

Risk prediction for locoregional recurrence in mutant-negative unresectable stage III non-small cell lung cancer after concurrent chemoradiotherapy: A retrospective study

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Received April 7, 2026; Accepted August 14, 2026

DOI: 10.3892/ol.2026.15930

Abstract. Locoregional recurrence (LRR) is a major factor affecting prognosis in patients with driver mutation-negative unresectable stage III non-small cell lung cancer (NSCLC) after concurrent chemoradiotherapy. The present study aimed to identify independent risk factors for LRR in this patient population and develop a simple predictive model. The present retrospective study included 134 patients with NSCLC treated between February 2020 and April 2025. Clinicopathological factors were analyzed using Cox regression, and notable predictors were integrated into a risk stratification model. Multivariate analysis identified T3-4 stage and persistently abnormal cytokeratin fragment antigen 21-1 levels after treatment as independent risk factors for LRR. A risk stratification model incorporating these two factors successfully stratified patients into low- and high-risk groups, with marked differences in time to recurrence. The findings of the present study indicate that high-risk patients can benefit from more intensive local treatment or closer surveillance to improve tumor control and clinical outcomes.

Introduction

Lung cancer represents the most frequently diagnosed malignancy and the leading cause of cancer-related mortality worldwide. According to GLOBOCAN 2022, ~2.5 million new lung cancer cases and 1.8 million lung cancer-associated deaths occur annually, with non-small cell lung cancer (NSCLC) accounting for 80-85% of all lung cancer diagnoses (1). It is estimated one-third of patients with NSCLC have stage III locally advanced disease (2). Most patients with stage III NSCLC are ineligible for surgical resection, primarily due to tumor extension to critical structures, such as the mediastinum and major vessels, or preexisting comorbidities (3). According to the National Comprehensive Cancer Network guidelines, concurrent chemoradiotherapy (CCRT) followed by consolidation immunotherapy is the standard treatment for unresectable locally advanced NSCLC (4). However, clinical outcomes associated with this strategy remain suboptimal, characterized by notably high locoregional recurrence (LRR) rates (31.8-45.7%) (5,6), short progression-free survival times (5.6-12 months) and low 5-year overall survival (OS) rates (15.1-36.0%) (2,5,7).

Consolidation immunotherapy after chemoradiotherapy has been reported to improve survival outcomes and has emerged as a cornerstone in the management of patients with unresectable locally advanced NSCLC (8-10). However, a previous study showed that immunotherapy did not markedly improve intrathoracic disease control, with LRR rates >38.5% (11). Furthermore, intrathoracic progression has been observed more frequently in patients receiving immunotherapy than in those in the placebo arm (80.6 vs. 74.5%) (8). These findings indicate that the most prominent benefit of immunotherapy lies in reducing the risk of distant metastasis (DM). Therefore, improving local disease control remains a primary focus of scientific research (12). Notably, locoregional control has been reported to strongly correlate with OS (13). The rate of tumor control in patients with NSCLC improves with increasing biological effect dose delivered to the primary lesion (14). However, data from the Radiation Therapy Oncology Group 0617 trial (15,16) and multiple radiation

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Abbreviations: NSCLC, non-small cell lung cancer; CCRT, concurrent chemoradiotherapy; HR, hazard ratio; PET-CT, positron emission tomography-CT; DM, distant metastasis; OS, overall survival; LRR, locoregional recurrence; CYFRA21-1, cytokeratin fragment antigen 21-1; IMRT, intensity-modulated radiation therapy

Key words: locoregional recurrence, NSCLC, CCRT, 3D interstitial high-dose-rate brachytherapy, neoadjuvant therapy

dose-escalation studies (17-20) have indicated that increasing radiation doses in conventional radiotherapy regimens inevitably elevates radiation exposure to organs at risk without improving OS in patients with locally advanced NSCLC. Exposure of the lung and esophagus to high doses contributes to elevated rates of acute and late toxicities, with 79.7-80.0% of patients developing severe adverse effects, including grade ≥ 3 radiation-related adverse events (17.4-30.0%) and grade ≥ 3 respiratory toxicity (13.0-23.8%). Conversely, a previous study showed that combining 3D interstitial high-dose-rate (HDR) brachytherapy with intensity-modulated radiation therapy (IMRT) for regional metastatic lymph nodes notably improved OS rates and reduced toxicity profiles in patients with locally advanced peripheral NSCLC (8).

