Published in final edited form as:

Cancer. 2019 September 15; 125(18): 3198–3207. doi:10.1002/cncr.32199.

Early Squamous Cell Carcinoma of the Oral Tongue With Histologically Benign Lymph Nodes: A Model Predicting Local Control and Vetting of the Eighth Edition of the American Joint Committee on Cancer Pathologic T Stage

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CONFLICT OF INTEREST DISCLOSURES

Robert L. Ferris has acted as a paid member of the advisory board for Amgen; has received research funding and personal fees from Astra-Zeneca/MedImmune; has acted as a paid consultant for Bain Capital Life Sciences; has received research funding and personal fees from Bristol-Myers Squibb; has acted as a paid member of the advisory board for EMD Serono and GlaxoSmithKline; has acted as a paid consultant for Iovance Biotherapeutics Inc; has acted as a member of the advisory board for Lilly; has received research funding and personal fees from Merck; has acted as a member of the advisory board for Numab Therapeutics AG and Oncorus Inc; has acted as a paid consultant for Ono Pharmaceutical Co Ltd; has acted as a paid member of the advisory board for Pfizer, PPD, and Regeneron Pharmaceuticals Inc; has acted as a paid member of the advisory board for and received research funding from Tesaro; has acted as a paid consultant for TTMS; and has received research funding from VentiRx Pharmaceuticals for work performed outside of the current study. The other authors made no disclosures.

Additional supporting information may be found in the online version of this article.

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Abstract

BACKGROUND: The eighth edition of the American Joint Committee on Cancer staging manual (AJCC8) added depth of invasion to the definition of pathologic T stage (pT). In the current study, the authors assess pT stage migration and the prognostic performance of the updated pT stage and compare it with other clinicopathologic variables in patients with early squamous cell carcinoma of the oral tongue (OTSCC; tumors measuring ≤4 cm) with histologically benign lymph nodes (pN0).

METHODS: A multi-institutional cohort of patients with early OTSCC was restaged as per AJCC8. Primary endpoints were local recurrence (LR) and locoregional recurrence (LRR). Influential variables were identified and an LR/LRR prediction model was developed.

RESULTS: There were a total of 494 patients, with 49 LR and 73 LRR. AJCC8 pT criteria resulted in upstaging of 37.9% of patients (187 of 494 patients), including 34.5% (64 of 185 patients) from pT2 to pT3, without improving the prognostication for LR or LRR. Both LR and LRR were found to be similar for patients with AJCC8 pT2 and pT3 disease. On multivariate analysis, LR was only found to be associated with distance to the closest margin (hazard ratio, 0.36; 95% CI, 0.20-0.64 [$P = .0007$]) and perineural invasion (hazard ratio, 1.92; 95% CI, 1.10-0.64 [$P = .046$]). Based on these 2 predictors, a final proportional hazards regression model (which may be used similar to a nomogram) was developed. The proposed model appeared to be superior to AJCC pT stage for estimating the probability of LR and LRR for individual patients with early OTSCC.

CONCLUSIONS: AJCC8 pT criteria resulted in pT upstaging of patients with pN0 disease without improved LR or LRR prognostication. The proposed model based on distance to the closest margin and perineural invasion status outperformed pT as a predictor of LR and LRR in patients with early OTSCC.

Keywords

American Joint Committee on Cancer (AJCC) staging; depth of invasion; glossectomy; local disease recurrence; oral tongue; pathologic T stage (pT); squamous cell carcinoma

INTRODUCTION

The eighth edition of the American Joint Committee on Cancer (AJCC8) staging incorporates depth of invasion (DOI) into pathologic T stage (pT) for oral cavity squamous cell carcinoma (SCC).[1] The inclusion of DOI in the pT category for oral cavity SCC may improve the prognostic performance of pT AJCC staging.[2-4] However, to our knowledge, it is unclear whether DOI offers new prognostic information for patients with known lymph node status. For example, a number of patients with oral tongue SCC undergo elective neck dissection and are shown to have histologically benign cervical lymph nodes (pN0). It remains unclear whether the expected pT upstaging[4] offers further prognostic information for patients with pN0 disease.

Although available data appear to support redefining pT stage,[4] the AJCC8 TNM oral cavity stage groupings remained unchanged and the committee called for further studies.[1] The prognostic performance of AJCC8 staging in patients with oral cancer recently was tested.[1,5,6] The new pT stage has been shown to correlate well with overall survival, but these findings reflect the prognostic performance of updated pT staging in a heterogeneous patient population with a variety of oral cavity subsites and pathologic T and N stages of disease (eg, clinically cN0 rather than pN0). The treatment and prognosis of patients with oral cavity carcinoma depends on the oral cavity subsite[7] and neck dissection.[8] Therefore, more focused studies are required to bridge personalized and population-based approaches to cancer staging.[9]

In addition, implementation of AJCC8 staging was complicated by numerous updates and corrections. For example, only with the third print run was it made clear that an oral SCC measuring ≤2 cm in largest dimension should not be categorized as pT3 if the DOI increases to >10 mm.[10] These and other corrections may affect the conclusions of earlier studies of AJCC8 staging of oral cavity cancer.

