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Research Paper

Genomic Profiling, Risk Stratification, and Post-Transformation Treatment Outcomes in Patients with Transformed Small-Cell Lung Cancer: A Multicenter Analysis

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ABSTRACT

Background: Transformed small-cell lung cancer (T-SCLC) is an increasingly recognized resistance mechanism in *EGFR*-mutant lung adenocarcinoma. This study aimed to identify early predictors of histologic transformation and evaluate post-transformation treatment outcomes.

Methods: We retrospectively collected 163 T-SCLC patients from five Chinese centers. Next-generation sequencing was performed on 60 *EGFR*-mutant patients, including 47 paired primary–transformed samples. Integrated genomic and clinical analyses were conducted to delineate molecular features and survival outcomes.

Results: Among 150 *EGFR*-mutant patients, the median time to SCLC transformation was 25.8 months and median post-transformation overall survival (OS) was 14.2 months. Clinical and survival data for the 13 *EGFR* wild-type patients are reported descriptively given the limited sample size. Among 108 treatment-evaluable patients, first-line *EGFR*-TKI plus chemotherapy, chemotherapy alone, and immune checkpoint inhibitors (ICIs) plus chemotherapy yielded median progression-free survival (PFS) of 6.2, 5.30, and 4.07 months ($P = 0.041$) and median OS of 21.2, 27.6, and 13.6 months ($P = 0.193$). In later-line therapy, taxane-based regimens achieved a median PFS of 6.93 months, outperforming camptothecin-based (1.13 months) and other regimens (1.90 months; $P = 0.049$). High evolutionary diversity was associated with shorter post-transformation OS (6.77 vs. 11.10 months), with restricted cubic spline analysis showing a nonsignificant trend toward a nonlinear association ($P = 0.055$). Age, *RB1/NTRK1* mutation, and secondary T790M mutation were identified as independent risk factors and integrated into a predictive model with high accuracy.

Conclusions: This study establishes a clinically applicable model for early prediction and risk stratification of SCLC transformation. Taxane-based regimens emerge as a promising later-line therapeutic option for T-SCLC.

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Background

Lung adenocarcinoma (LUAD) harboring epidermal growth factor receptor (*EGFR*) mutations constitutes a substantial proportion of non–small cell lung cancer (NSCLC), particularly in East Asian populations, where it accounts for nearly 50% of cases.([1]) The advent of *EGFR* tyrosine kinase inhibitors (*EGFR*-TKIs) has revolutionized the management of *EGFR*-mutant LUAD, markedly improving survival and quality of life.([2]) Nevertheless, acquired resistance remains inevitable, with histologic transformation to small-cell lung cancer (SCLC) emerging as a critical resistance mechanism in a subset of patients. Accumulating evidence indicates that approximately 3–14% of *EGFR*-mutant NSCLC patients undergo SCLC transformation during the disease course.([3])

Transformed SCLC (T-SCLC) is characterized by aggressive clinical behavior, poor prognosis, and the absence of an established standard treatment. Current expert consensus recommends etoposide plus platinum (EP), analogous to *de novo* SCLC; however, the clinical benefit is limited.([4]) In *EGFR*-mutant cases, continuation of *EGFR*-TKIs in combination with chemotherapy has been proposed, although supporting evidence remains sparse. Whole-exome sequencing studies have demonstrated persistence of *EGFR* pathway alterations in *EGFR*-mutant T-SCLC, providing a biological rationale for continued *EGFR*-TKIs use after transformation.([5]) Retrospective analyses have suggested that *EGFR*-TKIs combined with chemotherapy may prolong PFS compared with chemotherapy alone, yet no significant OS benefit has been observed.([6]) Consequently, the role of *EGFR*-TKI continuation after transformation remains controversial. Moreover, prior studies report median PFS of only 3–6 months with EP regimens, with or without *EGFR*-TKIs or programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors, highlighting the paucity of effective subsequent-line treatment options.([7–9])

Equally challenging is the early identification of patients at high risk for SCLC transformation. Potential predictive biomarkers, including co-mutations in *TP53* and *RB1*, have been proposed.([3,5,10]) However, most evidence derives from small cohorts or single-center studies, limiting robustness and generalizability. The absence of reliable predictive models impedes early intervention and individualized treatment strategies, underscoring the need for large, multicenter investigations.

In this study, we address the critical and understudied challenge of SCLC transformation in *EGFR*-mutant LUAD by leveraging a large multicenter cohort. We identify key clinical and molecular risk factors, develop a novel predictive model for early risk stratification, and propose optimized treatment strategies tailored to this unique and clinically challenging patient population.

Methods

Patients and data collection

We performed a multicenter retrospective chart review of patients with NSCLC who underwent re-biopsy at five cancer centers in China—Shandong Cancer Hospital and Institute, Shanxi Province Cancer Hospital, Guangdong Lung Cancer Institute, Beijing University Cancer Hospital, and the Cancer Hospital of the Chinese Academy of Medical Sciences—between June 2011 and July 2024. All slides and tissue specimens were obtained with prior informed consent and approval from the Ethics Committees of the participating institutions. Each participant provided written informed consent in accordance with the Declaration of Helsinki, and all methods were conducted in compliance with ethical standards. Collected data included demographics, tumor histology, molecular pathology, treatment histories, and clinical outcomes. SCLC transformation was independently confirmed by two pathologists based on histologic or cytologic evaluation using routine hematoxylin and eosin staining, in accordance with the 2015 WHO classification. Immunohistochemistry (IHC) was performed when required to clarify ambiguous morphologic features or resolve differential diagnoses, particularly in small biopsy specimens affected by crush artifacts.

