

## ORIGINAL ARTICLE

# Recategorization of tumor stage in patients with node-negative oral tongue cancer: Impact of the eighth edition American Joint Committee staging system

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## Abstract

**Background:** To evaluate recategorization of pT1-3N0 oral tongue cancer, from seventh to eighth editions of the American Joint Committee on Cancer (AJCC) staging classification, and impact on overall survival (OS).

**Methods:** Using the National Cancer Database, 1277 patients were categorized using tumor size and depth of invasion with seventh and eighth AJCC staging systems and evaluated for OS.

**Results:** Tumor-category was unchanged in 82.9% and upstaged in 17.1% patients with eighth AJCC. The 3-year OS was 85.3%, 76.6%, and 77.0% with seventh AJCC compared to 87.1%, 75.1%, and 81% with eighth AJCC, for patients with pT1N0, pT2N0, and pT3N0 disease, respectively. Improved discrimination of pT1N0 vs pT2N0 for OS on multivariate analysis was seen for eighth AJCC (hazard ratio [HR] = 1.43, 95% confidence interval [CI]: 1.03-1.98,  $P = .03$ ) but not for patients with pT3N0, with seventh AJCC (HR = 1.02, 95% CI: 0.53-1.98,  $P = .95$ ), and eighth AJCC (HR = 0.86, 95% CI: 0.52-1.42,  $P = .55$ ).

**Conclusion:** Eighth edition AJCC staging leads to improved discrimination of OS between pT1N0 and pT2N0 but not for patients with pT3N0.

## KEYWORDS

AJCC, depth of invasion, overall survival, tumor stage

## 1 | INTRODUCTION

The incorporation of depth of invasion (DOI) as a prognostic factor for oral cavity cancer in the new eighth edition American Joint Committee on Cancer (AJCC) classification has been a major change for primary tumor staging of oral cavity cancers, which has historically used single-dimension tumor size since 1977. The seventh edition AJCC classification was clinically valid, simple, and effective at estimating survival.<sup>1</sup> However, its prognostic value was limited by considering the primary tumor only in terms of its size/greatest surface

dimension while not incorporating in DOI.<sup>2</sup> DOI has important implications for management of the clinically node-negative neck, as a predictor of nodal involvement, and several authors have stressed the prognostic importance of DOI in staging oral cavity cancers. Hence, DOI has now been incorporated into the new eighth edition AJCC classification.<sup>2-6</sup> A DOI of 5 mm or greater predicts approximately a 15% to 20% risk of nodal involvement and studies have demonstrated that elective neck dissection to surgically stage the neck affects prognosis.<sup>7</sup> It is known that nodal disease drives survival,<sup>8</sup> however, the impact of tumor category (T) stage

incorporating tumor size and DOI and its impact on survival in the node-negative neck requires further study.

DOI is measured by noting the extent of tumor invasion in reference to the level of basement membrane of the closest adjacent normal mucosa<sup>6,9</sup>; it is distinct from tumor thickness. The AJCC seventh edition assigns tumor category according to the greatest dimension of tumor size in one dimension; T1:  $\leq 2$  cm in size, T2:  $>2$  and  $\leq 4$  cm; T3:  $>4$  cm; and T4 describing anatomic invasion into adjacent structures. According to the eighth edition AJCC, T1 category are tumors  $\leq 2$  cm in size with a DOI of  $\leq 5$  mm; T2 category are tumors  $\leq 2$  cm with a DOI between  $>5$  mm and  $\leq 10$  mm or tumors between  $>2$  and  $\leq 4$  cm and a DOI  $\leq 10$  mm; T3 category are tumors  $>4$  cm or any tumor with DOI  $>10$  mm; and T4 category unchanged.<sup>6</sup>

Recent study by Lydiatt et al has validated the tumor (T) classification changes using institutional dataset; however, they were unable to evaluate cancer registry data sets.<sup>9</sup> Similarly, several other authors have analyzed the eighth AJCC classification for prognosis and survival in patients with oral cancer; however, these studies included small institutional study populations and were likely underpowered.<sup>10-12</sup> When evaluating DOI, different anatomic oral cavity subsites may have different cut points for risk of occult nodal involvement, for example, floor of mouth compared to oral tongue cancer have smaller DOI cut points to predict nodal involvement.<sup>13</sup> Hence, for this study, we will evaluate the eighth edition AJCC staging classification for oral tongue cancer which comprises up to 40% to 50% of all oral cavity cancers<sup>14</sup> using the National Cancer Database (NCDB).

