How much can RT benefit from biomarkers of normal tissue response to RT?

Navita Somaiah, *MD, FRCR, DPhil*
Team leader, Translational Breast Radiobiology, ICR
Honorary Consultant Clinical Oncologist, RM

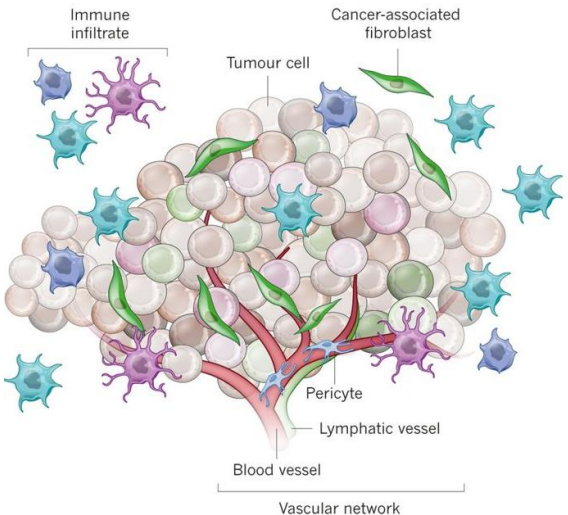
Workshop: Individual Response to Ionising Radiation, Stockholm 1-2 Sep 2022

Personalised radiotherapy

Normal tissue toxicity

Tumour control

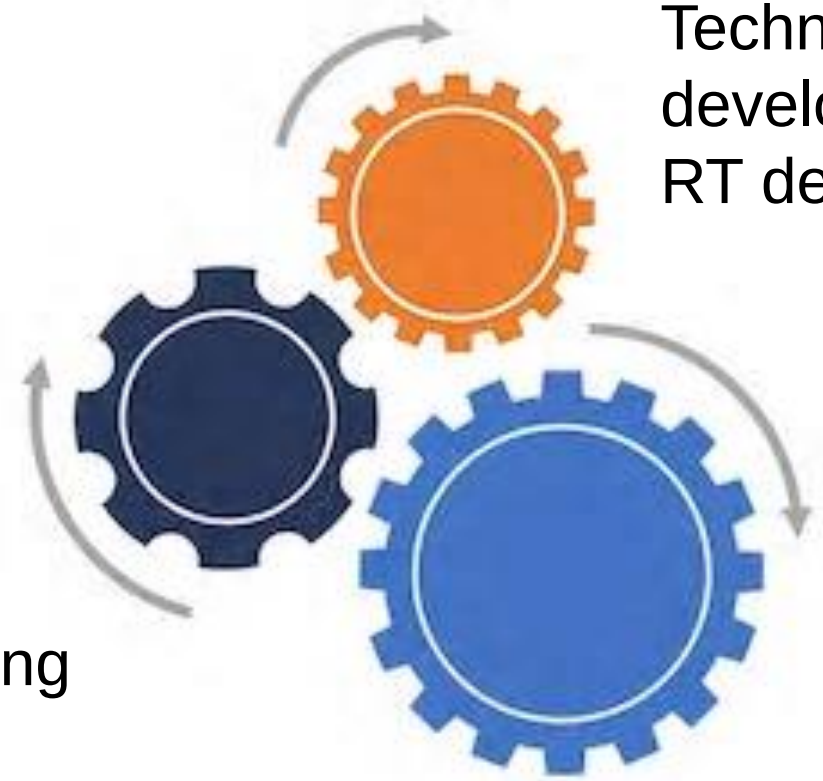
Tumour microenvironment



Why important?

- 50% of cancer patients receive RT in the curative setting
- Upto 20% experience late RT toxicity affecting QOL
- Most sensitive minority limit dose and cure prospects of the majority

Ultimate aim…



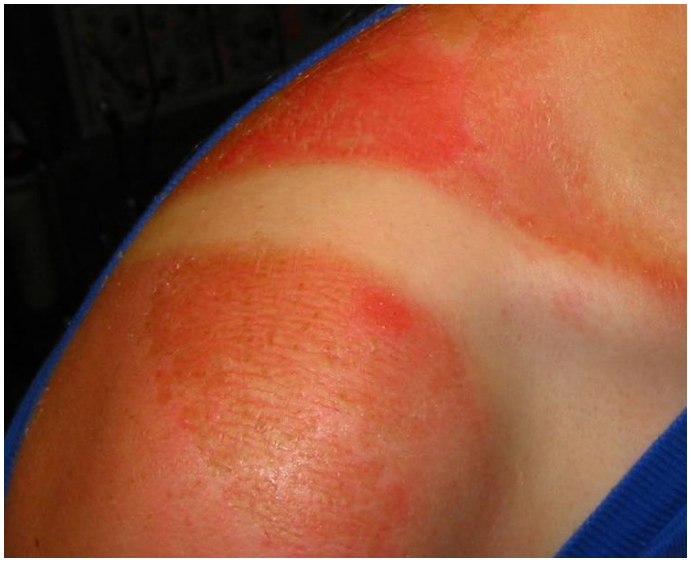
Technological developments in RT delivery

2D
3D CRT
IMRT
IGRT
SBRT
MRLinac
Protons

Understanding NT biology

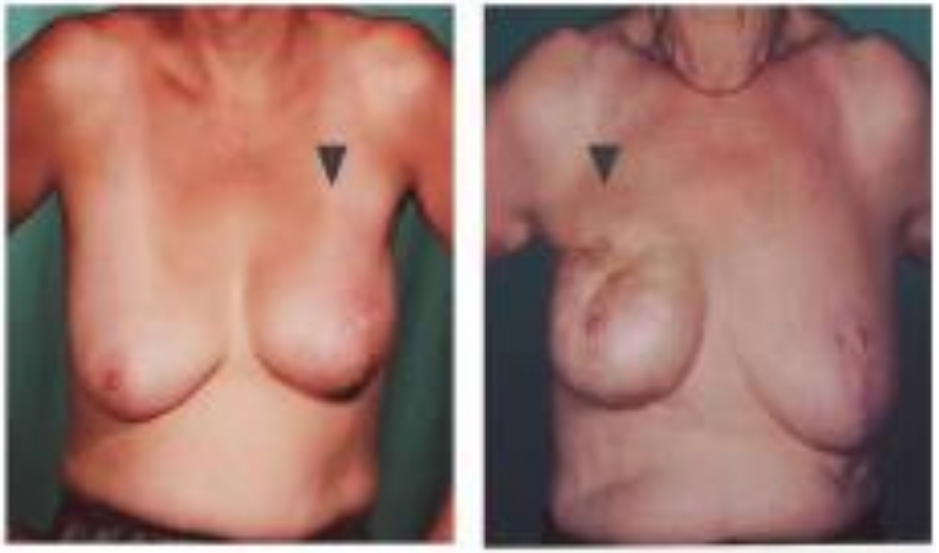
Improved therapeutic ratio in patients

Which side effects are we particularly worried about?



Before RT

After RT



Early reacting normal tissues

- Self-renewal tissues, rapidly proliferating
- Symptoms during/just after RT and resolve within weeks
- Usually not dose-limiting

Late reacting normal tissues

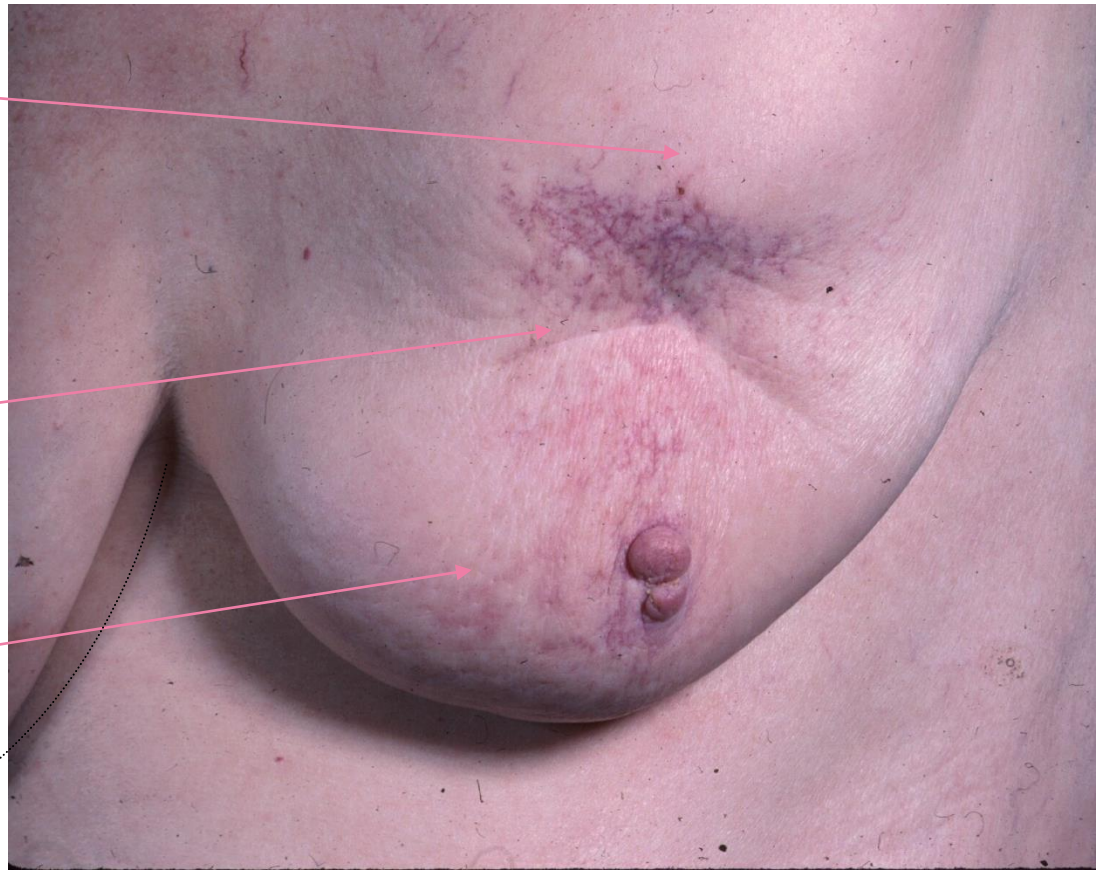
- Dormant/slowly proliferating
- Symptoms present months to years after RT
- Can be progressive
- Dose-limiting

Clinical Phenotypes: Several Pathologies

Hardness under skin (fibrosis?)

