Opportunities for high-quality real world research

Keynote lecture

Health Research Symposium

Hong Kong

26th November 2024

Prof Corinne Faivre-Finn

Finn_corinne

The Christie NHS Foundation Trust

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

<u>Founded in 1892, ‘Cancer Pavilion and Home of the Incurables’</u>
<u>renamed ‘The Christie Hospital & Holt Radium Institute’ in 1901</u>
Largest single site cancer centre in Europe - 3.2 million population - 60,000 treatments/yr

1901 - use of X-rays for therapy in UK
1905 - use of radium for therapy
1944 - world's first clinical trial of Stilboestrol
1970 - world's first clinical use of Tamoxifen
1986 - world's first use of cultured bone marrow for leukaemia treatment
1991 - world's first single harvest blood stem-cell transplant
2002- world’s first clinical use of image guided radiotherapy on a linac
2010-2020 - Real world data infrastructure

Outline of my talk

With examplars

- Definition of Real World Evidence (RWE)
- The Need for RWE
- Role of RWE
- Infrastructure for RWE Research
- Federated Learning
- Opportunities with high quality RWE

More tomorrow during workshop

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

EHR, healthcare databases, registries, mobile devices' health-related data

Claims databases

Social media, patient platforms

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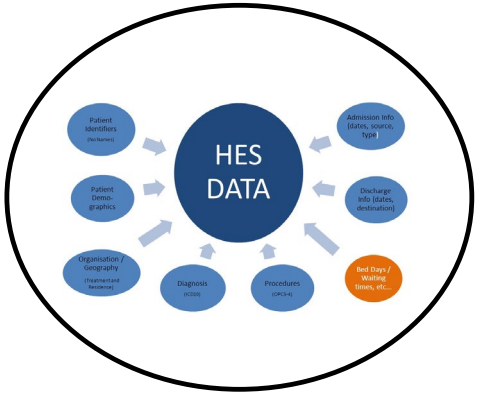
UK one of the best places for RWE research



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

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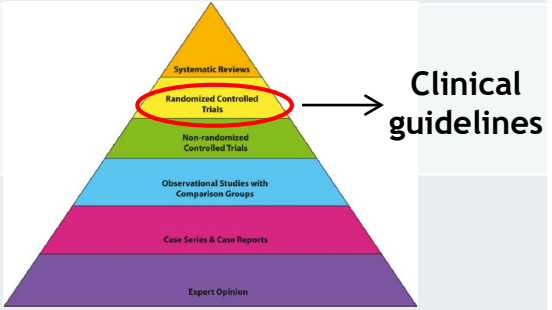
Why do we need Real World Evidence?

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	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

Randomised 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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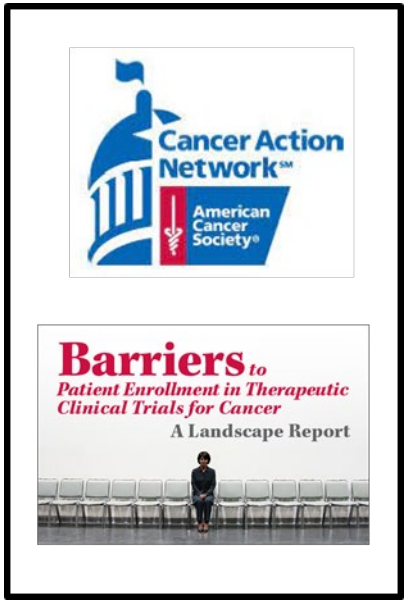
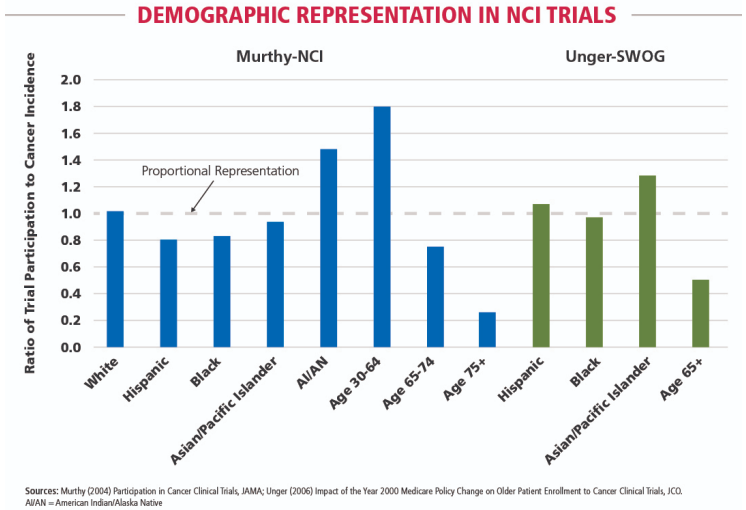
Lung cancer in Greater Manchester

- **~2200 new diagnosis** per year and ~1800 deaths
- First cause of mortality in the North West
- Median age at diagnosis **71 years**
- **Deprived postcodes, multimorbidity , polypharmacy**

MCRC
MANCHESTER 1824 The University of Manchester
CANCER RESEARCH UK
NHS The Christie NHS Foundation Trust

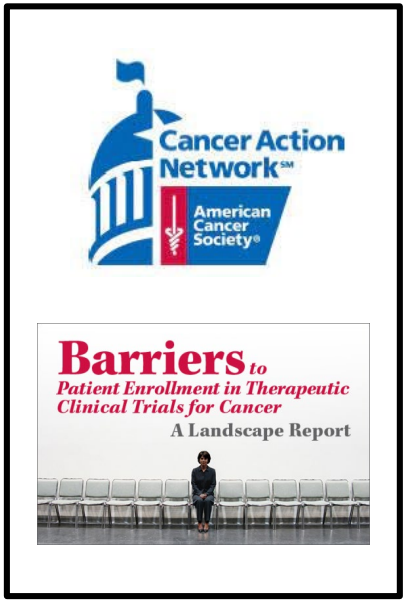
Patients under-represented in clinical trials

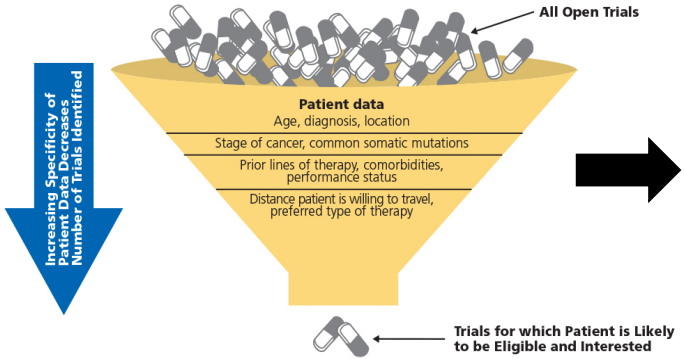


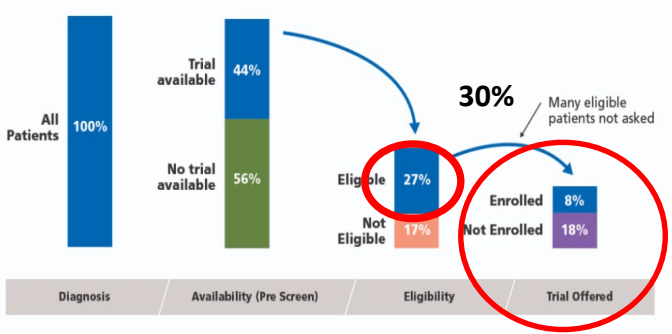


www.acscan.org/policy-resources/clinical-trial-barriers (2018)

