A nomogram with lymph node status predicts survival and the benefit of postoperative adjuvant therapy in IIIA-N2 Non-small cell lung cancer patients after surgery

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Research

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Abstract

Objective: This study aimed at establishing a novel nomogram predicting overall survival and investigating the survival benefit of various postoperative adjuvant treatments (POAT) in IIIA-N2 Non-small cell lung cancer (NSCLC) patients after surgery.

Methods: Data of IIIA-N2 NSCLC patients between 2004 and 2016 were collected from the Surveillance, Epidemiology, and End Results (SEER). Patients were excluded if the information regarding follow-up time and clinicopathological features were incomplete. Through Univariate and multivariate analyses, independent prognostic factors were identified and integrated into the construction of nomogram. The survival benefit of POAT was evaluated in model-defined low-risk, intermediate-risk, and high-risk subgroups, respectively.

Results: In total, 4389 patients were finally included for analysis. Patients' age, sex, T stage, differentiation grade, examined lymph nodes number (ELN), metastatic lymph nodes number (MLN), and metastatic lymph nodes ratio (LNR) were identified as independent prognostic factors and were integrated into the construction of nomogram. The C-index and calibration curves indicated that the predictive performance of the nomogram was satisfactory. Patients were then categorized into three prognostic groups with the increasing risk of all-cause of death. The prognosis of patients receiving POAT (POCT or PORT plus POCT) and patients receiving surgery alone was comparable in low-risk group, while POCT could significantly prolong survival for IIIA-N2 NSCLC patients after surgery in moderate-risk and high-risk groups. Only patients in high-risk group could benefit from the combination of postoperative radiotherapy (PORT) and postoperative chemotherapy (POCT).

Conclusion: In this large-cohort retrospective study, A survival-predicting nomogram and risk stratification model were established to estimate prognosis in IIIA-N2 NSCLC patients. Surgery alone was recommended as the first choice of treatment to patients in low-risk group. POCT was recommended for patients in moderate-risk group, and the combination of PORT and POCT was recommended for patients in high-risk group. This study may provide additional integration, introspection, and improvement for therapeutic decision-making.

Introduction

Lung cancer (LC) is the second most commonly diagnosed cancer in the United States and the leading cause of death in cancer both in women and men. There are an estimated more than 20,000 morbidity and 14,000 mortality due to lung cancer in 2019[1]. Non-small cell lung cancer (NSCLC) is the most common histopathological subtype of LC, accounting for about 85% of all LC, of which squamous cell carcinoma and adenocarcinoma are the most common subtypes[2, 3]. Although improvements have been made in diagnostic and therapeutic techniques, many cases were still diagnosed at an advanced stage with poor diagnosis[4].

Curative resection for primary lung cancer and metastatic lymph nodes is still the first choice for the majority of NSCLC patients. Nevertheless, for locally advanced NSCLC, especially N2 diseases, the optimal treatment after surgery remains controversial. The existing clinical guidelines hold distinct views on the application of postoperative treatment in IIIA-N2 NSCLC patients. NCCN guidelines recommend PORT for stage N2 NSCLC patients. While American Society of Clinical Oncology and American Society for Radiation Oncology guidelines suggest that PORT is considered unable to improve survival outcomes and is not routinely recommended for patients with IIIA-N2 NSCLC[5, 6].

In the real world, NSCLC is a heterogeneous tumor with diverse prognostic outcomes and can be affected by many demographic factors, including age, sex, marital status, and race, as well as clinicopathological features (such as lymph node status, grade, tumor size, and clinical treatment)[7, 8]. Additionally, not all patients with IIIA-N2 NSCLC could benefit from POAT. Thus, it is vital to integrate all potential information to accurately estimate the prognosis of each patient and select patients who could benefit from postoperative adjuvant therapy.

Recently, nomogram has been considered as a commonly convenient tool for assessing prognostic outcomes, especially in cancer patients. Several nomograms have been constructed to predict the risk of recurrence, metastatic risk, and radiotherapy response in lung cancer[9-11]. However, large population-based survival-predicting models for IIIA-N2 NSCLC patients have not been found. Herein, in this present study, we reported the first large population-based investigation into factors associated with the survival outcomes of patients suffering from IIIA-N2 NSCLC. Further, we established a survival-predicting model to assist the decision-making of postoperative adjuvant treatment.

Methods

Data source and case selection

This was a retrospective study base on the data collected from the Surveillance, Epidemiology, and End Results (SEER) database, an authoritative information source of the National Cancer Institute (NCI), which covered nearly 34.6 percent of the U.S. population[12]. In this present study, information for patients with IIIA-N2 NSCLC was collected based on the following exclusion and inclusion criteria.