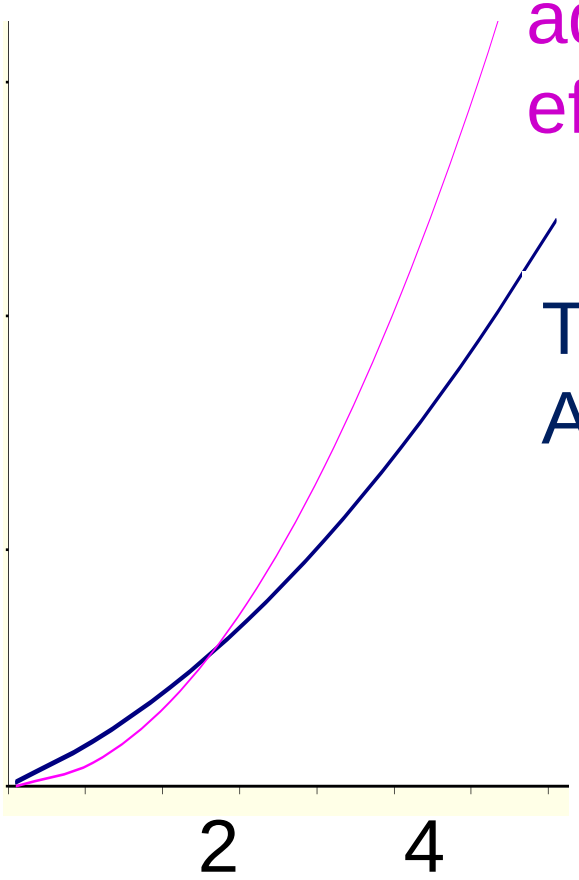
Telangiectasia

Breast atrophy & distortion



Traditional Model of Fractionation

Response



- Very sensitive to changes in daily dose
- Less sensitive to changes in daily dose

Size of daily dose (Gy) – fraction size

INSIGHT Study

Identification of *early* molecular & cellular processes predisposing to late normal tissue toxicity

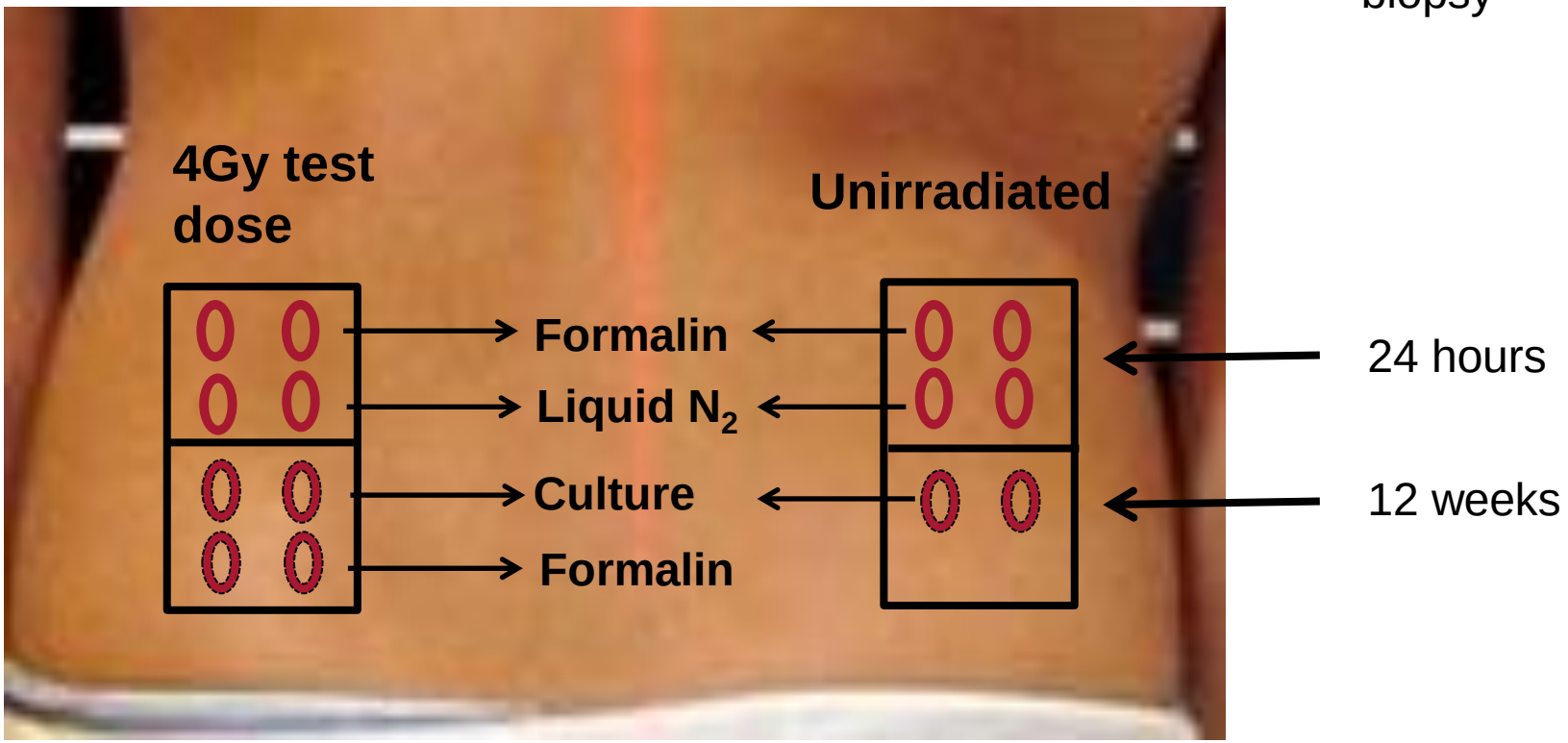
Aim:
To correlate residual double strand breaks (DSB) 24h after 4Gy test doses to skin in vivo & to lymphocytes in vitro with late toxicity

Collaboration with John Yarnold, Kai Rothkamm, Carsten Herskind, Melvin Chua

INSIGHT – novel methodology

Breast cancer patients – 15 cases (RS), 15 controls (RR)

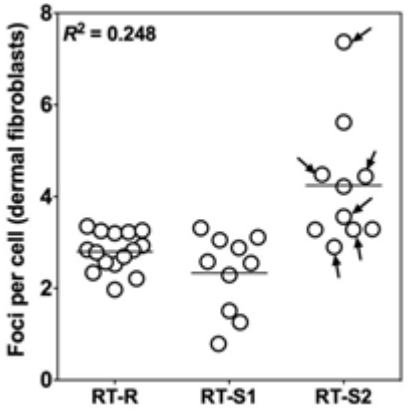
- Multiple skin punch biopsies
- Blood sample pre-RT – irradiated *ex vivo*



