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Patterns of Recurrence in Oral Tongue Cancer with Perineural Invasion

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Abstract

Background—Although perineural invasion (PNI) is recognized as an adverse prognostic factor in oral tongue squamous cell carcinoma (OTSCC), the patterns of failure are poorly defined.

Methods—Patients with OTSCC who received primary surgical treatment were identified. Specimens were reviewed by head and neck pathologists. Disease specific survival (DSS) and local, regional and distant recurrence free survival (LRFS, RRFS and DRFS) were calculated. PNI and PNI characteristics were analyzed as predictors of outcome.

Results—Patients with PNI had a decreased DSS however, PNI was not predictive of LRFS or RRFS. Patients with PNI were more likely to develop a distant recurrence and 19.40 (CI 6.70–56.14, $p < 0.001$) more likely to develop a distant recurrence if foci density was > 1 .

Conclusion—The presence of PNI in OTSCC predicts for worse DSS with distant recurrence as the most common pattern of failure. High foci density is associated with worse DRFS.

Keywords

oral tongue carcinoma; perineural invasion; distant metastasis; adjuvant therapy; head and neck squamous cell carcinoma

Introduction

The five-year survival rates of patients suffering from oral tongue squamous cell carcinoma (OTSCC) have not improved over the last 20 years.⁽¹⁾ Identifying factors, which put patients at risk for locoregional and distant failure, may affect therapeutic recommendations in an

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effort to improve survival. The histologic identification of perineural invasion (PNI) is generally considered a poor prognostic indicator and has been associated with an increase recurrence and a decrease in survival.^(2–5) The 2016 NCCN guidelines recommend adjuvant radiation (RT) when PNI is identified following surgical resection.⁽⁶⁾ Furthermore, because patients with PNI were included in EORTC 22931, a prospective randomized study comparing postoperative radiation alone versus the addition of chemotherapy in high risk squamous cell carcinomas of the head and neck ⁽⁷⁾ that showed a survival advantage for patients receiving adjuvant cisplatin concurrent with RT, the NCCN recommends considering adjuvant CRT for patients with adverse risk features, including PNI. Understanding patterns of failure associated with PNI warrants consideration when recommending adjuvant therapy for this adverse feature, particularly when PNI is identified in isolation. We sought to evaluate the effects of PNI on patterns of disease failure in a cohort of OTSCC.

One limitation of the current literature is the binary reporting of PNI as being simply present or absent, without any standardized definition or gradation of extent of PNI. We sought to evaluate the effects of PNI on patterns of disease failure in a cohort of OTSCC. Furthermore, we analyzed if grading the extent of PNI including percentage of the circumference of nerve involved by cancer, the caliber of nerve involved, intratumoral vs extratumoral PNI, intraneural vs. perineural location of PNI foci, and the number of foci detected per section (foci density) may improve risk stratification and propose a new, standardizing reporting characteristic, PNI foci density.

Methods

We identified a cohort of 381 patients treated with primary surgery for oral tongue squamous cell carcinoma (SCC) from January 1, 2000 through December 31, 2012 in our departmental database. We performed a retrospective review of medical records to obtain patient, tumor, treatment, and outcome data. Approval from the institutional review board of Memorial Sloan Kettering Cancer Center (MSKCC) for this study was obtained.

To be eligible for inclusion, patients were required to have histopathologic slides available for review. Three head and neck pathologists (B.X., N.K., R.A.G) reviewed all archived tumor specimens for PNI and all other histologic variables, and were blinded to clinical outcomes. PNI, defined as invasion in, around, or through peripheral nerve, presence or absence was assessed for each sample. For samples with PNI, further characterization was performed. The percentage of the nerve circumference involved by cancer, the diameter of the nerve involved (nerve caliber), intratumor vs extratumoral PNI, intraneural vs perineural location of PNI, and foci density were analyzed (Figure 1) Foci density was defined as the number of PNI foci observed divided by the number of tumor sections reviewed. Tumor size was defined as the greatest diameter of the invasive tumor based on gross and microscopic examination, and was categorized as 4.0 cm or less and greater than 4.0cm. Other pathologic variables that were assessed included surgical resection margin, lymph node metastases, histologic grade (well, moderately, or poorly differentiated), depth of invasion (DOI;<5mm or ≥ 5mm)⁽⁸⁾, and vascular invasion.

