, death within the early postoperative period) on overall survival. Only definitive surgical procedures were included—biopsy procedures were not counted as surgical treatment. Patients older than 70 were excluded to reduce the likelihood of bias against the older population, as death of unrelated causes is significantly more common in this patient population and most clinical trials exclude patients older than 70.

The primary objective of this study was to determine if young adults with OTSCC have worse survival than middle-aged adults. Secondarily, we aimed to assess if patterns of care varied significantly by age, as some previous studies have recommended escalation of treatment in young adults.[7,20] Subset cohorts of patients with negative extracapsular extension and negative surgical margins were additionally analyzed by age. The primary outcome endpoint was overall survival. Overall survival was estimated by method of Kaplan-Meyer. Univariate estimates of survival distributions were done by the log-rank test. Multivariate Cox regression adjusting for age, sex, race, comorbidities, stage, grade, lymphovascular invasion, extracapsular extension, treatment, surgical margins, and number of lymph nodes dissected was used to determine the impact of covariates on survival. All factors significantly associated with survival in multivariate analysis besides age were then used to create propensity score matched populations of young and middle-aged adults using the nearest neighbor algorithm.[21] Survival of this matched cohort was analyzed by log-rank test. An alpha of less than .05 was used as the threshold of statistical significance. Analyses were conducted using R version 3.5.1.[22]

3 | RESULTS

We identified 43 197 patients in the NCDB with OTSCC from the years 2004 to 2015. Patients were excluded if they were over age 70 (11 709, 27%), had unknown outcomes (3353, 8%), were not treated with surgery (4134, 9.5%), or died or had last follow-up within 6 months of diagnosis (1039, 2.4%). The remaining 22 930 (53%) patients comprised the study cohort. Two-thousand two-hundred and sixty-six (9.9%) of these patients were under 40 years of age (young adults). Clinicopathologic characteristics of the study population are described in Table 1. In the overall cohort, the median patient age was 56 (range: 18-70) and the majority of patients were male (13 713 59.8%). Most patients were white (19 600, 85.5%) and did not have comorbidities (18 685 81.5%, Charlson Comobidity Score of 0). The majority had stage I-II (12 754, 72.4%) and low-grade disease (17 384 84.0%). A minority of patients had nodal involvement (3895, 21.0%), distant metastases (65, 0.3%), or lymphovascular invasion (1566, 15.9%).

Some clinicopathologic factors varied by age (Table 1). A smaller percentage of young adults were male (1211, 53.4% vs 12 502, 60.5%, $P < .001$) and white (1875, 82.7% vs 17 725, 85.8%, $P < .001$) than the middle-aged group. Young adults had significantly fewer comorbidities (180, 7.9% vs 4065, 19.7%, $P < .001$), but had a 3.5% higher rate of nodal metastases (439, 24.3% vs 3456, 20.7%, $P < .001$) and lymphovascular invasion (174, 19.2% vs

TABLE 1 Clinicopathologic factors of 22 930 patients with oral tongue squamous cell carcinoma

	All patients		Young adults (<40)		Middle-aged adults (40-70)		
	Number	Percentage	Number	Percentage	Number	Percentage	*P* value[a]
Total	22 930	100	2266	100	20 664	100	
Age: median ± SD	56 ± 10.7		34 ± 5.3		58 ± 7.9		
Sex							**<.001**
Male	13 713	59.8	1211	53.4	12 502	60.5	
Female	9217	40.2	1055	46.6	8162	39.5	
Ethnicity							
White	19 600	85.5	1875	82.7	17 725	85.8	**<.001**
Black	1005	4.4	51	2.3	954	4.6	
Hispanic	971	4.2	162	7.1	809	3.9	
Asian	831	3.6	110	4.9	721	3.5	
Other	523	2.3	68	3.0	455	2.2	
Comorbidity							**<.001**
Comorbidity present	4245	18.5	180	7.9	4065	19.7	
No comorbidity	18 685	81.5	2086	92.1	16 599	80.3	
Tumor stage							.14
Stage I-II	12 754	55.6	1225	54.1	11 529	55.8	
Stage III-IVB	4811	21.0	510	22.5	4301	20.8	
Stage IVC	46	0.2	5	0.2	41	0.2	
Unknown	5319	23.2	526	23.2	4793	23.2	
Tumor grade							.09
Low grade	17 384	75.8	1725	76.1	15 659	75.8	
High grade	3318	14.5	362	16.0	2956	14.3	
Unknown	2228	9.7	179	7.9	2049	9.9	
Node status							**<.001**
No nodal metastases	14 621	63.8	1371	60.5	13 250	64.1	
Nodal metastases	3895	17.0	439	19.4	3456	16.7	
Unknown	4414	19.2	456	20.1	3958	19.2	
Distant metastases							.68
No distant metastases	21 812	95.1	2184	96.4	19 628	95.0	
Distant metastases	65	0.3	5	0.2	60	0.3	
Unknown	1053	4.6	77	3.4	976	4.7	
Lymphovascular invasion							**.005**
No invasion	8286	36.1	757	32.3	7910	36.6	
Invasion present	1566	6.8	179	7.6	1518	7.0	
Unknown	13 078	57.0	1406	60.0	12 199	56.4	
Extracapsular extension							.85
No extension	6450	28.1	651	28.7	5799	28.1	
Extension present	1236	5.4	122	5.4	1114	5.4	
Unknown	15 244	66.5	1493	65.9	13 751	66.5	