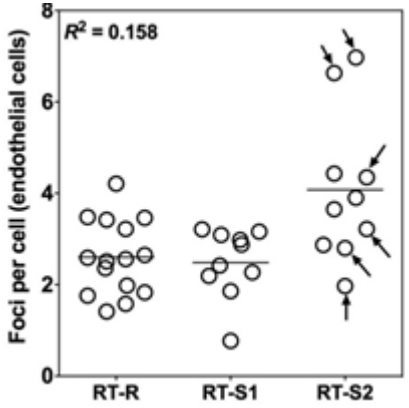
Results – Residual DSB in vivo

Residual DSB in fibroblasts significantly increased in most sensitive cases

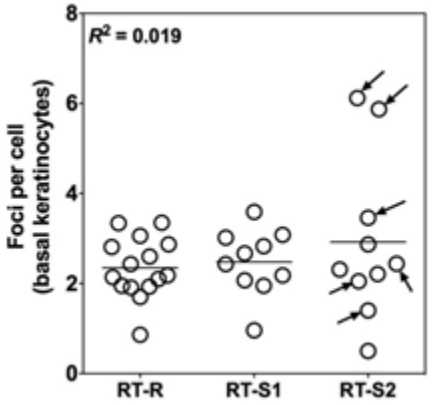
Fibroblasts



Endothelial cells



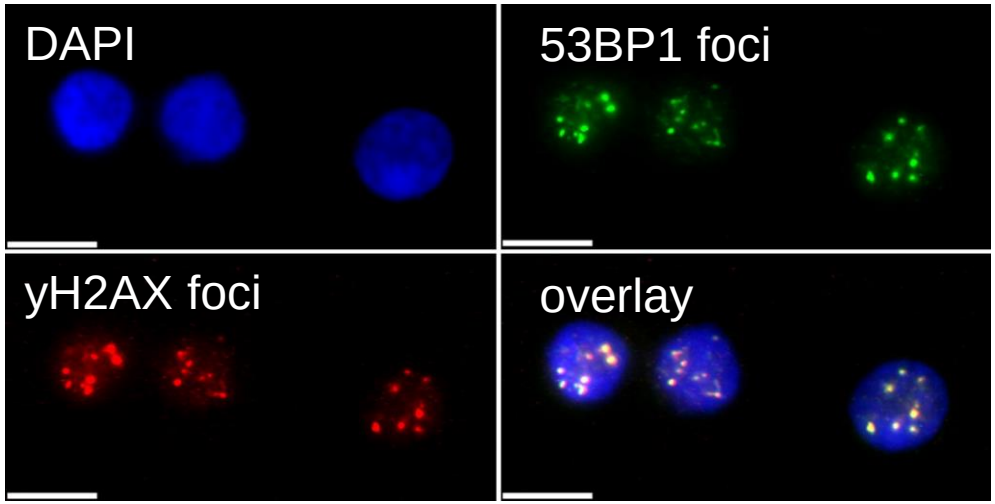
Basal keratinocytes

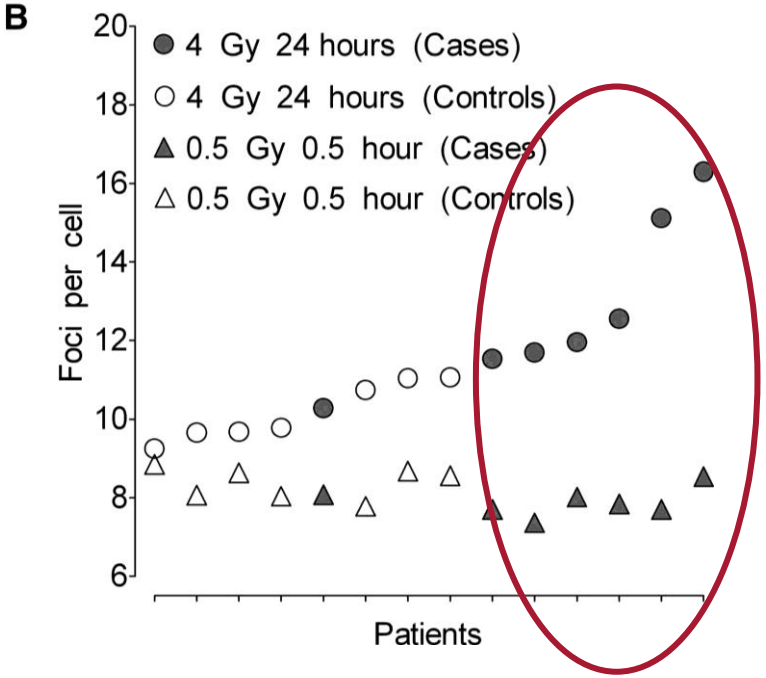


Arrows=severe cases

Somaiah et al, R&0 2016
Nuta, Somaiah et al, Cancer Letters 2016

Results – Residual DSB foci in lymphocytes



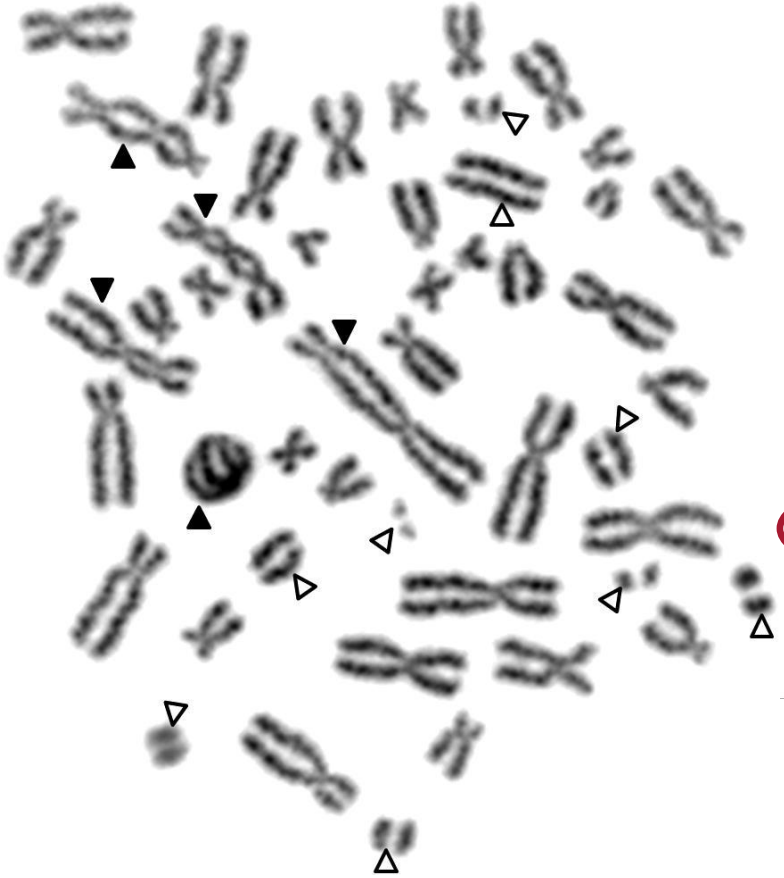


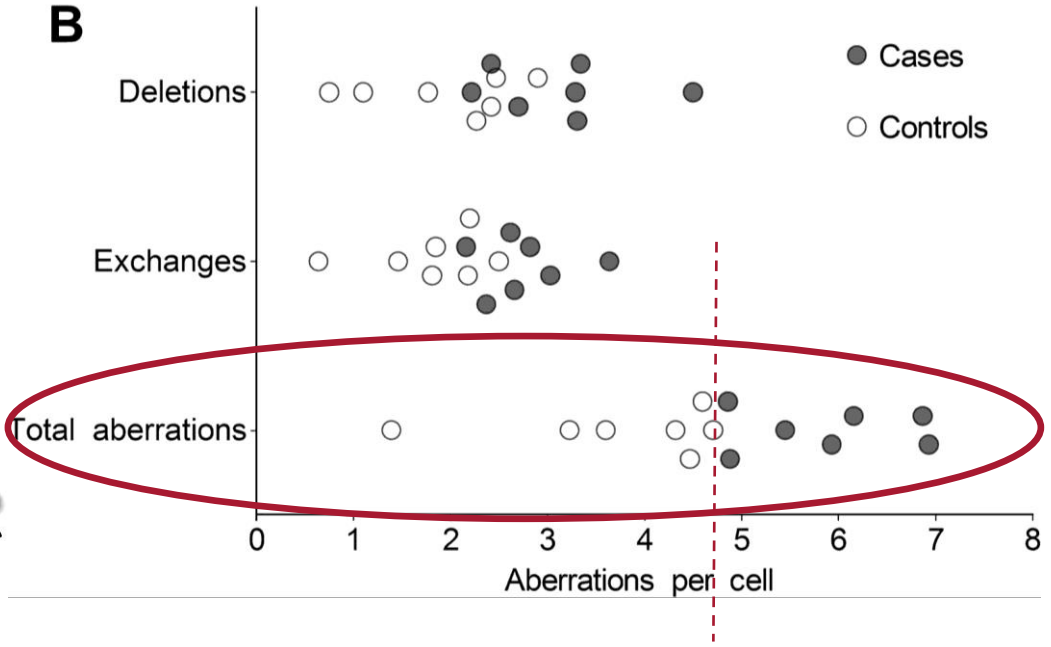
Statistically significant difference between cases and controls

Chua, Somaiah et al R&O Apr 2011

Chua, Somaiah et al R&O June 2011

Results – Chromosomal aberrations in lymphocytes





Chua, Somaiah et al R&O June 2011

Summary from INSIGHT

Main strengths

- Controlling for effects of tissue microenvironment on cell responses
- Recruitment of patients under prospective follow-up
- Able to associate the radiation response of fibroblasts & lymphocytes with late toxicity in most radiosensitive patients

Clinical translatability???

Micronucleus assay

RILA assay

Dicentric chromosome assay

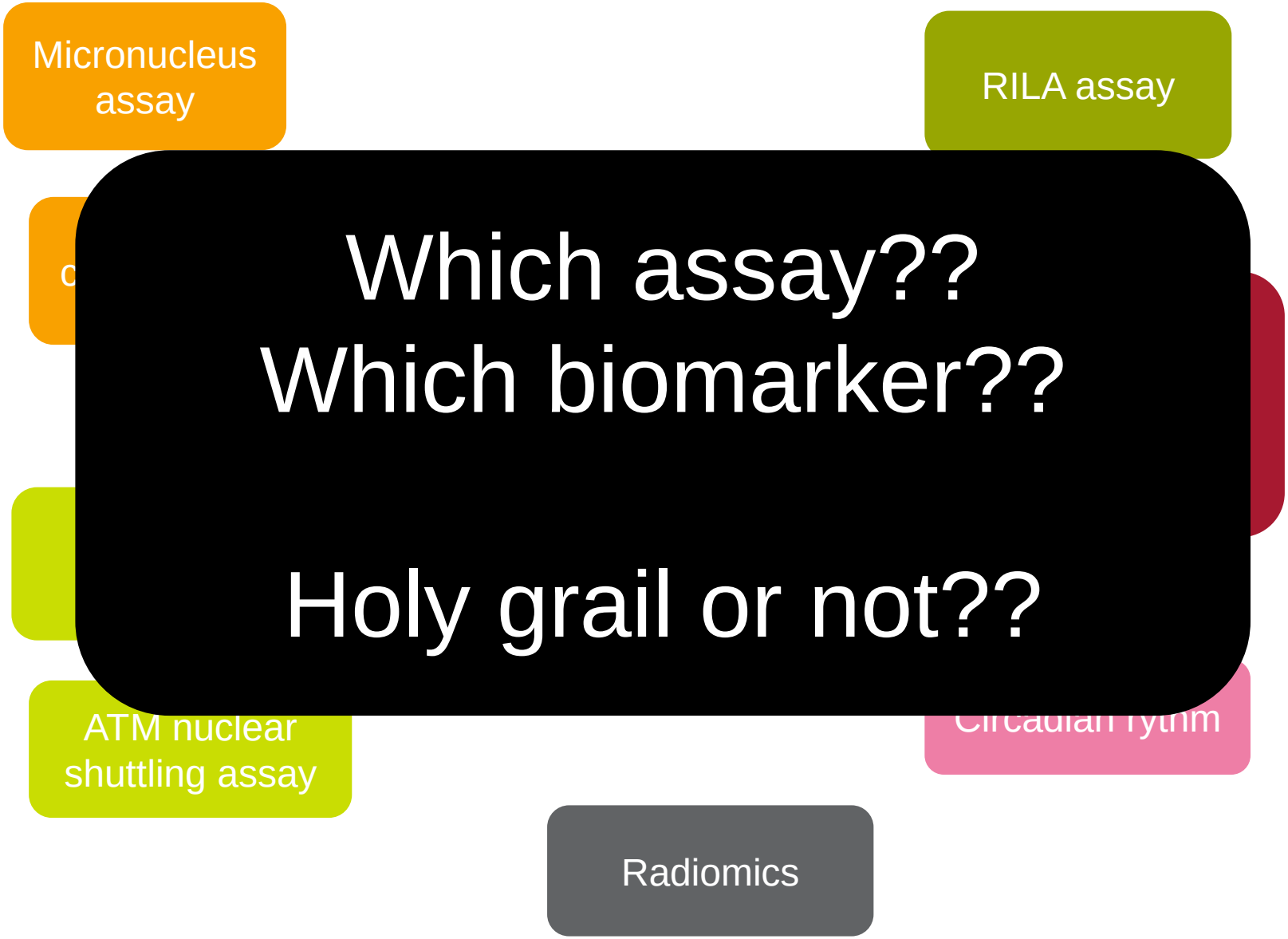
Genomic
Proteomic
Transcriptomic signatures

