Association of Post-Operative Radiotherapy With Survival in Resected N2 Non-Small Cell Lung Cancer Patients with Chemotherapy

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Abstract

Backgroup

The current staging system for completely resected pathologic N2 non-small-cell lung cancer (NSCLC) treated with chemotherapy is not suitable for predicting those patients most likely to benefit or not from post-operative radiotherapy (PORT). This study aimed to construct a survival prediction model that will enable individualized predictions of the net survival difference of PORT.

Methods

A total of 3094 cases between 2002 and 2014 were extracted from the Surveillance, Epidemiology, and End Results databases. Patient characteristics were included as covariates, and their association for overall survival (OS) with and witout PORT was assessed. Externally validate data of 602 patients were included from China.

Results

Age, gender, examined lymph node, positive lymph node, tumor size, extent of surgery, and visceral pleural invasion were significantly associated with OS ($P < .05$). The two nomograms were developed based on clinical variables to estimate an individual's net survival difference attributable to PORT. The calibration curve for OS showed great agreement between prediction by survival prediction model and actual observation. In the training cohort, the C-index for OS was 0.619 (95% CI, 0.598-0.641) in the PORT group and 0.627 (95% CI, 0.605-0.648) in the non-PORT group. We found that PORT could improve OS (HR, 0.861; $P = 0.044$) for patients with a positive PORT net survival difference.

Conclusions

We established a practical survival prediction model that can be used to make individualized estimate of the net survival difference of PORT and without PORT in patients with completely resected N2 NSCLC, treated with chemotherapy.

Background

The most generally diagnosed cancer is lung cancer, which is the leading cause of cancer based death (18.4% of total cancer deaths) worldwide.[1] Patients with resected pathologic N2 non-small-cell lung cancer (NSCLC) are a high risk group for regional recurrence and metastasis even with complete resection [2]. Adjuvant chemotherapy is now recommended as standard for those patients according to the NCCN (National Comprehensive Cancer Network) guidelines.[3] Two large databases including SEER [4] and NCBD [5] suggest that post-operative radiotherapy (PORT) can improve survival for patients with resected pathologic N2 NSCLC. Some meta-analysis studies [6, 7] also demonstrated a benefit of PORT in N2 nodal disease. However, there are also articles suggesting that PORT has no significant effect on survival. [8–10] Furthermore, the NCCN guidelines are themselves ambiguous [3]. Therefore, the role of PORT in completely resected N2 NSCLC patients is still highly controversial. Currently, physicians have little evidence to suggest that PORT will be beneficial to their patients. Moreover, the current staging system of completely resected pathologic N2 NSCLC treated with chemotherapy is not sufficient for identifying the patients who may most likely benefit or not from PORT. Consequently, there it remains necessary to develop a survival model exploring the potential individual difference of PORT.

In this study, we aim to develop a survival prediction model to calculate the probable overall survival(OS) differences of PORT and without PORT for patients with completely resected pathologic N2 NSCLC treated with chemotherapy.

Methods

Patient Selection Criteria

Information for patients with completely resected pathologic N2 NSCLC treated with chemotherapy between 2002 and 2014 was extracted from the Surveillance, Epidemiology, and End Results (SEER) database (http://seer.cancer.gov/). The inclusion criteria contained the following: pathologically confirmed primary N2 NSCLC between January 2002 and December 2014; completely resected history of lobectomy or pneumonectomy; treatment with chemotherapy; and only one malignant primary lesion. The exclusion criteria were as follows: distant metastasis; invasion of any of the following structures: heart, great vessels, trachea, diaphragm, mediastinum, recurrent laryngeal nerve, carina, vertebral body, and esophagus; Preoperative radiotherapy; radioactive implants; radioisotopes; no information on extracted data.

An external validation cohort who met the inclusion and exclusion criteria was presented to analyze the applicability of the model. The cohort composed of 602 patients between 2009 and 2014 from the First Affiliated Hospital of Guangzhou Medical University and Collaborative Innovation Center for Cancer Medicine of Sun Yat-sen University, China.