The aim of the present study was to evaluate the impact of the eighth edition of the AJCC classification, which incorporates tumor size and DOI, on stage recategorization and overall survival (OS) in patients with node-negative oral tongue squamous cell carcinoma (SCC).

## 2 | MATERIALS AND METHODS

### 2.1 | Data source

The NCDB is a clinical oncology database sourced from hospital registry data collected from more than 1500 commission on cancer-accredited facilities. These data represent more than 70% of newly diagnosed cancer cases nationwide and more than 34 million historical records.<sup>15</sup>

### 2.2 | Study design and population

We conducted a retrospective analysis of the NCDB, including patients diagnosed with oral tongue SCC between the years of 2010 and 2013, who underwent primary curative intent surgery with or without adjuvant treatment and who also had tumor size and DOI data. Primary site and histology were defined using the International Classification of Disease for Oncology third

edition, with the following primary sites included in the study population: C021 (Tongue: Border, Tip), C022 (Tongue: Ventral NOS), C023 (Tongue: Anterior NOS), and histology codes 8070-8078, which includes SCC.<sup>16</sup> Other oral cavity sites and oropharynx sites including base of tongue were not included in the study population. All patients with a pathological tumor category (pT) pT1-pT3, pathological or clinical N0, and a reported DOI were included in the study. Patients with pT4 disease were not included in the study, as incorporation of tumor spread into specific anatomic structures was not incorporated into the analysis. Exclusion criteria for the study are listed in Table 1.

### 2.3 | Study variables

Demographic variables included: age at the time of diagnosis (years), sex, race (white, black, or other), and insurance status (private insurance, Medicaid or other government insurance, Medicare, and uninsured). Patient comorbidities were recorded using the Charlson-Deyo comorbidity score (categorized as 0, 1, or  $\geq 2$ ). Cancer-related variables included: tumor grade (well differentiated, moderately differentiated, or poorly differentiated/undifferentiated) and pT classification based on seventh and eighth edition of AJCC. Treatment variables included: type of treatment received (surgery only or surgery with adjuvant treatment), need for neck dissection, and treatment at  $>1$  facility. In addition, tumor size (cm) and DOI (mm) was also collected.

### 2.4 | Statistical analysis

Frequencies were computed to describe demographic and clinicopathologic characteristics. The primary outcome of interest was OS from the time of diagnosis. One and 3 years OS rates were estimated using the Kaplan-Meier method, and log-rank tests were used to determine statistical significance in OS between groups. Cox proportional hazards regression modeling was used to compute crude and adjusted hazard ratios (HRs) for death with 95% confidence intervals (CIs). Following covariates were selected a priori for the multivariate analysis: age, sex, race, insurance status, tumor grade, Charlson-Deyo score, treatment at  $>1$  facility, neck dissection, and treatment received. Significance was determined at an alpha level of .05. The statistical software SAS version 9.4 or higher (SAS Institute Inc., Cary, North Carolina) was used to perform all data analysis.

## 3 | RESULTS

### 3.1 | Patient characteristics

A total of 1277 patients met the inclusion criteria. Within this population, patients were predominantly males (55.9%;  $n = 714$ ), white (91.2%;  $n = 1165$ ), privately insured (50.9%;  $n = 650$ ), and treated at a single facility (88.2%;  $n = 1126$ ). The

