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Prognostic nomograms for lung neuroendocrine carcinomas based on lymph node ratio: a SEER database analysis

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Abstract

Objective: The current study aimed to explore the prognostic value of the lymph node ratio (LNR) in patients with lung neuroendocrine carcinomas (LNECs).

Methods: Data for 1564 elderly patients with LNECs between 1998 and 2016 were obtained from the Surveillance, Epidemiology, and End Results database. The cases were assigned randomly to training (n = 1086) and internal validation (n = 478) sets. The association between LNR and survival was investigated by Cox regression.

Results: Multivariate analyses identified age, tumor grade, summary stage, M stage, surgery, and LNR as independent prognostic factors for both overall survival (OS) and lung cancer-specific survival (LCSS). Tumor size was also a prognostic determinant for LCSS. Prognostic nomograms combining LNR with other informative variables showed good discrimination and calibration abilities in both the training and validation sets. In addition, the C-index of the nomograms was statistically superior to the American Joint Committee on Cancer (AJCC) staging system in both the training and validation cohorts.

Conclusions: These nomograms, based on LNR, showed superior prognostic predictive accuracy compared with the AJCC staging system for predicting OS and LCSS in patients with LNECs.

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Introduction

Lung neuroendocrine carcinomas (LNECs), including small cell carcinoma and large cell neuroendocrine carcinoma, are among the most lethal malignant tumors with aggressive clinical behavior and a poor prognosis.[1–5] However, neuroendocrine tumors of the lung can be diagnostically and prognostically challenging due to their morphologic overlap with other conditions and their complex and heterogeneous biological behaviors.[6–8] The identification of patients with LNECs who are at high risk of a poor prognosis will thus ensure the implementation of appropriate treatments and have a substantial impact on their prognosis.

Tumor nodal status is regarded as one of the most important prognostic markers for solid-organ malignant neoplasms and is an important element affecting therapeutic decision-making and the prognosis of various cancers.[9–11] The lymph node ratio (LNR), defined as the ratio of the number of positive lymph nodes (PLNs) to the total number of resected lymph nodes (RLNs), has become an important prognostic factor for solid tumors, as well as neuroendocrine carcinomas in other sites.[12–18] However, little information is available regarding the prognostic role of LNR in patients with LNECs. This study thus aimed to explore the associations of LNR with overall survival (OS) and lung cancer-specific survival (LCSS) in patients with LNECs, and to develop and validate new prognostic models to predict 3-, 5-, and 10-year OS and LCSS based on the Surveillance, Epidemiology, and End Results (SEER) database.

Methods

Study population

This retrospective study included patients with newly diagnosed LNECs according to positive histology from 1998 to 2016, based on the International Classification of Diseases for Oncology, 3rd Edition '(ICD-O-3)/WHO 2008' (Lung and Bronchus) and 'ICD-O-3 Hist/bahav' (8013/3, large-cell neuroendocrine carcinoma, 8246/3: Neuroendocrine carcinoma, NOS and 8574/3, adenocarcinoma with neuroendocrine differentiation). The methods of data collection and patient follow-up are available on the SEER database. We excluded patients with a history of other malignancies and unknown variables, including race/ethnicity, age at diagnosis, TNM stage, American Joint Committee on Cancer (AJCC stage), marital status, survival months, number of PLNs, and number of RLNs. The included patients were randomly assigned to a training group or a validation group.

Variables

The following variables were identified from the dataset: year of diagnosis (1998–2003, 2004–2010, 2011–2016), age at diagnosis (<60 or ≥60 years), race (White, Black, or other), marital status (married or unmarried), primary site (main bronchus, upper lobe, middle lobe, lower lobe,

and overlapping lesion of lung), laterality (left, right, or bilateral), grade (I/II or II/IV), SEER summary stage (localized, regional, or distant), tumor size (<3, 3–5, or >5 cm), AJCC stage (I/II or III/IV), T stage (T0/T1/T2 or T3/T4), N stage (N0/N1 or N2/N3), M stage (M0 or M1), surgery for primary site (no/unknown, wedge resection, lobectomy, or pneumonectomy), chemotherapy (yes or no/unknown), and radiotherapy (yes or no/unknown). The LNR was stratified into three risk groups by X-tile[19] (0.0, 0.0–0.2, and >0.2). The primary outcome of this study was OS and the secondary outcome was lung cancer-specific survival (LCSS). All the information in the SEER database has been de-identified and is freely available to the public, and no ethics committee approval for the analysis was therefore required. The authors signed a data-use agreement and obtained permission from the SEER program to use these data. The study was conducted according to the Declaration of Helsinki (as revised in 2013).

Statistical analysis

Categorical variables were reported as number and percentage and continuous measurements were presented as mean and range. Categorical variables were compared using χ^2 tests and continuous variables were compared using *t*-tests or Mann–Whitney U tests. Survival differences among different LNR groups were compared by Kaplan–Meier survival analysis and log-rank tests. Multivariate analyses were conducted using Cox regression analysis. A nomogram was formulated with potential risk factors ($P < 0.05$) based on results of multivariate analysis. A time-dependent receiver operating characteristic curve (td-ROC), calibration curve, and decision curve analysis (DCA) were calculated to evaluate the predictive performance of the prognostic nomograms. All statistical analyses were performed using R (version 3.4.3; www.r-project.org). A two-sided P value <0.05 was defined as statistically significant.

Results

Patient characteristics

From 1998 to 2016, 1564 patients with LNECs were included in the study and assigned randomly to a training group and a validation group at a ratio of 7:3 (training cohort, n = 1086; validation cohort, n = 478). There were no significant differences between the two sets, according to analysis of variance (Table 1). The median survival times were 38.0 (10.0, 82.0) months in the training set and 41.0 (11.0, 92.5) months in the validation set. Other clinical and pathological features are listed in Table 1.

Independent prognostic factors for OS

Univariate and multivariate analyses were performed to identify factors that were significantly associated with OS (Table 2). In the training cohort, year of diagnosis, age at diagnosis, sex, primary site, laterality, tumor grade, SEER summary stage, AJCC stage, T stage, N stage, M stage, tumor size, chemotherapy, surgery primary site, radiation, and LNR were significantly associated with OS in univariate analysis ($P < 0.05$), while age at diagnosis, tumor grade, summary stage, M stage, surgery for primary site, and LNR were also autonomous prognostic determinants for OS in multivariate analysis.

