



Lung Cancer

Prognostic Impact of Baseline Liver Metastasis in ALK Fusion-Positive Metastatic Lung Cancer: A Retrospective Review

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Abstract



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Introduction The prognosis of anaplastic lymphoma kinase (ALK) fusion-positive metastatic non-small cell lung cancer (mNSCLC) patients has improved drastically since the introduction of targeted therapies. Apart from age, performance status, and type of driver mutation in a mNSCLC, prognosis also depends on baseline metastatic sites number as well as location with liver metastases being a poor prognostic factor. However, the clinical and prognostic association of baseline liver metastases in ALK fusion-positive mNSCLC is not well known.

Material and Methods We performed a retrospective analysis of ALK fusion-positive mNSCLC patients to assess prognostic impact of liver metastases. Records were obtained from lung cancer audit database and electronic medical records. Patients were started on either chemotherapy, ALK-directed tyrosine kinase inhibitors, or given best supportive care as per the clinical scenario. Radiological response was assessed every 2 to 3 months or earlier at clinical suspicion of progressive disease. Adverse events were evaluated as per Common Terminology Criteria for Adverse Events v4.02.

Results A total of 441 patients were screened, out of which 76 had baseline liver metastases. Median age was 49 years with 64.5% males. Median progression-free survival (mPFS) was 14.2 months (95% confidence interval [CI] 8.9–19.4) in patients with baseline liver metastases. In patients who received first-line ALK inhibitor therapy versus who received first-line chemotherapy, mPFS was significantly better in the ALK-directed therapy subgroup, 15.3 months (95% CI 11.7–18.9) versus 5.9 months (95% CI 2.7–9.1), respectively (hazard ratio [HR] 0.3 [95% CI 0.17–0.54]; $p < 0.001$). Median

Keywords

- ▶ ALK
- ▶ chemotherapy
- ▶ crizotinib
- ▶ liver metastases
- ▶ NSCLC

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overall survival (mOS) was 27.6 months (95% CI 17.4–37.7) in patients with baseline liver metastases which was not statistically significant from patients without baseline liver metastases which was 32.3 months (95% CI 28.8–35.7) (HR 1.32 [95% CI 0.91–1.9]; $p = 0.22$). Use of ALK-directed therapy in patients with baseline liver metastases resulted in better OS, mOS not reached versus 15.7 months (95% CI 2.7–28.8) in the chemotherapy group (HR 0.33 [95% CI 0.16–0.67]; $p < 0.001$).

Conclusion In patients with ALK fusion-positive mNSCLC, baseline liver metastases was not found to be an independent prognostic factor. However, the use of ALK-directed therapy resulted in a significantly better PFS and OS as compared with chemotherapy in patients with baseline liver metastases. This underscores the importance of the use of ALK-directed therapy whenever feasible in this group of patients.

Introduction

Anaplastic lymphoma kinase (ALK) gene rearrangements are seen in 3 to 5%^{1,2} of non-small cell lung cancer (NSCLC) patients. With the introduction of targeted therapies, the prognosis of ALK fusion-positive metastatic NSCLC (mNSCLC) has drastically changed, with median survival reaching beyond 5 years.³ Age, performance status (PS), and type of driver mutations are among the common prognostic factors for survival in NSCLC. Liver metastases is seen in 3 to 6% of NSCLC patients^{4,5} with a higher incidence in ALK or estimated glomerular filtration rate positive lung cancers as compared with the drive negative cases,⁶ with liver metastases being a poor prognostic factor.^{7,8} However, clinical and prognostic association of baseline liver metastases in ALK-positive mNSCLC has not been well studied.

To assess the prognostic impact of baseline liver metastases in ALK-positive mNSCLC, we did a retrospective analysis of prospectively collected data of patients from our institute from June 2012 to March 2018. This is the largest retrospective single-center data of ALK-positive mNSCLC patients analyzing the prognostic impact of liver metastases at baseline in this group of patients.