**TABLE 1** Exclusion criteria

	Exclusions	Patients remaining
<i>Total tongue cancer cases between 2010 and 2013</i>	—	37 807
Base of tongue (n = 20 189), dorsal surface of tongue (n = 1063), lingual tonsil (n = 348), overlapping lesion of tongue (n = 1035), or not otherwise specified (n = 6744)	29 379	8428
Histology codes except squamous cell carcinoma (8070-8078)	349	8079
Carcinoma in situ	449	7630
Metastatic disease	81	7549
History of cancer	1543	6006
Vital status/missing follow-up information	2	6004
Treatment other than surgery, radiation, or chemotherapy	139	5865
Chemoradiation only (n = 253), chemotherapy only (n = 35), or radiation only (n = 86)	374	5491
Missing treatment time information	113	5378
Radiation before surgery	20	5358
Chemotherapy before surgery	43	5315
Palliative intent	22	5293
Missing or unknown depth of invasion (n = 1874) or no mass found (n = 73)	1947	3346
Missing pN (n = 276), pNx (n = 664), pN1, (n = 341), pN2 (n = 537), or pN3 (n = 7)	1825	1521
pTx (n = 7), pT0 (n = 3), or pT4 (n = 42)	52	1469
Positive surgical margin	66	1403
Missing tumor size	10	1393
Misclassified AJCC seventh edition pT (based on tumor size)	41	1352
Missing insurance status (n = 19) and tumor grade (n = 56)	75	1277
<i>Final study population</i>	—	1277

Abbreviations: AJCC, American Joint Committee on Cancer; n = number of patients; pN = pathologic N classification; pT = pathologic T classification.

median age for the entire cohort was 59 years with an interquartile range of 50-69 years. Additionally, 83.6% (n = 1067) of patients received a neck dissection and 82.9% (n = 1058) of patients received surgical treatment only. The 16.4% (n = 210) patients who did not receive a neck dissection were all cN0; however, they were coded as pN0 in the database. Complete

demographic and clinicopathologic characteristics along with pathologic tumor classification based on both the seventh and eighth edition of AJCC is included in Table 2.

**TABLE 2** Demographic and clinicopathologic characteristics

(N = 1277)	
Age, y (median, IQR)	59 (50-69)
n (column percent)	
Sex	
Men	714 (55.9)
Women	563 (44.1)
Race	
White	1165 (91.2)
Black	31 (2.4)
Other	81 (6.3)
Insurance status	
Private	650 (50.9)
Medicaid/other govt.	91 (7.1)
Medicare	460 (36.0)
Uninsured	76 (6.0)
Tumor grade	
Well differentiated	404 (31.6)
Moderately differentiated	740 (58.0)
Poorly differentiated/undifferentiated	133 (10.4)
Charlson-Deyo score	
0	995 (77.9)
1	230 (18.0)
2 or more	52 (4.1)
Treatment at >1 facility	
No	1126 (88.2)
Yes	151 (11.8)
Neck dissection	
No	210 (16.4)
Yes	1067 (83.6)
Treatment received	
Surgery only	1058 (82.9)
Surgery with adjuvant treatment	219 (22.8)
T classification (AJCC seventh Edition)	
pT1	877 (68.7)
pT2	339 (26.6)
pT3	61 (4.8)
T classification (AJCC eighth Edition)	
pT1	719 (56.3)
pT2	412 (32.3)
pT3	146 (11.4)

Abbreviations: AJCC, American Joint Committee on Cancer; IQR, interquartile range; n, number of patients; N, total number of patients; pT, pathologic T classification.

**TABLE 3** AJCC eighth edition pT category based on tumor size and depth of invasion

Tumor size (cm)	Depth of invasion (mm)		
	≤5	>5 to ≤10	>10
≤2	719 (pT1)	133 (pT2)	25 (pT3)
>2 to ≤4	212 (pT2)	67 (pT2)	60 (pT3)
>4	41 (pT3)	4 (pT3)	16 (pT3)

Abbreviations: AJCC, American Joint Committee on Cancer; pT, pathologic T classification.