Kaplan–Meier survival curves demonstrated a significant association between poorer OS and an LNR >0.2, compared with groups with a lower LNR, in both the training and validation cohorts (Figure 1a, 1b).

Table 1. Clinicopathological characteristics of all patients.

Characteristic	Training set (n = 1086)	Validation set (n = 478)	P-value
Year of diagnosis, n (%)			0.411
1998–2003	291 (26.8)	127 (26.6)	
2004–2010	444 (40.9)	214 (44.8)	
2011–2016	351 (32.3)	137 (28.7)	
Age (years), n (%)			0.503
<60	374 (34.4)	173 (36.2)	
≥60	712 (65.6)	305 (63.8)	
Sex, male, n (%)	474 (43.6)	208 (43.5)	0.961
Race, n (%)			0.301
White	945 (87.0)	405 (84.7)	
Black	94 (8.7)	50 (10.5)	
Other	47 (4.3)	23 (4.8)	
Marital status, n (%)			0.517
Married	628 (57.8)	268 (56.1)	
Unmarried	458 (42.2)	210 (43.9)	
Primary site, n (%)			0.962
Main bronchus	40 (3.7)	19 (4.0)	
Upper lobe	500 (46.0)	209 (43.7)	
Middle lobe	94 (8.7)	48 (10.0)	
Lower lobe	325 (29.9)	156 (32.6)	
Overlapping lesion of lung	127 (11.7)	46 (9.7)	
Laterality, n (%)			0.688
Left	444 (40.9)	189 (39.5)	
Right	602 (55.4)	272 (56.9)	
Bilateral	40 (3.7)	17 (3.6)	
Histological grade, n (%)			0.503
Grade I/II	692 (63.7)	313 (65.5)	
Grade III/IV	394 (36.3)	165 (34.5)	
Summary stage, n (%)			0.499
Localized	435 (40.1)	197 (41.2)	
Regional	396 (36.5)	177 (37.0)	
Distant	255 (23.4)	104 (21.8)	
Tumor size, n (%)			0.316
<3 cm	606 (55.8)	262 (54.8)	
3–5 cm	222 (20.4)	85 (17.8)	
≥5 cm	258 (23.8)	131 (27.4)	
AJCC stage, n (%)			0.151
I/II	635 (58.5)	298 (62.3)	
III/IV	451 (41.5)	180 (37.7)	
T stage, n (%)			0.503
T0/T1/T2	826 (76.1)	356 (74.5)	
T3/T4	260 (23.9)	122 (25.5)	
N stage, n (%)			0.741
N0/N1	736 (67.8)	328 (68.6)	
N2/N3	350 (32.2)	150 (31.4)	

Table 1. Continued.

Characteristic	Training set (n = 1086)	Validation set (n = 478)	P-value
M stage, n (%)			0.323
M0	891 (82.0)	402 (84.1)	
M1	195 (18.0)	76 (15.9)	
Chemotherapy, n (%)			0.393
Yes	380 (35.0)	178 (37.2)	
No/unknown	706 (65.0)	300 (62.8)	
Surgery for primary site, n (%)			0.533
No/unknown	289 (26.6)	120 (25.1)	
Wedge resection	111 (10.2)	45 (9.4)	
Lobectomy	627 (57.7)	290 (60.7)	
Pneumonectomy	59 (5.5)	23 (4.8)	
Radiation, n (%)			0.635
Yes	256 (23.6)	118 (24.7)	
No/unknown	830 (76.4)	360 (75.3)	
RLN, mean (range)	6.8 (1–66)	6.8 (1–54)	0.965
PLN, mean (range)	0.8 (0–15)	0.7 (0–12)	0.199
LNR, n (%)			0.402
0	614 (56.5)	282 (59.0)	
0–0.2	98 (9.0)	40 (8.4)	
>0.2	374 (34.5)	156 (32.6)	
Survival months, M (1/4, 3/4)	38.0 (10.0, 82.0)	41.0 (11.0, 92.5)	0.065
OS, n (%)	591 (54.4)	258 (54.0)	0.871
LCSS, n (%)	476 (43.8)	194 (40.6)	0.233

AJCC, American Joint Committee on Cancer; RLN, resected lymph node; PLN, positive lymph node; LNR, lymph node ratio; OS, overall survival; LCSS, lung cancer-specific survival.

Table 2. Univariate and multivariate analyses of factors associated with overall survival.

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P	HR (95%CI)	P-value
Year of diagnosis				
1998–2003	Ref.	–	Ref.	–
2004–2010	0.59 (0.49–0.71)	<0.001	0.84 (0.69–1.31)	0.164
2011–2016	0.52 (0.42–0.66)	<0.001	0.69 (0.54–1.06)	0.068
Age, years				
<60	Ref.	–	Ref.	–
≥60	1.85 (1.54–2.23)	<0.001	1.53 (1.26–1.85)	<0.001
Sex, male	1.61 (1.37–1.89)	<0.001	1.58 (0.93–1.96)	0.096
Race				
White	0.94 (0.63–1.41)	0.779		
Black	1.22 (0.77–1.96)	0.400		
Other	Ref.	–		
Marital status				
Married	0.90 (0.76–1.06)	0.192		
Unmarried	Ref.	–		

Table 2. Continued.

