



Radiologic-Pathologic Correlation of Major vs. Minor Extranodal Extension in Oral Cavity Squamous Cell Carcinoma

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Abstract

Objective: We aim to evaluate the diagnostic performance of radiologic extranodal extension (rENE) in predicting major (>2mm) and minor ENE (<=2mm) pathologic ENE (pENE) and their differential prognostic value in patient with oral cavity squamous cell carcinoma (OCSCC).

Methods: All newly diagnosed OCSCC patients who underwent neck dissection with pathological nodal disease (pN+) treated between 2010-2015 were reviewed. Preoperative computed tomography (CT) and/or magnetic resonance (MR) imaging were reviewed for the presence of rENE. Sensitivity, specificity, and accuracy of rENE for pENE overall and for minor vs major pENE were calculated. Cox proportional hazards regression models were constructed to evaluate the prognostic significance of rENE and pENE on overall survival (OS).

Results: A total of 334 pN+ patients were eligible. ENE was present in 61 cases (18%), while pENE was identified in 157 (47%). The sensitivity and specificity of rENE were 37% [95%CI 29-44] and 98% [95%CI 96-100] respectively. The sensitivity of rENE for identifying major and minor pENE was 48% [95%CI 38-57] vs. 19% [95%CI 9-29], respectively (p<0.01). The presence of rENE was associated with inferior 3-year OS: 28% vs. 71% (p<0.01). In rENE-negative subset, major and minor pENE further stratified mortality risk (38% [95%CI 27-54] vs. 53% [95%CI 40-71], p<0.01). In multivariable analyses, rENE was an independent OS predictor [HR 1.84; 95%CI 1.24-2.74].

Conclusions: This large cohort study demonstrates high specificity, but low sensitivity for pre-operative imaging in the detection of pENE in patients with OCSCC. Sensitivity for pENE improved in the subset of patients with major ENE. Patients with rENE demonstrated poor OS, but the presence of pENE in the absence of rENE is still an adverse factor. Future research into improved methods of identifying pENE prior to surgery may help clinicians better counsel patients about treatment and prognosis.

Introduction

ENE has emerged as one of the most important adverse prognostic features in OCSCC, with implications for both adjuvant therapy and survival. Recent data suggest that classifying pENE into either major (>2mm invasion into surrounding tissue) or minor (≤2mm) may further stratify patients, with those having major pENE demonstrating worse disease-free survival.

As such, the ability to reliably identify major pENE on pre-treatment imaging may be critical. Although the sensitivity of rENE for identifying all types of pENE has been shown to be relatively poor, we aim to compare the sensitivity of rENE in patients with minor and major pENE and to better understand the significance of pENE in the absence of rENE.

Methods

A retrospective review was performed of pre-operative CT or MR imaging of all newly diagnosed OCSCC patients at the Princess Margaret Cancer Centre who had primary tumor resection and neck dissection for pathologically confirmed nodal disease between 2010-2015. Research ethics board approval was obtained. Exclusion criteria included poor imaging quality, a delay in surgery (>12 weeks from the time of imaging to surgery), or unavailability of pre-operative imaging.

Two head and neck neuroradiologists independently reviewed the presence of rENE on pre-operative imaging, defined as ill-defined lymph node borders. The presence and extent of pENE was reviewed by two head and neck pathologists using the AJCC 8th edition criteria.

Sensitivity, specificity, PPV, and NPV were calculated for rENE vs. pENE. Actuarial rate of OS was estimate using the Kaplan Meier method with log-ranks tests to compare mortality risk. Cox proportional hazard models were used to evaluate the prognostic significance of rENE and pENE adjusting for covariates.

Results

	n (%)
Age (mean, standard deviation)	62.3, 12.0
Sex	
M	215 (64)
F	119 (36)
ECOG Performance Status	
0	162 (48)
1	130 (39)
2	19 (6)
3	4 (1)
Unknown	19 (6)
Imaging Modality	
CT alone	180 (54)
MRI alone	118 (35)
CT + MRI	36 (11)
Subsite	
Oral tongue	168 (50)
Floor of mouth	72 (22)
Buccal	35 (10)
Mandibular alveolus	34 (10)
Maxillary alveolus	6 (2)
Mucosal lip	17 (5)
Palate	2 (1)
pENE	
None	117 (53)
Minor	58 (17)
Major	99 (30)
rENE	
cNO	57 (17)
rENE-	216 (65)
rENE+	61 (18)

Table 1 (above). Demographic and clinical characteristics of study cohort, n=334 patients.