The objective of the current study was to test the performance of AJCC8 pT staging in a population of patients with early SCC of the oral tongue who were classified as having pN0 disease after elective neck dissection. Second, while considering other relevant variables, we aimed to develop a prognostic model that could optimize risk stratification for patients with early oral tongue SCC.

MATERIALS AND METHODS

Clinical and pathologic data were reviewed for patients with oral tongue SCC who were treated between 1986 and 2016 at the study institutions (8 institutions). All studied patients satisfied the following criteria: 1) had primary SCC limited to the oral tongue with a largest tumor dimension of ≤4 cm (those patients with carcinomas extending to adjacent anatomic

sites [ie, the base of tongue, floor of mouth] were excluded); 2) had undergone elective neck dissection (ipsilateral to the tongue primary tumor) with histologically benign cervical lymph nodes (pN0); 3) had conventional SCC morphology; 4) only cases with residual carcinoma in the resection specimen (ie, glossectomy) were included; 5) cases with a history of prior head and neck cancer were excluded; and 6) only glossectomies that were processed in a manner that allowed measuring distance to margins were included (eg, type of margin sampling [perpendicular *versus* shave] was indicated or could be deduced from inking key and sections summary).

The current study was approved by the University of Pittsburgh Medical Center Total Quality Council and institutional review boards IRB991206, Cleveland Clinic Foundation IRB 15-023/17-1573, Mount Sinai 15-00007, 358-2017 for Sunnybrook Health Sciences Centre, National Healthcare Group Domain Specific Review Board Ref: 2018/00173 for Tan Tock Seng Hosptial, and IRB #5968 for Southern California Permanente Medical Group. A subset of these patients was described previously and follow-up information was updated.[11] Each institution supplied from 16 to 205 cases, which were reviewed centrally. Details regarding the measurement of DOI were described previously.[12]

The collected data included age, sex, perineural invasion (PNI), details regarding surgery (manner of surgical margin sampling[11,13]), and other variables (Table 1). pT stage classification was performed using the seventh edition of AJCC (AJCC7) and AJCC8.

In all cases, margin status (positive *versus* negative, distance to the closest margin) was assessed from the main resection and/or glossectomy specimen only. The presence of invasive or in situ carcinoma at the margin was interpreted as a “positive” margin. The manner of margin sampling was categorized as previously described[11,14]: group 1, en bloc resection, comprised patients with margins assessed from the glossectomy specimen only; group 2 comprised patients with additional margins taken from the tumor bed after a suboptimal glossectomy specimen margin was identified (revision group); and group 3 comprised patients with primary reliance on tumor bed margins only (if the tumor bed margin was positive for carcinoma and subsequently was revised, such cases were categorized as group 2).

Statistical Analysis

The primary endpoint was local recurrence (LR), measured as the time elapsed from the date of glossectomy until histologically confirmed disease recurrence/progression at the site of glossectomy. Regional recurrence was defined as SCC metastasis to cervical lymph nodes. Locoregional recurrence (LRR) was defined as local and/or regional recurrence. Patients who were alive at the time of last follow-up and developed a regional recurrence, developed distant metastasis, died of other causes, or developed a second primary SCC without a LR were censored and considered free of LR at the time of censoring. A second primary SCC was defined as SCC arising at a different site or that arising 4 years after the diagnosis of the index SCC. The probability of survival without LR or LRR was estimated using the Kaplan-Meier method. Group differences were examined using the log-rank test. Proportional hazards regression was applied to test the joint effect of covariates: pT, tumor size, DOI, PNI, distance to the closest margin, involvement of the intrinsic tongue musculature, blood

vessel invasion, lymphatic vessel invasion, tumor grade, patient age at the time of diagnosis, and sex. Two-way interactions among these variables also were evaluated. The selection of models was guided by the Akaike and Bayesian information criteria to balance fit and complexity. The final multivariate model for LR and LRR was found to meet proportional hazards assumptions using Schoenfeld residuals.[15] Survivor functions were estimated from final proportional hazards models using the discrete hazard method of Kalbfleisch and Prentice.[16]

Time-dependent receiver operating characteristic (ROC) analysis was used to evaluate and compare the discriminatory abilities of the AJCC7 and AJCC8 pT stage and of the proposed model.[17] The nearest neighbor estimator was used to guarantee monotonic operating characteristics. *P* values were adjusted for false discovery using the method of Benjamini and Hochberg.[18] All statistical analyses were conducted using R statistical software (version 3.5.1).[19]

RESULTS

Clinicopathologic Features of the Studied Population

A cohort of 494 patients who were treated with glossectomy with curative intent was assembled. Clinicopathologic features of the studied patients are summarized in Tables 1 and 2. There were 436 partial glossectomies and 58 hemiglossectomies performed. Intraoperative consultation (including Gross only examination) was performed in 445 of 494 cases (90%).

