Determination of the detection lead time for autoantibody biomarkers in early stage lung cancer using the UKCTOCS cohort

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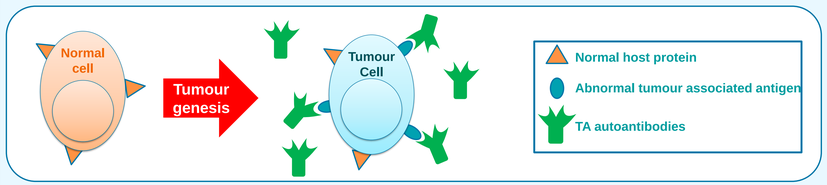
1. Background

- Tumour associated (TA) autoantibodies[1]
  - Serum Immuno-biomarkers amplify the corresponding TA antigen signal
  - Hundreds of TA autoantibodies identified at elevated levels for a **range of cancers**
  - Produced **early** in tumour genesis prior to clinical symptoms
    - Previously detected ≤5 years before diagnosis[2]
    - Detection lead time never accurately determined



- Can aid early detection and nodule patient stratification in **lung cancer** patients
  - Absent or low concentrations in healthy & benign cohorts
  - 7 panel ELISA available commercially since 2012 (EarlyCDT®-Lung[3-4]
    - ~40% sensitivity & 93% specificity for **all stages of lung cancer**
    - p53, NY-ESO-1, SOX2, HuD, GBU4-5, CAGE & MAGE A4
    - Technically & clinically validated on numerous high risk case control cohorts[5-7]
    - Randomised controlled clinical screening trial due to report 2018[8]

2. Aims

- Accurately determine the **detection lead time** for TA autoantibodies in lung cancer:
  - Using a cohort of cases with sequential pre-diagnostic blood samples and a matched healthy control cohort.
  - Applying an extended panel of 14 TA autoantibodies, now including:
    - CK8, CK20, LMYC2, p62, p16, SSX1, p53-N
  - Using personalized analysis which looks for changes in autoantibody profile across time rather than a population approach

3. Study Cohort

- UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)
  - Recruited 202,638, postmenopausal women aged >50 (2001-2005)
  - The multi modal screening arm (50,648 women) had annual blood draws
- **Lung Cancer Case Cohort:**
  - Average of seven serial pre-diagnostic samples per patient
  - 142 lung cancer cases diagnosed during the trial
  - Early and late stage disease at diagnosis
- **Control Cohort:**
  - UKCTOCS cases with no history of cancer during the study
  - Matched 1:1 to lung cancer cases by age, smoking history and sample collection year
- Cohort cases split into Training (n=100) and Validation (n=42) cohorts

4. Distribution of samples by pre-diagnosis time

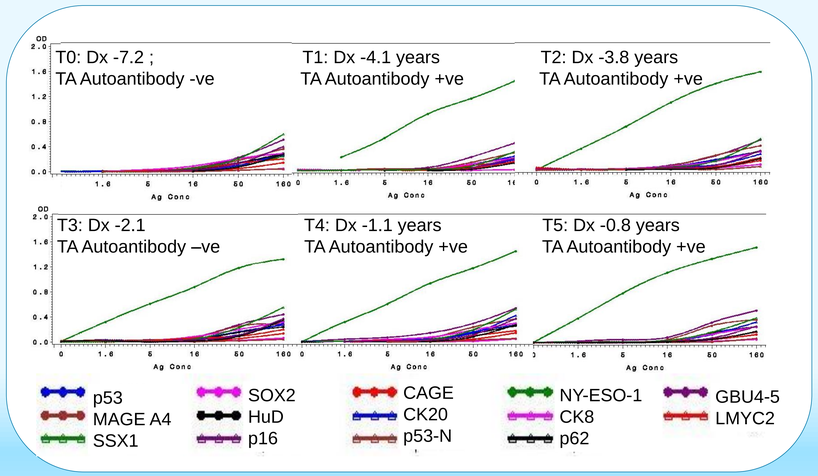
:	Samples by years before diagnosis									
CASES	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	Total samples
142	182	168	143	125	127	96	79	37	38	995

5. Methods

- **Testing procedure**
  - For each timepoint sample an autoantibody profile was observed as a vector of assay results
  - **Phase 1:** Test the first patient sample T0 versus a population negative profile (PNP) derived from control samples, to determine if the patient is already TA autoantibody positive, using an inter-subject cut-off
  - **Phase 2:** For patients negative at T0, compare each subsequent timepoint (T1, T2, etc) profile with T0 profile for the same patient using intra-subject cut-offs
- The autoantibody-specific cut-offs were optimised on the Training cohort then applied to the Validation cohort
- **Detection Lead time:**
  - Calculated for all lung cancer cases using Phase I and Phase II cut-offs:
    - If positive at T0 that pre-diagnosis time was assumed to be the detection lead time
    - If positive after T0 the detection lead time was calculated from the mid point between the pre-diagnosis time of the sample and the one preceding it

6. Results: Profile change over time

- TA autoantibodies were elevated for 60 of the 142 lung cancer cases
- **Example case** (age at Dx = 61.1 yrs): NY-ESO-1 TA autoantibody raised 4.1 years prior to diagnosis:



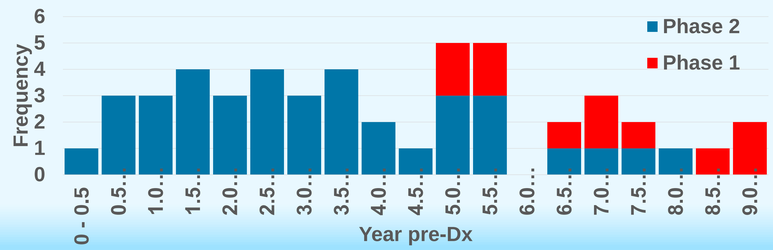
7. Results: Positivity summary

	Cohort	Phase 1 Positive	Phase 2 Positive	Total
Total (Training & Validation)	Case	14	46	142
	Control	3	14	142
	Total	17	60	284

8. Results: Detection lead time

Cohort	All positive cases (Phase 1 + Phase 2)			Phase 2 positive cases only		
	n	median	range	n	median	Range
Training	49	4.0	0.3 – 9.4	38	3.1	0.3 - 8.0
Validation	11	4.3	0.1 – 9.0	8	3.5	0.1 – 7.4
Total	60	4.1	0.1 – 9.4	46	3.2	0.1 – 8.0

9. Results: Detection lead time distribution



10. Conclusions

- **Detection lead time:**
  - Median detection lead time for TA autoantibodies was 4 years prior to clinical diagnosis of lung cancer:
    - 4 years for both Training and Validation cohorts
    - 3 years when T0 positives removed from cohorts
  - Detection lead time was as early as 9 years prior to diagnosis for some cases

11. Acknowledgments

The UKCTOCS study was run by UCL (University College of London, UK). The patient samples were accessed in a collaboration between Oncimmune and Abcodia Ltd, Cambridge UK, the latter maintaining exclusive access to the UKCTOCS samples in collaboration with UCL. The UKCTOCS trial was funded by the Medical Research Council, Cancer Research UK, the Department of Health and The Eve Appeal, all in the UK. We would particularly like to thank Sophia Apostolidou (UCL) and Dr Julie Barnes (Abcodia) for their excellent support in matching, retrieving and shipping the samples.

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