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Postoperative Radiotherapy and Survival in Oral Cavity Squamous Cell Carcinoma With Mandibulectomy

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IMPORTANCE Oral cavity squamous cell carcinoma (SCC) tumors with mandibular invasion are upstaged to pT4a regardless of their size. Even small tumors with boney invasion, which would otherwise be classified as pT1-2, are recommended for the locally advanced treatment pathway to receive administration of postoperative radiotherapy (PORT).

OBJECTIVE To evaluate the association of PORT with overall survival according to tumor size among patients who received mandibulectomy for pT4aN0 oral cavity SCC.

DESIGN, SETTING, AND PARTICIPANTS This was a retrospective analysis using data from the US National Cancer Database from January 1, 2004, through December 31, 2019. All patients who received mandibulectomy for treatment-naive pT4aN0 oral cavity SCC with negative surgical margins were included. Data analyses were performed in January 2023 and finalized in July 2023.

EXPOSURE PORT vs no PORT.

MAIN OUTCOMES AND MEASURES Entropy balancing was used to balance covariate moments between treatment groups. Weighted multivariable Cox proportional hazards regression was used to measure the association of PORT with overall survival associated with tumor size.

RESULTS Among 3268 patients with pT4aN0 oral cavity SCC (mean [SD] age, 65.9 [12.1] years; 2024 [61.9%] male and 1244 [38.1%] female), 1851 (56.6%) received PORT and 1417 (43.4%) did not receive PORT. On multivariable analysis was adjusted for age, insurance status, Charlson Comorbidity Index score, tumor site, tumor grade, tumor size, and PORT. Findings indicated that PORT was associated with improved overall survival and that this relative survival advantage trended upwards with increasing tumor size. That is, the larger the tumor, the greater the survival advantage associated with the use of PORT. For the 1068 patients with tumors greater than 4 cm, the adjusted hazard ratio (aHR) in favor of PORT was 0.63 (95% CI, 0.48-0.82); for the 1774 patients with tumors greater than 2 cm but less than or equal to 4 cm, the aHR was 0.76 (95% CI, 0.62-0.93); and for 426 patients with tumors less than 2 cm, the aHR was 0.81 (95% CI, 0.57-1.15).

CONCLUSIONS AND RELEVANCE In this retrospective analysis of patients who received mandibulectomy for pT4aN0 oral cavity SCC, PORT was associated with improved overall survival, the benefit of which improved relatively with increasing tumor size. These findings suggest that tumor size should be considered in guidelines for PORT administration in this patient population.

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Supplemental content

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Postoperative radiotherapy (PORT) plays an important role in the treatment of locally advanced oral cavity squamous cell carcinoma (SCC). The US National Comprehensive Cancer Network (NCCN) guidelines, version 1.2023, advise using radiation therapy for oral cavity malignant tumors resected with adverse pathologic features. These features include extranodal extension, positive or close margins, pN2a-N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular invasion, lymphatic invasion, or pT3-4 primary.[1] While the value of radiotherapy in disease with node positivity, positive margins, and extracapsular spread has been supported by level 1 data[2-4] as well as in general with risk-adapted approaches,[5,6] currently there are no prospective or randomized studies evaluating surgery with and without PORT among patients with locally advanced node negative oral cavity SCC who received mandibulectomy.

In oral cavity cancer, T stage is dictated by tumor size, depth of invasion, and invasion of adjacent structures (mandible, maxilla, or skin). Tumors staged as T4aN0 that invade the mandible can capture a heterogeneous patient group depending on the characteristics of the primary tumor. In this study, we sought to delineate the benefit of PORT and its association with increasing tumor size among a subgroup of patients with pT4a oral cavity SCC.

Key Points

Question In patients with pT4aN0 oral cavity squamous cell carcinoma (SCC) requiring mandibulectomy, does the therapeutic benefit of postoperative radiotherapy (PORT) change with respect to tumor size?

Findings This retrospective analysis including 3268 patients with pT4aN0 oral cavity SCC found that PORT was associated with improved overall survival and that its relative survival benefit tended to improve with increasing tumor size.