We assessed associations between variables using the chi squared test or Fisher exact test. The primary endpoints were disease-specific survival (DSS), local recurrence free survival (LRFS), regional recurrence free survival (RRFS), and distant recurrence free survival (DRFS). LRFS, RRFS and DRFS were calculated from the date of surgery to the date of local, regional, or distant recurrence, respectively. All recurrences were proven by biopsy. Survival was reported at the median follow-up. A death was considered a DSS event if the patient had active disease at the time of the last disease assessment. DSS was calculated from the date of surgery to the date of death or last disease assessment. To determine the optimal cut off of PNI foci density as related to DSS, maximal chi square analysis was used.

Cox proportional hazards regression model and Kaplan-Meier statistics were performed to assess outcomes. Log-rank test determined the univariate significance of a variable. Adjusting for pathologic and treatment variables, multivariable Cox proportional hazards regression models were created. Hazard ratio (HR) and 95% confidence intervals (CI) were used to report magnitude of difference and the strength of the association. P-values less than 0.05 were considered significant.

Results

Patient Characteristics

The study population consisted of 381 patients diagnosed with OTSCC, classifications T1–T4. A majority of the patients (58.3%) were males, and the median age was 57 years old (range 18–96). The median follow-up period was 39.8 months (0.03–150.1 months). The 5 year DSS, LRFS, RRFS, and DRFS for the entire cohort was 81.5%, 79.7%, 83.5% and 92.6%, respectively. Overall, there were 96 deaths, with 55 related to disease. Recurrent disease developed in 97 patients, including 58 local recurrences, 53 regional recurrences, and 23 distant recurrences. On pathologic review, we found that PNI was present in 105 cases (28%). Patients with PNI were more likely to also have a higher T-classification tumor and lymph node metastasis ($p<0.001$ and $p<0.001$, respectively). In addition, neck dissection and adjuvant radiation were more often part of the treatment plan in patients with PNI ($p<0.001$ and $p<0.001$, respectively). A summary of relevant demographic and clinicopathologic factors are provided in Table 1.

PNI Characteristics

In patients with PNI circumference of nerve involved by tumor was less than 100 percent in 37% patients. PNI was identified within the tumor in almost all cases; only one case observed outside the tumor. Tumor was also located around the nerve rather than intraneural in the majority of cases (92%). The caliber of nerve involved was less than 0.5mm in 90.4% of cases with only 10 tumors (9.6%) showing PNI involving nerves greater than 0.5mm.

Foci density was defined as the total number of foci of PNI identified, divided by the number tumor sections reviewed by the pathologist. The average number of tumor sections reviewed per case was 9, median is 8 (range 2–28 sections). The average and median number of tumor sections reviewed per cm of tumor was 4 (range 1–9 sections). The average number of slides per case was 32 (range 4–86). Using maximal chi square analysis, the optimal cut-

off associated with DSS was determined to be 1.17 foci density ($p=0.014$). We, therefore, used 1 as the optimal cutoff to differentiate lesions with high and low foci density. Any patient with greater than 1 focus per section was considered to have a high foci density. Most patients with PNI were found to have low foci density (84%).