Exclusion criteria: (1) autopsy/death certificate diagnosed only; (2) unknown/obscure follow-up time; (3) not first tumor; (4) No/Unknown surgery; (5) distant metastasis; (6) unknown/no information on the extracted data; (7) overall survival ≤ 3 months.

Inclusion criteria: (1) histologically confirmed diagnosis of IIIA-N2 non-small cell lung cancer; (2) active follow-up.

The time range of our study was determined based on the data availability of the sixth/ seventh AJCC TNM staging version. The collected information included basic demographics (age, race, gender), histopathologic characteristics of tumor (primary tumor location, differentiation grade, TNM stage(6th/7th)), details of treatment (record of surgery, chemotherapy and radiotherapy), and survival outcomes (follow-up time, and OS status). In this study, the endpoint for NSCLC patients was overall survival (OS), which was determined as the period from the date of histologic diagnosis to the date of death due to any cause or the last follow-up time.

Statistical analysis

The optimal cut-off values for examined lymph nodes number (ELN), metastatic lymph nodes number (MLN), and metastatic lymph nodes ratio (LNR) were determined using the X-tile software. Univariate and multivariate Cox proportional hazard analyses were used to identify independent prognostic variables through a backward stepwise method. Further, based on these variables, we finally built the survival-predicting nomogram with the SURVIVAL and RMS package in R software. The C-index was utilized to evaluate the discrimination ability and clinical utility of the model. We also generated the calibration curves to assess predicting accuracy of this model by comparing the actual OS with the model-predicting OS probability. Furthermore, based on the total scores of each patient, a risk stratification system was developed to divide all cases into three subgroups with different prognosis. the Kaplan–Meier method and Log-rank test were applied to compare the OS outcome between subgroups.

All statistical analyses were processed using R software (version 3.5.1; http://www.r-project.org) and SPSS 22.0 (IBM Corporation, Armonk, NY, USA). The risk stratification system was established using the X-tile software (Version 3.6.1.1, Yale University, New Haven, CT, USA). Two-side $P < 0.05$ was considered as statistical significance.

Results

Patient characteristics

In total, 4389 IIIA-N2 NSCLC patients receiving curative surgery were selected from the SEER database. Among all patients, the majority (93.3%) were older than 50 years of age. Most cases presented with pathological grade II (N = 1924) and III (N = 2085) at the time of diagnosis. In addition, 33.0% (N = 1449) of patients had T1 stage and 67.0% (N = 2940) had T2 stage. The median follow-up time was 40 months. The actuarial 1-year, 2-year, 3-year and 5-year OS were 85.3%, 73.3%, 54.0% and 39.1%, respectively. Detailed patients' clinicopathological characteristics were listed in Table 1.

Table 1. Demographic and clinicopathological characteristics of IIIA-N2 NSCLC patients after surgery

	All patients		PORT		No PORT		
	n=4389	%	n=1767	%	n=2622	%	P value
Age							0.000
<65	1915	43.6	885	50.1	1030	39.3	
≥65	2474	56.4	882	49.9	1592	60.7	
Gender							0.344
Female	2093	47.7	858	48.6	1235	47.1	
Male	2296	52.3	909	51.4	1387	52.9	
Race							0.289
White	3580	81.6	1435	81.2	2145	81.8	
Black	425	9.7	164	9.3	261	10.0	
Other	384	8.7	168	9.5	216	8.2	
Grade							0.086
Well	246	5.6	82	4.6	164	6.3	
Moderately	1924	43.8	764	43.2	1160	44.2	
Poorly	2085	47.5	865	49.0	1220	46.5	
Undifferentiated	134	3.1	56	3.2	78	3.0	
Laterality							0.739
Left	1998	45.5	799	45.2	1199	45.7	
Right	2391	54.5	968	54.8	1423	54.3	
T classification							0.528
T1	1449	33.0	593	33.6	856	32.6	

T2	2940	67.0	1174	66.4	1766	67.4	
ELN							0.008
Median(range)	9	1-90	9	1-82	9	1-90	
MLN							0.000
Median(range)	2	1-61	2	1-61	2	1-41	
LNR							0.000
Median(range)	0.28	0-1	0.33	0-1	0.24	0-1	

Independent OS-related prognostic factors

The optimal cutoff points of ELN, MLN and LNR were determined with the highest specificity and sensitivity using the X-tile software. For ELN, its optimal cutoff values were 6 (Figure 1A); For MLN, its optimal cutoff values were 3 and 6 (Figure 1B). For LNR, its optimal cutoff value was 0, 0.25, and 0.45 (Figure 1C). The log-rank tests confirmed that the survival differences between cohorts classified by ELN, MLN or LNR were statistically significant.