Genomic Profiling

EGFR mutation status was assessed in all baseline samples using DHPLC or ADx-ARMS. Comprehensive genomic profiling was conducted by next-generation sequencing across participating centers, with paired tumor–plasma–normal samples sequenced on Illumina platforms. Somatic variants, copy-number alterations, and mutational signatures were identified using established analytical pipelines, including Mutect2, CNVkit, and GISTIC2.0. Detailed sequencing protocols, quality metrics, and bioinformatic workflows are provided in the Supplementary Methods.

Clonal evolution and tumor heterogeneity analysis

Tumor purity was estimated using Allele-Frequency-based Imputation of Tumor Purity (All-FIT), an iterative weighted least-squares approach that infers purity from allele-frequency distributions derived from high-depth targeted sequencing. Cancer cell fractions (CCFs) were subsequently inferred with PyClone, incorporating All-FIT purity estimates and copy-number states from CNVkit. Variants detected at both pre- and post-transformation time points were classified as truncal mutations, whereas alterations present exclusively in either sample were designated as branch mutations. Patient-specific evolutionary trajectories were reconstructed using an in-house pipeline integrating CCF estimates, mutation timing, and clonal topology. Temporal tumor heterogeneity during transformation was quantified as the proportion of branch mutations among all detected mutations. Evolutionary diversity was measured using Shannon entropy calculated from CCF-weighted clonal proportions. Patients were stratified into high- and low-diversity groups using maximally selected rank statistics based on post-transformation overall survival.

Prediction model for SCLC transformation

Candidate risk factors were evaluated using univariate and multivariate binary logistic regression analyses. Patients were randomly assigned to a training cohort ($n = 107$) and a test cohort ($n = 45$) at a 7:3 ratio. Random forest and support vector machine (SVM) algorithms were trained on the training cohort, with model performance assessed in the test cohort. External validation was conducted in an independent cohort ($n = 34$). Predictive performance was evaluated using receiver operating characteristic (ROC) analysis.

Data comparison and Statistical analysis

Baseline clinicopathological characteristics were compared using the χ^2 test for categorical variables and the Mann–Whitney U test for continuous variables. A two-sided P-value < 0.05 was considered statistically significant. Progression-free survival (PFS) was defined as the interval from treatment initiation to documented disease progression or death, and overall survival (OS) was calculated from diagnosis to death. Time to transformation was measured from NSCLC diagnosis to histologically confirmed SCLC transformation, and post-transformation OS was defined from the date of transformation to death. The last follow-up date was June 23, 2025. Survival curves were estimated using the Kaplan–Meier method and compared with the log-rank test. Prognostic factors were assessed using univariate and multivariate Cox proportional hazards models.

For comparative genomic analyses, somatic mutation data from three independent cohorts were included: (1) the BENEFIT prospective cohort of *EGFR*-mutant lung adenocarcinoma (n = 162 at baseline, of whom 122 had post-progression biopsies with genomic profiling available);([11]) (2) a real-world internal cohort of *EGFR*-mutant LUAD patients (n = 27 at baseline, of whom 20 had post-progression biopsies with genomic profiling available); and (3) a *de novo* SCLC cohort from cBioPortal (George *et al.*, *Nature*, 2015; $n = 110$).([12]) Cohorts (1) and (2) together comprised a baseline non-transformed *EGFR*-mutant LUAD cohort of 189 samples and a post-progression non-transformed *EGFR*-mutant LUAD cohort of 142 samples. All post-progression biopsies in cohorts (1) and (2) were confirmed by histopathologic review to maintain LUAD morphology without evidence of SCLC transformation. Differences in mutation frequencies were evaluated using χ^2 or Fisher's

exact tests, as appropriate, with Benjamini–Hochberg correction to control the false discovery rate. Mutations with $P < 0.05$ and FDR < 0.1 were considered significant. To minimize bias arising from differences in sequencing coverage across centers, analyses were restricted to genes consistently captured by all platforms. Mutation burden was normalized to the median mutation count within each sequencing method, yielding a Normalized Mutation Count that was used for dichotomization (high *vs*. low) in subsequent risk modeling. All statistical analyses were performed using R software (v4.3.2).

Results

Cohort characteristics and clinical course of SCLC transformation

A total of 163 patients initially diagnosed with non–small cell lung cancer (NSCLC) who subsequently developed histologic transformation to small-cell lung cancer (SCLC) were included in this study (Fig. 1). The median age at diagnosis was 56 years (range, 24–77), including 86 females (52.8%) and 77 males (47.2%). Among these patients, 150 (92.0%) harbored *EGFR* mutations, whereas 13 (8.0%) were *EGFR* wild-type. Within the *EGFR*-mutant cohort, exon 19 deletions were identified in 94 patients, L858R point mutations in exon 21 in 47 patients, L861Q mutations in exon 21 in three patients, G719A and G719X mutations in exon 18 in two and one patients, respectively, and T790M mutations in exon 20 in two patients (Table 1).

In the *EGFR*-mutant cohort, the median interval from NSCLC diagnosis to SCLC transformation was 25.8 months (Fig. 2A). The median overall survival following SCLC transformation was 14.2 months (95% CI: 11.2–18.5) (Fig. 2B). Among the 13 *EGFR* wild-type patients, none had received prior *EGFR*-targeted therapy before transformation; their median time to transformation was 24.4 months, and median post-transformation OS was 10.4 months (95% CI: 9.33–NA).

