National Cancer Research Institute

REPORT OF THE RADIOTHERAPY AND RELATED RADIOBIOLOGY PROGRESS REVIEW GROUP

January 2003

TABLE OF CONTENTS

EXECUTIVE SUMMARY

1. The NCRI secretariat was asked to set up a review with the following remit:

- To review the current state of radiotherapy/radiobiology (RT/RB) research in the UK.
- To identify: UK's strengths and weaknesses; scientific opportunities for the UK; barriers to progress; recommendations for overcoming these barriers.
- To identify: what research evidence is required to underpin the advancement of services in the UK.
- To report to the NCRI Board.

2. The review was designed to cover all clinical radiotherapy research plus underpinning medical physics research and underpinning radiobiology research that was directly relevant to clinical application. The review was not designed to include very basic radiobiology, unrelated to cancer therapy such as certain aspects of DNA damage/ repair, carcinogenesis, radiation chemistry etc, nor radiobiology underpinning other fields.

3. A review process built around the Progress Review Group (PRG) model used by the NIH NCI was developed. This was the first such review carried out by the NCRI and the process was designed to act as a pilot exercise for PRG methodology. The PRG process was carried out in three stages: an initial meeting, a questionnaire survey and a larger Roundtable discussion.

4. The PRG and Roundtable discussion groups identified important therapeutic research opportunities for RT/RB in the fields of molecular radiosensitivity; predictive testing; radiosensitisation; imaging; applied physics; targeting of systemic isotopes. The dual training of UK clinical oncologists in both chemotherapy and radiotherapy creates particular potential for clinical research.

5. RT/RB research in the UK has declined over the last decade. Although important and relevant scientific questions are there, the critical mass of people active in RB is heading towards the point where it will no longer be sustainable as an academic discipline. The major clinically applied RB groups in the Gray Laboratories, the Institute of Cancer Research (ICR), and recently in Manchester, have either retired, departed or moved to other research fields. There are also few Academic (i.e. university) Radiotherapy consultant appointments in the UK, an estimate of 26 in total. Some of these appointments, especially in Scotland, are funded by the NHS and have substantial service responsibilities greatly limiting research time. This is also limited for NHS Consultants due to service pressures.

6. There is a threat that the lack of RB research will be self-perpetuating as neither academic clinicians nor scientists can enter a UK laboratory for appropriate training.

7. Funding for radiotherapy and radiobiological research in open competition with other areas of cancer research has in general not competed well. In part this may be because "classical radiobiology" was categorised as low priority by one funding body in the mid 1990s. There is a perception in the RT/RB research community that an under-representation on peer-review committees has contributed to a reduction in funding.

8. Many RT/RB groups have not collaborated with molecular biologists and clinicians developing associated therapeutic modalities. This means that the UK RT/RB research community has not been well placed to capitalise on advances in other areas of cancer research.

9. A range of modern cancer research topics have relevant applications in RT/RB. An inability to exploit these would be to the detriment of both the public and of the scientific community. These include: DNA repair; angiogenesis; apoptosis; hypoxia and other stress responses; cell cycle control; stem cell research; growth factors and receptors. At the same time there is the opportunity to gain a more sophisticated understanding of RT problems, such as cellular radiosensitivity and mechanisms of normal tissue injury.

10. RT/RB research needs to be developed as an integrated component of more broad-based biological research. This has major implications for the way funding is organised and how we train the next generation of researchers.

11. Re-growth of RT/RB research in the UK would be valuable but will require a coherent approach from key stakeholders to effect a change in the culture and profile of the subject. These include, not only the NCRI funding bodies, but also the Royal Colleges, the radiotherapy/radiobiology community itself and the wider research community. Particular issues are:

- Promoting multidisciplinary working
- Establishing critical mass and stability of funding in a number of research groups
- Major change in the approach to training in the area
- Improved communication and networking and profile within the research community

12. Multidisciplinary collaborations are key to the future of radiotherapy research in the UK. The challenge is to encourage integration while maintaining a skill base in cellular and animal models for RB.

