MRO. ART
INNOVATIVE TREATMENTS AND PATIENTS COMPLIANCE
31° RESIDENTIAL COURSE

What is considered innovation in 21st century radiotherapy?

Anna Kirby
Royal Marsden/ Institute of Cancer Research, UK

18 "Everyone acquainted with the subject will recognize it as a conspicuous failure." - -Henry Morton, president of the Stevens Institute of Technology, on Edison's light bulb, 1880

20 "I think there is a world market for maybe five computers." - Thomas Watson, chairman of IBM, 1943

[25 Famous Predictions That Were Proven To Be Horribly Wrong (list25.com)]

MRO. ART
INNOVATIVE TREATMENTS AND PATIENTS COMPLIANCE
31° RESIDENTIAL COURSE

What is considered innovation in 21st century radiotherapy?

Or what can the radiation oncology community learn from the history of innovation?

Anna Kirby
Royal Marsden/ Institute of Cancer Research, UK

Overview

- What do we mean by innovation?
- Why and how does innovation happen?
- How can we innovate better in radiation oncology?
- What does this mean for patient compliance?
- The innovation pathway: a case example
- Some closing thoughts

What is innovation?

- Finding new ways to apply energy to create improbable things and see them catch on
- More than just invention because it has to be sufficiently practical, affordable, reliable and ubiquitous to be worth using

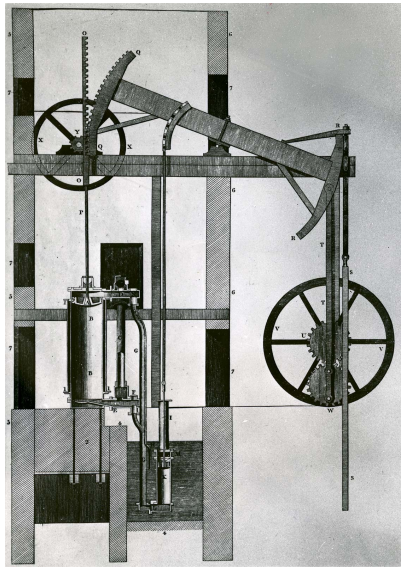
"A new method or new product that becomes a new practice somewhere in the world"
Edmund Phelps

Why and how does innovation happen?

- “Technical progress is the most essential characteristic of modern growth and one that is most difficult to explain”
- “Scholars know remarkably little about the kind of institutions that foster and stimulate technological progress”

M Ridley, How Innovation Works

The concept of “innovationism”



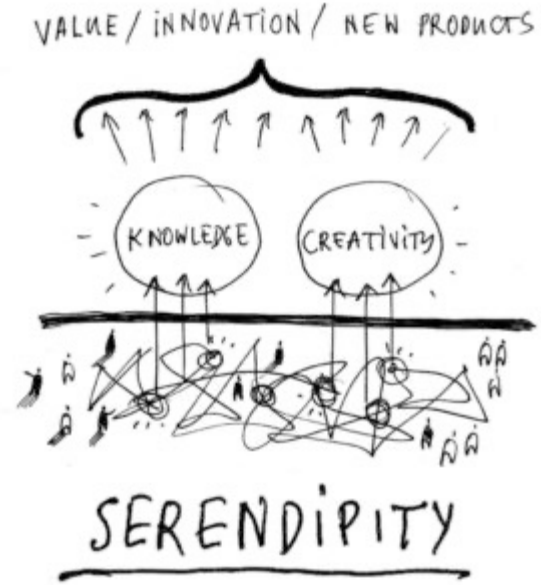
- Industrial revolution
- The habit of applying new ideas to raising living standards
- Not achieved by “piling of brick on brick, or bachelor’s degree on bachelor’s degree” but by curiosity, trade and exchange
- Few of the innovators who drove the changes were trained scientists
- Much innovation preceded the science that underpinned it (eg smallpox inocculation)
- Innovation as autocatalytic eg steam engines, coal mining, cheaper energy etc

So how does innovation work?

- Innovation is evolution
  - Innovation is recombinant
    - “It’s what happens when ideas have sex”
    - “Ideas are like rabbits. You get a couple and learn how to handle them, and pretty soon you have a dozen” (John Steinbeck)
    - Interfaces are key
      - Llopis, Research Policy, 2016- contact with patients facilitates biomedical scientists medical innovation output
    - It is more likely when people meet, exchange ideas, services and goods
      - Eg computers needed ENIAC vacuum tubes and Mark 1 storable programmes

How does innovation work?

- Innovation is evolution
  - Innovation is more like natural selection than intelligent design
    - Iteration- Newcomen engine- several people working on similar problems with slightly different technical solutions
    - Patents that are too broad kill innovation
      - Competition is beneficial- risk that pandemic removes smaller companies from the genetic pool
    - Innovation is often random/ serendipitous
      - Yahoo/ Google/ Instagram/ GPS systems