Outcomes

PNI was found to be associated with a worse DSS on univariate analysis. (HR 5.63 C.I. 3.27–9.87, $p<0.001$, Table 2). On multivariable analysis, when adjusting for tumor size, adjuvant therapy and lymph node status, patients with PNI demonstrated a decreased DSS (HR 2.40 CI 1.32–4.37, $p=0.004$; Table 2). Although PNI was predictive on univariate analysis for local (HR 2.24 CI 1.31–3.85, $p=0.003$) and regional recurrence (HR 2.27 CI 1.31–3.95, $p=0.004$), it was not predictive on multivariable analysis (Table 3). For distant recurrence on univariate analysis when PNI was present, patients were 6.39 (CI: 2.70–15.10, $p=0.003$) times more likely to have a distant recurrence. Too few distant recurrent events precluded multivariable analysis on distant recurrence free survival.

When analyzing PNI characteristics including circumference of nerve involved, caliber of nerve, intra vs extratumoral PNI, and location of PNI foci (intraneural vs perineural), subclassification of PNI characteristics was not predictive of DSS, LRFS or RRFS (Table 4). In contrast, foci density was predictive of DSS (foci density ≤ 1 61.8% vs foci density > 1 37.1%, $p=0.006$) (Table 4). In a subgroup analysis of T1 and T2 tumors (336), high foci density PNI was predictive of a worse DSS (HR 6.03; CI 1.78–20.49 $p=0.004$). In all tumors, on multivariable analysis, patients who had foci density greater than 1 had a significantly poorer DSS compared with patients without PNI (HR 3.49; CI 1.53–7.95 $p=0.007$, Table 5). The impact of foci density on DSS is illustrated in Figure 2a.

On univariate analysis, foci density was associated with a difference in LRFS, RRFS, and DRFS (Table 6). For local recurrence, patients with high foci density had a HR of 4.07 when compared to patients with no PNI. When adjusting for tumor size, foci density, margin status, and post-operative adjuvant therapy, foci density was not an independent predictor of LRFS. For regional recurrence, patients with high foci density had a HR of 4.32 when compared to patients with no PNI. When adjusting for DOI, LN status, and postoperative adjuvant therapy, PNI was not an independent predictor of RRFS. When high foci density was present, patients were 19.40 (CI 6.70–56.14, $p<0.001$) times more likely to have a distant recurrence on univariate analyses when compared to having no PNI. The rate of distant recurrence at 5 years stratified by foci density was 39.4% patients with a foci density of greater than one, 12.2% for patients with a foci density of less than or equal one and 4.1% for patients without PNI (Figure 2b). Too few distant recurrence events precluded multivariable analysis for DRFS. For T1 and T2 tumors, PNI was not associated with differences in the pattern of failure including LRFS, RRFS and DRFS.

Discussion

Several studies have shown that the presence of PNI alters prognosis in oral cavity squamous cell carcinoma (SCC) negatively ^(2–5). While these findings support PNI as an adverse risk feature, it remains unclear exactly how PNI should be measured, whether PNI should be

quantified rather than reported as a binary outcome, and how the identification of PNI should affect clinical management. In the present study, PNI as quantified by foci density in OTSCC was associated with a decrease in DSS. In this patient cohort, the dominant pattern of failure was distant metastasis, without a significant difference in local or regional control rates.

Previously reported patterns of failure with PNI in oral cavity SCC varies across retrospective studies. Chinn et al identified a worse DSS in patients with early OTSCC with PNI, which was associated with a significantly worse local regional control. ⁽³⁾ Fagan attributed PNI associated disease related mortality to local failure without differences in regional or distant recurrences. ⁽²⁾ Increased nodal metastasis and regional recurrence with local control has also been observed in PNI positive OTSCC. ^(4, 9) In this current study, consistent with previously reported studies, PNI positive tumors were associated with a worse DSS. But in contrast, these findings were not associated with differences in local or regional control rates on multivariate analysis. Interestingly, presence of PNI did increase risk of distant metastasis by 6.4 fold. This pattern was even more striking when foci density was analyzed, with high foci cases being associated with a 19.4 fold higher risk of distant metastasis. Distant events in the high foci PNI cohort plateaus early, occurring within the first 12 months, supporting that the adverse prognostic implication of high foci density PNI is biologically realized very rapidly. Rates of distant metastasis in oral cavity cancer range from 2% in early stage tumors ⁽¹⁰⁾ to 21% in high risk head and neck SCC ⁽¹¹⁾ and confers a significantly worse survival. ^(12, 13) Consistent with previously published literature, incidence of distant metastasis across all tumor stages was 16% in this cohort. Median survival in this study population was 7.66 months (1.01–49.08). Identifying risk factors for DM represents a strategy to select patients for whom novel chemotherapy regimens might be employed with a goal of improving survival. PNI has also been identified as a risk factor for distant metastatic disease in other solid organ cancers. ^(14–19) Specifically, associations between squamous cell carcinoma PNI and distant metastases have been reported for esophageal, rectal, and oropharynx cancer. ^(14, 16, 17, 20)