Options for action:

- Fund high quality RT/RB research groups within existing multi-disciplinary cancer research centres
- Encourage interdisciplinary research collaborations by offering funding incentives – this could be done through partnerships between different funders (MRC/EPSRC/ BBSRC/CCLRC/ DoH, CR UK)
- Build up a small number of multidisciplinary centres of excellence alongside clinical centres, which would address the problems of critical mass and links with more basic biology, and would promote multidisciplinary and translational research
- Organise a series of cross-disciplinary research conferences/workshops that promote interdisciplinary working

13. Funding is an influential lever to attract and retain key researchers, and the funding process needs to take account of the special needs of long-term translational research. Clinical research in RT/RB has less recourse to commercial funding than chemotherapeutics. There is a need to ensure a viable network of centres with the appropriate configuration of expertise, personnel, equipment and equipment time to underpin multi-centre clinical trials.

Options for action:

- Strategic/targeted funding initiatives in key RT/RB areas
- NCI model of separate funding stream for RT/RB research with strategic leadership
- Provide core funding for a number of Centres for RT/RB Research in appropriately multi-disciplinary environments
- Coordinate joint funding between different agencies, in particular MRC/EPSRC/BBSRC/CCLRC/CRUK
- Review the representation of RT/RB on key peer-review panels
- Examine the infrastructure issues underpinning RT/RB clinical trials

14. Flexibility of clinical training in RT is an issue for the Royal College of Radiologists though additionally laboratory-based research training fellowships need funding support. Overseas fellowships for clinicians and scientists may be optimal in the short term for subjects not available in the UK.

Options for action:

- Review training and career structure for radiotherapists specified by the Royal College of Radiologists and ensure dialogue with NCRI
- Review the career structure for scientists in Radiotherapy /Radiobiology Research
- Protect research time for NHS clinicians and other research-active NHS staff such as physicists and radiographers
- Consider how to improve attractiveness of academic consultant posts in RT/RB research
- Create appropriate training environments in large multidisciplinary centres
- Extend support of core Clinical Research Fellowships to departments with training capacity
- Create a number of five-year Fellowships for laboratory research workers and of clinicians preparing to devote their careers to translational RT/RB research and consider their long term career structure

15. RT/RB communication, networking and profile would gain from strategic leadership with the responsibility to report on progress to the

NCRI. The US model within the NCI is seen as effective. This has bearing on collaboration with industry and new structures such as NTRAC, as well as on problems of applying research findings in the NHS.

Options for action:

- Explore models for providing ongoing strategic direction for the field
- Discuss dissemination and implementation of results with key stakeholders (radiotherapy community, Royal Colleges, NHS)
- Run workshops with industry to explore closer interactions (NTRAC?)
- Consider the need for establishing further networks and consortia
- Review the role of existing networks (NTRAC, NCRN, NCRI CSG)

16. The profile of RT/RB research has been raised by the PRG process and will gain further from a declared strategic prioritisation by NCRI.

Options for action:

- Organise a high profile conference on 'Radiotherapy Research in the NHS'
- Establish an initiative within the Royal College of Radiologists to promote research, perhaps building on the model developed by the Royal College of Surgeons

1. PURPOSE & ACTIVITIES OF THE PROGRESS REVIEW GROUP

1.1. Purpose and Terms of Reference of the Review

A number of NCRI member organisations had noted decrease in research activity and a dwindling cohort of senior researchers in the fields of radiotherapy and underpinning radiobiology. The issue was discussed at the NCRI Board and members agreed that advice was needed on the future direction of research in this area and identification of barriers to progress. NCRI members were particularly interested in identifying the key scientific questions facing the field in coming years. The NCRI secretariat was asked to set up a review with the following remit:

- *To review the current state of radiotherapy/radiobiology research in the UK.*
- *To identify: UK's strengths and weaknesses; scientific opportunities for the UK; barriers to progress; recommendations for overcoming these barriers.*
- *To identify: what research evidence is required to underpin the advancement of services in the UK.*
- *To report to the NCRI Board.*

1.2. Scope of the Review

The review was designed to cover all clinical radiotherapy research plus underpinning medical physics research and underpinning radiobiology research (RT-RB) that was directly relevant to clinical application. The review was not designed to include very basic radiobiology unrelated to cancer such as DNA damage/ repair, carcinogenesis or radiation chemistry etc, nor radiobiology underpinning other fields such as radiation carcinogenesis and risk assessment.