A total of 43 patients developed LR only, 24 patients developed regional recurrence only, and 6 patients developed both LR and regional recurrence, thereby producing 49 LRs and 73 LRRs. Among the 30 regional recurrences, 13 were contralateral to neck dissection.

The median follow-up for patients without a LRR was 45 months (range, 1-348 months) and at the time of last follow-up, 160 patients without recurrence had been followed for <3 years. Forty-one patients developed a second primary SCC of the upper aerodigestive tract or lung. Of the 97 patients who had died by the time of last follow-up, 54 patients died of other causes. Of the remaining 43 patients who died of SCC, 8 died of a second primary SCC that was unrelated to the index SCC. Overall, the probability of 3-year LR-free survival was 0.89 (95% CI, 0.86-0.92) and the probability of 3-year LRR-free survival was 0.84 (95% CI, 0.81-0.88).

pT Stage Migration

AJCC8 pT criteria resulted in the upstaging of 37.9% of all patients (187 of 494 patients), including 39.8% (123 of 309 patients) upstaged from pT1 to pT2 and 34.5% (64 of 185 patients) upstaged from pT2 to pT3 (Table 2). The rates of pT upstaging were comparable to those of prior studies.[4-6] The association between the AJCC7 or AJCC8 pT staging and LR and LRR is shown in Figure 1 and Table 3. The AJCC8 pT classification did not improve the prognostic performance of pT stage for patients with pN0 with early oral tongue SCC.

Usefulness of the DOI as an Adjunct to Tumor Size

There was a strong correlation noted between the tumor size and DOI (Spearman correlation coefficient, 0.646; $P < .0001$), suggesting that DOI does not add substantial new information to tumor size–derived pT stage.

The largest tumor size and the DOI were examined individually as continuous variables, without preconceived thresholds, and were not found to be associated with LR (Figs. 2A and 2C). Both the largest tumor size and the DOI were associated with LRR (Figs. 2B and 2D). The association between the largest tumor size and the log relative hazard of LRR was nonlinear (Fig. 2B): an increase from 2 mm to 18 mm was associated with an increased hazard of LRR. A tumor size >18 mm did not appear to increase the risk of LRR further.

The association between DOI and the log relative hazard of LRR was linear across the entire range of DOI, from 2 mm to 17 mm, suggesting that discrete categorization of tumor DOI at 5 mm or 10 mm may define categories of increasing risk (Fig. 2D).

Even in patients with pN0 disease, DOI (as a continuous variable) was associated with LRR ($P = .006$). The median DOI was similar in cases with contralateral regional only (9 cases; median DOI, 10 mm) and ipsilateral regional only (15 cases; median DOI, 8 mm) recurrences (Wilcoxon test $P = .4009$). Despite the small sample sizes, DOI was associated with an increased risk of regional ipsilateral recurrence (ie, after neck dissection; $P = .0976$) and contralateral disease recurrence (without neck dissection at the time of glossectomy; $P = .0382$). None of the patients with SCC with a DOI <6 mm developed contralateral regional only disease recurrence.

Treatment Course of Patients Who Would Be Upstaged by the AJCC8

Of the total of 494 patients, 114 patients (23%) received radiotherapy (RT). Among the 187 patients whose pT stage was upstaged by AJCC8 (37.9%), 65 patients (34.8%) received adjuvant RT (Tables 4 and 5). Patients upstaged from pT2 to pT3 were more likely to have received RT compared with patients with pT2 who were not upstaged (56.2% [36 of 64 patients] vs 28.9% [35 of 121 patients]; $P = .0005$). Similarly, patients upstaged from pT1 to pT2 were more likely to have received RT than patients with pT1 who were not upstaged (23.9% [29 of 121 patients] vs 7.6% [14 of 185 patients]; $P = .0001$).

A logistic regression model identified 4 risk factors associated with the decision to administer RT: PNI (odds ratio [OR], 3.9; 95% CI, 2.4-6.2), pT2 (AJCC7: 2.8; 95% CI, 1.8-4.5), positive glossectomy specimen margin (OR, 1.9; 95% CI, 1.1-3.2), and lymphatic invasion (OR, 1.8; 95% CI, 1.1-3.1).

Predicting LR and LRR

Clinicopathologic parameters that were tested individually using proportional hazards regression for the association with LR or LRR are summarized in Table 3.

Final multivariate proportional hazards regression models for both LR and LRR established the importance of distance to the closest margin and PNI. On multivariate analysis, LR was found to be associated only with distance to the closest margin (hazard ratio, 0.36; 95% CI,

0.20-0.64 [P = .0007]) and PNI (hazard ratio, 1.92; 95% CI, 1.10-0.64 [P = .046]). Conditional on distance to the closest margin and PNI, pT stage using the AJCC7 or AJCC8, tumor size, and DOI were insignificant contributors to the models.

