Opportunities with high quality real-word data

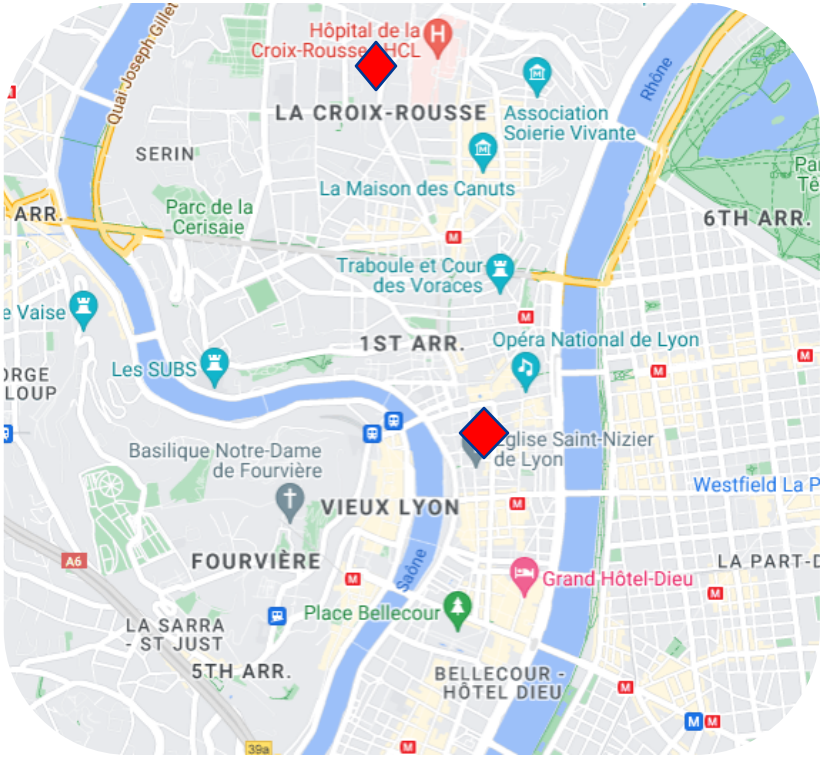
08/07/2024

ICCR Lyon

Prof Corinne Faivre-Finn

Finn_corinne

The Christie
NHS Foundation Trust


Hôpital de la Croix-Rousse - HCL
LA CROIX-ROUSSE
Association Soierie Vivante
Rhône
SERIN
La Maison des Canuts
Parc de la Cerisaie
6TH ARR.
Traboule et Cour des Voraces
Opéra National de Lyon
1ST ARR.
Les SUBS
Basilique Notre-Dame de Fourvière
Église Saint-Nizier de Lyon
Westfield La P
VIEUX LYON
FOURVIÈRE
A6
Saône
Grand Hôtel-Dieu
LA PART-D
Place Bellecour
LA SARRA - ST JUST
5TH ARR.
BELLECOUR - HÔTEL DIEU

Disclosures

I am a clinical trialist

Passionate about evidence-based medicine

Frustrated after 2 decades of leading ‘explanatory’ clinical trials

Many of my examples come from the field of lung cancer

What is Real World Evidence (RWE)?

Information on healthcare derived from **real-world data** settings
Its defining characteristics are the **routine care settings** in which data are collected and the **degree of pragmatism**

Royal College of Physicians | National Lung Cancer Audit

RCS NPCA National Prostate Cancer Audit

ukiacr United Kingdom and Ireland Association of Cancer Registries

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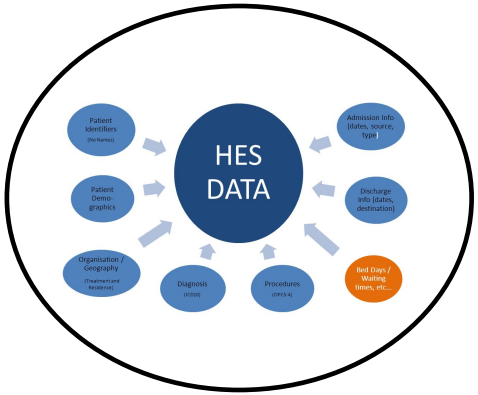
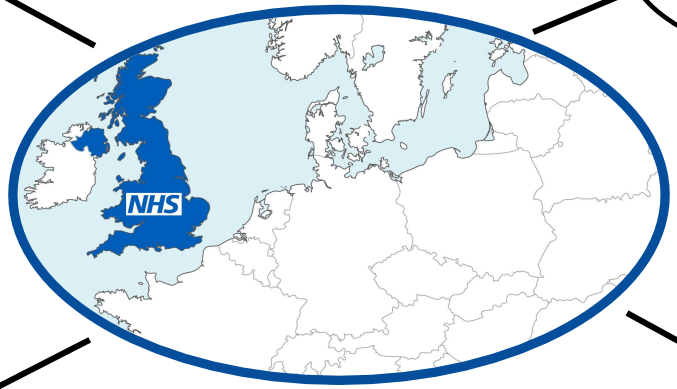
UK one of the best places for RWE research





SACT Systemic Anti-Cancer Therapy Chemotherapy Dataset

Royal College of Physicians | National Lung Cancer Audit

RCS NPCA National Prostate Cancer Audit

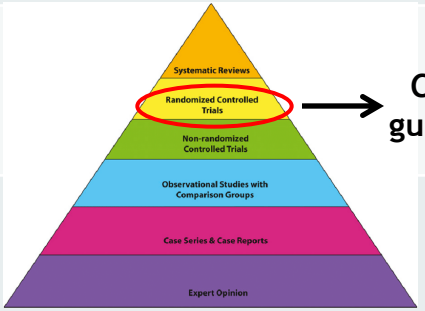
The Radiotherapy Dataset (RTDS)

ukiacr United Kingdom and Ireland Association of Cancer Registries

The Christie NHS NHS Foundation Trust

Why do we need Real World Evidence?