Materials and Methods

ALK fusion-positive mNSCLC patients with baseline liver metastases with or without other sites of metastases planned for palliative treatment from June 2014 to December 2018 were selected for analysis. ALK fusion was reported either by immunohistochemistry (IHC) using Ventana (D5F3) CDx Assay or break-apart fluorescence in situ hybridization (FISH).

The demographic details of patients were obtained from the prospective lung cancer audit database and relevant clinical details were obtained from hospital electronic medical records. The lung cancer audit is an Institutional Ethics Committee-approved observational protocol, is registered with the Clinical Trials Registry India (registration number: CTRI/2013/01/003335), and patients sign a written informed consent prior to their information being recorded as part of the lung cancer audit. Staging was performed by contrast-enhanced computed tomography (CECT) thorax and abdo-

men or whole body fluorodeoxyglucose positron emission tomography-CECT.

Therapy decision was based on age, PS, comorbidities, disease burden, affordability for 2nd or 3rd generation tyrosine kinase inhibitor (TKI), and patient preference. Following treatment regimens were used:

1. Chemotherapy.
2. Crizotinib 250 mg orally twice a day.
3. Ceritinib 450 mg orally twice a day with meals.
4. Alectinib 600 mg orally twice a day with meals.
5. Best supportive care.

Radiological response assessment (RECIST 1.1) was done every 2 to 3 months or at symptomatic progression. Treatment regimen was discontinued at disease progression, intolerable side effects, or patient decision. The adverse events were evaluated in accordance with the Common Terminology Criteria for Adverse Events version 4.02. At progression, further therapy was considered based on standard recommendations.

Statistical Analysis

All statistical calculations were performed using SPSS version 20 (Armonk, New York, United States). Descriptive statistics were performed. Median value with interquartile range was provided for continuous variables. Progression-free survival (PFS) was calculated in months from the date of start of therapy till the date of progression or death from any cause on therapy. Patients who had not progressed at the time of last follow-up were censored. Overall survival (OS) was calculated in months from the date of start of therapy till the date of death from any cause. Patients who had not died at the time of last follow-up were censored. Kaplan–Meier method was used for time to event analysis. Log-rank test was used for univariate analysis of PFS and OS. Cox proportional hazard model was used for multivariate analysis.

Results

Baseline Characteristics

A total of 441 patients with ALK positive advanced NSCLC were screened for analysis, out of which 76 patients were

selected for analysis who had liver metastases at baseline. The median age of the cohort was 49 years. Forty-nine (64.5%) were males and 35.5% females; elderly patients (≥ 60 years) comprised 18.4% of total cohort; 81.6% had Eastern Cooperative Oncology Group PS 0 to 1 while 18.5% were PS 2 to 3. Thirteen (17.1%) patients were ever smokers, and 36.8% had some comorbidities (**Table 1**).

ALK was detected by IHC in 73.7% patients, FISH in 18.4%, and by both the methods in 7.9% of patients. Majority patients (96.1%) had adenocarcinoma histology. The median duration of follow-up was 18.7 months (95% confidence interval [CI] 8.4–29.1). Out of 76 patients, 13 patients were lost to follow-up.

Progression-Free Survival

Median PFS (mPFS) in patients with baseline liver metastases was 14.2 months (95% CI 8.9–19.4) (**Fig. 1**) which was similar to mPFS in entire cohort of ALK-positive patients in our study which was previously published.⁹ In patients who received first-line ALK inhibitor therapy versus who received first-line chemotherapy, mPFS was significantly better in the ALK-directed therapy subgroup, 15.3 months (95% CI 11.7–18.9) versus 5.9 months (95% CI 2.7–9.1), respectively (hazard ratio [HR] 0.3 [95% CI 0.17–0.54]; $p < 0.001$) (**Fig. 2**). Patients who were switched to ALK inhibitor after ALK report or were given ALK-directed therapy as switch maintenance were considered as having received ALK therapy in first line and were excluded from the first-line chemotherapy subgroup.

