HHS Public Access

Author manuscript

Otolaryngol Head Neck Surg. Author manuscript; available in PMC 2020 December 14.

Published in final edited form as:

Otolaryngol Head Neck Surg. 2018 June ; 158(6): 1035–1041. doi:10.1177/0194599817751888.

Perineural Invasion in Parotid Gland Malignancies

Phillip Huyett, MD[1], **Umamaheswar Duvvuri, MD, PhD**[1], **Robert L. Ferris, MD, PhD**[1], **Jonas T. Johnson, MD**[1], **Barry M. Schaitkin, MD**[1], **Seungwon Kim, MD**[1]

[1]Department of Otolaryngology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

Abstract

Objectives.—To investigate the clinical predictors and survival implications of perineural invasion (PNI) in parotid gland malignancies.

Study Design.—Case series with chart review.

Setting.—Tertiary care medical center.

Subjects and Methods.—Patients with parotid gland malignancies treated surgically from 2000 to 2015 were retrospectively identified in the Head and Neck Cancer Registry at a single institution. Data points were extracted from the medical record and original pathology reports.

Results.—In total, 186 patients with parotid gland malignancies were identified with a mean follow-up of 5.2 years. Salivary duct carcinoma (45), mucoepidermoid carcinoma (44), and acinic cell carcinoma (26) were the most common histologic types. A total of 46.2% of tumors were found to have PNI. At the time of presentation, facial nerve paresis (odds ratio [OR], 64.7; P <.001) and facial pain (OR, 3.7; P = .002) but not facial paresthesia or anesthesia (OR, 2.8, P = .085) were predictive of PNI. Malignancies with PNI were significantly more likely to be of advanced T and N classification, be high-risk pathologic types, and have positive margins and angiolymphatic invasion. PNI positivity was associated with worse overall (hazard ratio, 2.62; P = .001) and disease-free survival (4.18; P < .001) on univariate Cox regression analysis. However, when controlling for other negative prognosticators, age, and adjuvant therapy, PNI did not have a statistically significant effect on disease-free or overall survival.

Corresponding Author: Phillip Huyett, MD, Department of Otolaryngology, University of Pittsburgh Medical Center, 203 Lothrop St, Suite 500, Pittsburgh, PA 15213, USA. huyettpa@upmc.edu.

Author Contributions

Phillip Huyett, study conception/design, data acquisition/analysis/interpretation, manuscript preparation/final approval, accountability for accuracy and integrity; **Umamaheswar Duvvuri**, study design, data acquisition, critical revisions and final approval of manuscript, accountability for accuracy and integrity; **Robert L. Ferris**, study design, data acquisition, critical revisions and final approval of manuscript, accountability for accuracy and integrity; **Jonas T. Johnson**, study design, data acquisition, critical revisions and final approval of manuscript, accountability for accuracy and integrity; **Barry M. Schaitkin**, study design, data acquisition, manuscript preparation/final approval, accountability for accuracy and integrity; **Seungwon Kim**, study conception/design, data acquisition/analysis/interpretation, manuscript preparation/final approval, accountability for accuracy and integrity.

Competing interests: National Cancer Institute, National Institute of Health.

Sponsorships: None.

This article was presented at the 2016 AAO-HNSF Annual Meeting and OTO EXPO; September 18-21, 2016; San Diego, California.

Conclusions.—PNI is strongly correlated with more aggressive parotid gland malignancies but is not an independent predictor of worse survival. Facial paresis and pain were predictive of PNI positivity, and facial paresis correlated with worse overall and disease-free survival.

Keywords

parotid gland; salivary gland malignancy; perineural invasion; facial nerve paresis/paralysis

Tumors of the parotid gland represent approximately 70% to 80% of salivary gland neoplasms, 10% to 20% of which are found to be malignant.[1,2] Despite higher malignant to benign ratios found in the minor salivary, sublingual, and submandibular glands, the parotid gland represents the most common primary site of salivary gland malignancies.