The baseline demographics for the patients (age, sex, and race), characteristics of tumors (size, location, differentiation grade and histological type), examined lymph node, positive lymph node, extent of surgery and VPI (visceral pleural invasion) were gathered from the SEER database. The

TNM category was based on the IASLC 8th edition staging system. [11] PORT was categorized as received or not received.

Construction of the Nomogram

In the training set for PORT and non-PORT groups, OS was predicted by the Kaplan-Meier method and analyzed applying the log-rank test. Multivariable Cox proportional hazard regression was applied to identify independent prognostic factors. On the basis of the significant independent factors of two groups, nomograms were formulated by R 3.5.3 with the rms and survival packages.[12] Rms is the package that goes along with the book Regression Modeling Strategies. All survival models were constructed using the rms R library by Harrell (http://cran.r-project.org/web/packages/rms).

Validation and Calibration of the Nomogram

The model was subjected to 1,000 bootstrap resamples for internal validation in the training cohort and external validation with the cohort from the Chinese Institute. Calibration for one, three, and five year OS was determined by comparing the predicted survival with the observed survival on 1000 bootstrap resamples. The ability to discriminate was determined using the concordance index (C-index). The values of the C-index ranged from 0.5 to 1.0, and higher C-index values suggested a better outcome with the nomogram.[13] The C-index for two different models were compared using the methods previously described [14].

Statistical Analyses

The chi-square test was applied to examine the statistical significance of the differences for the clinical variables between the PORT and non-PORT groups. OS was calculated using the Kaplan-Meier method and compared by applying the log-rank test. The independent prognostic factors were identified using the multivariate cox proportional hazard regression. The hazard ratio (HR) and corresponding 95% confidence interval (CI) were determined. Nomograms were developed using the rms package of R version 3.5.3. All statistical analyses were performed by SPSS 22.0, and $P < 0.05$ was regarded statistically significant.

Results

Clinical Characteristics

A total of 3094 patients with completely resected pathologic N2 NSCLC and treated with chemotherapy derived from the SEER database (Figure S1), and 602 patients from a multicenter hospital in China met the inclusion criteria. The demographics and clinicopathological characteristics assessed for the training cohort and external validation cohort are listed in Table 1. The median interquartile range (IQR) and follow-up times on OS were 27 months (13, 52) and 36 months (22, 49) for the training cohort and external validation cohort, respectively.

Table 1
Demographics and Clinicopathologic Characteristics of the Training and External Validation Cohort.

	Training cohort					External Validation cohort				
	PORT (n = 1519)		NO-PORT (n = 1575)			PORT (n = 69)		NO-PORT (n = 533)		
Characteristic	No.	%	No.	%	P	No.	%	No.	%	P
Age					0.001					0.127
< 60	517	34	495	31.4		47	68.1	295	55.3	
60–70	594	39.1	558	35.4		17	24.6	177	33.2	
≥ 70	408	26.9	522	33.1		5	7.2	61	11.4	
Gender					0.272					0.25
Male	734	48.3	730	46.3		45	65.2	309	58	
Female	785	51.7	845	53.7		24	34.8	224	42	
Race					0.674					
White	1236	81.4	1285	81.6		-	-	-	-	
Black	138	9.1	152	9.7		-	-	-	-	
Other	145	9.5	138	8.8		-	-	-	-	
Location					0.732					0.856
Upper	875	57.6	896	56.9		31	44.9	258	48.4	
Middle	75	4.9	72	4.6		7	10.1	41	7.7	
Lower	516	34	548	34.8		28	40.6	206	38.6	
other	53	3.3	59	3.7		3	4.3	28	5.3	
Examined lymph node					0.035					0.837
0–9	696	45.8	649	41.2		7	10.1	46	8.6	
10–15	404	26.6	453	28.8		13	18.8	114	21.4	
≥ 16	419	27.6	473	30		49	71	373	70	
Positive lymph node					0.007					0.963
1–3	876	57.7	995	63.2		26	37.7	210	39.4	
4–9	531	35	478	30.3		28	40.6	211	39.6	
≥ 10	112	7.4	102	6.5		15	21.7	112	21	
Tumor size										
≤ 3 cm	715	47.1	719	45.7	0.305	30	43.5	259	48.6	0.524
> 3 to 5 cm	522	34.4	525	33.3		29	42	183	34.3	
> 5 to 7 cm	187	12.3	230	14.6		5	7.2	58	10.9	
> 7 cm	95	6.3	101	6.4		5	7.2	33	6.2	
Extent of surgery					0.01					0.3
Lobectomy	1385·	91.2	1392	88.4		68	98.6	512	96.1	
Pneumonectomy	134	8.8	183	11.6		1	1.4	21	3.9	
Differentiation grade					0.834					0.126
Grade I	72	4.7	83	5.3		1	1.4	17	3.2	
Grade II	633	41.7	663	42.1		33	47.8	289	54.2	
Grade III or IV	713	46.9	733	46.5		19	27.5	158	29.6	