Currently, tumor size, lymph node involvement and specific histological features, such as tumor differentiation grade, lymphovascular invasion and pleural invasion, are the most recognized risk factors for poor outcomes. However, most of these factors are based on clinical experience rather than rigorous evidence. Accurate identification of patients at high risk of recurrence is important for guiding optimal treatment selection. Therefore, the present study aimed to identify risk factors for LRR after CCRT in patients with driver mutation-negative unresectable stage III NSCLC and to develop a risk stratification model to identify patients at high risk for LRR. The findings of the present study may provide clinical guidance for managing patients with driver mutation-negative unresectable stage III NSCLC.

Materials and methods

Study design and population. For the present retrospective study, consecutive patients diagnosed with NSCLC who were referred for genetic testing at the Department of Oncology, The Second Affiliated Hospital of Chongqing Medical University (Chongqing, China), between February 2020 and April 2025 were included. Medical records were retrospectively accessed for this study from May 2025 to January 2026. The inclusion criteria were as follows: i) Histologically confirmed mutant-negative NSCLC; and ii) histologically proven stage III NSCLC, with variable imaging modalities adopted for staging. A subset of patients received contrast-enhanced chest computed tomography (CT), abdominal CT, brain magnetic resonance imaging (MRI) and whole-body bone scintigraphy. The remaining patients underwent whole-body fluorine-18 fluorodeoxyglucose positron emission tomography (PET)-CT supplemented by contrast-enhanced brain MRI to identify occult brain metastases. Comprehensive integration of imaging findings and pathological results confirmed stage III disease without DM. iii) All cases required discussion by a multidisciplinary team, led by physicians from the Departments of Medical Oncology, Pulmonology, Radiation Oncology and Thoracic Surgery. The resectability of tumors was comprehensively determined with additional input from pathology and imaging specialists. iv) CCRT and immunotherapy consolidation treatment. The detailed regimens of CCRT and immunotherapy are presented in Table SI. Patients who underwent lung surgery or other treatments were excluded from the study. The staging was based on the 8th edition of the American

Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system (21).

N substaging. N substaging data were collected for analysis as a potential risk factor for LRR. Pretreatment CT/PET-CT and pathology reports were reviewed to confirm unresectable stage III NSCLC. They were further sub-staged as minimal N2/single station, and bulky and/or multilevel N2, according to the AJCC/UICC 8th staging criteria.

Genetic testing. Tissues were fixed in 10% neutralbuffered formalin at room temperature for 12-24 h, embedded in paraffin, and sectioned at 4 μ m thickness for subsequent genetic testing. Formalin-fixed paraffin-embedded tissue specimens from patients with NSCLC were analyzed using the commercial MaiFeiJie[®] Lung Cancer Multigene Joint Detection Kit (Guangzhou Maijing Gene Medical Technology Co., Ltd.), covering 13 clinically actionable genes: EGFR, HER2, BRAF, KRAS, neuroblastoma RAS viral oncogene homolog, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α , anaplastic lymphoma receptor tyrosine kinase (ALK), c-ros oncogene 1 (ROS1), rearranged during transfection, MNNG HOS transforming gene (MET), neurotrophic receptor tyrosine kinase (NTRK)1, NTRK2 and NTRK3. The proprietary full-length primer and probe sequences of the integrated multiplex panel are subject to the confidential intellectual property restrictions of the manufacturer. The primers, probes and internal loading control sequences for the core target genes are publicly documented in a series of authorized Chinese invention patents from the same developer (22-25). All assays adopted unified VIC-fluorescent labeled internal DNA/RNA loading controls for reaction validity monitoring, consistent with the patented detection systems. All standardized reverse transcription-quantitative PCR/amplification refractory mutation systems-PCR conditions were strictly implemented as described in the Multigene Joint Detection Kit manual and patent protocols.

Tumor marker levels. Peripheral venous blood samples were collected after completion of CCRT. Serum carcinoembryonic antigen (CEA) and cytokeratin fragment antigen 211 (CYFRA211) were quantitatively measured by electrochemiluminescence immunoassay using the cobas e601 analyzer with matching Elecsys[®] kits (Roche Diagnostics) at the Department of Clinical Laboratory, the Second Affiliated Hospital of Chongqing Medical University. All detections were performed strictly following the manufacturer's operating instructions. The institutional reference ranges were 0-5.2 ng/ml for CEA and 0-3.3 ng/ml for CYFRA211. These tumor-marker values were used as indicators for surveillance of tumor recurrence and progression.