RCTs- Pros and Cons

Advantages of RCTs	Disadvantages of RCTs
Comparative	Logistics – sample size, multisite, time , cost
Minimises bias e.g. selection and allocation bias . Homogeneous population	Applicability/generalisability- Results may not always mimic real life treatment situation (eg age, PS, comorbidities)
Minimises confounding factors	Ethical limitations-lack of equipoise
Statistical reliability Avoids both type 1 error (null hypothesis is incorrectly rejected) and type 2 error (null hypothesis is incorrectly accepted)	
High quality data collection protocols, Publishable	

LET'S BE CLEAR

Randomized controlled trials and real-world evidence are not mutually exclusive

…but…

RCTs only enrol approximately 5-10% of the cancer patient population

RCT participants are >6-10 years younger than the general population

Lack of external validity - i.e. limited ability to GENERALISE results

Lack of diversity

Aim of RWE - Learn from every patients

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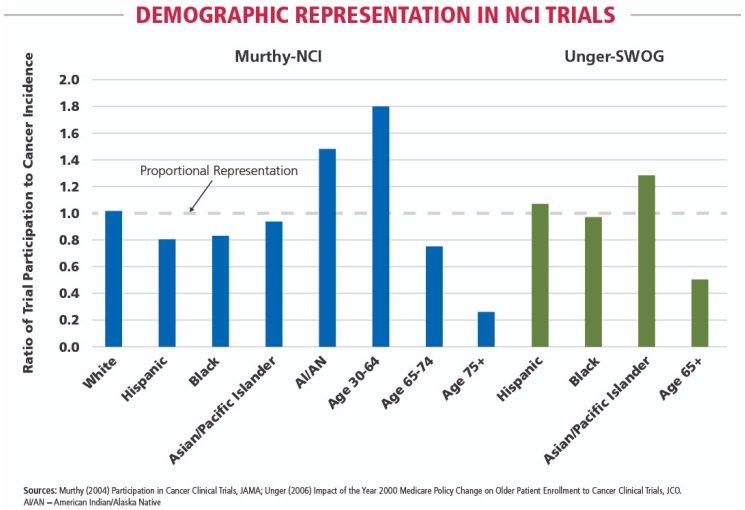
Patients under-represented in clinical trials

Cancer Action Network℠
American Cancer Society®

Barriers *to*
Patient Enrollment in Therapeutic Clinical Trials for Cancer
A Landscape Report



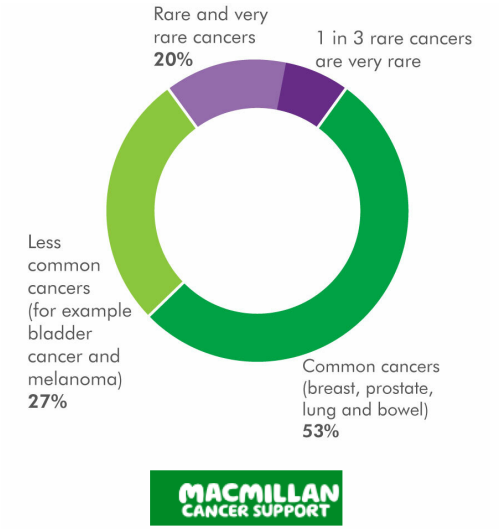
BIAS

Eligibility criteria too stringent

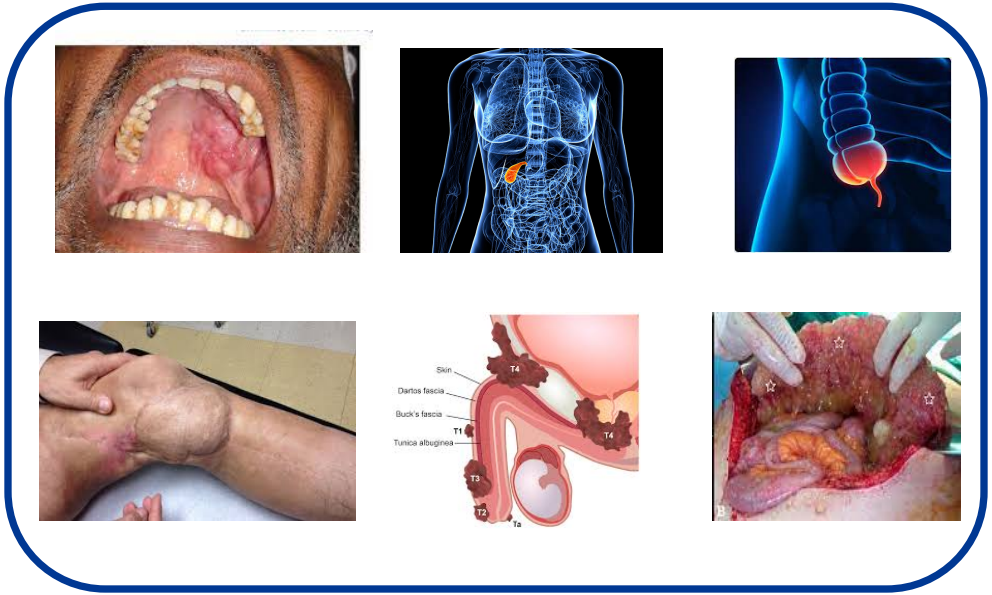
<5% of patients with cancer are enrolled in RCTs

www.acscan.org/policy-resources/clinical-trial-barriers (2018)

Cancers under-represented in clinical trials

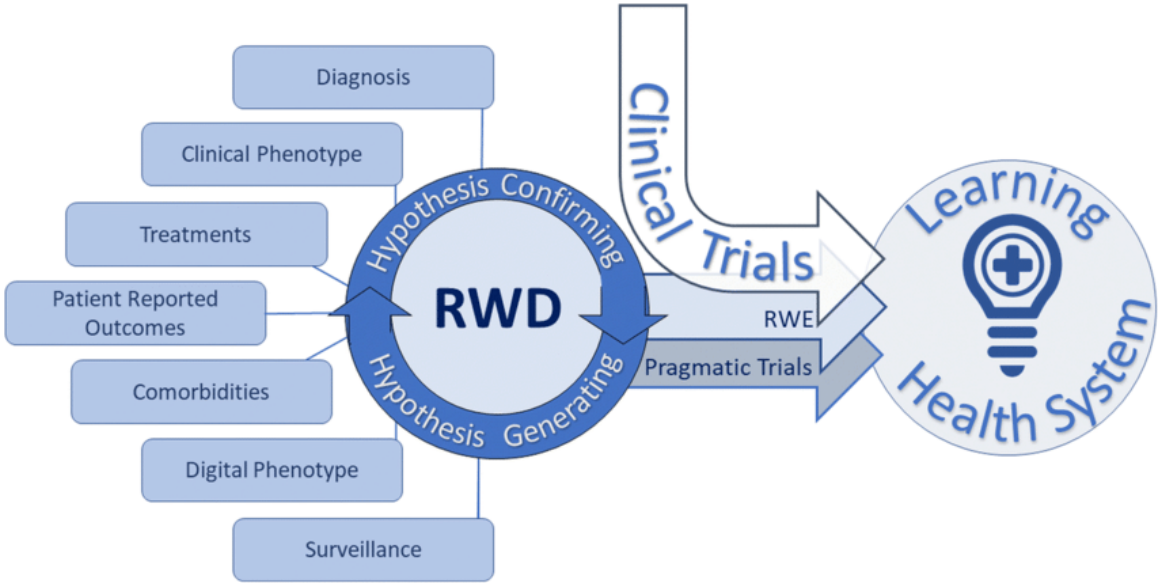


Proportions of common, less common, rare and very rare cancers



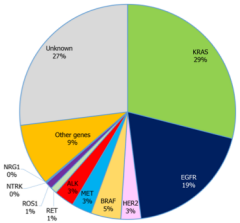
A cancer is rare if < 6 in 100,000 people are diagnosed each year
~ 24% of all cancer cases diagnosed in Europe and the UK