Clinical trial entry criteria are too rigid







8% of patients with cancer are enrolled in RCTs

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

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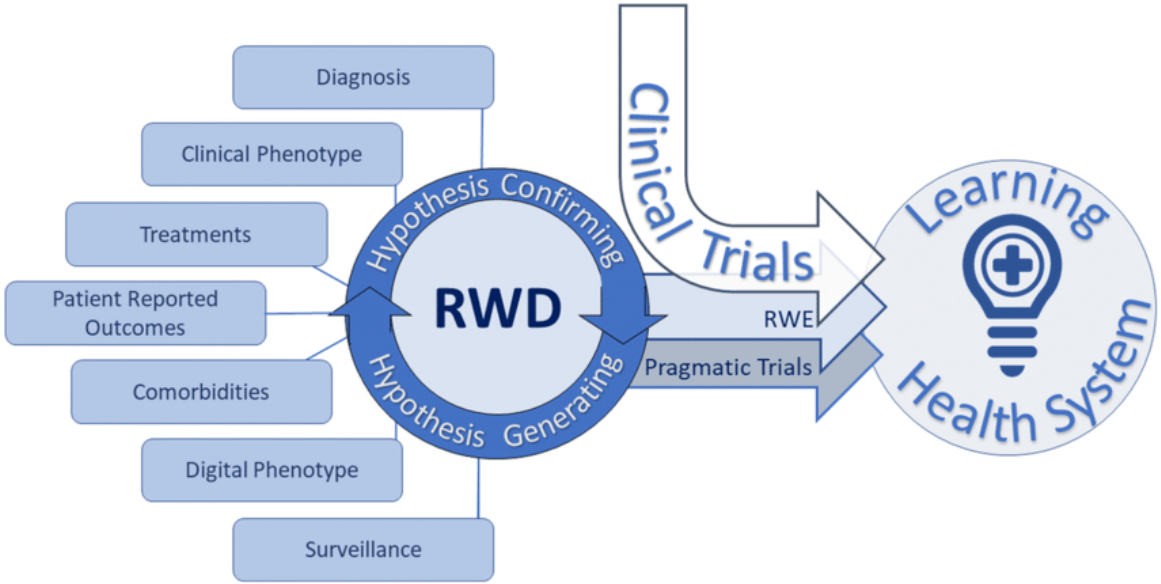
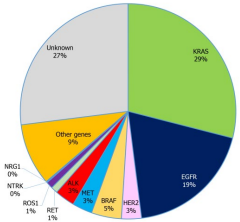
So….what is the role of RWE?
Alternative to RCTs in specific scenarios

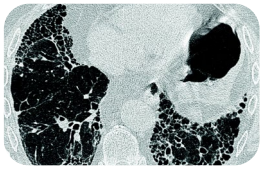


Alternative to RCTs in specific scenarios

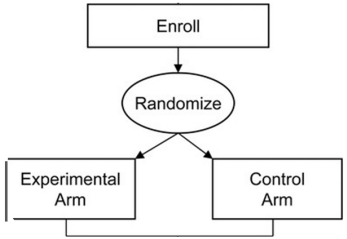
Underrepresented patients



Rare cancers or populations



Long term follow-up



Standard RCTs not suitable

No consensus on control arm

Lack equipoise

Rapid changes in technology

RWE → More inclusive and representative research

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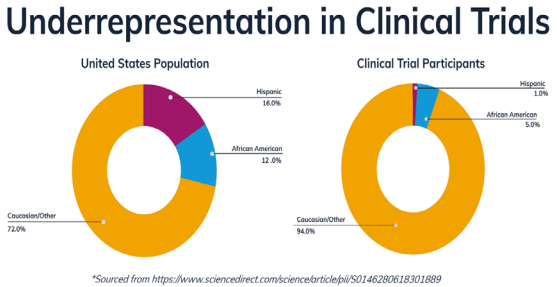
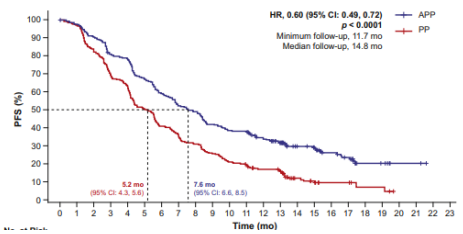
Underrepresented patients or populations



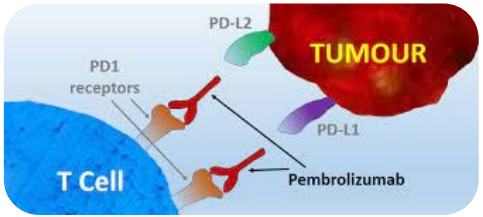
16% Hispanic and 12% African American
6% total in clinical trials

Impower 132



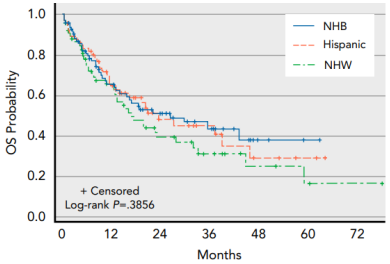
Race, n (%)	
White	193 (66.1)
Black or African American	2 (0.7)
Asian	71 (24.3)
American Indian or Alaska Native	1 (0.3)

Impact of immunotherapy in underrepresented populations

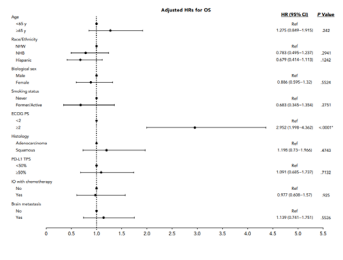


248 patients treated
with pembrolizumab

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



OS/PFS similar
among race groups and
comparable to Impower 132



No effect of race in
multivariable OS model

Lee. J Natl Compr Canc Netw 2023

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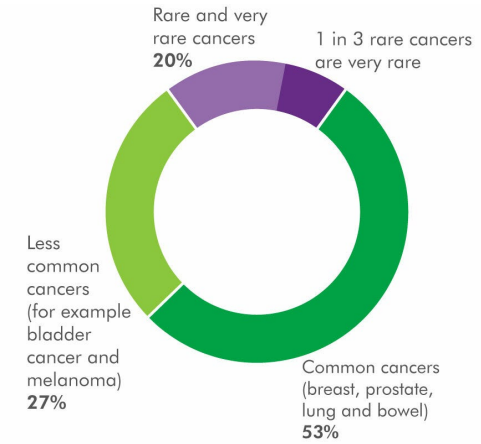
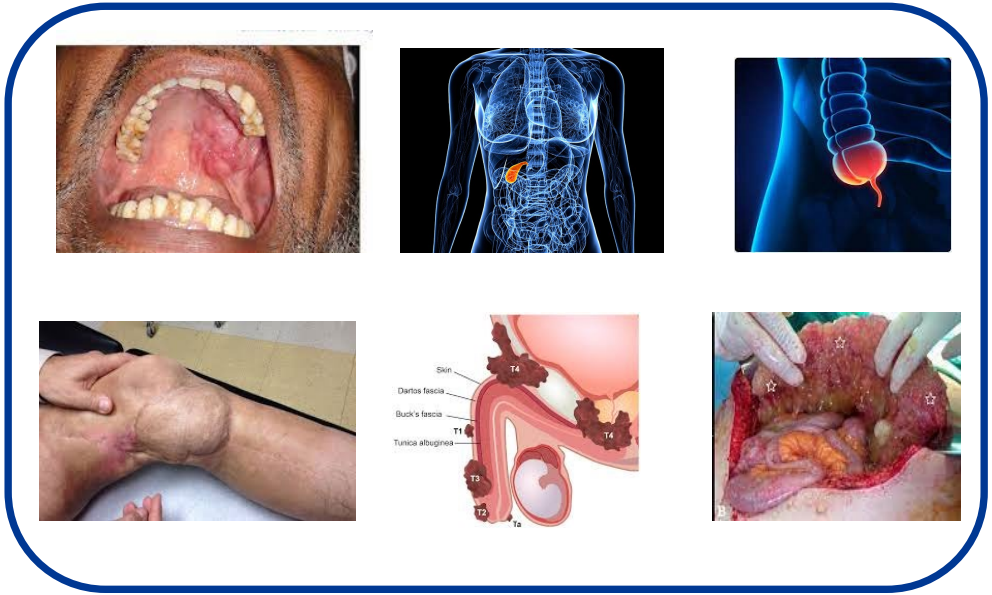
Cancers under-represented in clinical trials

