

Rapid Review of Radiotherapy and Associated Radiobiology 2008



NCRI

National
Cancer
Research
Institute



National Cancer Research Institute
**Rapid Review of Radiotherapy
and Associated Radiobiology
2008**

Contents

Executive Summary	2
1. Introduction	3
1.1 Background	3
1.2 Need for a further review	3
1.3 NHS environment	3
1.4 Scientific opportunities	3
2. Discussion of opportunities, barriers and possible solutions	5
2.1 Radiobiological research underpinning advances in radiotherapy	5
2.2 Experimental radiotherapy	5
2.3 Phase III trials in radiotherapy	6
2.4 Current and future leadership	7
2.5 Training and career structures	7
3. Action Plan	8
3.1 Identify a national champion and remodel the NCRI Radiotherapy Clinical Studies Group (CSG) with a wider remit	8
3.2 Physics and radiography support for trials	9
3.3 Trial methodology	10
3.4 Patterns of radiotherapy care and late effects	10
3.5 Clinical fellowships	10
3.6 Training for research radiographers	10
3.7 Engagement with industry	10
3.8 Support for Chief Investigators	11
3.9 Implementation of new technologies and their use	11
3.10 Support for radiobiology	11
Appendix A: Participants in the NCRI Rapid Review meeting held on 28 April 2008	12
Appendix B: Glossary of Terms and Acronyms	13

Executive Summary

A group of research funders and experts met in April 2008 to consider and update the actions which had been undertaken as a result of NCRI's first review of radiotherapy and associated radiobiology in 2003. A 10-point action plan has been agreed by the NCRI Board and implementation has begun in the autumn of 2008:

1. National leadership will be provided through a senior clinical oncologist with dedicated time and scientific support, working through a new multi-workstream Clinical and Translational Radiotherapy Research Working Group which he will chair. The first national leader will be Professor Tim Maughan, Professor of Cancer Studies at Cardiff University. The work of this group will be broad-ranging in scope and ambitious in intent. The expertise and resources hereby created will provide direction and impetus to all other actions in this plan.
2. Steps will be taken to break down barriers to access to funds for physics and radiotherapy support for radiotherapy trials within the NHS, and where necessary to provide additional resources.
3. The Medical Research Council (MRC) will organise a workshop on research methodology for the evaluation of new radiotherapeutic techniques.
4. The National Cancer Intelligence Network (NCIN) will undertake a study of patterns of radiotherapy practice, and how these impact on outcomes in terms of both survival and late effects of radiotherapy treatment.
5. Cancer Research UK, the MRC and the Royal College of Radiologists will review resources and incentives for academic career development in radiation oncology, and take steps accordingly.
6. The Society and College of Radiographers, the National Cancer Research Network (NCRN) and UK Clinical Research Network (UKCRN) will work together to develop new training and career development resources for radiographers.
7. Greater engagement of the pharmaceutical industry in the opportunities for combined drug and radiotherapy trials will be promoted.
8. Resources to provide incentives for NHS-employed clinical oncologists to engage in research will be reviewed, and new actions initiated where necessary.
9. The national leader and the Working Group will work with NHS service providers to ensure a timely and evidence-based approach to the implementation of new radiotherapy technologies for the benefit of patients.
10. Following the last review, Cancer Research UK and MRC have recently invested heavily in radiation oncology and biology research, specifically by establishing a new Institute in Oxford. They will continue to explore opportunities to support excellent research in this important area.

Progress will be actively monitored by the NCRI Board and progress reports published on the NCRI website.

1. Introduction

1.1 Background

In 2003 a report was published by NCRI detailing the barriers and opportunities for radiation-associated research in the UK. The report resulted in a number of actions, the most substantial of which was the establishment of the Gray Institute for Radiation Oncology and Biology (ROB) in Oxford, jointly funded by Cancer Research UK and MRC.

Other actions from the report included Cancer Research UK and MRC each funding clinical training fellowships jointly with the Royal College of Radiologists (RCR) (a total of 8 to date). The Academic Clinical Oncology and Radiobiology Research Network (ACORRN) was also established to encourage grass-roots connections to be made in the community to promote research.