As illustrated, the main pattern of failure attributing a worse prognosis to patients with PNI varies across studies. One possible explanation may be the variable clinical behavior of numerous oral cavity subsites, and potential varying influences of PNI in these different settings. Consolidating all oral cavity sites together may lead to heterogeneous findings. Another possible contributing factor includes different rates of adjuvant radiation therapy applied across these studies, ranging from 0–48%. ^(9, 21) In a homogenous group of OTSCC, we show here that the presence of PNI significantly affects DSS without affecting local or regional recurrence independent of receiving adjuvant RT.

Furthermore, variable reporting of PNI in a binary fashion may also contribute to varied published results for the prognostic significance of PNI in oral cancer. Liebig et al. specified that the presence of tumor cells within any of the three nerve sheath layers constitutes PNI ⁽²²⁾. However, others have broadened this definition to include any tumor cells touching a nerve. ⁽²⁾ In the pathology department at MSKCC, we use the classic definition of invasion in, around, or through peripheral nerves, ⁽²³⁾ but do not require a certain circumference around the nerve or that the nerve be outside the bulk of the tumor. Chi et al. found

interobserver agreement in assessing PNI status was only “fair” and suggested a “more widely accepted, objective, and reproducible criteria is needed for evaluating PNI in oral cavity.”⁽²⁴⁾ The number of tumor sections examined may also directly impact on the frequency of PNI detection. In our department, two to three sections per centimeter of tumor are sampled. Some studies have identified multifocal PNI as a risk feature of worse DSS and an increase in local failure.⁽⁵⁾ However, measuring the number of foci without adjusting for tumor size or the number slides examined may bias the PNI sampling, and affect conclusions. In this current work, we propose the use of foci density to control for the number of sections examined for each specimen.

This current work is limited by the number of distant metastatic events in this cohort of patients making it underpowered to use multivariable analysis to control for potential confounding variables. However, comparing across univariate analysis, we found that patients with a high foci density had a 19-fold increased risk of distant metastasis, as compared to a 4-fold risk of local or regional recurrence. This finding suggests that with an increased sample size study, high foci density might be independently associated with distant metastasis. PNI may therefore reflect a biological process that reflects a propensity for distant metastatic spread, leading to diminished DSS in high foci tumors.

This study is subject to the limitations associated with any retrospective study, including selection bias. This data does not necessarily advocate for adjuvant standard chemotherapy for all patients with a high foci density. Importantly while EORTC 22931, a trial comparing the addition of adjuvant chemotherapy to postoperative radiation in squamous cell carcinomas of the head and neck with high risk features, including PNI, overall survival was not improved with the addition of standard adjuvant chemotherapy and there was no impact on distant metastases. Rather, our aim is to highlight patterns of failure so that more effective novel adjuvant regimens may be developed to improve survival for patients with OTSCC and PNI. Additionally, recognizing that PNI may represent a distant metastatic phenotype provides clinical rationale to study biologic mechanisms that may be driving this process.