So….what is the role of RWE?
Alternative to RCTs in specific scenarios

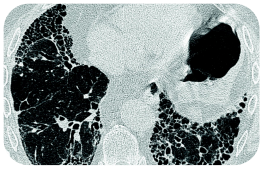


Specific scenarios

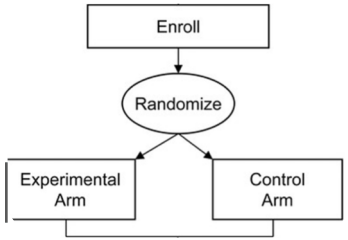
Underrepresented patients

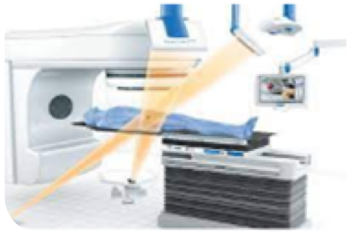


Rare cancers or populations



Long term follow-up





Rapid changes in technology

Standard RCTs not suitable

No consensus on control arm

Lack equipoise

→ More inclusive and representative research

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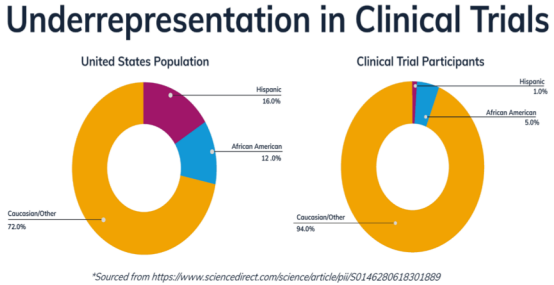
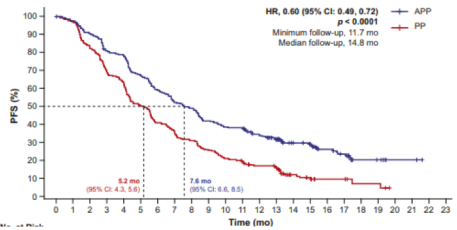
Underrepresented patients or populations

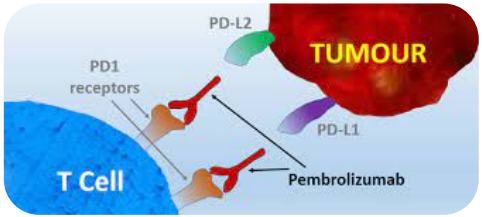


Impower 132



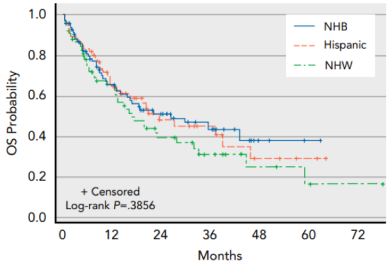
Race, n (%)	
White	193 (66.1)
Black or African American	2 (0.7)
Asian	71 (24.3)
American Indian or Alaska Native	1 (0.3)

Impact of immunotherapy in underrepresented populations

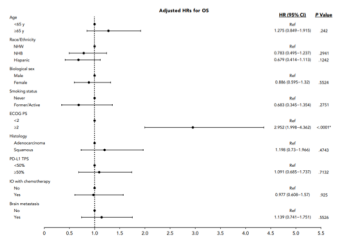


248 patients treated with pembrolizumab

Non-Hispanic Black, Hispanic, and Non-Hispanic White patients



OS/PFS similar among race groups

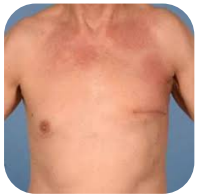


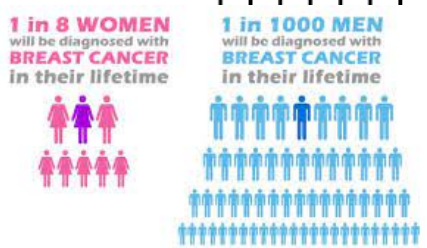
No effect of race in multivariable model

Lee. J Natl Compr Canc Netw 2023

The Christie NHS Foundation Trust

Real-World Data of Palbociclib in Combination With Endocrine Therapy for the Treatment of Metastatic Breast Cancer in Men- selective inhibitor of CDK4/6





~ 370 men diagnosed each year with breast cancer in the UK

vs. 55,500 diagnoses in women

Efficacy and safety of Palbociclib in women with M+ hormone receptor+/HER2− breast cancer established

1139 men with M+ breast cancer, 146 treated with Palbociclib

Benefit from palbociclib plus ET, safety profile consistent with observations in women

FDA expanded the palbociclib indication to include men with HR+/ HER2− M+BC

Kraus. Clin Pharmacol Ther. 2022

Conventional RCTs not suitable

First Linac

Cerrobend blocks

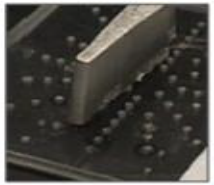
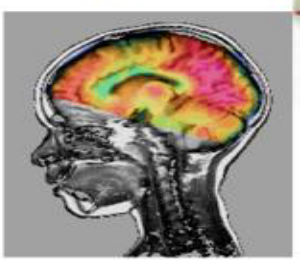
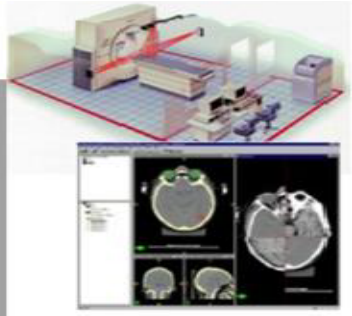
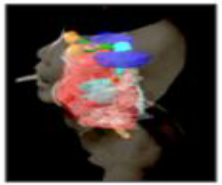