Table 2 showed the hazard ratios for overall survival according to all factors (including lymph node status) in the univariate and multivariate Cox proportional hazards model. Variables, including age, sex, T stage, differentiation grade, ELN, MLN, and LNR were significantly associated with prognosis in univariate analysis (Table 2, left panel), and were then enrolled into the multivariate analysis to confirm the association. Finally, age ($p < 0.0001$), sex ($p < 0.0001$), T stage ($p < 0.0001$), differentiation grade ($p < 0.0001$), ELN ($p < 0.0001$), MLN ($p < 0.0001$), and LNR ($p < 0.0001$) were identified as the independent overall survival-related prognostic factors (Table 2, right panel).

Table 2. Univariate and multivariate analysis for all-cause of death in IIIA-N2 NSCLC patients after surgery

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age				
<65	**Ref.**		**Ref.**	
≥65	1.436(1.332-1.550)	0.000	1.444(1.338-1.558)	0.000
Gender				
Female	**Ref.**		**Ref.**	
Male	0.757(0.703-0.815)	0.000	0.766(0.711-0.826)	0.000
Race				
White	**Ref.**			
Black	**0.954(0.839-1.086)**	0.478		
Other	0.852(0.744-0.976)	0.021		
Grade				
Well	**Ref.**		**Ref.**	
Moderately	1.260(1.053-1.507)	0.012	1.257(1.050-1.504)	0.013
Poorly	1.444(1.209-1.725)	0.000	1.396(1.168-1.669)	0.000
Undifferentiated	1.487(1.142-1.937)	0.003	1.480(1.136-1.928)	0.004
Laterality				
Left	**Ref.**			
Right	0.999(0.927-1.076)	0.976		
T classification				
T1	**Ref.**		**Ref.**	
T2	1.325(1.222-1.436)	0.000	1.296(1.195-1.406)	0.000
ELN				
<6	**Ref.**		**Ref.**	
≥6	0.840(0.771-0.914)	0.000	0.831(0.742-0.930)	0.001
MLN				
<3	**Ref.**		**Ref.**	

[3,6)	1.175(1.078-1.279)	0.000	1.085(0.980-1.202)	0.115
≥6	1.619(1.468-1.785)	0.000	1.343(1.168-1.545)	0.000
LNR				
0	**Ref.**		**Ref.**	
(0,0.25]	1.258(1.026-1.543)	0.027	1.301(1.059-1.598)	0.012
(0.25,0.45]	1.588(1.291-1.953)	0.000	1.501(1.209-1.863)	0.000
>0.45	2.213(1.797-2.724)	0.000	1.971(1.571-2.472)	0.000

The generation of nomogram and risk stratification system

According to the multivariate Cox proportional hazards model, age, sex, T stage, differentiation grade, ELN, MLN, and LNR were finally identified and integrated into the construction of a predictive nomogram for 1-, 3- and 5-year survival. Each element of these variables included was allotted a score, for example, LNR > 0.45 had a score of 100. The total point was calculated by adding all scores on the basis of the clinicopathologic characteristics of each patient. Finally, the likelihood of all-cause of death could be read by drawing a plummet line (Figure 2A).

The C-index values of the OS-predicting nomogram were 0.71 (95% CI: 0.699-0.721). The calibration curves showed that the nomogram-predicted survival outcomes had satisfying consistency with the actual prognosis results (Figure 2B).

Furthermore, based on the total scores of each patient, a novel risk stratification system was proposed to divide all IIIA-N2 NSCLC patients into three prognostic subgroups (Figure 2C), including low-risk group (total score < 160, N = 1327), intermediate-risk group (total score: [160, 215], N = 1618) and high-risk group (total score > 215, N = 1444). Among all the cases, the median OS time was 68 months in low-risk group, 40 months in intermediate-risk group, and 26 months in high-risk group. The Kaplan-Meier analysis and the log-rank test indicated that this risk stratification system could accurately distinguish survival outcomes in the three prognostic subgroups (Figure 2C).

