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Time to Sustained CEA Elevation Predicts First-Line Treatment Efficacy and Clinical Outcomes in Lung Adenocarcinoma

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Introduction

Lung adenocarcinoma represents the predominant pathological subtype within non-small cell lung cancer (NSCLC), and its incidence remains persistently high worldwide. Although genomics-guided precision medicine and immunotherapy have markedly improved survival in a subset of patients, developing simple and effective tools for response monitoring and prognostication remains a key focus of clinical research. Carcinoembryonic antigen (CEA), a classical serum tumor marker,is a cell-adhesion-related glycoprotein that is normally produced during fetal development but ceases to be secreted before birth; Accordingly, it is typically absent from the circulation of healthy adults. CEA is a glycosylphosphatidylinositol (GPI)-anchored glycoprotein whose sialylated glycans serve as functional ligands for L-selectin and E-selectin in colorectal cancer,potentially facilitating metastatic dissemination. In lung adenocarcinoma, CEA has attracted sustained attention because of its relatively high positivity rate, particularly among patients with advanced disease.

Methods

This retrospective study enrolled 225 pathologically confirmed, first-line treatment-naïve lung adenocarcinoma patients with complete clinical and follow-up data. Defining ΔT as the time interval from first-line therapy start to the first documented sustained CEA elevation (two consecutive measurements with ≥20% increase). Patients were dichotomized based on ΔT median value=242 days and the optimal cut-off value for therapeutic efficacy determined by ROC curve analysis (134days). Baseline characteristics, objective response rate (ORR), and disease control rate(DCR) were compared between groups. Median PFS (mPFS) and Median OS (mOS) were estimated using the Kaplan-Meier method and compared by log-rank test. Univariate and multivariate survival analyses were performed using Cox proportional-hazards models.

Conclusion

The time interval from first-line therapy start to sustained CEA elevation remains a key predictor of therapeutic efficacy and prognosis in lung adenocarcinoma; A longer ΔT is correlated with better treatment response and more favorable survival outcomes.

Patient demography and clinical characteristics:

The median age of the 225 enrolled patients was 67years.Using the two ΔT thresholds (242 days and 134 days), we compared baseline characteristics between subgroups,including sex,median age at diagnosis, smoking history, and Performance status (PS), driver mutation status, clinical stage, presence of brain, liver or other distant metastases, and first-line treatment modality. When patients were grouped by ΔT median value (243days), sex and smoking history showed statistically significant differences; when grouped by either ΔT median value(243days) or ΔT cut-off value (134days), mutation status and treatment modality also differed significantly. Details of the intergroup comparisons of clinical features are presented in Table 1.

Table1 comparison clinical features between groups with varying durations since first-line treatment and sustained CEA elevation (ΔT median value(243days) or ΔT cut-off value (134days)).