	Training cohort					External Validation cohort				
	PORT (n = 1519)		NO-PORT (n = 1575)			PORT (n = 69)		NO-PORT (n = 533)		
Unknown	101	6.6	96	6.1		16	23.2	69	12.9	
Histology					0.71					0.007
SC	273	18	305	19.4		23	33.3	93	17.4	
Adenocarcinoma	1028	67.7	1038	65.9		42	60.9	405	76	
Others	218	14.4	232	14.7		4	5.8	35	6.6	
VPI					0.195					0.968
Yes	537	35.4	522	33.1		34	49.3	264	49.5	
No	982	64.6	1053	66.9		35	50.7	269	50.5	
Abbreviation: PORT, post-operative radiotherapy; SC, squamous carcinoma; VPI, visceral pleural invasion;										

Independent Prognostic Factors in the Training Cohort

The survival analysis using the log-rank test found no significant differences in OS (HR = 1.006, 95% CI: 0.915 to 1.106; P = 0.9) between the PORT and non-PORT groups (Fig. 1a). Results from the multivariate regression model are listed in Table 2. For patients with PORT, the multivariate analyses indicated that age (P < 0.001), gender (P = 0.011), examined lymph node (P < 0.001), positive lymph node (P < 0.001), tumor size (P = 0.037), extent of surgery (P < 0.032), and differentiation grade (P = 0.001) are independent prognostic factors for OS. For patients in the non-PORT group, the multivariate analyses indicated that age (P < 0.001), gender (P < 0.001), examined lymph node (P = 0.013), positive lymph node (P < 0.001), tumor size (P = 0.005), and VPI (P = 0.046) are independent prognostic factors for OS.

Table 2
Multivariate Cox Regression Analysis of Factors Associated With Overall Survival.

	PORT (n = 1519)				NO PORT (n = 1575)				
Univariable Analysis P	Multivariable Analysis				Univariable Analysis P	Multivariable Analysis			
		Characteristic	Hazard Ratio	95% CI		P	Hazard Ratio	95% CI	P
	Age	0.001			0.001	0.001			0.001
	< 60		1(reference)				1(reference)		
	60–70		1.203	1.019 to 1.419	0.029		1.100	0.927 to 1.306	0.274
	≥ 70		1.531	1.283 to1.828	0.001		1.642	1.387 to 1.944	0.001
	Gender	0.003				0.001			
	Male		1(reference)				1(reference)		
	Female		0.835	0.727 to 0.959	0.011		0.702	0.613 to 0.803	0.001
	Race	0.238				0.011			0.107
	White						1(reference)		
	Black						0.983	0.779 to 1.242	0.981
	Other						0.759	0.587 to 0.980	0.034
	Location	0.046			0.301	0.069			0.814
	Upper		1(reference)				1(reference)		
	Middle		0.982	0.694 to 1.388	0.916		1.040	0.74 to 1.461	0.82
	Lower		1.034	0.889 to 1.203	0.663		1.073	0.928 to 1.242	0.34
	other		0.650	0.313 to 1.350	0.248		0.995	0.692 to 1.432	0.98
	Examined lymph node	0.075			0.001	0.435			0.013
	0–9		1(reference)				1(reference)		
	10–15		0.792	0.666 to 0.942	0.008		0.842	0.714 to 0.993	0.041
	≥ 16		0.660	0.546 to 0.797	0.001		0.775	0.649 to 0.927	0.005
	Positive lymph node	0.001			0.001	0.001			0.001
	1–3		1(reference)				1(reference)		
	4–9		1.423	1.218 to 1.662	0.001		1.345	1.155 to 1.568	0.001