Efficacy assessment after CCRT. Efficacy evaluation was performed 4-8 weeks after CCRT completion, with systematic examination methods encompassing chest and upper abdominal CT scans, bone scans, brain MRI and, in select cases, PET-CT scans. According to the RECIST 1.1 criteria (26), the efficacy evaluation focused on changes in target and non-target lesions. Target lesions were defined as measurable primary lung tumors and thoracic regional (hilar and

mediastinal) lymph nodes with a longest diameter of ≥ 10 mm, whereas non-target lesions were defined as non-measurable abnormalities, such as pleural thickening and sub-centimeter lymph nodes. Treatment responses were classified as complete response, partial response and stable disease.

Follow-up. For post treatment follow-up, chest and upper abdominal CT, and brain MRI were performed 1-2 months after treatment completion, at intervals of 3-6 months during the first 2 years and every 6-12 months thereafter (27). Bone scans, PET-CT scans and biopsies were performed only under clinically necessary circumstances, such as suspected disease progression. LRR was defined as any relapse occurring within the ipsilateral hemithorax (excluding multiple recurrent lesions in the ipsilateral lung) or involving regional lymph nodes. Relapse detected in any other anatomical sites was classified as DM (28). All instances of ultimate disease progression, whether localized or distant, were thoroughly documented.

Statistical analysis. Time from CCRT to the first locoregional relapse, first DM and the date of last follow-up were recorded. Univariate Cox regression analysis was performed to screen potential prognostic factors, and variables with statistical significance in univariate analysis were further included into multivariate Cox regression to identify independent prognostic factors. Statistical analyses were performed using R Studio (embedded R 4.5.1; Posit Software, PBC) and SPSS 22.0 (IBM Corp.). A nomogram was constructed to develop a prediction model, and receiver operating characteristic (ROC) curves were plotted. Internal validation was performed using bootstrap resampling with 1,000 iterations to generate calibration and decision curve analysis (DCA) curves. Timetoevent recurrence curves were plotted using the Kaplan-Meier method, and subgroup comparisons were performed using the log-rank test. Two-sided $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 1,044 patients were screened in the present study. Among them, 134 consecutive patients met the eligibility criteria and were included in the present study (Fig. 1). Baseline demographic characteristics of all included unresectable stage III driver-gene-negative patients with NSCLC are summarized as follows: A total of 84 male patients and 50 female subjects were included, and the median age of the whole cohort was 68 years old, with an age range from 48-81 years old. Table I shows the clinicopathological characteristics and treatment-related parameters. Of the 134 patients, 54 (40%) had T1-2 disease and 80 (60%) had T3-4 disease. Furthermore, 68 (51%) patients had normalized CYFRA21-1 levels after CCRT, whereas 66 (49%) patients did not.

Patterns of recurrence. During the present study, the median follow-up duration was 20 months (range, 8-34 months). Of the 134 patients, 131 (97.7%) experienced relapse. Ultimately, 66 (49.2%) patients had local recurrence only, 53 (39.5%) had DM only and 12 (8.9%) had both. The locoregional and distant relapse sites are shown in Table SII. Of note, the counts in

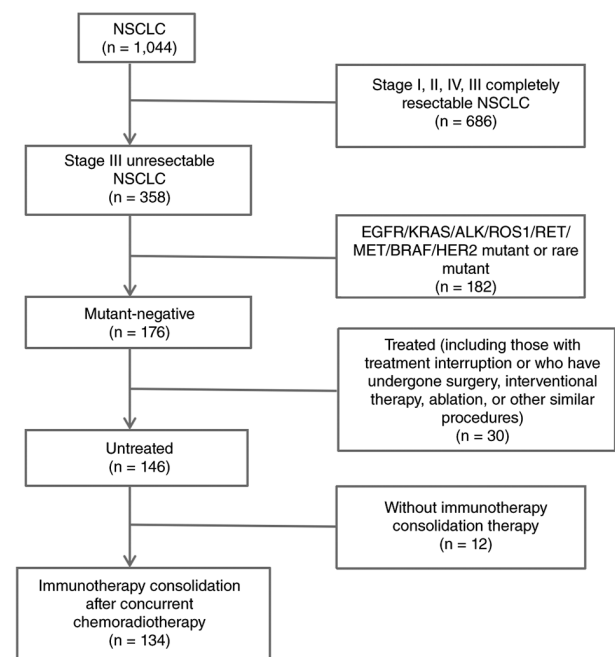


Figure 1. Flowchart for patient enrollment. ALK, anaplastic lymphoma kinase; ROS1, c-ros oncogene 1; RET, rearranged during transfection; MET, MNNG HOS transforming gene; NSCLC, non-small cell lung cancer.