Overall Survival

Median OS (mOS) in patients with liver metastases versus those who did not have liver metastases, irrespective of the type of therapy received, was poorer in liver metastases subgroup; however, it was not statistically significant, 27.6 months (95% CI 17.4–37.7) versus 32.3 months (95% CI 28.8–35.7) (HR 1.32 [95% CI 0.91–1.9]; $p = 0.22$) (**Fig. 3**). Among patients with liver metastases, use of first-line ALK inhibitor therapy was associated with significantly better OS, mOS not reached versus 15.7 months (95% CI 2.7–28.8) in the chemotherapy group (HR 0.33 [95% CI 0.16–0.67]; $p < 0.001$) (**Fig. 4**).

Response Rate

Forty patients (52.6%) had a partial response to TKI, 18.4% had stable disease, complete response was seen in 1 patient, and 7 patients had progressive disease as their best response whereas response was not evaluable in 14 (18.4%) patients. This translated to an overall response rate of 54% and clinical benefit rate of 72.3%.

Adverse Events (**Table 2**)

Adverse events were evaluable for patients treated with crizotinib (61 patients). It was fairly well tolerated with the majority of patients having grade 1 to 2 side effects. Note that 44.7% experienced grade 1 to 2 anemia and grade 1 to 2 transaminitis. Fatigue was the second most common side effect in 18 patients (grade 1–2). QTc prolongation was seen

Table 1 Baseline characteristics of patients

Characteristics	Number (percentage)
Age	Median: 49 y
	Range: 32–75 y
Gender	
Male	49 (64.5)
Female	27 (35.5)
Histology	
Adenocarcinoma	73 (96.1)
Adenosquamous	1 (1.3)
Large cell neuroendocrine	1 (1.3)
Squamous	1 (1.3)
ECOG PS	
0–1	62 (81.5)
2	10 (13.2)
3	4 (5.3)
Smoking	
Ever smoker	13 (17.1)
Never smoker	63 (82.9)
Comorbidities (diabetes, hypertension, COPD, dyslipidemia)	
None	48 (63.2)
Yes	28 (36.8)
Elderly	
Yes (≥ 60 y)	14 (18.4)
No	62 (81.6)
ALK detection	
IHC	56 (73.7)
FISH	14 (18.4)
Both	6 (7.9)
1st line therapy	
ALK-directed TKI	51 (67.1)
Crizotinib	49 (64.4)
Ceritinib	2 (2)
Chemotherapy	20 (26.3)
Best supportive care	5 (6.6)
Sites of metastases	
Opposite lung	24 (31.5)
Pleural effusion	32 (42.1)
Brain	10 (13.2)
Bone	47 (61.8)

Abbreviations: ALK, anaplastic lymphoma kinase; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; PS, performance status; TKI, tyrosine kinase inhibitor.

in 15.7% patients which did not lead to interruption of therapy. Out of 61 patients who received crizotinib in first or subsequent lines, dose modification or brief interruption was required in 11 patients (18%).