[a]Result of chi-squared comparisons between young adult and middle-aged cohorts. Bold text indicates a statistically significant difference.

TABLE 2 Treatment of 22 930 patients with oral tongue squamous cell carcinoma

	All patients		Young adults (<40)		Middle-aged adults (40-70)		
	Number	Percentage	Number	Percentage	Number	Percentage	*P* value[a]
Treatment							
Surgery only	13 974	60.9	1303	57.5	12 671	61.3	**<.001**
Surgery with adjuvant RT	4070	17.7	360	15.9	3710	18.0	**.016**
Surgery with RT and CT	3791	16.5	502	22.2	3289	15.9	**<.001**
Surgery with chemotherapy	267	1.2	30	1.3	237	1.1	.52
Surgery with unknown additional treatments	828	3.6	71	3.1	757	3.7	
Surgical margins							.46
Negative	20 241	88.3	1990	87.8	18 251	88.3	
Positive	1855	8.1	172	7.6	1683	8.1	
Unknown	834	3.6	104	4.6	730	3.5	
Number of lymph nodes dissected							**<.001**
Median ± SD	14 ± 22.7		20 ± 24.0		13 ± 22.5		

[a]Result of chi-squared comparisons between young adult and middle-aged cohorts. Bold text indicates a statistically significant difference.

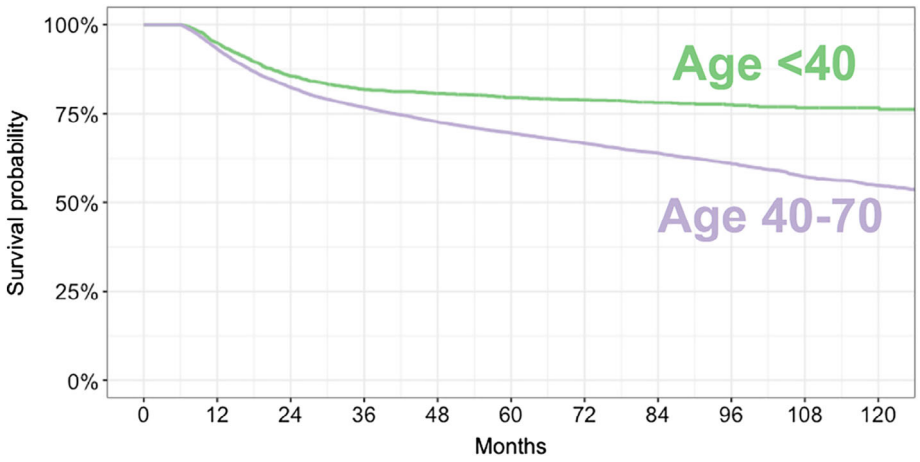

FIGURE 1 Overall survival of patients with oral tongue squamous cell carcinoma, young adults vs middle-aged adults [Color figure can be viewed at wileyonlinelibrary.com]

1392, 15.6%, $P = .005$) compared to middle-aged adults. Tumor stage, grade, extracapsular extension, and rates of distant metastases did not differ significantly between age groups.