Table SII represent all patients with locoregional or distant relapse (including overlapping cases with concurrent events), rather than exclusive mutually exclusive categories. Of the 131 patients who experienced relapse, 8 (6.1%) received traditional Chinese medicine or palliative therapy due to economic or personal reasons, while the remaining 123 patients received firstline systematic or combined therapy. Detailed postrelapse treatment information is summarized in Table SIII.

Risk factors and predictive nomogram for LRR. An association between the T stage and LRR was reflected by a median LLR of 23 months for T3-4 patients, while median timetoLRR was not reached for T1-2 patients within the followup period (Fig. 2A). Another risk factor was the level of CYFRA21-1 after CCRT (23 vs. 26 months; Fig. 2B). The multivariate analysis identified T3-4 stage disease [hazard ratio (HR), 16.187; 95% confidence interval (CI), 2.052-127.696; $P=0.008$] and abnormal CYFRA21-1 level after CCRT (HR, 2.396; 95% CI, 1.296-4.430; $P=0.005$) as independent risk factors for LRR (Table II).

ROC curve analysis identified a total score cut-off point of 100 to stratify patients into high- and low-risk groups. Patients with a total score < 100 were classified as low risk, and those with a total score ≥ 100 were classified as high risk. When stratified by nomogramderived risk groups, the median timetoLRR was 23 months for the highrisk group; median timetoLRR was not reached for the lowrisk group (Fig. 2C).

A nomogram predicting the cumulative incidence of LRR was created by incorporating T stage and level of CYFRA21-1 after CCRT (Fig. 3A). The internal validation showed that the nomogram had a concordance index of 0.986 (95% CI; 0.968-1.000) and was well calibrated (Fig. 3B). The area under the curve was 0.989 (95% CI; 0.971-1.000), sensitivity was

Table I. Patient characteristics (n=134).

Characteristics	Patients, n (%)
Age, years	
≥60	110 (82)
<60	24 (18)
Sex	
Male	84 (63)
Female	50 (37)
Karnofsky performance status	
90-100	130 (97)
80	4 (3)
Tumor type	
Squamous cell carcinoma	101 (75)
Adenocarcinoma	33 (25)
Pre-treatment T stage	
T1-2	54 (40)
T3-4	80 (60)
Pre-treatment N stage	
N0-1	16 (12)
N2-3	118 (88)
Smoking	
Yes	91 (68)
No	43 (32)
Carcinoembryonic antigen returns to normal after concurrent chemoradiotherapy	
Yes	85 (63)
No	49 (37)
Cytokeratin fragment antigen 21-1 returns to normal after concurrent chemoradiotherapy	
Yes	68 (51)
No	66 (49)
Stable disease after concurrent chemoradiotherapy	
Yes	65 (49)
No	69 (51)
Local recurrence	
Yes	78 (58)
No	56 (42)
Distant metastasis	
Yes	65 (49)
No	69 (51)
N classification ^a	
Minimal N2/single station	69 (62)
Bulky and/or multilevel N2	42 (38)

^an=111.

that the model has high clinical practical value and performance (Fig. 3D).

Discussion

LRR is the most common mode of treatment failure among patients with driver mutation-negative unresectable stage III NSCLC treated with CCRT plus consolidation immunotherapy. The key drivers of failure are tumor heterogeneity, subclinical residual disease, insufficient local radiation dose, inherent radioresistance of tumor cells and a defective anti-tumor immune microenvironment (29-31). Currently, reliable tools to screen individuals at risk of early LRR around the time of treatment completion are lacking. Without risk stratification, standardized one-size-fits-all protocols cannot achieve individualized management. The present study investigated the patterns of recurrence and risk factors for LRR in patients with driver mutation-negative unresectable stage III NSCLC after CCRT. To the best of our knowledge, this is the first large retrospective study focusing on LRR status in this specific patient population.