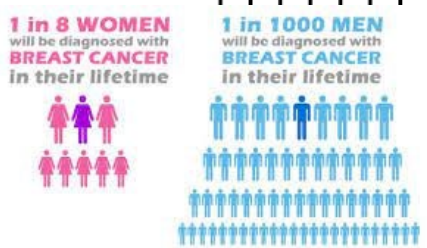


Proportions of common, less common, rare and very rare cancers



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

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

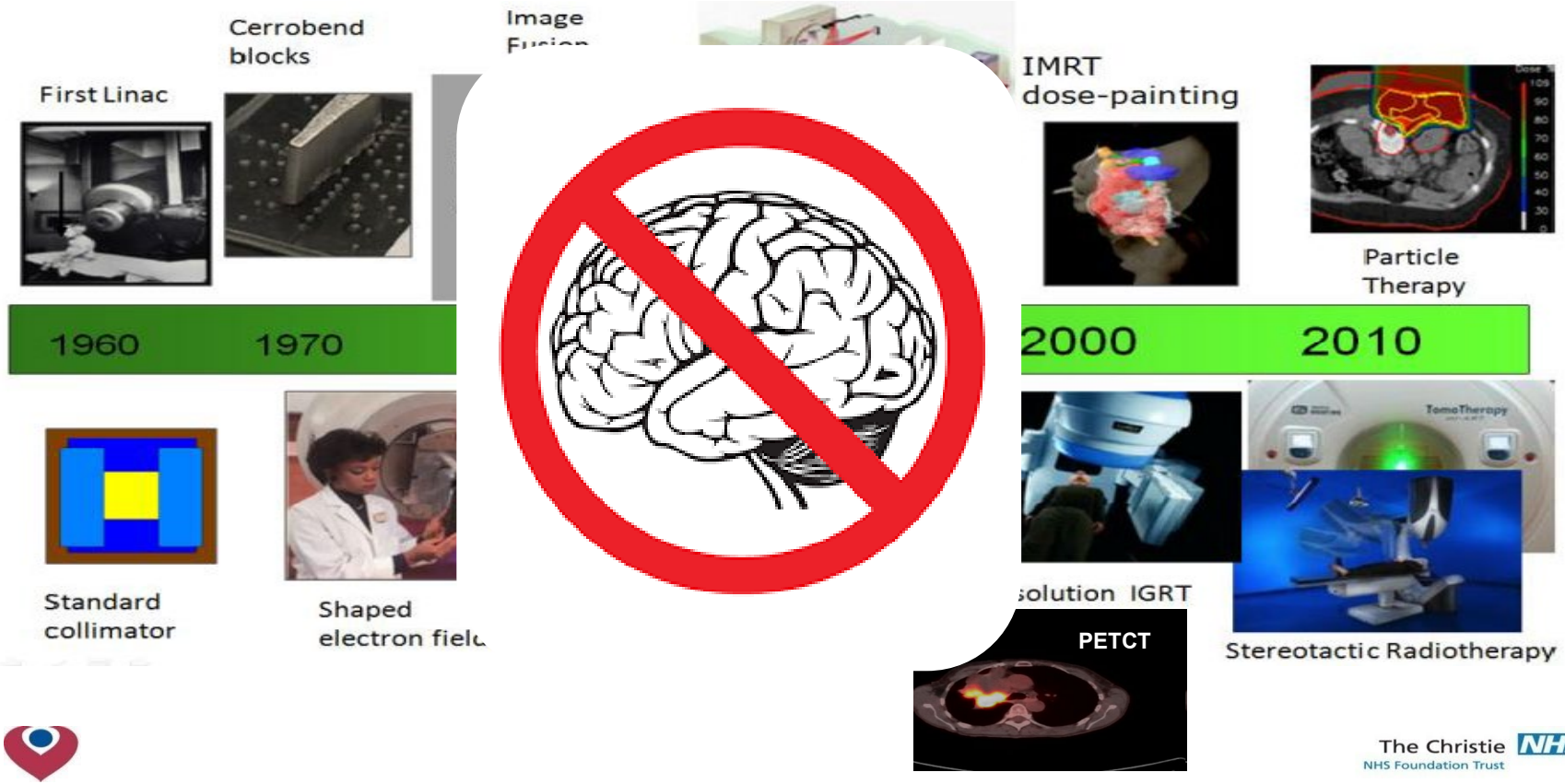
1139 men with M+ breast cancer, 146 treated with Palbociclib

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

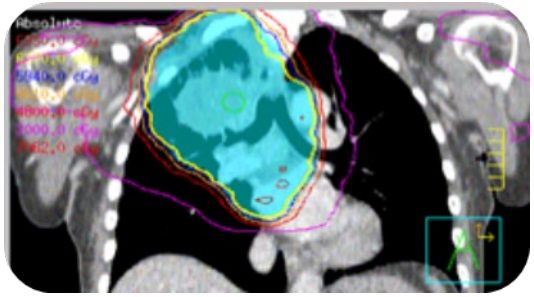
FDA expanded the palbociclib indication to include men with HR+/ HER2− M+BC

Kraus. Clin Pharmacol Ther. 2022

Conventional RCTs not suitable



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

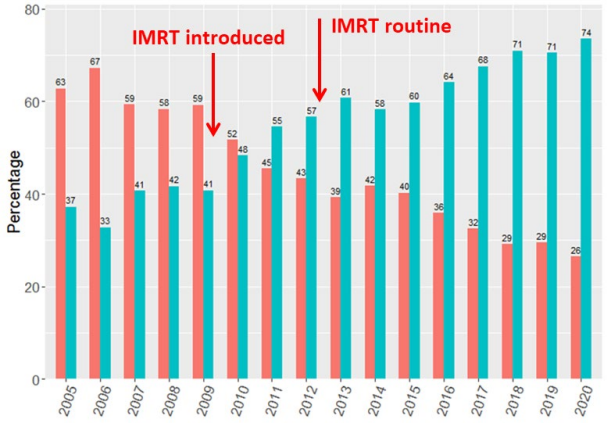
- 2005 -2008 — Pre-IMRT
- 2009-2012 — Some availability IMRT
- 2013-2020 — Full access IMRT

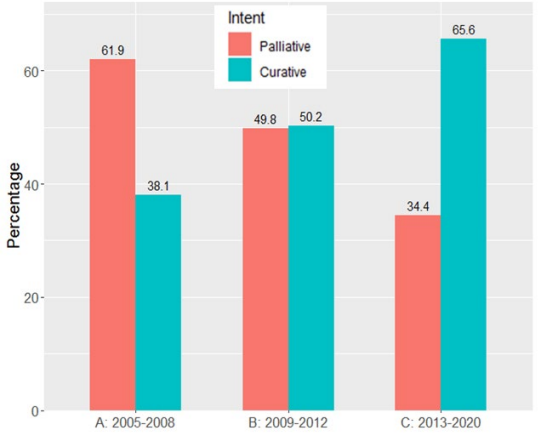
Hypothesis 1 - IMRT is allowing us to treat more patients with curative-intent radiotherapy