In conclusion, we demonstrate that a novel PNI histologic characteristic reporting system, foci density, has prognostic utility for OTSCC. High foci density is strongly associated with a decrease in DSS on multivariate analyses, and the dominant pattern of failure in this cohort was through distant metastasis. These results support a study of PNI, using a graded and non-binary reporting system, in a larger cohort of patients powered to determine the risk and patterns of failure associated with PNI in OTSCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Microscopic pictures of Hematoxylin and Eosin section from specimen harboring perineural (PNI) and intraneural invasion by squamous cell carcinoma. A: Large extra-tumoral 5 mm in diameter nerve with intraneural invasion by carcinoma (arrows). B: Small (<0.5 mm) nerve (n) with PNI partially wrapped by tumor (arrow). C: Several foci (>1) of intratumoral PNI in a single tumor section (n: nerve, arrow: tumor). D: Small (<0.5 mm) nerve (n) with PNI completely surrounded by tumor (arrow).

Figure 2.

A) Survival estimates of a Multivariable Cox Proportional Hazard Regression Model showing the difference of foci density while holding the tumor size and lymph node status at their reference variables. B) Univariate distant disease survival analysis showing the difference of foci density

Table 1

Demographics of patients broken down by Perineural Invasion

Variable	Total No. of Pts	No. of Pts with No PNI	No. of Pts with PNI	p-value
Gender				
Female	159 (41.7%)	117 (30.7%)	42 (11.0%)	0.672
Male	222 (58.3%)	159 (41.7%)	63 (16.5%)	
Age				
<60	212 (55.6%)	151 (39.6%)	61 (16.0%)	0.632
60	169 (44.6%)	125 (32.8%)	44 (11.5%)	
pT-Classification				
T1	260 (68.2%)	217 (57.0%)	43 (11.3%)	<0.001
T2	76 (20.0%)	48 (12.6%)	28 (7.35%)	
T3	21 (5.51%)	6 (1.6%)	15 (3.94%)	
T4	22 (5.77%)	3 (0.79%)	19 (4.99%)	
Unknown	2 (0.52%)			
pN- Classification				
N0	296 (77.7%)	241 (63.3%)	55 (14.4%)	<0.001
N+	85 (22.3%)	35 (9.18%)	50 (13.1%)	
Adjuvant Therapy				
No	286 (75.1%)	238 (62.5%)	48 (12.6%)	<0.001
Yes	95 (25.0%)	38 (9.97%)	57 (15.0%)	
Neck Dissection				
No	100 (26.2%)	95 (24.9%)	5 (1.31%)	<0.001
Yes	281 (73.8%)	181 (47.5%)	100 (26.2%)	

Abbreviations: pT- Classification, pathological T- Classification; pN- Classification, pathological N- Classification, PNI, Perineural Invasion, No.-Number, Pts- Patients

Table 2

Cox Proportional Hazard Regression Analysis for Disease Specific Survival

Variable	Univariate		Multivariable	
	HR (CI)	P-value	HR (CI)	P-value
Tumor Size	4cm	Reference	Reference	<0.001
	>4 cm	9.79 (5.34–17.33)	3.87 (2.11–7.10)	
	<5mm	Reference		
DOI	5mm	7.202 (3.26–15.93)		
	No	Reference	Reference	0.004
PNI	Yes	5.63 (3.27–9.87)	2.40 (1.32–4.37)	
	No	Reference		
VI	Yes	4.30 (2.34–7.89)		
	Negative	Reference		
Margin	Positive	4.43 (2.09–9.39)		
	No Positive Nodes	Reference	Reference	<0.001
LN Status	Positive Nodes	11.02 (6.24–19.46)	5.10 (2.50–10.40)	
	No	Reference	Reference	0.269
Adjuvant Therapy	Yes	6.91 (3.98–12.02)	1.48 (0.74–2.95)	
	WD	Reference		
Grade	MD	7.48 (1.03–54.25)		
	PD	15.96 (2.02–126.04)		

Abbreviations: DOI, depth of invasion; PNI, Perineural Invasion; VI, Vascular Invasion; LN Status, Lymph Node Status