	PORT (n = 1519)				NO PORT (n = 1575)			
≥ 10		1.849	1.397 to 2.448	<0.001		1.841	1.400 to 2.423	<0.001
Tumor size	<0.001			0.037	<0.001			0.005
≤ 3 cm		1(reference)				1(reference)		
> 3 to 5 cm		1.145	0.978 to 1.340	0.92		1.150	0.984 to 1.345	0.08
> 5 to 7 cm		1.341	1.083 to 1.660	0.007		1.241	1.007 to 1.528	0.042
≥ 7 cm		1.245	0.934 to 1.661	0.135		1.605	1.221 to 2.109	0.001
Extent of surgery	0.007				0.016			
Lobectomy		1(reference)				1(reference)		
Pneumonectomy		1.308	1.024 to 1.671	0.032		1.117	0.896 to 1.391	0.326
Differentiation grade	0.011			0.001	0.142			0.317
Grade I		1(reference)				1(reference)		
Grade II		1.338	0.895 to 2.000	0.156		1.254	0.906 to 1.735	0.173
Grade III or IV		1.721	1.154 to 2.565	0.008		1.335	0.966 to 1.846	0.08
Unknown		1.639	1.010 to 2.660	0.045		1.365	0.903 to 2.063	0.14
Histology	0.374	-	-	-	0.825	-	-	-
SC		-	-	-		-	-	-
Adenocarcinoma		-	-	-		-	-	-
Others		-	-	-		-	-	-
VPI	0.029				0.012			
Yes		1(reference)				1(reference)		
No		1.146	0.991 to 1.326	0.66		1.157	1.003 to 1.335	0.046
Abbreviation: PORT, post-operative radiotherapy; SC, squamous carcinoma; VPI, visceral pleural invasion;								

Development of a Prognostic Nomogram

Nomograms were constructed from the coefficients of the multivariate regression model. Significant independent factors of the two groups, including age, gender, examined lymph node, positive lymph node, tumor size, extent of surgery, differentiation grade, and VPI were included to develop the nomogram. To estimate the net survival differernces for PORT, the two nomograms were utilized together (Fig. 2). The first nomogram (Fig. 2A) estimated OS with PORT, and the second nomogram (Fig. 2B) estimated OS without PORT. The difference between the two estimates represented the expected net survival difference from the addition of PORT. Each factor was given a score on the point scale. By gathering the total score and finding it on the total point scale, it was a simple process to determine the estimated probability of survival at each score point using a straight line.

Calibration and Validation of the Nomogram

The calibration curve (Fig. 3A and B) showed a great agreement between the nomogram prediction and actual observation for one, three, and five year OS in the training cohort. In the PORT group, the Harrell's C-index for the established nomogram to predict OS (0.619; 95% CI, 0.598 to 0.641) was significantly greater than that of the IASLC 8th edition staging system (T1, T2, T3 and T4, 0.566; 95% CI, 0.521 to 0.610; P < 0.01). In the non-PORT group, the C-index was higher for the nomogram prediction 0.627 (95% CI, 0.605–0.648) than for the T category prediction (0.559; 95% CI, 0.540 to 0.610; *P* < 0.01). In the external validation cohort, the calibration plots also presented an acceptable agreement between the nomogram predictions and actual observations for one, three and five year OS (Fig. 3C and D). The C-index was 0.599 (95% CI, 0.485 to 0.713) for the PORT group and 0.595 (95% CI, 0.544 to 0.646) for the non-PORT group.

Clinical Use

For an individual patient, first use nomogram A to calculate the expected OS with PORT; then use nomogram B to calculate the expected OS without PORT. The difference between the two estimates represents the expected net survival difference from the addition of PORT. The three year survival rates of each patient were calculated using these two nomograms. The net survival difference was computed according to the value of the three-year survival rates of each patient. There are 1434 patients with a positive PORT net survival difference and 1475 patients with a negative PORT net survival difference for SEER. The multivariate analyses showed that PORT could improve OS (HR, 0.861; 95% CI, 0.744 to 0.996; *P* = 0.044) for patients with a positive PORT net survival difference. For patients with a negative PORT net survival difference, PORT was not associated with OS (HR, 1.113; 95% CI, 0.978 to 1.267; *P* = 0.105). The Kaplan-Meier curves for OS are shown in Figure S2.