Meaning These findings suggest that tumor size should be considered in guidelines for PORT administration in the setting of pN0 oral cavity SCC requiring mandibulectomy.

Methods

This study was deemed exempt from review by the University of Pittsburgh Institution Review Board. Informed consent was waived because the data were derived from a deidentified dataset, and the study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data Source

Data for this study were extracted from the US National Cancer Database (NCDB). The NCDB is a nationwide cancer registry jointly sponsored by the American College of Surgeons and the American Cancer Society. NCDB is a clinical oncology database sourced from more than 1500 Commission on Cancer-accredited facilities and includes approximately 70% of the newly diagnosed malignant neoplasms in the US annually.[7,8]

Study Cohort

This retrospective cohort analysis included all adult patients who received margin-negative mandibulectomy (marginal or segmental) for treatment-naive pT4aN0 oral cavity SCC from January 1, 2004, through December 31, 2019. Appropriate patients were identified using the World Health Organization *International Classification of Diseases for Oncology*, third edition (*ICD-O-3*) codes. Eligible topographic codes for the oral cavity were lip (C00.0-6 and C00.8-9), tongue (C02.0-3 and C02.8-9), gingiva (C03.0-1 and C03.9), floor of mouth (C04.0-1 and C04.8-9), palate (C05.0-1 and C05.9), buccal (C06.0-1), retromolar trigone (C06.2), and unspecified mouth (C06.8-9). **Figure 1** details the inclusion and exclusion criteria.

Restaging Criteria

In 2017, the American Joint Committee on Cancer (AJCC) released the eighth edition of its cancer staging guidelines,[9] with major changes to the T classification in oral cavity tumors. The new system primarily relies on depth of invasion and tumor size. Extrinsic muscle invasion was removed as a criterion for pT4a disease. NCDB does not reclassify tumors based on AJCC updates, and therefore, this must be done manually. The largest dimension of the diameter of the primary tumor is measured in millimeters. Site-specific factor 11 provides information regarding depth of tumor invasion. The variable CS_EXTENSION provides information regarding direct extension of the primary tumor into nearby structures. These 3 variables were used to manually reclassify all tumors according to the AJCC newest guidelines.[9]

Variables and Outcome Measures

The primary outcome measure was overall survival (OS). Follow-up intervals were reported as number of months between date of diagnosis and date of patient last contact or death. The primary predictor variables were PORT and tumor size (≤2 cm, >2-4 cm, and >4 cm). Other independent variables analyzed were sociodemographic characteristics (age, sex, race and ethnicity, insurance status, urban or rural residence, education level, and income level) and clinicopathologic features (Charlson Comorbidity Index [CCI] score, facility type, facility location, site of primary tumor, tumor grade, tumor extension, and chemotherapy status) per NCDB data.

Entropy Balancing

Entropy balancing is a data preprocessing method that achieves covariate balance in observational studies with binary treatments.[10] This method reweights observations by directly balancing the moments of covariates between the treatment and control conditions. Seminal work by Rosenbaum and Rubin[11] identifies how within observational cohorts, propensity score methods are essential to estimate the mean causal effect. Robins et al[12] first demonstrated that outcome regression models can be augmented by propensity score weighting methods to provide a robust estimation of treatment effect. Zhao and Percival[13] further demonstrated that incorporation of entropy balancing weights into a regression model is doubly robust if either the propensity score model or

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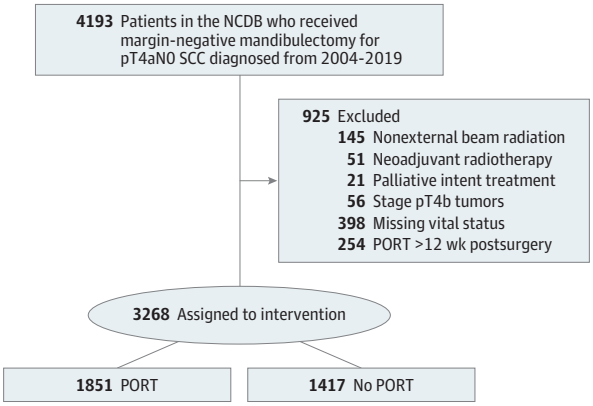
Figure 1. CONSORT Diagram With Inclusion and Exclusion Criteria



NCDB indicates the US National Cancer Database; PORT, postoperative radiotherapy; and SCC, squamous cell carcinoma.

the outcome regression model is correctly specified, the mean causal effect estimator is statistically consistent.