Surgical resection remains the mainstay of treatment for parotid gland neoplasms, but several negative prognostic indicators have been identified that often dictate the need for adjuvant treatment. Perineural invasion (PNI) has historically been one such negative prognosticator. PNI is a common finding in head and neck cancers, of salivary origin or otherwise, given the rich network of small (non-named) and large (named) nerves within this anatomic region. Occasionally (~10%-30%), the manifestations of PNI are clinically apparent, as seen in the patient presenting with facial nerve paresis.[3-5] In the patient with facial nerve weakness at the time of presentation, a number of studies have demonstrated worse survival and increased frequency of distant and regional metastases.[4-13]

More often, histologic PNI is asymptomatic, and in this setting, the importance of PNI is less clear.[14] Although many studies have shown worse survival and disease control rates in salivary gland tumors demonstrating PNI,[4,15-20] several studies have found the opposite to be true, especially when multivariable analysis is performed.[21-24] The objectives of this study were to review the survival implications and clinical predictors of PNI in patients with parotid gland malignancies.

Methods

Institutional review board approval was obtained from the University of Pittsburgh. The Head and Neck Cancer Registry at the University of Pittsburgh Medical Center (UPMC) was queried for all tumors of primary parotid gland origin from January 1, 2000, to December 31, 2015. Each case was subsequently reviewed to confirm the primary site and pathologic type of the tumor, removing benign and metastatic neoplasms. All cases of parotid gland malignancies were otherwise included if the patient was treated with primary surgery with curative intent.

Patient records were then reviewed to confirm demographic data and the use of adjuvant treatment contained within the database. The history and physical exam at the initial clinic encounter was used to determine facial nerve function, facial anesthesia or paresthesia, and facial pain. The original definitive surgical pathology reports were reviewed to confirm the histopathologic diagnosis, size, grade and the presence of PNI, angiolymphatic invasion (ALI), positive margins, or lymph node involvement. In cases performed in part outside of our hospital system, the final pathology interpretation made by the UPMC pathologists was

used. Cases in which PNI was not explicitly commented on were excluded. Immediately prior to data analysis, the database was updated with the most recent follow-up information as well as the most recent vital and cancer status.

Statistical analysis was performed with SPSS, version 23 (SPSS, Inc, an IBM Company, Chicago, Illinois). *P* values of less than .05 were considered significant. High- and low-risk type stratification was assigned according to Seethala.[25] T classification was divided into T1/2 and T3/4 to account for frequent minor discrepancies between clinical and pathologic staging. If a discrepancy was encountered that precluded assignment to only one of these groups, the case was assigned according to final pathologic T classification. Positive nodal status was defined as 1 or more cervical lymph nodes involved with the same tumor type as the primary parotid cancer. ALI and margin status had to be specifically commented on by the pathologists; otherwise, it was considered missing rather than negative.

Univariate analysis of categorical and numerical variables was performed with the 2-sided Pearson χ^2 test and independent 2-sample *t* test, respectively. We performed Cox proportional hazards model analysis of overall survival for patient demographics, negative pathologic features, and adjuvant treatment. The same analysis was performed for disease-free survival with death from other causes as competing risk taken into account. Multivariate analysis using the Cox regression model was performed to examine the independent contributions of the negative pathologic features (PNI, positive margins, positive nodal status, advanced T classification, and high-risk cancer types) on overall and disease-free survival while controlling for the adjuvant therapies and patient demographics found to be significant on univariate analysis. Collinearity between variables was tested using the variance inflation factor, and only ALI was found to have an unsatisfactorily high collinearity and was thus excluded from multivariate analysis. Cox proportional hazards model analysis was also used to compare overall and disease-free survival in PNI-positive tumors treated with and without radiation therapy (RT).

Results

Over the 15-year study period, 215 patients were identified with primary parotid gland malignancies that were treated surgically. Overall, 186 cancers were evaluated histopathologically for PNI, 86 (46.2%) of which were found to be positive. There were no statistically significant differences in any variable examined between the 29 cases that were not evaluated for PNI (and were therefore excluded from further analysis) and the 186 cases that were evaluated for PNI.

Although the patients with PNI positivity were significantly older (61.4 vs 55.6 years, *P* = .014), there were no other demographic differences compared to those with PNI-negative tumors (Table 1). Patients who presented with facial paresis or pain but not paresthesias or anesthesia showed higher rates of PNI. With regard to other negative prognosticators examined—high-risk pathologic types, advanced T classification, cervical lymph node involvement, ALI, and positive margins—the cancers with PNI positivity were significantly more advanced. Accordingly, these tumors were more frequently treated with adjuvant radiation and chemotherapy.