Figure 3 demonstrates the model results. The underlying equations are shown in Supporting Figure 1. The model allowed for the estimation of the probability of LR or LRR for patients with pN0 disease with early oral tongue SCC. The curves shown in Figure 3 also may be used similar to a nomogram to determine, in 2 steps, the estimated model-derived probability of 3-year LR-free survival and LRR-free survival for an individual patient with known distance to the closest margin and PNI status. Bootstrap cross-validation with 100 bootstrap samples demonstrated the original slope for plotting observed *versus* predicted decreased from 1.0 to 0.994 (ie, an optimism of only 0.006).

Prognostication by the AJCC7 and AJCC8 pT Staging and Proposed Model

To compare the predictive ability of the AJCC7 and AJCC8 pT staging, we calculated the area under a time-dependent ROC curve (AUC) for disease recurrence at 3 years. We also compared these with the ROC derived from our proposed prognostic model. As shown in Figure 4, AJCC8 pT staging is marginally better than that of AJCC7 at predicting LR and LRR at 3 years (AUC, 0.56 vs AUC, 0.52 for LR and AUC, 0.57 vs AUC, 0.55 for LRR). The AUC of the proposed model was 0.71 for LR at 3 years and 0.7 for LRR at 3 years. It is important to note that the model's 95% CI did not overlap with the AUC of 0.5. The prognostic model relying on distance to the closest margin and PNI status was found to be superior to pT staging of either AJCC7 or AJCC8 (Fig. 4).

DISCUSSION

The AJCC staging manual has had many traditional roles, including education, cancer advocacy, and facilitating interaction between patients, physicians, statisticians, and registrars.[9] AJCC8 also attempts to transition from classic population-based staging to a more personalized staging to assist with therapeutic decisions for individual patients.

The pT staging of patients with oral cavity SCC was adjusted by including the DOI to reflect the correlation between DOI and cervical lymph node status.[3,4] In the current study, we vetted the new pT staging in a multi-institutional cohort of patients with pN0 early oral tongue SCC. The objective was to test whether the DOI offers any additional prognostic information to patients with pN0 disease that would justify pT upstaging. In addition, although the AJCC8 changed the pT definition, the overall TNM grouping update is pending. Our data may help to optimize TNM grouping for patients with pN0 disease.

Generally, the DOI is not considered when deciding on the postoperative treatment of patients with pN0 disease with early oral tongue SCC. However, through pT upstaging, the AJCC8 may influence therapeutic decision making in patients with pN0 disease. Compared with AJCC7, AJCC8 staging leads to pT upstaging in approximately 38% of patients, including to pT3. In the current study, we demonstrated that a higher pT stage (AJCC8) was not associated with worse LR or LRR. However, because TNM overall stage has not been modified in AJCC8, a higher pT stage would directly lead to the assignment of a higher

overall clinical stage. For example, approximately 34.5% of patients formerly classified as having pT2N0 clinical stage II disease (AJCC7) will be upstaged to pT3N0, clinical stage III disease, without the suggested higher LR or LRR rates. An updated TNM grouping is needed to reflect similar outcomes in patients with pT2pN0 and pT3pN0 disease (AJCC8) (Figs. 1C and 1D). Overall, the results of the current study have demonstrated that the prognostic value of DOI is blunted in patients with pN0 disease, and individuals with pT3pN0 disease will likely have a clinical course more similar to that of patients with stage II disease rather than that of patients with stage III disease.

Patients with early oral tongue SCC with PNI or lymphatic invasion and positive glossectomy margins already are considered to be at higher risk of disease recurrence and will be selected for RT, irrespective of the staging criteria used. Therefore, AJCC8 pT criteria do not appear to identify a novel pN0 patient population prone to worse local control.

In the current study of 494 patients with surgically treated, early-stage pN0 tongue cancers, the outcomes were consistent with those of prior reports of similar patient populations.[3] The rate of contralateral neck failure was low, suggesting that close surveillance alone is an adequate approach and would not justify bilateral elective neck dissection at the time of glossectomy or postoperative RT.[3,20] This paradigm would not apply to patients with tumors that cross the tongue's midline or encroach onto adjacent subsites.

Several factors were found to be associated with LR and LRR in the pN0 patient population. On univariate analysis, LR and LRR were associated with surgical margin sampling workflow,[11] surgical margin status (with these 2 parameters being reflected in "distance to the closest margin"), and PNI, among other variables (Table 3). For example, tumor bed sampling and the need for margin revision correlated with higher rates of LR. These findings are in agreement with previously published data.[11,13,21,22]

A prognostic risk model for early oral tongue SCC may facilitate the prediction of LR and LRR and guide therapeutic choices after glossectomy for patients with pN0 disease. The AJCC decided on a checklist of 16 items necessary for their endorsement of any risk model.[23] The discussion of the model proposed herein will center on the AJCC checklist.

Several prognostic calculators applicable to oral cavity SCC recently were evaluated.[24] To the best of our knowledge, none of the other oral cavity SCC models accounts for oral cavity subsite, margin status, or PNI.[24] The discriminatory ability of the model proposed herein is higher than that of the 5 known risk calculators for oral cavity SCC, for which the AUC ranged from 0.652 to 0.706.[24] More detailed comparison with other models is difficult because they predict 5-year overall survival for patients with oral cavity SCC across all TNM stages. We have considered numerous other clinicopathologic variables (Table 3) and, ultimately, did not include them in the risk model due to the lack of incremental predictive ability.