In this analysis, we elected to use entropy balancing to improve the comparability between treatment groups. This doubly robust method, incorporating entropy balancing weights into a multivariable Cox proportional hazards model, provides 2 opportunities to close noncausal backdoor paths between treatment and outcome created by confounding variables. We used an Average Treatment Effect on the Treated model that reweights the control group (no PORT) to match the treatment group (PORT). This allowed us to achieve near perfect balance of covariate moments between treatment groups (SD $<1.0 \times 10^{-15}$) with respect to age, sex, race and ethnicity, health insurance status, urban or rural residence, education level, income level, CCI status, facility type, facility location, site of primary tumor, tumor grade, tumor extension, and chemotherapy status. Tumor size was not included in the entropy balancing given our aim to stratify outcomes across this variable.

Statistical Analysis

Descriptive statistics, including proportions and means (SDs), were used to report the sociodemographic and clinicopathologic features of the population. The Average Treatment Effect on the Treated entropy balancing weights were incorporated into Cox proportional hazards regressions. All independent variables were considered to be significant at $\alpha < .05$ on weighted univariate Cox proportional hazards regression included in the final multivariable model. Doubly robust estimation was achieved by incorporating weights within multivariable Cox proportional hazards model. A priori post hoc subgroup analysis was performed to evaluate the association of treatment with tumor size. A power analysis was conducted using the power Cox method of Hsieh and Lavori[14] to determine the minimum detectable effect size given the current sample size in each subgroup. The squared multiple-correlation coefficient (R^2) was used to account for multiple covariates (eTable in Supplement 1).

Statistical tests were 2-tailed and P values < .05 were considered statistically significant. Data analyses were performed using Stata, version 17.0 (StataCorp LLC), in January 2023 and finalized in July 2023.

Results

Patient Characteristics

The study included a total of 3268 patients (mean [SD] age, 65.9 [12.1] years; 1244 [38.1%] female and 2024 [61.9%] male; 103 [3.2%] Asian, 218 [6.7%] Black, 111 [3.4%] Hispanic, and 2771 [84.8%] White individuals). **Table 1** summarizes the sociodemographic and clinicopathologic features of the study population according to NCDB data. Overall, PORT was administered to 1851 patients (56.6% of the cohort).

Factors Associated With Overall Survival

In our weighted univariate model, we found that age, insurance status, CCI, site of primary tumor, tumor grade, tumor size, and PORT were significantly associated with OS. In our doubly robust multivariable model, we found that age, insurance status, CCI, site of primary tumor, tumor grade, tumor size, and PORT were independently associated with OS. Patients who received PORT (adjusted hazard ratio [aHR], 0.72; 95% CI, 0.62-0.84) demonstrated improved OS compared with patients who did not receive PORT. Tumor size greater than 2 cm to 4 cm (aHR, 1.26; 95% CI, 1.01-1.57) and tumor size greater than 4 cm (aHR, 1.52; 95% CI 1.19-1.94) were associated with worse OS compared with tumors 2 cm or less. Primary tumors occurring within the floor of mouth (aHR, 1.37; 95% CI 1.12-1.66) and retromolar trigone (aHR, 1.27; 95% CI, 1.04-1.56) demonstrated worse OS compared to gingival tumors (**Table 2**).

PORT and OS by Tumor Size

We found that PORT was associated with a 24% reduction in risk of death for patients with tumors greater than 2 to 4 cm (aHR, 0.76; 95% CI, 0.62-0.93) and a 37% reduction in risk of death for patients with tumors greater than 4 cm (aHR, 0.63; 95% CI, 0.48-0.82). PORT was not independently associated with survival in patients with tumors that were 2 cm or less (aHR, 0.81; 95% CI, 0.57-1.15; **Figure 2**).

