RWD54

Real-world evidence for patient outcomes and mutational burden in non-small cell lung (NSCLC) cancer patients in England using EGFR biomarker test data from routine clinical care

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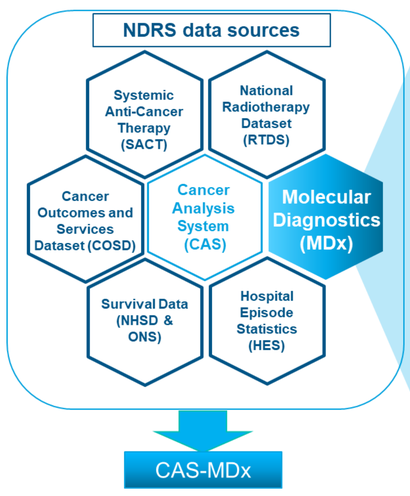
Background

- Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancers in England and generally has poor prognosis[1]. Over the past decades, significant advances have been made in the understanding of molecular drivers for tumor progression and in the development of personalized treatments based on genetic biomarkers.
- Genetic biomarkers can serve as predictors of cancer survival and play a pivotal role in guiding treatment choices.
- The development of EGFR-targeted therapies for NSCLC has significantly enhanced patient outcomes. However, the efficacy of these drugs is highly dependent on the EGFR mutational variant patients carry, emphasizing the importance of understanding the EGFR mutational variants among NSCLC populations.
- The recent development of a Molecular Diagnostics dataset by the National Disease Registration Service (NDRS), part of NHS England, holds the potential to support future studies in identifying new prognostic and predictive markers

This study aimed to explore unmet need using novel biomarker data collated by the NDRS within NHS England

Methods

Study design: This study employed a retrospective observational cohort design using data from the NDRS Cancer Analysis System (CAS), including the Molecular Diagnostics dataset (MDx).



Real-world somatic testing data:
- Somatic tests directly from tumour samples
- Captures >300 different biomarkers
- From small DNA variants to chromosomal abnormalities
  - As well as RNA and protein testing methodologies

Unparalleled coverage:
- Data from >400 testing laboratories across England
- Nationally representative biomarker data for the MMR genes and PD-L1 biomarker from 2019 onwards
  - Other biomarkers do not yet have a nationally representative coverage, however improving representation with each data refresh

Study cohort: Patients aged ≥18 years with an incident diagnosis of NSCLC between 2012-2019 were included if they had an EGFR biomarker test record between 2016-2019. Study time period was based on available data at time of analysis.

Analysis

- Patient demographics, clinical characteristics and biomarker testing interval for the cohort were described**.**
- Cox regression models were used to estimate overall survival by EGFR test result status, excluding patients with missing stage at diagnosis. Patients were followed up from diagnosis until death from any cause, lost to follow-up or 31 December 2020.
- Findings were presented as crude and adjusted hazard ratios (HR) for age, sex and stage at diagnosis.
- Sequence variants identified for NSCLC patients with EGFR biomarker test results will be described. Variant mapping was performed using ClinVar (a sequence variant online database) to report categories of 'Types of variant' and 'Clinical significance'

Figure 1. Data flow of patients in study cohort

A. Patients with records in MDx from 1 January 2016 to 31 December 2019
N = 94,430 (100%)

B. Patients with incident diagnosis of NSCLC from 1 January 2012 to 31 December 2019
N = 53,360 (55% of A)

C. Patients with an EGFR-test record
N = 35,470 (65% of B)

Final study cohort
N = 30,110 (85% of C)

Exclusions
- Patients aged <18 at diagnosis
- Patients receiving treatment under Cancer Drugs Fund
- Patients with prior malignancy
- Patients with a prior record of systemic anticancer treatment.
- Patients with EGFR test >60 days before NSCLC diagnosis

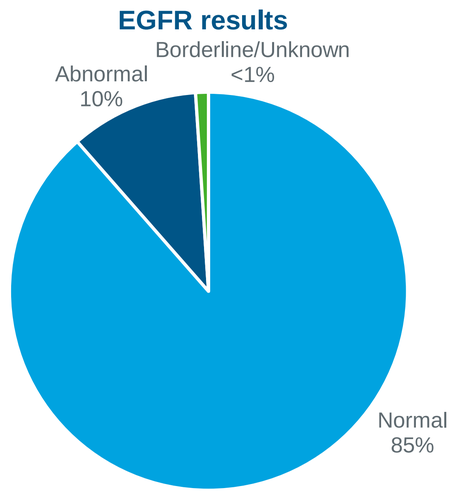
Results

Study population
N = 30,110 EGFR-tested NSCLC patients, of which **N = 3,410 (~10%)** had an abnormal EGFR result

Time from diagnosis to biomarker test
Median time between diagnosis to overall test result was **19 days (IQR: 11-36)**.
85% of patients had their EGFR test within 3 months of diagnosis.

