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ctDNA Dynamics and TCR Diversity in Patient Selection for Unresectable Stage III NSCLC Consolidation Therapy

Yan Xu^a, Hui Guan^b, Yuan Wu^c, Siyuan Yu^a, Huiyu Huang^a, Xiaolu Yin^{c#}, Mengzhao Wang^{a#}

^a Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, 100730. ^b Department of Radiation Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, 100730. ^c Precision Diagnostics Development, Oncology R&D, AstraZeneca, Shanghai, China

Introduction

- Concurrent chemoradiotherapy (cCRT) followed by immune checkpoint inhibitor (ICIs) is the standard of care for unresectable stage III non-small cell lung cancer (NSCLC).
- The different strategies of combined radiotherapy (RT), chemotherapy and ICIs are being actively explored, such as sequential CRT (sCRT) followed by ICI, ICI concurrently with CRT, or induction strategies.
- Definitive RT primes the immune system, yet its suppressive impact on the systemic immune repertoire is often underappreciated.
- We aimed to identify the optimal early window for efficacy prediction and characterize immune activation potential through longitudinal monitoring of ctDNA and TCR dynamics.

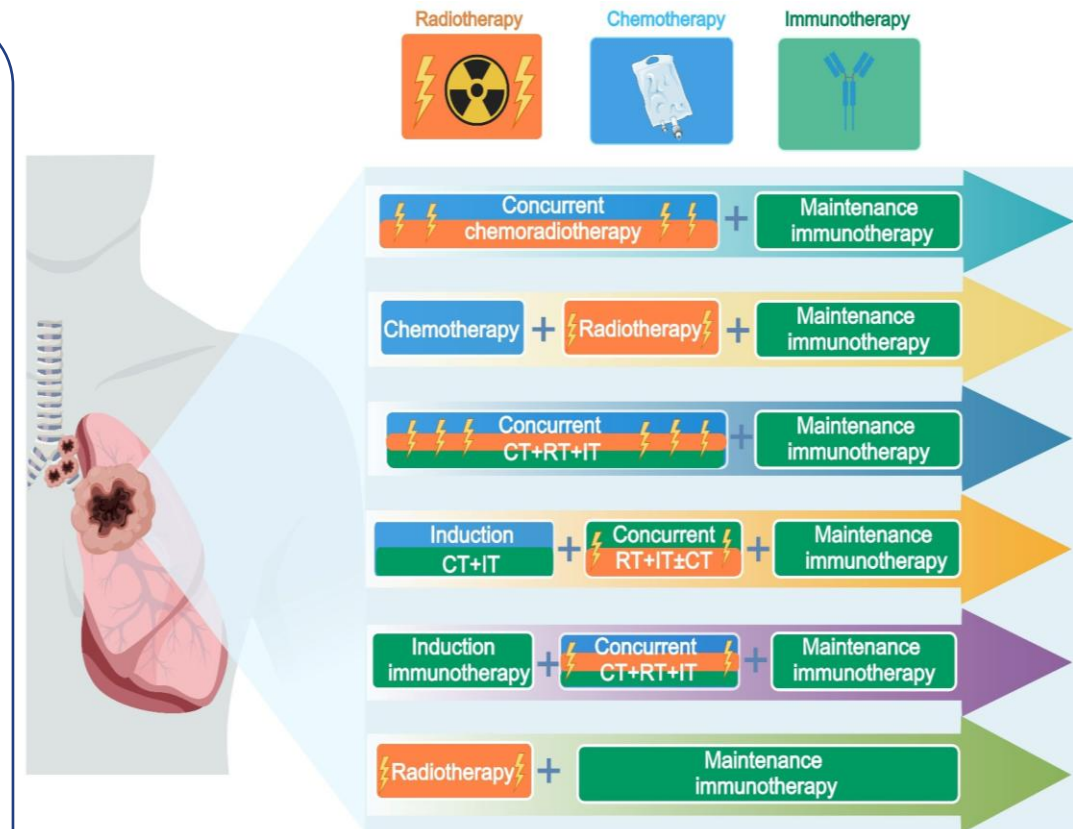


Figure 1: Multimodal combination strategies of anti-tumor immunotherapy, radiotherapy, and chemotherapy in unresectable, locally advanced lung cancer.