Discussion

This study used a doubly robust estimation, combining entropy balancing and multivariable Cox proportional hazards regression to better estimate the association of PORT with OS among patients who received margin-negative mandibulectomy for pT4aN0 oral cavity SCC.

Within this population, we found that PORT was associated with improved survival, and that the relative benefit of PORT tended to rise with increasing tumor size. These findings indicate that decisions regarding postoperative management of pT4aN0 oral cavity SCC tumors with PORT should include consideration of tumor size.

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Table 1. Demographic and Clinical Characteristics of Participants With pT4aN0 Oral Cavity Squamous Cell Carcinoma

Variable	No. (%)		
	Total (N = 3268)	No PORT (n = 1417)	PORT (n = 1851)
Age, mean (SD), y	65.9 (12.1)	68.8 (12.4)	63.6 (11.3)
Sex			
Female	1244 (38.1)	599 (42.3)	645 (34.8)
Male	2024 (61.9)	818 (57.7)	1206 (65.2)
Race and ethnicity			
Asian	103 (3.2)	42 (3.0)	61 (3.3)
Black	218 (6.7)	86 (6.1)	132 (7.1)
Hispanic	111 (3.4)	41 (2.9)	70 (3.8)
White	2771 (84.8)	1222 (86.2)	1549 (83.7)
Missing data	65 (2.0)	26 (1.8)	39 (2.1)
Health insurance status			
Private insurance	1030 (31.5)	367 (25.9)	663 (35.8)
Medicare/Medicaid	2084 (63.8)	983 (69.4)	1101 (59.5)
No insurance	97 (3.0)	34 (2.4)	63 (3.4)
Missing data	57 (1.7)	33 (2.3)	24 (1.3)
Charlson Comorbidity Index score			
0	2336 (71.5)	959 (67.7)	1377 (74.4)
1	619 (19.0)	300 (21.2)	319 (17.2)
2	194 (5.9)	94 (6.6)	100 (5.4)
3	119 (3.6)	64 (4.5)	55 (3.0)
Site of primary tumor			
Gum	1377 (42.1)	643 (45.4)	734 (39.6)
Floor of mouth	849 (26.0)	341 (24.1)	508 (27.4)
Retromolar trigone	376 (11.5)	138 (9.7)	238 (12.9)
Cheek mucosa	188 (5.8)	72 (5.1)	116 (6.3)
Tongue	125 (3.8)	56 (4.0)	69 (3.7)
Mouth, NOS	353 (10.8)	167 (11.8)	186 (10.1)
Tumor grade			
Well differentiated	663 (20.3)	292 (20.6)	371 (20.1)
Moderately differentiated	1743 (53.4)	752 (53.0)	991 (53.5)
Poorly differentiated	390 (11.9)	185 (13.1)	205 (11.1)
Undifferentiated	7 (0.2)	3 (0.2)	4 (0.2)
Missing data	465 (14.2)	185 (13.1)	280 (15.1)
Tumor size, cm			
≤2	426 (13.0)	234 (16.5)	192 (10.4)
>2	1774 (54.3)	760 (53.6)	1014 (54.8)
>4	1068 (32.7)	423 (29.9)	645 (34.8)
Chemotherapy status			
No	2805 (85.8)	1355 (95.6)	1450 (78.3)
Yes	402 (12.3)	23 (1.6)	379 (20.5)
Missing data	61 (1.9)	39 (2.8)	22 (1.2)

Abbreviations: NOS, not otherwise specified; PORT, postoperative radiotherapy.