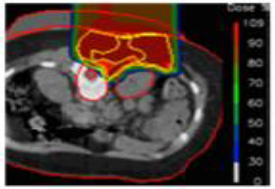
Image Fusion





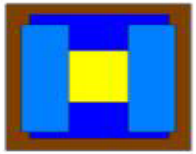
IMRT dose-painting





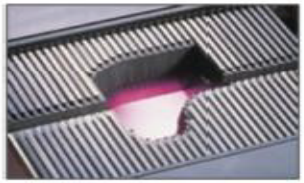
Particle Therapy

1960 1970 1980 1990 2000 2010

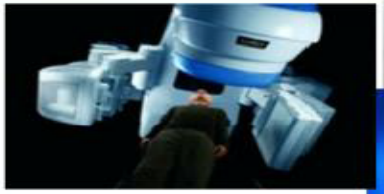


Standard collimator

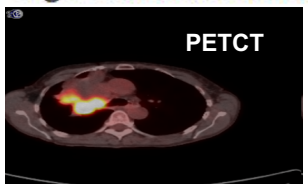
Shaped electron fields



Multileaf collimator

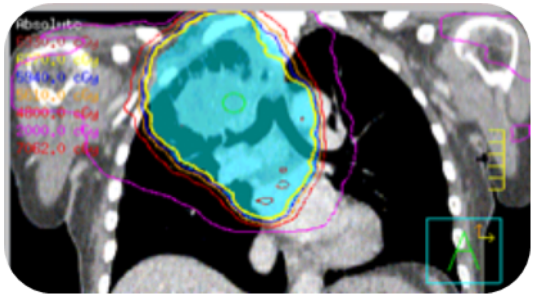


High resolution IGRT



Stereotactic Radiotherapy

Impact of introducing IMRT on curative-intent RT and survival for lung cancer



Lung cancer patients treated with thoracic radiotherapy 2005-2020 retrospectively identified

n=12499

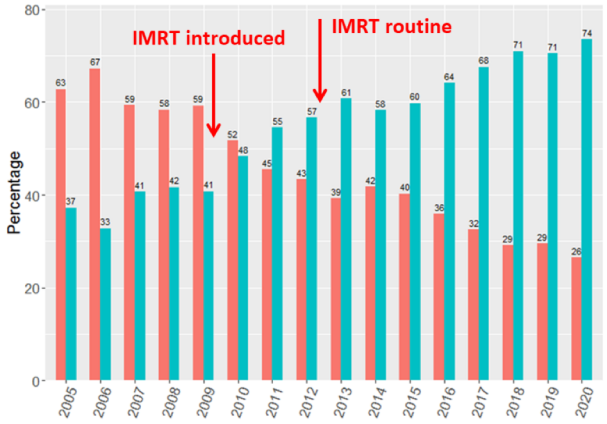
- 2005 -2008 — Pre-IMRT
- 2009-2012 — Some availability IMRT
- 2013-2020 — Full access IMRT

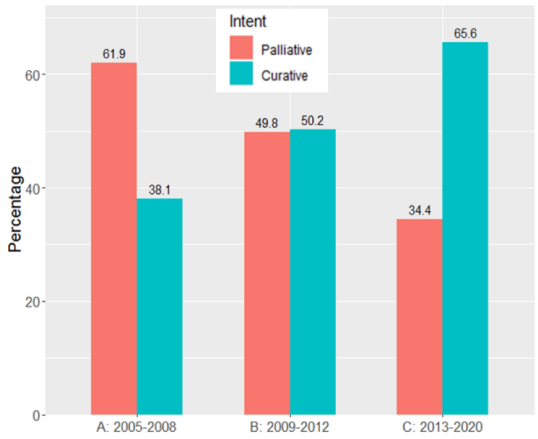
Hypothesis 1 - IMRT is allowing us to treat more patients with curative-intent radiotherapy

Hypothesis 2 - Survival will increase following the introduction of IMRT, after adjustment for known prognostic factors

Chan. Frontiers Oncol 2022

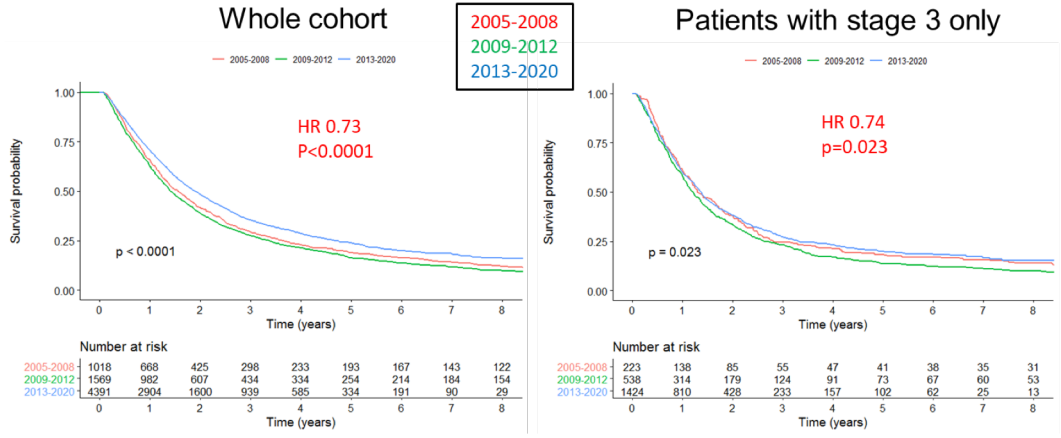
Proportion of patients receiving curative-intent radiotherapy





n= 12499

Impact on overall survival



Adjusted for known prognostic factors

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Experience with RWE
at the
Christie NHS Foundation Trust

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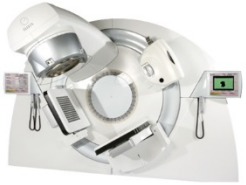
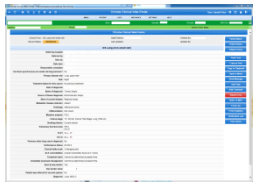
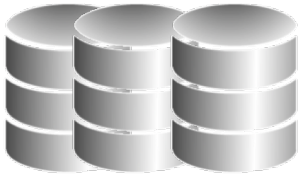
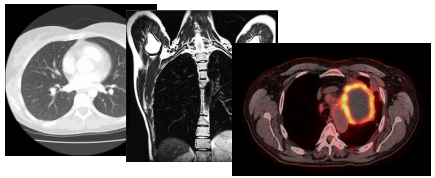
Radiotherapy real world data- UK CAT