Treatment outcomes in the first-line and later-line settings after transformation

Clinical treatment data were available for 108 patients, including 96 *EGFR*-mutant and 12 *EGFR* wild-type patients. Among *EGFR*-mutant patients receiving first-line therapy after transformation, 23 were treated with *EGFR*-TKIs combined with chemotherapy (TKIs+C), 38 with chemotherapy alone (C), and 11 with an immune checkpoint inhibitor plus chemotherapy (ICI+C) (Table S1). To minimize treatment-related confounding, all chemotherapy regimens were uniformly based on etoposide/platinum (EP). Median progression-free survival (mPFS) for TKIs+C, C, and ICI+C was 6.2 months (95% CI: 5.13–11.33), 5.30 months (95% CI: 3.77–6.27), and 4.07 months (95% CI: 2.67–NA), respectively ($P = 0.041$; Fig. 2C). Median OS was 21.2 months (95% CI: 12.2–NA) for TKIs+C, 27.6 months (95% CI: 26.7–NA) for C, and 13.6 months (95% CI: 11.2–NA) for ICI+C ($P = 0.193$).

Table 1
Clinical characteristics of patients with NSCLC transforming to SCLC.

	EGFR-mut(n = 150), %	*EGFR*-wt(n = 13), %	Total(n = 163), %	P
Age, median (range)	55 (24–77)	69 (56-75)	56 (24–77)	< 0.001
Sex, *n* (%)				
Female	86 (57.3%)	0	86 (52.8%)	< 0.001
Male	64 (42.7%)	13 (100%)	77 (47.2%)	
Smoking history, *n* (%)				< 0.001
Never smoker	121 (80.7%)	3 (23.1%)	124 (76.1%)	
Smoker	29 (19.3%)	10 (76.9%)	39 (23.9%)	
EGFR mutation at diagnosis, *n* (%)				
19del	94 (62.7%)	-	94 (57.7%)	
20ins	1 (0.7%)	-	1 (0.6%)	
G719A	2 (1.3%)	-	2 (1.2%)	
G719X	1 (0.7%)	-	1 (0.6%)	
L858R	47 (31.3%)	-	47 (28.8%)	
L858R+T790M	2 (1.3%)	-	2 (1.2%)	
L861Q	3 (2%)	-	3 (1.8%)	
WT	-	13 (100%)	13 (8%)	
First line TKI				
1st	99 (66.4%)	-	99 (66.4%)	
2nd	13 (8.7%)	-	13 (8.7%)	
3rd	37 (24.8%)	-	37 (24.8%)	
3rd generation TKI before transformation				
No	42 (28.2%)	-	42 (28.2%)	
Yes	107 (71.8%)	-	107 (71.8%)	
Lines of TKIs pre-transformation				
1	76 (51%)	-	76 (51%)	
≥ 2	73 (49%)	-	73 (49%)	

Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; *EGFR*-mut, *EGFR*-mutant; *EGFR*-wt, *EGFR* wild-type; TKI, tyrosine kinase inhibitor;

In the second-line and later treatment settings, seven patients received taxane-based regimens, eight received camptothecin-based regimens, and nine received other therapies (Table S2). The mPFS was 6.93 months (95% CI: 1.63–NA) with taxane-based regimens, compared with 1.13 months (95% CI: 1.00–NA) for camptothecin-based regimens and 1.90 months (95% CI: 1.13–4.1) for other treatments ($P = 0.049$, Fig. 2D). Given the limited sample size and treatment heterogeneity of the EGFR–wt subgroup, their clinical courses are described in

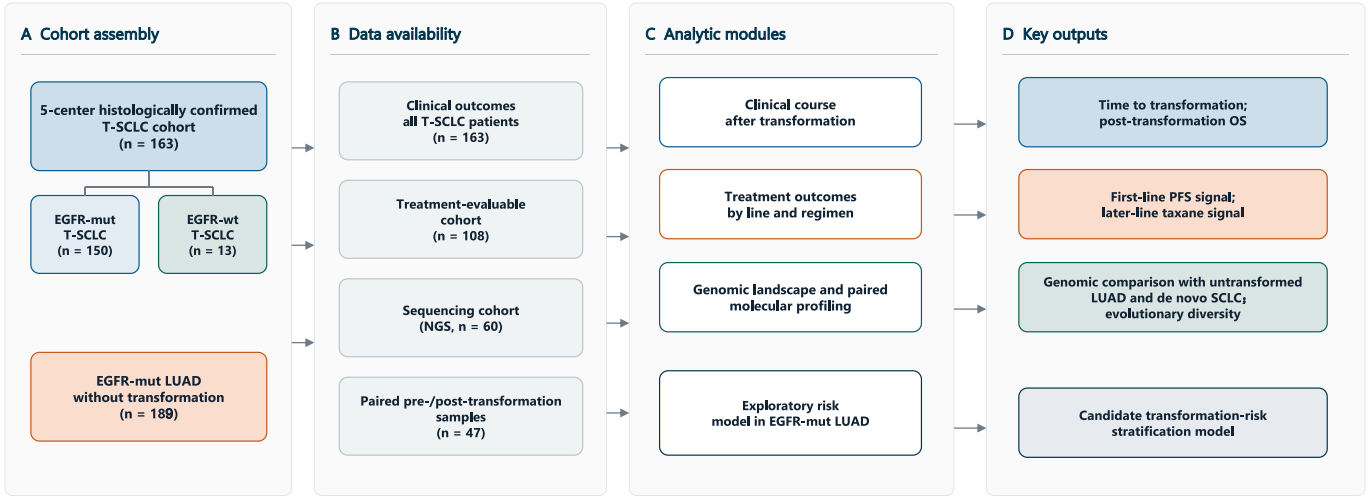

Fig. 1. Study design and patient selection workflow.