Patients and Methods

- 26 unresectable stage III NSCLC patients from PUMCH were prospectively enrolled.
- Patients received cCRT/sCRT $\pm$ ICI maintenance, or induction ICI+chemotherapy with definitive RT.
- Baseline tumor tissues underwent whole exome sequencing via next-generation sequencing (NGS).
- Plasma ctDNA and PBMC TCR were longitudinally monitored through treatment and follow-up.
- The correlation between ctDNA clearance, TCR diversity, and progression-free survival (PFS) was analyzed.

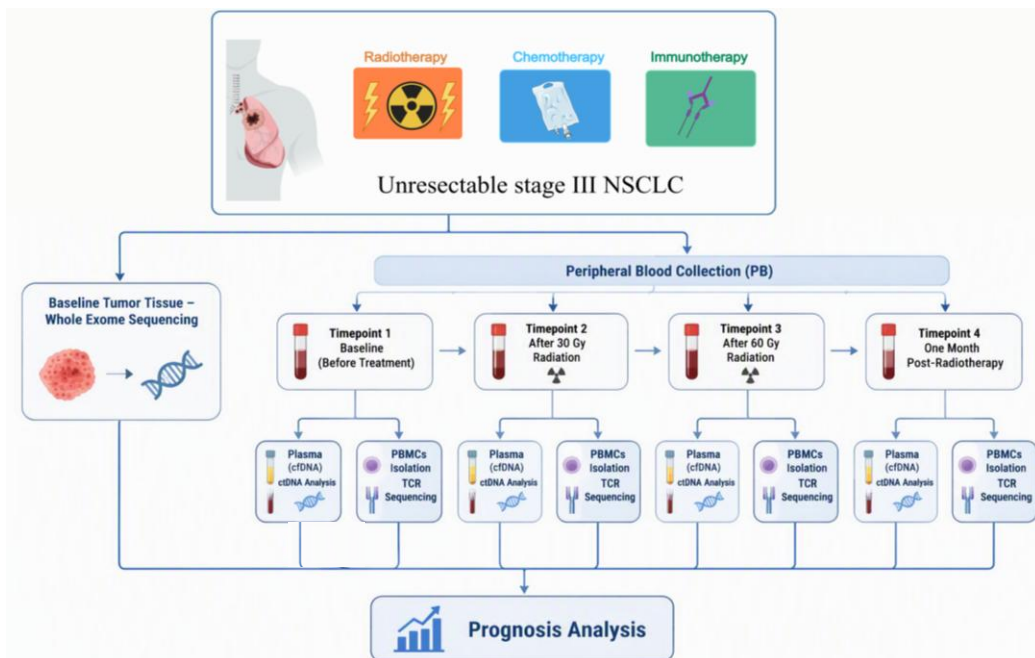


Figure 1: cancer treatment and sample disposition & testing Methods

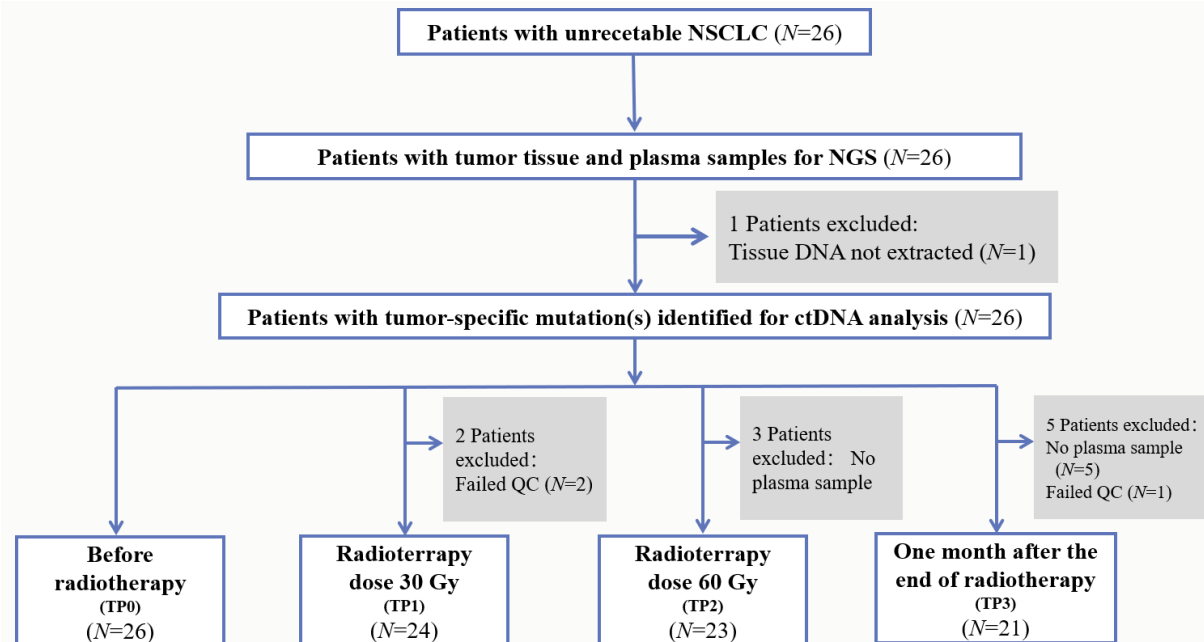


Figure 2: patients' disposition and samples collection

Results

- Baseline ctDNA positivity was 54% (14/26).
- Patients achieving ctDNA clearance at TP1 had significantly longer PFS ($p=0.016$, HR=3.77).
- Peripheral TCR diversity declined during radiotherapy, while ICI-RT was associated with partial post-treatment recovery.
- Patients with response or no progression tended to maintain higher diversity across treatment.
- ICI treatment promoted diversity recovery at TP3, where diversity often exceeds the baseline.

Table 1. Clinical characteristics of stage III NSCLC

Characteristics	N=26
Gender	
F	2(7.69%)
M	24(92.31%)
Age	
Mean±SD	63.92±9.66
Median[min-max]	64.00[45.00,81.00]
Pathological type	
LUAD	4(15.38%)
LUSC	18(69.23%)
NSCLC	4(15.38%)
Treatment options	
Concurrent CRT	10(38.46%)
Sequential CRT	5(19.23%)
ICI+chemotherapy with definitive RT (ICI-RT)	11(42.31%)
Best response	
PR	17(65.38%)
SD	9(34.62%)
Disease progression	
N	12(46.15%)
Y	14(53.85%)