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P	HR (95%CI)	P-value
Primary site				
Main bronchus	0.45 (0.28–0.73)	0.001	0.90 (0.54–1.50)	0.693
Upper lobe	0.50 (0.40–0.63)	<0.001	1.14 (0.86–1.51)	0.376
Middle lobe	0.28 (0.19–0.41)	<0.001	1.11 (0.71–1.74)	0.642
Lower lobe	0.33 (0.25–0.42)	<0.001	1.15 (0.83–1.58)	0.401
Overlapping lesion of lung	Ref.	–	Ref.	–
Laterality				
Left	0.33 (0.23–0.48)	<0.001	1.03 (0.66–1.59)	0.910
Right	0.40 (0.28–0.57)	<0.001	1.30 (0.84–2.00)	0.241
Bilateral	Ref.	–	Ref.	–
Histological grade				
Grade I/II	Ref.	–	Ref.	–
Grade III/IV	2.05 (1.74–2.41)	<0.001	1.76 (1.48–2.10)	<0.001
Summary stage				
Localized	Ref.	–	Ref.	–
Regional	2.43 (1.97–3.00)	<0.001	1.38 (1.01–1.91)	0.048
Distant	7.58 (6.10–9.43)	<0.001	1.67 (1.03–2.71)	0.039
Tumor size				
<3 cm	Ref.	–	Ref.	–
3–5 cm	1.29 (1.04–1.60)	0.021	0.88 (0.70–1.10)	0.267
≥5 cm	3.09 (2.57–3.71)	<0.001	1.42 (0.92–1.75)	0.059
AJCC stage				
I/II	Ref.	–	Ref.	–
III/IV	4.04 (3.42–4.78)	<0.001	1.27 (0.90–1.81)	0.179
T stage				
T0/T1/T2	Ref.	–	Ref.	–
T3/T4	2.79 (2.35–3.31)	<0.001	1.08 (0.86–1.37)	0.505
N stage				
N0/N1	Ref.	–	Ref.	–
N2/N3	4.22 (3.57–4.98)	<0.001	1.04 (0.73–1.47)	0.846
M stage				
M0	Ref.	–	Ref.	–
M1	4.88 (4.05–5.87)	<0.001	1.57 (1.13–2.18)	0.007
Chemotherapy				
Yes	0.44 (0.37–0.51)	<0.001	0.89 (0.73–1.09)	0.259
No/unknown	Ref.	–	Ref.	–
Surgery for primary site				
No/unknown	Ref.	–	Ref.	–
Wedge resection	0.33 (0.26–0.44)	<0.001	0.57 (0.41–0.78)	<0.001
Lobectomy	0.17 (0.14–0.20)	<0.001	0.39 (0.29–0.52)	<0.001
Pneumonectomy	0.30 (0.21–0.43)	<0.001	0.60 (0.39–0.91)	0.015
Radiation				
Yes	2.39 (2.01–2.83)	<0.001	0.78 (0.63–1.07)	0.127
No/unknown	Ref.	–	Ref.	–

Table 2. Continued.

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P	HR (95%CI)	P-value
LNR				
0	Ref.	–	Ref.	–
0–0.2	1.64 (1.21–2.21)	0.001	1.17 (0.81–1.69)	0.403
>0.2	4.09 (3.44–4.87)	<0.001	1.57 (1.14–2.17)	0.006

HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; LNR, lymph node ratio.

Development and validation of prognostic nomogram for OS

Based on the results of multivariate analysis, we formulated a prognostic nomogram to predict 3-, 5-, and 10-year OS in the training cohort (Figure 1c). td-ROC analyses (Figure 1d, 1e) revealed that the prognostic nomogram could accurately predict 3-year (area under the curve [AUC] = 0.821), 5-year (AUC = 0.857), and 10-year (AUC = 0.870) OS in the training set, and 3-year (AUC = 0.876), 5-year (AUC = 0.874), and 10-year (AUC = 0.876) OS in the validation set in patients with LNECs. The calibration curves of the survival nomogram are shown in Figure 2a–2f. The plots were close to the 45° line, indicating that the survival nomogram was well-calibrated in the training and validation sets.

Development and validation of prognostic nomogram for LCSS

Multivariate analysis identified age at diagnosis, tumor grade, summary stage, M stage, surgery for primary site, tumor size, and LNR as autonomous prognostic determinants for LCSS in the training cohort (Table 3). Moreover, Kaplan–Meier curves also demonstrated a significant association between poorer LCSS and an LNR >0.2 compared with groups with a lower LNR, in both the training and validation cohorts (Figure 3a, 3b).

Based on the results of multivariate analysis, we formulated a prognostic nomogram to predict 3-, 5-, and 10-year LCSS in the training cohort (Figure 3c). td-ROC analyses (Figure 3d, 3e) revealed that the prognostic nomogram could accurately predict 3-year (AUC = 0.855), 5-year (AUC = 0.866), and 10-year (AUC = 0.876) LCSS in the training set, and 3-year (AUC = 0.895), 5-year (AUC = 0.905), and 10-year (AUC = 0.884) LCSS in the validation set in patients with LNECs. The calibration curves of the survival nomogram are shown in Figure 4a–4f. The plots were very close to the 45° line, indicating that the survival nomogram was well-calibrated in the training and validation sets.