### 3.2 | Comparison of pT classification using the seventh vs eighth edition of AJCC

The AJCC eighth edition pT classification (based on tumor size and DOI) for the entire cohort is shown in Table 3. A comparison of pT classification between the two AJCC editions is shown in Table 4. Overall, tumor category was unchanged in 82.9% (n = 1059), upstaged in 17.1% (n = 218), and none were downstaged with eighth AJCC staging. Percentage of patients with pT1 disease based on the seventh and eighth edition was 68.7% (n = 877) and 56.3% (n = 719), respectively. According to the new distribution, 18.1% (n = 158) of the AJCC seventh edition patients with pT1 were upstaged in the AJCC eighth edition. Similarly, percentage of patients with pT2 disease was 26.6% (n = 339) in the seventh AJCC edition and 32.3% (n = 412) in the eighth AJCC edition. About 17.7% (n = 60) of those patients in the AJCC seventh edition pT2 subset were upstaged. Lastly, percentage of patients with pT3 disease was 4.8% (n = 61) in the seventh edition and 11.4% (n = 146) in the eighth edition.

### 3.3 | Overall survival

After a median follow-up of 29.4 and 31.4 months for all and surviving patients, respectively, 188 deaths were reported. For entire cohort, 1- and 3-year actuarial survival rates were 96.6% and 82.6%, respectively. The 3-year OS was 85.3%, 76.6%, and 77.0% with seventh AJCC staging system compared to 87.1%, 75.1%, and 81% with eighth AJCC staging system for patients with pT1N0, pT2N0, and pT3N0, respectively; Table 5 and Figure 1. Table 5 further describes the patients categorized based on tumor size (for seventh edition) and tumor size and DOI (for the eighth edition) and their corresponding survival.

### 3.4 | Univariate and multivariate analysis

Pathologic classification pT1 was used as reference category for the univariate and multivariate cox proportional hazards regression analyses. The multivariate analysis model was adjusted for age, sex, race, insurance status, tumor grade, CDS, treatment at >1 facility, neck dissection, and treatment received. In the

**TABLE 4** Comparison of pT category classification between seventh and eighth AJCC editions

Seventh edition	Eighth edition			Total
	pT1	pT2	pT3	
pT1	719 (82.0, 100)	133 (15.2, 32.3)	25 (2.9, 17.1)	877
pT2	—	279 (82.3, 67.7)	60 (17.7, 41.1)	339
pT3	—	—	61 (100, 41.8)	61
Total	719	412	146	1277

Note: Results are presented as number of patients (row, column percent).

Abbreviations: AJCC, American Joint Committee on Cancer; pT, pathologic T classification.

eighth edition of AJCC, patients with pT2 disease noted worsening OS (adjusted HR 1.43, 95% CI 1.03-1.98,  $P = .03$ ). In comparison, no such difference in noted when analysis was performed using seventh edition of AJCC (adjusted HR 1.19, 95% CI 0.85-1.65,  $P = .31$ ). Patients with pT3 disease had no survival difference compared to pT1 using both editions of AJCC. Complete results are presented in Table 6.

## 4 | DISCUSSION

In the present study, our group obtained data from the NCDB pertaining to node-negative SCC of the oral tongue and compared OS rates in patients as they relate to both the seventh and eighth editions of the AJCC classification. Our results provide evidence that the eighth edition of AJCC classification better predicts OS among patients with pT1 and pT2 node-negative oral tongue cancer. The prognosis for patients staged as pT1 using the new eighth edition of AJCC classification is improved (in comparison to the seventh edition) as lesions with a greater DOI have been removed from the pT1 category and upstaged to a pT2 classification. Regarding the pT2 subset, the addition of lesions with a greater DOI may also be responsible for the marginally worse HZ and 3-year survival using the new classification. Both the seventh and eighth edition AJCC are unable to discriminate between the T3 subset, which is problematic in both the systems. Based on the eighth edition, the pT is unchanged for 1059 patients (82.9%), upstaged in 218 patients (17.1%), and none were down staged in our sample. In a series by Tirelli et al, 174 patients were categorized using both seventh and eighth edition AJCC systems and found that pT category was upstaged in 31% of the patients.<sup>12</sup> They also demonstrated a statistically significant association between increasing pT category and disease specific survival ( $P = .01$ ) along with improved discrimination between pT categories based on the eighth edition of AJCC. Similar improved prognostication based on the impact of T-stage modifications in the new system has also been found by Lydiatt et al, using institutional data from Memorial Sloan Kettering Cancer Center