The distribution of the histologic types (Table 2) is consistent with prior reports in the literature in that mucoepidermoid carcinoma and acinic cell carcinoma were the most common subtypes. The exception to this is the disproportionately high number of patients with salivary duct carcinoma treated at UPMC. The frequency of PNI positivity by histologic type is shown in Table 2.

Thirty-five patients (18.8%) presented with facial nerve paresis or paralysis. Of these, 34 were found to have pathologic evidence of PNI (positive predictive value [PPV] = 97.1%; Table 3). This compares to 34.4% (1 – negative predictive value [NPV]) of patients found to be PNI positive when facial nerve weakness was absent (odds ratio [OR], 64.7; 95% confidence interval [CI], 8.6-486.4; $P < .001$). Of the 34 cases with PNI positivity and facial nerve paresis, PNI of the facial nerve itself was specifically commented on in 22 patients. In the remaining 12, the nerve with PNI was not specifically named. Facial nerve weakness at the preoperative visit was also predictive of worse overall survival and disease-free survival (Table 4).

Facial paresthesia or anesthesia and facial pain at presentation were found in 7.0% and 15.6% of patients, respectively. Facial pain (OR, 3.7; 95% CI, 1.6-8.9; $P = .002$) but not facial numbness (OR, 2.8; 95% CI, 0.8-9.5; $P = .085$) predicted higher rates of PNI positivity (Table 3). Facial pain at presentation had negative prognostic implications in terms of disease-free survival. Otherwise, facial numbness and pain were not found to be statistically related to survival (Table 4).

In 58 cases (31.2%), the facial nerve was sacrificed during parotidectomy. Thirty-two of these patients had documented facial nerve weakness and therefore facial nerve sacrifice was planned preoperatively. In the remaining 26 patients (16.9%), the decision to sacrifice the facial nerve was made intraoperatively, and in these instances, PNI was identified in 80.8% (OR, 11.6; 95% CI, 4.0-33.2; $P < .001$). Tables 3 and 4 summarize the predictability of PNI and survival implications of cases that underwent intraoperative cranial nerve (CN) VII sacrifice.

On univariate analysis of overall survival using the Cox regression model, all prognostic parameters examined, including PNI, were strongly related to poorer outcomes. Univariate analysis was similarly performed to determine predictors of worse disease-free survival, and all 6 pathologic parameters were again strongly related (Table 4).

Multivariate analysis revealed that patient age >60 years, advanced T classification, and positive nodal status correlated with worse overall survival (Table 5). Disease-free survival was likewise significantly worse in cases with positive nodes and advanced T classification, as well as positive margin status. PNI did not independently correspond to an overall or disease-free survival disadvantage. Radiation therapy was found to be protective in both the overall and disease-free survival multivariable analysis.

Of the 86 patients with PNI, 76 received postoperative radiation and 10 were treated with surgery alone. Those treated with adjuvant radiotherapy had improved disease-free survival (hazard ratio [HR], 2.58; 95% CI, 1.19-5.60; $P = .016$). Overall survival was no different

between PNI-positive tumors treated with or without RT (HR, 1.69; 95% CI, 0.65-4.37; *P* = .279).

Discussion

This study found that nearly half (46.2%) of parotid gland malignancies at our tertiary care referral center demonstrate PNI upon histopathologic examination. Of the negative pathologic prognosticators examined (ALI, PNI, high-risk subtype, positive margin status, positive nodal status, advanced T classification), only high-risk subtype (51.6%) was encountered more frequently than PNI. Neural invasion is thus exceptionally common, and therefore predictors of PNI as well as the survival implications of PNI positivity are of significant importance.

The cause of facial nerve paresis in parotid gland malignancies has been historically attributed to malignant neural infiltration rather than facial nerve compression or other causes of nerve dysfunction. Correspondingly, in this study, a high number of tumors were found to have pathologic nerve invasion when the patient presented with facial nerve weakness (PPV = 97.1%). Facial nerve weakness in this and prior studies also correlated with worse overall and disease-free survival as well as all other negative pathologic prognosticators. As such, facial nerve dysfunction should prompt preoperative counseling not just for facial nerve sacrifice but also an expected need for adjuvant therapy. The NPV and sensitivity were both low, limiting the value of preoperative facial nerve paresis in ruling PNI out based on physical exam.