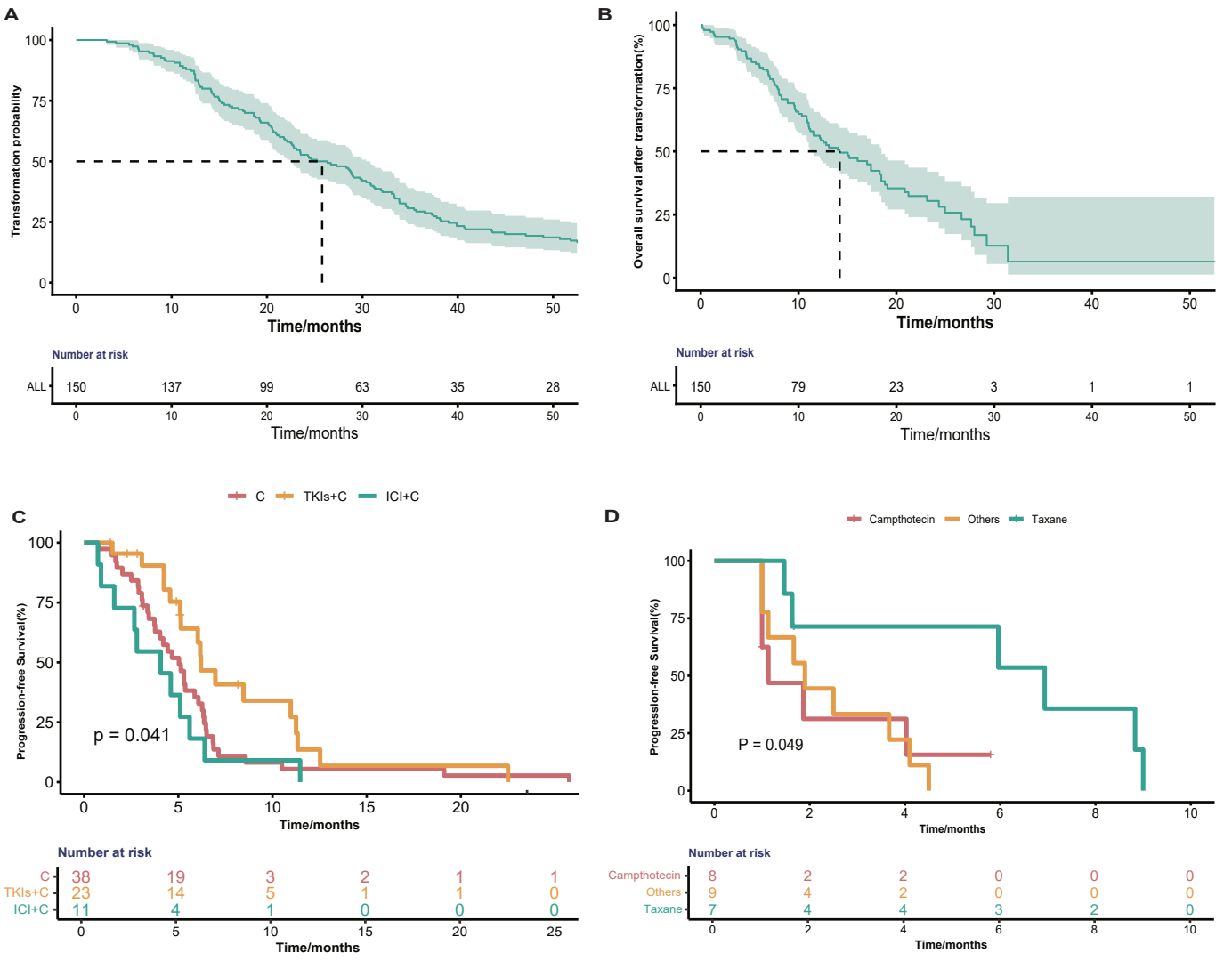

Fig. 2. Survival outcomes and treatment responses in patients with *EGFR*-mutant transformed SCLC. (A) Time to SCLC transformation in patients with *EGFR*-mutant NSCLC; (B) Overall survival from the time of SCLC transformation in patients with *EGFR*-mutant transformed SCLC; (C) Progression-free survival following first-line therapy in *EGFR*-mutant patients after SCLC transformation; (D) Progression-free survival according to treatment regimens in second-line and subsequent therapies among patients with *EGFR*-mutant transformed SCLC. Abbreviations: SCLC, small-cell lung cancer; TKIs+C, EGFR-TKIs combined with chemotherapy; ICI+C, immune checkpoint inhibitor combined with chemotherapy; C, chemotherapy.