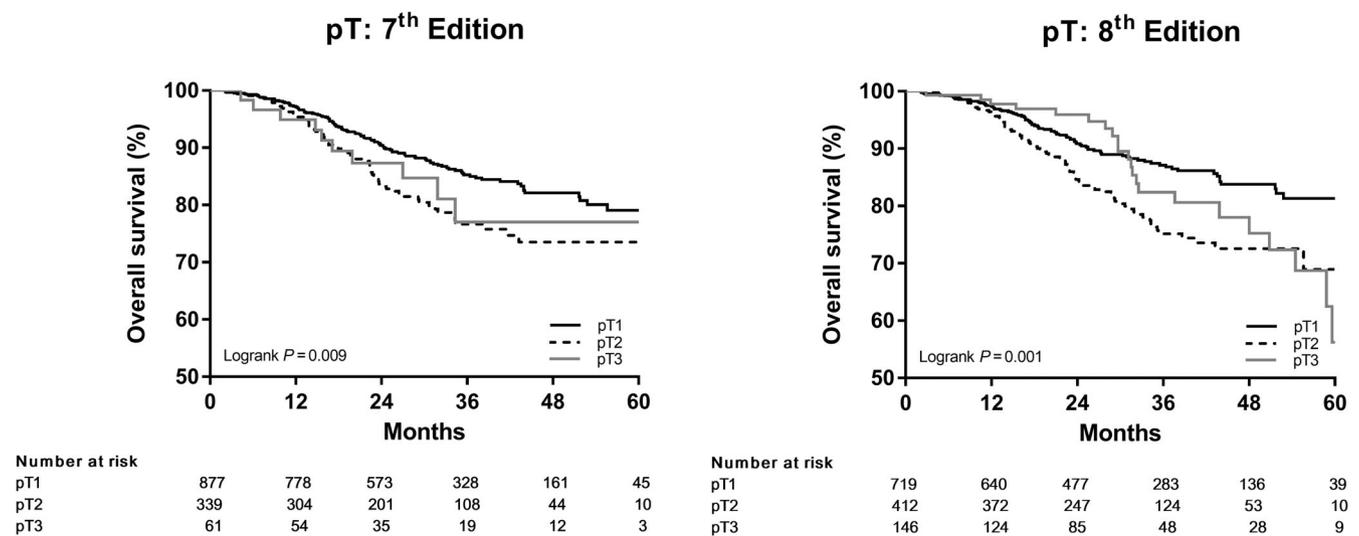
**TABLE 5** Survival analysis by pT category classification (seventh and eighth AJCC edition)

	N	Events	Actuarial survival rate		P value
			1 y	3 y	
Overall	1277	188	96.6%	82.6%	—
Seventh edition					.009
pT1	877	113	97.1%	85.3%	
pT2	339	64	95.7%	76.6%	
pT3	61	11	94.9%	77.0%	
Eighth edition					.001
pT1	719	85	97.4%	87.1%	
pT2	412	80	96.2%	75.1%	
pT3	146	23	94.2%	81.0%	
Seventh – eighth edition pT (size, depth of invasion) <sup>a</sup>					.009
pT1 – pT1 (≤2 cm, ≤5 mm)	719	85	97.4%	87.1%	
pT1 – pT2 (≤2 cm, >5-≤10 mm)	133	25	96.8%	74.6%	
pT1 – pT3 (≤2 cm, >10 mm)	25	3	91.3%	86.7%	
pT2 – pT2 (>2-≤4 cm, ≤10 mm)	279	85	95.9%	75.5%	
pT2 – pT3 (>2-≤4 cm, >10 mm)	60	9	94.5%	82.2%	
pT3 – pT3 (>4 cm, all depths)	61	11	94.9%	77.0%	

Note: Hundred eighty-eight deaths were reported during the follow-up period (median = 29.4 months) with an overall 3-y survival rate of 82.7%. Surviving patients had median follow-up of 31.4 months.

Abbreviations: AJCC, American Joint Committee on Cancer; pT, pathologic T classification.

<sup>a</sup>Describes patients who were categorized per the seventh and eighth edition AJCC staging, respectively, and corresponding survival.



