#1154P Circulating tumor DNA analysis integrating tumor clonality detects minimal residual disease in resectable non-small-cell lung cancer

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Background

- Circulating tumor DNA (ctDNA) has been proven as a marker for detecting minimal residual disease (MRD) in mid-to-late stage non-small-cell lung cancers (NSCLCs) that received radio-, chemo-, immuno-, and/or targeted therapies. [1,2, 3]
- The usefulness of ctDNA in monitoring MRD in resectable stage I-III NSCLC patients after curative surgeries has not been validated.
- It also remains not fully understood whether tracking clonal evolution of tissues in ctDNA could further improve the risk stratification.[3]
- We attempt to evaluate MRD using ctDNA and tumor clonality information in NSCLC patients that received surgeries with curative intent.

Methods

- We profiled tissue mutations of 127 patients with stage I-III NSCLCs in the Lung Cancer Tempo-spatial Heterogeneity (LuCaTH) prospective cohort, and reconstructed individual clonal phylogenetics based on a total of 591 tissue samples.
- We collected plasma samples at baseline, 7 days post surgery, and every 3 months thereafter, and performed deep targeted sequencing (median: 4086X) on a total of 611 plasma samples using a panel covering 425 cancer-associated genes.
- All patients were monitored for at least two time points after surgeries and followed up for a median of 894 days.
- Plasma mutations were matched to tissue profiles, polished with a control pool of healthy individuals, and filtered for clonal mutations and highly confident subclonal mutations.

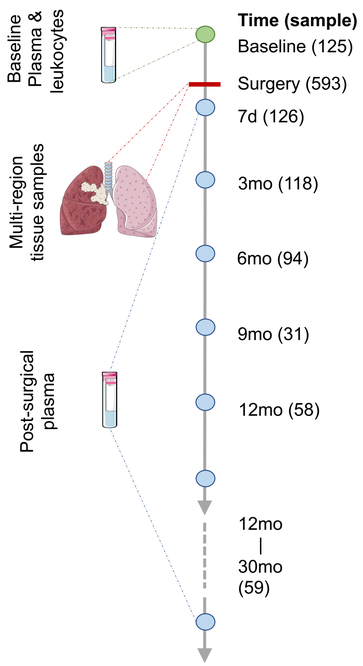
References

1. Chaudhuri, Aadel A., et al. Cancer discovery 7.12 (2017): 1394-1403.
2. Pécuchet, Nicolas, et al. *PLoS medicine* 13.12 (2016): e1002199.
3. Abbosh, Christopher, et al. Nature 545.7655 (2017): 446-451.
4. smart.servier.com

Disclosure

M.W., H.B., X.W., and Y.S. are employees of Nanjing Geneseeq Technology Inc.

Figure 1. Overview of sample collection and patient demography



Pictures of tubes and lung are from an online library[4]

Characteristics	Patients (n = 127)
Age (years)	
Mean ± SD	62.2 ± 8.3
Median (min - max)	63 (39 - 79)
Sex	
Female	55 (43.3%)
Male	72 (56.7%)
Smoking history	
Ever	33 (26.0%)
Never	94 (74.0%)
Histology	
LUAD	100 (78.7%)
LUSC	21 (16.5%)
Other	6 (4.8%)
Focality	
Multifocal	44 (34.6%)
Unifocal	83 (65.4%)
Stage	
I	55 (43.3%)
II	24 (18.9%)
III	47 (37.0%)
IV	1 (0.8%)
Lymph node metastasis	
Positive	57 (44.9%)
Negative	70 (55.1%)