Comparison with AJCC TNM staging system

The C-index of the nomogram for OS in the training cohort was 0.834 (95% confidence interval [CI]: 0.810–0.858), which was significantly higher than that of the AJCC TNM staging system (0.702, 95% CI: 0.670–0.733). The C-index of the current nomogram for OS (0.874, 95% CI: 0.843–0.905) remained superior to that of the AJCC staging system (0.723, 95% CI: 0.677–0.768) in the validation cohort. Moreover, the nomogram for LCSS performed better than the AJCC staging system in the training set (0.844 vs. 0.725) as well as in the validation set (0.861 vs. 0.756).
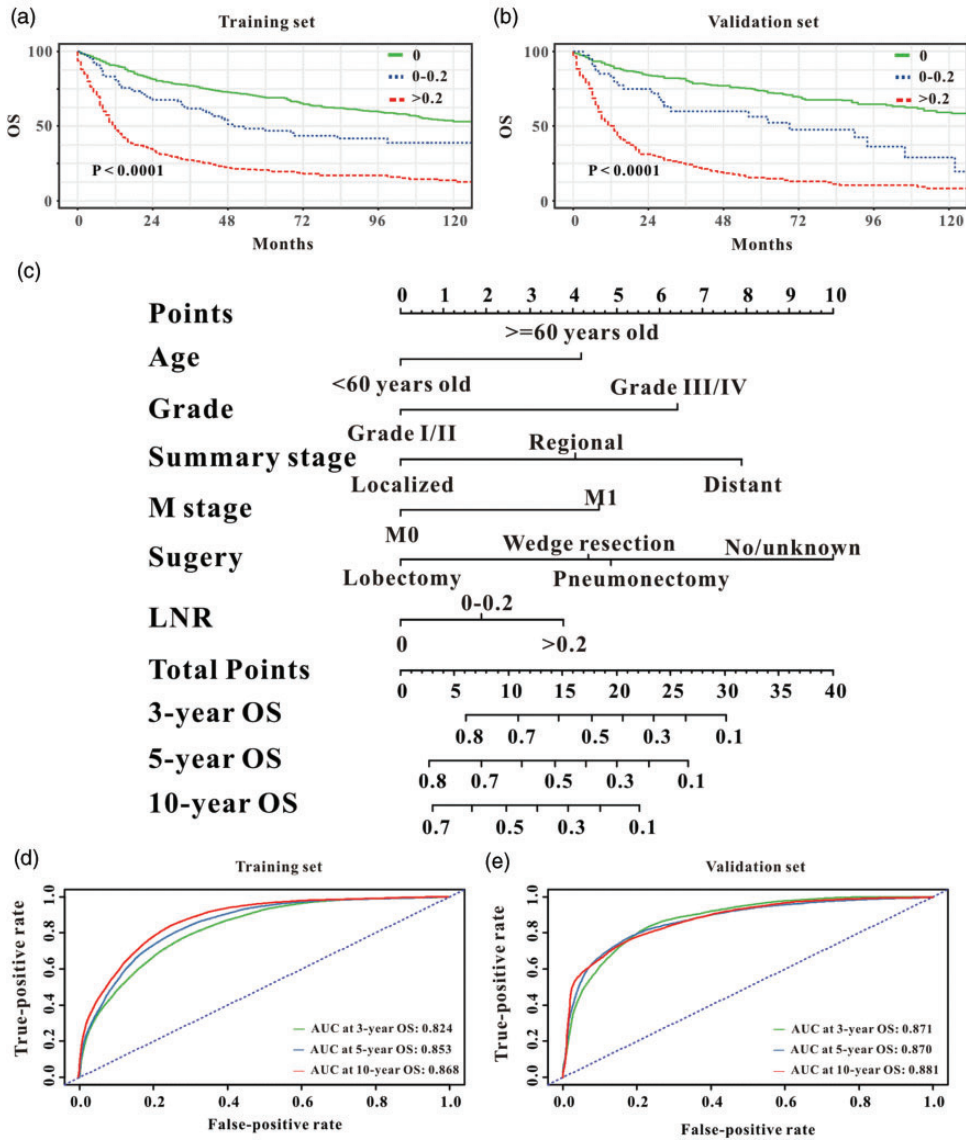
Figure 1. Prognostic importance of lymph node ratio (LNR) in patients with lung neuroendocrine carcinomas. Kaplan–Meier curves for overall survival (OS) for all patients stratified by LNR in the (a) training and (b) validation cohorts. Prediction of 3-year, 5-year, and 10-year OS (c) in patients with LNECs using a survival nomogram. Predictive ability of survival nomograms measured by time-dependent receiver operating characteristic (td-ROC) curves. td-ROC curves for 3-year, 5-year, and 10-year OS in patients in the (d) training and (e) validation cohorts.

In DCA, the current nomograms presented greater net benefits and a wider field of threshold probability compared with the AJCC staging system for both OS and LCSS in the training (Figure 5a, 5c) and validation cohorts