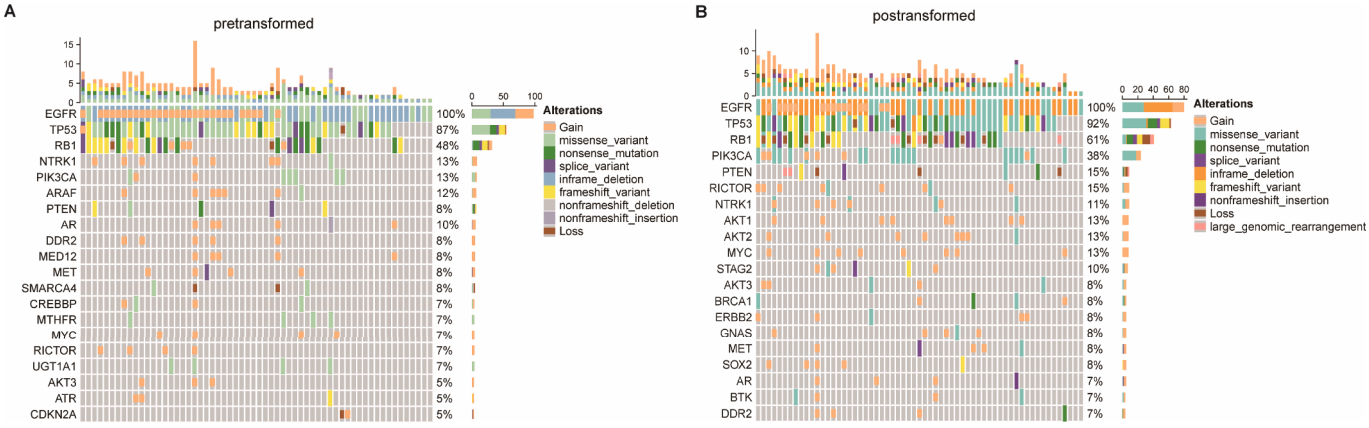

Fig. 3. Genomic landscape of *EGFR*-mutant patients before and after SCLC transformation. (A) Heatmap showing recurrent genetic alterations in 60 pre-transformation samples from patients with *EGFR*-mutant lung adenocarcinoma; (B) Heatmap showing recurrent genetic alterations in the 60 post-transformation SCLC samples. Genetic alterations are color-coded according to alteration type, as indicated in the legend. The bar plots above each heatmap indicate the number of alterations per sample, and the percentages on the right denote the frequency of alterations in each gene.

Supplementary Table S3.

Genomic landscape and paired molecular profiling of primary and transformed tumors

Among the 163 patients with histologic transformation, 63 underwent NGS/WES testing prior to transformation, including 60 *EGFR*-mutant and three *EGFR* wild-type tumors. Another 63 patients underwent NGS testing after transformation, again comprising 60 *EGFR*-mutant and three *EGFR* wild-type cases.

In *EGFR*-mutant samples analyzed before transformation, the most frequent co-occurring alterations were *TP53* (52/60, 87%) and *RB1* (29/60, 48%) (Fig. 3A). Analysis of paired pre- and post-transformation samples (n = 47) revealed a trend toward increased *PIK3CA* alterations after transformation (40.43% *vs.* 8.51%, P_{adj} =0.089) (Table S4). Compared with the baseline non-transformed *EGFR*-mutant LUAD samples (n =189, Fig. S3A), *EGFR*-mutant pre-transformation LUAD samples (n = 60, Fig. 3A) exhibited significantly higher mutation frequencies of *RB1* (48.33% *vs*. 19.05%, $P_{adj} < 0.001$), *NTRK1* (13.33% *vs*. 1.06%, $P_{adj} < 0.001$), and *PMS2* (11.67% *vs*. 0.53%, $P_{adj} < 0.001$) (Table S5).

Relative to the *de novo* SCLC cohort, transformed SCLC samples demonstrated markedly higher frequencies of *EGFR* (93.33% *vs*. 3.64%, $P < 0.001$), *PIK3CA* (38.33% *vs*. 3.64%, $P < 0.001$), *AKT2* (13.33% *vs*. 0.91%, $P = 0.02$), and *MYC* (13.33% *vs*. 0.91%, $P = 0.02$) mutations, alongside a significantly lower frequency of *LRP1B* alterations (5.00% *vs*. 48.18%, $P < 0.001$) (Table S6).

Comparisons between transformed SCLC samples and post-progression non-transformed samples further identified significant differences in mutation frequencies for *RB1* (60.00% *vs*. 14.79%, $P < 0.001$), *TP53* (91.67% *vs*. 52.82%, $P < 0.001$), *PIK3CA* (38.33% *vs*. 5.63%, $P < 0.001$), *NTRK1* (11.67% *vs*. 0.70%, $P = 0.011$), *AKT1* (13.33% *vs*. 1.41%, $P = 0.011$), *PTEN* (15.00% *vs*. 2.82%, $P = 0.023$), and *STAG2* (10.00% *vs*. 0.70%, $P = 0.023$) (Table S7).

Among the 3 *EGFR* wild-type patients with SCLC transformation who had genomic sequencing data available, all 3 harbored *TP53* mutations, and 1 also had an *RB1* mutation.

Evolutionary diversity and its association with post-transformation survival

Clonal reconstruction of the 47 paired samples revealed extensive genomic remodeling during SCLC transformation, characterized by the emergence of numerous branch mutations in transformed tumors. Evolutionary diversity varied substantially among patients, reflecting heterogeneous clonal complexity. Using the optimal cutoff, 10 patients were classified as having high evolutionary diversity and 37 as having low diversity. Patients in the high-diversity group experienced significantly worse post-transformation survival, with a median OS of 6.77 months (95% CI: 5.20–NA) compared with 11.10 months (95% CI: 7.97–18.3) in the low-diversity group ($P = 0.007$) (Fig. S3).

Restricted cubic spline analysis showed a trend toward an overall association between evolutionary diversity and post-transformation OS ($P = 0.070$), with a suggestion of a nonlinear relationship that did not reach statistical significance (P for nonlinearity = 0.055).

