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Impact of postoperative radiation therapy for deeply invasive oral cavity cancer upstaged to stage III

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Abstract

Background—This article is about the eighth edition staging guidelines for upstaged patients with oral cavity squamous cell carcinoma (OCSCC) with >10 mm depth to pT3. This upstages some patients from stage I-II to stage III, a point at which patients are traditionally considered for postoperative radiation therapy (PORT). The role of PORT in patients upstaged for >10 mm depth is unknown.

Methods—We identified patients with surgically resected stage I-II OCSCC with >10 mm depth who were upstaged to stage III. We used Cox proportional hazard modeling to compare patients who received PORT to those who did not (median follow-up 38.6 months).

Results—We observed that 3.6% of patients with OCSCC were upstaged to stage III for depth >10 mm including 823 eligible patients. On adjusted analyses, PORT was associated with improved overall survival in patients upstaged to stage III (adjusted hazard ratio [aHR] 0.47, 95% confidence interval [CI] 0.30–0.73).

Conclusion—PORT is associated with improved survival for patients with OCSCC upstaged to stage III for >10 mm depth.

Keywords

mouth neoplasms; oral cavity cancer; radiotherapy; squamous cell carcinoma; staging

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

1 | INTRODUCTION

Since its inception in 1959, the American Joint Committee on Cancer (AJCC) staging system has become the universal language to describe the extent of cancer and is essential for prognostication, research, and treatment planning.¹ AJCC staging guidelines for oral cavity squamous cell carcinoma (OCSCC) have remained fundamentally the same over nearly 30 years from the third through the seventh editions.² On January 1, 2018, the eighth edition staging guidelines for OCSCC went into effect, which instituted major changes by incorporating both depth of invasion (DOI) and extranodal extension (ENE).³ These changes in the staging system create new dilemmas related to long-standing treatment paradigms. While there is robust evidence to guide adjuvant treatment recommendations for patients who change stage groups due to ENE,⁴ the same cannot be said for patients who change stage groups due to DOI.

The eighth edition staging guidelines will upstage patients with pT1–2 disease with DOI >10 mm to pT3, upstaging some patients from stage I-II to stage III. Traditionally, treatment guidelines recommended that patients with stage III or stage I-II disease with adverse prognostic features be considered for postoperative radiation therapy (PORT).⁵ However, DOI >10 mm was not previously considered to be an adverse feature that warranted PORT by treatment guidelines.⁵ This calls into question if this new group of patients with stage III disease would benefit from PORT.

As clinicians and patients are left without evidence to guide management regarding this issue, we set out to investigate the role of PORT in patients with pT1–2 OCSCC with DOI >10 mm who will be upstaged from stage I-II to stage III. We used a large observational data set, as a randomized trial of this subpopulation of OCSCC is not practically feasible. Our primary objective was to determine if PORT is associated with an improvement in overall survival (OS) in this population after adjusting for differences in patient characteristics.

2 | PATIENTS AND METHODS

2.1 | Data source and variables

We identified adult patients with OCSCC diagnosed in the National Cancer Database (NCDB) from January 1, 2009, to December 31, 2015. Briefly, the NCDB is a cancer registry containing information on tumor characteristics, staging, treatment, and survival information from over 1500 Commission on Cancer Hospitals.⁶ This includes approximately 70% of all cancers diagnosed in the United States each year.⁶

We identified patients with OCSCC based on the International Classification of Diseases for Oncology, third edition (ICD-O-3). Supporting Information Supplemental Table 1 shows the ICD-O-3 codes that were used to select patients with oral cavity cancer and squamous cell carcinoma histology. We included patients with non-metastatic OCSCC that underwent surgical resection with information available on T, N, M classification and information on depth yielding 28 480 patients (Figure 1). We excluded pT3–4 patients based on the seventh edition staging guidelines (7183 excluded), N-positive disease (2239 excluded), or primary tumor depth <10 mm (16 046 excluded). This yielded 1012 patients out of whom we further

excluded those with other indications for PORT as per The National Comprehensive Cancer Network (NCCN) guidelines⁵ including lymphovascular invasion (100 excluded) or positive margins (87 excluded). We finally excluded 2 patients who received radiation prior to surgery for the index oral cavity cancer case, as they would not be candidates for conventional PORT. Primary tumor depth is recorded in the NCDB for OCSCC as the pathologically measured depth of invasive tumor. We considered postoperative radiation as adjuvant if started within 90 days of surgery.

2.2 | Outcomes

We divided our cohort into one group that received PORT and a second group that did not receive PORT. Our primary outcome was if there was a difference in adjusted hazard of death with or without PORT.