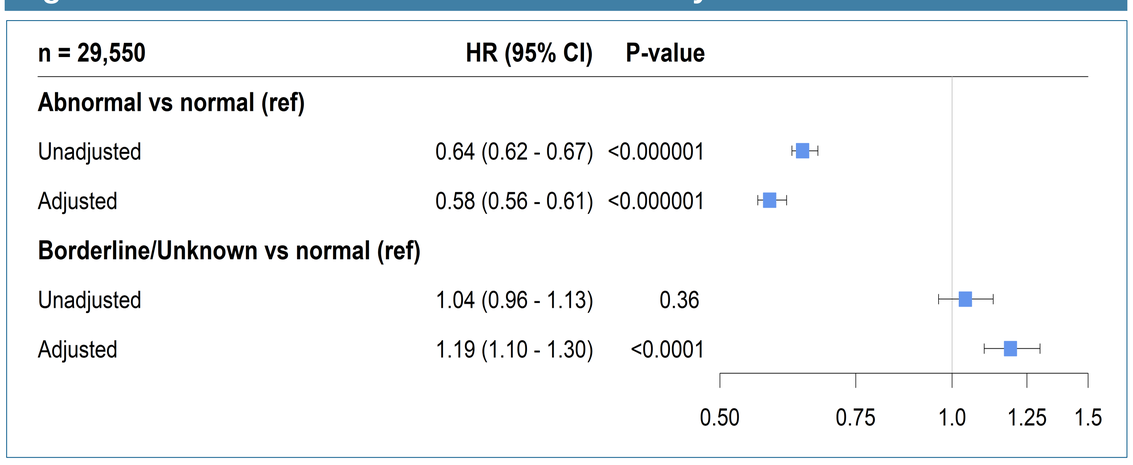
Figure 2. Patient and clinical characteristics

Total patients		30,110
Mean (SD) age in years at diagnosis		69 (10)
Sex	Female	50%
Stage at diagnosis	1	10%
	2	5%
	3	20%
	4	60%
	Unknown	<1%
Socio-economic status based on index of multiple deprivation	1 – Least deprived	25%
	2	20%
	3	20%
	4	20%
	5 – Most deprived	15%



Overall survival
- Abnormal EGFR test result in NSCLC patients was significantly associated **(P<1*10^{-6})** with lower unadjusted risk of death compared to normal EGFR.
- The survival advantage for abnormal EGFR vs normal EGFR persisted after adjusting for age, sex and stage at diagnosis **(P<1*10^{-6})**.
- Patients with unknown/borderline EGFR had a survival disadvantage vs. normal EGFR after accounting for covariates **(P<1*10^{-4})**.

Figure 3. Hazard ratios for overall survival by EGFR test result



Types of sequence variants among abnormal EGFR test results
- **>99% (N=3,410)** of patients with abnormal EGFR have DNA sequence variants; the remaining have copy number loss/gain.
- Genetic locations and details of DNA sequence variants are available for **N=2,200** patients.
- **75% (N=1660)** of NSCLC patients with sequence variant data for EGFR had single nucleotide variants, with small numbers of other types of variants.
- **75% (N=1680)** of NSCLC patients with sequence variant data for EGFR had a variant associated with drug response.

Table 4. EGFR sequence variants

Total patients tested		N=30,110	100%
Patients with sequence variant identified		3,410	10%
Patients with variant genetic location available		2,200	65%
Type of EGFR sequence variant	Single nucleotide variant	1,660	75%
	Deletion	190	10%
	Duplication	30	0%
	Indel	60	5%
	Insertion	*	-
	Unmapped	260	10%
Clinical significance of EGFR sequence variant	Benign	*	-
	Pathogenic	340	15%
	Drug response	1,680	75%
	Conflicting interpretations	*	-
	Uncertain significance	40	0%
	Unmapped	260	10%

Conclusion

- **Within this NSCLC patient cohort in the CAS-MDx data, abnormal EGFR test results were associated with higher survival. The majority of EGFR variants corresponded to known drug response targets, suggesting the potential role of personalised treatments in these outcomes.**
- **Very few data sources contains the detail required to support research into unmet needs in emerging targeted cancer therapies.**
- **This study shows that real-world biomarker data in CAS-MDx contains the combination of depth and breadth required to conduct associations between mutational variant level to outcomes, as exemplified by the EGFR biomarker stratification.**

References: 1. Zappa C, Mousa SA. Non-small cell lung cancer: current treatment and future advances. Transl Lung Cancer Res. 2016 Jun;5(3):288-300. doi: 10.21037/tlcr.2016.06.07. PMID: 27413711; PMCID: PMC4931124.
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Note: All small numbers 1-9 are replaced with ' * '. All numbers above 10 are rounded to the nearest 10. Percentages are presented rounded to the nearest 5%.
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