**FIGURE 1** Kaplan-Meier OS estimates for pT stage based on AJCC seventh and eighth edition. Abbreviations: AJCC, American Joint Committee on Cancer; OS, overall survival; pT, pathological tumor category

(New York, New York) and Princess Margaret Hospital (Toronto, Ontario).<sup>9</sup> They interrogated the influence of DOI on OS on 1792 patients with the combined datasets from the above two mentioned centers and examined the interplay of the new N and T criteria by a stage group analysis which showed that the seventh edition AJCC did not discriminate well

between stages II and III. In a similar analysis of the NCDB by Cramer et al, compared the two AJCC staging systems using the NCDB in 39 361 patients with oral SCC, which showed that 10% of the patients were upstaged in the new classification with marginally improved prognostication value between the seventh and eighth edition (survival concordance index for

**TABLE 6** Univariate and multivariate analysis of overall survival by pT classification (seventh and eighth AJCC edition)

	N	Events	Univariate		Multivariate <sup>a</sup>	
			Hazard ratio (95% CI),	P	Hazard ratio (95% CI),	P
Seventh edition						
pT1	877	113	Ref		Ref	
pT2	339	64	1.59 (1.17-2.16)	.003	1.19 (0.85–1.65)	.31
pT3	61	11	1.50 (0.81-2.79)	.20	1.02 (0.53-1.98)	.95
Eighth edition						
pT1	719	85	Ref		Ref	
pT2	412	80	1.81 (1.33-2.46)	.0002	1.43 (1.03–1.98)	.03
pT3	146	23	1.47 (0.93-2.33)	.10	0.86 (0.52-1.42)	.55

Abbreviations: AJCC, American Joint Committee on Cancer; pT, pathologic T classification.

<sup>a</sup>Multivariate model includes following factors: age, sex, race, insurance status, tumor grade, Charlson-Deyo score, treatment at >1 facility, neck dissection, and treatment received.

pathological staging 0.699 and 0.704, respectively).<sup>17</sup> Their study looks at all stages I-IV of the disease when comparing stage migration including in the node positive neck. They also showed worsening HRs in the increasing pT categories based on the eighth edition AJCC. Similarly, Matos et al, in their validation of an independent cohort of 298 patients showed a worsening disease-free survival (51.1% vs 80.4%) and OS (31.5% vs 58.6%) in the upstaged pT subgroup with better stratification noted in the new system.<sup>11</sup> Amit et al in a study of 244 patients demonstrated that 25% of the patients with early oral tongue cancer were upstaged based on the eighth edition AJCC and that incorporation of DOI into the T-classification lead to better risk stratification for T1-T3 disease but these also included node positive patients.<sup>18</sup> Most of these studies involve patients with nodal involvement and its impact on OS and prognosis cannot be understated.

The authors believe that there are multiple possible reasons to explain why the eighth edition AJCC is unable to discriminate well the pT3 stage subset in the study. The integrity of the data from NCDB must be kept in mind as the DOI was not available for all oral tongue cases and was missing in 1874 cases, which may introduce bias into the sample. Patients with T3N0 category staging may represent a rarer cohort of patients, as DOI predicts nodal involvement, and patients with T3 disease are more likely to have nodal involvement, and these patients were not included in this study. The higher survival rates in the T3N0 cohort may be reflective of small sample size. The new classification may be underestimating the impact tumor geometry and volume. Gross tumor volume evaluated on diagnostic imaging such as positron emission tomography with computed tomography (PET/CT), and CT alone have been shown to be important prognostic indicators for local control and survival in patients with head and neck cancer.<sup>19-21</sup> Lastly other risk factors such a smoking, alcohol history, and other patient

factors not available in the NCDB, which may affect survival outcome, were not part of our multivariate analysis.

## 5 | CONCLUSION

The eighth edition of AJCC classification has incorporated significant new changes to its system. Our study evaluated the effect of T-stage modifications using a national cancer registry. Based on the eighth edition, the pT was unchanged for 82.9%, upstaged in 17.1%, and none were down staged. The new system leads to improved discrimination with respect to OS between the T1 and T2 subsets, but T3 remains problematic in both the staging systems.

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