Residual yH2AX foci

ATM nuclear shuttling assay

Circadian rythm

Radiomics


Micronucleus assay
RILA assay
Which assay??
Which biomarker??
Holy grail or not??
ATM nuclear shuttling assay
Radiomics

The Problem

SO FAR

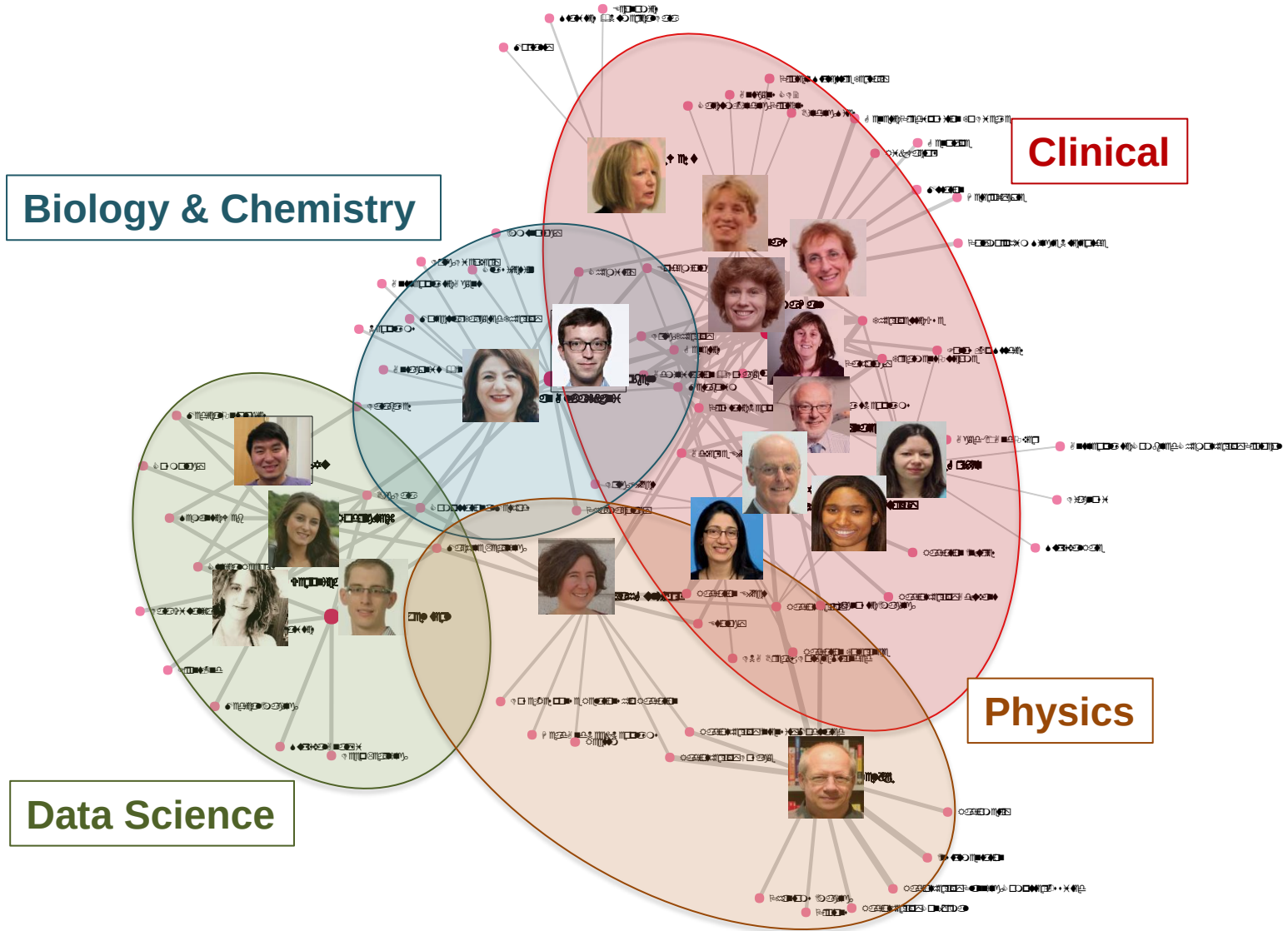
- Dosimetry or biology alone cannot explain toxicity
- Recognise that pathogenesis of RT-induced toxicity is complex & multi-factorial
- Limited combined analyses of clinical, dosimetric, genetic factors

CHALLENGES

- Rarity of large studies with complete, prospectively collected data
- Difficulty to integrate, analyse & interpret large, multi-modal data

Can Big Data/AI Analysis help?

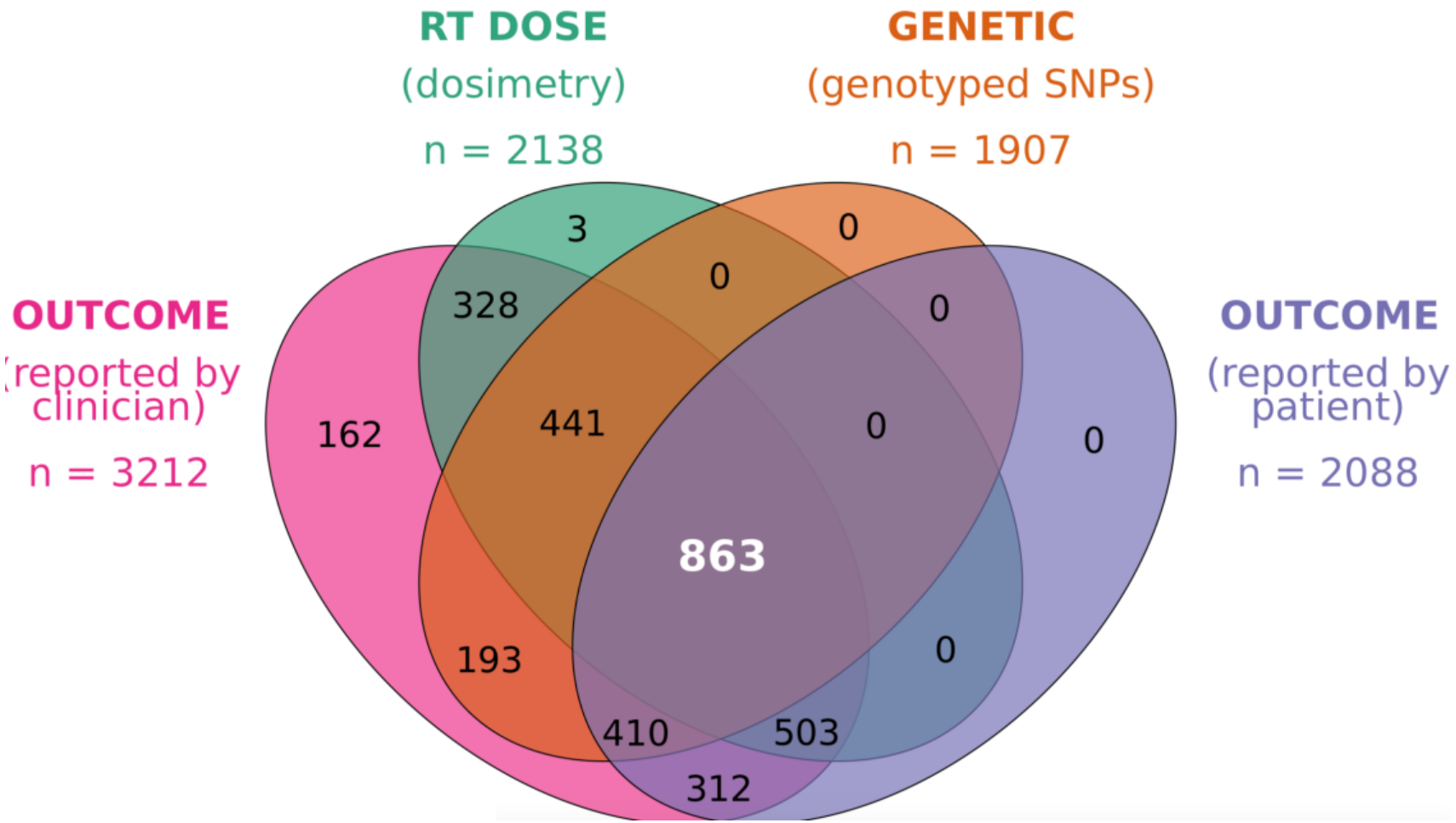
Multidisciplinary Team- Big RT



CHHiP: Prostate Hypofractionation Trial

Chief investigator: Prof David Dearnaley
ICR-CTSU Lead: Prof Emma Hall

3216 patients recruited



Data Processing: Inclusion Criteria

Focus on Rectal Bleeding endpoint

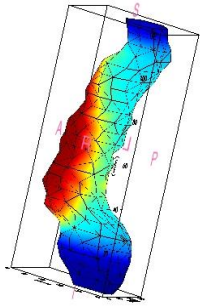
928 have all CRO, dosimetry, genetic data - included in the combined analysis