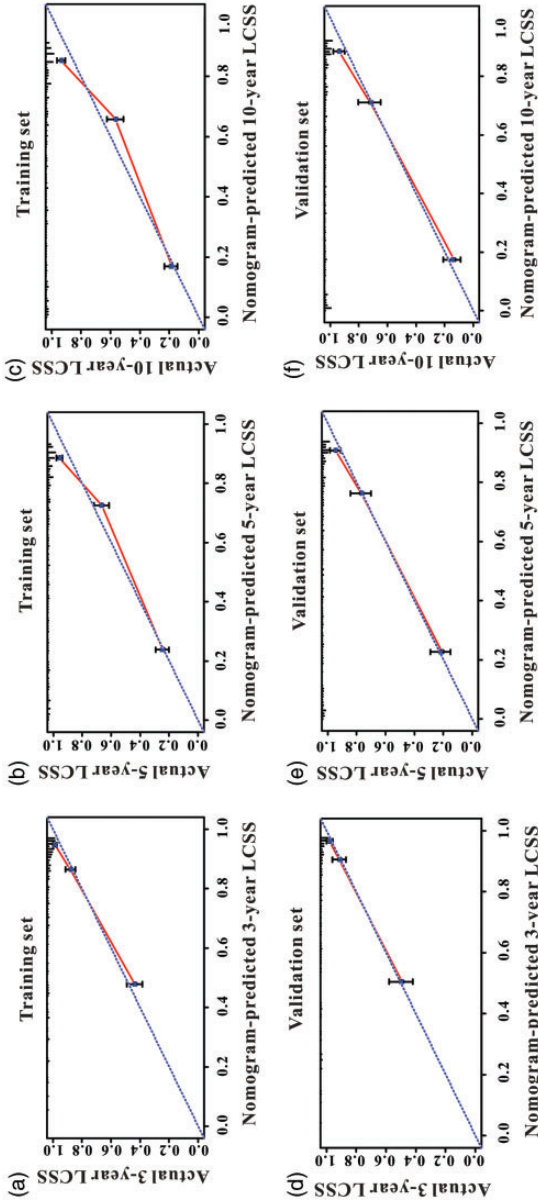**Figure 2.** Calibration curves for predicting overall survival (OS) in the training (a–c) and validation sets (d–f).
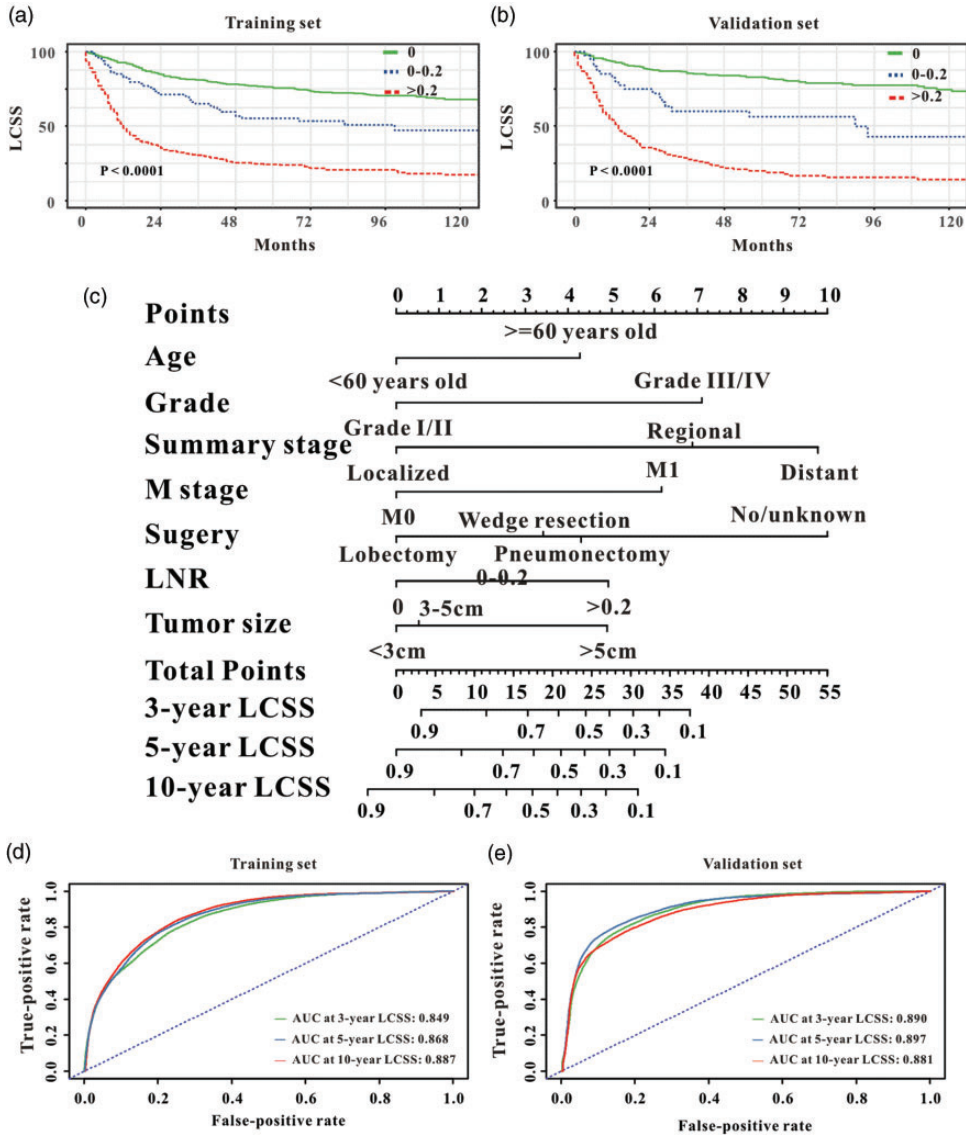
Figure 3. Prognostic importance of lymph node ratio (LNR) in patients with lung neuroendocrine carcinomas. Kaplan–Meier curves for LCSS for all patients stratified by LNR in the (a) training and (b) validation cohorts. Prediction of 3-year, 5-year, and 10-year LCSS (c) in patients with LNECs using a survival nomogram. Predictive ability of survival nomograms measured by time-dependent receiver operating characteristic (td-ROC) curves. td-ROC curves for 3-year, 5-year, and 10-year LCSS in patients in the (d) training and (e) validation cohorts.

(Figure 5b, 5d), indicating that these nomograms had superior predictive abilities for the prognosis of patients with LNECs. A higher threshold probability resulted in a more robust estimation of decision results. The results indicated that the formulated nomograms provided better predictions of survival in patients with LNECs.
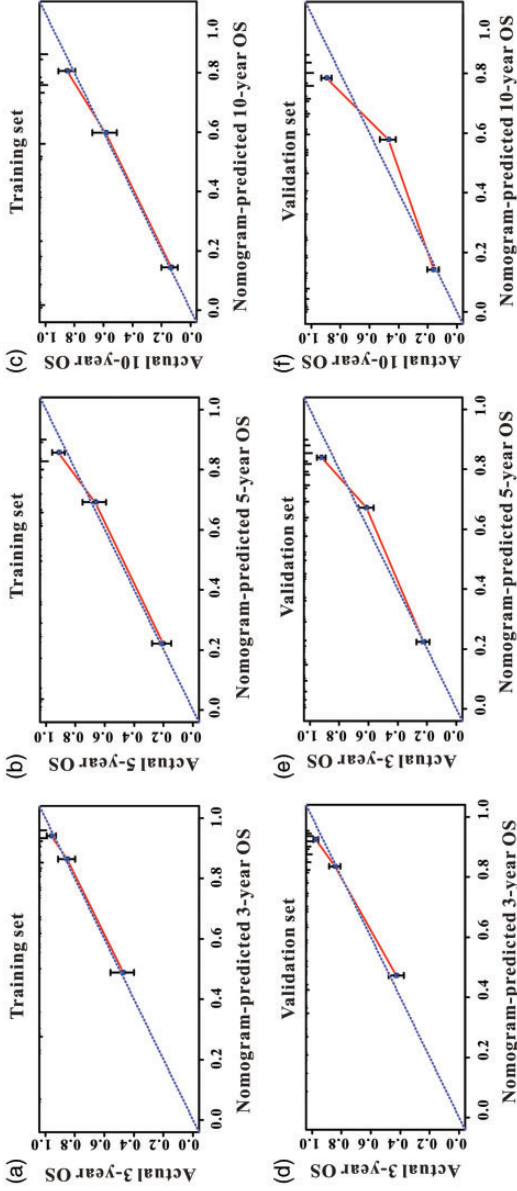
Figure 4. Calibration curves for predicting overall survival (OS) and lung cancer-specific survival (LCSS) in the training and validation sets. The 3-year, 5-year, and 10-year OS calibration plots in the (a–c) training and (d–f) validation cohorts.

Table 3. Univariate and multivariate analyses of factors associated with lung cancer-specific survival.