1.2 Need for a further review

NCRI Partners acknowledge that whilst there has been good progress in some areas, it has been slow in others. The convergence of the completion of funding for ACORRN and the review of the NCRI Radiotherapy Clinical Studies Group prompted the NCRI Board to instigate a brief but penetrating examination of how the field has developed in the 5 years since the 2003 report, and to identify priorities for the next phase of development.

Consulting with a small group of representatives and experts, the research funders sought to further understand the reasons for the slow progress in some areas, with a view to devising an action plan to engender change in key areas. They then met privately to consider options for action.

1.3 NHS environment

Capacity for radiotherapy in the NHS has been growing, though is not yet sufficient to fully meet demand. The 2007 Cancer Reform Strategy for England announced the intention to almost double the number of fractions delivered per million patients by 2016 and to provide more staff. It is hoped that this will enable timely radiotherapy treatment for all who need it, without interruptions or constraints on the dose-fractionation prescribed. Applying current knowledge should improve cure rates. In addition, this increase in capacity along with new structures to support clinical research provides an opportunity to increase research activity in radiotherapy, and to create a stronger trials portfolio.

1.4 Scientific opportunities

All present at the review agreed that the chances of achieving a cure through radiotherapy are now greater than ever, due largely to techniques such as image-guided radiotherapy (IGRT) and intensity-modulated radiotherapy (IMRT), which target the radiation more effectively to the tumour and thus reduce damage to healthy tissue. These techniques need further in-depth evaluation in tumour-specific studies. Other areas with potential include:

- Finding the most effective combinations of radiotherapy and chemotherapy
- The development of agents to protect normal cells from radiation and/or to sensitise tumour cells
- Uncovering the genetic basis of how patients respond to radiotherapy, enabling more personalised treatment programmes
- Next generation techniques, such as proton therapy

The invited experts spoke of a field where research opportunities are increasing due to technological advancements and better understanding of the biological response to

radiation. However it was also clear that there are a number of barriers particular to radiation-associated research that are hindering the progress of this field in the UK.

2. Discussion of opportunities, barriers and possible solutions

2.1 Radiobiological research underpinning advances in radiotherapy

Prof Gillies McKenna reported that, three years after his appointment, the Oxford Radiation Oncology and Biology Institute comprising 17 independent research groups is now fully operational. The Institute has initiated a doctoral training programme currently with 9 DPhil students and 3 clinical fellows. In the longer term it is expected that ROB will provide academic leaders of the future, particularly in clinically relevant radiobiological research though it could take up to ten years for this rejuvenation to be felt outside Oxford.

Whilst the Oxford initiative was welcomed, there are dangers in concentrating all expertise in one location; young talent may leave the country in search of further career opportunities. It was agreed that one institute, no matter how well funded, could not cover the full spectrum of research nor could it be considered to constitute the critical mass needed for a field to flourish on a national level. A small number of additional centres may be needed in addition, ideally with collaborative links to Oxford. Professor McKenna said he would welcome this.

2.2 Experimental radiotherapy

It was agreed that there is scope for advancing radiotherapy by boosting the number of Phase I / II trials. Trials are needed to determine how radiotherapy should best be combined with new chemotherapy agents, while the advanced radiotherapy techniques need to be evaluated for new indications. There is also the prospect

of using biological agents to either increase the sensitivity of tumour cells or protect normal cells from radiation.

In 2007 a network of 19 Experimental Cancer Medicine Centres (ECMCs) was established, jointly funded by Cancer Research UK and the government Health Departments. Centres are provided with infrastructure posts to support Phase I / II trials. At present, the network has very limited activity in radiotherapy - none of the centre leads is a clinical oncologist and radiotherapy trials account for less than 2% of the total portfolio.