Patient labelled as having rectal bleeding toxicity if:
Grade ≥ 2 at ≥ 12 months

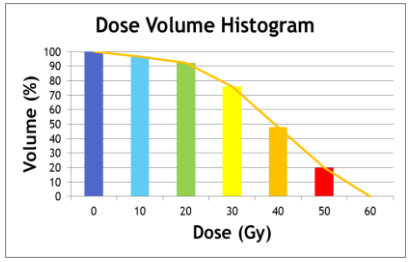
7.8% incidence

Analysis: Features Selected

Dosimetric



Rectal volume receiving RT dose



Dose Volume Histogram (80 bins)

Clinical (12 variables)

Age, hypertension, pelvic surgery, diabetes, IBD, previous TURP, risk group, Gleason score, pre- and post-hormone PSA, RT dose

Genetic

300k–500k **genetic variants (SNPs)** from RAPPER & PRACTICAL consortia:

- **~9 million** after imputation
- **~100-500** pre-selected

Analysis

Results: Combined multiparametric, multimodal data better identifies patients with long-term toxicity

Genetics

CRO

Dosimetry

PRO

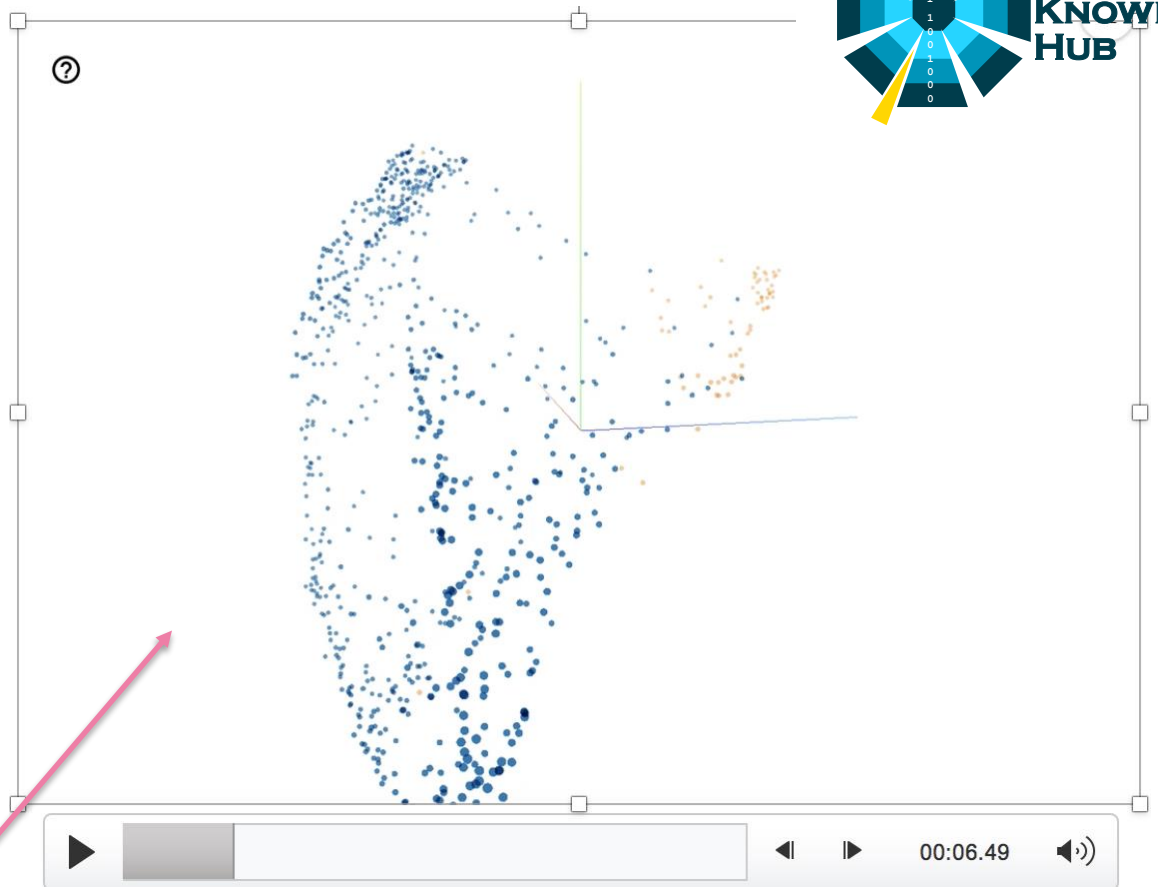
450 million data points

Refine data

Deep learning

74 latent parameters

Cluster patients



THE KNOWLEDGE HUB

Patients with severe rectal bleeding

Patients without

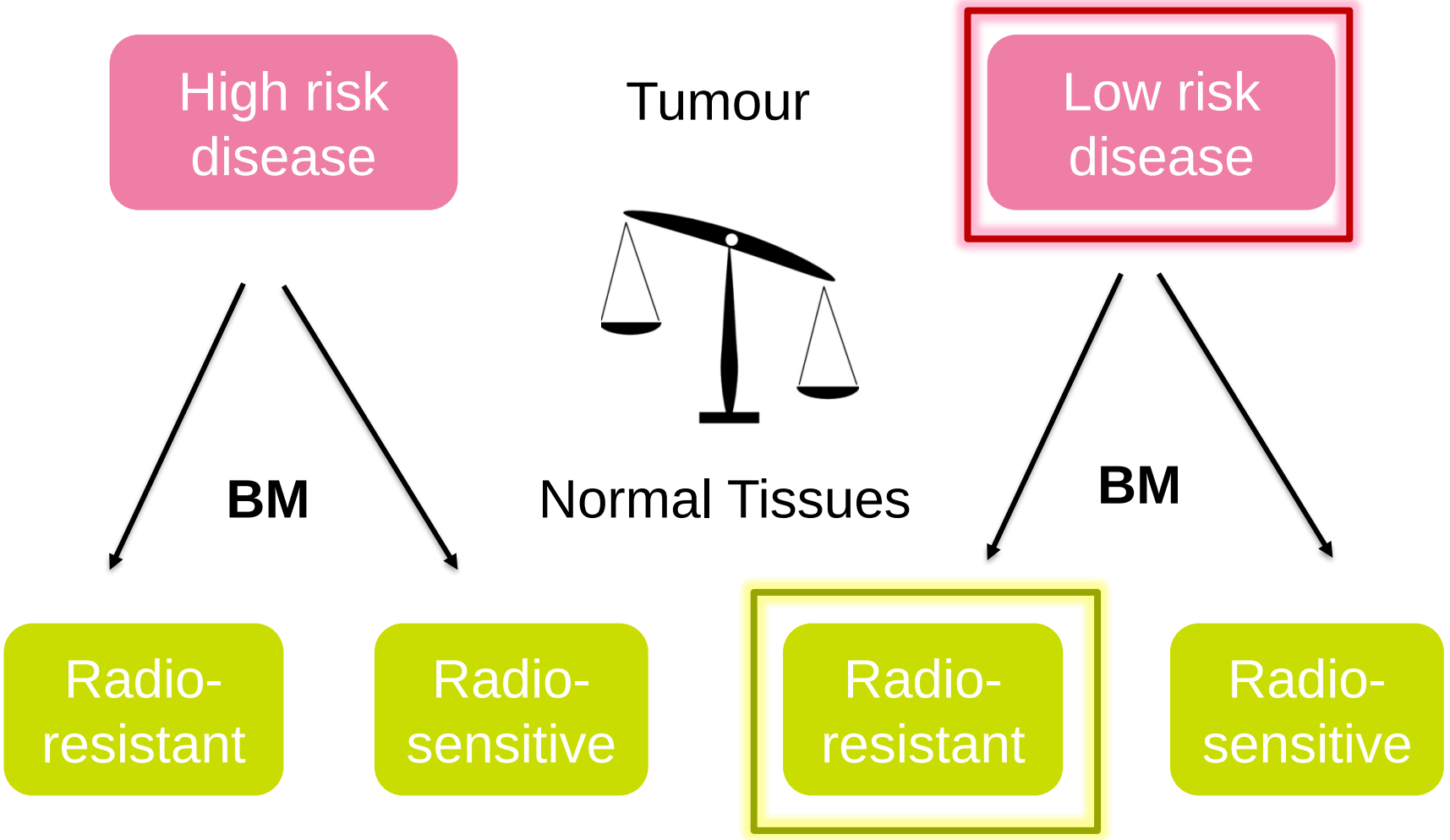
So far…

- Developed a bespoke integrative model to *jointly* analyse *all* datasets
- Allows integration of other data types eg: radiomics
- Identified some novel markers combining variables from all datasets
- Predictive power typically increased by combining datasets

Next steps

- Validation in progress with independent data set

If we find a reproducible/reliable/validated BM that can accurately predict individual NT toxicity can RT be beneficially modified?


High risk disease
Tumour
Low risk disease
BM
Normal Tissues
BM
Radio-resistant
Radio-sensitive
Radio-resistant
Radio-sensitive

Low risk disease, Radio-resistant NT

Current standard of care OK?