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P	HR (95%CI)	P-value
Year of diagnosis				
1998–2003	Ref.	–	Ref.	–
2004–2010	0.55 (0.45–0.67)	<0.001	0.79 (0.64–1.28)	0.133
2011–2016	0.53 (0.41–0.67)	<0.001	0.63 (0.46–1.04)	0.054
Age, years				
<60	Ref.	–	Ref.	–
≥60	1.79 (1.46–2.20)	<0.001	1.49 (1.21–1.85)	<0.001
Sex, male	1.59 (1.33–1.91)	<0.001	1.53 (0.75–2.84)	0.167
Race				
White	0.87 (0.56–1.33)	0.514		
Black	1.17 (0.71–1.94)	0.536		
Other	Ref.	–		
Marital status				
Married	0.94 (0.78–1.13)	0.515		
Unmarried	Ref.	–		
Primary site				
Main bronchus	0.51 (0.31–0.83)	0.007	0.96 (0.57–1.63)	0.878
Upper lobe	0.47 (0.37–0.60)	<0.001	1.10 (0.81–1.48)	0.548
Middle lobe	0.22 (0.14–0.34)	<0.001	0.93 (0.56–1.55)	0.784
Lower lobe	0.29 (0.22–0.39)	<0.001	1.11 (0.79–1.56)	0.561
Overlapping lesion of lung	Ref.	–	Ref.	–
Laterality				
Left	0.34 (0.23–0.51)	<0.001	1.16 (0.72–1.85)	0.545
Right	0.40 (0.27–0.59)	<0.001	1.48 (0.93–2.36)	0.097
Bilateral	Ref.	–	Ref.	–
Histological grade				
Grade I/II	Ref.	–	Ref.	–
Grade III/IV	2.10 (1.75–2.51)	<0.001	1.75 (1.44–2.12)	<0.001
Summary stage				
Localized	Ref.	–	Ref.	–
Regional	3.35 (2.58–4.34)	<0.001	1.72 (1.18–2.51)	0.005
Distant	11.02 (8.47–14.33)	<0.001	1.96 (1.14–3.38)	0.015
Tumor size				
<3 cm	Ref.	–	Ref.	–
3–5 cm	1.51 (1.18–1.92)	0.001	0.99 (0.77–1.27)	0.945
>5 cm	3.67 (2.99–4.51)	<0.001	1.50 (1.19–1.89)	<0.001
AJCC stage				
I/II	Ref.	–	Ref.	–
III/IV	5.15 (4.24–6.25)	<0.001	1.23 (0.84–1.81)	0.293
T stage				
T0/T1/T2	Ref.	–	Ref.	–
T3/T4	3.24 (2.69–3.90)	<0.001	1.12 (0.87–1.43)	0.382
N stage				
N0/N1	Ref.	–	Ref.	–
N2/N3	5.22 (4.34–6.28)	<0.001	1.13 (0.77–1.66)	0.524

(continued)

Table 3. Continued.

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P	HR (95%CI)	P-value
M stage				
M0	Ref.	–	Ref.	–
M1	5.62 (4.61–6.85)	<0.001	1.70 (1.20–2.40)	0.003
Chemotherapy				
Yes	0.36 (0.30–0.43)	<0.001	0.94 (0.75–1.17)	0.577
No/unknown	Ref.	–	Ref.	–
Surgery for primary site				
No/unknown	Ref.	–	Ref.	–
Wedge resection	0.26 (0.19–0.36)	<0.001	0.51 (0.36–0.73)	<0.001
Lobectomy	0.14 (0.11–0.17)	<0.001	0.43 (0.31–0.59)	<0.001
Pneumonectomy	0.28 (0.19–0.42)	<0.001	0.64 (0.40–0.91)	0.036
Radiation				
Yes	2.76 (2.29–3.32)	<0.001	0.85 (0.68–1.07)	0.167
No/unknown	Ref.	–	Ref.	–
LNR				
0	Ref.	–	Ref.	–
0–0.2	1.91 (1.36–2.69)	<0.001	1.13 (0.75–1.71)	0.557
>0.2	5.20 (4.26–6.34)	<0.001	1.61 (1.13–2.29)	0.008

HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; LNR, lymph node ratio.

Discussion

The current study aimed to evaluate the association between LNR and survival status in patients with LNECs. To the best of our knowledge, this is the first study to demonstrate that elevated LNR may be an independent prognostic factor for OS, as well as LCSS, in patients with LNECs. Notably, survival nomograms incorporating LNR and other significant clinical variables showed good ability for predicting OS and LCSS in patients with LNECs.

Lymph node involvement is regarded as one of the most important indicators informing therapeutic decision-making and the prognosis of patients with malignant tumors. Norifumi et al. demonstrated that lymph node metastasis was significantly associated with disease-free survival in a retrospective study of 95 consecutive patients with pancreatic neuroendocrine tumors undergoing pancreatic resection, and patients required lymph node dissection to improve prognosis.[20] Using data from the National Cancer Database and SEER database, Adam et al. concluded that the number of positive locoregional lymph nodes was an independent prognostic factor in patients with colon neuroendocrine tumors, and they developed a new nodal staging system that could predict survival more accurately than current staging systems.[21] In the current study, LNR was considered an independent predictive factor for OS and LCSS in 1564 patients with LNECs, based on univariate and multivariate analyses. We then generated two prognostic nomograms by combining LNR with other informative clinical features, which showed good predictive values for OS and LCSS, respectively, in patients with LNECs.