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

Fornacon-Wood . Frontiers Oncol 2022

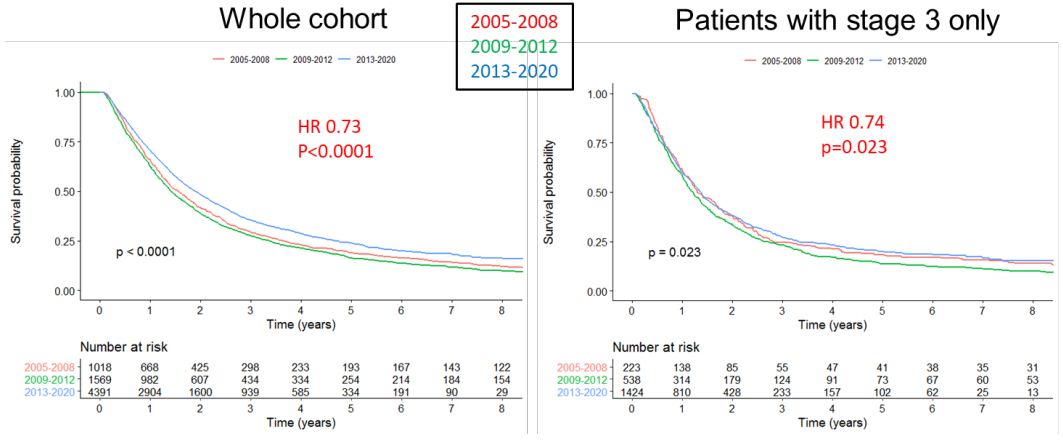
Proportion of patients receiving curative-intent radiotherapy





n= 12499

Impact on overall survival



Adjusted for known prognostic factors

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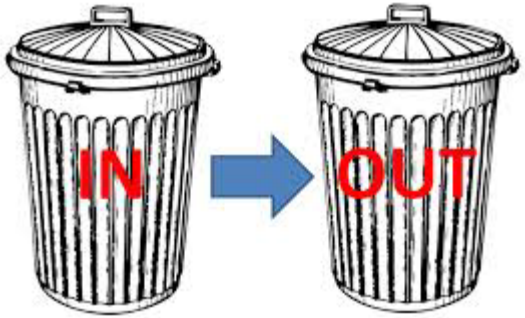
RWE Infrastructure
at the
Christie NHS Foundation Trust



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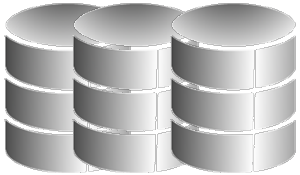
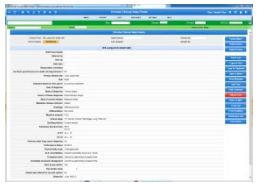
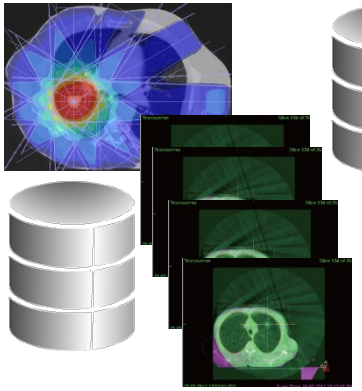
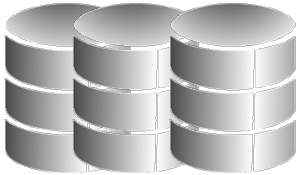
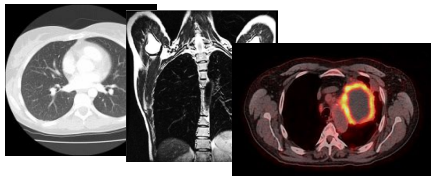
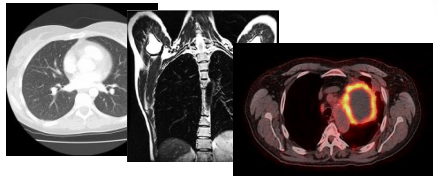
Christie real world data- UK CAT

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

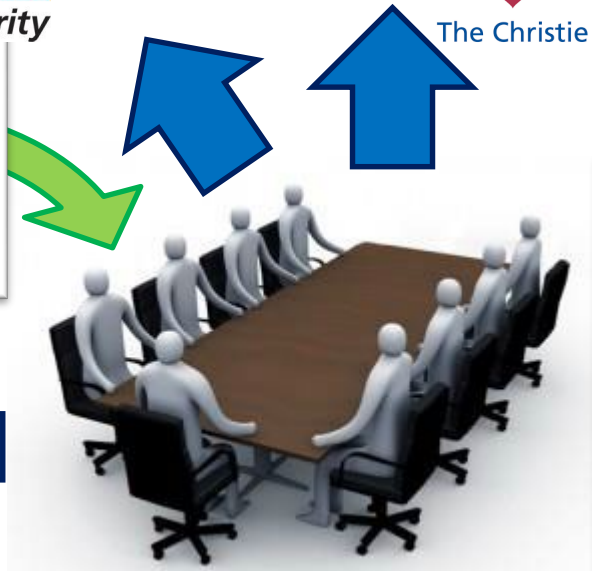
Large digital footprint
Links and enables access to various data sources

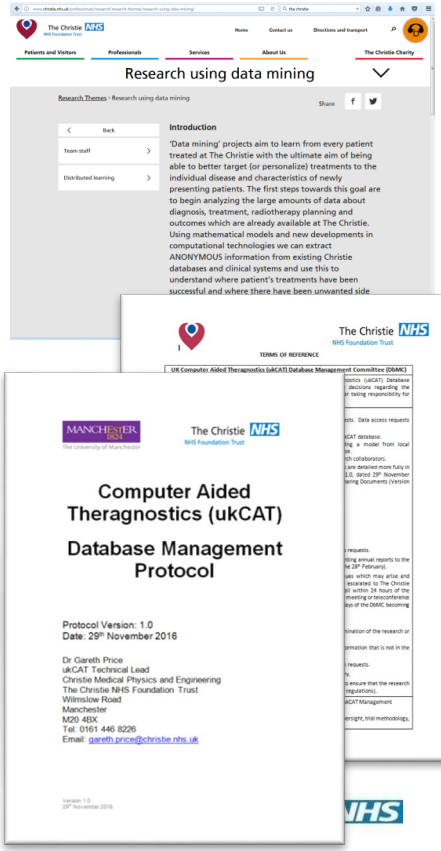
Governance

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[c]
T1b	Tumour more than 1 cm but not more than 2 cm in greatest dimension[c]
T1c	Tumour more than 2 cm but not more than 3 cm in greatest dimension[c]
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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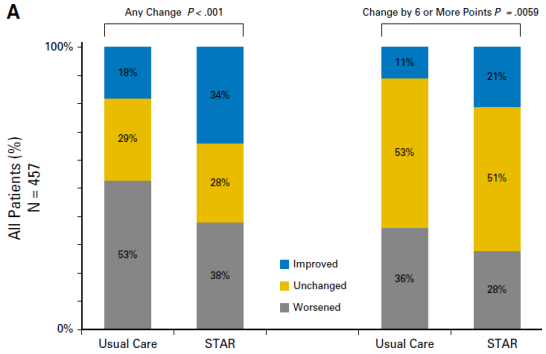
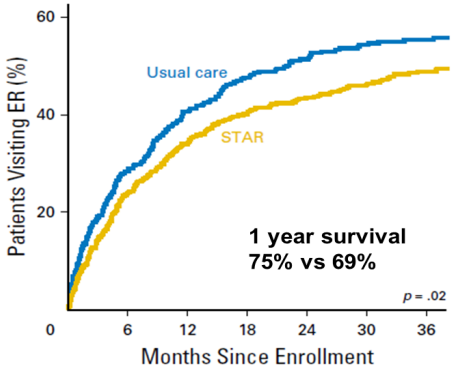
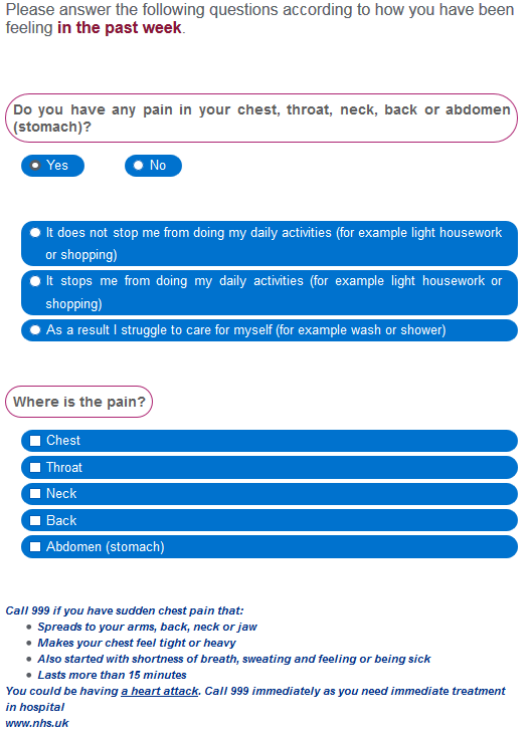
Electronic patient reported outcomes