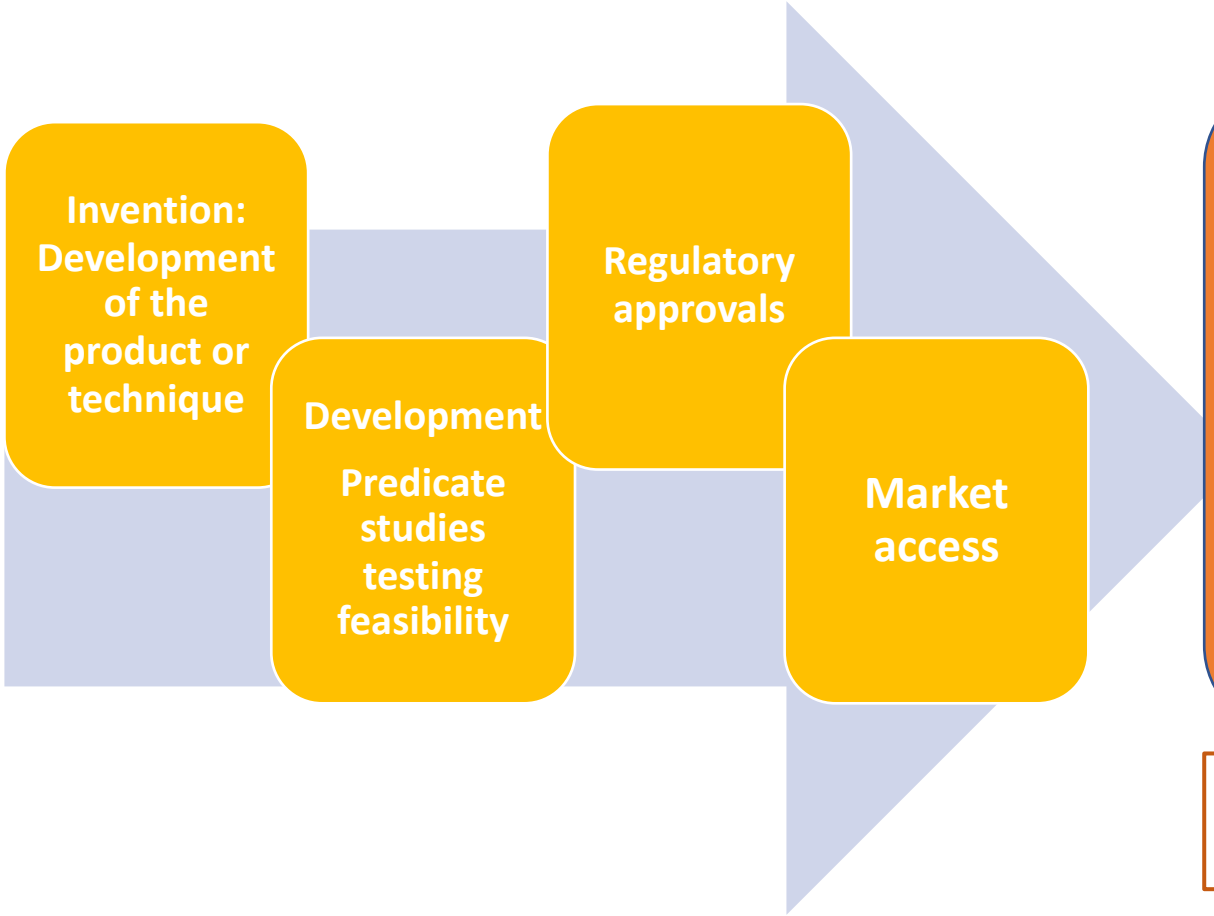
How does innovation work?

- It involves trial and error
  - Edison: ”I’ve not failed. I’ve just found 10,000 ways that won’t work.”
  - Wright brothers multiple failed attempts
- It doesn’t have to be complicated
  - Again and again in history it is those who simplify and drive down costs that make the biggest difference (Eg mobile phones in 1990s)
- Innovation is teamwork (either multiple individuals or multiple teams working towards similar goals) eg lightbulbs, Newcomen engines etc
- The hype cycle: Most people overestimate the short-term impact of an invention but underestimate its long-term impact eg GPS systems

But how does this translate to radiation oncology?

- Inventions that aren't delivered to patients aren't innovations
- The impact of effective innovation will be significant
  - RT will save one million lives saved by 2035 but the impact of technological advances will be greatest if supported by political decision-making around infrastructure funding and transfer of knowledge
- Innovation should provide benefit for patients and value for society:
  Y Lievens, European Cancer Summit, 2021

The innovation pathway in radiation oncology



Treatment Optimisation

Applied multidisciplinary clinical research

Clinical trials defining benefits in specific populations

Publication/ discussion

Potential implementation in specialist centres

Health System Optimisation

Health services and implementation research

Access/ cost

Acceptability

Value

Reimbursement

Integration into treatment guidelines and policy

Widespread integration into clinical practice

Adapted from Denis Lacombe

How can the RO community innovate better?

- Invention
  - Recombination
    - The magic happens at interfaces: connect, meet, network, read, question, challenge
  - Simplify and drive down costs
    - Will we invest in expensive tools for a small subgroup of patients or mainstream and accessible tools that improve RT quality for the majority? (Verellen 2021)
  - Frugal innovation
    - Simplified, cost-effective solutions that offer patient experience with ease of access and reduced travel
    - Given increasing costs of regulation, clinical trials and market access, companies could benefit from having a “minimally viable” product which delivers patient and user benefits without being over-engineered

How can the RO community innovate better?

- Development
  - Honesty around likely impact: eg MRL game-changing for particular indications, insufficient added value to justify expense in other areas
  - Technologies as vehicles for focussed multiprofessional engagement in radiotherapy pathway

It's the team not the beam that makes the difference (Swisher-McLure et al, IJROBP, 2019)

- Clinical trials
  - Ground-breaking, practice-changing, robust
  - Slow, bureaucratic, expensive
  - Smarter design using same infrastructure
    - Umbrella, Basket, Platform