NCCN treatment guidelines (version 1.2023) recommend PORT for oral cavity SCC with adverse features (extranodal extension, positive or close margins, pT3-4 primary, pN2-N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular invasion, and lymphatic invasion).[1] However, these guidelines do not provide a specific pathway for oral cavity tumors with mandibular invasion. Of particular interest are tumors of 2 cm or less that would otherwise be staged as pT1-2. To date there are 3 studies evaluating pT4aN0 oral cavity SCC involving the mandible.[15-17] In a single-institution retrospective study of 64 patients with pT4aN0 oral cavity SCC and boney invasion, Stanford-Moore et al[15] found that postoperative radiation or chemoradiation was associated with improved outcomes with respect to disease-free survival and OS. These authors adjusted for tumor size but did not evaluate the effect of adjuvant for each size group separately. In a NCDB study of 1559 patients with pT4aN0 oral cavity SCC who underwent mandibulectomy, Namin et al[16] identified that PORT was as-

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Table 2. Doubly Robust Cox Proportional Hazards Model for Overall Survival

Predictor	Univariate analysis, HR (95% CI)	Multivariable analysis, aHR (95% CI)
Age (continuous), y	1.02 (1.02-1.03)	1.01 (1.00-1.02)
Sex		
Female	1.07 (0.90-1.27)	NA
Male	1 [Reference]	NA
Race and ethnicity		
Asian	1.06 (0.45-2.51)	NA
Black	0.89 (0.54-1.46)	NA
Hispanic	0.78 (0.39-1.55)	NA
White	1 [Reference]	NA
Missing data	0.88 (0.55-1.41)	NA
Health insurance status		
Private insurance	1 [Reference]	1 [Reference]
Medicare/Medicaid	2.41 (2.01-2.87)	2.09 (1.68-2.60)
No insurance	0.74 (0.38-1.44)	0.75 (0.37-1.53)
Missing data	2.41 (1.57-3.70)	2.28 (1.47-3.55)
Charlson Comorbidity Index score		
0	1 [Reference]	1 [Reference]
1	1.34 (1.13-1.58)	1.17 (1.01-1.37)
2	1.49 (1.06-2.10)	1.22 (0.89-1.68)
3	2.10 (1.59-2.77)	1.91 (1.44-2.52)
Site of primary tumor		
Gum	1 [Reference]	1 [Reference]
Floor of mouth	1.27 (1.03-1.58)	1.37 (1.12-1.66)
Retromolar trigone	1.26 (1.02-1.56)	1.27 (1.04-1.56)
Cheek mucosa	1.05 (0.76-1.45)	1.11 (0.81-1.51)
Tongue	0.85 (0.51-1.43)	0.83 (0.50-1.39)
Mouth, NOS	1.19 (0.87-1.64)	1.18 (0.87-1.60)
Tumor grade		
Well differentiated	1 [Reference]	1 [Reference]
Moderately differentiated	1.16 (0.97-1.38)	1.15 (0.98-1.35)
Poorly differentiated	1.58 (1.14-2.19)	1.72 (1.27-2.34)
Undifferentiated	1.57 (0.35-6.98)	2.07 (0.50-8.58)
Missing data	0.96 (0.70-1.30)	0.90 (0.69-1.19)
Tumor size, cm		
≤2	1 [Reference]	1 [Reference]
>2 to 4	1.30 (0.98-1.72)	1.26 (1.01-1.57)
>4	1.53 (1.14-2.05)	1.52 (1.19-1.94)
Postoperative radiotherapy		
No	1 [Reference]	1 [Reference]
Yes	0.78 (0.66-0.92)	0.72 (0.62-0.84)
Chemotherapy status		
No	1 [Reference]	NA
Yes	1.03 (0.74-1.42)	NA
Missing data	1.10 (0.77-1.59)	NA

Abbreviations: HR, hazard ratio; aHR, adjusted hazards ratio; NA, not applicable; NOS, not otherwise specified.

sociated with OS. In a subgroup analysis by tumor size, these authors further demonstrated that this association was maintained for tumor size of 2 cm or less, more than 2 cm to 4 cm, and greater than 4 cm. In contrast, Lee et al[17] found that within their cohort of 28 patients with pT4aN0 oral cavity SCC tumors with mandibular invasion, PORT was not significantly associated with disease-free survival (DFS) or OS. The variability in these retrospective series may in part be due to baseline differences between patients who received PORT and those who did not. Our current study evaluates whether any of these associations are maintained after baseline characteristics are balanced between the groups.