Clinical benefit of various postoperative treatments

First, we assessed the survival benefits of several postoperative therapy strategies (i.e. surgery alone, postoperative radiotherapy (PORT), postoperative chemotherapy (POCT), and PORT plus POCT) in all patients. The results showed that for the entire, patients receiving POCT or PORT plus POCT had better survival outcomes than patients receiving surgery alone or PORT ($p < 0.001$, Figure 3A). Similarly, the Kaplan-Meier curves and log-rank tests were then generated in the three prognostic subgroups respectively. In low-risk group, the prognosis of patients receiving POAT (POCT or PORT plus POCT) and patients receiving surgery alone was comparable, while in moderate-risk and high-risk groups, POCT could significantly prolong survival for IIIA-N2 NSCLC patients after surgery. Additionally, in moderate-risk subgroup, the difference was not statistically significant in the OS of IIIA-N2 NSCLC patients who received POCT in view of whether underwent PORT (Figure 3B,3C). For patients in high-risk subgroup, the combination of PORT and POCT showed a significant advantage in prolonging OS in IIIA-N2 NSCLC patients compared with receiving POCT alone (Figure 3D).

Discussion

Accurate prediction of survival prognosis is critical for better management of NSCLC patients, and to date, this mainly relied on the AJCC TNM staging system. However, the predictive performance of the existing systems for NSCLC remains unsatisfactory[13]. In fact, even in patients with the same TNM stage, the survival outcomes remain heterogenous[14]. In this study, for the first time, a novel nomogram with lymph node status was established and validated for predicting overall survival outcomes in IIIA-N2 NSCLC patients, which is user-friendly, accurate, and practical.

Various studies had reported several variables associated with the prognosis of patients with lung cancer. Li et al found that T stage, N stage, the number of examined lymph nodes and age were statistically prognostic factors for surgical resected carcinoma of the lung[15]. In the present study, the prognostic values of the lymph node status in IIIA-N2 NSCLC patients receiving curative surgery were investigated. The X-tile software was utilized to explore the optimal cutoff points of ELN, MLN, and LNR. The combination of ELN, MLN, and MLNR could effectively reflect the involvement of regional metastasis and the extent of surgery, and the result of univariate analysis confirmed that these variables were prognostic predictors for IIIA-N2 NSCLC patients.

Notably, only variables of lymph node status are not sufficient to accurately reflect the postoperative prognosis of IIIA-N2 NSCLC patients. In the present study, all variables of interest were included into the multivariate analysis, and seven clinicopathologic features were finally identified as independent prognostic factors, including age, sex, T stage, pathologic grade, ELN, MLN, and LNR. Among all these variables, LNR > 0.45 made the greatest contribution to poorer prognosis followed by undifferentiated grade and MLN > 6. C-index and calibration curves indicated that the predictive performance of the nomogram was satisfactory.

The goal of systemic therapy in NSCLC patients is to mitigate symptom burden from NSCLC and improve survival outcomes, with a co-occurrent aim of improving the quality of life[16]. Whether adjuvant therapy is suitable for NSCLC patients was kept controversial for decades, especially since the results reported by PORT Meta-analysis Trialists Group in 1998[17]. Some previous studies reported that PORT could not prolong the survival rate of NSCLC patients compared with surgery alone[18]. In the meantime, some studies revealed that with the progress of radiotherapy technology, PORT could significantly improve the prognosis of IIIA-N2 NSCLC patients, resulting in reduced local-regional recurrence and better OS[19]. Notably, even in IIIA-N2 NSCLC patients, the survival outcomes are heterogeneous, and not all IIIA-N2

NSCLC patients could benefit from the treatment of POAT. The role of POAT in prolonging overall survival should be further investigated in NSCLC patients, especially in those with IIIA-N2 NSCLC.

Personal clinicopathologic features should be considered carefully when making a therapeutic decision for each patient. And it is critical to integrate these factors to identify IIIA-N2 NSCLC patients who can benefit from various postoperative treatments. Based on the survival-predicting model, we proposed a novel risk stratification system and the survival benefits of various postoperative treatments were analyzed in each risk subgroup. The results showed that surgery alone was recommended as the first choice of treatment to patients in low-risk group. POCT was recommended for patients with IIIA-N2 NSCLC in moderate-risk and high-risk groups. Additionally, only patients in high-risk group, instead of those in low-risk and moderate-risk groups, could benefit prognostically benefit from the combination of PORT and POCT, which provided more valuable information for therapeutic decision-making.

To the best of our knowledge, this is the first comprehensive attempt to develop a population-based nomogram that predicts the prognosis of IIIA-N2 NSCLC patients after surgery. Our survival-predicting nomogram can be practically applied to the clinical works to predict the prognosis of IIIA-N2 NSCLC patients and facilitate clinical consultation, which is able to help to make therapeutic plans ahead on follow-up and surveillance. Furthermore, we proposed a novel patient classification strategy, which could assess the survival benefits of various postoperative treatments for each patient.