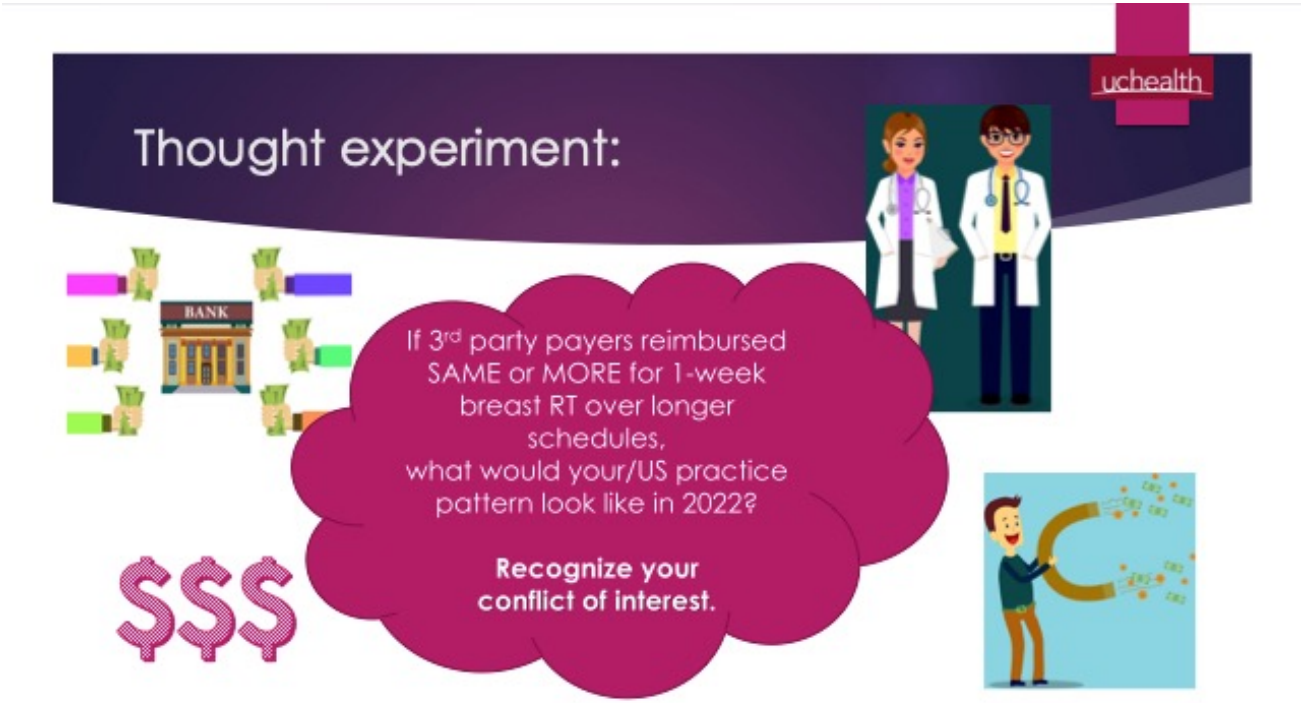
How can the RO community innovate better?

- Health Systems & Treatment Optimisation Network
  - To help health systems meet the decision-making challenges related to new treatment options
- Advocacy document being prepared around “The Great Reset in European Cancer Research and Care”
  - To help inform political decision makers on the routemap to health systems and treatment optimisation
  - Key recommendations:
    - Independently assess and publish key questions in cancer research
    - Reorientate funding to address gaps in cancer research continuum

Denis Lacombe, European Cancer Summit 2021

How can the RO community innovate better?

- Healthcare System “readiness”



Rachel Rabinovitch

Current issues in RO innovation

- Need for research and care to go hand in hand
- There is a global need for more affordable and equitable access to cancer care
- We know what works but the value gap is increasing
  - Delinkage between costs to healthcare systems and outcomes
  - For some countries, increased healthcare spend- worse outcomes
- Need better relationships between structures and processes, benefits and outcomes
- Need site-specific audits within nations to understand whether or not innovations are reaching the shop floor eg PBI in UK
- In context of ageing population, new technologies become less relevant than what is feasible and pretty good (the best is the enemy of the good)
- Chronic underfunding of implementation science/ health services research

Richard Sullivan, European Cancer Summit 2021

Current issues in RO innovation

- We need the bandwidth to define and deliver standard of care before we can deliver R&D- human capacity issue
  - Need for a more skilled and mobile workforce
    - Innovations in education and training (virtual learning, subtitles etc) can support this
  - Machine learning & AI critical to improving efficiency in hospital care (leverage digital technology to strengthen health care delivery eg automatic blood testing at home, remote monitoring etc
- Healthcare policy: EU Beating Cancer Plan all well and good but has it learnt from previous plans/ initiatives? Need to build on structures and processes that are already there. Need to balance EU funding and individual member state funding
- Need to rebalance research agenda across or EU or risk increasing inequalities

Richard Sullivan, Kim Benstead, Berfu Yaziyurt European Cancer Summit 2021

What about patient compliance in relation to innovation?

- If patients cannot clearly see the benefits to them, they can be distrustful of new technologies*
- Co-producing with end users and citizens can improve the technology itself and its adoption into healthcare systems*
- Beware of herd behaviours in groups¥
- As individuals, humans are by nature altruistic

*HealthcareGlobal.com; ¥InnovationManagement.se

Are patients interested in clinical trials?

- The general public is keen to participate in cancer trials
  - 2000 Cancer Clinical Trials Study
  - Survey of 1000 US adults
    - Around 1/3 willing to participate in a cancer trial if asked
    - Another 1/3 interested to participate if reservations could be addressed
  - Conclusion: Substantially more people are willing to participate in clinical trials than are actually accrued indicating that lack of availability of studies together with narrow recruitment criteria are key barriers

Comis et al, 2003, JCO

What do patients want from clinical trials?

- Factors influencing decisions to participate in clinical trials:
  - Trial offers best treatment available
  - Trial results could benefit others
  - >3/4 willing to donate blood or tissue for research
  - Patients treated with palliative intent more willing to donate tissue
  - Patients want as much information about the novel treatment as possible, around half of patients declaring that they would have liked more information

Moorcraft et al, 2016, Trials

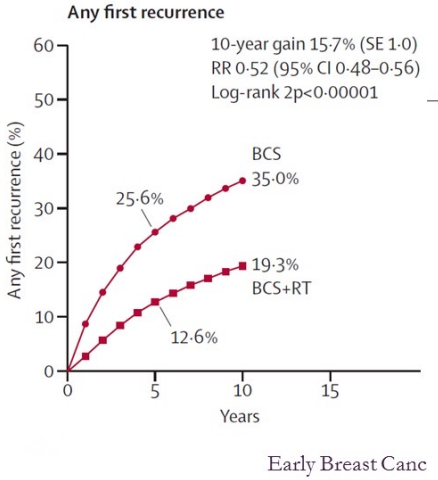
Recruitment to/ retention in RCTs

- Participants' top ten research questions
  - Which aspects of trial recruitment could be changed to improve retention?
  - Which aspects of clinical trials to patients find most burdensome and how can these be reduced?
  - How does relationship of patients to trial staff influence recruitment/ retention?
  - How does sense of belonging influence recruitment/ retention?
  - What are the best approaches for designing and communicating with trial participants?
  - To what extent to feasibility studies lead to improvements in retention in main trial?
  - Which strategies make participants feel valued and how does this influence recruitment/ retention?
  - How should incentives be used (if at all)?
  - How does continuity of care affect retention?
  - What behaviours of trial staff improve retention?