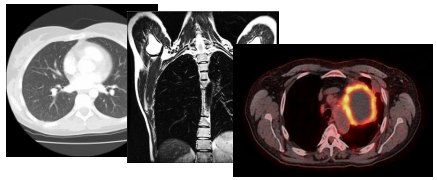


Diagnostic tests | Prescription | Plan and treat | Follow up tests | PROMs









Large digital footprint

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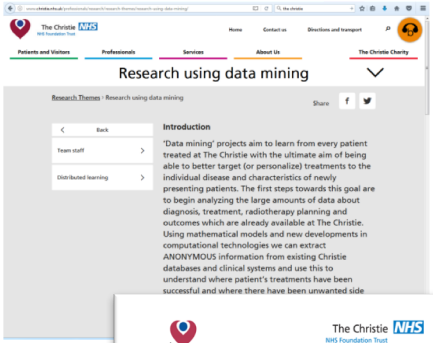
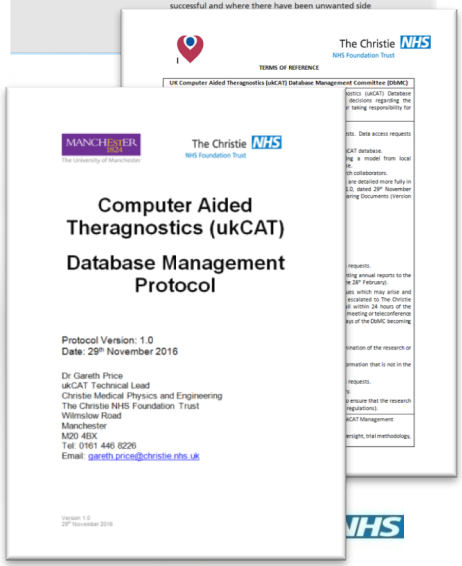
Governance

Ethical permission from Health Research Authority to run as a research database
Management of data use for research devolved to a local management committee

NHS
Health Research Authority

The Christie





1-2 weeks

Disease and staging (DS) Lung form

* Date seen: 28-Dec-2022

* Responsible consultant: FAIVRE-FINN C

Are there synchronous non-small cell lung tumours? ○ Yes ◉ No

* Primary disease site: Lung, upper lobe

* Side: ◉ Right ○ Left

* Treatment status for this cancer: This is about any previous treatment at all for this cancer (not just from this team)

◉ No previous treatment
○ Post previous treatment

* Histology

* Differentiation

* Clinical stage
ie, at time of original treatment

Smoking history

Pack years
Record if current or ex-smoker

Pulmonary function tests
Mark all that apply

Clinical TNM Stage: Lung (TNM v8)	
NA	Not applicable for this case
Awaited	The TNM stage is not currently available
T Stage	**Primary Tumour: Click on one T stage description to select** (then scroll down to select the N stage)
TX	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma in situ[a]
T1	Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus)[b]
T1mi	Minimally invasive adenocarcinoma[c]
T1a	Tumour 1 cm or less in greatest dimension[b]
T1b	Tumour more than 1 cm but not more than 2 cm in greatest dimension[b]
T1c	Tumour more than 2 cm but not more than 3 cm in greatest dimension[b]
T2	Tumour more than 3 cm but not more than 5 cm; or tumour with any of the following features[d] - Involves main bronchus regardless of distance to the carina, but without involvement of the carina - Invades visceral pleura - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region either involving part of or the entire lung
T2a	Tumour more than 3 cm but not more than 4 cm in greatest dimension
T2b	Tumour more than 4 cm but not more than 5 cm in greatest dimension
T3	Tumour more than 5 cm but not more than 7 cm in greatest dimension or one that directly invades any of the following: parietal pleura, chest wall (including superior sulcus tumours) phrenic nerve, parietal pericardium; or separate tumour nodule(s) in the same lobe as the primary
T4	Tumour more than 7 cm or of any size that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary
N Stage	**Regional Lymph Nodes: Click on one N stage description to select** (then scroll down to select the M stage)
NX	Regional lymph nodes cannot be assessed

ECOG PERFORMANCE STATUS	
Grade	**ECOG Description - Click on the description to select**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

Click to select the patient comorbidities:
Myocardial Infarct grade 2
Arrhythmias grade 1
Respiratory disease grade 1
Obesity grade 2

* Treatment intent: Curative

* Immediate proposed management
Indicate the first element of the management plan: SABR

Sites of planned radiotherapy: ◉ Primary ○ Primary and regional nodes ○ Metastasis ○ Other

* Verbal patient consent obtained for HIV/hepatitis screening: ○ Yes ○ No

Entry into a clinical trial: Trial discussed, patient decision awaited

Filled in by clinical teams

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Out-patient review (lung) form

Responsible consultant*

FAIVRE-FINN C

Diagnosis*

Lung, NSCLC

Summary of consultation

This can be filled in now or completed by secretary later.

Toxicity present*

Yes | No

Record of toxicity (CTCAE)

Click to select or remove any toxicity

Conduction disorder, grade 2
Esophagitis, grade 2
Fatigue, grade 2

Current disease status*

Pre treatment

- Pre-treatment planning

On treatment

- Stable disease
- Partial response
- Progressive disease
- Not assessed at this appointment/cycle

Not on treatment

- No evidence of progression
- Disease present
- Disease progressing
- Within 6 months of radical XRT (too early to assess response).
- Not assessed

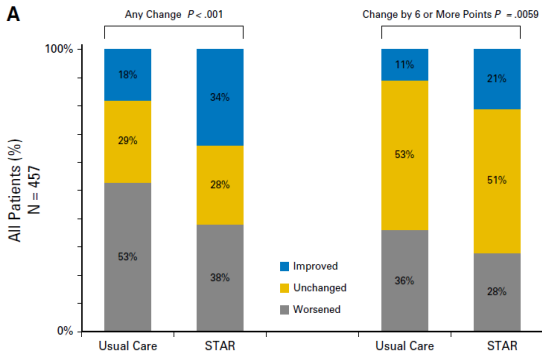
Respiratory, thoracic and mediastinal disorders				
Atelectasis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., dyspnea, cough); medical intervention indicated (e.g., chest physiotherapy, suctioning); bronchoscopic suctioning	Oxygen indicated; hospitalization or elective operative intervention indicated (e.g., stent, laser)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
Bronchial fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated
Bronchial obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., mild wheezing); endoscopic evaluation indicated; radiographic evidence of atelectasis/lobar collapse; medical management indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
Bronchial stricture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., rhonchi or wheezing) but without respiratory distress; medical intervention indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
Bronchopleural fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated
Bronchopulmonary hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated

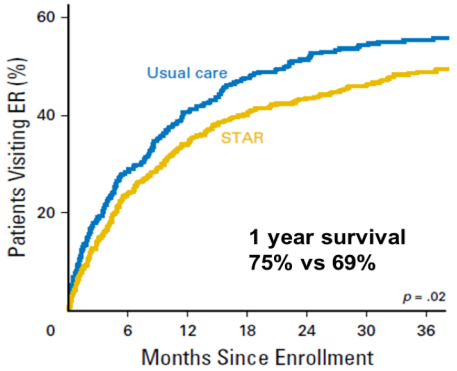
Performance Status

ECOG 2

The Christie NHS
NHS Foundation Trust

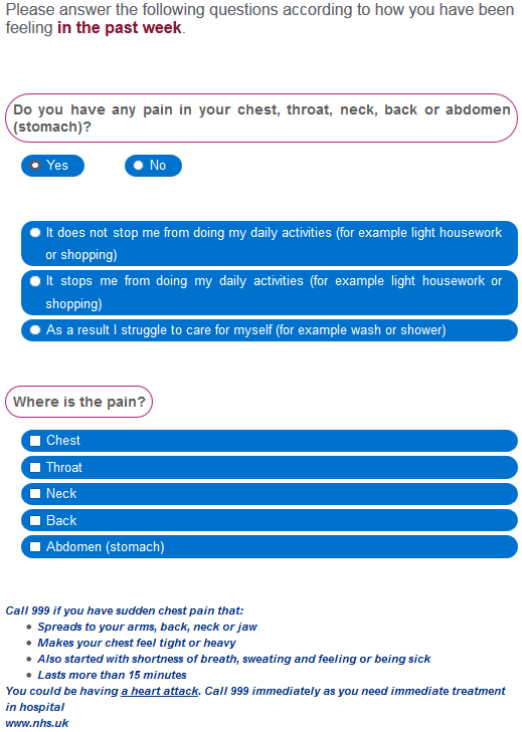
Electronic patient reported outcomes





Basch. JCO 2016

Crockett. Clin Oncol 2022

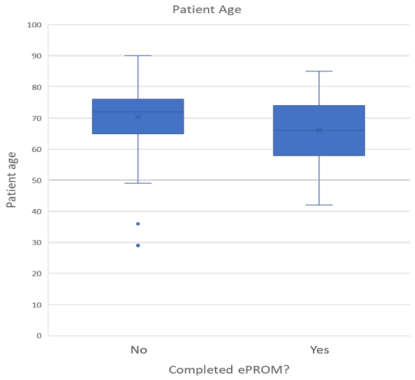


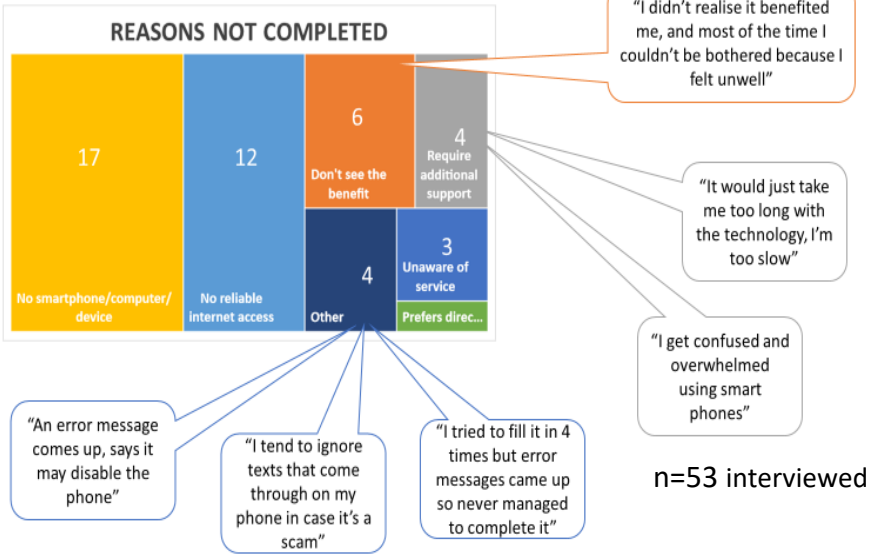
➢ 53,000 ePROMs collected from >20,000 patients (Jan 2020-June 2024)

The Christie NHS
NHS Foundation Trust

ePROMs - Patients engagement

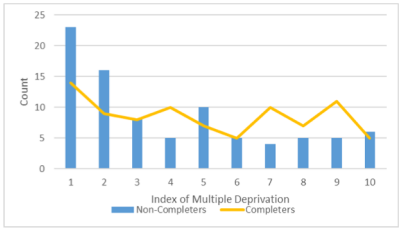
200 patients-100 completers and 100 non-completers

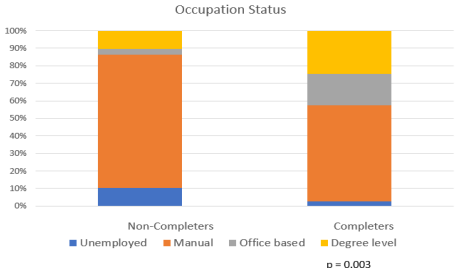




n=53 interviewed

Most deprived





Importance of feedback during clinic

Opportunities with high quality RWD

From discovery to implementation

Alternative trial methodology

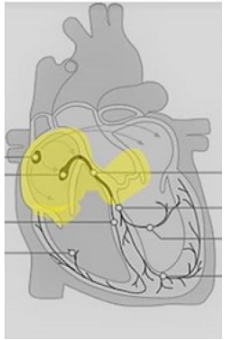
Short-term mortality prediction in SIII NSCLC: What do clinicians want and can models provide it?