Figure 2. Detection of ctDNA at different pathological stages

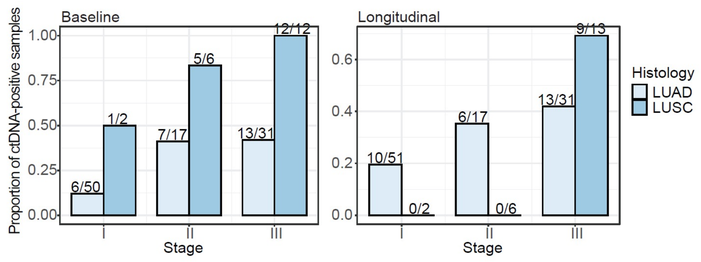
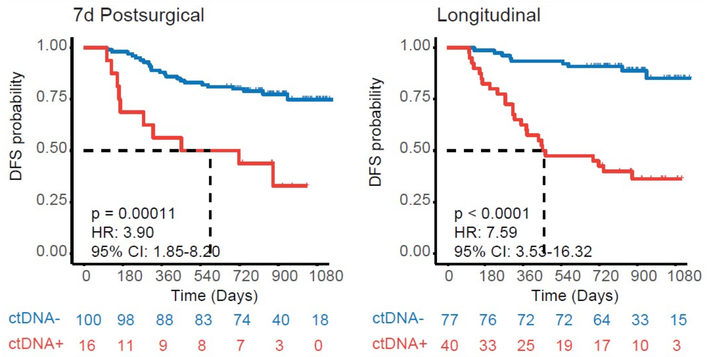


Figure 2: ctDNA was more frequently detected in patients with more advanced diseases both pre- and post-surgically.

Figure 3. Post-surgical ctDNA detection indicated higher risk of relapse



Group	7d Postsurgical		Longitudinal	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
LUAD	26.1 (6/23)	94.4 (68/72)	73.9 (17/23)	81.9 (59/72)
LUSC	37.5 (3/8)	88.9 (8/9)	77.8 (7/9)	88.9 (8/9)
Overall*	30.3 (10/33)	92.8 (77/83)	73.5 (25/34)	81.9 (68/83)

**including other types of pathological histology*

Figure 3: ctDNA detection at 7 days post surgeries and during longitudinal monitoring indicated higher risk of relapse (HR = 3.90 & 7.59, respectively). Longitudinal ctDNA monitoring achieved 73.5% sensitivity for predicting relapse occurrence while maintaining 81.9% specificity.

Figure 4. Detection of ctDNA during longitudinal monitoring in relapse cases

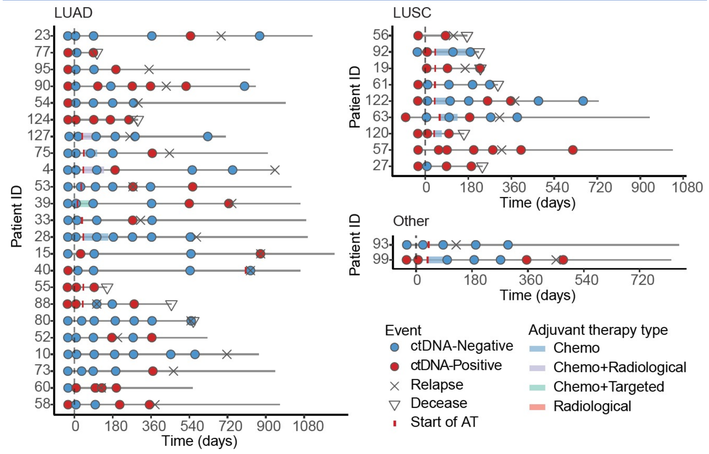
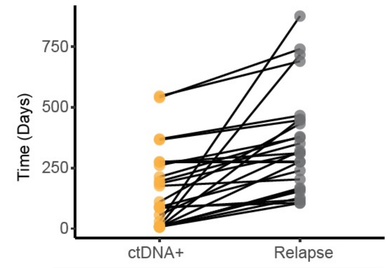


Figure 5. ctDNA detection led radiological relapse



Histology	Lead day median (min - max)
LUAD	144 (0-847)
LUSC	150 (33-264)
Overall*	145 (0-847)

**including other types of pathological histology*

Figure 5: ctDNA detection during longitudinal monitoring led radiological relapse by a median of 144 days in LUAD cases and 150 days in LUSC cases.

Results

- Both baseline and postsurgical ctDNA were more frequently detected in patients with more advanced diseases.
- The detection of postsurgical ctDNA at 7 days and during longitudinal monitoring indicated higher risk of relapse (HR: 3.90 and 7.95; P = 0.00011 and P < 0.0001, respectively).
- ctDNA detection during longitudinal monitoring had 73.5% sensitivity at 81.9% specificity for predicting relapse occurrence in the investigation period.
- ctDNA detection during longitudinal monitoring led radiological relapse by a median of 145 days.

Conclusions

- ctDNA analysis integrating tumor clonality may provide evidence for minimal residual disease in NSCLC patients who receive curative surgeries.