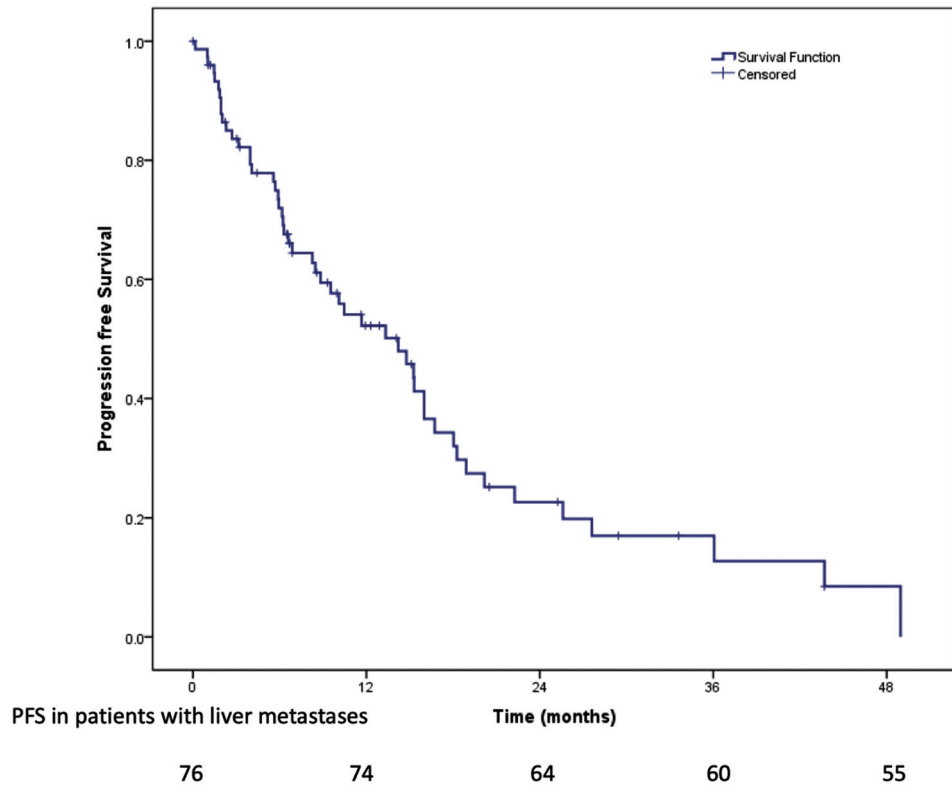


Fig. 1 Progression-free survival (PFS) overall in patients with liver metastases.