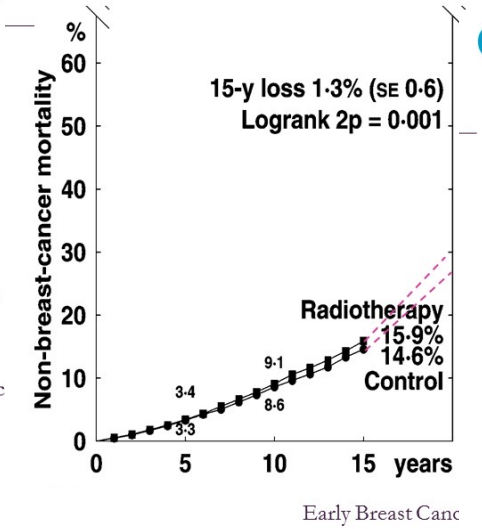
James Lind Alliance

Innovation in action: Heart-sparing in breast RT

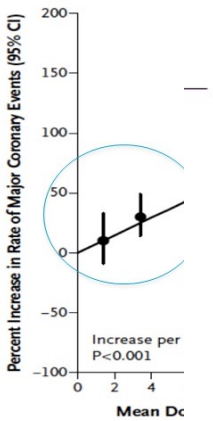
RT after BCS reduces recurrence rates and improves survival



but increases non-breast-ca mortality

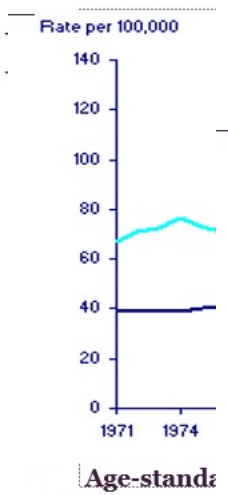


Quantifying the dose-effect relationship



Potential benefit of heart-sparing breast RT for an individual patient

More women are surviving breast cancer



Potential population benefits of heart-sparing breast RT

- Small risk reduction × large number of patients
  = large population benefit
- Assuming:
  - 1.7 million breast cancer survivors in 2040
  - Mean heart doses reduced from 3Gy to 1Gy
- Number of radiation-related acute coronary events reduced from around 20,000 to 6000
- Number of IHD deaths from 9000 to 2000

HeartSpare

↓

HeartSpare-Plus

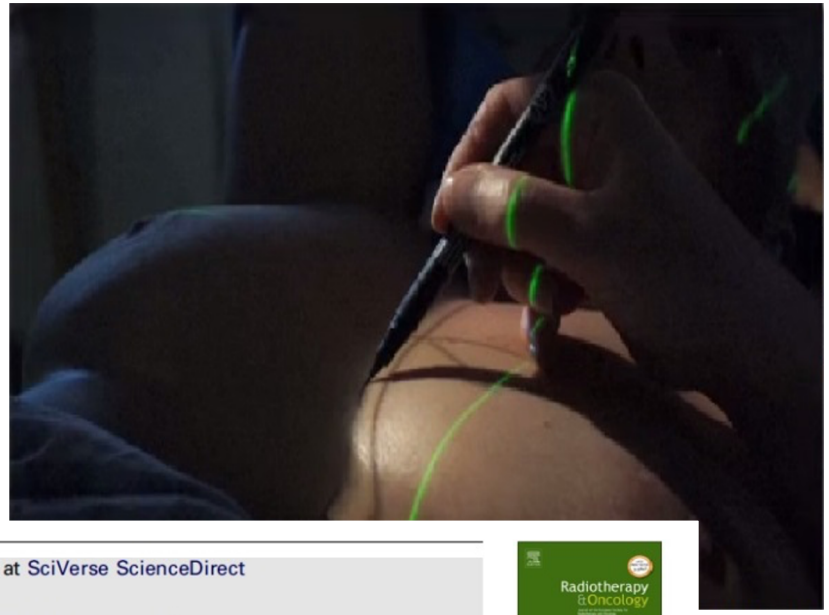
↓

PARABLE

Bartlett, Yarnold & Kirby, Clin Onc, 2013

HeartSpare

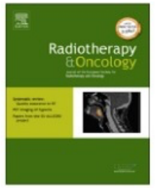
NHS National Institute for Health Research



Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

ELSEVIER



Locally practice-changing

Original article

The UK HeartSpare Study: Randomised evaluation of voluntary deep-inspiratory breath-hold in women undergoing breast radiotherapy