2.3 | Statistical analysis

Categorical variables were compared with a chi-square test, and continuous variables were compared with a two-sided *t* test. We calculated 1-year, 2-year, 3-year, 4-year, and 5-year OS rates based on the date of diagnosis to the date of death or last follow-up. Unadjusted OS was compared between groups using a log-rank test. We used Cox proportional hazard modeling to examine if PORT was associated with improved OS after adjusting for age, sex, race, comorbidities, T classification, oral cavity subsite, and depth (10–15, 15–20, or >20 mm). We used sensitivity analyses based on the dose of radiation delivered to test the rigor of the results. Statistical analyses were performed using SPSS, version 24 (IBM, Armonk, NY). The UPMC Institutional Review Board approved a waiver for this study.

3 | RESULTS

3.1 | Patient characteristics

We initially identified 28 480 patients with surgically resected, non-metastatic OCSCC. Of this population, we identified 1012 patients (3.6%) with pT1–2N0M0 OCSCC with depth >10 mm who were upstaged to pT3N0M0 using the eighth edition staging guidelines that fit the inclusion criteria for this study question. We excluded 187 patients with other indications for PORT yielding a final cohort of 823 patients. The final cohort included 612 patients (74.4%) who did not undergo PORT and 211 (25.6%) who underwent PORT.

Table 1 shows the patient characteristics of our study cohort. The PORT group was significantly younger than the no PORT group (mean 61.1 vs 65.1 years, respectively) and had greater proportion of tongue and floor of mouth disease. Importantly, the PORT group had less favorable tumor characteristics, including a higher proportion of pT2 primary disease (79.1% vs 54.2%, $P < .001$) and poorly differentiated histology (19.4% vs 10.0% $P < .001$). Rates of adjuvant chemotherapy were higher in the PORT group (8.9% vs 0.3%, $P < .001$). In the PORT group, the regional dosage of radiation was as follows: 127 patients (67.9%) received >60 Gy, 49 patients (26.2%) received 45–60 Gy, 11 patients (5.9%) received <45 Gy, and 24 patients had missing information on radiation dose.

3.2 | Unadjusted OS

Median follow-up was 38.6 months (range 0.1–82.3 months). Unadjusted OS is shown in Table 2. On unadjusted analysis, there was not a significant difference in OS between the PORT and the no PORT groups (81.1% vs 71.3%, 3 years, respectively; $P = .10$).

3.3 | Adjusted OS

Results of the full Cox proportional hazard model are shown in Table 3. After adjusting for differences in clinical, pathological, and treatment characteristics, PORT was associated with improved survival (adjusted hazard ratio [aHR] 0.47, 95% confidence interval [CI] 0.30–0.73). We additionally found that 75 years or older age, male sex, >1 comorbidity, and floor of mouth subsite were all associated with worse OS. Figure 2 demonstrates the adjusted OS probability curves stratified by the use of PORT.

3.4 | Subgroup analysis

Subgroup analyses were performed first based on the dose of PORT delivered to determine if there was a dose-response relationship and second stratified for tumor differentiation. In this subgroup analysis, we only included patients who underwent radiation therapy ($n = 187$). After adjusting for differences in clinical, pathological, and treatment characteristics, PORT between 1 and 45 Gy was associated with an increase hazard of mortality (aHR 4.22, 95% CI 1.42–12.55) compared with 45–60 Gy (aHR 0.85, 95% CI 0.32–2.28) or >60 Gy (aHR 1.00, Figure 3). We then performed a second subgroup analysis stratified by tumor differentiation as some literature suggests that patients with poorly differentiated tumors and high DOI should receive PORT. Cox proportional hazard models stratified by tumor differentiation revealed a decreased hazard of death in both the well-moderately differentiated group (aHR 0.45, 95% CI 0.27–0.75) and poorly differentiated group (aHR 0.19, 95% CI 0.06–0.61) for patients with PORT (Table 4).

4 | DISCUSSION

The addition of depth to the eighth edition staging guidelines will upstage some patients from stage I-II to stage III, creating new dilemmas about whether or not PORT is indicated. We studied this group upstaged to pT3 for DOI >10 mm to provide an evidence basis to guide practice. The results of this study show that PORT was associated with a significant improvement in OS suggesting that clinicians and patients should consider PORT in this setting.