The majority of patients were treated with surgery alone (13 973, 63.2%), followed by surgery with adjuvant radiation (4070, 18.4%), and surgery with adjuvant radiation and chemotherapy (3791, 17.2%, Table 2). Treatment regimens varied by age group (Table 2). Surgery alone was less common in young adults (1303, 59.4% vs 12 671, 63.7%, $P < .001$); and adjuvant chemoradiation was more common (502, 22.9% vs 3289, 16.5%, $P < .001$). In subanalysis of 5682 patients with negative margins and negative extracapsular extension and similar stage disease ($P = .14$), adjuvant chemoradiation was more common in young adults (92, 16.1% vs 657, 12.9%, $P = .038$). Rates of positive surgical margins were 8.1% and did not vary by patient age. The median number of lymph nodes dissected in young adults (20 ± 24.0) was significantly higher than that of the middle-aged adults (13 ± 22.5, $P < .001$).

Median length of follow-up was 45 months (interquartile range: 23-77). Among all patients, 3- and 5-year overall survival (OS) was 77.2% (95% confidence interval [CI] = 76.6%-77.7%) and 70.6% (95% CI = 69.9%-71.2%), respectively. Five-year OS was significantly higher for the young adults (79.6%, 95% CI = 77.9%-81.4%) compared to middle-aged adults (69.5%, 95% CI = 68.8%-70.2%, $P < .001$, Figure 1). In univariate Cox regression, older age, male sex, black race, comorbidities, advanced stage, high grade, lymphovascular invasion, extracapsular extension, all treatments other than surgery alone, and positive margins, were associated with worse outcomes (Table 3). All of these factors remained significant in multivariable regression, and additionally dissection of ≥18 lymph nodes became associated with improved survival (hazard ratio [HR] = 0.88, 95%

TABLE 3 Univariate and multivariate analysis of clinicopathologic and treatment factors and overall survival in oral tongue squamous cell carcinoma

	Univariate			Multivariate		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age under 40	**0.59**	0.54-0.65	**<.001**	**0.59**	0.54-0.65	**<.001**
Male sex	**1.38**	1.31-1.45	**<.001**	**1.26**	1.20-1.33	**<.001**
Ethnicity (reference: white)						
Black	**1.69**	1.54-1.86	**<.001**	**1.37**	1.24-1.51	**<.001**
Hispanic	1.06	0.94-1.19	.38	0.94	0.84-1.07	.40
Asian	**0.84**	0.73-0.97	**.01**	0.89	0.75-1.05	.10
Other	**0.84**	0.71-0.99	**.04**	0.89	0.75-1.05	.20
Comorbidity	**1.58**	1.49-1.67	**<.001**	**1.50**	1.41-1.58	**<.001**
Tumor stage (reference: stage I-II)						
Stage III-IVB	**2.66**	2.52-2.82	**<.001**	**1.60**	1.50-1.71	**<.001**
Stage IVC	**6.70**	4.80-9.35	**<.001**	**3.61**	2.57-5.06	**<.001**
Unknown	**1.32**	1.24-1.40	**<.001**	**1.17**	1.10-1.25	**<.001**
Tumor grade (reference: low grade)						
High grade	**1.73**	1.63-1.84	**<.001**	**1.33**	1.25-1.41	**<.001**
Unknown	**0.63**	0.57-0.70	**<.001**	**0.74**	0.67-0.82	**<.001**
Lymphovascular invasion (reference: no invasion)						
Invasion present	**2.48**	2.27-2.72	**<.001**	**1.46**	1.33-1.61	**<.001**
Unknown	**1.11**	1.05-1.18	**<.001**	1.05	0.97-1.13	.20
Extracapsular extension (reference: no extension)						
Extension present	**3.17**	2.89-3.48	**<.001**	**1.74**	1.57-1.93	**<.001**
Unknown	1.00	0.94-1.06	1.00	**1.22**	1.12-1.34	**<.001**
Treatment (reference: surgery only)						
Surgery with RT	**2.12**	2.00-2.25	**<.001**	**1.63**	1.53-1.74	**<.001**
Surgery, RT, and CT	**2.96**	2.80-3.14	**<.001**	**1.78**	1.66-1.91	**<.001**
Surgery with CT	**3.67**	3.11-4.32	**<.001**	**2.30**	1.94-2.73	**<.001**
Surgery, adjuvant therapy unknown	**1.21**	1.05-1.39	**<.001**	1.01	0.88-1.15	.90
Surgical margins (reference: negative margins)						
Positive margins	**2.20**	2.05-2.36	**<.001**	**1.59**	1.48-1.71	**<.001**
Unknown	**1.23**	1.09-1.39	**<.001**	1.06	0.93-1.20	.40
Lymph nodes examined (reference: 1-17 nodes)						
≥18 lymph nodes evaluated	1.04	0.98-1.11	.17	**0.88**	0.83-0.94	**<.001**
No nodes evaluated	**0.64**	0.60-0.69	**<.001**	**0.82**	0.76-0.88	**<.001**
Unknown	**1.22**	1.05-1.43	**.01**	1.12	0.95-1.31	.20

Abbreviations: CI, confidence interval; CT, chemotherapy; HR, hazard ratio; RT, radiotherapy.
Bold text indicates a statistically significant association.