Variables	Total (n=225)	ΔT < 134d (n=99)	ΔT ≥ 134d (n=126)	P-value (134d cutoff)	ΔT < 242d (n=112)	ΔT ≥ 242d (n=113)	P-value (242d cutoff)
Gender, n(%)				0.105			0.032
Female	93(41.33)	23(33.33)	70(44.87)		37(33.04)	56(49.56)	
Male	132(58.67)	46(66.67)	86(55.13)		75(66.96)	57(50.44)	
Smoking history, n(%)				0.295			0.024
No	173(76.89)	50(72.46)	123(78.85)		79(70.54)	94(83.19)	
Yes	52(23.11)	19(27.54)	33(21.15)		33(29.46)	19(16.81)	
Performance status, n(%)				0.798			0.316
0-1	207(92.00)	63(61.30)	144(92.31)		101(90.18)	106(93.81)	
>1	18(8.00)	6(6.70)	12(7.69)		11(9.82)	7(6.19)	
Gene mutation status, n(%)				<0.001			0.002
Mutation-negative	58(25.78)	28(40.58)	30(19.23)		42(37.50)	21(18.58)	
Other actionable alterations	167(74.22)	41(59.42)	126(80.77)		70(62.50)	92(81.42)	
Median age at diagnosis (years), n(%)				0.950			0.448
<65	133(59.11)	41(59.42)	92(56.97)		69(61.61)	64(56.64)	
≥65	92(40.89)	28(40.58)	64(41.03)		43(38.39)	49(43.36)	
Clinical stage, n(%)				0.687			0.200
III	177(56)	68(70)	117(93)		11(9.82)	6(5.31)	
IV	208(92.44)	63(61.30)	145(92.95)		101(90.18)	107(94.69)	
Liver metastases, n(%)				0.380			0.881
No	188(83.56)	60(86.96)	128(92.05)		94(83.93)	94(83.19)	
Yes	37(16.44)	9(13.04)	28(17.95)		18(16.07)	19(16.81)	
Adrenal metastases, n(%)				0.932			0.676
No	195(86.67)	60(86.96)	135(86.54)		96(85.71)	99(87.61)	
Yes	30(13.33)	9(13.04)	21(13.46)		16(14.29)	14(12.39)	
Brain metastases, n(%)				0.846			0.744
No	132(58.93)	40(57.97)	92(59.35)		65(58.04)	68(60.18)	
Yes	92(41.07)	29(42.03)	63(40.65)		47(41.96)	45(39.82)	
Bone metastases, n(%)				0.959			0.831
No	131(58.22)	40(57.97)	91(58.33)		66(58.93)	65(57.52)	
Yes	94(41.78)	29(42.03)	65(41.67)		46(41.07)	48(42.48)	
Treatment modality, n(%)				<0.001			<0.001
Non-targeted therapy	80(35.56)	36(52.17)	44(28.21)		54(48.21)	26(23.01)	
Targeted therapy	145(64.44)	33(47.83)	112(71.79)		58(51.79)	87(76.99)	

Table 2. Objective response rate (ORR) and disease control rate (DCR) according to the time interval (ΔT) from first- line therapy to sustained CEA elevation in 225 patients with lung adenocarcinoma.

Variables	N	ORR	Statistic	P	DCR	Statistic	P
Overall rate	225	103			197		
Time from first-line therapy to sustained CEA rise			$\chi^2=18.96$	<0.001		$\chi^2=27.84$	<0.001
<134d	112(49.78)	35(33.98)			85(43.15)		
≥134d	113(50.22)	68(66.02)			112(56.85)		
Time from first-line therapy to sustained CEA rise			$\chi^2=18.96$	<0.001		$\chi^2=27.84$	<0.001
<242d	112(49.78)	35(33.98)			85(43.15)		
≥242d	113(50.22)	68(66.02)			112(56.85)		

Table 2 presents patients were divided by ΔT cutoff values of 134 days and 242 days. The ORR and DCR were compared using the chi-square test. ΔT ≥ 134 days and ΔT ≥ 242 days were associated with significantly higher ORR and DCR (all P < 0.001).