Facial paresthesia, anesthesia, and pain similarly may to be secondary to malignant neural invasion of the auriculotemporal nerve, greater auricular nerve, and other sensory branches. In this study, both numbness and pain at presentation corresponded to higher rates of PNI, although this finding was not significant in the case of facial numbness. The etiology of facial pain may also be related to rapid tumor enlargement, necrosis, or hemorrhage, and the high frequency of PNI may simply reflect a more aggressive tumor. In terms of survival, only facial pain had an effect on disease-free survival, making the prognostic implications of facial numbness and pain less clear than facial motor weakness.

In this series, 58 patients underwent facial nerve sacrifice in conjunction with parotidectomy, 32 of which were planned preoperatively based on facial nerve paresis or paralysis. To assess the accuracy of intraoperative identification of nerve infiltration on the part of the surgeon, we examined the remaining 26 patients in whom facial nerve sacrifice was not planned preoperatively. Twenty-one (80.8%) of these patients were found to have PNI on final histopathology, indicating that the perception of intraoperative gross neural invasion seems to correlate well with microscopic invasion. This finding is important in that the patient is potentially spared a revision surgery or accepting a positive neural or tumor margin when the surgeon is less aggressive.

Decision making regarding facial nerve sacrifice is of significant functional and cosmetic consequence, especially in the patient who is not anticipating it. Given the importance of facial nerve weakness and the implications of facial nerve sacrifice, there may be a role for

preoperative objective facial nerve assessment. This would be especially appropriate in patients with other concerning tumor features (positive nodes, large size) but no clinically apparent facial nerve weakness.[26]

PNI was found to be very strongly correlated to worse overall and disease-free survival on univariate analysis (Table 4); however, this relationship did not hold true when controlling for other factors (Table 5). While this could be attributed to the high degree of concomitant poor prognosticators (Table 1), testing for collinearity between variables indicated that the multivariate analysis was statistically appropriate to run (with ALI excluded). Based on the results of this analysis, the thinking of PNI alone as a high-risk feature in regard to disease-free and overall survival should be reconsidered.

With that said, PNI in isolation of other negative prognosticators was uncommon in this study cohort—only 5 cases had PNI without ALI, positive margins, positive nodes, high-risk type, or T classification 3 or 4. Furthermore, the effect on disease-free survival approached significance in multivariate analysis (HR, 2.32; $P = .069$), and a shift in conventional thinking of PNI as a negative prognosticator is therefore not recommended based on this evidence alone. Further research in this area is needed with attention to the location and extent of the neural invasion (eg, intratumoral vs extratumoral; named vs nonnamed nerve), as well as the effects of adjuvant therapy.

Positive cervical lymphadenopathy and advanced T classification were negative prognosticators for both disease-free and overall survival on multivariable analysis, which supports the use of the American Joint Committee on Cancer TNM staging system for parotid gland cancers. Positive margin status was also noted to be predictive of worse disease-free survival.

There are several limitations to this study. First, 29 cases were excluded as they were not evaluated for PNI. The cases that were and were not evaluated for PNI were reviewed, and no differences between the groups were found. When discussing the relationship between physical exam findings and PNI, the PNI was not necessarily of the facial nerve. In 22 cases (64.7%), the pathology report specifically commented on PNI of the facial nerve, but in the remaining cases, the nerve was not specified. While it is most likely that PNI of the facial nerve is being evaluated, the lack of nerve specificity likely stems from the inherent challenges of specimen orientation by the pathologists, especially in the case of partial facial nerve sacrifice. Even if the neural invasion is not of the facial nerve specifically, the tumors at least demonstrate an intrinsic proclivity toward PNI.

The unusually high number of salivary duct carcinoma cases treated at UPMC may affect the generalizability of the results, especially the univariable results. The particularly high percentage of negative pathologic prognosticators in these cancers is, however, controlled for in the multivariable analysis. This may also artificially increase the frequency of the concerning physical exam features and rates of PNI, although our findings are consistent with prior reports in the literature.

On the other hand, as these represent cases taken to surgery as the primary treatment, advanced tumors that were taken for open biopsy or fine needle aspiration biopsy (FNAB)

prior to palliative or therapeutic chemoradiation were not included. It is likely that these cases of parotid malignancy treated nonsurgically had high rates of PNI, presenting facial nerve symptoms, other negative pathologic features and poor outcomes that were excluded from the data.