Basch. JCO 2016

Crockett. Clin Oncol 2022



- 65,000 ePROMs collected from >24,000patients (Jan 2020-Oct 2024)

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JC STEM Lab: Oncology Care Enhancement (DOCE)

Director, Professor Janelle Yorke
Hong Kong SAR Global STEM Scholar, Head, School of Nursing, PolyU

VISION: To lead the transformation of personalized oncology care using digital technology

1. Routine integration of ePROMs into oncology clinics

1. Real-World Big Data and AI analysis to build predictive models

1. Development and validation of digital self-management interventions

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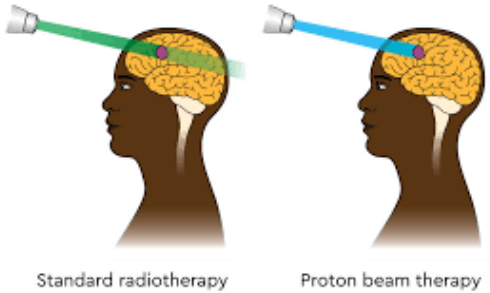
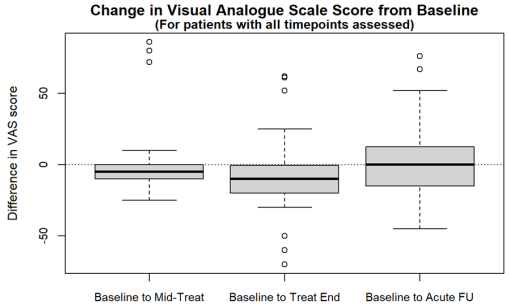
JC STEM Lab of Digital Oncology Care Enhancement
賽馬會「數碼提升腫瘤照護」創科實驗室

捐助機構 Funded by
香港賽馬會慈善信託基金
The Hong Kong Jockey Club Charities Trust

Impact of ePROM collection on RWE

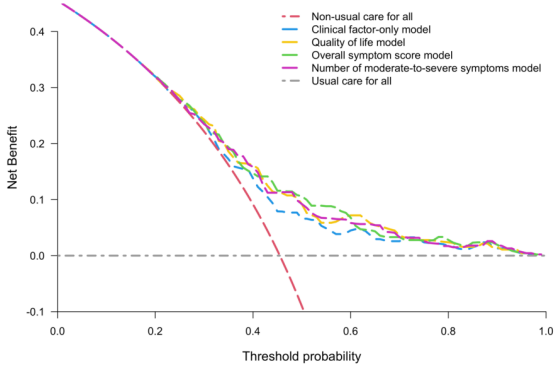
UK National proton facility





Li. PTCOG 2024

Integration in predictive models of outcome



Compared with the clinical factor-only model, an ePROM-enhanced models better predict 1-year OS in 464 patients with advanced NSCLC receiving immunotherapy
→potential clinical utility for informing treatment

Liao. BMJ Oncol 2024

NHS Foundation Trust

VIGILANCE: Developing Circulating and Imaging Biomarkers Towards Personalised Radiotherapy in Lung Cancer

University of Manchester, The NHS Christie Foundation Trust, Manchester

Dr. Ashley Horne

ClinicalTrials.gov Identifier: NCT06086574

Introduction:

- ❑ Outcomes for patients diagnosed with stage III NSCLC remain poor
- ❑ Paucity of biomarkers supporting treatment decisions tailored to the individual patient

Key study strengths:

- ✓ Prospective data collection
- ✓ **Real world population**
- ✓ Longitudinal follow-up
- ✓ Combining multiple novel biomarker technologies:
  - Radiomics
  - Circulating tumour DNA methylation assay
- ✓ Patient reported outcomes collected

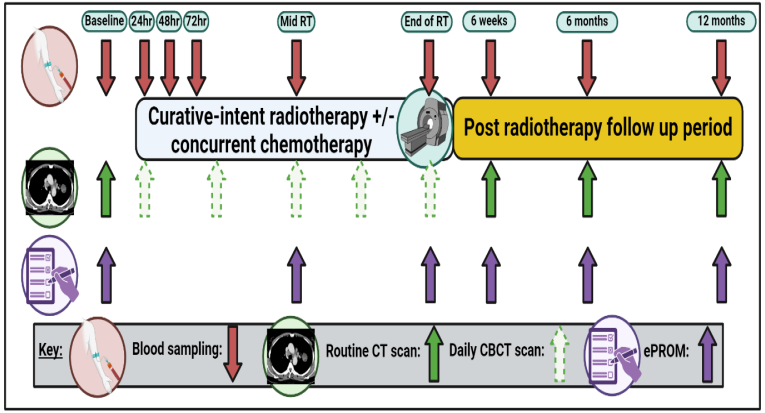
Exploratory objectives:

- To build a model using longitudinal circulating tumour DNA, radiomics features and patient reported outcomes to predict survival, tumour control and early tumour relapse
- To identify features associated with to benefit from consolidation immunotherapy

Progress to date:

- 60 patients recruited
- Data collection will be completed September 2025

Trial schema:



Key eligibility:

- ❑ Inoperable stage III NSCLC
- ❑ Treated with:
  - ➢ Radical radiotherapy (RT)
  - ➢ Sequential chemo-RT
  - ➢ Concurrent chemo-RT with or without consolidation durvalumab

Study supported by:

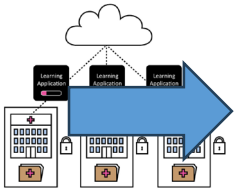
Rosetrees Trust

CANCER RESEARCH UK

AstraZeneca

Methods for distributed learning

Local modelling
global integration
(Federated learning)



Deist et al (2020)
doi:10.1016/j.radonc.2019.11.019

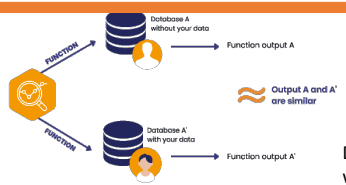
Type of machine learning approach where multiple decentralized devices or servers collaboratively train a model without sharing raw data with a central server

Secure
Comp

a to preserve

Opportunities for improved collaboration
Improve study set-up process
Speed of study set-up and execution