It was agreed that the ECMC network is the most suitable avenue through which to promote Phase I / II radiotherapy trials but that given the current low levels of activity, additional funding and/or other incentives will be needed to encourage centres to pursue this direction. Suggested incentives included having a network target for number of radiotherapy trials, or awarding additional credit for recruitment into radiotherapy trials. To increase trial activity, additional funding is likely to be required for specialist staff such as physicists and radiographers. It was agreed that if such additional funding were to be provided this resource should be concentrated in a small number of centres most likely to deliver. It was also thought that participating centres would benefit from having a locally appointed clinical oncology lead.

In the UK, current engagement with industry focuses mostly around drug therapy and it is likely that opportunities for combining radiotherapy and chemotherapy are being missed. It was proposed that NCRN and ECMCs should include radiotherapy in their discussions with industry.

2.3 Phase III trials in radiotherapy

Obtaining funding for high quality trials does not seem to be an issue and some world-class studies have been completed. Despite these signs of progress, there remain concerns about the ability to recruit to multi-centre radiotherapy trials.

Several radiotherapy trials have recently terminated early due to difficulties in trial recruitment (e.g. INCH, SOCCAR). Radiotherapy in a trial setting will nearly always be more resource-intensive than treatment outside a trial. It was reported that centres are having difficulty finding the additional per-patient resources required for planning and quality assurance, particularly for trials involving complex radiotherapy (IGRT, IMRT) or hyperfractionation. There is some confusion as to whether these costs should be met by the research funder, or if they should be considered as treatment costs and met by the Trust, or are service support costs to be met from funds distributed through the Comprehensive Local Research Networks (CLRNs). Dr Helen Campbell (DH) reported that in England it had recently been agreed that QA needed specifically for trials (as opposed to the routine QA that would continue when the newly proven treatment is introduced into service) should be regarded as a service support cost. This still left a question over how radiotherapy planning should be resourced. In principle this should be a treatment cost and this would imply a need for increased tariffs for techniques that require more planning time. Those engaged in such work thought the distinction between planning and QA was artificial, but welcomed the fact that a decision on funding the latter has been made.

In addition to the per-patient planning and

QA cost, there is a significant start-up cost for each centre entering a trial (e.g. REC approval, training of staff, new software, standardisation of treatment protocols). These costs may not be included in the trial funding, or be available from any NHS funding stream. Finding the resources for this start-up phase can delay the ability to enter patients into trials by months, resulting in a 'holding pattern' of radiotherapy trials that are 'active' in multiple centres but not actually recruiting. It was agreed that this funding issue will need to be solved if trials are to meet their recruitment targets.

At present tariffs for radiotherapy treatment do not increase when more resource-intensive techniques are used. It was argued that this will need to change for new advances to be adopted across the NHS. Concern was also expressed that the degree of disparity in the UK in how radiotherapy is delivered makes it very difficult to deliver the standardised care needed for trial participation. It was thought that the National Cancer Intelligence Network (NCIN) could be asked to consider the feasibility of a study in the patterns of radiotherapy care in the UK and how these relate to outcomes and the late effects of treatment.

Participants reported that in the rest of the world advanced radiotherapy techniques are implemented with a limited base of evidence for safety or efficacy, with the rationale that the benefits of some advances are a step-change that do not need to be tested in a randomised controlled trial (RCT). The danger in insisting on the rigour of an RCT which takes a number of years to deliver a result, is that implementation proceeds by a process of 'creep' with very little evidence at all. This dilemma is not particular to radiotherapy, as similar questions are being asked about imaging techniques and other aspects of healthcare delivery. It was suggested

that some guidance needs to be developed to help investigators determine when an RCT is warranted or when an observational study would be more appropriate.

2.4 Current and future leadership

Participants thought that the field would benefit from a champion within the radiation oncology community, with a remit to promote radiation associated research. Such an individual would need to be of sufficient stature to command respect from the research funders as well as his peers. The recent review of the NCRI Radiotherapy Clinical Studies Group (CSG) recommended that it should be remodelled to take a more active role in trial development and also to identify and nurture young investigators. To achieve this it would be necessary for the new group to have a wider role and remit than the CSG has had. It is likely that this would require more than the usual time commitment from the Chair, and careful consideration would need to be given to this appointment.