1.3. Description of the Progress Review Process

A review process built around the Progress Review Group model used by the NIH NCI was developed. This was the first such review carried out by the NCRI and the process was designed to act as a pilot exercise for PRG methodology.

The PRG process was carried out in three stages: an initial meeting of the Progress Review Group, a questionnaire survey and a larger Roundtable discussion meeting.

Initial meeting of the PRG - The NCRI invited Professor Horwich and Professor Goodhead to Co-chair the Progress Review Group. The Co-Chairs selected membership of the PRG from among prominent members of the scientific and clinical communities. Membership was chosen to represent a spectrum of expertise required to make comprehensive recommendations for the RT/RB agenda. At the PRG planning meeting on 29th April PRG members were asked to give short presentations on the range of relevant topics. This initial meeting served to map out the content, limits and scientific structure and identify membership and format of the subsequent Roundtable Meeting.

Questionnaire Survey - Before the Roundtable meeting, all invitees and all members of the NCRI Radiotherapy Clinical Studies Group were asked to fill in a questionnaire identifying: a) scientific opportunities in RT/RB research over the next ten years, b) RT/RB research evidence to have the most impact in improving services for cancer patients, c) current barriers to conducting research in the UK.

Roundtable Meeting – The Roundtable Meeting was held on 28th June. The structure of the meeting included presentations, Roundtable breakout groups and plenary sessions. The meeting was facilitated by Mr George Binney and was opened with an international perspective given by Dr Norman Coleman (Director of Radiation Research at the NCI, Bethesda) who summarised the current activities and strategic approach adopted in the US. There was further international perspective from Dr G McKenna (USA) and from Dr Jens Overgaard (Denmark).

Initially, each of the 56 Roundtable participants was assigned to one of 6 breakout groups designed to cover all of the relevant research areas. These were:

- *Cellular and Molecular Radiobiology*
- *Radiosensitisation*
- *Predictive Tests*
- *Radiation Physics and Imaging*
- *Fractionation*
- *Targeted Radiation*

Within each group, participants were provided with the results of the questionnaire survey and asked to identify the three most important

scientific questions/issues in each of the RT/RB research areas they had been assigned to.

In the second set of breakout groups, participants were assigned to different groups and asked to identify one/two key research questions addressing the Patient and Health Service need that had not been identified during the first exercise. The breakout groups were organised to cover the following stages of the 'Cancer Patient Journey'.

- *Defining the target*
- *Treatment Planning Techniques*
- *Technology of Delivering Treatment*
- *Fractionation*
- *Short-term effects (acute toxicity and symptom relief)*
- *Long-term side-effects and outcomes*

Questions from both of these breakout sessions were posted on display boards for informal discussion. Any gaps, overlaps and changes were noted. Participants were then asked to vote on what they felt were the three most important questions/issues facing radiotherapy research. The results of this voting are presented in Section 2.3. In the third breakout session, members discussed key issues relating to the organisation of RT/RB research in the UK. This was followed by a plenary discussion on this issue.

1.4. Organisation of the Report

This Report has been drafted so that all of the input received at various stages of the review process has been captured in a single document. All the input and ideas captured during the process are therefore available to be used by individuals and organisations in developing their research strategies in this area.

Section 2 of the Report is a record of the PRG Roundtable Meeting held on 28th June. Appendix A shows the results of a Questionnaire analysis addressing the most important scientific opportunities in radiotherapy/radiobiology research over the next ten years. Appendix B provides a listing of the results of a questionnaire analysis addressing the RT/RB research evidence, which would have the most impact in improving services for cancer patients. Appendix C provides a listing of a questionnaire analysis addressing the barriers (e.g. Organisational, cultural, financial, and institutional) to conducting research in these areas. Details of the Progress Review Group and all attendees are given at Appendix D.