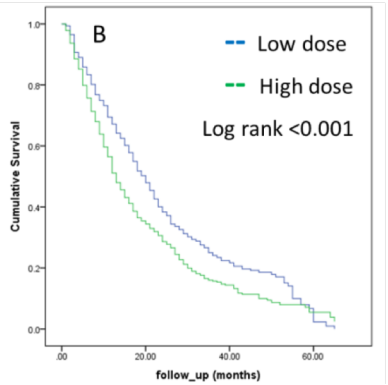
Matt Craddock
TOMORROW - Rising Stars Competition

Scientific discovery using RWD

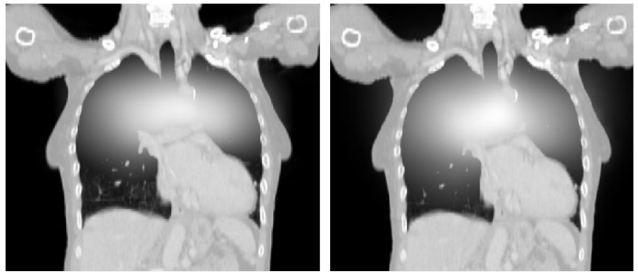
Radiation dose to heart base linked with poorer survival in lung cancer patients European Journal of Cancer 85 (2017) 106–113

Alan McWilliam [a,b,*], Jason Kennedy [b], Clare Hodgson [c], Eliana Vasquez Osorio [a], Corinne Faivre-Finn [a,b,1], Marcel van Herk [a,b,d,1]



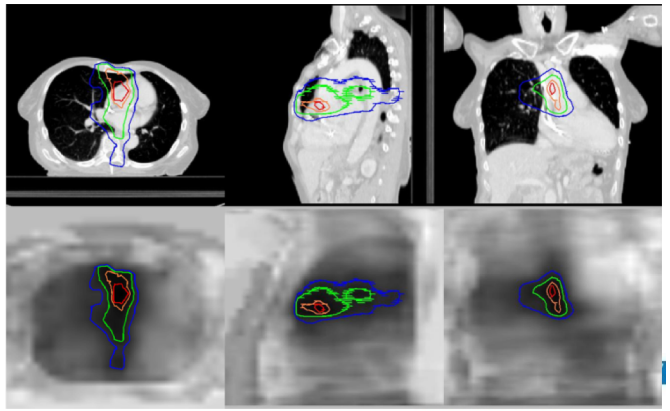


1101 patients
NSCLC
Image-based data mining
Curative intent RT
55Gy/20 fractions



Alive – 12 months Dead – 12 months

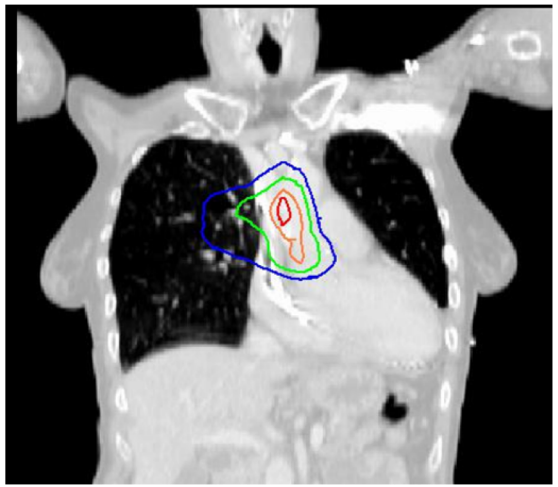
Radiotherapy planning CT scans from the routine setting

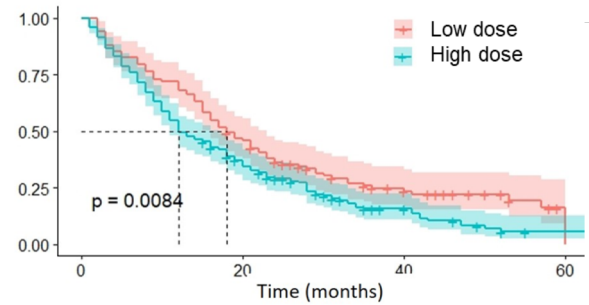


Base of the heart identified as the anatomical area associated with poor survival