CI = 0.83-0.94, $P < .001$, Table 3). After controlling for all covariates, age under 40 years was associated with a significant reduction in the risk of mortality (HR = 0.59, 95% CI = 0.55-0.65, $P < .001$).

We then performed a propensity score matched pair analysis, matching 1464 young adults with 1464 middle-aged patients. Apart from age, patients were matched by all factors that were significant in multivariate cox regression namely sex, race, comorbidities, stage, grade, lymphovascular invasion, extracapsular extension, treatment, margins, and dissection of ≥18 lymph nodes (Table 4). Following initial matching, chi-squared comparisons were utilized to assess the

TABLE 4 Characteristics of propensity score matched patients with oral tongue squamous cell carcinoma

	Young adults (n = 1464)	Middle-aged adults (n = 1464)	*P* value
Sex			.94
Male	794 (54.2%)	797 (54.4%)	
Female	670 (45.8%)	667 (45.6%)	
Ethnicity			.49
White	1218 (83.2%)	1241 (84.8%)	
Black	34 (2.3%)	23 (1.6%)	
Hispanic	100 (6.8%)	86 (5.9%)	
Asian	71 (4.9%)	73 (5.0%)	
Other	41 (2.8%)	41 (2.8%)	
Comorbidity			1.0
No comorbidity	1345 (91.9%)	1344 (91.8%)	
Comorbidity present	119 (8.1%)	120 (8.2%)	
Tumor stage			.97
Stage I	662 (45.2%)	656 (44.8%)	
Stage II	364 (24.9%)	364 (24.9%)	
Stage III	213 (14.5%)	222 (15.2%)	
Stage IV	225 (15.4%)	222 (15.2%)	
Tumor grade			.57
Well differentiated	384 (26.2%)	366 (25.0%)	
Moderately differentiated	823 (56.2%)	850 (58.1%)	
Poorly differentiated	256 (17.5%)	248 (16.9%)	
Undifferentiated	1 (0.1%)	0 (0.0%)	
Lymphovascular invasion			.84
No invasion	583 (39.8%)	599 (40.9%)	
Invasion present	139 (9.5%)	136 (9.3%)	
Unknown invasion	742 (50.7%)	729 (49.8%)	
Extracapsular extension			.94
No extension	522 (35.7%)	531 (36.3%)	
Extension present	98 (6.7%)	96 (6.6%)	
Unknown extension	844 (57.7%)	837 (57.2%)	
Treatments			.96
Surgery only	853 (58.3%)	861 (57.8%)	
Surgery with adjuvant RT	253 (17.3%)	245 (16.7%)	
Surgery with RT and CT	340 (23.2%)	342 (23.4%)	
Surgery with chemotherapy	18 (1.2%)	16 (1.1%)	
Margins			.40
No residual tumor	1366 (93.3%)	1378 (94.1%)	
Residual tumor	98 (6.7%)	86 (5.9%)	
Lymph nodes examined			.96
1-17 lymph nodes	261 (17.8%)	256 (17.5%)	
≥18 lymph nodes	854 (58.3%)	859 (58.7%)	
No dissection	349 (23.8%)	349 (23.8%)	

matched cohorts and confirmed there were no significant differences in terms of demographic, clinocopathologic, or treatment factors. In this matched population, 5-year OS for young adults remained greater compared to middle-aged adults (77.1%, 95% CI = 74.8%-79.5%, vs 68.2%, 95% CI = 65.6%-70.9%, $P < .001$, Figure 2).