Construction and validation of a predictive model for SCLC transformation

To develop a robust predictive model for SCLC transformation, clinical variables and genomic features derived from NGS/WES data were systematically evaluated. Univariate and multivariate logistic regression analyses identified age, *RB1* mutation, *NTRK1* mutation, and secondary *EGFR T790M* mutation as independent risk factors for transformation (Fig. 4B; Table S8). Based on these variables, predictive models were constructed using Random Forest (RF) and Support Vector Machine (SVM) algorithms. The internal cohort (n = 152) was randomly divided into a training set (70%, n = 107) and a test set (30%, n = 45). Model performance was assessed in the test set and subsequently validated in an independent external cohort (n = 34).

Receiver operating characteristic (ROC) analysis demonstrated superior discriminative performance of the RF model compared with the SVM model, with an ROC of 0.957 in the test cohort and 0.986 in the external validation cohort (Fig. 4E; Fig. 4F). In the test cohort, the RF model achieved a sensitivity of 93.3% and a specificity of 96.7%. Robust performance was further confirmed in the external validation cohort, which included seven transformed and 27 untransformed cases, yielding a sensitivity of 100% and a specificity of 92.6%. The performance of the SVM model is detailed in Supplementary Material 1 and Fig. S2.

Discussion

This retrospective study—the largest to date examining NSCLC with small-cell transformation—highlights the aggressive clinical course and poor prognosis of transformed SCLC (T-SCLC), underscoring the critical need for early identification. Although prior studies have reported genetic and signaling alterations associated with transformation, their limited sample sizes and lack of external validation have constrained clinical translation. By analyzing a substantially larger, multicenter cohort, we identified and validated key risk factors for transformation and developed a predictive model for T-SCLC. Clinically, our findings suggest that *EGFR*-TKIs may be considered a preferred first-line option in *EGFR*-mutant T-SCLC, while taxane-based regimens represent a rational second-line strategy, with important implications for optimizing treatment sequencing.

Most previous investigations have focused on *EGFR*-mutant disease, with sparse data on *EGFR* wild-type cases. Although Ding et al. reported longer post-transformation survival in *EGFR* wild-type compared with *EGFR*-mutant patients (10.0 *vs*. 6.0 months, $P = 0.016$),([13]) the single-center nature of the study underscores the need for larger multicenter datasets to better define the prognostic impact of *EGFR* status after transformation. In our cohort, 13 *EGFR* wild-type patients developed SCLC transformation, with a median time to transformation of 24.4 months. Given the limited number of *EGFR* wild-type cases, observations in this subgroup should be interpreted cautiously. By contrast, the larger *EGFR*-mutant cohort allowed a more robust characterization of clinical outcomes, with a median time to transformation of 25.8 months and a median post-transformation OS of 10.4 months. These findings provide clinically relevant benchmark data for *EGFR*-mutant t-SCLC.

At present, no standard therapy exists for T-SCLC. Current guidelines generally recommend treatment analogous to *de novo* SCLC, with platinum–etoposide–based chemotherapy combined with immune checkpoint inhibitors as first-line therapy.([14–16]) However, in our cohort, chemo-immunotherapy conferred limited benefit in T-SCLC. In contrast, *EGFR*-TKI plus chemotherapy achieved the most favorable PFS, suggesting that *EGFR* signaling may persist in a subset of transformed tumors and that TKI-based combinations may be more effective in this setting. The absence of a corresponding OS benefit nonetheless reflects the aggressive biology of SCLC, in which the transformed phenotype rapidly predominates and TKI responses are transient.

The role of immunotherapy in *EGFR*-mutant NSCLC with SCLC transformation remains controversial. Multiple studies have demonstrated minimal activity of PD-1/PD-L1 inhibitors, with median PFS ranging from 1.3 to 1.6 months, although Wu et al. reported a modestly longer mPFS of 5.1 months in a small cohort.([7]) Consistent with these data, the poor outcomes observed with immune checkpoint inhibitors—either alone or combined with chemotherapy—in our study reinforce their limited efficacy in transformed SCLC. This inferior response may reflect the intrinsically “immune-cold” phenotype of EGFR-driven tumors,([17]) in which immune checkpoint blockade provides limited benefit and the expected synergy between chemotherapy and immunotherapy is attenuated.([18,19]) Consequently, chemotherapy remains the therapeutic backbone, while novel approaches targeting lineage plasticity or tumor microenvironment reprogramming merit further investigation.([4])

To date, etoposide–platinum (EP) remains the only clinically validated regimen for SCLC transformation following EGFR-TKI failure.([6]) Therapeutic options beyond EP are exceedingly limited. Emerging