Discussion

We established a practical survival prediction model that can be used to make individualized predictions about the expected survival difference of PORT and without PORT for patients with completely resected pathologic N2 NSCLC treated with chemotherapy. The model is more predictive than the T category prediction of the IASLC 8th edition staging manual with higher C-index. The model is practical for individual recommendations for the use of PORT.

As adjuvant chemotherapy is recommended for patients with completely resected pathologic N2, in the NCCN guidelines [3]. Our study excluded patients who had not undertaken chemotherapy. In this large population-based study, our results suggest that there were no statistical difference in OS between the PORT and non-PORT groups (Fig. 1). Similarly, an early closed randomized controlled trial [9] indicated PORT increased both local/regional and distant disease-free survival (DFS) rate, but not the OS rate. A Randomized Phase III study [8] with 37 patients and Phase II trial with 101 patients [10], also showed that there were no statistical differences between the observation and PORT arms for OS. The randomized controlled trial (NCT00410683) announced the results that postoperative radiotherapy has no PFS or OS benefit for R0 resection N2 (IIIA) of NSCLC in the recent ESMO congress. However, previous retrospective studies [4, 5] and meta-analyses studies [6, 7] revealed that PORT could significantly improve the survival of patients. Therefore, the role of PORT in completely resected N2 patients is still controversial. Our model can provide individual predictions of OS for patients with PORT and non-PORT. This suggests that our nomograms may also be valuable at picking out patients who are most likely to gain from PORT. In addition, we have found that approximately half of the patients may have benefited from PORT (figure S2).

It is unclear why the results of our study were different from others [4, 5], but a possible explanation is the difference in the prognostic factors included in the multivariate analyses. The numbers of positive lymph nodes and examined lymph nodes were not reported in previous NCDB studies [5, 15]. Especially, the number of positive lymph nodes is an essential prognostic factor in many kinds of cancer, and comparable studies [16, 17] also suggested that the higher number of positive lymph nodes (n > 3) are associated with a worsening survival rate. In addition, examined lymph node count was an important prognostic factor for NSCLC [18]. The independent prognostic factors consisting of age, gender, tumor size, extent of surgery in our outcomes, were comparable to those discovered in some prior studies for NSCLC [5, 19, 20]. Histology was not selected as a candidate factor because it is not an independent prognostic factor. This finding is consistent with other findings for stage II or III [4] and IIIA-N2 [20] NSCLC from SEER. Furthermore, we found that VPI is associated with poor prognosis in N2 stage NSCLC. The cutoff points are mostly based on our previous studies[18, 19]. A cutoff point of 3 positive lymph nodes was recommended. Therefore, age, sex, examined lymph node, positive lymph node, tumor size, extent of surgery, differentiation grade, and VPI were the final factors applied in the nomogram.

The calibration plots in the training and external validation cohorts indicated ideal agreement between actual OS and prediction, indicating that predictive functionality of the nomograms was excellent. The C-indices from our nomograms (0.63 and 0.66 for PORT and non-PORT cohorts, respectively) were superior to that of TNM staging (0.56 and 0.55), with *P* < .001 in OS. Therefore, by combining multiple clinical risk factors, the nomogram had a better discrimination ability than the TNM staging system. Moreover, the nomograms can be generally applied considering that the data gathered from the United States multi-center SEER database and the two centers in China might reduce the impact of patient history backgrounds and hospital differences.

Despite there being several NSCLC prognostic models had been reported previously[18–22], no nomogram has been developed for completely resected pathologic N2 NSCLC with and without PORT. We previously developed a survival model to predict OS for patients with stage I - IIIA resected NSCLC, but it only included 24% of N2 patients and was not related to PORT [18]. A recent study [20] reported a nomogram to predict the

survival of stage IIIA-N2 NSCLC after surgery. However, it lacked chemotherapy data and cannot guide the choice of PORT. Jiang et al.[23] reported a similar survival prediction model in patients with stage II or III gastric cancer. Their nomgrams can be applied to calculate individualized predictions of the probable OS advantage from adjuvant chemotherapy for these patients. We also established practical nomograms to predict OS and identified a subset of patients who might benefit from PORT.

