Pre-radiotherapy ctDNA liquid biopsies can precisely risk-stratify oligometastatic non-small cell lung cancer

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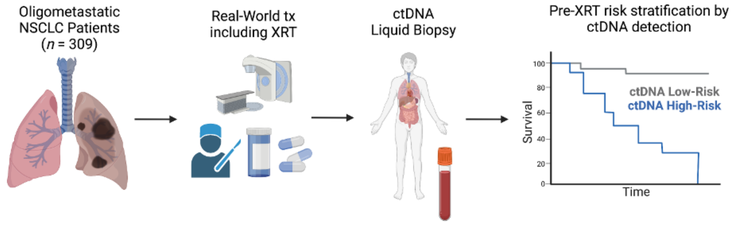
Background

- The optimal treatment approach for oligometastatic non-small cell lung cancer is unclear, and its diagnosis is frustratingly subjective.
- Some patients with oligometastatic disease experience prolonged remission (or even cure) after local therapy.
- Other patients harbor micrometastatic disease, below the limit of detection of current imaging techniques.
- We have previously shown that post-radiation therapy (RT) plasma circulating tumor DNA (ctDNA) is powerfully prognostic in localized NSCLC.

Study Design

Question: Can pre-radiotherapy (pre-RT) circulating tumor DNA (ctDNA) risk-stratify patients with oligometastatic non-small cell lung cancer and identify those most likely to benefit from RT versus systemic therapies?

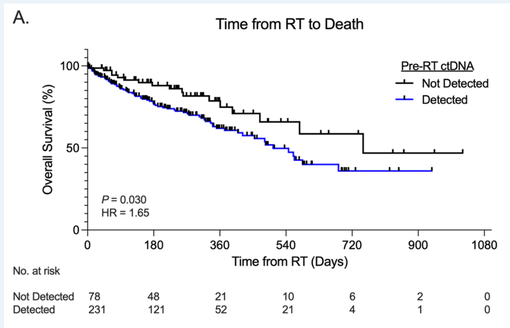


Cohort Characteristics

Characteristic	Entire Cohort (n=1,487)	Sub-cohort (n=309)
Age, mean (SD), y	64.7 (10.1)	63.1 (10.1)
Sex		
Male	703 (47.3%)	149 (48.2%)
Female	784 (52.7%)	160 (51.8%)
Race and ethnicity		
Asian	93 (6.3%)	20 (6.5%)
Black	150 (10.1%)	38 (12.3%)
White	835 (56.1%)	176 (57.0%)
Other	44 (3.0%)	11 (3.5%)
Unknown	365 (24.5%)	64 (20.7%)
Primary Tumor Histology		
Adenocarcinoma	1,078 (72.5%)	233 (75.4%)
Squamous	267 (18.0%)	50 (16.2%)
Other/Not Specified	142 (9.5%)	26 (8.4%)
Metastatic sites, mean* (SD, range)	1.3 (0.64, 1–8)	1.3 (0.56, 1–5)
PD-L1 Status		
Positive	302 (20.3%)	59 (19.1%)
Negative	202 (13.6%)	48 (15.5%)
Unknown	983 (66.1%)	202 (65.4%)
Smoking Status		
Current/Former Smoker	1,006 (67.7%)	221 (71.5%)
Never Smoker	323 (21.7%)	73 (23.6%)
Unknown	158 (10.6%)	15 (4.9%)
Documented Radiotherapy	975 (66%)	309 (100%)

The sub-cohort was defined as those patients who underwent a liquid biopsy ctDNA test prior to receiving radiation therapy and after their diagnosis of oligometastatic NSCLC. Data are presented as the number (percentage) of patients, unless otherwise noted. *Metastases were reported at the organ system level.

Fig 1. Oligometastatic NSCLC PFS and OS by Pre-RT ctDNA Detection



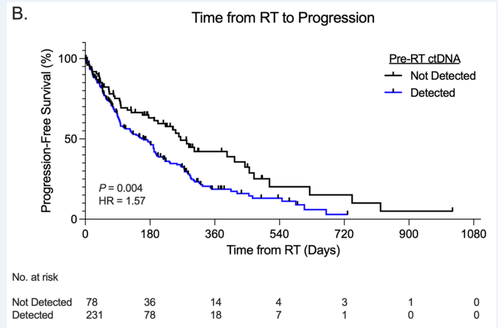
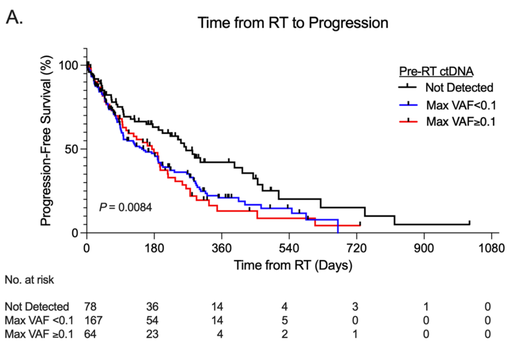