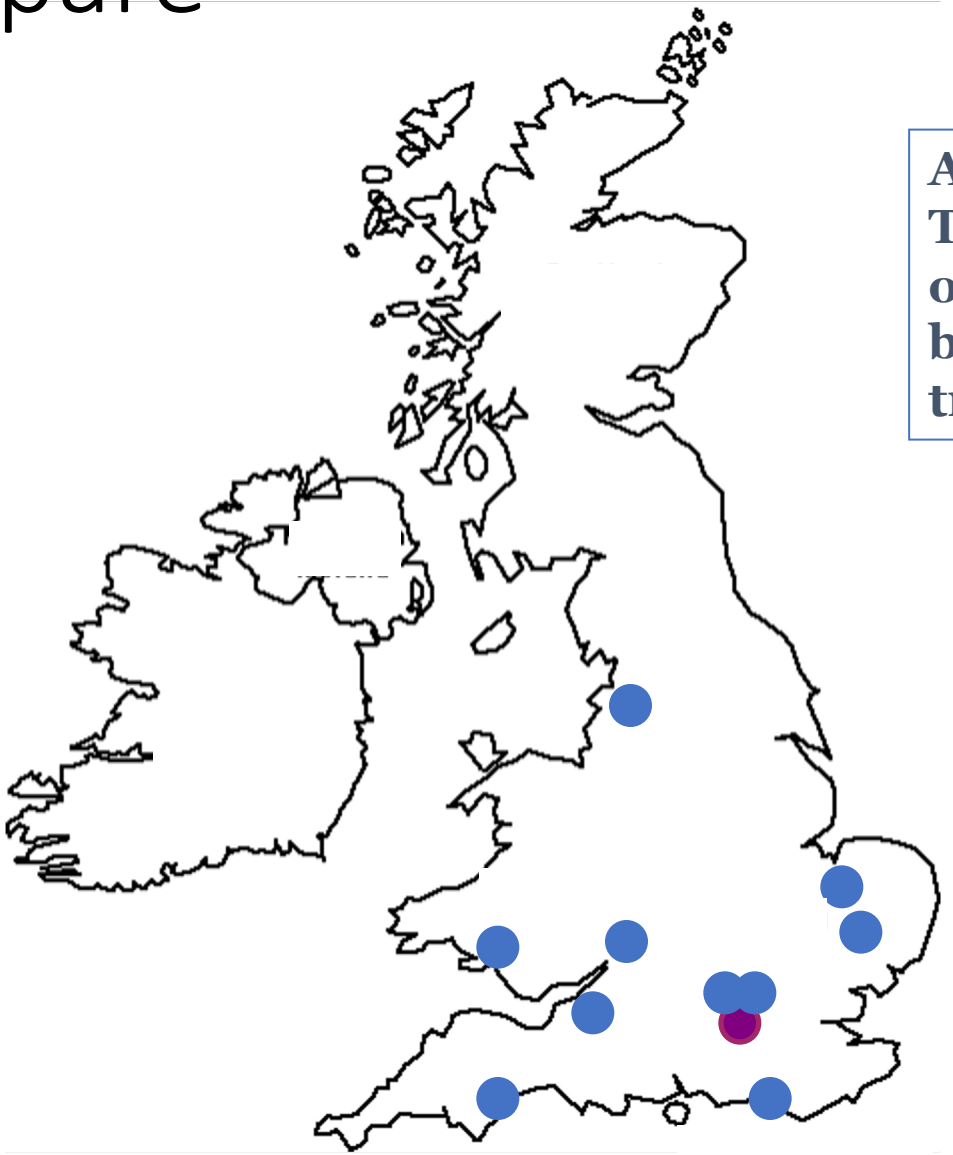
Frederick R. Bartlett [a,*], Ruth M. Colgan [b], Karen Carr [a], Ellen M. Donovan [b], Helen A. McNair [a], Imogen Locke [a], Philip M. Evans [b,c], Joanne S. Haviland [d], John R. Yarnold [a,e], Anna M. Kirby [a]

[a] Department of Academic Radiotherapy, Royal Marsden NHS Foundation Trust; [b] Joint Department of Physics, Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Sutton; [c] Centre for Vision, Speech and Signal Processing, Faculty of Engineering and Physical Sciences, University of Surrey, Guildford; [d] Clinical Trials and Statistics Unit (ICR-CTSU); and [e] Division of Radiotherapy and Imaging, Institute of Cancer Research, Sutton, UK

HeartSpare

HeartSpare II: Multi-centre non-randomised evaluating implementation of VBH
10 UK centres, n=101

Is VBH in other people's hands still heart-sparing & reproducible?