Ultimately, the main implication of identifying perineural invasion and other negative prognosticators is in recommending adjuvant chemotherapy and especially radiation therapy. It is thus worth noting the positive survival influence of adjuvant radiation therapy on the cohort overall found in the multivariate analysis. The data regarding the efficacy of radiation therapy in parotid gland malignancies[8,12,27,28] and specifically PNI in parotid gland malignancies[29,30] are limited by small case numbers, retrospective design, and nonrandomization.

In the largest study reporting on the effects of adjuvant RT on PNI-positive salivary gland tumors (predominantly parotid), a benefit was seen in univariate but not multivariate analysis for local disease control.[30] Although not statistically significant, Frankenthaler et al[29] demonstrated improved overall survival in PNI-positive tumors treated with surgery and RT compared to surgery alone. Conversely, another large study of 207 parotid gland cancers treated exclusively with surgery (no RT) found there to be no difference in local-regional control at 10 years between PNI-positive and PNI-negative tumors. In our cohort, there was a disease-free but not overall survival benefit to postoperative radiation therapy in PNI-positive tumors. However, a small group (n = 10) of PNI-positive patients not treated with RT as well as the lack of control for other prognosticators limits the analysis. Regardless, it is clear that future work is needed to clarify the effect of adjuvant therapies on PNI in parotid gland cancers prior to a change in current practice.

Conclusion

PNI was identified in 42.6% of parotid gland cancers. While PNI was strongly correlated with worse overall and disease-free survival on univariate analysis, it was not an independent predictor of worse survival when other negative prognosticators were controlled for. Facial nerve dysfunction at presentation was found to be predictive of both PNI and poorer survival. Further work is needed to examine the influence of the size, location, and extent of PNI as well as the impact of adjuvant therapies on PNI.

Acknowledgments

Funding source: T32 training grant CA060397-21, National Institutes of Health through grant UL1-TR-001857 (statistical support).

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Table 1.

Demographics of Patients Overall, with and without Perineural Invasion.[a]

Characteristic	All (n = 186)	PNI+ (n = 86)	PNI− (n = 100)	*P* Value
Patient demographics				
Mean age, y	58.3	61.4	55.6	.014
Male, %	51.1	53.5	49.0	.542
Smoker, %	44.6	50.0	40.0	.171
White, %	90.3	90.7	90.0	.873
Presentation characteristics, %				
Facial paresis	18.8	39.5	1.0	<.001
Facial numbness	7.0	10.5	4.0	.085
Facial pain	15.6	24.4	8.0	.002
Tumor characteristics, %				
Percent T3/4	36.6	58.1	18.0	<.001
Positive nodes	33.3	55.8	14.0	<.001
Angiolymphatic invasion	42.8	70.8	20.0	<.001
High risk	51.6	81.4	26.0	<.001
Positive margins	40.2	58.3	24.2	<.001
Adjuvant treatment, %				
Radiation therapy	60.2	87.2	37.0	<.001
Chemotherapy	18.3	33.7	5.0	<.001

Abbreviation: PNI, perineural invasion.

[a]Statistical comparisons are between PNI-positive and PNI-negative cases.

Table 2.

Frequency of Parotid Malignancies and Rates of Perineural Invasion.[a]

Histology	Total No.	PNI, No.	% PNI
Salivary duct carcinoma[b]	45	36	80.0
Mucoepidermoid (all)	44	14	31.8
High grade[b]	9	6	66.7
Intermediate grade	20	6	30.0
Low grade	12	1	8.3
Acinic cell carcinoma	26	6	23.1
Epithelial-myoepithelial carcinoma	13	0	0.0
Adenoid cystic carcinoma[b]	14	11	78.6
Adenocarcinoma[b]	10	8	80.0
Carcinoma NOS[b]	4	4	100.0
Basal cell adenocarcinoma	7	3	42.9
Carcinoma ex-PA[b]	5	0	0.0
Myoepithelial carcinoma	6	1	16.7
Low-grade cribiform cystadenocarcinoma	2	0	0.0
Hybrid carcinoma[b]	2	1	50.0
Large cell carcinoma[b]	1	0	0.0
Lymphoepithelial carcinoma[b]	1	0	0.0
Mammary analogue secretory carcinoma	2	0	0.0
Neoplasm NOS[b]	1	1	100.0
Leiomyosarcoma[b]	1	0	0.0
Neuroendocrine carcinoma[b]	1	0	0.0
Polymorphous low-grade adenocarcinoma	1	1	100.0
Total	186	86	46.2

Abbreviations: NOS, not otherwise specified; PA, pleomorphic adenoma; PNI, perineural invasion.