There remain some limitations to our study. Firstly, the clinical characteristics of patients with and without PORT were slightly different between the training and external validation cohorts (Table 1), especially the proportion and number of PORT in the Chinese patients was very low. Therefore, our results should be further validated by larger multi-center data from other countries. Secondly, our study is limited by its retrospective design, which represents an unavoidable bias. Furthermore, the SEER program lacks data on some relevant molecular factors, chemotherapy regimen, tumor recurrence, RT dose, surgical margin status, and comorbidity. In addition, the C-indices of the nomogram were only 0.619 and 0.627, which was not inspiring. Obviously, future studies using prospective data collection and additional prognostic variables are needed to improve performance and reliability of the model.

Conclusion

We established a practical nomogram that can produce an individualized estimate of the net survival difference of PORT and without PORT for patients with completely resected pathologic N2 NSCLC treated with chemotherapy. This model can help us to quantify the survival benefit of PORT after surgical resection of N2 NSCLC with chemotherapy and to make individualized therapeutic suggestions.

Abbreviations

Non-small-cell lung cancer (NSCLC); post-operative radiotherapy (PORT); Overall survival (OS); National Comprehensive Cancer Network (NCCN); Surveillance, Epidemiology, and End Results (SEER); Visceral pleural invasion (VPI); Confidence interval (CI); Interquartile range (IQR)

Declarations

Ethics approval and consent to participate

The study was approved by the First Affiliated Hospital of Guangzhou Medical University, and informed consent was waived because of the retrospective nature of this study.

Consent for publication

Not applicable

Availability of data and material

The datasets analyzed during the current study are available from the corresponding author on reasonable request

Competing interests

We have no conflicts of interest to declare.

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Authors' contributions

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Figures

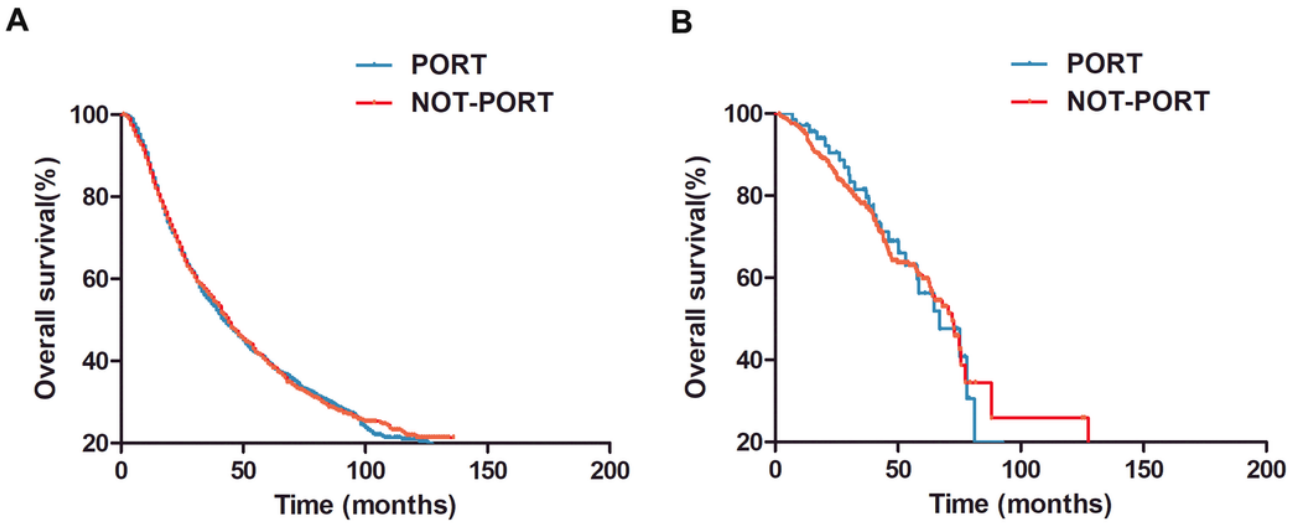

Figure 1

Kaplan-Meier Estimates of Overall Survival (OS) for all patients in the training (A) and external validation cohorts (B).