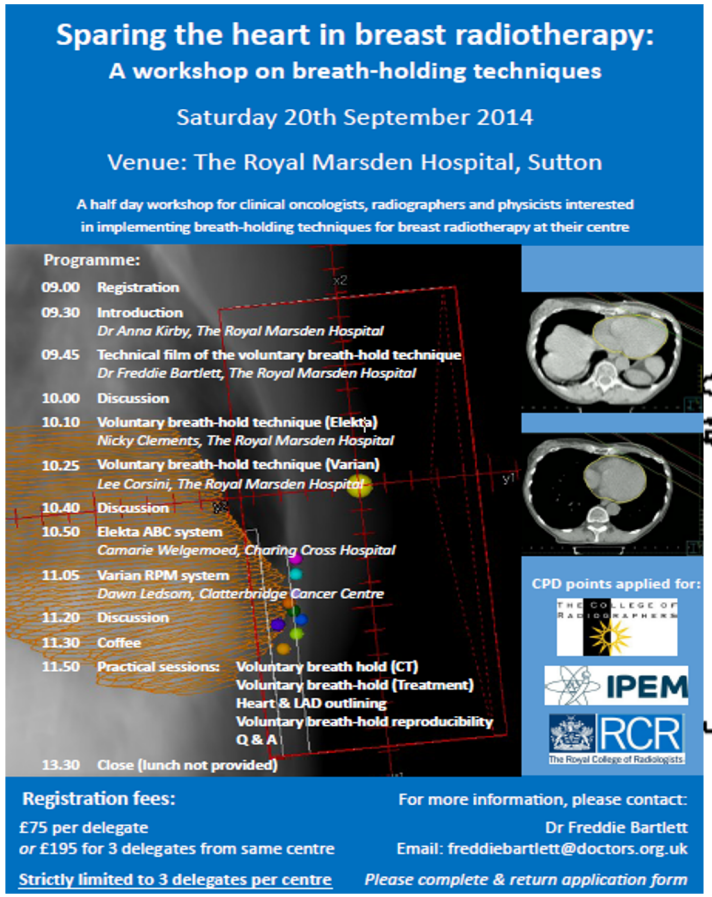


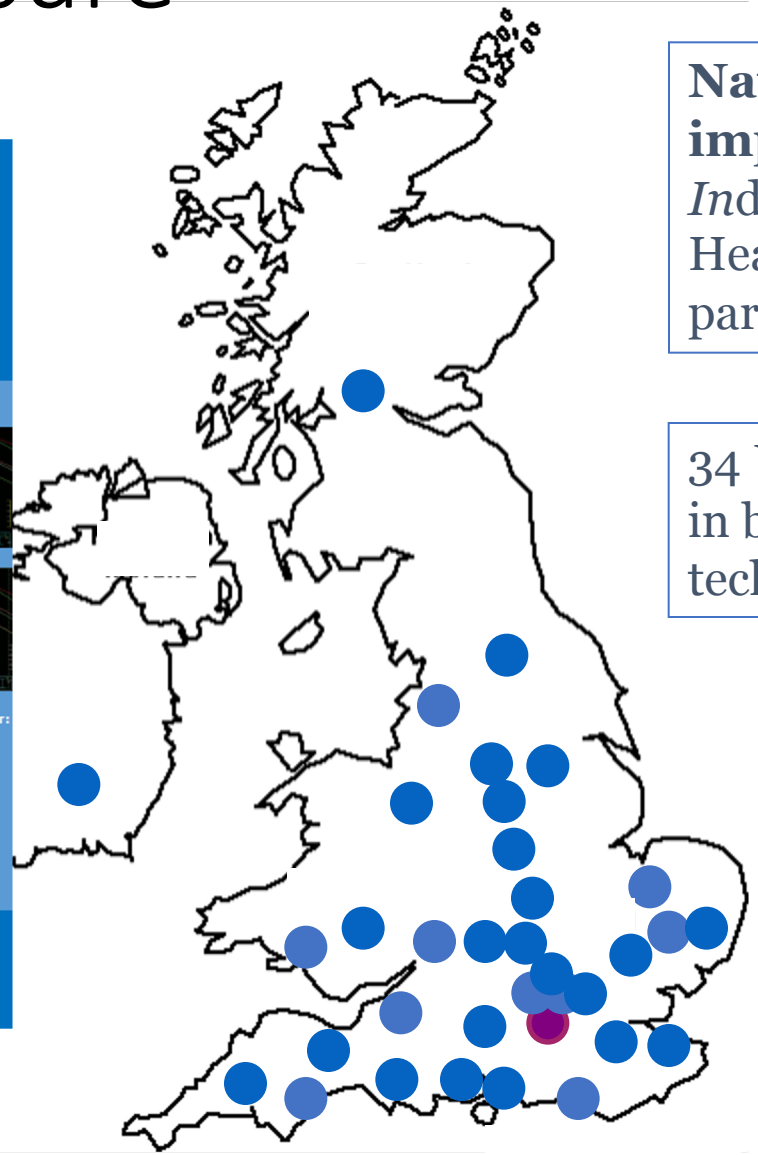
Aim:
To increase UK use of heart-sparing breast RT through trial participation

Outcome: 10/10 HeartSpare II centres implemented VBH into routine practice

Bartlett et al, Clin Onc 2017

Beyond HeartSpare





National implementation:
*In*direct effect of HeartSpare II on participating centres

34 UK centres trained in breath-holding techniques

Clinical Oncology
The Royal College of Radiologists

UK consensus statements

Cardiac sparing

UK standard of care

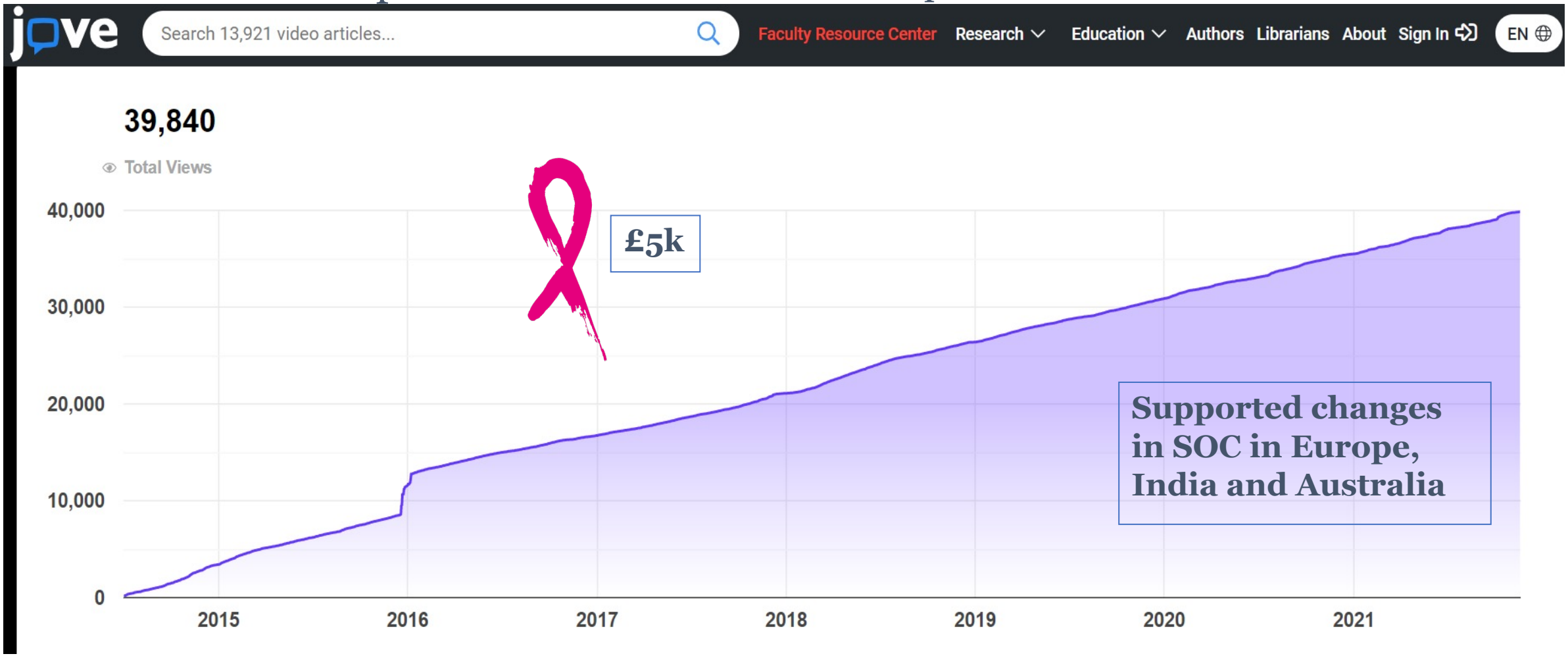
Cardiac-sparing radiotherapy should be considered the standard of care for patients with left-sided breast cancer.