In the 1970s, Breslow first identified a link between tumor thickness and survival in cutaneous melanoma.⁷ Breslow's hypothesis regarding the link between tumor thickness and survival was later validated in OCSCC in 1986 by Spiro et al.⁸ Over time, alternative terminology and methods of measuring the pattern of deeply invasive OCSCC have been used to describe the pattern of deeply invasive cancers.⁹ All terminologies have consistently identified deeply invasive behavior as a predictor of poor prognosis.⁹ The International Consortium for Outcome Research in Head and Neck Cancer investigated a potential modification to the T classification system for OCSCC by incorporating depth and selected DOI as the preferred measure.¹⁰ They examined 3149 patients with OCSCC from 11

different centers and identified optimal prognostic cutoffs of DOI of ≤ 5 , 5–10, and >10 mm for T1, T2, and T3 disease, respectively.¹⁰ This prompted the AJCC to adopt the above T classification system and cutoffs in the eighth edition guidelines. The cutoffs were designed to optimize prognostic prediction and were not designed to reflect ideal treatment. Hence, modifications to the staging system need to be investigated to determine if the treatment of patients who changed stage groups should also change.

Although there is robust evidence that deeply invasive cancers have a poor prognosis,^{10–15} there is little evidence to determine if treatment for deeply invasive cancers should be altered. The few studies that have evaluated the use of PORT in the adjuvant setting for deeply invasive cancers are predominantly retrospective, single-institution studies that did not include a comparison group.^{11,12,14} These studies have varying cutoffs to consider PORT including tumor thickness ≤ 4 mm,¹⁴ DOI >5 mm,^{11,12} and tumor depth ≤ 10 mm,¹³ and others have considered depth when associated with a variety of adverse features.^{12,13} One study concluded that tumor thickness ≤ 4 mm combined with poorly differentiated histology for pT1–2N0M0 OCSCC was associated with a significantly worse 5-year survival potentially warranting PORT.¹⁴ Another study advocated that patients with four or more adverse features, including DOI/tumor thickness ≤ 5 mm, should consider PORT.¹² These authors have concluded that PORT may be considered for these patients based on the poor prognosis associated with deeply invasive cancers; however, none of these studies provided a comparison group to establish the effectiveness of PORT. Chen et al. completed the only study to include both a group treated with PORT and a comparison group that did not receive PORT.¹³ They examined 567 patients and identified that patients with two or more minor adverse features, including tumor depth ≤ 10 mm and other traditional adverse features, experienced improved survival with PORT or postoperative chemoradiotherapy.¹³ The literature has not assessed if depth >10 mm alone should be an indication for PORT and NCCN guidelines also do not address if DOI >10 mm is an adverse feature enough to warrant PORT.⁵ We specifically examine this question that arises due to the inclusion of depth into the eighth edition staging guidelines. We found that PORT was associated with improved OS for patients upstaged to pT3 based on depth >10 mm without other adverse features after adjusting for clinical differences between the groups. The adjusted hazard ratio of 0.47 indicates a magnitude of effect that is also clinically important. In support of our conclusion, when we analyzed our cohort based on the dose of radiation delivered, we also identified a dose-response relationship. Patients who received 45–60 or >60 Gy of PORT had a significantly reduced adjusted hazard of death compared with those who received PORT with <45 Gy. On subset analysis, we found that when stratified by tumor differentiation, both patients with well-moderately and poorly differentiated tumors benefited from PORT, suggesting that this benefit is not limited to patients with multiple adverse features such as those with deeply invasive cancer and poorly differentiated histology, as some of the previously referenced studies suggested.^{11,13}

Although the subpopulation examined in this study is small, it is highly relevant to discussions at head and neck tumor boards as clinicians try to implement the new staging system. We identified that 3.5% of patients with non-metastatic surgically resected OCSCC were upstaged to pT3 based on tumor depth >10 mm. Among those who were upstaged to stage III, 81.3% did not have another indication for PORT and would be in a group without

clear evidence to guide adjuvant therapy. We estimate that of the 275 000 patients diagnosed with oral cavity cancer each year world-wide, around 9400 globally¹⁶ or around 600 in the United States¹⁷ would be upstaged to stage III for depth >10 mm. Based on our findings, we would suggest that patients and clinicians consider PORT for those upstaged to pT3 based on DOI >10 mm that do not have other indications for PORT. Our data are from a single study using a national tumor registry, and it will be helpful to replicate these findings in other data sets.