RT dose fractionation already modelled on keeping NT toxicity low

High risk disease

Tumour

Low risk disease

Normal Tissues

Radio-resistant

Radio-sensitive

Radio-resistant

Radio-sensitive

Low risk disease, Radio-sensitive NT

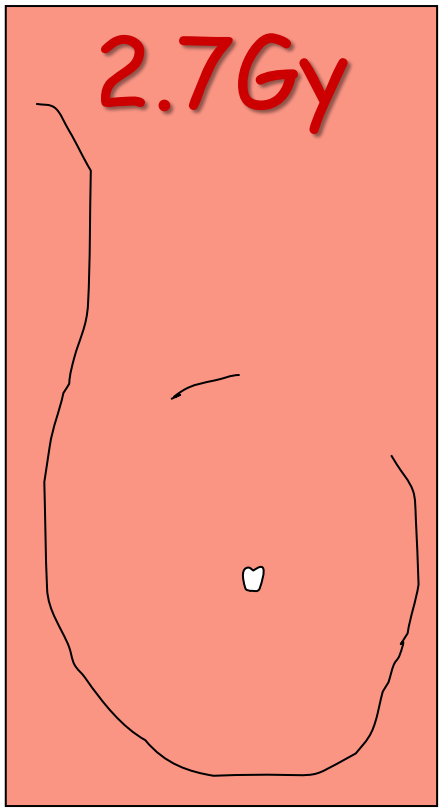
Avoidance of RT all-together (eg: active surveillance, surgery, hormone therapy)

If no oncological alternative to RT

- Stringent dose constraints for NT (accept tumour compromise)
- Dose de-escalation strategies
- Use of Image guided RT/Adaptive RT strategies to keep NT dose to a minimum

Partial breast RT in low risk -IMPORT LOW

Control Group:
Whole breast



15 Fractions

Test Groups: **Partial breast**

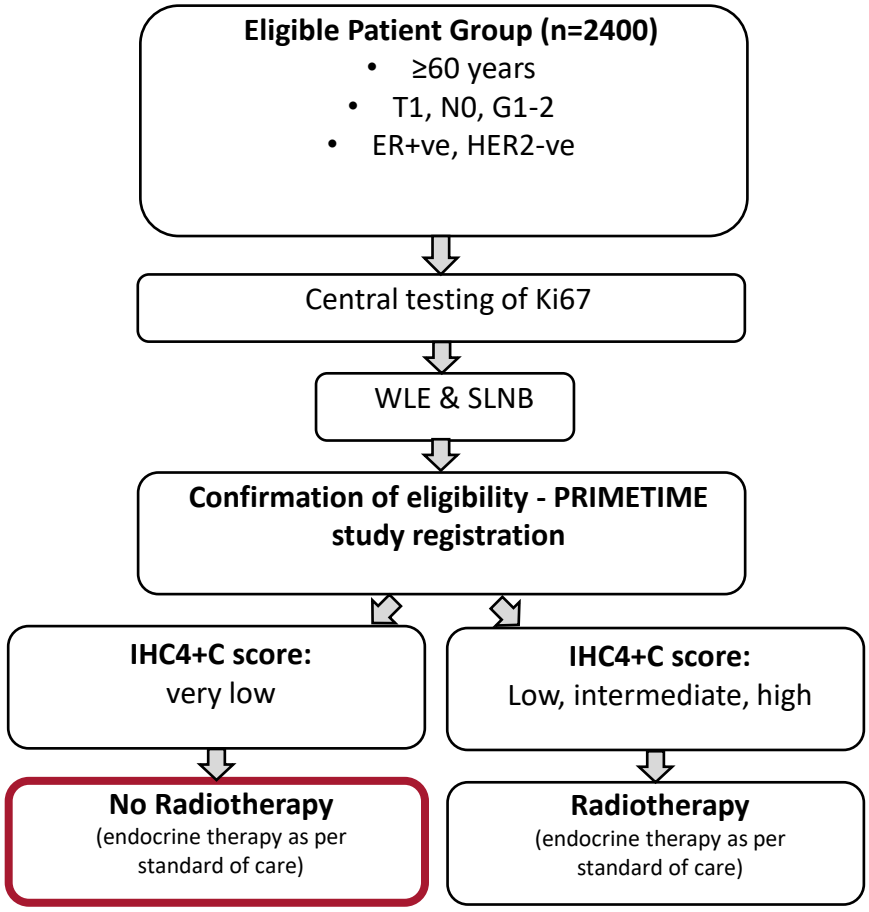
Group 1

15 Fractions

Group 2

15 Fractions

PRIMETIME



AIM: develop low cost accurate biomarkers to test omission of radiotherapy in very low risk population

No radiotherapy side effects for very low risk patients
Save NHS >£12M/year treatment costs

Courtesy Charlotte Coles

High risk disease

Tumour

Low risk disease

Normal Tissues

Radio-resistant

Radio-sensitive

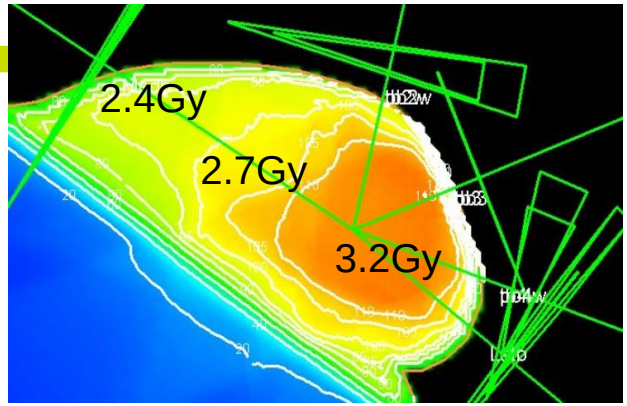
Radio-resistant

Radio-sensitive

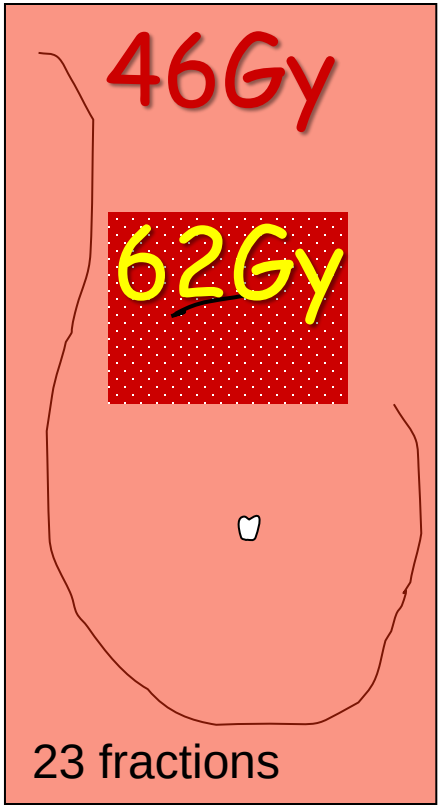
High risk disease, Radio-resistant NT

- Relax dose constraints to NT in favour of tumour coverage
- Dose escalation strategies
- Hypofractionation strategies with a view to accelerated RT
- Combination strategies with radiosensitisers – chemotherapy/novel drugs

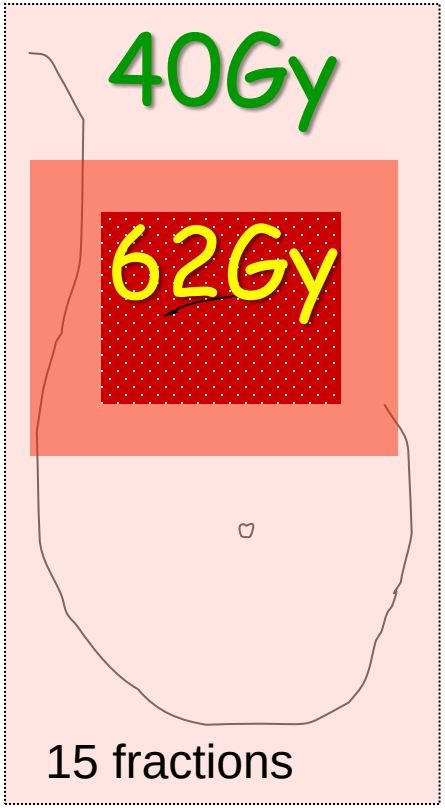
Dose escalation to tumour bed in high-risk breast patients –IMPORT HIGH