[a] Note that some mucoepidermoid carcinoma cases were not graded.

[b] Denotes high-risk histopathologic subtype.

Table 3.

Sensitivity, Specificity, and Positive and Negative Predictive Value of Preoperative Facial Nerve Weakness, Facial Numbness, Facial Pain and Intraoperative Facial Nerve Sacrifice to Pathologic Perineural Invasion.

	PNI+	**PNI−**	
Facial weakness	34	1	PPV = 97.1%
Normal motion	52	99	NPV = 65.6%
	Sensitivity = 39.5%	Specificity = 99.0%	
	PNI +	**PNI−**	
Facial anesthesia/paresthesia present	9	4	PPV = 69.2%
Facial anesthesia/paresthesia absent	77	96	NPV = 55.5%
	Sensitivity = 10.5%	Specificity = 96.0%	
	PNI+	**PNI−**	
Facial pain present	21	8	PPV = 72.4%
Facial pain absent	65	92	NPV = 58.6%
	Sensitivity = 24.4%	Specificity = 92.0%	
	PNI+	**PNI−**	
CN VII sacrificed	21	5	PPV = 80.8%
CN VII preserved	34	94	NPV = 73.4%
	Sensitivity = 38.2%	Specificity = 95.0%	

Abbreviations: CN, cranial nerve; NPV, negative predictive value; PNI, perineural invasion; PPV, positive predictive value.

Table 4.

Univariate Cox Proportional Hazard Regression Analysis of Overall and Disease-Free Survival.[a]

		Overall Survival		Disease-Free Survival	
Characteristic	**n**	**HR**	***P* Value**	**HR**	***P* Value**
Age >60 years	92	**3.14**	**<.001**	**1.76**	**.030**
Female	95	0.68	.161	**0.48**	**.006**
Facial weakness	35	**3.21**	**<.001**	**2.78**	**<.001**
Facial numbness	13	0.65	.556	0.73	.590
Facial pain	29	1.78	.079	**1.86**	**.040**
CN VII sacrifice	26	1.78	.124	**2.50**	**.007**
Radiation therapy	112	**1.86**	**.047**	**1.94**	**.025**
Chemotherapy	34	1.43	.290	**2.34**	**.003**
High-risk malignancy	96	**2.97**	**<.001**	**4.12**	**<.001**
Positive nodes	62	**3.04**	**<.001**	**3.49**	**<.001**
T classification 3/4	68	**2.05**	**<.001**	**3.02**	**<.001**
ALI present	62	**2.46**	**.004**	**3.68**	**<.001**
PNI present	86	**2.62**	**.001**	**4.18**	**<.001**
Positive margins	72	**2.21**	**.005**	**2.76**	**<.001**

Abbreviations: ALI, angiolymphatic invasion; CN, cranial nerve; HR, hazard ratio; PNI, perineural invasion.

[a]Bold numbers indicate statistical significance.

Table 5.

Multivariable Cox Proportional Hazard Regression Analysis of Overall and Disease-Free Survival.[a]

	OS		DFS	
Characteristic	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Age >60 years	**3.04 (1.65-5.58)**	**<.001**	1.18 (0.66-2.11)	.580
Chemotherapy			1.02 (0.49-2.10)	.970
Radiation therapy	**0.35 (0.14-0.88)**	**.025**	**0.26 (0.10-0.65)**	**.005**
High-risk type	1.87 (0.83-4.22)	.131	2.62 (0.93-7.33)	.068
Perineural invasion	1.62 (0.78-3.35)	.194	2.32 (0.94-5.77)	.069
Positive margins	1.68 (0.91-3.09)	.098	**2.16 (1.20-3.87)**	**.010**
Positive nodes	**2.13 (1.15-3.96)**	**.016**	**2.02 (1.10-3.70)**	**.023**
T classification 3/4	**1.85 (1.31-2.61)**	**<.001**	**2.06 (1.03-4.12)**	**.041**

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

[a]Note that angiolymphatic invasion excluded from analysis for high degree of multicollinearity. Bold numbers indicate statistical significance.