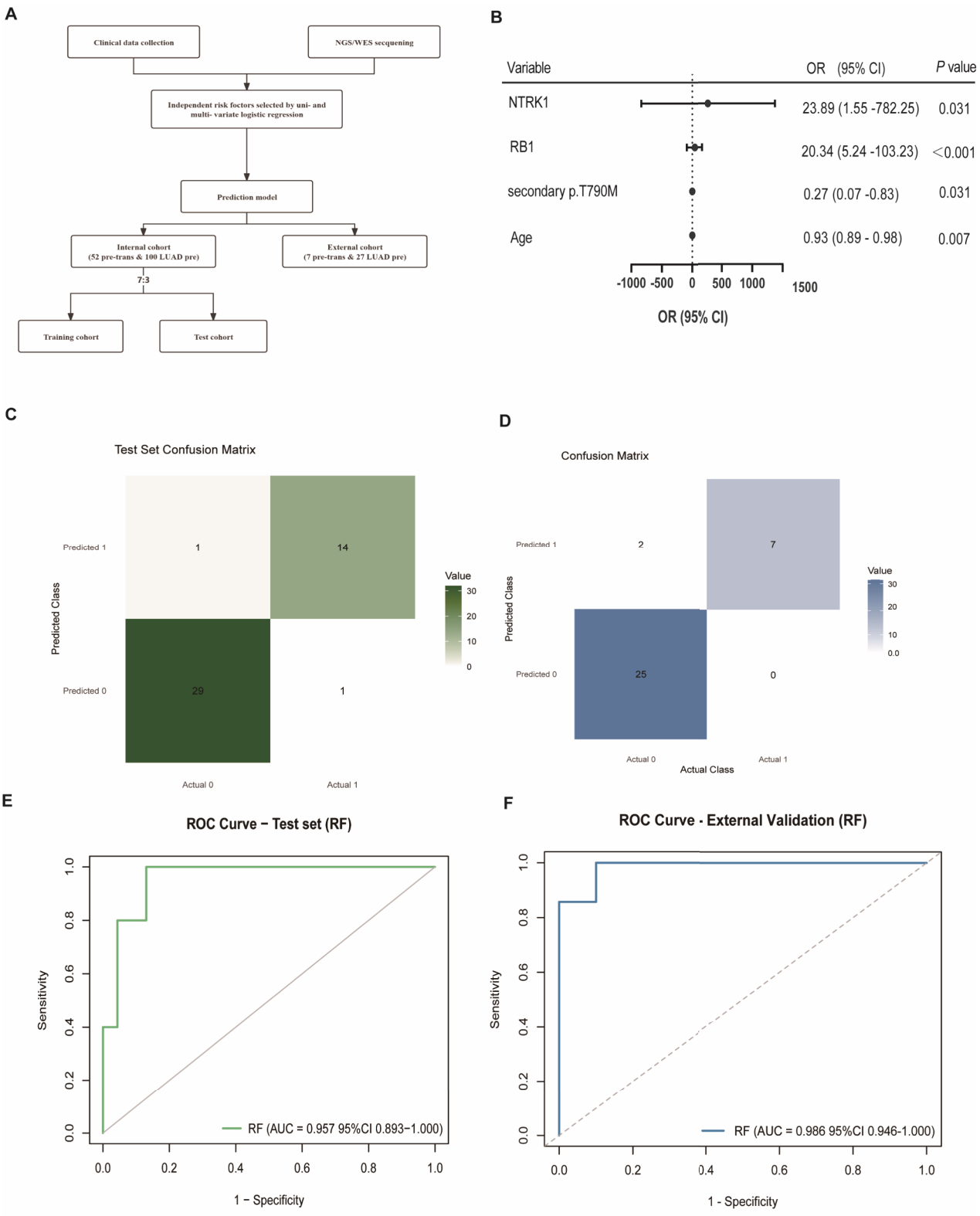

Fig. 4. Development and validation of the prediction model. (A) Flowchart illustrating the process of developing the prediction model. Clinical data and NGS sequencing were used to identify independent risk factors selected by univariate and multivariate logistic regression, followed by model construction with internal and external cohorts; (B) Forest plot showing the odds ratios (OR) and 95% confidence intervals (CI) for the independent risk factors identified in the prediction model; (C) Confusion matrix for the test set, showing the model's predicted versus actual classification outcomes; (D) Confusion matrix for external validation, demonstrating the model's performance on the external cohort; (E) Receiver operating characteristic (ROC) curve for the test set, with area under the curve (AUC) reported for the random forest model. (F) ROC curve for external validation, showing the AUC for the random forest model on the external cohort.

evidence, however, suggests that taxane-based therapies may have clinically meaningful activity in *EGFR*-mutant T-SCLC. A prior study reported a response rate of 71% with paclitaxel or nab-paclitaxel, whereas no responses were observed with docetaxel, indicating potential heterogeneity within the taxane class.([9]) In line with these findings, taxane-based regimens in our cohort achieved a median PFS of 6.93 months in later-line settings—a notable benefit given the scarcity of effective salvage therapies. Collectively, these data support taxanes as a promising therapeutic option, either alone or in combination strategies, beyond first-line treatment. Other novel approaches are also being explored. A recent study by Cooper et al. reported limited clinical benefit with tarlatamab in EGFR-mutant T-SCLC, suggesting that the activity of DLL3-directed therapy in this setting may be less favorable than that observed in de novo SCLC.([20]) Further studies are needed to better define the role of DLL3-targeted treatment in transformed SCLC.

Beyond treatment considerations, our findings also raise questions regarding subgroup-specific susceptibility to transformation. Although only one patient in our cohort harbored an EGFR exon 20 insertion mutation and did not receive an exon 20-specific TKI, the recent availability of agents such as sunvozertinib has made sustained targeted therapy feasible in this previously undertreated population.([21,22]) This evolving treatment landscape raises the possibility that prolonged TKI-mediated selective pressure could increase the incidence of SCLC transformation in this subgroup, an issue that warrants prospective surveillance.