The AJCC staging system has been widely used for prognostic prediction in
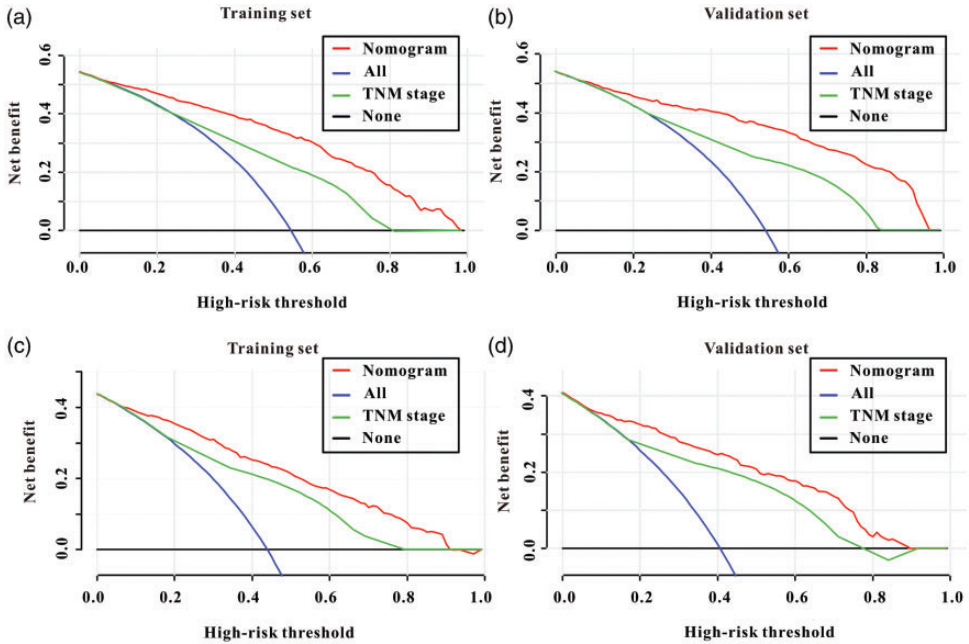
Figure 5. Decision curve analysis (DCA) of survival nomograms to determine their clinical use. DCA of survival nomogram for overall survival in the (a) training and (b) validation sets. DCA of lung cancer-specific survival nomogram in the (c) training and (d) validation sets.

patients with lung cancer and other malignant tumors.[22–25] However, previous studies have shown that lymph node status in the AJCC staging system might not adequately reflect the extent of disease, due to the influence of surgery.[26] LNR, which reflects not only nodal disease but also the quality and extent of lymphadenectomy, has recently been demonstrated to be a good prognostic factor for malignant tumors.[26–29] Li et al. reported that patients with gastric neuroendocrine tumors with an LNR >0.132 had an increased likelihood of all-cause mortality and cancer-specific death compared with patients with an LNR value ≤0.132.[30] The prognostic significance of LNR was also verified in a retrospective study of 1778 patients with resected N2 stage lung squamous cell carcinoma.[31] Consistent with those results, our study also suggested that a higher LNR value was

associated with poorer OS and LCSS in patients with LNECs. In addition, we combined LNR with other significant variables to create survival nomograms, which showed better predictive abilities for OS and LCSS compared with the AJCC staging system, implying that these combined indexes might be useful for accurately predicting the prognosis in patients with LNECs.

As an easy-to-use statistical predictive instrument, nomograms can digitize risk by creating an intuitive graph and have been widely used in clinical practice.[32–35] A nomogram merging some conducive variables is a readily accessible tool to help clinicians clarify a diagnosis,[32] predict survival,[36] and decide the follow-up interval for their patients.[37] In the current study, we successfully created two survival nomograms based on the LNR and other

informative factors to predict OS and LCSS in patients with LNECs. These survival nomograms achieved better predictive performances than the AJCC staging system, as reflected by the C-index and DCA curves for both the training and validation sets. These survival nomograms might thus be applied in a clinical setting to reliably predict OS and LCSS in patients with LNECs.

This study had some limitations. First, it was a retrospective study using data from the SEER database and may have selection bias due to the ethnic homogeneity of the patient population. Second, some prognostic factors, including serum tumor markers, vascular infiltration, laboratory results, and detailed treatment strategies, which may have had an impact on patient prognosis, were not accessible in the SEER database. Moreover, the limitations of the SEER database meant that we could not obtain information on the exact chemotherapeutic drugs used for LNEC patients. In addition, patients were first diagnosed with LNECs over a considerable period of time and chemotherapy drugs may change over time. We therefore classified chemotherapy as performed or not to investigate its prognostic role for LNECs, but this might not be an accurate reflection of the role of chemotherapy. This might also explain why chemotherapy and radiotherapy were not included in the final nomogram for the prognosis of LNEC patients. Finally, although the prognostic nomograms performed better than the AJCC staging system in the current study, further studies are needed to validate our survival nomograms in patients with LNECs.

Conclusions

The novel survival nomograms provide an applicable tool with good discrimination and calibration abilities for predicting the prognosis of LNECs. These nomograms may have superior prognostic capabilities for patients with LNECs compared with the current AJCC staging system. Further studies are needed to validate and improve this model.

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References

1. Dasari A, Mehta K, Byers LA, et al. Comparative study of lung and extrapulmonary poorly differentiated neuroendocrine carcinomas: A SEER database analysis of 162,983 cases. *Cancer* 2018; 124: 807–815.
2. Deng C, Wu SG and Tian Y. Lung large cell neuroendocrine carcinoma: an analysis of patients from the Surveillance, Epidemiology, and End-Results (SEER) database. *Med Sci Monit* 2019; 25: 3636–3646.
3. Gu J, Gong D, Wang Y, et al. The demographic and treatment options for patients with large cell neuroendocrine carcinoma of the lung. *Cancer Med* 2019; 8: 2979–2993.
4. Oliver AL. Lung cancer: epidemiology and screening. *Surg Clin North Am* 2022; 102: 335–344.

5. Frost N, Griesinger F, Hoffmann H, et al. Lung cancer in Germany. *J Thorac Oncol* 2022; 17: 742–750.

6. Galffy G. [Diagnosis and treatment of the neuroendocrine tumors of the lung]. *Magy Onkol* 2018; 62: 113–118.

7. Zombori T, Juhasz-Nagy G, Tiszlavicz L, et al. [Large-cell neuroendocrine carcinoma of the lung – challenges of diagnosis and treatment]. *Orv Hetil* 2020; 161: 313–319.

8. Scoazec JY. Lung and digestive neuroendocrine neoplasms. From WHO classification to biomarker screening: which perspectives?. *Ann Endocrinol (Paris)* 2019; 80: 163–165.

9. Dijksterhuis W, Hulshoff JB, Van Dullemen HM, et al. Reliability of clinical nodal status regarding response to neoadjuvant chemoradiotherapy compared with surgery alone and prognosis in esophageal cancer patients. *Acta Oncol* 2019; 58: 1640–1647.

