Mapping the pattern and pace of tumour dissemination using longitudinal imaging and ctDNA in the TRACERx lung study

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Wing Kin Liu[1,2], Boyue Ding[3], Sonya Hessey[1,2], Jeanette Kittel[1] , Cristina Naceur-Lombardelli[1,2], Hyothaek Lee[3], Catarina Veiga[3],, Ariana Huebner[2,4], Allan Hackshaw[5], Christopher Z. Abbosh[2], Alexander M. Frankell[2,4], Gary Royle[3], Charles Swanton[2,4,6] on behalf of TRACERx Consortium and Mariam Jamal-Hanjani[1,2,6] on behalf of the PEACE Consortium

Cancer Metastasis Laboratory, University College London Cancer Institute, London, UK[1], Cancer Research UK Lung Cancer Centre of Excellence[2], Department of Medical Physics and Biomedical Engineering, University College London, UK[3], Cancer Evolution and Genome Instability Laboratory, The Francis Crick Institute, London, UK[4], Cancer Research UK and UCL Cancer Trials Centre, London, UK[5], Department of Medical Oncology, University College London Hospitals, London, UK[6]

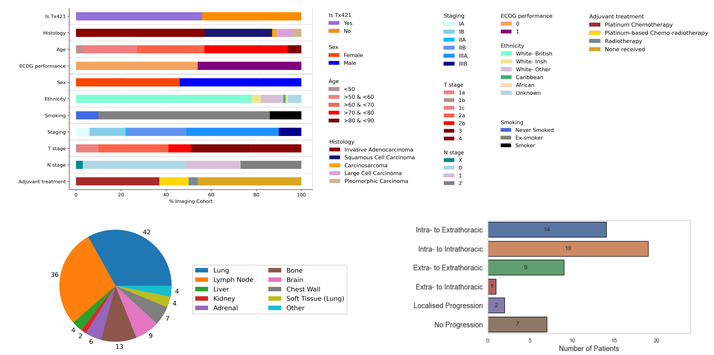
Overview

- ❖ Longitudinal computerised tomography (CT) imaging can be leveraged to map patterns of metastatic spread and track tumour growth rates lesion-by-lesion.
- ❖ Large-scale studies with longitudinal imaging and clinical annotation such as TRACERx can map the pattern of cancer progression from diagnosis to relapse and beyond.
- ❖ Circulating tumour DNA (ctDNA) in longitudinal plasma samples can be mapped to imaging to assess their role in monitoring cancer progression and the impact of therapy.
- ❖ ctDNA shedding was higher per unit volume in patients with extrathoracic relapses compared to intrathoracic-only relapse possibly suggesting a greater burden of micro metastatic disease.

Introduction

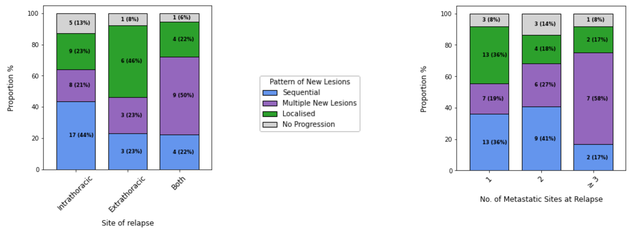
- ❖ TRACERx is a multicentre, prospective cohort study recruiting patients with early-stage non-small cell lung cancer.
- ❖ CT scanning is routinely performed during adjuvant follow up for surveillance, at points of relapse and/or progression and during treatment to assess response.
- ❖ ctDNA levels were detected using patient bespoke multiplex-PCR assay-panels based on tissue exome sequencing tracking up to 600 mutations per patient.
- ❖ The emergence and dynamics of metastasis specific subclones were tracked within ctDNA samples to further investigate ctDNA shedding.

Patterns of metastatic dissemination at relapse and subsequent progression



Result 1. Clinical demographics and patterns of metastasis at relapse

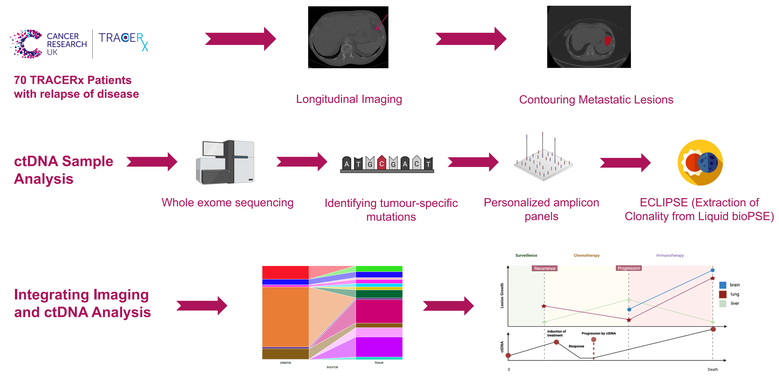
- ❖Common sites of relapse were lung, lymph node, bone and adrenal.
- ❖Sites of new metastasis upon cancer progression after relapse for patients with either intrathoracic-only or extrathoracic-only disease was highly variable (n=52).



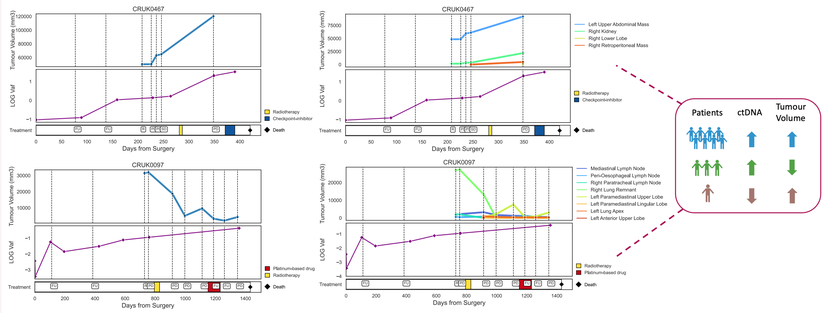
Result 2. Number of new lesions during cancer progression

- ❖Patients are more likely to progress with multiple new lesions simultaneously if they have extrathoracic relapse or had 3 or more metastasis at relapse.