An AUC of 0.71 (with 95% CIs not overlapping with the AUC of 0.5) for the current study model is of greater usefulness than pT using AJCC8. The model-derived curves (Fig. 3) function similar to a nomogram and may be used to derive 3-year LR-free survival and

LRR-free survival for an individual patient with known distance to the closest margin and PNI status. When validated, our risk assessment model will be applied after surgery (glossectomy and neck dissection) when a pathology report confirms the early stage of oral tongue SCC, pN0, and distance to the closest margin and PNI status become available. The risk model would predict the probability of LR and LRR. If, for example, the predicted LR and LRR probability at 3 years is <5% to 10%, RT would not be recommended.

There were several limitations to the current study. We excluded patients with histological variants of SCC, such as verrucous carcinoma, in which the distinction between tumor thickness and DOI is more significant. The current study was a retrospective analysis of pathologic specimens and outcome data for patients treated over decades. However, the improvement in cure rates for patients with oral cavity SCC over this time period was only slight, arguing against significant changes in treatment strategies. A subset of patients (23%) received RT. However, the lack of critical details concerning RT, such as dose, timing, and volume, preclude confident assessment of its efficacy.

The model presented herein has not been validated and should be viewed as a training set for future validation. However, bootstrap validation of model fit statistics demonstrated negligible optimism, which suggests the model is well calibrated and could be generalized successfully to other study populations.

In conclusion, AJCC8 pT criteria lead to upstaging without offering new clinically meaningful prognostic information regarding local or locoregional control in patients with pN0 early oral tongue SCC. The local control rates for patients with pT2pN0 and pT3pN0 disease are similar and individuals with pT3pN0 disease are perhaps more accurately categorized as having stage II, rather than stage III, disease. In patients with pN0 early oral tongue SCC, the prognostic relevance of DOI is blunted. In contrast, distance to the closest margin and PNI status are prognostically more informative, and a risk model relying on these 2 parameters will have to be validated in future patients treated over a more contemporary time frame.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

FUNDING SUPPORT

This project used the University of Pittsburgh Medical Center Hillman Cancer Center Biostatistics Facility, which is supported in part by award P30CA047904.

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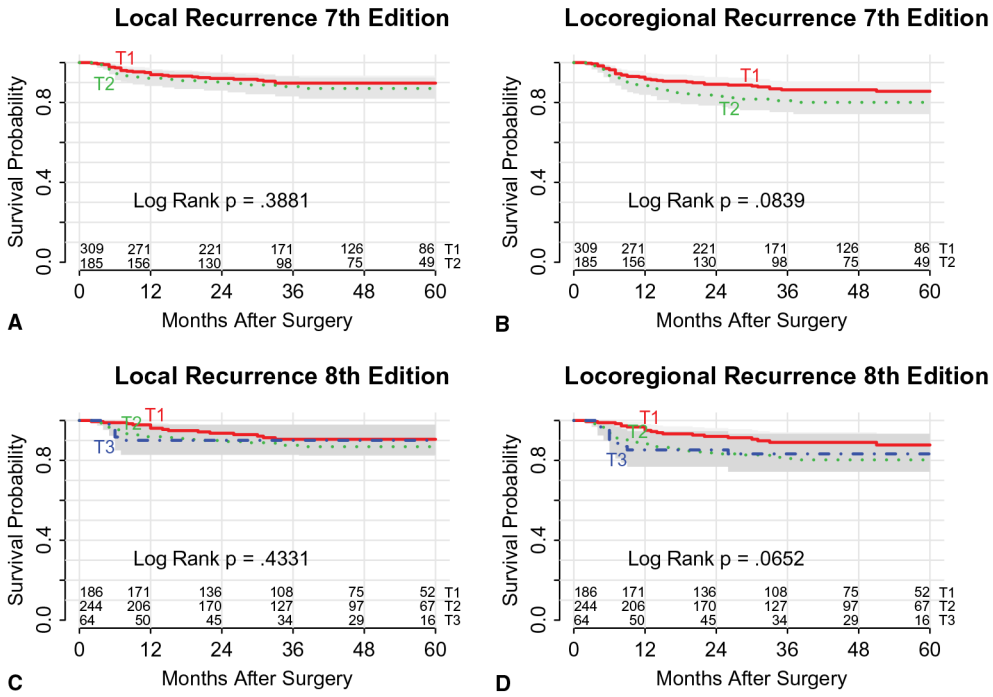

Figure 1.

pT stage according to the seventh and eighth editions of the American Joint Committee on Cancer (AJCC). Kaplan-Meier plots of (A and C) local recurrence-free survival and (B and D) locoregional recurrence-free survival. Patients were grouped by pT1 and pT2 disease when staged using the (A and B) seventh edition and by pT1, pT2, or pT3 disease when staged using the (C and D) eighth edition. Each plot included a *P* value resulting from a log-rank test, gray 95% CIs (all 95% CIs overlapped), and the number of patients at risk at 1-year intervals along the x-axis. pT staging according to the seventh and eighth editions of AJCC was not found to be associated with (A and C) local recurrence, and was only modestly associated with (B and D) locoregional recurrence.