4.1 | Limitations

There are several limitations to consider when interpreting these results. First, like all large tumor registries, there is potential for errors in coding. Second, retrospective evaluation of treatment is prone to confounding, as patients are not randomly assigned to treatment. Although a randomized controlled trial would be ideal, one would be impractical in this small subpopulation of OCSCC. Therefore, to account for the observational nature of our study, we used adjusted analyses and further subgroup analyses to examine the treatment effect. Third, our analyses are limited by the data collected in the cancer registry. The NCDB does not have information on perineural invasion for OCSCC and some patients may have received PORT for this adverse feature. Fourth, the NCDB records information on the depth of the primary tumor; however, in such a large dataset, there is likely to be variability in this measurement with some institutions reporting tumor thickness. DOI has been shown to be a better predictor of survival, and once this is measured more precisely after final staging guideline implementation, we would expect the magnitude of the clinical effect to only increase. Finally, many patients were excluded from our study because of missing information on depth, and this may have biased our results. Despite these limitations, we feel that the NCDB offers a powerful tool to study the role of PORT in this subset of patients with OCSCC that would be difficult to study using other study designs.

In conclusion, the eighth edition AJCC staging guidelines upstage patients with DOI >10 mm to pT3, calling into question whether or not this population should receive PORT. We examined this group upstaged to pT3 based on DOI >10 mm without other indications for adjuvant radiation therapy. We found that PORT was associated with improved survival. We recommend considering PORT for patients upstaged to pT3 (stage III) based on DOI >10 mm without other indications for PORT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The data used in the study are derived from a de-identified National Cancer Data Base (NCDB) file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigators.

REFERENCES

1. Greene FL, Sobin LH. The TNM system: our language for cancer care. *J Surg Oncol.* 2002;80:119–120. [PubMed: 12115792]

2. Edge SB. American Joint Committee on Cancer. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.
3. Amin MB, Edge SB. American Joint Committee on Cancer AJCC Cancer Staging Manual. Eighth ed.
4. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent post-operative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck*. 2005;27:843–850. [PubMed: 16161069]
5. National Comprehensive Cancer Network. Head and Neck Cancer Clinical Practice Guidelines in Oncology 2017; 2017
6. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol*. 2008;15:683–690. [PubMed: 18183467]
7. Thickness Breslow A., cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg*. 1970;172:902–908. [PubMed: 5477666]
8. Spiro RH, Huvois AG, Wong GY, Spiro JD, Gnecco CA, Strong EW. Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. *Am J Surg*. 1986;152:345–350. [PubMed: 3766861]
9. Huang SH, Hwang D, Lockwood G, Goldstein DP, O’Sullivan B. Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity: a meta-analysis of reported studies. *Cancer*. 2009;115:1489–1497. [PubMed: 19197973]
10. International Consortium for Outcome Research in Head and Neck Cancer, Ebrahimi A, et al. Primary tumor staging for oral cancer and a proposed modification incorporating depth of invasion: an international multicenter retrospective study. *JAMA Otolaryngol Head Neck Surg*. 2014;140:1138–1148. [PubMed: 25075712]
11. Shim SJ, Cha J, Koom WS, et al. Clinical outcomes for T1–2N0–1 oral tongue cancer patients underwent surgery with and without postoperative radiotherapy. *Radiat Oncol*. 2010;5:43. [PubMed: 20504371]
12. Low TH, Gao K, Gupta R, et al. Factors predicting poor outcomes in T1N0 oral squamous cell carcinoma: indicators for treatment intensification. *ANZ J Surg*. 2016;86:366–371. [PubMed: 26991038]
13. Chen WC, Lai CH, Fang CC, et al. Identification of high-risk subgroups of patients with Oral cavity cancer in need of postoperative adjuvant radiotherapy or chemo-radiotherapy. *Medicine*. 2016;95:e3770. [PubMed: 27258508]
14. Liao CT, Lin CY, Fan KH, et al. Outcome analyses of unusual site neck recurrence in oral cavity cancer. *Ann Surg Oncol*. 2013;20:257–266. [PubMed: 22872292]
15. Fan KH, Wang HM, Kang CJ, et al. Treatment results of postoperative radiotherapy on squamous cell carcinoma of the oral cavity: coexistence of multiple minor risk factors results in higher recurrence rates. *Int J Radiat Oncol Biol Phys*. 2010;77:1024–1029.
16. Warnakulasuriya S Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol*. 2009;45:309–316. [PubMed: 18804401]
17. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin*. 2013;63:11–30. [PubMed: 23335087]

FIGURE 1.
Flow diagram of cohort selection

FIGURE 2.

Adjusted overall survival probability stratified by postoperative radiation therapy (PORT). Curves adjusted for age, sex, race, comorbidities, subsite, T classification, differentiation, tumor depth, and hospital type. aHR, adjusted hazard ratio; CI, confidence interval [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 3.