- The heart should routinely be excluded from the radiotherapy field.
- All UK radiotherapy departments should have a breath-hold technique available.
- A target mean heart dose would help departments to implement breath-hold.
- In left-breast-affected patients undergoing radiotherapy not including the internal mammary chain (IMC), >90% of patients should be treated to a mean heart dose of <2 Gray (Gy).

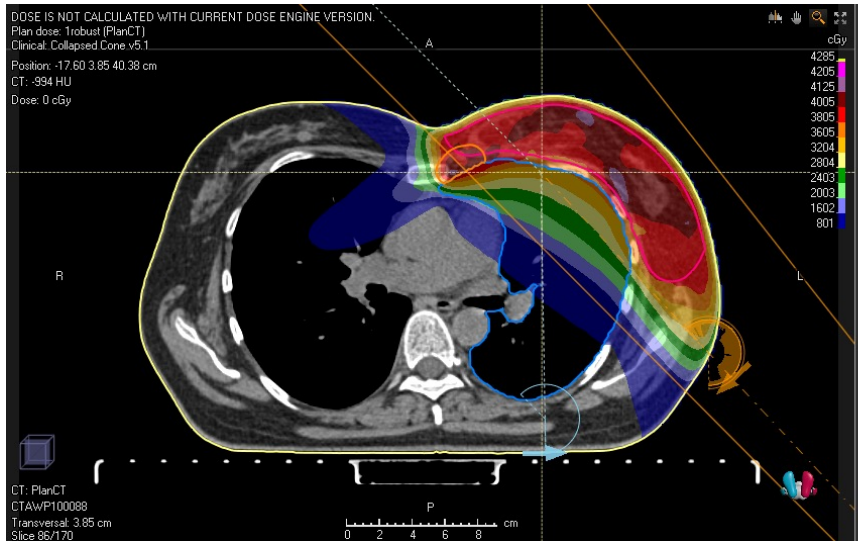
Cardiac sparing from zero to UK SOC
Cost: £250k
Time: 5 years

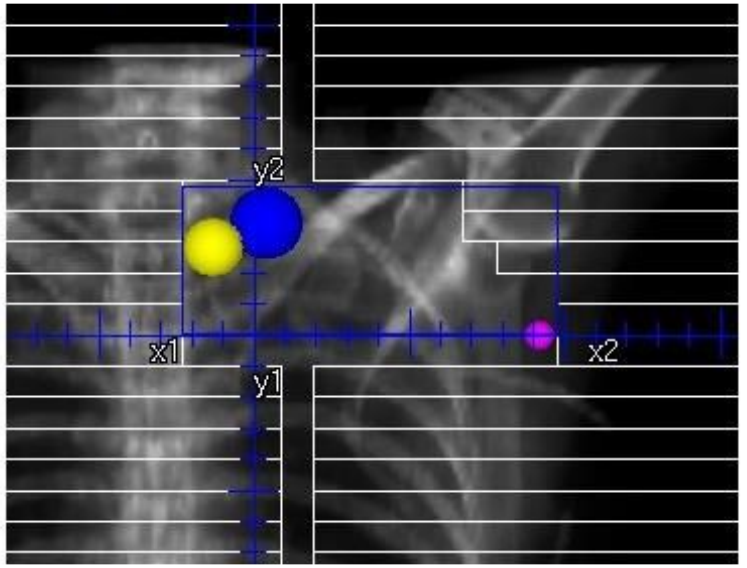
Beyond HeartSpare

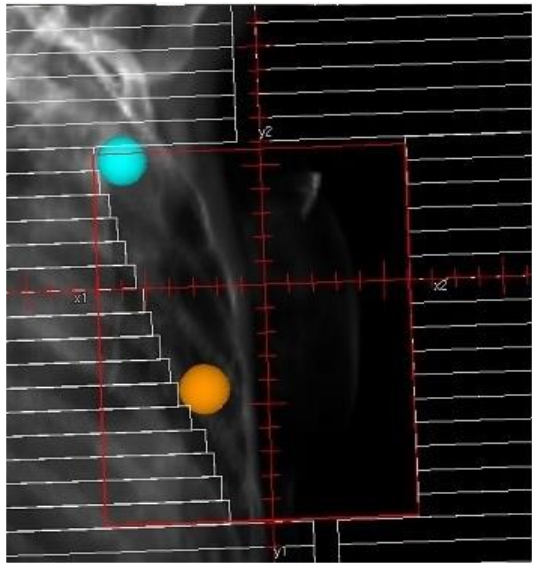
- Video publication: Journal of Visual Experimentation