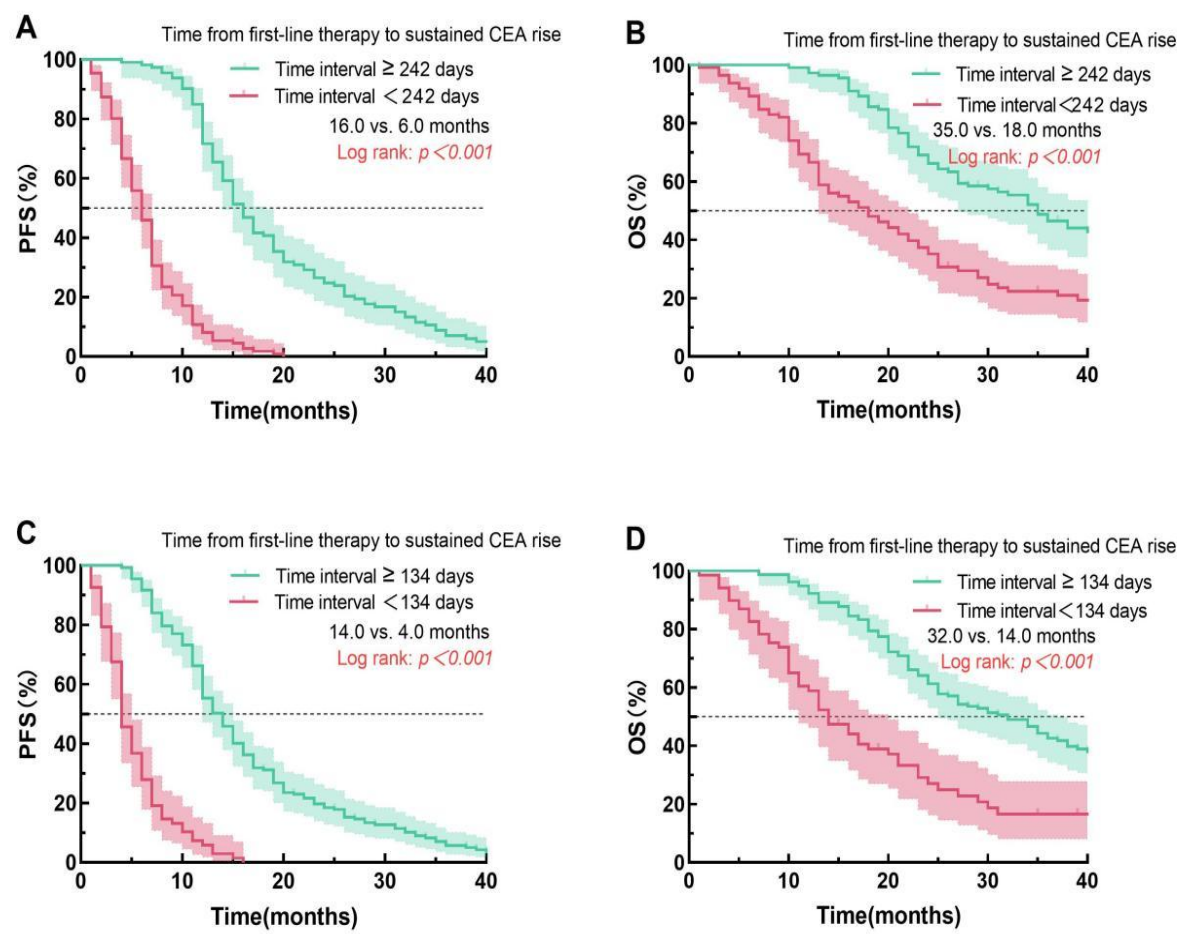


Figure 1. Progression-free survival (PFS) and overall survival (OS) according to the time interval (ΔT) from first-line therapy to sustained CEA elevation in lung adenocarcinoma patients.