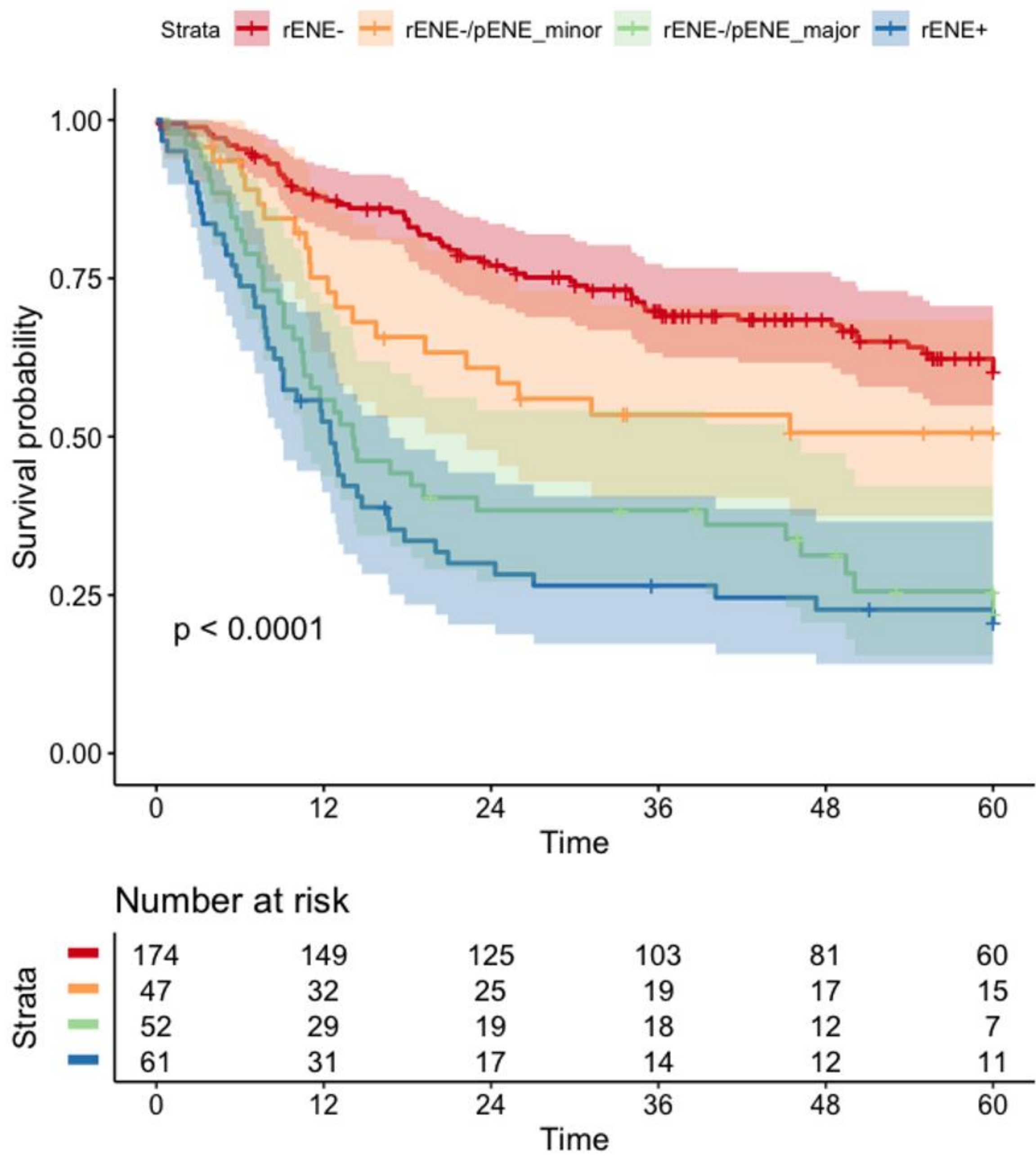


Figure 1 (left). Overall Survival for OSCC cohort stratified by both pENE and rENE status (rENE-, rENE-/pENE minor, rENE-/pENE major, rENE+). Vertical bar represents censoring event. Shaded area corresponds to 95% confidence interval.