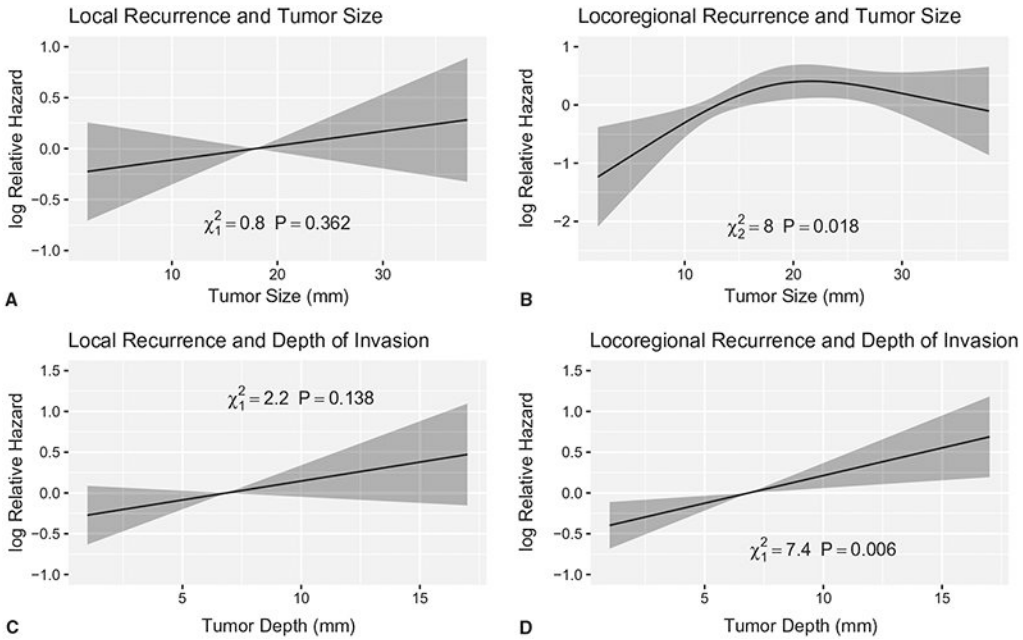

Figure 2.

Univariate effect of tumor size and depth of invasion on local and locoregional recurrence-free survival. Results were plotted as the log relative hazard of (A and B) tumor size and (C and D) depth of invasion. The association between size and locoregional recurrence was nonlinear and a restricted cubic spline function was fit to the data. The likelihood ratio chi-square statistic and associated *P* value for the association are shown.