There are still several limitations in the present study which should be highlighted, including its retrospective nature and potential selection biases[20]. Furthermore, information about some potential prognostic factors, such as the detailed chemotherapy protocol, molecular or genomic data, were not available in this database. Accordingly, we failed to incorporate these parameters into our model. Future studies are warranted to improve this model by incorporating more valuable prognostic features. In addition, the majority of patients enrolled in this study were Caucasian and black, so this nomogram is expected to externally validated, especially in the Asian population. Last, the recent development of immune checkpoint inhibitors (ICIs) has profoundly changed the treatment strategy of patients with IIIA-N2 NSCLC, but our study failed to reveal the survival benefits of ICIs on these patients. Nevertheless, we agree with the viewpoint of the SEER database that despite the limitations in the population-based analysis, “big data” will definitely continue to be an indispensable part of medical studies for the purpose of hypothesis-generating exploratory analyses[21].

In conclusion, a novel survival-predicting nomogram and risk stratification system were established for predicting individual OS in IIIA-N2 NSCLC. This study may help physicians in making therapeutic decisions and contribute to the design of future prospective researches.

Abbreviations

NSCLC: Non-small cell lung cancer; SEER: The Surveillance, Epidemiology, and End Results; POAT: postoperative adjuvant treatments; PORT: postoperative radiotherapy; POCT: postoperative chemotherapy; ELN: examined lymph nodes number; MLN: metastatic lymph nodes number; LNR: metastatic lymph nodes ratio; OS: overall survival

Declarations

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Authors' contributions

Conception, design, and acquisition of data: Y.C., W.C., C.Q., L.D., M.L., F.H. Data collection, analysis, and interpretation: Y.C., W.C., L.D. Manuscript draft and revision: All authors. All authors read and approved the final manuscript.

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Availability of data and materials

The authors declare that all datasets generated and analyzed are available in the SEER database (https://seer.cancer.gov/).

Ethics approval and consent to participate

As this database is open-source and informed consent of patients is not re- quired, ethics committee approval by the institutional review board was not needed for this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

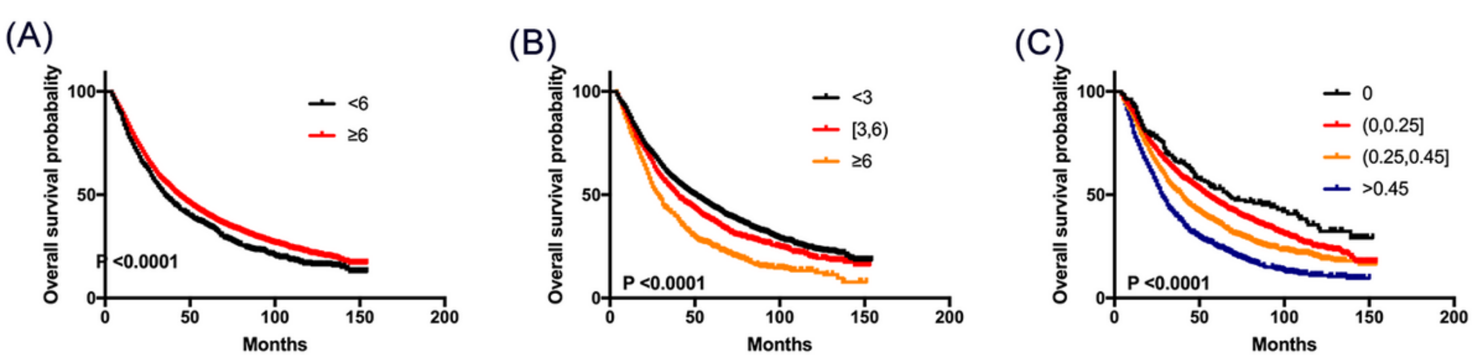
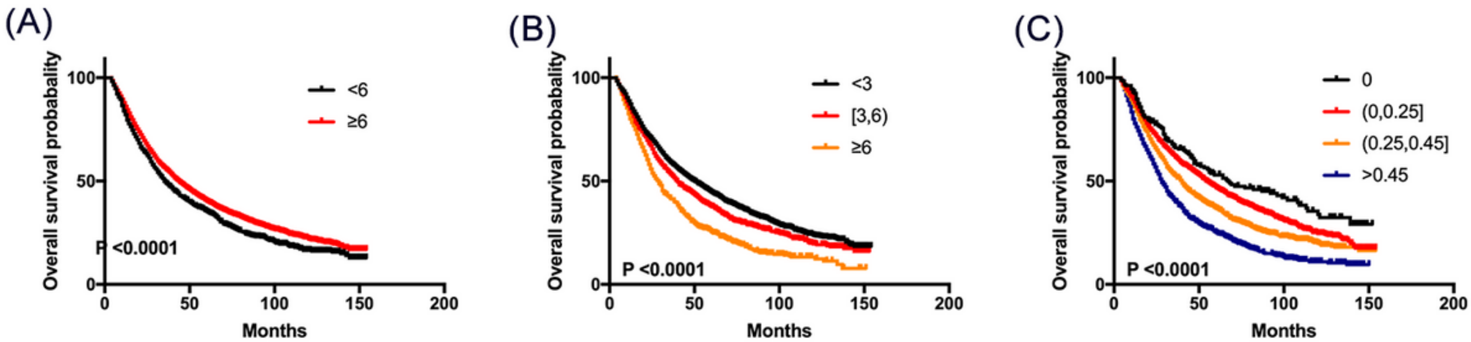