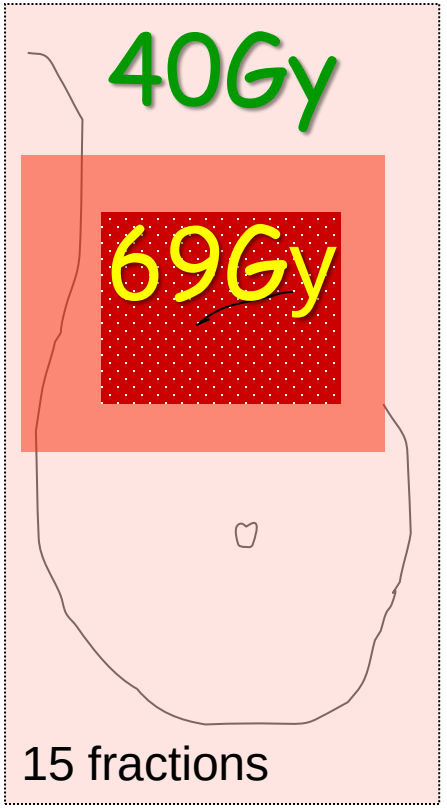
Control



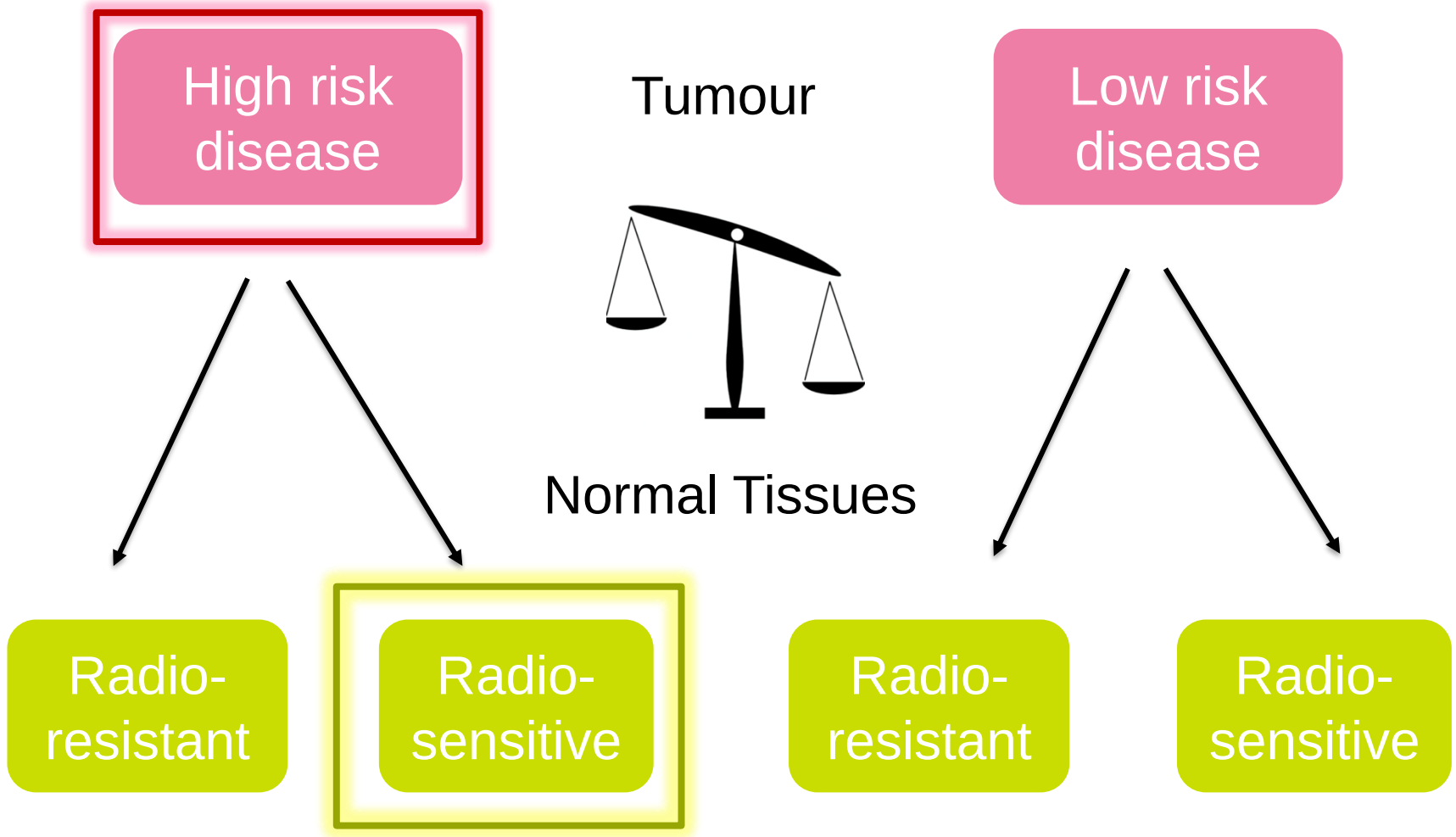
Test 1



Test2



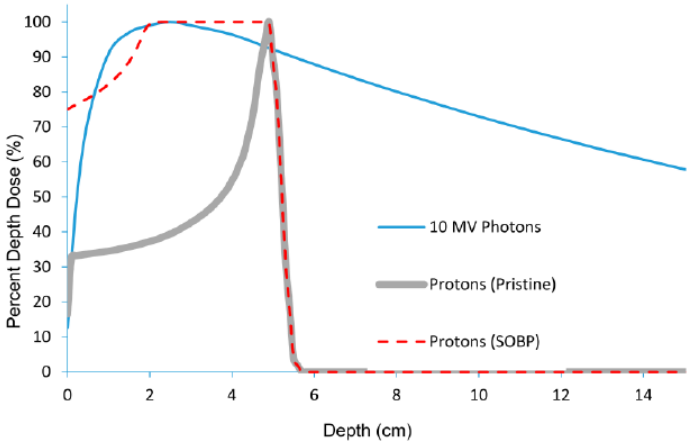
Courtesy Charlotte Coles

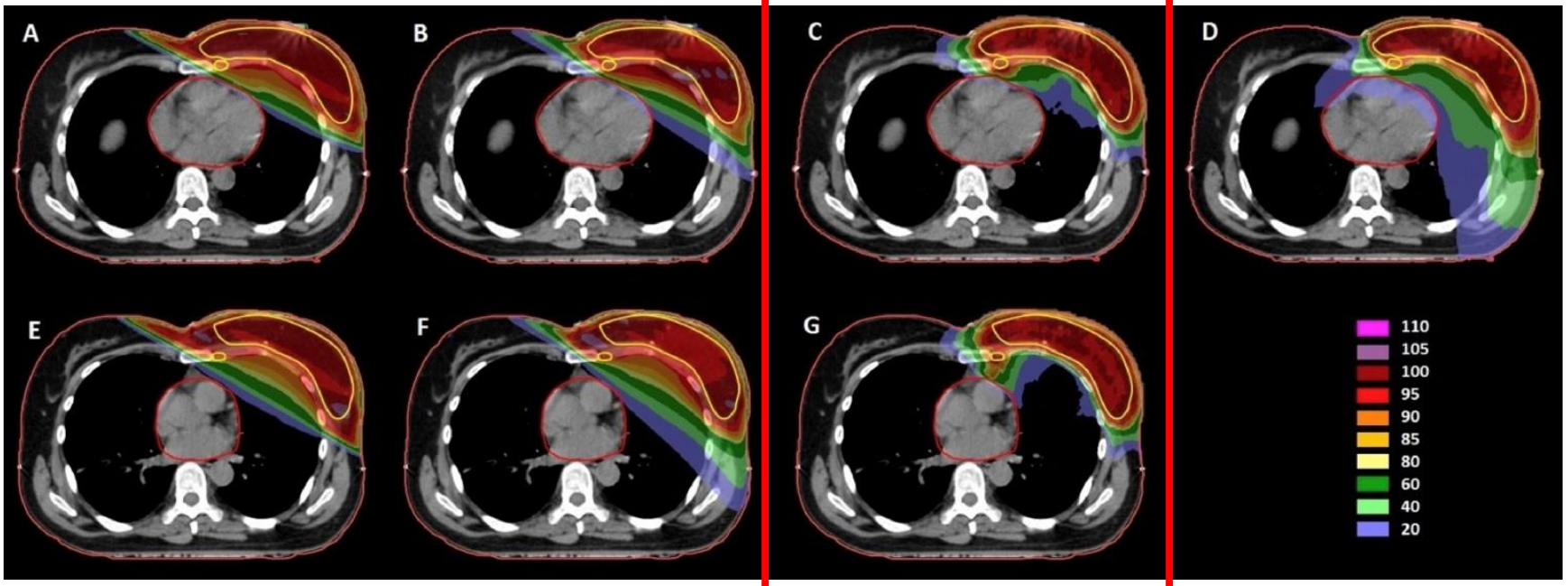

High risk disease
Tumour
Low risk disease
Normal Tissues
Radio-resistant
Radio-sensitive
Radio-resistant
Radio-sensitive

High risk disease, Radio-sensitive NT

- Very stringent dose constraints for NT
- Favour conventional/hyper-fractionation instead of hypofractionation
- IGRT/ART/MR-Linac/Protons/Gating/Spacers – strategies to minimise NT dose
- More closer follow-up of these patients for early interventions for NT toxicity management
- Use of novel radio-protectors

High risk breast disease
Internal mammary chain RT





Wide tangents | Arc therapy | Protons | Tomotherapy

Ranger et al Clin Oncol (R Coll Radiol) 2018

PARAMLE

Proton beAm theRApy in patients with Breast cancer: evaluating early and Late Effects

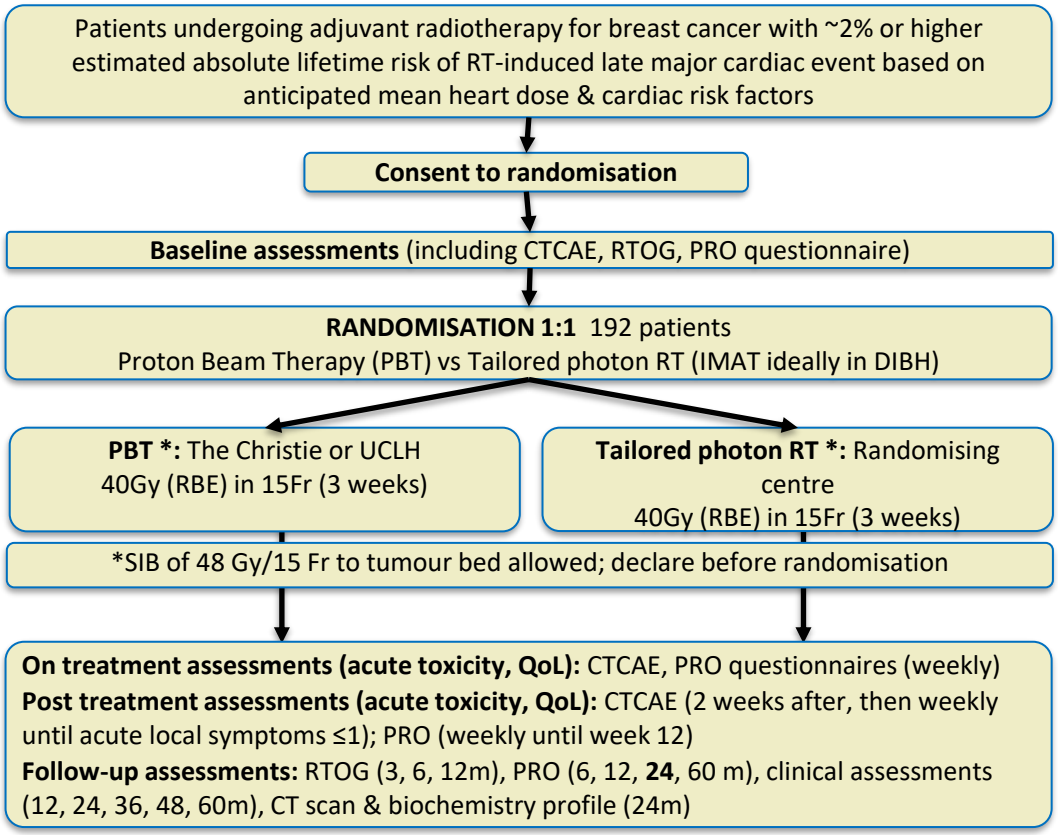
Aim: To show that PBT reduces predicted risk of late serious heart toxicity with no increase in other shorter-term side effects