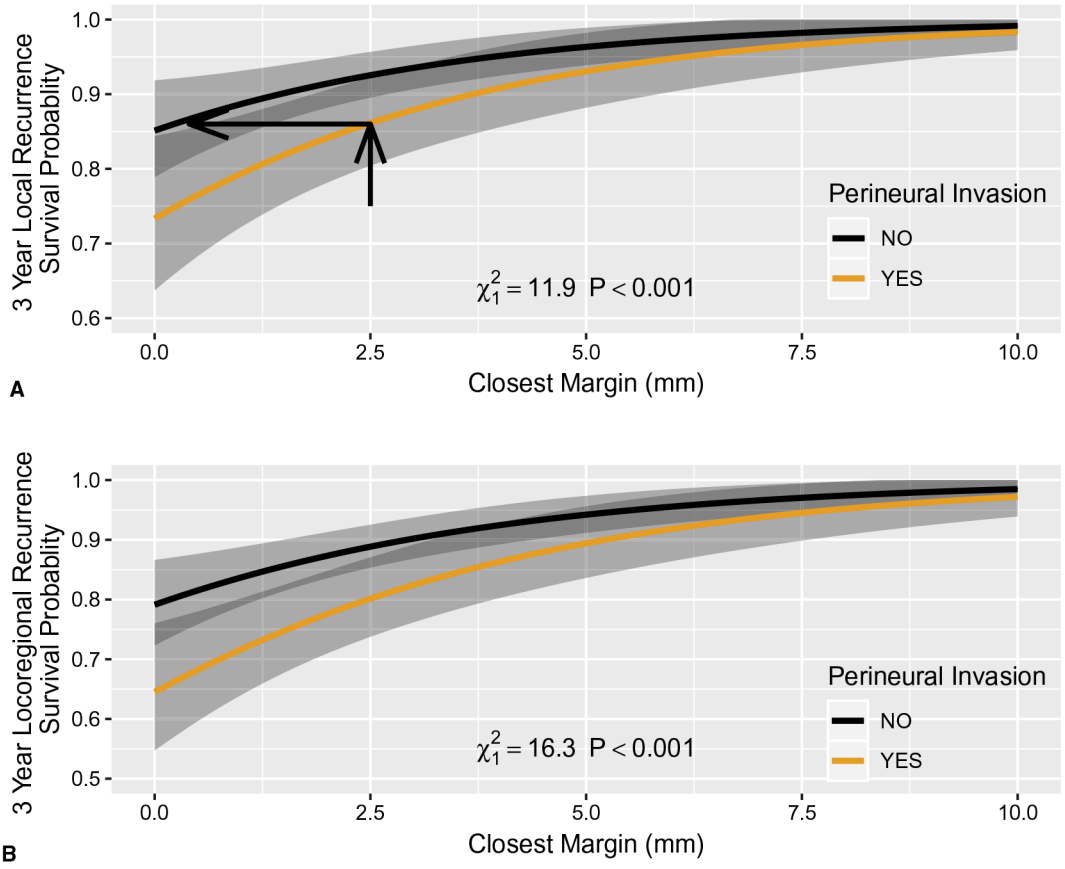

Figure 3.

Multivariate model-derived estimated probability of 3-year local recurrence-free survival (A) and locoregional recurrence-free survival (B) is plotted against the distance to closest margin separately by perineural invasion status. The displayed curves may also function similarly to a nomogram. For instance, a patient with a closest margin of 2.5 mm and positive for perineural invasion would have an estimated probability of local recurrence free survival of about 0.86. Arrows illustrate how referencing for individual patients can be done. A vertical line (see vertical arrow) is drawn from the point corresponding to the distance to closest margin on *x*-axis until the line crosses the orange Kaplan-Meier curve (with PNI). From this point on Kaplan-Meier curve, horizontal line (horizontal arrow) towards the *y*-axis will point out the estimated probability of 3-year local recurrence free survival. Survival probabilities are calculated from the hazard functions of proportional hazards regression equations which used two covariates, distance to closest margin and presence or absence of perineural invasion. Text shows the likelihood ratio chi-square statistic and associated *P* value for overall model fit.

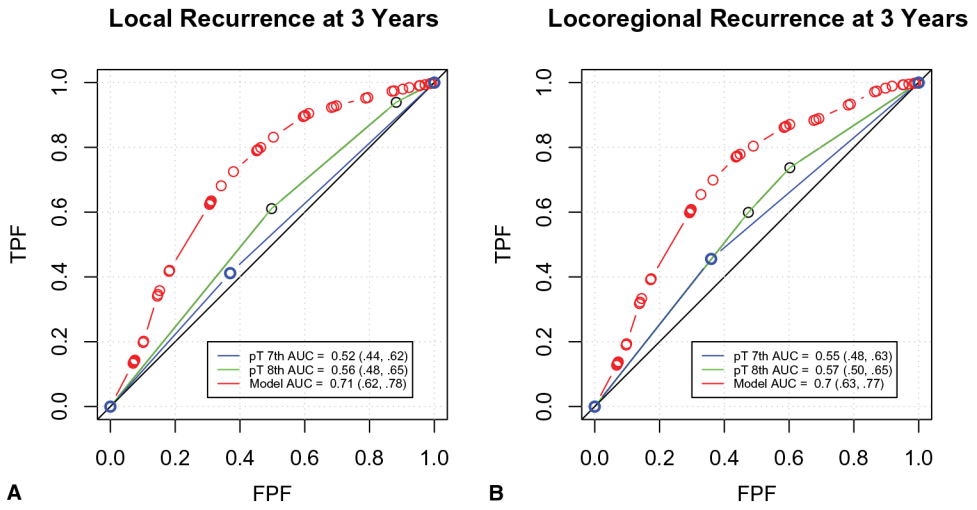

Figure 4.

Receiver operating characteristic (ROC) curves for predicting 3-year (A) local recurrence and (B) locoregional recurrence using the seventh and eighth editions of the American Joint Committee on Cancer (AJCC) pT stage, and the proposed prognostic model accounting for distance to the closest margin and perineural invasion status. Areas under the curve (AUCs) and 95% CIs were computed for each ROC curve. The 95% CIs for the model-based predictions were distinct from the diagonal AUC of 0.5 and suggested that model-based prediction has real value. The 95% CIs for the seventh or eighth AJCC edition staging of pT overlapped with the diagonal AUC of 0.5 and suggested that prognostication by pT status using either the seventh or eighth AJCC edition for pT was poor. The prognostic model based on proportional hazards regression as a function of distance to the closest margin and perineural invasion status provided substantial improvement. FPF indicates false-positive fraction; TPF, true-positive fraction.

TABLE 1.