Figure 1

Optimal cut-off values determined by X-tile software for ELN (A), MLN (B), and LNR (C).



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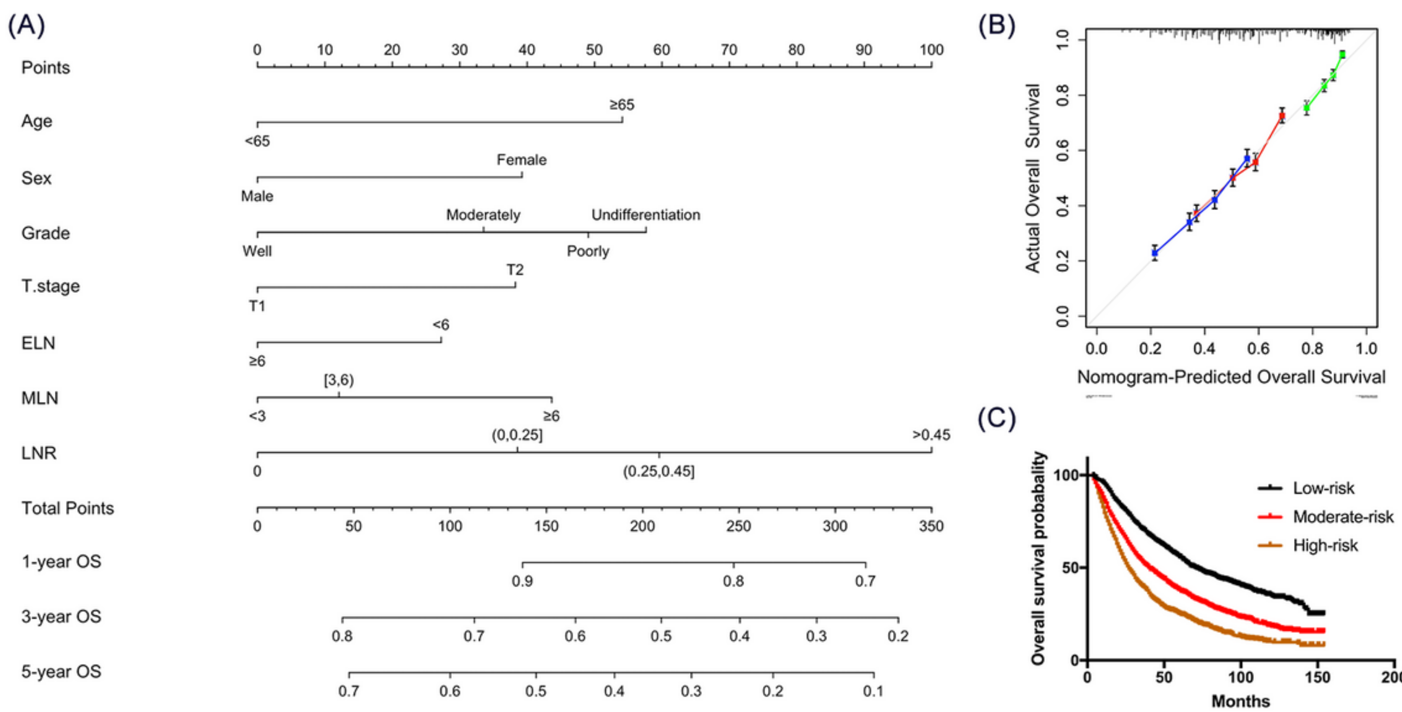
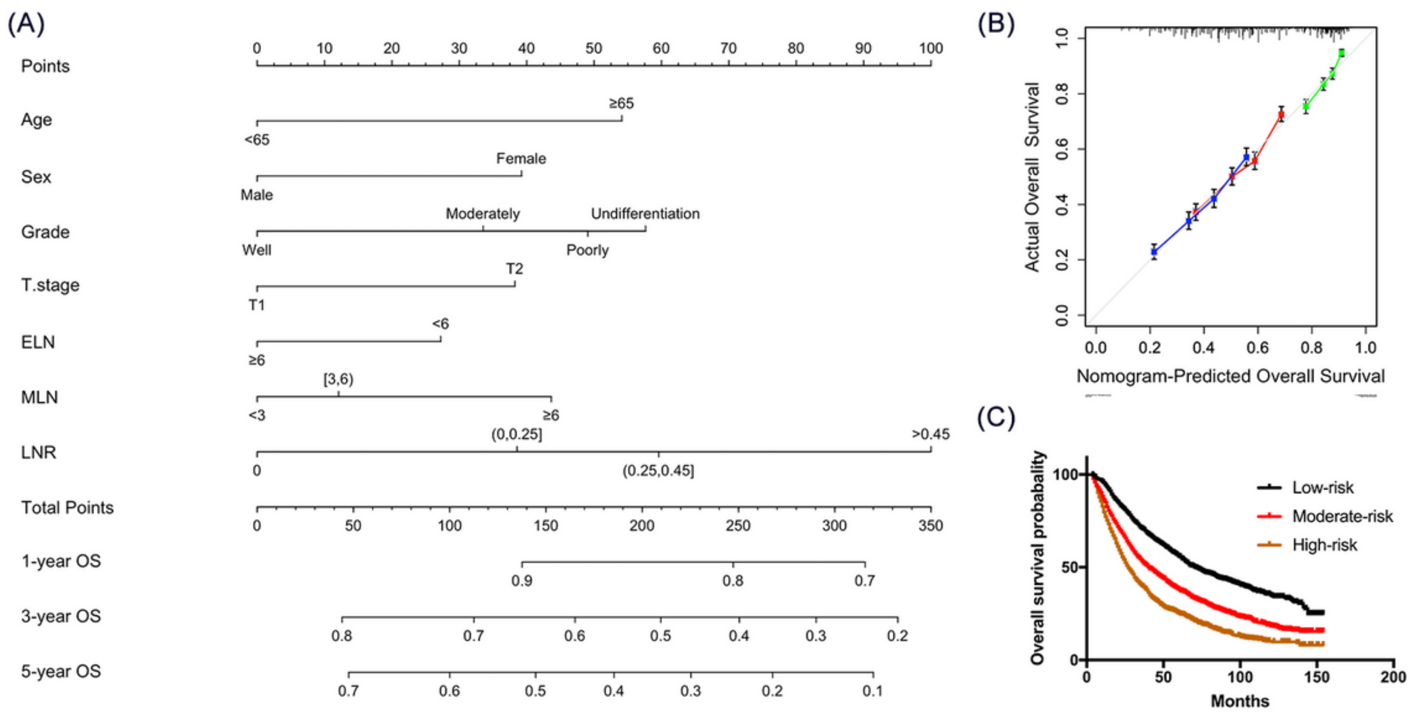