Adjusted overall survival probability stratified by dose of postoperative radiation. Curves adjusted for age, sex, race, comorbidities, subsite, T classification, differentiation, tumor depth, and hospital type [Color figure can be viewed at wileyonlinelibrary.com]

Table 1

Patient characteristics in study cohort

Variable	No postoperative radiation (n = 612) N (%)	Postoperative radiation (n = 211) N (%)	P-value
Age, mean (SD)	65.1 (14)	61.1 (14)	.01
Sex			.08
Male	353 (57.7)	136 (64.5)	
Female	259 (42.3)	75 (35.5)	
Race			.82
White	525 (85.8)	179 (84.8)	
African American	28 (4.6)	12 (5.7)	
Hispanic	26 (4.2)	7 (3.3)	
Other	33 (5.4)	13 (6.2)	
Charlson/Deyo comorbidity index			.18
0	453 (74.0)	147 (69.7)	
1	123 (20.1)	44 (20.9)	
>1	36 (5.9)	20 (9.5)	
Pathological T classification (7th edition)			<.001
T1	280 (45.8)	44 (20.9)	
T2	332 (54.2)	167 (79.1)	
Depth, mean (SD), mm			.12
10–15	360 (58.8)	132 (62.6)	
15–20	113 (18.5)	45 (21.3)	
>20	139 (22.7)	34 (16.1)	
Subsite			.001
Lip	77 (12.6)	8 (3.8)	
Tongue	322 (52.6)	129 (61.1)	
Upper or lower gum	42 (6.9)	9 (4.3)	
FOM	69 (11.3)	36 (17.2)	
Hard palate	21 (3.4)	8 (3.8)	
Buccal	44 (7.2)	11 (5.2)	
RMT or other mouth	37 (6.0)	10 (4.7)	
Grade			<.001
Well/intermediate differentiation	551 (90.0)	170 (80.6)	
Poorly differentiated	61 (10.0)	41 (19.4)	
Chemotherapy			<.001
No	610 (99.7)	193 (91.5)	
Yes	2 (0.3)	18 (8.5)	

Abbreviations: FOM, floor of mouth; RMT, retromolar trigone.

Table 2

Overall survival with or without PORT

	1-y	2-y	3-y	4-y	5-y	Log rank
No PORT	89.1%	78.5%	71.3%	67.1%	65.2%	0.10
PORT	95.7%	86.9%	81.1%	72.5%	72.5%	

Abbreviations: PORT, postoperative radiation therapy.

Table 3

Cox proportional hazard regression analysis of survival of adjuvant radiation vs no radiation

Variable	aHR	95% CI
Radiation		
No adjuvant radiation	1.00	
Adjuvant radiation	0.47	0.30–0.73
Age, y		
<55	1.00	
55–64	1.68	0.94–3.01
65–74	1.64	0.91–2.95
75	3.93	2.25–6.89
Sex		
Male	1.00	
Female	0.55	0.37–0.81
Race		
White	1.00	
African American	0.94	0.40–2.20
Hispanic	0.81	0.38–1.71
Other	0.64	0.27–1.51
Comorbidity		
0	1.00	
1	1.41	0.93–2.16
>1	2.13	1.23–3.69
Pathological T classification (7th edition)		
T1	1.00	
T2	1.91	1.29–2.85
Subsite		
Tongue	1.00	
Lip	0.74	0.39–1.41
Upper or lower gum	1.34	0.65–2.78
FOM	1.66	1.04–2.63
Hard palate	1.66	0.58–4.74
Buccal	0.81	0.38–1.71
RMT or other mouth	0.78	0.31–1.95
DOI, mm		
10–15	1.00	
15–20	1.29	0.82–2.03
>20	1.00	0.63–1.60
Differentiation		
Well to moderate	1.00	
Poor	1.74	1.09–2.78
Hospital type		

Variable	aHR	95% CI
Nonacademic		
Academic	0.67	0.47–0.95

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; DOI, depth of invasion; FOM, floor of mouth; RMT, retromolar trigone.

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Table 4

Cox models stratified by tumor differentiation and predicting hazard of mortality by postoperative radiation

Tumor differentiation	aHR	95% CI
Well-differentiated or moderately differentiated		
No postoperative RT	1.00	Reference
Postoperative RT	0.45	0.27–0.75
Poorly differentiated		
No postoperative RT	1.00	Reference
Postoperative RT	0.19	0.06–0.61

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; RT, radiation therapy.

Adjusted for age, sex, race, comorbidities, T classification, oral cavity subsite, tumor depth, and hospital type.