Validated in multiple external datasets

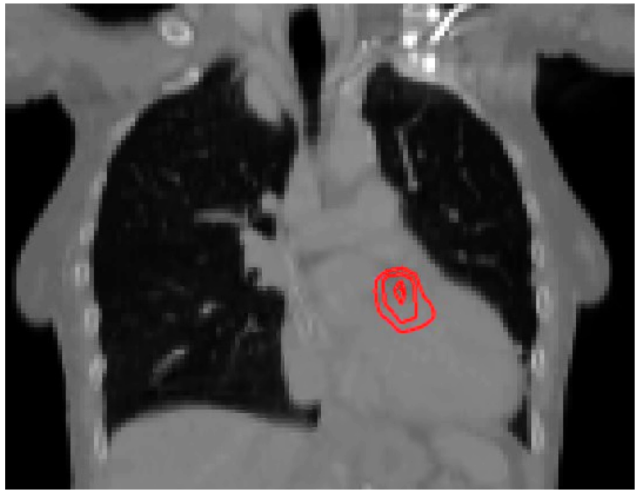
Christie cohort

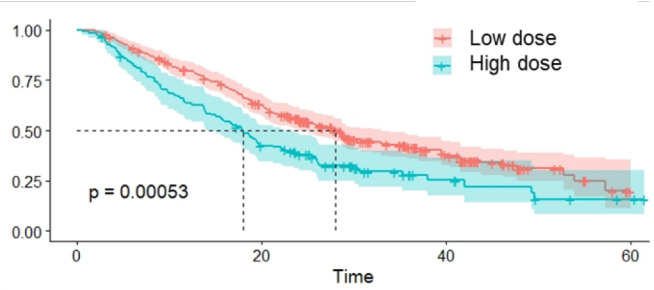




McWilliam et al. EJC 2017

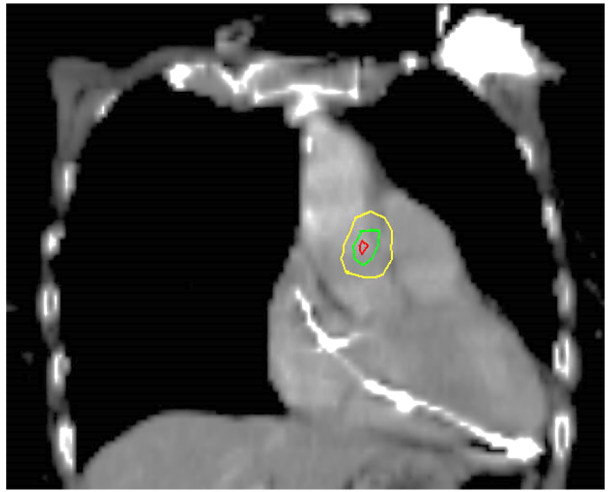
RTOG 0617 trial

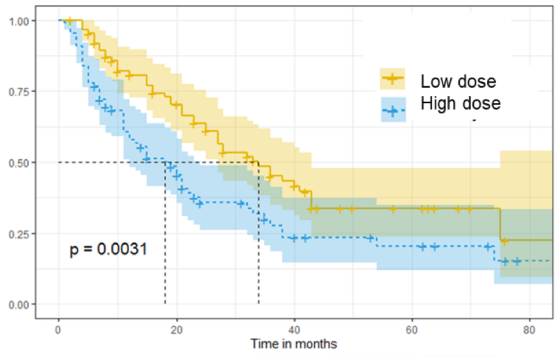




McWilliam et al. JTO 2023

PET-plan trial



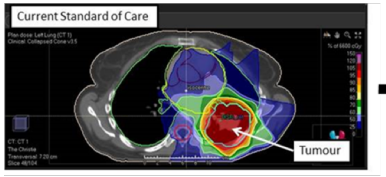


Craddock et al. JTO 2022

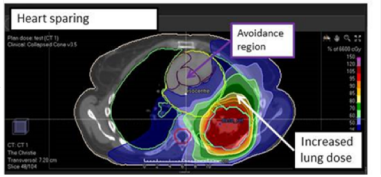
RAPID-RT

Using RWD and rapid learning to drive improvements in lung cancer survival

Feb 2022



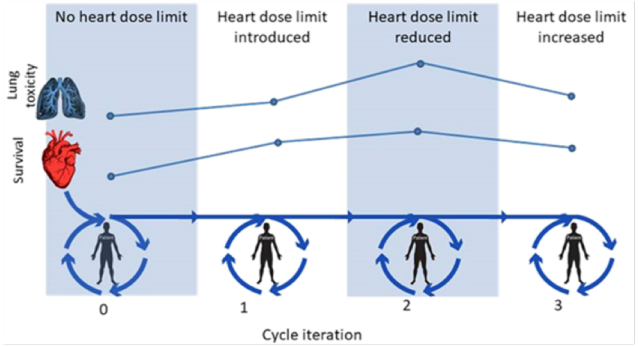
Change heart dose for all lung cancer patients treated at the Christie



Use real-world routinely collected data to look at impact of change on patient outcomes

April 2023

Supported by the lung team
Extensive PPIE input



Primary outcome – overall survival
Secondary outcome - acute toxicity

Multiple **rapid learning cycles** will be performed, balancing improved survival vs. side effects
Bayesian statistical design

No strict eligibility criteria- routinely collected data from EPR in real time - no CTU
Pragmatic consent process- patients can opt-out

Alternative pragmatic methodology to RCTs

FUNDED BY
NIHR National Institute for Health and Care Research

NICE National Institute for Health and Care Excellence

The Christie NHS
NHS Foundation Trust

Price et al. Clin Oncol 2022

RAPID-RT cohorts

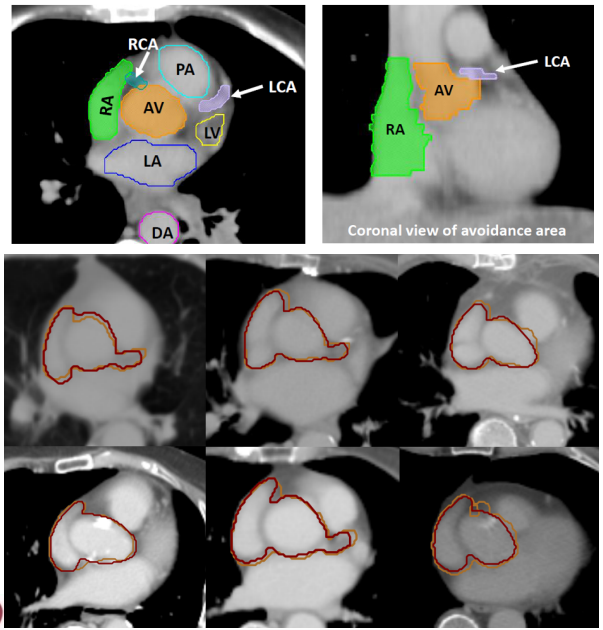
Cohort 1 – no dose limit for base of heart

RT between Jan 2021-Feb 2023
n=895

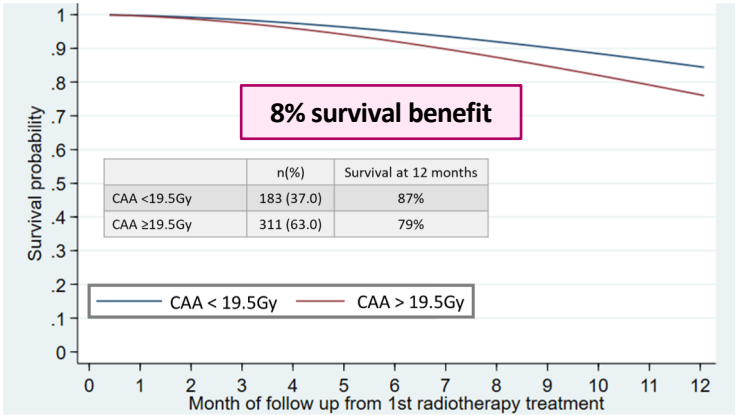
Cohort 2 – dose limit base of heart 19.5 Gy

RT after 17th April 2023
n=586 (01/07/24)

Only 1/586 patients opted-out



Marchant. BJR open 2024



Cohort 1
Standardised parametric model survival curve at 12 months
(Complete case, n=494, deaths n=121)

RAPID-RT programme

Determine the challenges and opportunities associated with the **use of rapid-learning and real-word data for the evidence-based introduction of changes in radiotherapy practice** within the NHS and beyond

Methodology's applicability for diverse cancers and changes in RT treatments

Ethical acceptability of rapid-learning from the perspective of diverse groups of patients and stakeholders

Understand the challenges to the implementation of rapid-learning across different NHS hospitals

European Groundshot report on current cancer research landscape (Lancet Oncol)

All-Party Parliamentary Group report on radiotherapy in the UK

LET'S BE CLEAR

Randomized controlled trials and real-world evidence are not mutually exclusive

Alternative methodology is needed for more inclusive research

High-quality real-world and real-time structured data

Governance and quality control structure

Particularly in populations often under-represented in conventional research

Randomisation is possible →pragmatic clinical trials

"NICE's ambition is to facilitate the adoption and implementation of RWE in health care decision-making in Europe"

NICE National Institute for Health and Care Excellence

"RWD and RWE are playing an increasing role in health care decisions"

FDA U.S. FOOD & DRUG ADMINISTRATION

The way forward - pragmatic trials

Make trials more accessible to ALL patients with cancer

Patient-centred clinical question

Population reflect usual practice

Appropriate setting

Pragmatic design

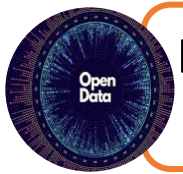
Minimal resources

Simple PIS and consent process

FU mirrors routine care

Simplified CRFs

Use of EHR for data collection



Data publicly available for further analyses

Learn as much as possible from clinical trials

The Christie NHS
NHS Foundation Trust