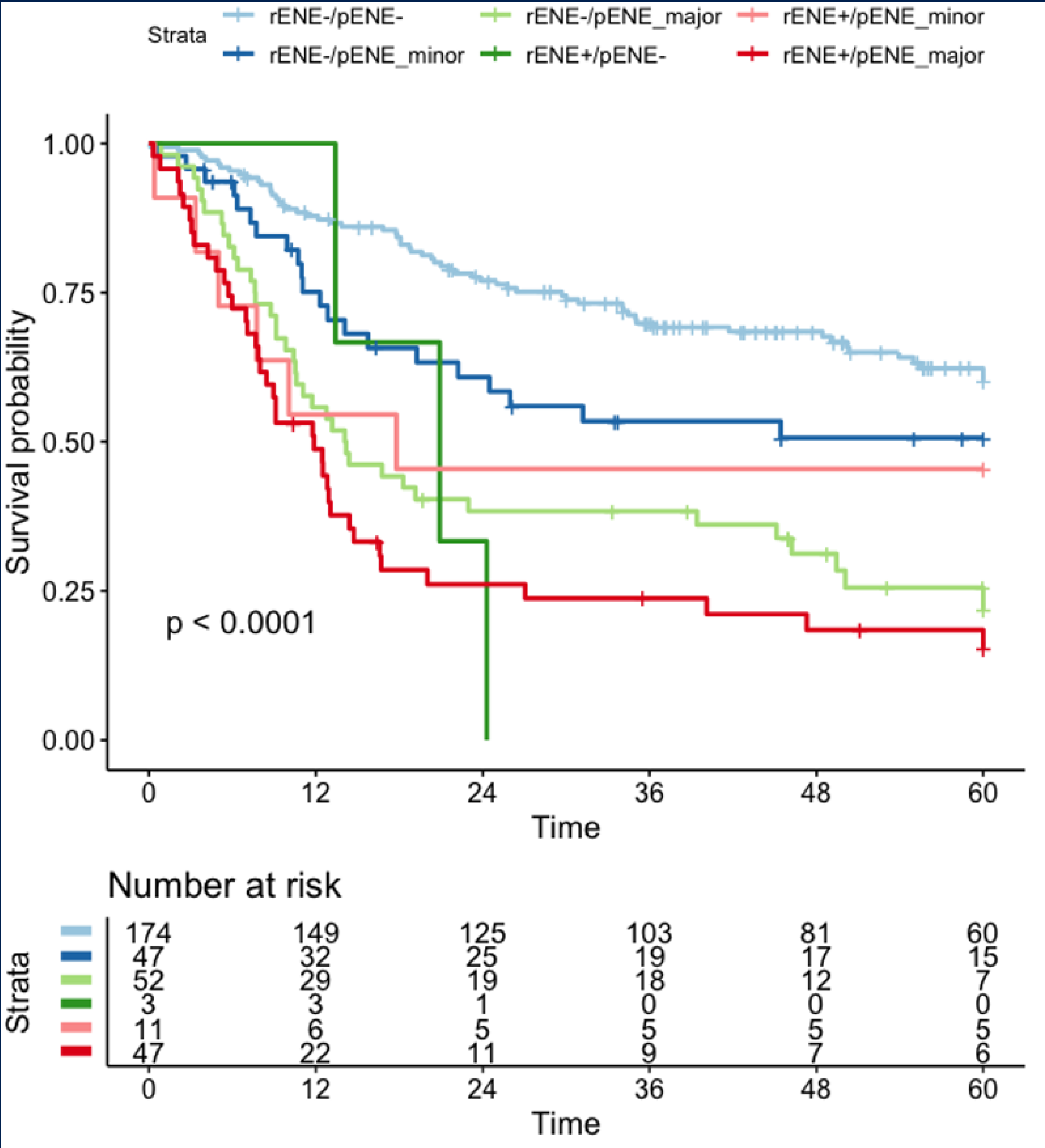


Figure 2 (right). Overall Survival for OSCC cohort stratified by both pENE and rENE status. Vertical bar represents censoring event.

	Major + Minor (n=157)	Major (n=99)	Minor (n=58)	p-value*
True Positive: n, (%)	58 (17)	47 (17)	11 (3)	-
True Negative: n, (%)	174 (52)	174 (63)	174 (74)	-
False Positive: n, (%)	3 (1)	3 (1)	3 (1)	-
False Negative: n, (%)	99 (30)	52 (19)	47 (20)	-
Sensitivity: %, [95%CI]	37 [29-44]	48 [38-57]	19 [9-29]	<0.01
Specificity: %, [95%CI]	98 [96-100]	98 [96-100]	98 [96-100]	1.00
PPV: %, [95%CI]	95 [90-100]	94 [87-100]	79 [57-100]	0.11
NPV: %, [95%CI]	63 [58-69]	77 [72-82]	78 [73-84]	0.73
Accuracy: %, [95%CI]	69 [65-74]	80 [75-85]	79 [73-84]	0.74

Table 2 (above). Diagnostic performance of rENE in pre-operative imaging at identifying major and minor pENE.

Table 3 (right). Cox proportional hazards model for OS by rENE and pENE.

	Unadjusted			Multivariable		
	HR	95%CI	p-value	aHR*	95%CI	p-value
MODEL 1 – including rENE						
rENE (yes vs. no)	2.73	[1.95-3.83]	<0.01	1.84	[1.24-2.74]	<0.01
MODEL 2 – including pENE						
pENE			<0.01			<0.01
None	1	REF		1	REF	
Minor	1.59	[1.01-1.25]		1.08	[0.60-1.94]	
Major	3.52	[2.52-4.94]		2.49	[1.52-4.06]	
MODEL 3 – including rENE + pENE						
rENE (yes vs. no)	1.50	[1.01-2.22]	0.04	1.43	[0.94-2.17]	0.09
pENE			<0.01			<0.01
None	1	REF		1	REF	
Minor	1.48	[0.93-2.33]		1.06	[0.59-1.92]	
Major	2.95	[2.00-4.34]		2.25	[1.34-3.79]	

Conclusions

Our data suggest that the presence of rENE is reliably predictive of pENE. This information may help treating teams counsel patients about likely adjuvant therapies that may be recommended. Not surprisingly, minor ENE is difficult to identify on pre-operative imaging, and the absence of imaging features of ENE does not rule out neither minor nor major pathologic ENE.

This large cohort study demonstrated excellent specificity and positive-predictive value in the detection of pENE using pre-operative imaging assessment of patients with surgically resected OCSCC. Sensitivity for pENE was greatly improved in patients with major pENE. Patients with major pENE formed a distinct subgroup with worse overall survival compared to the remainder of the cohort.