Differential Privacy /
Data Perturbation

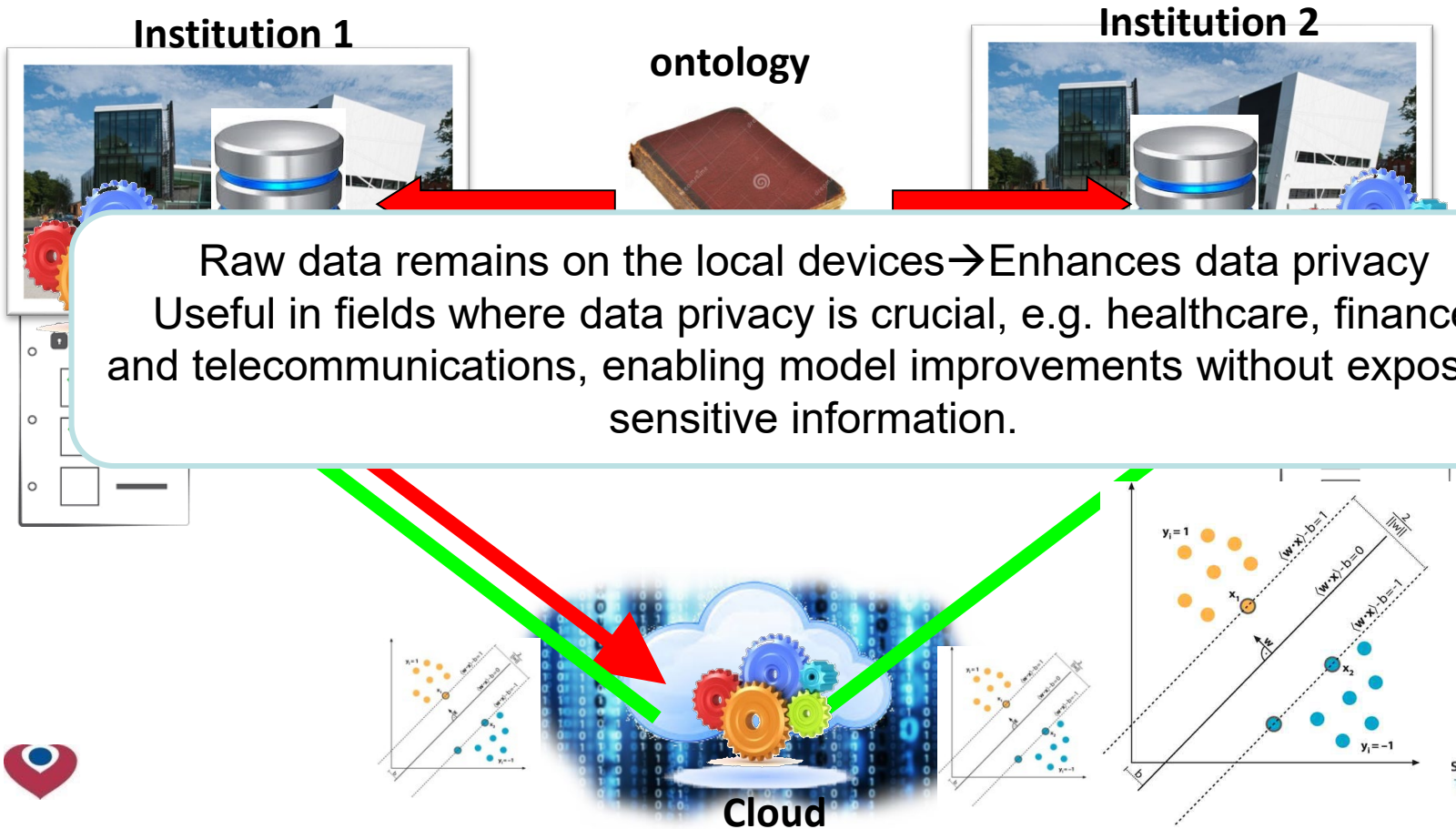


Devaux (2022)
www.statice.ai

Uses cryptographic approaches to keep data secret

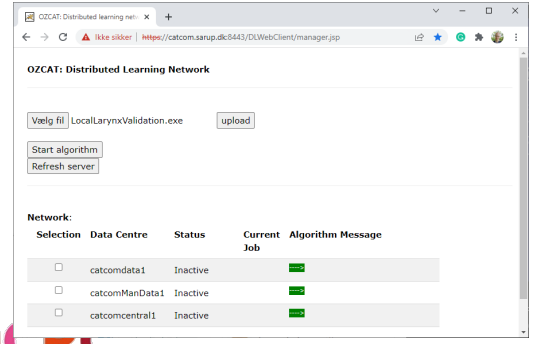
Sun et al, Data Sci. (2021) doi:10.3233/ds-210036

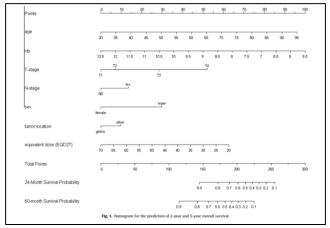
Federated learning



Case study: Prognostic modelling

- Using Distributed learning with centre-specific stratified Cox model
- Christie, UK; Odense, DK; Liverpool, Aus
- 1745 Larynx cancer patients treated with RT (2005-2018)



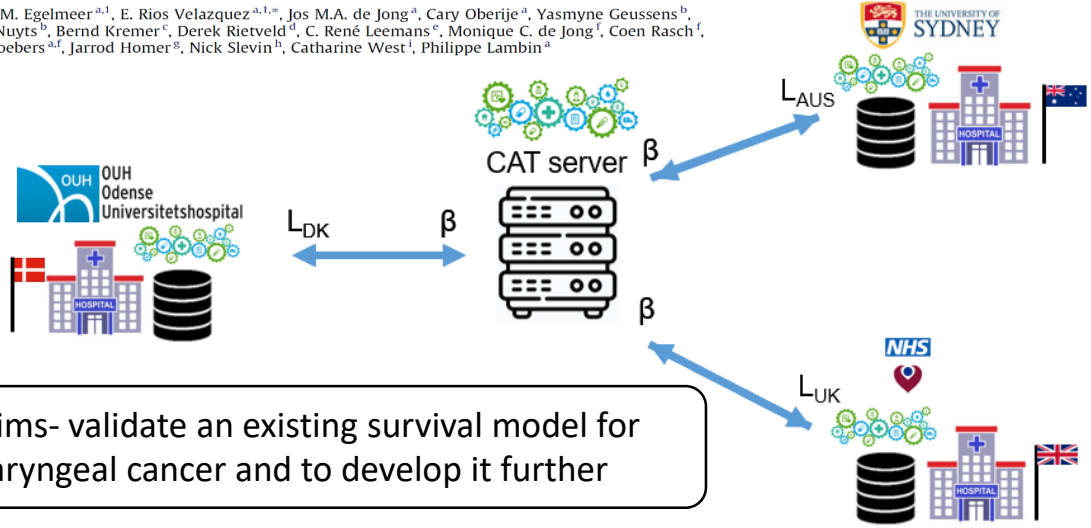


Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

Laryngeal carcinoma

Development and validation of a nomogram for prediction of survival and local control in laryngeal carcinoma patients treated with radiotherapy alone: A cohort study based on 994 patients

Ada G.T.M. Egelmeer [a,1], E. Rios Velazquez [a,1,*], Jos M.A. de Jong [a], Cary Oberije [a], Yasmyne Geussens [b], Sandra Nuyts [b], Bernd Kremer [c], Derek Rietveld [d], C. René Leemans [e], Monique C. de Jong [f], Coen Rasch [f], Frank Hoebers [a,f], Jarrod Homer [g], Nick Slevin [h], Catharine West [i], Philippe Lambin [a]



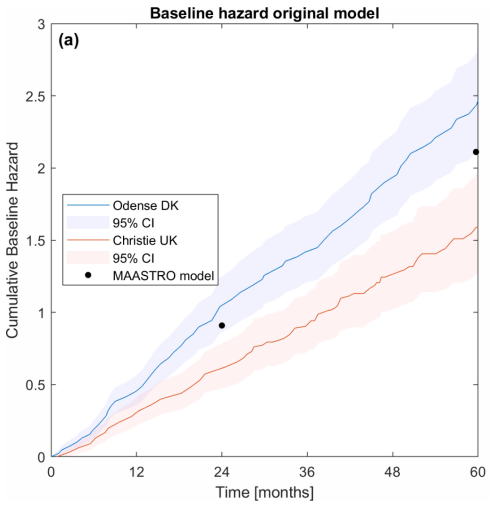
2 Aims- validate an existing survival model for laryngeal cancer and to develop it further

Hansen CR et al, Radiother Oncol (2022)
doi:10.1016/j.radonc.2022.06.009

Case study: 2 & 5 year survival prognostic modelling

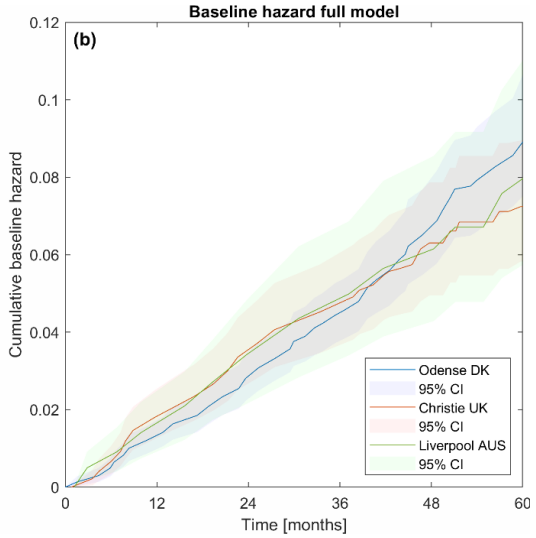
Regression variables

Age
Hb
T-classification
N-classification
Sex
Tumour location
Dose



Regression variables

Age
Hb
T-classification
N-classification
Sex
Tumour location
Dose
Tumour volume
ECOG PS
smoking status