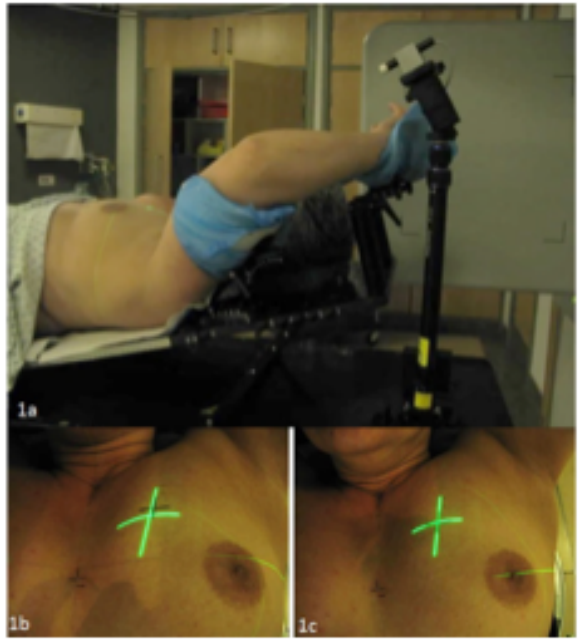


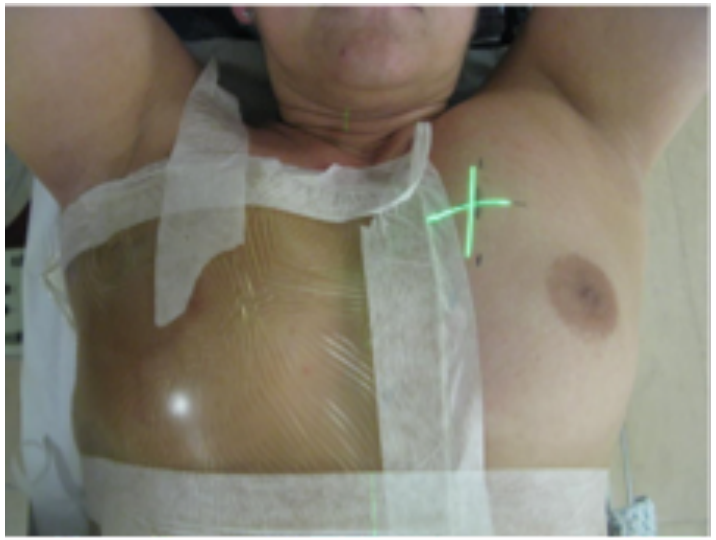
HeartSpare Plus











HeartSpare Plus
£135k
VMAT and BH
Dosimetry & treatment studies
VMAT implemented
Contouring shortcut
3rd laser

Local practice improved but what about national practice?

National training

The UK Breast Radiotherapy Trials Journey…

Cambridge Cancer Centre
UNIVERSITY OF CAMBRIDGE · Cambridge University Hospitals NHS Foundation Trust · CANCER RESEARCH UK
ICR The Institute of Cancer Research

Whole breast

50Gy - 2Gy in 25Fr over 5 weeks

Dose level variable in UK clinical practice

Hypofractionation

1990s	2004	2011
START A&B	FAST	FAST-Forward
>2Gy fractions	5Fr/1 week	5Fr/1week
(N=4451)	Vs. 50Gy/25Fr (N=915)	Vs. 40Gy/15Fr (N=4110)

Intensity modulated / risk adapted RT

2007	2009	2017
IMPORT Low	IMPORT High	PRIMETIME
Partial breast	Partial breast	RT avoidance
Low risk of recurrence	Higher risk of recurrence	very low risk of recurrence
(N=2018)	(N=2621)	(Recruiting N=1550)

Heart-Sparing Breast RT

HeartSpare-I	HeartSpare-II	HeartSpare-Plus
(N=23)	(N=101)	(N=37)

Future generation of breast RT trials

2019-2020s

FAST-Forward / IMPORT High
5-year analyses

HYPORT-Adjuvant
5Fr/1week
simultaneous integrated boost
(Recruiting N=2100)

PARABLE application
Hypofractionated proton RT
Heart dose reduction

Technology enabled

Efficient delivery

Rapid global recruitment

Fast adoption in practice

ICR-CTSU Scientific Lead: J Bliss

Chief Investigators: J Yarnold (START, FAST), C Coles (IMPORT, PRIMETIME, PARABLE), M Brunt (FAST-Forward) and S Chatterjee (HYPORT-Adjuvant) A M Kirby (HeartSpare Studies)

The Christie
Oncologists
Physicists Radiographers

ICR The Institute of Cancer Research
CTU, Trials methodologists

UCLH NHS
Oncologists
Physicists Radiographers

UNIVERSITY OF OXFORD
Health Economists
Epidemiologists
Cardiologists

Breast
Radiotherapy
Clinical Trials

PATIENTS

The ROYAL MARSDEN NHS Foundation Trust
Radiobiologists
Technical expertise

QUEEN'S UNIVERSITY BELFAST
Radiobiologists
Technical expertise

RTTQA
Radiotherapy Trials Quality Assurance


International partner for meta-analysis


Technical expertise in Breast PBT


International partner for NTCP modelling development

TEAM SCIENCE: Multidisciplinary UK Team

International Research Partners

Phase III multi-centre randomised controlled trial with internal pilot

PARABLE

- UK trial PARABLE: Proton beAm theRApy in patients with Breast cancer: evaluating early and Late-Effects
- Inclusion criteria: Estimated lifetime risk of radiation-induced late cardiac toxicity ≥2%* Calculated from tables of mean heart dose, age &cardiovascular risk factors
- **1:1 randomization to optimal photon RT versus proton beam therapy 40Gy/15#**
- **Research question:** Compared with standard photon RT for women with breast cancer, does PBT reduce mean heart dose (a predictor of serious heart toxicity many years later) without increasing shorter-term side effects?

5-years from concept to funding
Cost: £1.4 million (NIHR funded)
Primary analysis due 2026

Parallel aims
To increase uptake of IMC RT across UK
To implement breath-hold and arc therapy across UK

Joint Leads: Coles C, Kirby AM, Haviland J

Innovation in action: take home messages

- Impact is not proportional to investment
- You can do a lot with a little
  - Leverage investment
  - Build on collaborations
- Clinical trials in themselves are not enough to change practice
  - But they can be used to introduce technology safely and effectively
- Virtual learning has huge potential to increase impact
- Integration with national evidence-based and consensus guidelines and commissioning is critical to implementation

What is considered innovation in 21st century radiotherapy?

- Identify the problems that really need solving
  - Patients at the heart
  - “The better the question, the better the answer, the better the world works”*
- Find the most fruitful and efficient pathway for solving them
- Keep reading, thinking & talking
- Pay attention to implementation

For instance, on the planet Earth, man had always assumed that he was more intelligent than dolphins because he had achieved so much — the wheel, New York, wars and so on — whilst all the dolphins had ever done was muck about in the water having a good time. But conversely, the dolphins had always believed that they were far more intelligent than man — for precisely the same reasons.

Douglas Adams, The Hitchhiker’s Guide to the Galaxy