2.5 Training and career structures

As was highlighted in the original NCRI report, training remains an issue for all the professions involved in radiation associated research. For clinical oncologists there are concerns that research activity is not given sufficient training credit by the Royal College of Radiologists. This is seen as a major deterrent to the pursuit of an academic career that needs to be changed to encourage young doctors to consider an academic career.

This long-standing lack of incentives to pursue a career in academia has resulted in cohorts of capable clinical oncologists being lost to research. It was suggested that efforts should

be made to help this 'lost generation' to engage in research from their positions in the NHS.

Whilst there have been increases in the number of clinical training fellowships awarded, there are questions about the impact that these have had. Participants were unclear how many of the joint RCR / Cancer Research UK / MRC fellowships had been in clinical oncology and how many were in radiology and there is no knowledge of whether past fellows have progressed with a career in research. More information is needed on how National Institute for Health Research (NIHR) training awards fit in to the national picture. Without this knowledge participants could not judge if there is a need for more fellowships.

Training issues are not confined to clinical oncologists. There are only approximately 70 research radiographers in the UK and there is no centrally recognised training programme for them. It was argued that radiographers knowledgeable about research are needed if trial recruitment is to gain pace. They would also have a role in protocol development and improving treatment processes for patients.

It was reported that young radiobiologists have few options in the UK for post-doctoral positions, and even less chance of getting independent funding. At present many either leave the country or change fields. This will only be addressed by supporting existing units with strength in radiobiology to develop further.

3. Action Plan

3.1 Identify a National Champion and remodel the NCRI Radiotherapy Clinical Studies Group (CSG) with a wider remit

The need

Leadership and coordination across all aspects of radiotherapy research.

Action

A new NCRI Clinical and Translational Radiotherapy Research Working Group is being established to continue and expand the work of the former Radiotherapy Clinical Studies Group (CSG). It will have a broader, more strategic remit which will draw on a wider range of expertise than the CSG, all with the aim of developing a more ambitious portfolio of practice-changing trials. It will oversee the pursuit of the remaining points in this action plan and will take responsibility for issues that cut across workstreams, for example training and career development. It will also be responsible for ensuring coordination across all aspects of radiobiology and radiotherapy and for actively promoting the translation of new discoveries into practice. The new Working Group will develop 4 workstreams:

Workstream 1: Science base

This workstream will

- Monitor developments in the relevant basic science disciplines including radiobiology, DNA repair, microenvironment and imaging.
- Encourage further collaborative working in these areas between UK institutions.
- Feed in relevant developments to workstreams 2 and 3 to enhance trial development and improve translational studies within those trials.

This activity will subsume the current role of the translational sub-group of the Radiotherapy CSG in terms of the bedside to bench studies, and developing studies such as the currently funded RAPPER study (Radiogenomics: assessment of polymorphisms for predicting the effects of radiotherapy).

Workstream 2: Phase I / II trials

This workstream will

- Identify new chemotherapeutic agents which should be given priority for evaluation in conjunction with radiotherapy and the development of early phase studies of these combinations.
- Lead on non-invasive imaging for tumour assessment and monitoring of treatment effect in these and subsequent larger scale studies.
- Assist in the design of phase I/II trials for pure radiotherapy studies.

The group will have cross membership with relevant tumour-specific CSGs for specific disease site protocols. These activities will require linkage with pharmaceutical companies, ECMCs which have an interest in radiotherapy, the Cancer Research UK / EPSRC, with additional support from MRC and Department of Health (England), Cancer Imaging Centres and the NCRI PET Research Initiative. Specific issues will include development of guidelines on the required pre-clinical and clinical package for new drug-RT combination studies and optimal methodologies for phase 1 and 2 studies of combinations with radiotherapy.

Workstream 3: Phase III trials

This workstream will

- Synthesise information from the three other workstreams to review where the most promising new ideas may be coming from, in radiobiology, new agents,

imaging and physics/technology.