The Co-Chairmen and members of the Progress Review Group have brought together the key themes emerging from the PRG Process in '*Section 3 – Discussion of Key Issues and Options Emerging from the Progress Review Process*'. It identifies and discusses the key scientific, health and organisational issues emerging from the Review Process and suggests a number of options for action to address the key issues.

1.5. Development of the PRG report

After the RT/RB Progress review workshop, a draft report was prepared and reviewed by the PRG members. Upon completion of the final draft, the report will be submitted to the NCRI Board for consideration.

1.6. Next Steps

The PRG Report will be presented to NCRI Member Organisations and discussed at the NCRI Board. A Board subgroup has been set up where key NCRI Members will map out the key recommendations against current research activity identified in the NCRI Cancer Research Database, consider the options for action identified in the Report and formulate a response. Recommendations will be discussed at the NCRI Board. A follow-up meeting will bring together representatives from the NCRI Partners and the PRG to discuss this response.

2. OUTCOMES OF THE PRG ROUNDTABLE BREAKOUT GROUPS

2.1. Reports and recommendations of the Roundtable Breakout groups

2.1.1. Cellular and Molecular Radiobiology

The general aim of this field for radiotherapy is to assist optimisation of killing of tumour cells while minimising harmful effects to normal tissue of individual patients. Ultimately tumour and normal tissue response are affected by cell death. It is increasingly recognised that the molecular response to radiation is highly complex. How the molecular pathways link to cellular responses that determine key clinical end-points is fundamental to the future of this field. The interference with these processes for positive clinical benefit is clearly the major aim. It is important that this country has a group of scientists that are involved in developments in our molecular understanding of cell biology and relate them specifically to radiotherapy.

The field seeks to identify the radiation, biochemical and genetic factors responsible for tumour and normal tissue responses to radiotherapy. The responses differ because the former are highly abnormal cells with many mutations, and often a lasting predisposition to further genetic changes ('genomic instability'), while the latter are genetically "normal" cells, where polymorphisms or changes in gene expression may produce measurable variations in important biochemical activities. The techniques in this field may include standard biochemical approaches to quantify these activities, molecular biology approaches to identify abnormal genes and to manipulate genes to determine the effect of changes in function, and the use of cells, animal models or model organisms with defined mutations.

It is critical that advances in this field are related back to the clinic, to test the hypotheses developed from the laboratory, in patients, but also to use observations in the clinic to suggest areas in which laboratory research might be pursued. Models from human syndromes, transgenic animals and cell lines suggest that defective response to DNA damage and DNA repair are critical factors in rendering individuals susceptible to normal tissue radiation injury. The key factors, that are involved in determining tumour responses to radiation, are much less clear, in part because of the greater genetic complexity of the changes in tumours compared to normal tissues. However, it is known that radiosensitivity can be increased by interventions aimed at modifying repair of radiation DNA damage via relevant genes and proteins.

Opportunities exist to: a) dissect repair and response pathways in order to identify and characterise all the proteins involved, and the genes encoding these proteins and identify those components most involved in radiosensitivity, b) investigate the effects of inhibiting the level and activity of these proteins, c) investigate clinical correlations of naturally occurring mutations and polymorphisms in these genes and investigate the biochemical activity of gene products with normal tissue reactions, d) use of available animal models to test the role of molecular intervention in clinical radiosensitivity and where one or more factors can be manipulated to determine the effect of radiosensitivity, e) use of tissue culture models to investigate cell and organ specificity of repair pathways. These opportunities should lead to better understanding of the cytotoxic effects of radiation to tumours relative to normal tissue and to identifying possible molecular interventions for enhanced radiosensitivity of tumours or radioprotection of normal tissue. They should also assist in adapting treatment to individual patients.