Overall, our findings are consistent with NCCN guidelines as far as patients with pT4aN0 oral cavity SCC do benefit from PORT. The relative magnitude of benefit received, however, tends to be less as tumor size decreases. Our find-

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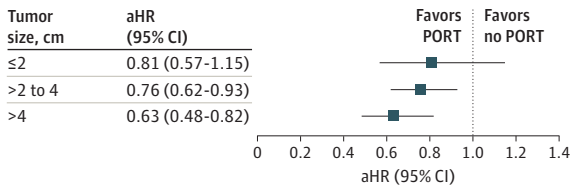
Figure 2. Treatment Effect of Postoperative Radiotherapy With Respect to Tumor Size



PORT indicates postoperative radiotherapy; aHR, adjusted hazard ratio.

ings suggest that the relative benefit of PORT changes with tumor size. Perhaps this also indicates that treatment can be modified by considering tumor size, even among patients with pT4aN0 disease. Tumor size of 2 cm or less without invasion of adjacent structures would otherwise be classified as pT1/2N0—for which there is no evidence to support administration of PORT. When boney invasion is identified this recommendation changes. In reality, the true severity of these tumors likely lies outside of the current T stage classifications. For patients concerned about the adverse effects of PORT on quality of life, those with pT4aN0 tumors of 2 cm or less may still be good candidates for single-modality surgical therapy.

Limitations

This retrospective study is not without limitations. NCDB relies on accurate coding of variables by health professionals and is susceptible to misclassification bias. The surgical code for mandibulectomy was used as a proxy for mandibular invasion, given that not all patients had documentation of local tumor extension. There may be patients included who met pT4a criteria due to invasion of the skin or extrinsic tongue muscles. Doubly robust estimation can theoretically identify the causal effect of a given intervention, but the accuracy of this estimation is dependent on inclusion of important clinicopathologic features. NCDB does not provide information for some adverse features that require PORT, eg, perineural invasion, vascular invasion, and lymphatic invasion. Additionally, the definition of a positive surgical margin can vary between institutions. Changes in staging criteria following the 2017 AJCC eighth edition update may have introduced further variability. Due to missing documentation of depth of invasion and/or tumor extension, we were unable to manually restage all patients. These limitations may touch on the question of why not all pT4a patients in this cohort received PORT. With further clinicopathologic information, we might have seen that only patients with more severe disease received additional treatment. On one hand, this could indicate that despite having more severe disease at baseline, patients who received PORT still had superior survival. On the other hand, it is possible that tumor size is a proxy for some of the missing information.

Regarding radiation therapy quality assurance, we did not adjust for 3-dimensional vs intensity-modulated radiation therapy, treatment fields, duration of treatment, time to initiation of radiotherapy postsurgery, as well as dose and fractionation schedule, which we know is an important aspect in radiotherapy treatment and treatment outcomes.

Finally, without DFS data, we cannot evaluate whether PORT is associated with improved locoregional disease control or improved survival through a nononcologic mechanism. There is also the consideration of patterns of failure. Cancer survivors can experience profoundly different clinical courses. We were unable to appreciate other benefits of locoregional control outside of survival, such as improved quality of life.

Conclusions

In this retrospective cohort study, we estimated the treatment effect of PORT on OS among patients who received margin-negative mandibulectomy for pT4aN0 oral cavity SCC. We found that the use of PORT was strongly associated with increased OS and that the relative survival benefit of PORT increased with increasing tumor size. Precise estimates of the true benefit with PORT are limited by the relatively small sample size, especially for tumor size less than 2 cm. At a minimum, the findings of this robust analysis are certainly hypothesis-generating and may aid future multidisciplinary clinical decision-making among specific patient populations.

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Concept and design: Harley, Faraji, Sridharan, Kubik.
Acquisition, analysis, or interpretation of data: Harley, Iheagwara, Kubik.
Drafting of the manuscript: Harley, Sridharan, Kubik.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Harley, Faraji, Sridharan.
Administrative, technical, or material support: Harley.
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