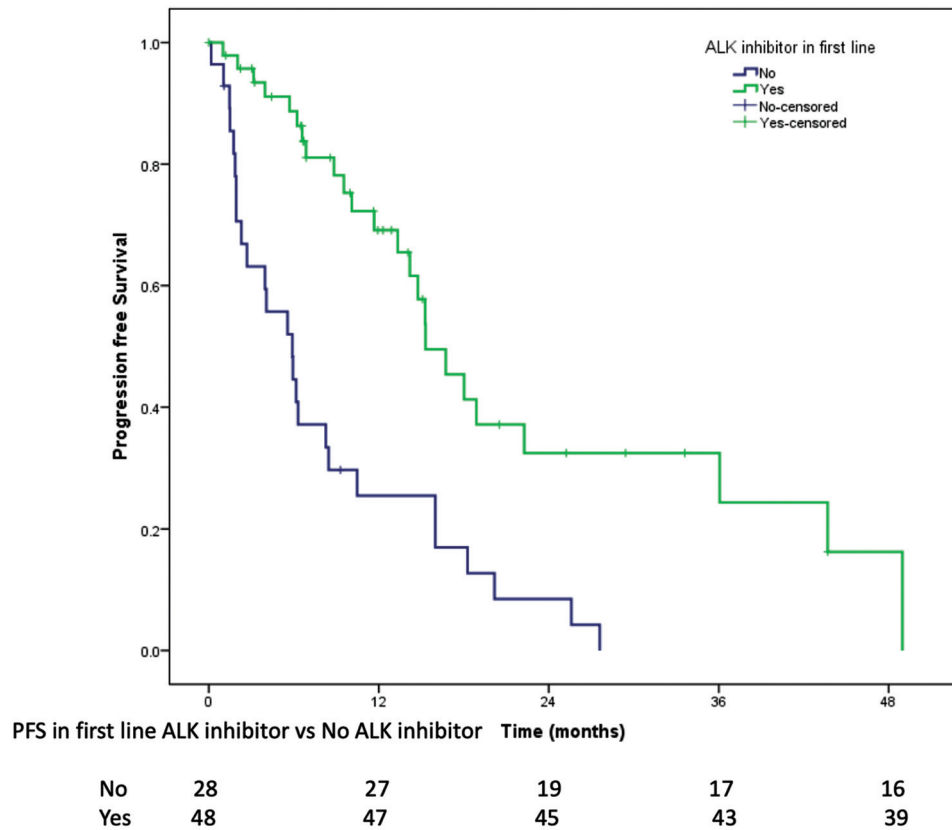


Fig. 2 Progression-free survival (PFS) in first-line anaplastic lymphoma kinase (ALK) inhibitor versus no ALK inhibitor.

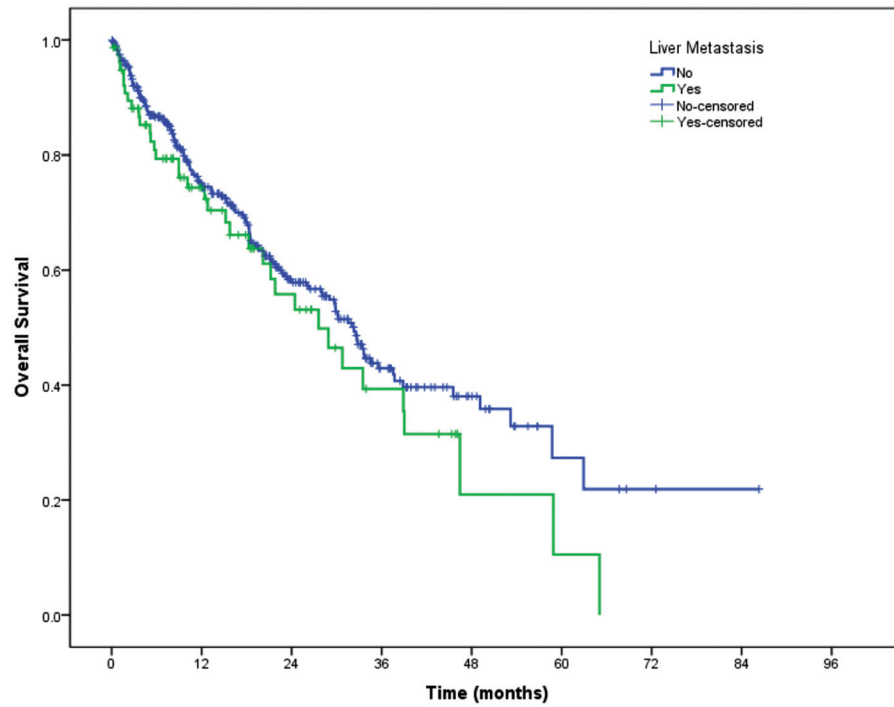


Fig. 3 Overall survival as per liver metastasis versus no liver metastasis.