10. Dutta SW, Volaric A, Morgan JT, et al. Pathologic evaluation and prognostic implications of nodal micrometastases in breast cancer. *Semin Radiat Oncol* 2019; 29: 102–110.

11. Leong SP, Zuber M, Ferris RL, et al. Impact of nodal status and tumor burden in sentinel lymph nodes on the clinical outcomes of cancer patients. *J Surg Oncol* 2011; 103: 518–530.

12. Occhionorelli S, Andreotti D, Vallese P, et al. Evaluation on prognostic efficacy of lymph nodes ratio (LNR) and log odds of positive lymph nodes (LODDS) in complicated colon cancer: the first study in emergency surgery. *World J Surg Oncol* 2018; 16: 186.

13. Elhusseiny KM, Abd-Elhay FA, Kamel MG, et al. Examined and positive lymph nodes counts and lymph nodes ratio are associated with survival in major salivary gland cancer. *Head Neck* 2019; 41: 2625–2635.

14. Xiao C, Song B, Yi P, et al. Deaths of colon neuroendocrine tumors are associated with increasing metastatic lymph nodes and lymph node ratio. *J Gastrointest Oncol* 2020; 11: 1146–1154.

15. Gaitanidis A, Patel D, Nilubol N, et al. A lymph node ratio-based staging model is superior to the current staging system for pancreatic neuroendocrine tumors. *J Clin Endocrinol Metab* 2018; 103: 187–195.

16. Wu L, Chen F, Chen S, et al. The lymph node ratio optimizes staging in patients with small intestinal neuroendocrine tumors. *Neuroendocrinology* 2018; 107: 209–217.

17. Liao Y, Yin G and Fan X. The positive lymph node ratio predicts survival in T1-4N1-3M0 non-small cell lung cancer: A nomogram using the SEER database. *Front Oncol* 2020; 10: 1356.

18. Liao Y, Wang X, Zhong P, et al. A nomogram for the prediction of overall survival in patients with stage II and III non-small cell lung cancer using a population-based study. *Oncol Lett* 2019; 18: 5905–5916.

19. Camp RL, Dolled-Filhart M and Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cutpoint optimization. *Clin Cancer Res* 2004; 10: 7252–7259.

20. Harimoto N, Hoshino K, Muranushi R, et al. Significance of lymph node metastasis in resectable well-differentiated pancreatic neuroendocrine tumor. *Pancreas* 2019; 48: 943–947.

21. Fields AC, Mccarty JC, Lu P, et al. Colon neuroendocrine tumors: A new lymph node staging classification. *Ann Surg Oncol* 2019; 26: 2028–2036.

22. Kutob L and Schneider F. Lung cancer staging. *Surg Pathol Clin* 2020; 13: 57–71.

23. Feng SH and Yang ST. The new 8th TNM staging system of lung cancer and its potential imaging interpretation pitfalls and limitations with CT image demonstrations. *Diagn Interv Radiol* 2019; 25: 270–279.

24. Eggermont A, Blank CU, Mandala M, et al. Prognostic and predictive value of AJCC-8 staging in the phase III EORTC1325/KEYNOTE-054 trial of pembrolizumab vs placebo in resected high-risk stage III melanoma. *Eur J Cancer* 2019; 116: 148–157.

25. Zhang Y, Shang L, Zhang PP, et al. Clinicopathological features and prognostic validity of the European Neuroendocrine Tumor Society (ENETS) and American Joint Committee on Cancer (AJCC) 8th staging systems in colonic neuroendocrine neoplasms. *Cancer Med* 2019; 8: 5000–5011.

26. Lei L, Tan L, Zhao X, et al. A prognostic nomogram based on lymph node ratio for postoperative vulvar squamous cell carcinoma from the Surveillance, Epidemiology, and End Results database: a retrospective cohort study. *Ann Transl Med* 2020; 8: 1382.

27. Teng J, Abdygametova A, Du J, et al. Bayesian inference of lymph node ratio estimation and survival prognosis for breast cancer patients. *IEEE J Biomed Health Inform* 2020; 24: 354–364.

28. Yao W, Lu N, Cui M, et al. [Positive lymph node ratio >/=0.16 is an independent risk factor affecting the prognosis of patients with esophageal cancer]. *Nan Fang Yi Ke Da Xue Bao* 2020; 40: 837–842.

29. Lei BW, Hu JQ, Yu PC, et al. Lymph node ratio (LNR) as a complementary staging system to TNM staging in salivary gland cancer. *Eur Arch Otorhinolaryngol* 2019; 276: 3425–3434.

30. Li J, Lin Y, Wang Y, et al. Prognostic nomogram based on the metastatic lymph node ratio for gastric neuroendocrine tumour: SEER database analysis. *ESMO Open* 2020; 5: e000632.

31. Bi G, Lu T, Yao G, et al. The prognostic value of lymph node ratio in patients with N2 stage lung squamous cell carcinoma: a nomogram and heat map approach. *Cancer Manag Res* 2019; 11: 9427–9437.

32. He Y, Zhu Z, Chen Y, et al. Development and validation of a novel diagnostic nomogram to differentiate between intestinal tuberculosis and Crohn's disease: a 6-year prospective multicenter study. *Am J Gastroenterol* 2019; 114: 490–499.

33. Dong YM, Sun J, Li YX, et al. Development and validation of a nomogram for assessing survival in patients with COVID-19 pneumonia. *Clin Infect Dis* 2021; 72: 652–660.

34. Jiang X, Su Z, Wang Y, et al. Prognostic nomogram for acute pancreatitis patients: An analysis of publicly electronic healthcare records in intensive care unit. *J Crit Care* 2019; 50: 213–220.

35. Su TW, Zhong X, Ye L, et al. A nomogram for predicting the presence of germline mutations in pheochromocytomas and paragangliomas. *Endocrine* 2019; 66: 666–672.

36. Jiang Y, Yuan Q, Lv W, et al. Radiomic signature of (18)F fluorodeoxyglucose PET/CT for prediction of gastric cancer survival and chemotherapeutic benefits. *Theranostics* 2018; 8: 5915–5928.

37. Yang Z, Gao Y, Fan X, et al. A multivariate prediction model for high malignancy potential gastric GI stromal tumors before endoscopic resection. *Gastrointest Endosc* 2020; 91: 813–822.