Table 3

Multivariable Cox Proportional Hazard Regression for Local Recurrence Free Survival and Regional Recurrence Free Survival

Variable		Local Recurrence Free Survival		Regional Recurrence Free Survival	
		HR (CI)	P-value	HR (CI)	P-value
Tumor Size	4cm	Reference	0.013	NA	
	>4 cm	2.69 (1.23–5.89)			
DOI	<5mm	NA		Reference	0.039
	5mm			2.21 (1.04–4.68)	
PNI	No	Reference	0.416	Reference	0.496
	Yes	1.30 (0.69–2.44)		1.24 (0.67–2.29)	
Margin	Negative	Reference	0.001	NA	
	Positive	3.91 (1.77–8.65)			
LN Status	No positive nodes	NA		Reference	<0.001
	Positive node/s			4.85 (2.12–11.08)	
Adjuvant Therapy	No	Reference	0.004	Reference	0.195
	Yes	2.51 (1.34–4.70)		0.57 (0.25–1.33)	

Abbreviations: DOI, depth of invasion; PNI, Perineural Invasion; VI, Vascular Invasion; LN Status, Lymph Node Status

Table 4

Univariate analysis of PNI variables for DRFS, LRFS, RRFS, and DSS

Variable		No. of Pts	DRFS		LRFS		RRFS		DSS	
			5yr Survival	P- value	5yr Survival	P- value	5yr Survival	P- value	5yr Survival	P- value
Circumference		39	93.8%	0.044	68.5%	0.963	83.9%	0.149	61.1%	0.137
	< 100%									
	100%	66	77.2%		75.6%		74.9%		55.6%	
Peri neural vs Intra neural		97	83.3%	0.896	73.6%	0.252	78.6%	0.338	59.6%	0.051
	Perineural only									
	Peri and Intra	8	85.7%		60.0%		70.0%		38.9%	
Location		1		0.878		0.829		0.465		0.756
	Outside Tumor									
	Intra Tumor	97	83.2%		71.4%		76.5%		55.9%	
	Both	7	83.3%		80.0%		100%		66.7%	
Caliber *		94	83.6%	0.637	71.6%	0.930	76.6%	0.462	56.5%	0.924
	0.5									
	>0.5	10	77.8%		80.0%		88.9%		63.5%	
Foci Density		88	87.8%	0.003	74.3%	0.163	78.8%	0.190	61.8%	0.006
	1									
	>1	17	60.6%		65.5%		74.3%		37.1%	

* 1 missing pt

Abbreviations: No.-Number, Pts- Patients, LRFS- Local Recurrence Free Survival, RRFS-Regional Recurrence Free Survival, DRFS -Distant Recurrence Free Survival, DSS-Disease Specific Survival

Table 5

Multivariable Disease Specific Survival using Foci Density.

Variable		Disease Specific Survival	
		HR (CI)	P-value
Tumor Size	4cm	Reference	<0.001
	>4 cm	3.73 (2.02–6.87)	
Foci Density	No PNI	Reference	0.007
	1	2.13 (1.12–4.04) ^a	
	>1	3.49 (1.53–7.95) ^a	
LN Status	N0	Reference	<0.001
	N+	4.63 (2.21–6.70)	
Adjuvant Therapy	No	Reference	0.182
	Yes	1.62 (0.80–3.30)	

Abbreviations: DOI, depth of invasion; LN Status, Lymph Node Status

^aP-value comparing DSS foci density 1 to >1 was 0.218

Table 6

Univariate analysis of Foci Density for LRFS, RRFS, and DRFS

Variable	LRFS			RRFS			DRFS		
		HR(CI)	p-value		HR (CI)	p-value		HR (CI)	p-value
	No PNI	Reference	0.002		Reference	0.004		Reference	<0.001
	1	1.95 (1.08–3.52)			2.00 (1.10–3.65)			4.42 (1.70–11.48)	
	>1	4.32 (1.69–11.09)			4.07 (1.58–10.49)			19.40 (6.70–56.14)	