Results

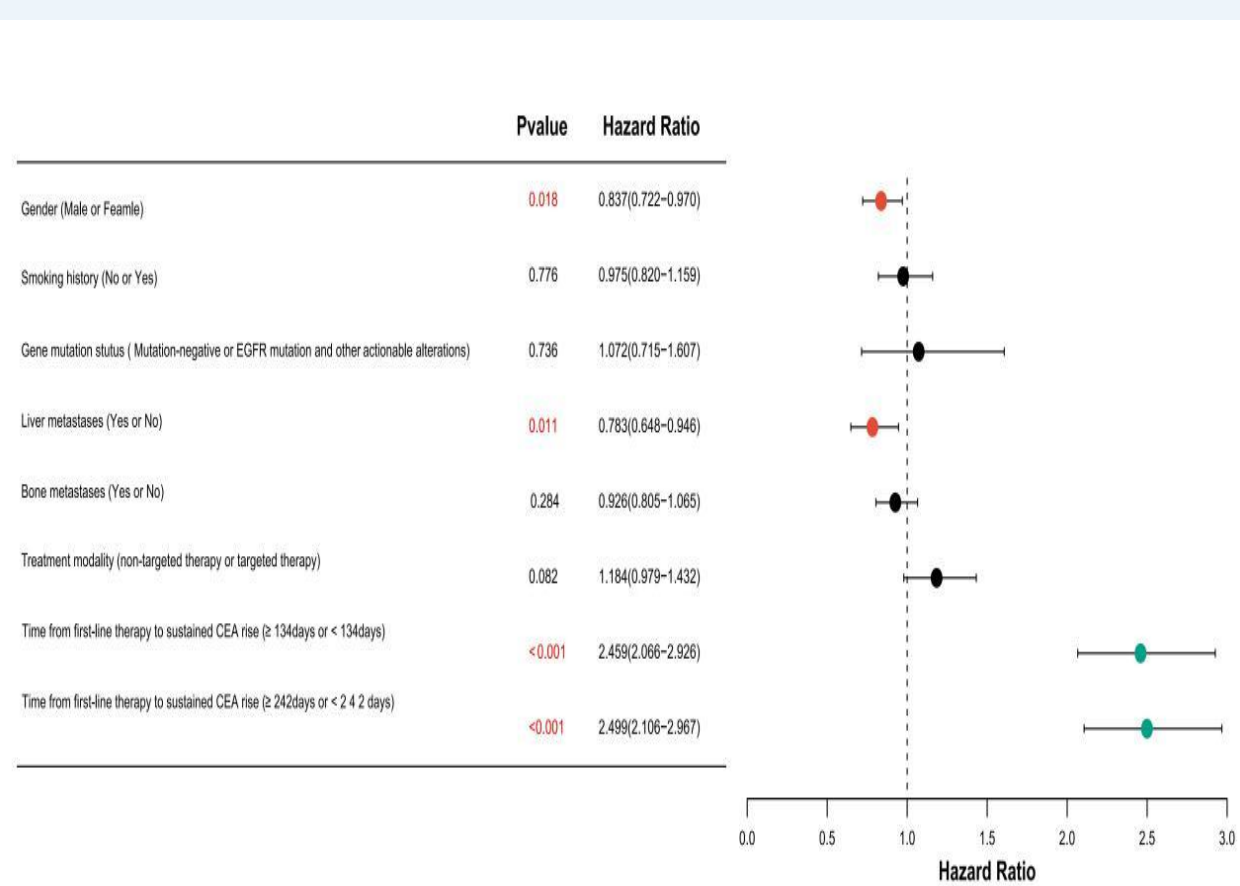


Figure 2. Forest plot of univariate/multivariate Cox regression analyses forProgression-free survival (PFS) in lung adenocarcinoma patients.