4 | DISCUSSION

Previous studies have had inconsistent and conflicting findings regarding the differences in clinicopathologic features and prognosis of OTSCC in young and middle-aged adults. One limitation of the previous literature is that there is not a uniform definition of young age and previous studies have used cutoffs ranging from 30 to 45 years of age.[9,15,19] It is possible that this lack of standardization has contributed to the inconsistent findings in the literature. In this study, young adulthood was defined as age below 40 years, as this was the cutoff most frequently used in prior studies of OTSCC.[9,19]

The demographic characteristics of our study's population were similar to other large cohort studies of OTSCC with the majority of patients being in their fifth and sixth decade of life (69.3%), male (59.8%), and white (85.5%).[23,24] Some demographic factors varied by age, with young adults being significantly more likely to be female and Hispanic, and less likely to have comorbidities compared to middle-aged adults. Having less comorbidity is not a surprising finding in younger patients; however, the higher proportion of women in the young adult population is an interesting observation that might warrant further investigation.

Most patients had stage I-II (72.4%) and low-grade disease (84.0%). Nodal (21.0%) and distant metastases (0.3%) were uncommon. These tumor characteristics were generally consistent with the prior OTSCC literature.[8-11,21,22] In our cohort, there was no difference in stage of presentation between young and middle-aged adults ($P = .14$). This contrasts with some smaller OTSCC studies of 150 to 500 patients, which found that young adults were significantly more likely to present with high-stage disease.[9,11,25,26] However, other studies have reported young and older adults present with similar stage disease.[2,27,28] Given our much larger cohort of size 22 930 patients, it is likely our results better represent the true epidemiology of OTSCC than these previous small cohort studies.

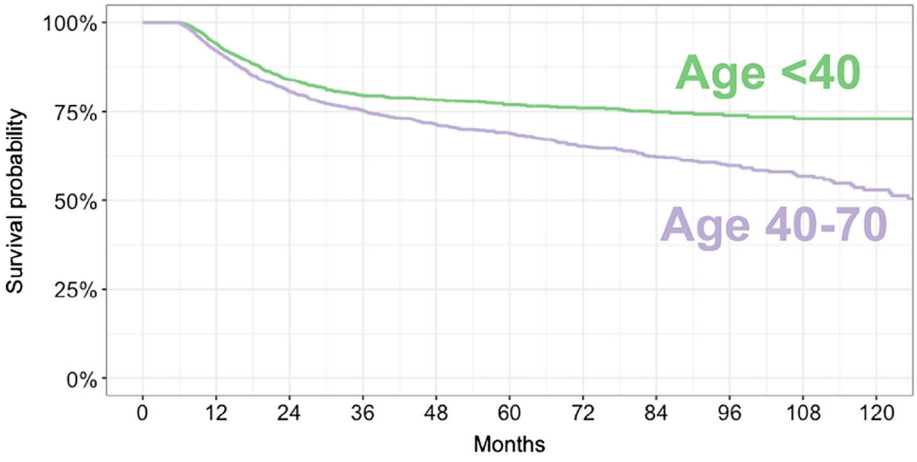

FIGURE 2 Overall survival of 3046 propensity score matched patients with oral tongue squamous cell carcinoma, young adults vs middle-aged adults [Color figure can be viewed at wileyonlinelibrary.com]

Clinicopathologic comparisons by age also revealed no differences in tumor grade, extracapsular extension, or rates of distant metastases. However, young adults had a significantly higher rate of nodal metastases (24.3% vs 20.7%, $P < .001$) and lymphovascular invasion (19.2% vs 15.6%, $P = .005$), than middle-aged adults. Higher rates of nodal metastases in young adults have been reported previously in the OTSCC literature.[2,29] Although significant, the rates of nodal involvement and lymphovascular invasion were only 3.5% higher in our cohort of young adults. Interestingly, treatment comparisons revealed the median number of lymph nodes dissected in young adults (20 ± 24.0) was significantly higher than that of middle-aged adults (13 ± 22.5, $P < .001$). Because of this, it is difficult to determine if these rates of nodal and lymphovascular involvement represent a true difference in the clinicopathologic nature of OTSCC in young adults, or are the result of more aggressive treatment (more neck dissections) or more vigorous investigation (closer scrutiny of the pathology specimens) that led to these findings.