- Engage with proposals for radiotherapy trials from tumour specific CSGs to help optimise radiotherapy related aspects of the trial.
- Take the lead in methodological development in radiotherapy trials in conjunction with an MRC-funded methodology hub.

This workstream will also have cross-membership with tumour-specific CSGs, who will continue to assess priorities and develop trials in their own areas. Tumour-specific groups will then consider the implications and applicability of the radiotherapy developments in their own areas. One issue that requires consideration is when RCTs are needed for evaluation of technological development and when more pragmatic approaches could be taken.

Workstream 4: New technology, Physics and Quality Assurance

This workstream will

- Encompass the current quality assurance in radiotherapy trials activity.
- Horizon scan for new developments in physics and radiotherapy technologies and, as appropriate, promote their evaluation and inclusion in clinical trials.
- Provide the reference group for developing the case for enhancing the infrastructure for radiotherapy research, together with the overarching working group, led by the Chair and programme manager.

The work programme will be complex in the variety of activities that need integration and the wide range of stakeholders whose interests must be considered. In the first instance the new Working Group will be chaired by Professor Tim Maughan, Professor of Cancer

Studies, and Director of the Wales Cancer Trials Unit in Cardiff. Professor Maughan will devote one day per week to this role for a period of 18 months and will be supported by a full-time research manager. Professor Maughan has agreed to take on this key leadership role on an interim basis, pending the conduct of a fully open process for appointment of a permanent chair, and so that the new structures can be set up without delay.

3.2 Physics and radiography support for trials

The need

Trials are being developed and funded but there tends to be a blockage at the initiation stage due to a lack of NHS infrastructure at the trial centres. The need for physics support is particularly acute, whilst research radiographers are also needed to inform patients and obtain consent.

Action

Mechanisms for the provision of NHS infrastructure for trials are already in place in each of the four countries in the UK. However, there is a lack of clarity as to exactly how the costs of radiotherapy trials should be attributed to direct research costs (met by the research funder), treatment costs (provided as part of cancer services) and service support costs (provided as part of NHS R&D). There is a need for a detailed analysis of needs, the availability of funding streams, and blockages in access to them. This will include identification of key trial centres where access to additional resources will have the greatest impact on trial recruitment. This analysis will be undertaken by the new research manager, under the direction of Professor Maughan and in consultation with relevant professionals and

the Government Health Departments. Solutions will be devised and implemented. Success will be judged primarily on the level of recruitment of patients to all phases of radiotherapy trials

3.3 Trial methodology

The need

Guidance is needed on methodologies for the evaluation of new radiotherapeutic technologies. This need is not confined to radiotherapy, so a solution could have much wider applicability. While RCTs remain the gold standard for scientific rigour, more pragmatic approaches ('evaluate as you implement') are needed where there is a danger of implementation occurring before evidence has been obtained, for example due to patient demand or political pressure.

Action

The Medical Research Council have agreed to organise a workshop to develop a guidance framework and identify methodological development needs.

3.4 Patterns of radiotherapy care and late effects

The need

To understand how variations in radiotherapy practice impact on clinical outcomes in terms of both survival and late effects of the radiotherapy treatment. This will be with a view to identifying best practice and improving radiotherapy standards.

Action

The National Cancer Intelligence Network (NCIN) has agreed to consider the feasibility of a study based on data across England in the first place. This will be included in their workplan

for 2009/10 and funded from existing NHS resources.

3.5 Clinical fellowships

The need

Incentives to develop a career in academic clinical oncology.

Action

Cancer Research UK, MRC and the Royal College of Radiologists will meet to review the joint fellowship scheme against the background of other training opportunities such as NIHR fellowships, and consider the scope for expanding or extending the current scheme. The RCR should consider whether greater credit should be given for periods of oncology research. The research manager to be appointed will facilitate such a meeting in the first instance.

3.6 Training for research radiographers

The need

More radiographers need to be trained in research.

Action

The Society and College of Radiographers, NCRN and UKCRN will work together to develop the new training and career development resources needed.