The present study identified pretreatment bulky tumors (T3-4) and persistently abnormal CYFRA21-1 levels after CCRT as independent risk factors for LRR in patients with driver mutation-negative unresectable stage III NSCLC after CCRT. These findings are consistent with and extend existing evidence (32,33) on LRR risk stratification in locally advanced NSCLC, providing valuable insights into clinical decision-making.

Consistent with present findings, a previous study demonstrated that the LRR rate remains as high as 40% in patients with unresectable stage III NSCLC after receiving CCRT (34). Larger tumor volume or extensive local invasion, such as chest wall or mediastinal invasion, compromises the efficacy of CCRT. Mechanistically, bulky tumors are prone to developing a hypoxic microenvironment, a well-recognized mediator of radioresistance and chemoresistance (35). A total of 20-30% of radiotherapy and chemotherapy treatment failures are attributed to tumor hypoxia (36). Additional DNA repair processes are triggered under hypoxic conditions. Hypoxia-inducible factor 1 subunit α boosts the production of DNA-dependent protein kinase, which is vital for repairing radiation-induced double-strand breaks (36). Additionally, T3-4 tumors often involve important anatomical structures, such as the aorta or main bronchus. The definitive radiation dose in standard CCRT is typically limited to 60-66 Gy to avoid severe normal tissue toxicity, such as esophageal fistula, which can compromise local disease control (8).

The detection of CYFRA21-1 in the blood is a reliable indicator of NSCLC, and its concentration can be used to monitor disease progression and treatment response. This biomarker has high sensitivity and specificity for detecting NSCLC (37). In the present study, the level of CYFRA21-1 gradually increased with lung cancer progression, consistent with the results of a previous study (38). CYFRA21-1 has been reported to notably positively correlate with stages I-III and negatively correlate with stage IV (39). The present study further confirmed that persistent abnormality of this marker (>3.3 ng/ml) after CCRT independently predicted LRR (HR, 2.396; 95% CI, 1.296-4.430; P=0.005), which is highly consistent with

98.7% and specificity was 98.2%, indicating that the model had strong discriminative performance (Fig. 3C). The DCA revealed that the net benefit rate of the clinical prediction model was relatively high across all risk thresholds, indicating

Table II. Prognostic factors for locoregional recurrence.

Variable	Univariable analysis (P-value)	Multivariable analysis	
		HR (95% CI)	P-value
Age (≥ 60 vs. < 60 years)	0.127		
Sex (male vs. female)	0.695		
Karnofsky performance status (90-100 vs. 80)	0.694		
Pathological type (squamous vs. adenocarcinoma)	0.234		
Pre-treatment T stage (T3-4 vs. T1-2)	0.010	16.187 (2.052-127.696)	0.008
Pre-treatment N stage (N0-1 vs. N2-3)	0.575		
Smoking (yes vs. no)	0.330		
Carcinoembryonic antigen returns to normal after concurrent chemoradiotherapy (not normal vs. normal)	0.560		
Cytokeratin fragment antigen 21-1 returns to normal after concurrent chemoradiotherapy (not normal vs. normal)	0.011	2.396 (1.296-4.430)	0.005
N2 classification (minimal N2/single station vs. bulky and/or multilevel N2)	0.552		
Stable disease after concurrent chemoradiotherapy (yes vs. no)	0.186	1.008 (0.493-2.060)	0.982

HR, hazard ratio; CI, confidence interval.