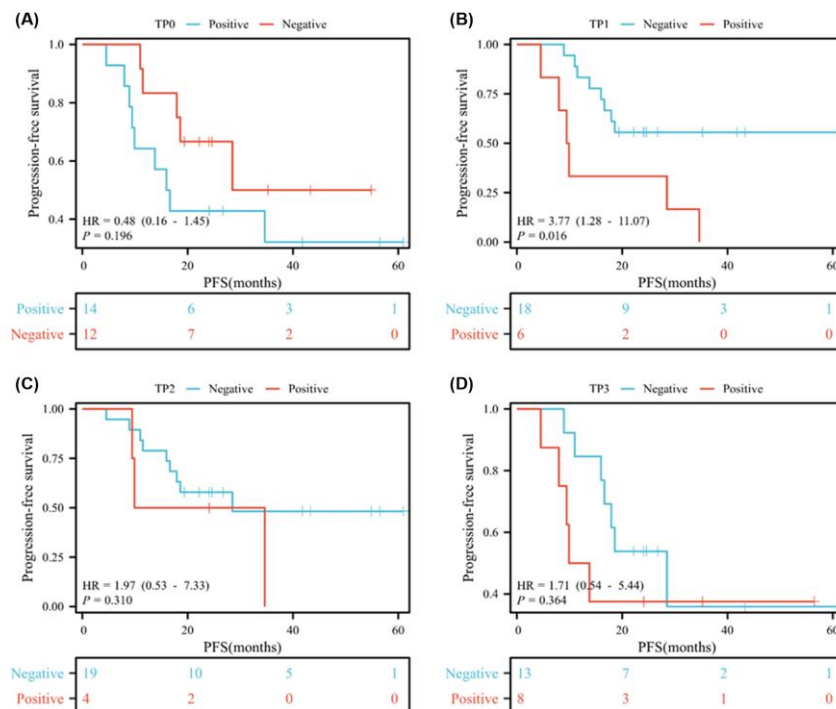


Figure 1: dynamic clearance of ctDNA and its correlation with PFS

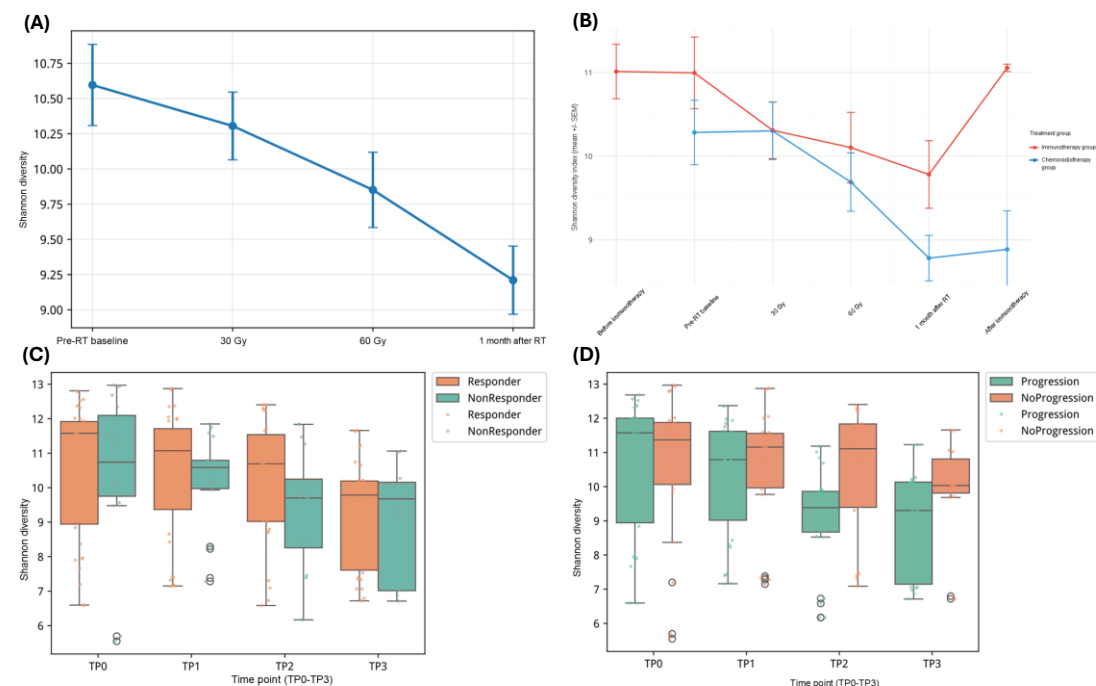
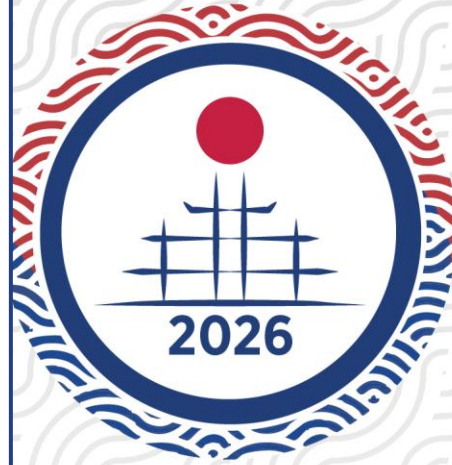


Figure 2: TCR repertoire diversity during radiotherapy

Conclusion

- Mid-RT ctDNA dynamics enables early survival prediction for stage III NSCLC.
- TCR repertoire evolution indicates “activatable” immune states.
- By combining ctDNA with TCR repertoire monitoring might guide patient selection.



Acknowledgement

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Thank You.