Objectives:

- Change international practice for breast PBT early with a primary outcome analysis at 2 years' follow-up
- Improve understanding of PBT biological models via a mechanistic study with potential benefit for all cancer patients needing PBT

Co-primary endpoints:

- Mean heart dose
- Patient-reported normal tissue toxicity in the breast (EORTC QLQ-BR23 breast symptoms score) at 2 years



Chief Investigator – Prof Charlotte Coles
Technical RT and Mechanistic Study Lead – Dr Anna Kirby

ICR The Institute of Cancer Research

FUNDED BY NIHR | National Institute for Health and Care Research

PARABLE

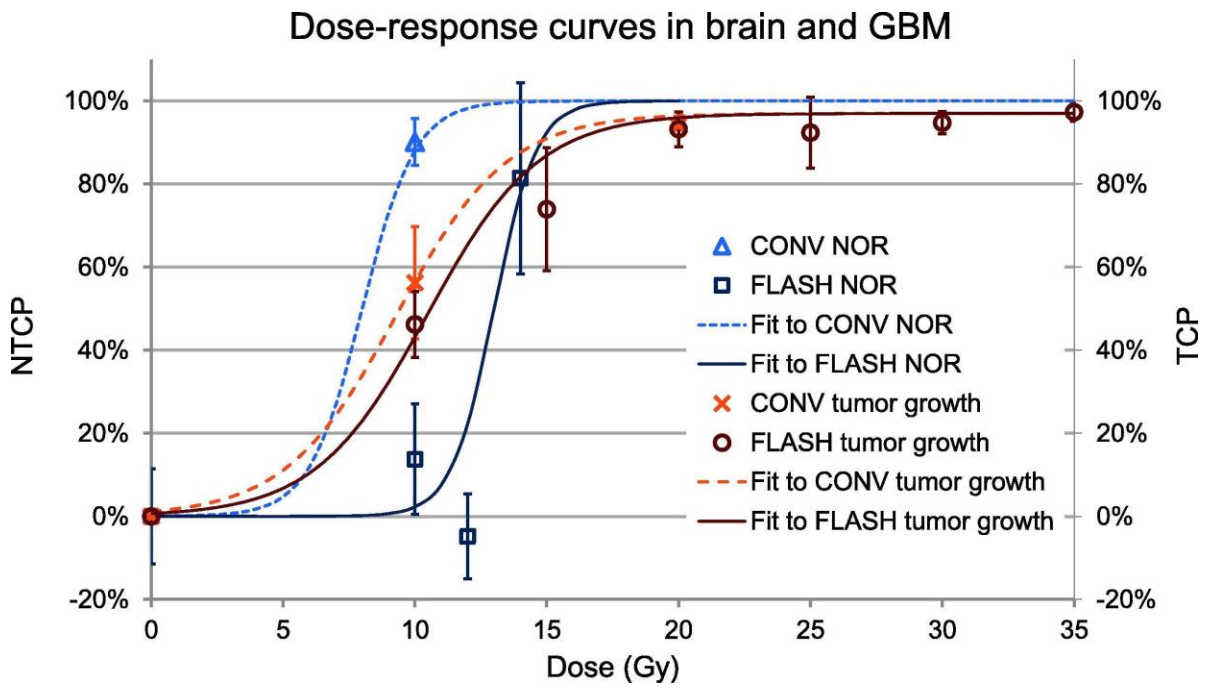
Who is eligible?

- For inclusion in PARABLE the estimated **lifetime risk of radiation-induced late cardiac toxicity** for a patient should be **around 2% or greater**
- This is calculated using **mean heart dose (MHD), age and cardiovascular risk factors** as per table below:

Age (years) at study registration	Mean heart dose (Gy) needed for ≥2% risk of radiation-related heart disease by aged 80 years	
	No Cardiac Risk Factor	At Least One Cardiac Risk Factor*
≤44¶	≥4Gy	≥2.5Gy
45-54	≥6 Gy#	≥4 Gy
55-64	≥6 Gy#	≥4.5 Gy
65+	≥6 Gy#	≥5.5 Gy

¶ Incorporating data for women <40 years (Henson et al).* Risk factors: pre-existing cardiac or circulatory disease, diabetes, COPD, BMI >30 kg/m^2, smoking (long term continuous within previous year). # Clinically acceptable threshold for MHD based on RCR UK consensus

What about FLASH-RT?



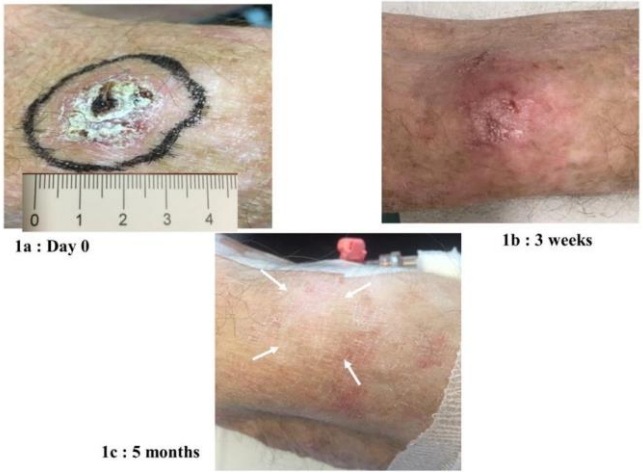
Normal tissue sparing; similar tumour control

Bourhis, Vozenin et al 2019 R&O

Contents lists available at ScienceDirect

Radiotherapy and Oncology

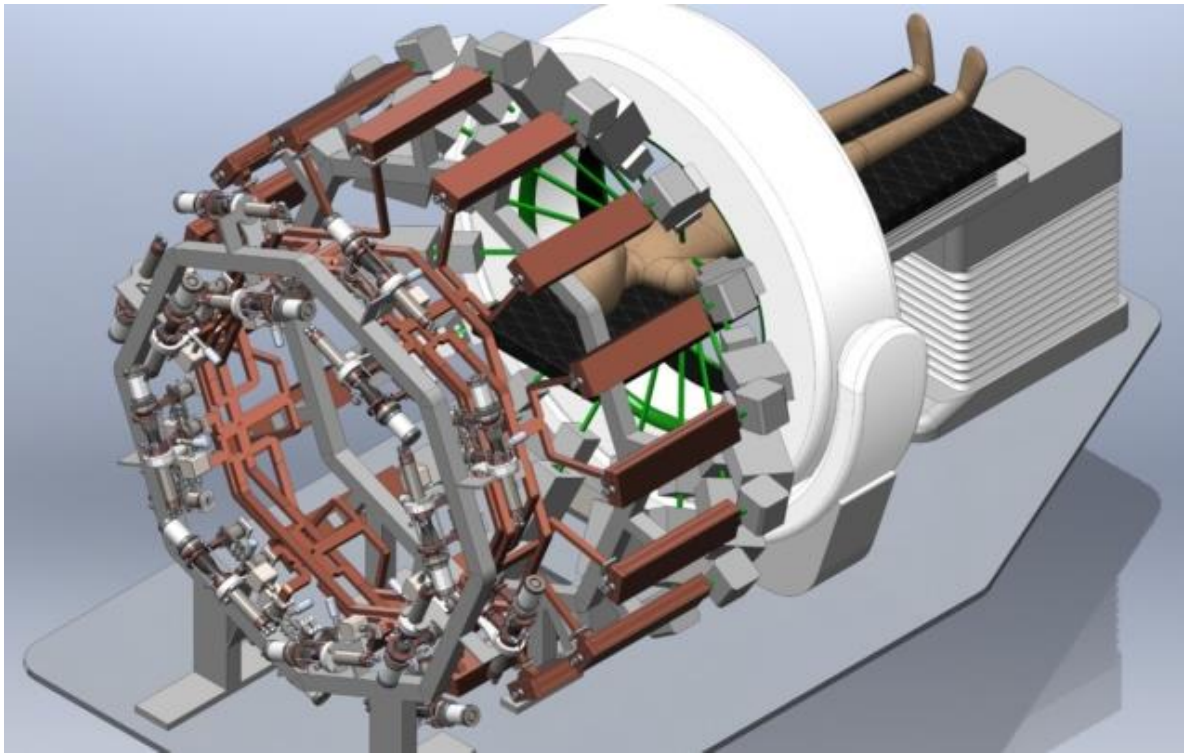
journal homepage: www.thegreenjournal.com



Original Article

Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis [a,b,*], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a,b,c], Olivier Gaide [d], Claude Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c], Jean-François Germonc Raphaël Moeckli [c,1], Marie-Catherine Vozenin [a,b,1]



PHASER Linac
Stanford's clinical prototype

Early (non-RT) intervention strategies in RS patients

- **Smoking cessation**
- Modifying gut biome
- Radioprotectors- Amifostine, Antioxidants (Vit E, Pentoxyphylline)
- Circadian rhythm- timing of RT delivery
- Hyperbaric Oxygen

Ultimately it is about informed patient discussions/shared decision making

Radiother Oncol. 2016 December ; 121(3): 440–446. doi:10.1016/j.radonc.2016.11.003.

Optimal design and patient selection for interventional trials using radiogenomic biomarkers: A REQUITE and Radiogenomics consortium statement

Dirk De Ruysscher[1,2], **Gilles Defraene**[2], **Bram L.T. Ramaekers**[3], **Philippe Lambin**[1], **Erik Briers**[4], **Hilary Stobart**[5], **Tim Ward**[6], **Søren M Bentzen**[7], **Tjeerd Van Staa**[8], **David Azria**[9], **Barry Rosenstein**[10], **Sarah Kerns**[11], and **Catharine West**[12]