Figure 2

Nomogram for predicting 1-, 3- and 5-year overall survival in ⅢA-N2 NSCLC patients after surgery (A); Calibration curve for predicting 1-, 3- and 5-year overall survival (B); Optimal cut-off values to classified patients into three prognostic subgroups by the X-tile software, including low-risk: 160< ; intermediate-risk: [160, 215)High-risk: ≥215 (C).



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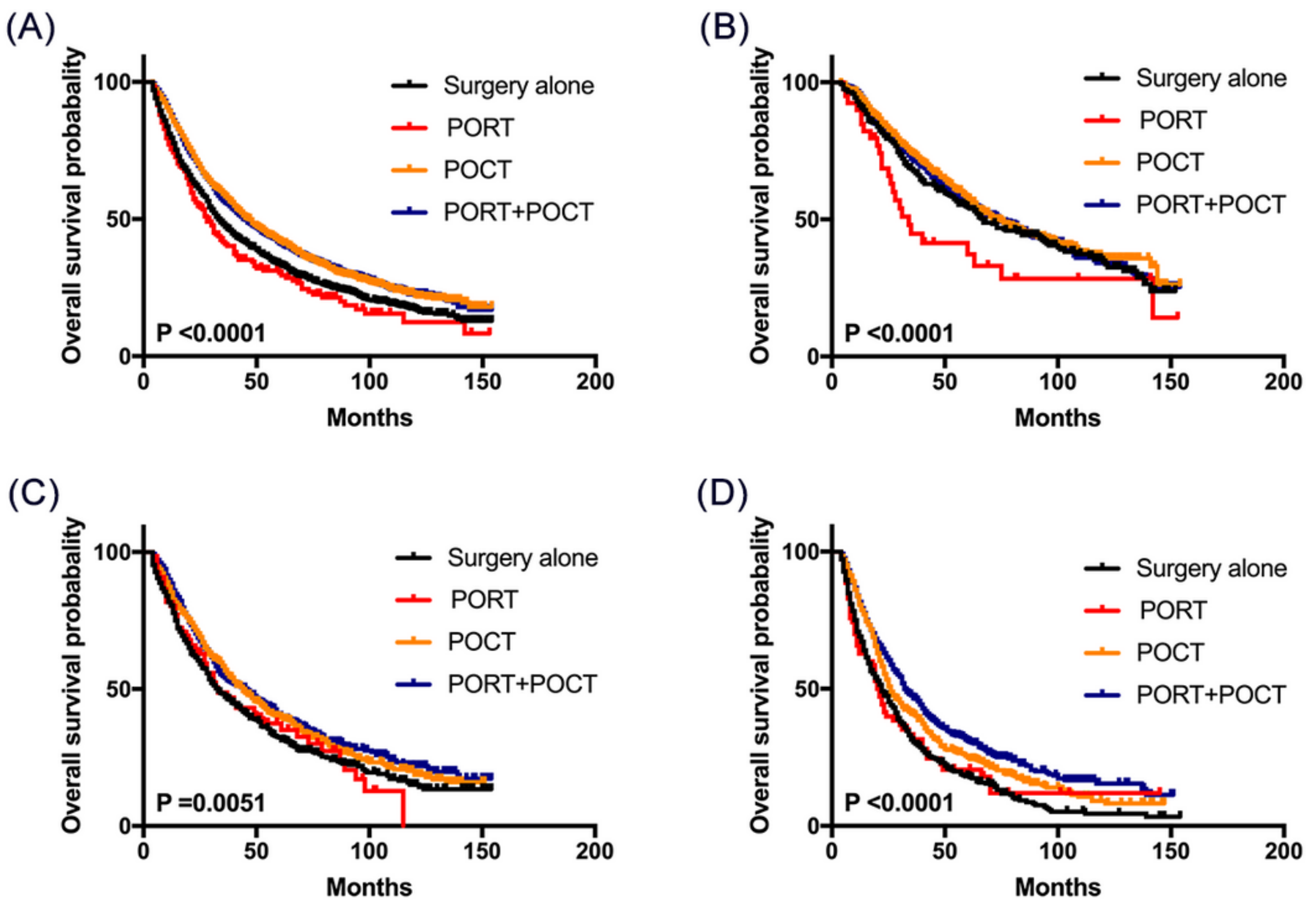
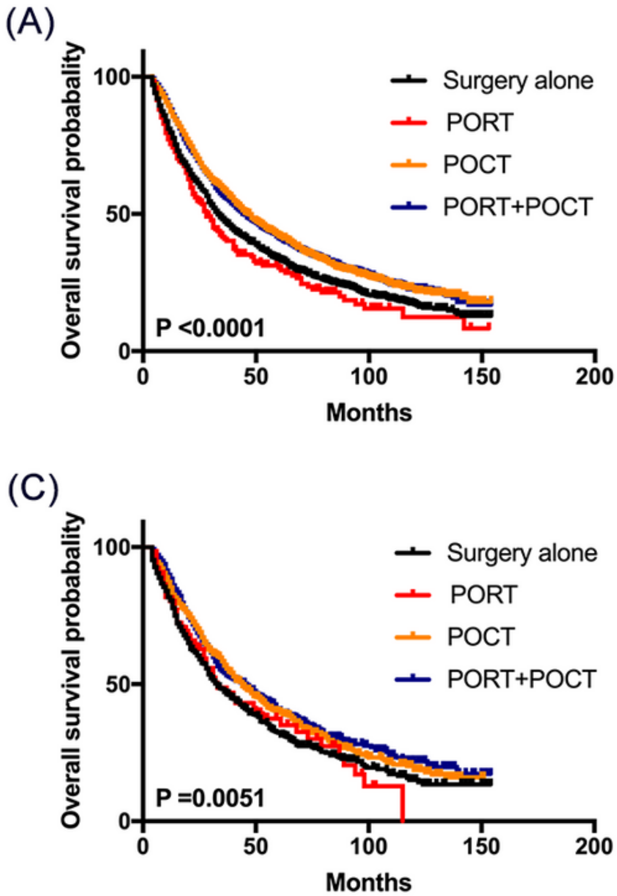


Figure 3

The survival outcomes of four therapy strategies (i.e. surgery alone, PORT, POCT, and PORT plus POCT) in all patients (A), low-risk group (B), moderate-risk group (C), and high-risk group (D).



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