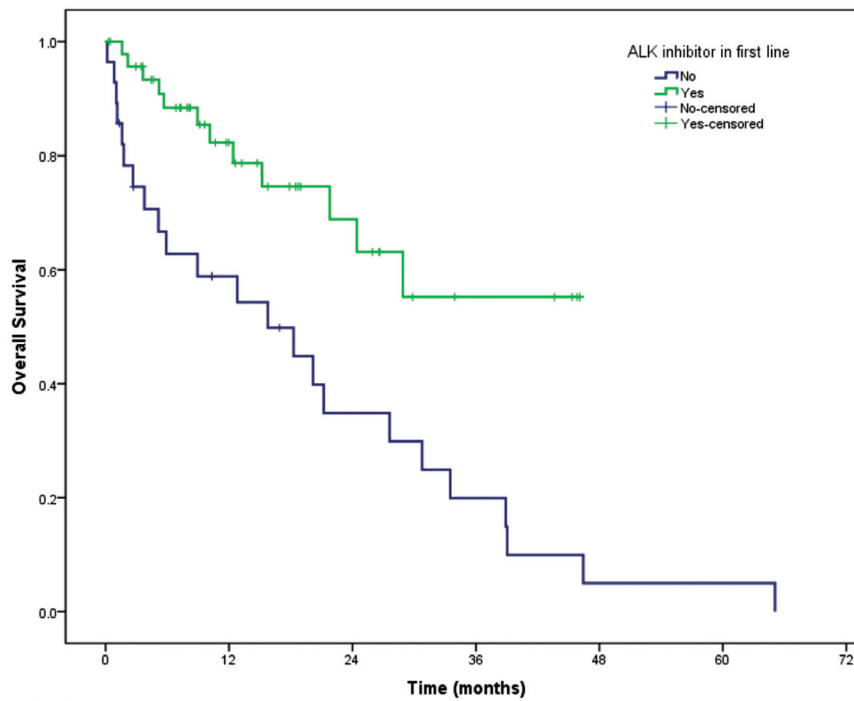


Fig. 4 Overall survival by use of anaplastic lymphoma kinase (ALK) inhibitor in first line.

Table 2 Adverse events to crizotinib

Adverse event	Grading	
	Grade 1–2 Number (%)	Grade 3–4 Number (%)
Hematological		
Anemia	34 (55.7)	3 (4.9)
Neutropenia	5 (8.1)	6 (9.8)
Thrombocytopenia	3 (4.9)	1 (1.6)
Nonhematological		
Transaminitis	34 (55.7)	5 (8.1)
Creatinine raised	6 (9.8)	0
Fatigue	18 (29.5)	3 (4.9)
Vomiting	18 (29.5)	1 (1.6)
QTc prolongation	12 (19.6)	0
Peripheral edema	19 (31.1)	0
Visual disturbance	12 (19.6)	0
Crizotinib-induced rash	6 (9.8)	1 (1.6)
Renal cyst	4 (6.5)	0

Discussion

Patients with ALK-positive mNSCLC represent a favorable subgroup when compared with patients without a driver mutation.¹⁰ However, certain prognostic features separate the poorer risk subgroup of patients from others. Here, we have presented a retrospective analysis of 76 patients of ALK-positive mNSCLC who had liver metastases at baseline. To our knowledge, this is the largest single-center experience in this subgroup of patients.

mPFS as well as mOS was similar to other reported real-world data.^{11–13} The difference between mOS in our study and clinical trials of ALK inhibitors³ can be attributed to the limited availability of 2nd and 3rd generation ALK inhibitors which lead to a majority of patients receiving chemotherapy in further lines of treatment. Forty-nine patients received crizotinib in first line, five out of these were unfit for second-line therapy and were planned for supportive care alone on progression, rest of them received chemotherapy.

Among the adverse events with crizotinib, when compared with PROFILE 1014 trial,¹³ higher percentage of patients experienced anemia, thrombocytopenia, and transaminitis, fewer patients had visual disturbances and edema, whereas fatigue was comparable. This could be attributed to different patient profile and ethnicity as compared with the reference study.

Overall, liver metastases was not a poor prognostic factor; however, the use of first-line ALK inhibitor therapy was associated with significant survival benefit as compared with chemotherapy in patients with liver metastases underscoring the importance of the use of ALK-directed therapy whenever feasible in such patients.

Our study had several limitations. Being a retrospective study, information bias was inevitable. Also, single-center

experience and lost to follow-up were other shortcomings. Nonfeasibility of next-generation ALK inhibitors such as ceritinib, alectinib, and lorlatinib impacted the treatment outcomes in our study population.

In conclusion, in treatment-naïve ALK positive mNSCLC patients, liver metastases was not shown to be a poor prognostic factor and the use of ALK-directed therapy resulted in better response rates and survival which was consistent with previously reported studies.

Further real-world studies with better availability of ALK inhibitors are needed to better define the outcomes in patients with liver metastases.

Conflict of Interest

None declared.

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