Generation of a longitudinal imaging and ctDNA pipeline



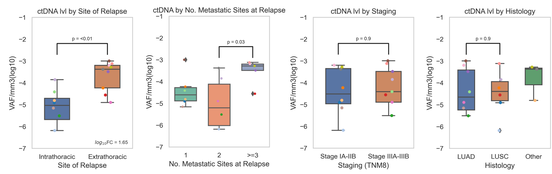
The pace and nature of radiological disease progression can be related to dynamic changes in ctDNA



*Each dotted vertical line corresponds to an imaging scan, treatment bar show radiologist reported outcome of scan; R= disease relapse, S = stable disease, PD= progression of disease, Days from surgery= date of surgery to remove primary tumour, LOG Vaf = mean clonal ctDNA fraction present in the plasma sample to the log10. For summary table; arrow represents an increase or decrease from ctDNA sample/ scan taken at relapse to the last registered ctDNA sample/ scan.

Result 3. ctDNA rises with total tumour volume for the majority of cases

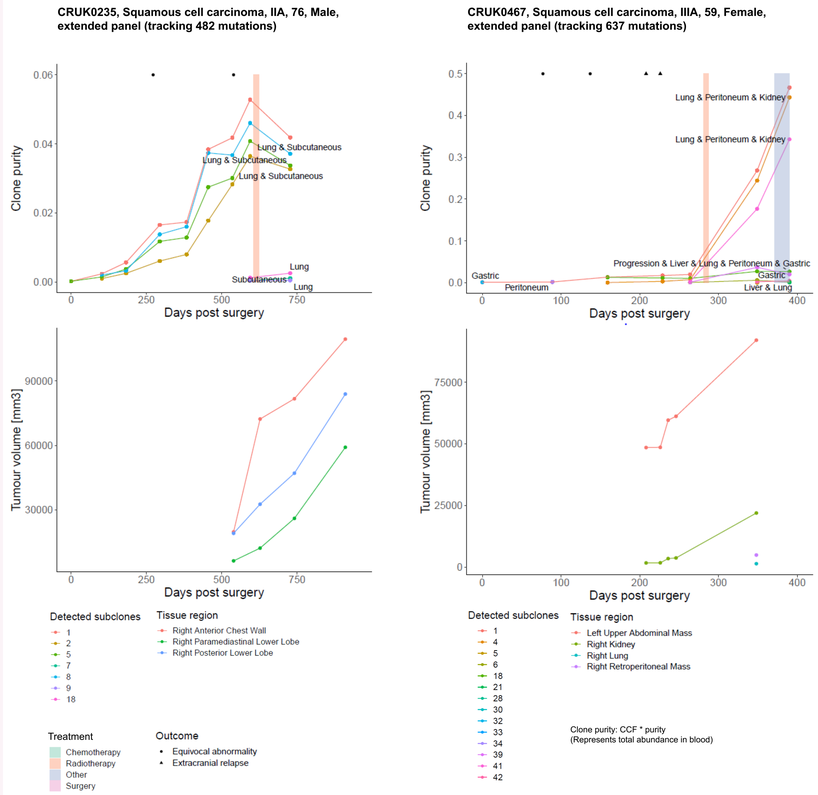
- ❖A 59-year old female smoker with lung squamous carcinoma stage IIIA. For most patients (8/12) ctDNA correlates with increasing tumour volume.
- ❖A 76-year old male ex-smoker with large cell carcinoma stage IB. ctDNA inversely correlated with tumour volume possibly suggesting disproportionate shedding of micro-metastatic disease.



Result 4. ctDNA shedding is higher for patients with extrathoracic relapse

- ❖ctDNA at relapse was paired with total tumour volume to calculate ctDNA /mm^3 (n=17).
- ❖More ctDNA/mm^3 was shed for patients with extrathoracic relapse compared to intrathoracic-only.
- ❖More ctDNA/mm^3 was shed for patients with more metastatic sites at relapse.
- ❖No correlation was found for ctDNA shedded with staging at diagnosis or histology.

Early detection of metastasis specific subclones in ctDNA



Result 5. Dynamics of subclonal circulating tumour DNA shedding during metastasis together with metastatic lesion specific tumour volumes

- ❖ Subclones were detected in ctDNA before or soon after surgery that were otherwise only identified in autopsy tissue.
- ❖ Subclones can be detected in ctDNA several hundred days prior to matched subclones from lesions tracked on imaging scans.

Conclusions and further work

- ❖Large-scale studies with longitudinal imaging and clinical annotation can map the pattern of cancer progression adding further insight into the clinical disease course.
- ❖ctDNA fraction usually tracks with total tumour volume but for rarer cases may instead track with lesions that disproportionately shed ctDNA.
- ❖Analysis of subclones detected in ctDNA can show metastatic divergence occurring earlier than would be suggested by tissue analysis.
- ❖Longitudinal imaging can be mapped to the detection of subclones in ctDNA to give further insights into cancer evolution.
- ❖Further work will involve expanding this cohort to systemically analyse treatment effects on ctDNA shedding and further investigate the clonal or lesion-specific shedding of ctDNA.

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