Clinicopathologic Characteristics of Patients in the Current Study (N = 494)

Characteristic	No. (%)
Sex	
Male	271 (55%)
Female	223 (45%)
Median age at diagnosis (range), y	59 (23-88)
Depth of invasion, mm	
Median (IQR)	6 (4-10)
Largest tumor size, mm	
Median (IQR)	18 (11-25)
Positive for intrinsic tongue muscle involvement	428 (87%)
Positive for lymphatic invasion	95 (19%)
Positive for blood vessel invasion	13 (3%)
Positive for perineural invasion	159 (32%)
Margin sampling groups	
Group 1 (no tumor bed margins)	157 (32%)
Group 2 (revision, by sampling tumor bed)	167 (34%)
Group 3 (primary reliance on tumor bed margins)	170 (34%)
Status of the tumor bed margin	
Positive	15 (3%)
Negative	322 (65%)
Tumor bed not sampled	157 (32%)
Median distance to closest margin (IQR), mm	2.0 (0.5-4.0)
Type of closest margin	
Deep	226 (46%)
Mucosal	268 (54%)
Margin status assessed from main resection specimen, permanent/final pathologic evaluation	
Positive	103 (21%)
Negative	391 (79%)
Tumor differentiation	
Well	56 (11%)
Moderate	394 (80%)
Poor	44 (9%)
Adjuvant chemotherapy[a]	26 (5%)
Adjuvant radiotherapy[a]	114 (23%)

Abbreviation: IQR, interquartile range.

[a]Three patients had unknown postoperative treatment status. A total of 22 patients received chemoradiotherapy.

TABLE 2.

Eighth and Seventh Editions of AJCC and pT Stage Migration

		Eighth Edition			
		T1	**T2**	**T3**	**Total**
Seventh edition	T1	186	123	0	309
	T2	0	121	64	185
	Total	186	244	64	494

TABLE 3.

Clinicopathologic Variables and Association With Local or Locoregional Recurrence: Univariate Analysis

Covariate		Local Recurrence		Locoregional Recurrence	
		HR (95% CI)	Adjusted P^a	HR (95% CI)	Adjusted P^a
Margin clearance/distance to closest margin, continuous[b]		0.73 (0.62-0.86)	.004	0.75 (0.66-0.85)	<.001
Margin sampling	Revision vs en bloc resection	1.87 (0.83-4.19)	.040	1.77 (0.92-3.40)	.010
	Tumor bed sampling vs en bloc resection	2.66 (1.23-5.74)		2.53 (1.36-4.71)	
Margin status assessed from main resection specimen, permanent/final pathologic evaluation: positive vs negative		2.12 (1.18-3.82)	.040	2.09 (1.29-3.38)	.010
Perineural invasion		2.3 (1.31-4.03)	.019	2.22 (1.40-3.51)	.004
Depth of invasion[b]		1.05 (0.99-1.11)	.229	1.07 (1.02-1.12)	.015
Largest tumor size[b]		1.01 (0.98-1.05)	.420	1.02 (1.00-1.05)	.071
Radiotherapy		1.86 (1.03-3.36)	.102	2.06 (1.28-3.32)	.010
Chemotherapy		3.74 (1.68-8.35)	.010	4.02 (2.11-7.565)	.0002
pT Seventh edition		1.29 (0.73-2.27)	.420	1.5 (0.94-2.37)	.099
pT Eighth edition			.259		.030
T2:T1		1.51 (0.81-2.83)		1.87 (1.09-3.21)	
T3:T1		1.28 (0.50-3.29)		1.69 (0.78-3.63)	
Differentiation of carcinoma (grade)			.250		.028
Moderately: well		2.04 (0.63-6.59)		2.2 (0.8-6.05)	
Poor: well		2.58 (0.62-10.81)		3.9 (1.22-12.44)	
Vascular invasion		2.65 (0.83-8.54)	.202	3.05 (1.23-7.56)	.028
Lymphatic invasion		1.63 (0.87-3.08)	.228	1.83 (1.1-3.04)	.030
Invasion of the intrinsic tongue muscle		3.92 (0.95-16.15)	.133	3.9 (1.23-12.4)	.030
Age at diagnosis[b]		0.99 (0.97-1.01)	.259	0.99 (0.97-1.0)	.155
Male sex		0.85 (0.48-1.48)	.563	0.88 (0.56-1.4)	.594

Abbreviation: HR, hazard ratio.

[a] *P* values were adjusted for false discovery using the method of Benjamini and Hochberg.[18]

[b] For continuous variables (distance to the closest margin, depth of invasion, tumor size, and age at diagnosis), the HR reference is the interquartile range.

TABLE 4.

Radiotherapy and Upstaging From pT2 (AJCC Seventh Edition) to pT3 (AJCC Eighth Edition)

	Receipt of Radiotherapy	
	Yes	**No**
pT2 (seventh edition) remained pT2 (eighth edition) (N = 121)	35	86
pT2 (seventh edition) upstaged to pT3 (eighth edition) (N = 64)	36	28

Abbreviation: AJCC, American Joint Committee on Cancer.

TABLE 5.

Radiotherapy and Upstaging From pT1 (AJCC Seventh Edition) to pT2 (AJCC Eighth Edition)

	Receipt of Radiotherapy[a]	
	Yes	**No**
pT1 (seventh edition) remained pT1 (eighth edition) (N = 186)	14	171
pT1 (seventh edition) upstaged to pT2 (eighth edition) (N = 123)	29	92

Abbreviation: AJCC, American Joint Committee on Cancer.

[a]Radiotherapy data were not available for 3 patients.