Suda *et al.* described a complementary relationship between SCLC transformation and acquisition of the *EGFR* T790M secondary mutation.([23]) Lesions undergoing SCLC transformation rarely harbor T790M, whereas this mutation is more frequently detected in residual adenocarcinoma components after therapy,([24]) suggesting divergent evolutionary pathways: T790M preserves *EGFR* dependency, whereas SCLC transformation reflects a shift toward *EGFR* independence. A subsequent multicenter retrospective study similarly reported the absence of T790M mutations in patients with SCLC transformation after first- or second-generation TKI therapy, with 15 of 19 previously T790M-positive cases reverting to wild-type status upon transformation.([25]) Consistent with these observations, T790M mutations were detected in only 10 of 59 cases in our cohort. Together, these findings indicate that secondary T790M acquisition and SCLC transformation are largely mutually exclusive resistance mechanisms, underscoring distinct evolutionary trajectories under *EGFR*-TKI selective pressure and emphasizing the importance of re-biopsy to guide subsequent treatment decisions.

Baseline alterations in *TP53* and *RB1* have been implicated as predictors of SCLC transformation. Lee *et al.* reported that concurrent loss-of-function mutations in both genes increased the risk of transformation by 43-fold,([26]) while other studies observed RB1 loss in all transformed cases but none in untransformed tumors, with no transformation occurring in *EGFR*-mutant lung cancers lacking *TP53/RB1* alterations.([10]) In our cohort, *TP53* and *RB1* mutations were highly prevalent both before (87% and 48%) and after transformation (92% and 61%). Beyond these canonical tumor suppressors, alterations in the PI3K/AKT pathway—central to cell growth and metabolism—were also frequent.([27]) Prior transcriptomic analyses have shown upregulation of PI3K/AKT-related genes (*PIK3CA*, *PIK3R1*, *AKT3*) in transformed SCLC,([27]) consistent with our identification of recurrent *PTEN* and *AKT1/2/3* alterations.

Notably, *NTRK1* alterations appeared enriched in paired pre- and post-transformation samples, raising the possibility that this pathway may be involved in the evolution of transformed SCLC. Recent studies have shown that SCLC exhibits neuronal-like transcriptional programs and engages in neuron–cancer interactions through neurotransmitter-mediated signaling that promotes tumor growth and plasticity, providing a biologically relevant context for this observation.([28]) As the detected events were mainly copy-number gains or missense mutations rather than canonical NTRK fusions, further validation and mechanistic studies are needed to clarify their functional and therapeutic relevance.

Several predictive models for SCLC transformation have been reported previously. Huang *et al.* developed a model based on 55 *EGFR*-mutant cases from the Guangdong Lung Cancer Institute, while Xing *et al.* proposed an RNA-based transcriptomic model derived from 36 cases.(30,31) In contrast, our study leveraged a larger cohort and employed a DNA-based approach, which may offer greater clinical practicality given its compatibility with routine genomic testing. These features enhance the robustness and translational relevance of our model for identifying patients at high risk of SCLC transformation.

This study has several limitations. Its retrospective design may have introduced bias in treatment selection and response assessment. Post-transformation treatment data were available for only a limited number of patients, precluding multivariable adjustment for treatment regimen in the evolutionary diversity analysis; the observed survival difference between high- and low-diversity groups should therefore be interpreted with caution, as treatment heterogeneity cannot be excluded as a contributing factor. In addition, the number of *EGFR* wild-type patients with SCLC transformation was small, and clinical and molecular data in this subgroup were limited, precluding meaningful conclusions regarding their genomic features or treatment implications. Finally, mechanistic insights into the functional role of NTRK1 alterations in SCLC transformation require validation through *in vivo* models and functional assays.

Conclusions

In summary, by integrating clinical and molecular features, we establish a predictive model for early identification of SCLC transformation, providing a clinically actionable tool to inform surveillance and therapeutic decision-making. We further identify taxane-based regimens as a promising later-line treatment option for this challenging disease. Together, these findings advance the understanding of T-SCLC biology and support precision medicine–oriented strategies for its management.

List of abbreviations

T-SCLC	Transformed Small-cell Lung Cancer
EGFR	Epidermal Growth Factor Receptor
NSCLC	Non–small Cell Lung Cancer
LUAD	Lung Adenocarcinoma
EP	Etoposide plus Platinum
PD-1	Programmed Death-1
PD-L1	Programmed Death-ligand 1 Inhibitors
IHC	Immunohistochemistry
CCFs	Cancer Cell fractions
SVM	Support Vector Machine
PFS	Progression-free survival
OS	overall survival

CRediT authorship contribution statement

Ruolin Gao: Writing – original draft, Methodology, Formal analysis, Conceptualization. **ZhenXiang Li:** Writing – review & editing, Funding acquisition, Formal analysis. **Jie Huang:** Data curation. **Jun Zhao:** Data curation. **Yan Wang:** Data curation. **Qinxiang Guo:** Data curation. **Guangchuan Deng:** Data curation. **Hua Bai:** Data curation. **Xu Yang:** Formal analysis, Data curation. **Jianchun Duan:** Data curation. **Zhijie Wang:** Data curation. **Yuyan Wang:** Data curation. **Jingjing Wang:** Data curation. **Jiachen Xu:** Data curation. **Rui Wan:** Data curation. **Boyang Sun:** Data curation. **Kailun Fei:** Data curation. **Zixiao Ma:** Data curation. **Jia Zhong:** Writing – review & editing, Funding acquisition, Conceptualization. **Jie Wang:** Data curation.

Ethics approval and consent to participate

All slides and tissue specimens were obtained with prior informed consent and approval from the Ethics Committees of the participating institutions. All participants were informed about the purpose of the study, assured of confidentiality. Each participant provided written informed consent in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2026.109566.

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