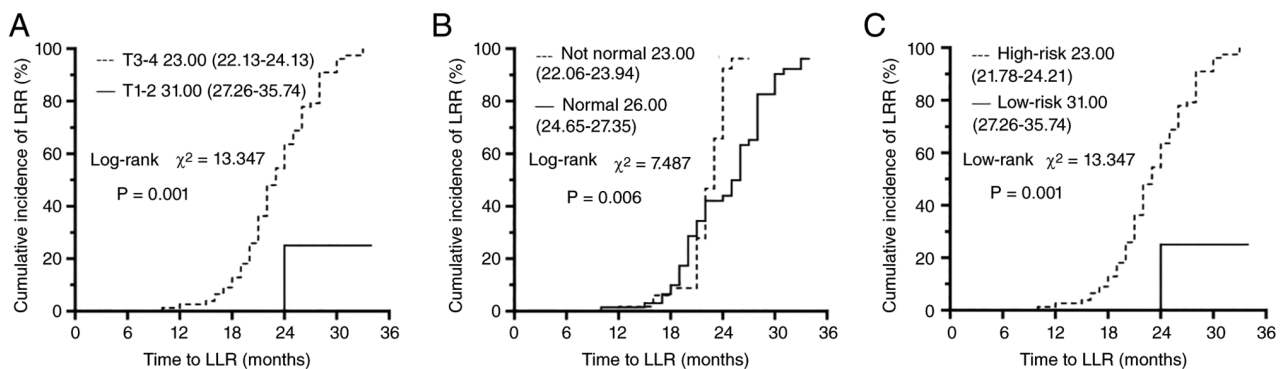


Figure 2. Prognostic factors of LRR. Cumulative incidences of LRR by (A) T stage (T1-2 vs. T3-4); (B) level of carcinoembryonic antigen and cytokeratin fragment antigen 21-1 after concurrent chemoradiotherapy (normal vs. not normal); and (C) risk-group (low-risk vs. high-risk group). LRR, locoregional recurrence.

existing literature (39). From a clinical practice perspective, CYFRA21-1 offers a distinct advantage. Compared with CT or PET-CT, which may miss microresidual lesions < 1 cm, serial serum CYFRA21-1 testing (performed every 4 weeks) enables dynamic monitoring, thereby facilitating the identification of high-risk patients before radiologically evident recurrence.

Unlike previous studies that focused on risk factors (40,41), such as N stage or programmed death-ligand 1 expression, the present study is the first to identify T3-4 tumors and persistently abnormal CYFRA21-1 levels after CCRT as predictive risk factors for LRR through multivariate analysis. The present study has notable clinical implications. First, a visualized nomogram was developed to predict the risk of LRR for driver mutation-negative unresectable stage III NSCLC after CCRT. The model, constructed using easily obtainable

clinical variables, achieved favorable discrimination and calibration. Second, this predictive tool supported individualized risk stratification either before or immediately after CCRT, enabling early identification of patients at risk of early LRR. Third, the independent prognostic factors identified in the present analysis can help improve clinicians' understanding of the population features associated with local treatment failure. This risk stratification strategy may help clinicians implement differentiated surveillance and therapeutic management for distinct risk subgroups.

Intensified surveillance with shortened imaging follow-up intervals is recommended for patients stratified as high risk for LRR. Furthermore, these patients may be eligible for innovative therapeutic strategies, such as local brachytherapy combined with regional nodal IMRT and