The majority of patients in this study were treated with surgery alone (60.9%), which is consistent with the previous literature.[9,11,14,30] Comparisons of treatment regimens by age revealed that young adults in this study were significantly more likely to be treated with trimodal therapy (22.2%) compared to middle-aged adults (15.9%, $P < .001$) and significantly less likely to receive surgery alone (57.5% vs 61.3%, $P < .001$). Even among patients with similar stage disease without clear indications for adjuvant chemotherapy (negative extracapsular extension and negative surgical margins), young adults were still more likely to be treated with adjuvant chemoradiation (16.1% vs 12.9%, $P = .038$). Previous OTSCC studies have reported more adjuvant treatment utilization in young adults as well,[9,11,26] but these studies also compared young adults to middle-aged adults with less aggressive disease. Based on our data, young adults in the United States with OTSCC are more likely to be treated with trimodal therapy than middle-aged adults with similar stage disease, even in the absence of standard indications for adjuvant chemotherapy. It is unclear why these patients undergo intensification and further studies are needed to examine if practitioners are electing to recommend adjuvant chemoradiotherapy despite no clear indication for adding chemotherapy.

Three-year OS was 77.2% and 5-year OS was 70.6%. In univariate analysis, older age (40-70), male sex, black race, comorbidities, advanced stage, high grade, lymphovascular invasion, extracapsular extension, all treatments other than surgery alone, and positive margins, were associated with worse prognosis. All of these factors remained significant in multivariable regression, and additionally dissection of ≥18 lymph nodes became significantly associated with improved survival. Most of these results are consistent with the previous literature, which has similarly observed worse outcomes in patients of male sex, black race, advanced stage, high grade, and positive margins.[16,21,22,31,32] Several recent studies have similarly reported an association between dissection of ≥18 lymph nodes and improved survival for patients with head and neck SCC.[33-36]

Both univariate and multivariate analyses demonstrated higher survival in the young adult cohort. Propensity score matched analysis controlling for all influential prognostic factors in multivariate analysis (sex, race, comorbidities, tumor stage, tumor grade, lymphovascular invasion, extracapsular invasion, treatment regimen, surgical margins, and number of lymph nodes dissected) was used to create two matched cohorts of 1464 young and middle-aged adults. Survival analysis of these matched cohorts also demonstrated higher survival in young adults compared to middle-aged adults (HR = 0.66, $P < .001$).

The literature regarding the prognosis of oral tongue SCC in young adults is mixed, with some studies reporting worse outcomes,[8-13] and others reporting better outcomes in this population.[3,14-16] Some weaknesses of the previous literature include small cohort sizes of fewer than 200 patients,[8,10-13] as well as comparisons of young adults to middle-aged adults with significantly lower stage disease.[9,11] Conclusions from these studies may be influenced by selection biases and sampling error.

Interestingly, stratification of the previous literature by sample size revealed that studies analyzing populations of more than 500 patients all observed better outcomes in young adults.[3,14,16] In the present study, we conducted the largest age stratified propensity score matched survival analysis of OTSCC to date. Through all of our analyses, we found nothing to suggest that young age is associated with reduced survival.

Based on our findings, young adults in the United States present with similar stage OTSCC to middle-aged adults, but despite this similarity, have a 6% higher rate of undergoing treatment intensification with adjuvant chemotherapy. Even among patients with negative extracapsular extension and negative surgical margins, young adults have a 3% higher rate of treatment with adjuvant chemoradiation. Considering the prevalence of this disease, the intensification of treatment could be a source of significant increases in morbidity and cost of treatment, without any proven benefits at this time. This finding might require further investigation in a prospective controlled fashion.

There are limitations inherent to performing a study with the NCDB. ICD-O-3.1 codes were used to identify patients with OTSCC from the database, and this may have introduced the possibility of inaccuracy through miscoding of cases, however, that possibility for a common diagnosis such as SCC is low. The NCDB does not document substance use, and as a result, we could not analyze or control for history of alcohol or tobacco use. Given the recent changes in smoking habits of young adults, an analysis controlling for the evolving patterns of substance use is worthwhile. In addition, the NCDB does not document patterns of failure (local, regional, or distant) or disease-specific survival, and our analysis is limited to all-cause mortality. Although it is true that middle-aged adults are more likely to die from other causes compared to young adults, we limited our comparison group to 40 to 70 year olds, controlled for medical comorbidities as well as other prognostic variables available in the NCDB. Despite such limitations, our large sample size enabled us to control for multiple factors and reduce sources of error and bias as much as possible.

5 | CONCLUSION

Young and middle-aged adults in the United States present with similar stage OTSCC and have similar rates of extracapsular extension and positive surgical margins; but despite this, young adults (under 40) are more likely to be treated with adjuvant radiotherapy and chemotherapy. Age alone was not a negative factor in multivariable regression and in a propensity score matched population. These results suggest young age alone might not be a factor for consideration of intensification of treatment beyond the standard of care.

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