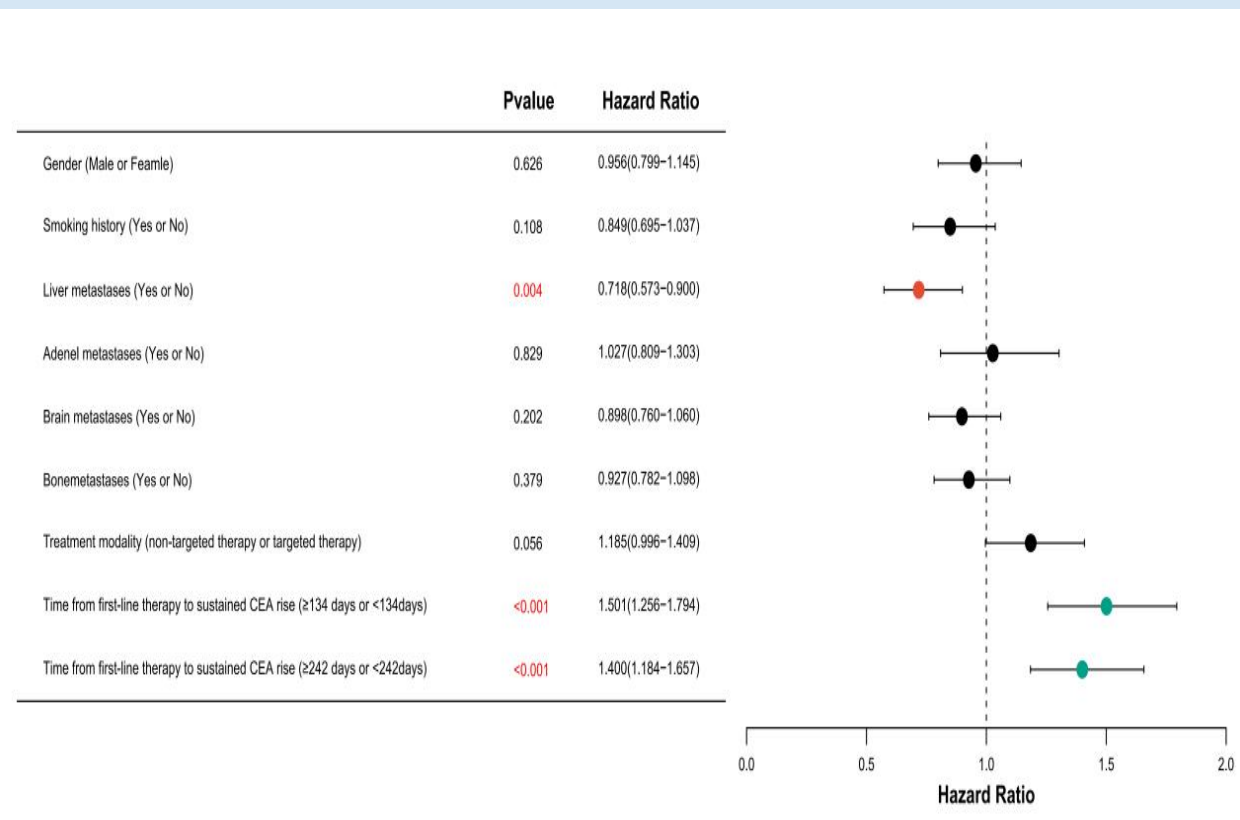


Figure 3. Forest plot of univariate/multivariate Cox regression analyses for overall survival (OS) in lung adenocarcinoma patients.

In univariate analysis, we included clinical characteristics and the time interval to sustained CEA elevation (ΔT, stratified by median = 242 days or optimal cutoff = 134 days). Variables with P < 0.2 were entered into multivariate analysis, which identified gender, liver metastasis status, and ΔT grouping as independent predictors of PFS (all P < 0.05). Other covariates (smoking history, gene mutation status, bone metastases, treatment modality) were not statistically significant.

Specifically, female gender was associated with a lower progression risk (the only factor specific to PFS). Liver metastases conferred a higher risk of progression (aHR ≈ 0.78, 95% CI: 0.64–0.95, P = 0.011) and also impacted OS, indicating patients with liver metastases had a ~1.28-fold higher progression risk. Importantly, ΔT served as a dynamic prognostic marker: early sustained CEA elevation (<134 or <242 days) indicated a high progression risk, warranting intensified surveillance and early evaluation for therapeutic intervention.

Multivariate analysis identified liver metastasis and time to sustained CEA elevation (using 134- day and 242- day cutoffs) as independent prognostic factors for OS. Other variables (gender, smoking, gene mutation, bone/brain metastases, treatment modality) were not significant. Patients with liver metastasis had a 39% higher mortality risk. Time to sustained CEA elevation serves as a dynamic prognostic tool: elevation before 134 or 242 days indicates high mortality risk, warranting closer monitoring and early treatment re- evaluation. The adverse impact of liver metastasis on OS is independent, justifying more intensive management upfront.

Discussion

Previous studies focused on baseline CEA levels, changes, and kinetics in relation to survival. Elevated baseline CEA or insufficient decline during treatment was associated with worse PFS and OS across chemotherapy, targeted therapy, and immunotherapy. CEA kinetics may even precede radiological progression. CEA elevation reflects higher tumor burden, invasiveness, and clonal evolution, while a delayed sustained CEA rise indicates better tumor control and delayed resistance. Multivariate analyses identified gender, liver metastasis, and time to sustained CEA elevation as independent predictors of PFS; liver metastasis and time to sustained CEA elevation independently predicted OS. Liver metastasis increased mortality by 39% and progression risk by 1.28-fold. Using 134-day and 242-day thresholds as monitoring milestones is clinically practical: early sustained CEA elevation justifies closer surveillance and early treatment adjustment before radiological progression, matching guideline-recommended personalized management.