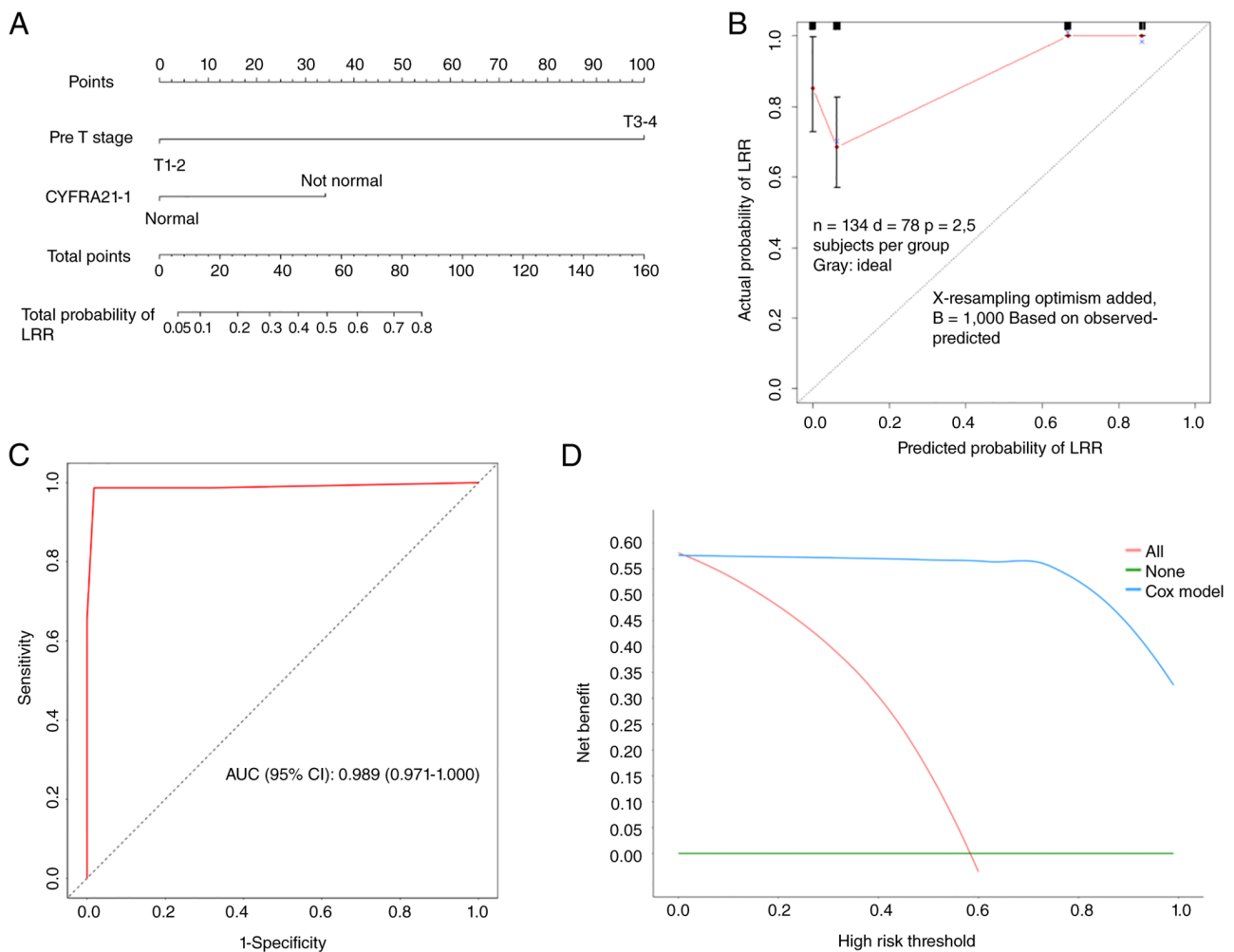


Figure 3. LRR nomogram, calibration curves, ROC curves and DCA curves. (A) The nomogram is created to estimate the cumulative incidence of LRR. The value of one individual patient is located at each variable axis. A straight line drawn upward determines the points received for each variable value. The sum of points is located on the total point axis, and then a straight line is drawn downward to the cumulative incidence of LRR axes to determine the cumulative incidence of LRR. (B) The calibration curves predict the cumulative incidence. (C) The ROC curves and (D) the DCA curves reflect the performance of the model. LRR, locoregional recurrence; CYFRA21-1, cytokeratin fragment antigen 21-1; ROC, receiver operating characteristic; AUC, area under the curve; DCA, decision curve analysis.

neoadjuvant chemotherapy combined with immunotherapy. Brachytherapy offers unique and complementary advantages in the multidisciplinary treatment paradigm for NSCLC. A core strength of brachytherapy lies in its steep dose gradient outside the target volume, thereby overcoming the normal organ dose constraints associated with conventional external beam radiotherapy within the thoracic cavity. Endobronchial brachytherapy and radioactive seed implantation are the primary brachytherapy modalities widely adopted in clinical practice. Endobronchial brachytherapy can achieve curative intent for early-stage tumors limited to the tracheobronchial lumen and deliver effective palliative relief for patients with advanced NSCLC complicated by central airway obstruction and refractory hemoptysis (42). Intraoperative seed implantation has been used as an adjuvant local therapy for early NSCLC with high-risk surgical resection margins. Particularly, CT-guided seed implantation assisted by 3D-printed templates fulfills three critical clinical indications: Definitive radical treatment for early-stage patients who cannot tolerate surgical resection, a local dose-boost technique for locally advanced lesions and

salvage radiotherapy for recurrent tumors after prior surgery or chemoradiotherapy failure (42). Consistent with these clinical merits of interstitial brachytherapy, Xiang *et al* (8) conducted a phase II prospective trial to assess the efficacy and safety of combined 3D interstitial HDR brachytherapy and IMRT targeting regional metastatic lymph nodes in patients with locally advanced NSCLC. During the entire follow-up period, no grade ≥ 2 late radiation-related adverse events were observed. The 2- and 5-year OS rates were 68.0 and 44.5%, respectively. This combined regimen was associated with superior survival outcomes and a favorable toxicity spectrum compared with standard radiotherapy alone. Compared with previous trials (43,44), the present study showed improved survival and toxicity. Patients with any of the high-risk factors (pretreatment T3-4 bulky tumors or persistently abnormal CYFRA21-1 levels after CCRT) may be considered for 3D interstitial HDR brachytherapy.