Baseline hazards are different→model doesn't capture all explanatory factors

Enable the model to select new factors

The baseline hazards are in better agreement

Hansen CR et al, Radiother Oncol (2022)
doi:10.1016/j.radonc.2022.06.009

Opportunities with high quality RWD

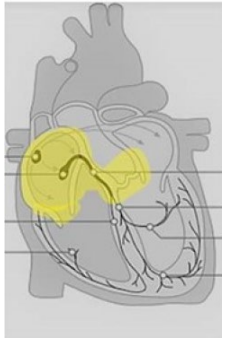
Alternative trial methodology

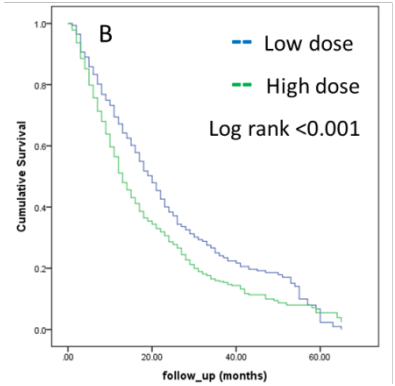
Learn from every patients

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]

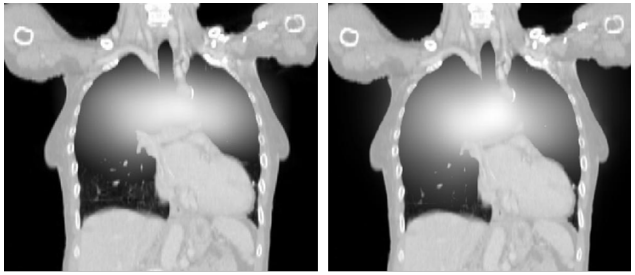




1101 patients
NSCLC

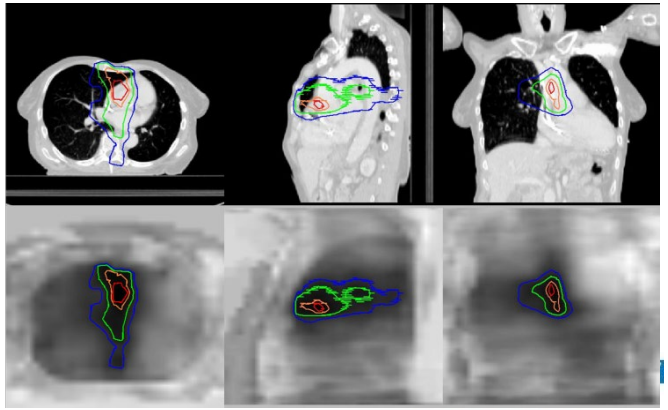
Image-based data mining

Curative intent RT
55Gy/20 fractions



Alive – 12 months **Dead – 12 months**

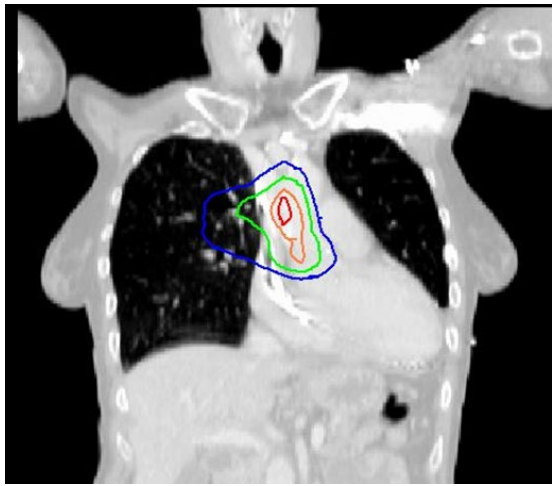
Radiotherapy planning CT scans from the routine setting

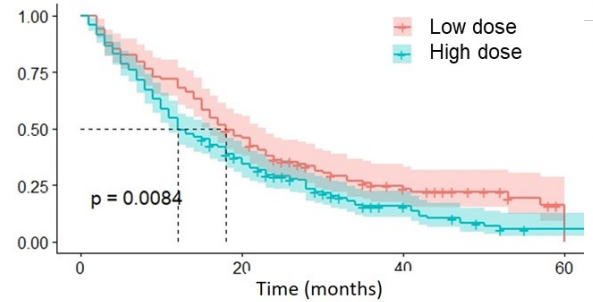


Base of the heart identified as the anatomical area associated with poor survival

Validated in multiple external datasets

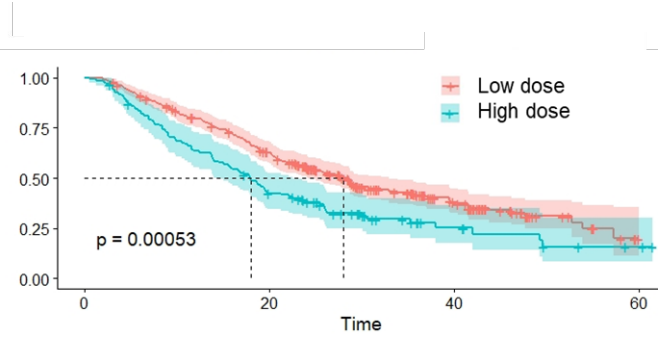
Christie cohort





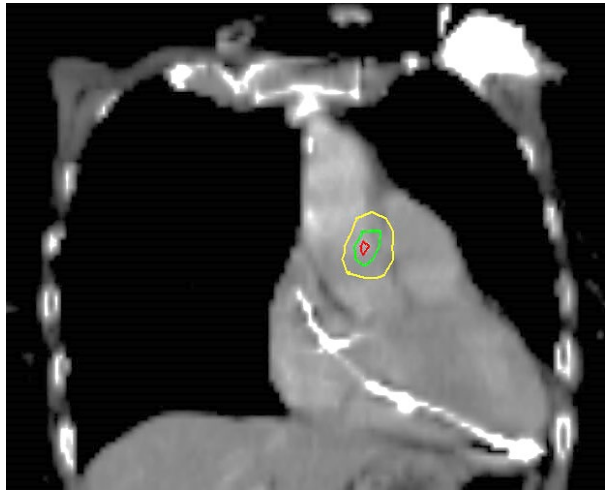
McWilliam et al. EJC 2017

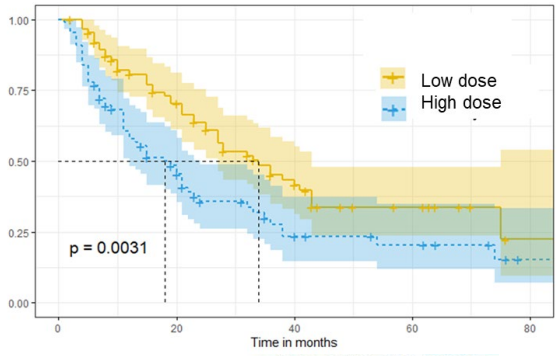
RTOG 0617 trial



McWilliam et al. JTO 2023

PET-plan trial



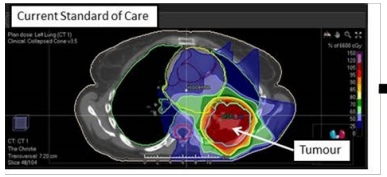


Craddock et al. JTO 2022

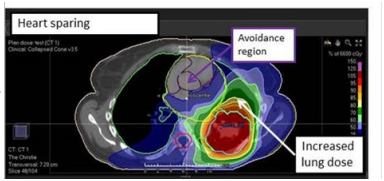
RAPID-RT

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

Feb 2022

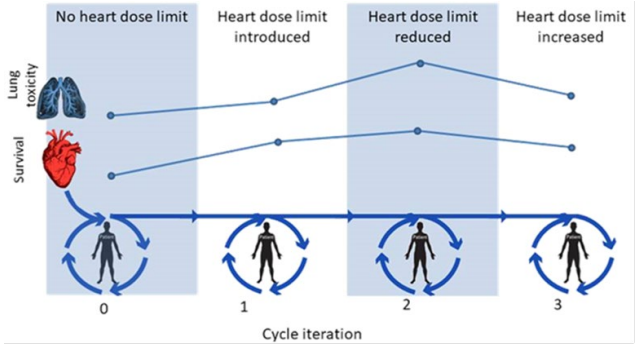


Change heart dose for all lung cancer patients treated at the Christie



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

Feb 2023



Primary outcome – overall survival
Secondary outcome - acute toxicity

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

No strict eligibility criteria- routinely collected data from EPR in real time - no CTU
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 Foundation Trust