Fig 2. Oligometastatic NSCLC PFS and OS by Pre-RT ctDNA Levels



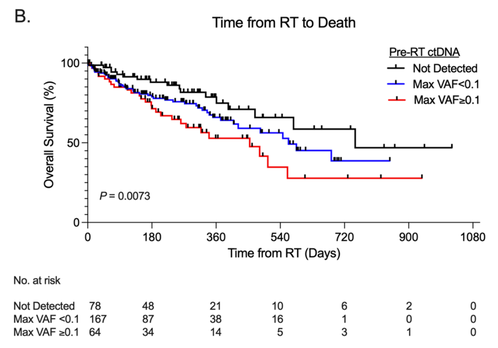
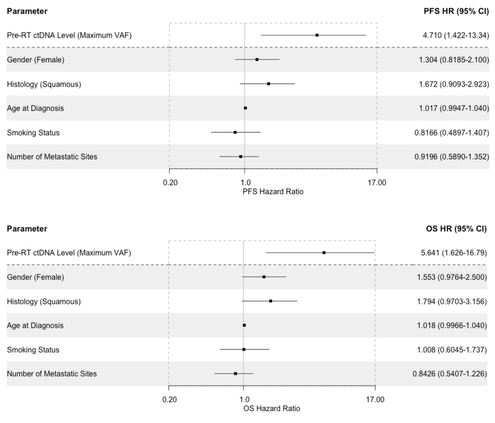
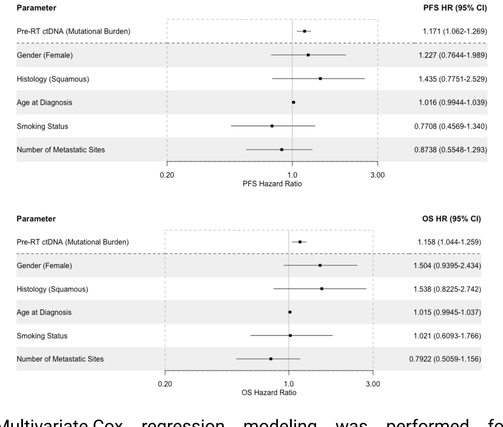


Fig 3. Multivariate Cox Model of ctDNA Levels



Multivariate Cox regression modeling was performed for progression-free survival and overall survival with parameters including the maximum ctDNA variant allele frequency (VAF) prior to radiotherapy, as well as clinically relevant co-variates.

Fig 4. Multivariate Cox Model of ctDNA Mutational Burden



Multivariate Cox regression modeling was performed for progression-free survival and overall survival with parameters including the number of detected mutations in ctDNA (mutational burden) prior to radiotherapy, as well as clinically relevant co-variates.

Variant Detection

Characteristic	Entire Cohort	Sub-cohort
Liquid Biopsies Performed	1,880	434
Variants Detected, (mean per ctDNA test)	38,546 (20.5)	9,069 (20.9)
Pathogenic / Likely Pathogenic	3,503 (9.1%)	828 (9.1%)
Conflicting Evidence	17 (0.04%)	10 (0.11%)
Benign/Likely Benign	30,911 (80.2%)	7,254 (80.0%)
Uncertain Significance	4,115 (10.7%)	977 (10.8%)
Fusions Detected†	18	4
Copy Number Variations Detected†	34	11

All patients underwent at least one ctDNA liquid biopsy test. †Fusion and CNV numbers reflect only pathogenic or likely pathogenic findings. For fusions, these encompassed *CD74-ROS1*, *EML4-ALK*, *FGFR2-TACC2*, *KIF5B-RET*, *SOD2-ROS1*,and *SPTBN1-ALK*. For CNVs, these included *CCNE1*, *EGFR*, *ERBB2*, *MET*, and *MYC*.

Results

Median follow-up time after initial blood collection for liquid biopsy analysis was 10.3 months. Of the sub-cohort of 309 patients who underwent liquid biopsy after the diagnosis of oligometastatic disease and before RT, 48% (n=151) experienced progressive disease and 11% (n=34) died during the study period.

Overall survival was significantly worse in oligometastatic NSCLC patients with detectable ctDNA from pre-RT liquid biopsies, as compared to those without detectable ctDNA pre-RT, with a median OS of 16.8 months versus 25 months (p=0.030, hazard ratio [HR]=1.65, confidence interval [CI]=1.05–2.61) **[Figure 1A]**. Similar findings were also observed for PFS, which was worse in patents with detectable ctDNA pre-RT, with a median PFS of 5.4 months versus 8.8 months (p=0.004, HR=1.57, CI=1.15–2.13) **[Figure 1B]**.

ctDNA levels demonstrated significant risk correlations, with the maximum pre-RT ctDNA VAF associated with increased risk of both disease progression (p=0.0084) **[Figure 2A]** and death (p=0.0073) **[Figure 2B]**. These findings were corroborated by multivariate Cox proportional hazards modeling for PFS (p=0.04, PFS HR=4.71, CI=1.42–13.34) and OS (p=0.005, HR=5.64, CI=1.63–16.79) **[Figure 3]**. Notably, multivariate modeling did not show significant impacts of other clinical parameters, including gender, age at diagnosis, smoking status, squamous histology, and number of metastatic sites. Additionally, the ctDNA mutational burden was significantly associated with risk for both PFS (p=0.006, HR=1.17, CI=1.06–1.27) and OS (p=0.003, HR=1.16, CI=1.04–1.26) **[Figure 4]**.

Conclusions

Pre-radiotherapy ctDNA may be a useful tool for shared decision-making in oligometastatic NSCLC when deciding between radiation therapy versus systemic therapy, and provides an opportunity to objectively redefine oligometastatic disease.

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