3.7 Engagement with industry

The need

Greater engagement of the pharmaceutical industry in the opportunities for combined drug and radiotherapy trials.

Action

It will be part of the role of the Clinical and Translational Radiotherapy Research Working Group to ensure such engagement through active involvement of industry in their work.

3.8 Support for Chief Investigators

The need

To provide incentives for NHS-employed clinical oncologists in particular to engage in research.

Action

Some schemes already exist, for example within the National Institute of Health Research (NIHR) in England. More analysis is needed on how far this problem requires new resource or the unblocking of existing resource. This will be another task for the research manager.

3.9 Implementation of new technologies and their use

The need

Research will only have an impact if the outcomes can be implemented. For technologies like IGRT and IMRT, the infrastructure needs for physics (planning and QA) and radiography (highlighted in 3.2 above) will carry through into practice.

Action

Representatives of service providers will be involved in relevant workstreams of the NCRI Clinical and Translational Radiotherapy Research Working Group, to ensure that this aspect of translation is taken forward in all countries of the UK.

3.10 Support for radiobiology

The need

A critical mass of radiobiology research related to radiotherapy in the UK. The Gray Institute for Radiation Oncology and Biology in Oxford has already gone some way to providing a solution. On its own, it may not be able to provide the entire national need.

Action

Cancer Research UK and MRC will consider this further in the first instance, facilitated by the NCRI Secretariat.

Appendix A: Participants in the NCRI Rapid Review meeting held on 28 April 2008

Chair

***Professor Mike Richards CBE**, National Cancer Director for England

Invited experts

Julie Davies, Christie Hospital Manchester
Professor Peter Hoskin, Chair, Radiotherapy Clinical Studies Group (CSG)

Professor Gillies McKenna, Director, Radiation Oncology & Biology Unit, Oxford
***Professor Tim Maughan**, Velindre Hospital Cardiff

Dr Philip Mayles, Clatterbridge Centre for Oncology

Professor Chris Nutting, Institute of Cancer Research

Dr Catharine West, University of Manchester

Dr Michael Williams, Royal College of Radiologists

Professor John Yarnold, Institute of Cancer Research

Funders

- ***Dr Roma Armstrong**, Scottish Executive
- ***Dr Helen Campbell**, Department of Health
- ***Dr Karen Finney**, Medical Research Council
- ***Dr Frances Rawle**, Medical Research Council
- ***Dr Mags Sara**, Cancer Research UK
- ***Dr David Scott**, Cancer Research UK

NCRI

- ***Dr Jane Cope**
- ***Dr Aoife Regan**

All participants were present for the general discussion. Those marked * were also present for formulation of the action plan.

Invited but unable to attend

- Professor Sir Kenneth Calman** (NCRI Chair)
- Professor David Cameron** (NCRN)
- Dr David Grant** (Leukaemia Research Fund)

Appendix B: Glossary of Terms and Acronyms

ACORRN	Academic Clinical Oncology and Radiobiology Research Network
CLRNs	Comprehensive Local Research Networks
CSG	Clinical Studies Groups
DH	Department of Health
ECMCs	Experimental Cancer Medicine Centres
IGRT	Image-Guided Radiotherapy
IMRT	Intensity Modulated Radiation Therapy
MRC	Medical Research Council
NCIN	National Cancer Intelligence Network
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NHS	National Health Service
NIHR	National Institute for Health Research
PET	Positron Emission Tomography
QA	Quality Assurance
RCR	Royal College of Radiologists
RCT	Randomized Controlled Trial
REC	Research Ethics Committee
ROB	Gray Institute for Radiation Oncology and Biology, Oxford
UKCRN	UK Clinical Research Network

NCRI Partners:



Visit us at
www.ncri.org.uk

National Cancer Research Institute

61 Lincoln's Inn Fields

P O Box 123

London WC2A 3PX

tel: +44 (0)20 7061 8460

fax: +44 (0)20 7061 8461

web: www.ncri.org.uk

email: info@ncri.org.uk