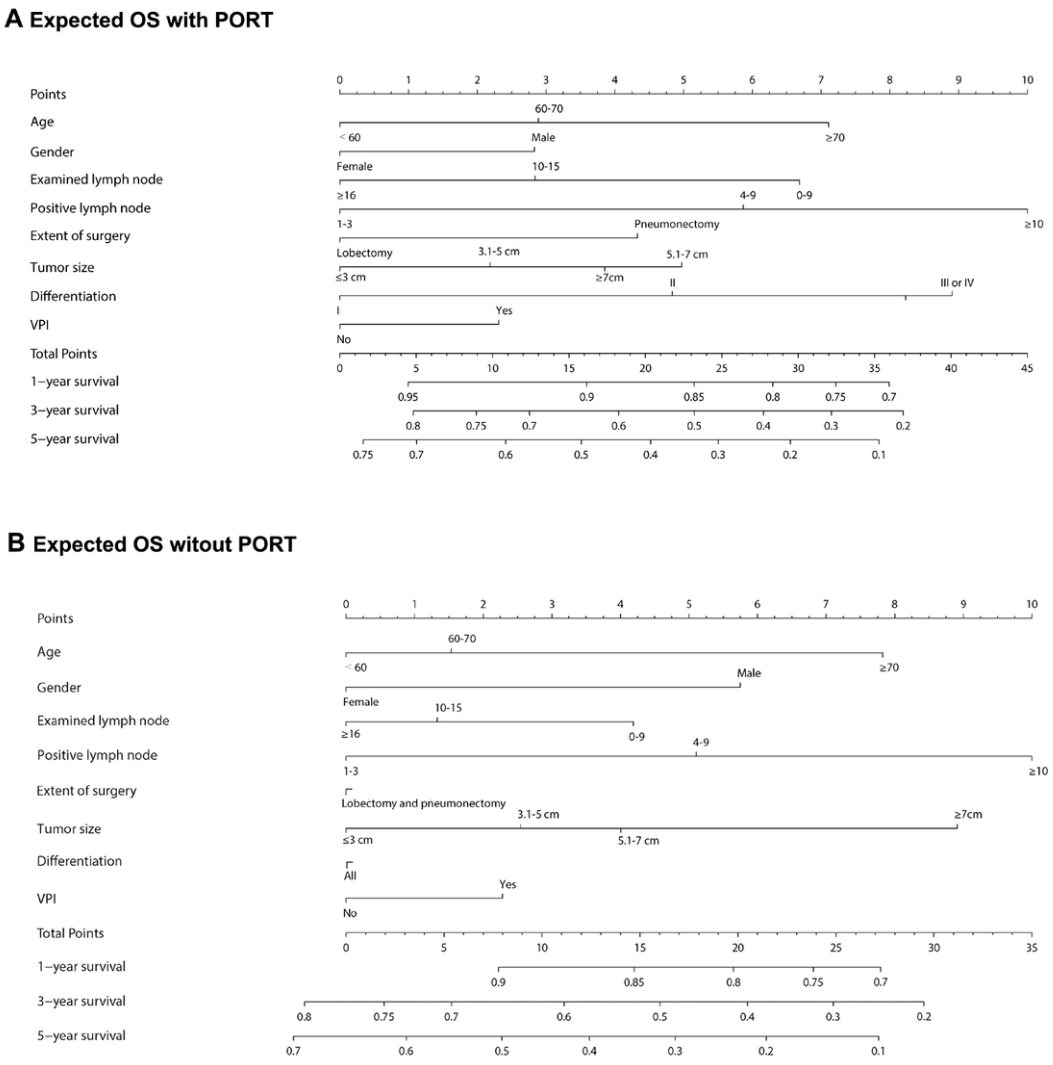

Figure 2

Nomograms for the Comparison of Expected Overall Survival (OS) With and Without post-operative radiotherapy (PORT). For an individual patient, first use nomogram A to calculate the expected OS with PORT; then use nomogram B to calculate the expected OS without PORT. The difference between the two estimates represents the expected net survival impact from PORT and without PORT. PORT, post-operative radiotherapy; VPI, visceral pleural invasion.