Price et al. Clin Oncol 2022

RAPID-RT cohorts

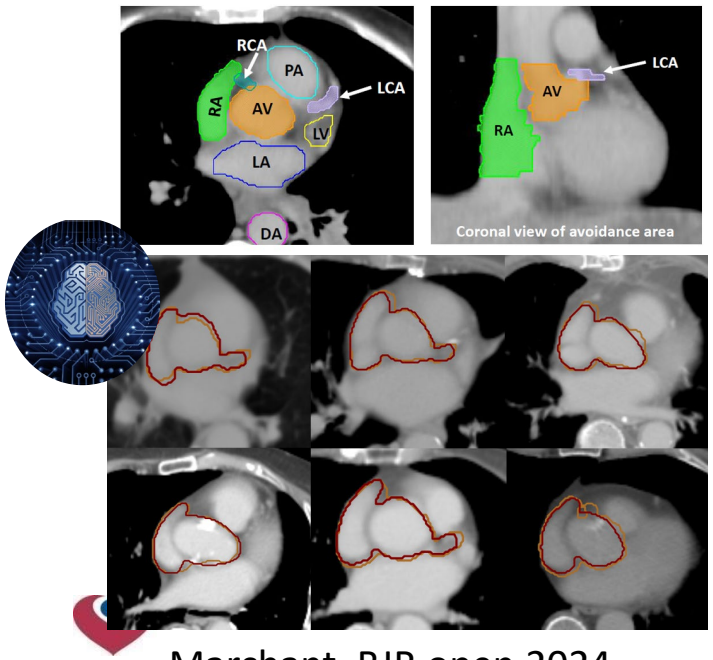
Cohort 1 – no dose limit for base of heart

RT between Jan 2021-Feb 2023
n=895

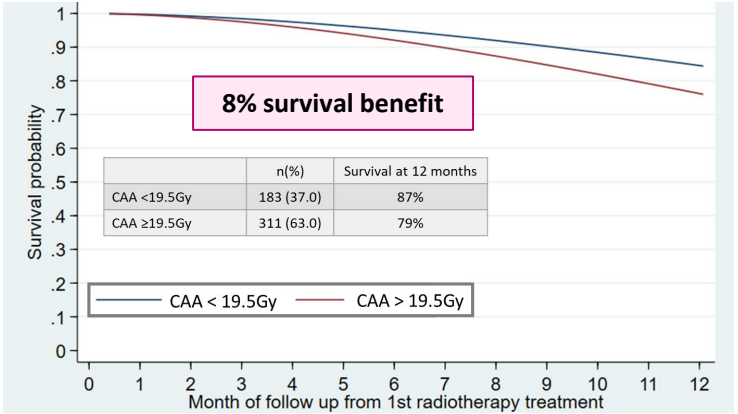
Cohort 2 – dose limit base of heart 19.5 Gy

RT after 17th April 2023
n=742 (11/11/24)

Only 1/742 patients opted-out



Marchant. BJR open 2024

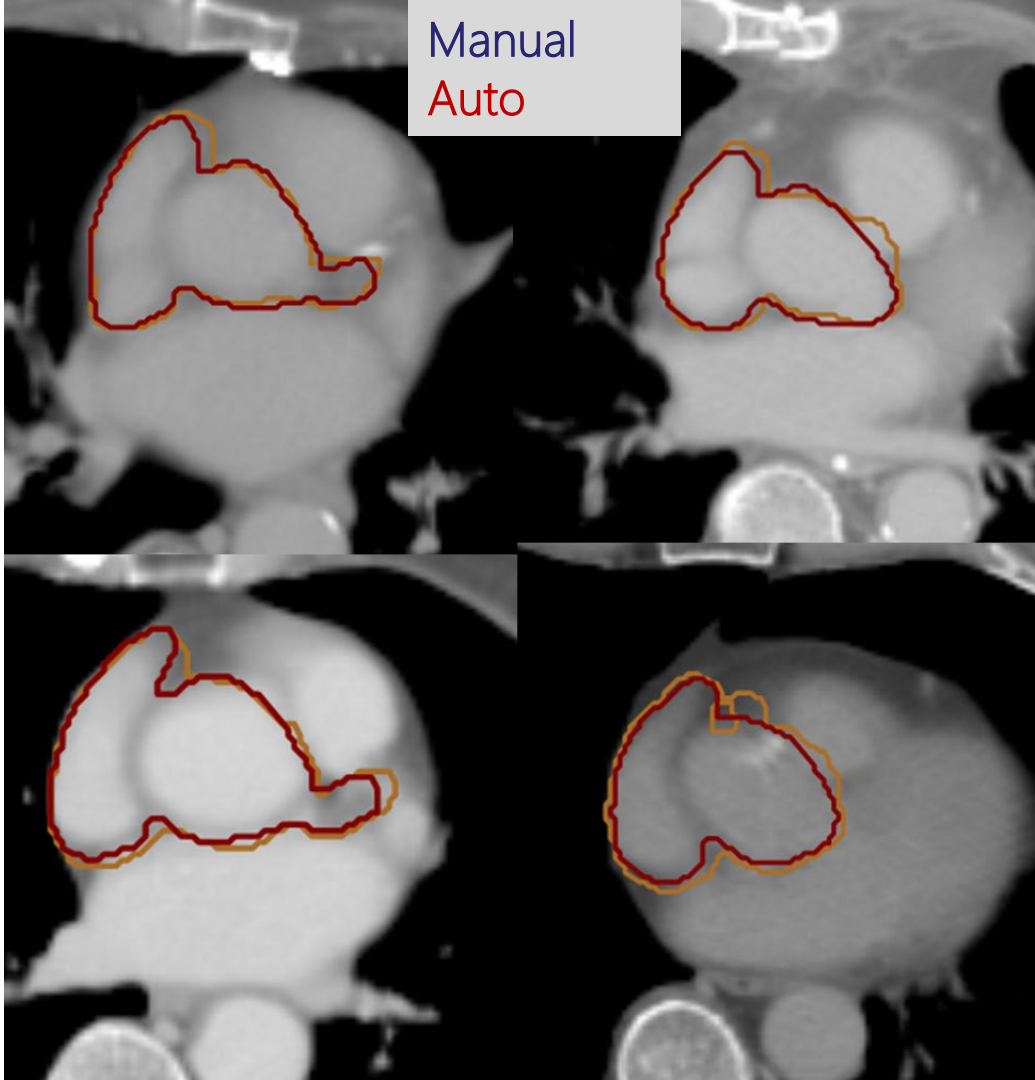


Standardised parametric model survival curve at 12 months (Complete case, n=494, deaths n=121)

AI CAA Autocontouring

- AI-based autocontouring tool developed
  - CAA and substructures contours
  - Runs automatically for all lung RTP scans
    - Checked and edited by clinician
- Geometric validation vs manual contour for 20 patients
  - Mean DSC = 0.80
  - Mean surface distance = 1.9mm
- Dosimetric validation
  - Plans generated with autocontour compared to manual contour

- Differences between auto and manual contours consistent with inter-observer differences between manual contours



LET'S BE CLEAR

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

GOLD STANDARD

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

"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 Christie NHS
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