Neoadjuvant chemotherapy combined with immunotherapy may delay the administration of definitive radiotherapy. However, systemic therapy marks the initiation of local treatment. In the CheckMate-816 trial (45), the

pathological complete response rate reached 24% after 3 cycles of nivolumab plus platinum-based chemotherapy, and the major pathological response rate was 37%. In the AEGEAN (46), KEYNOTE-671 (47) and NADIM II studies (48), the pathological complete response rates ranged from 18 to 37%, whereas the major pathological response rates ranged from 30 to 53%. These findings indicate that upfront systemic therapy does not compromise local control and improves local efficacy in patients with unresectable disease. Therefore, neoadjuvant therapy serves as one of the 'efficacy-enhancing strategies' for unresectable T3-4 stage III NSCLC.

The present study has several limitations. First, the retrospective single-center design may introduce selection bias. The nomogram was only internally validated via bootstrap resampling. Therefore, prospective multicenter external validation is needed to verify its generalizability. Second, the prediction model was constructed using routinely accessible clinical, imaging and therapeutic variables. Peripheral blood biomarkers and standardized physical status metrics were not included due to limitations in the archived retrospective data. Incorporating these parameters may enhance the performance of the model. Third, the study population was limited to patients with driver mutation-negative unresectable stage III NSCLC treated with CCRT followed by consolidation immunotherapy, which may restrict extrapolation to other NSCLC populations. Fourth, the optimal CYFRA21-1 cutoff has not been established, and variability in reference ranges across testing platforms may impede widespread clinical application. Finally, genomic testing used a targeted multigene PCR panel instead of whole-genome sequencing. Such hotspot-focused assays fail to identify rare or unreported structural variants outside the predefined gene regions. Further studies with prospectively collected biomarker and physical status data from subsequent cohorts are needed for external validation and model refinement.

Collectively, the established nomogram and identified risk factors facilitate risk stratification of LRR, which may support individualized surveillance and optimized therapeutic strategies for mutation-negative unresectable stage III NSCLC after CCRT.

In conclusion, pretreatment T3-4 bulky tumors and persistently abnormal CYFRA21-1 levels after CCRT are high-risk factors for LRR in patients with driver mutation-negative unresectable stage III NSCLC. High-risk patients may require neoadjuvant therapy or 3D interstitial HDR brachytherapy to reduce LRR. Further prospective studies are needed to validate these findings and translate this risk stratification model into effective interventions to improve survival outcomes.

Acknowledgements

Not applicable.

Funding

The present study was supported by grants from the National Natural Science Foundation of Chongqing (grant no. CSTB2022NSCQ-MSX1239) and the National Reserve Talents Program in the Field of Health of Chongqing (grant no. HBRC202404).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YS and ZY were responsible for the study conception and research design. ZY was involved in the establishment of research framework and experimental workflows. JL and YQ performed experimental verification and data reproducibility checks. JL performed the statistical analysis and bioinformatics data processing, the clinical sample collection and case data acquisition. JL and YQ were responsible for dataset sorting, cleaning and management. Code programming and computational tool operation was performed by YQ. JL drafted the original manuscript and revised the manuscript. YS provided overall study supervision and project coordination and management. Funding was acquired by JL and YS. YS and JL confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

All experiments in the present retrospective study were reviewed and approved by the Institutional Ethics Committee of The Second Affiliated Hospital of Chongqing Medical University [approval no. 2025(168)]. The Ethics Committee granted a formal waiver of written informed consent from individual participants, given that only retrospective archival clinical data were analyzed in this research. The present work is an extended retrospective sub-analysis under ethics approval no. 2025(168). While the original ethical protocol primarily focused on stage IV driver-negative NSCLC, the same treatment framework and archived de-identified patient cohort also included unresectable stage III cases, which were separately analyzed in the present study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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