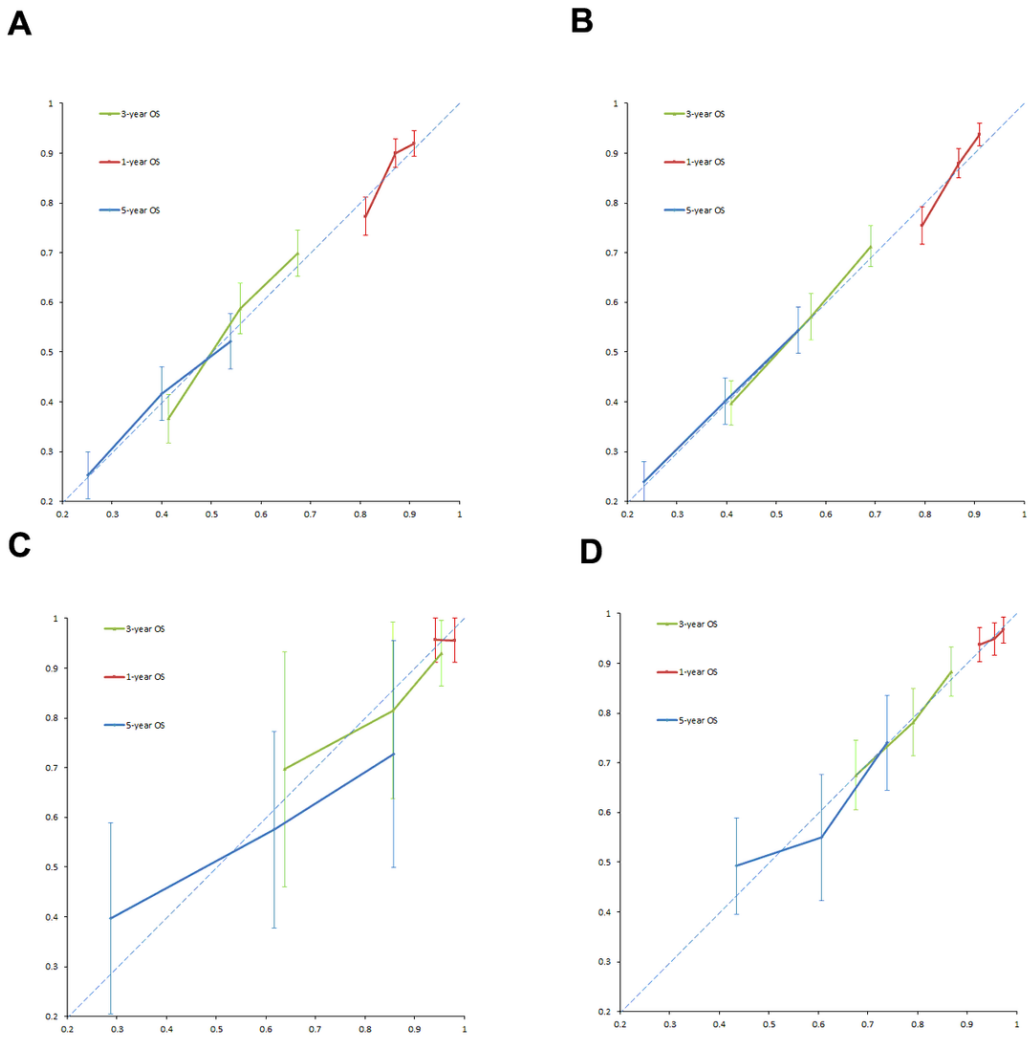

Figure 3

Calibration of the Nomograms in the Training and External Validation Cohorts. The x-axis represents the nomogram-predicted survival, the y-axis represents actual survival, and 95% CIs are measured by Kaplan-Meier analysis. Calibration curves of PORT (A) and non-PORT (B) group in the training cohort. Calibration curves of PORT (C) and non-PORT (D) group in the external validation cohort.

Supplementary Files

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