Over the past decade much research has been directed towards defining sub-cellular and biochemical events occurring after irradiation. Much of this work has relied on *in vitro* model systems in which cells are considered as autonomous units, responding to damage as independent entities. However, tissues are highly integrated systems in which cell-cell interactions play major functional roles under physiological and pathological conditions. The response of individual cells in an artificially isolated situation can be misleading in predicting *in vivo* responses and to understand cytotoxic and general tissue effects of radiation it is necessary to understand multiple response pathways at each of the cell, tissue and whole organism levels. An understanding of each level of response along with the translation of *in vitro* systems to *in vivo* and clinical studies is needed to predict adverse health outcomes following radiation exposure and to develop interventions to ameliorate or prevent injury to normal tissue or enhance toxicity in tumours. To address experimentally the complexity of cell-cell communication and cell-

microenvironment interactions it is necessary to employ new and existing *in vivo* experimental models, develop new *in vitro* models and approaches and/or adapt models that are used to study other types of tissue injury. The use of mouse strains, or other animal models, that have genetically determined differences in radiation responses or mice genetically modified in their expression of potentially critical molecules in various pathways can be used to investigate *in situ* responses at cellular, tissue and whole organism levels. Explant culture and organ culture techniques together with co-culture models in which cells from different types of tissues and/or cells plus matrix are grown together can be used for functional and molecular analyses of tissue radiation responses that depend on cell responses, cell-cell interactions and micro-environmental factors. To delineate the inter- and intra-signalling pathways in normal and tumour cells and tissues and investigate the role of genetic factors in modifying responses will require all these various types of model systems.

Tumour cell lines routinely show different responses to radiation compared to primary cells, occasionally showing elevated radio resistance. The genetic basis underlying this difference is not well understood and yet has the potential to provide important information that could yield insight into factors influencing radiosensitivity in all cell types. Moreover, the basis underlying the response to radiation of tumour cells is of fundamental importance in drug targeting. Tumour cell lines differ from primary cells in aspects of their cell cycle control, in their proliferative status, in their ability to effect apoptosis and in some aspects of their repair mechanisms.

Major physiological differences between tumours and normal tissues stem primarily from differences in vascular properties; hypoxia is a prime characteristic distinguishing tumours from normal tissues in this context. While hypoxia has long been a target for therapeutic intervention (e.g. hypoxia-specific chemical radiosensitisers), in the last decade there have been several unequivocal demonstrations of the importance of tumour oxygenation for successful radiotherapy of common tumours, the development of diagnostic methods for hypoxia that are nearing routine clinical application, and the identification of links between hypoxia and metastatic spread. At the same time an understanding of the nature and causes of hypoxia has increased considerably (e.g. acute and chronic hypoxia), along with knowledge of a number of genes and transcription factors promoting metabolic adaptation and angiogenesis (e.g. VEGF, HIF-1). Parallel advances have been made in imaging tumour vasculature and real-time visualisation of the effects of vascular-targeted drugs; imaging pH gradients and an appreciation of the effects on drug distribution; and hypoxia-specific chemotherapeutic drugs. With this background of demonstrated clinical importance, new imaging techniques, and the opportunities for discovering new molecular targets linked to these physiological differences by gene array technologies, the time is ripe to build on this solid knowledge base to develop new treatment modalities. Illustrative opportunities include hypoxia- and radiation-targeted gene therapy as well as novel radiosensitisers (e.g. targeted by hypoxic-specific drug delivery or DNA sequence-specificity, or cyclooxygenase inhibitors).

Key Scientific Questions and Opportunities

1. **To understand and exploit the genetic and biochemical differences between tumour and normal tissues in DNA damage responses.**

- Analyse response to radiotherapy using microarray technology.
- Exploit the basic knowledge of DNA damage/repair for modulation of radiation sensitivity or prediction.
- Identify molecular targets to be used for predictive assays and therapeutic targets.

2. **To exploit the physiological differences between normal & tumour tissues and search for new causal and consequential molecular targets.**

- Investigate bystander effects and cell-to-cell interactions.
- Identify targets to alter radiation responses e.g. Small molecule repair inhibitors.
- Develop radio-protectors for normal tissue.

3. **To develop appropriate models to relate molecular and cellular events to clinical outcomes**.

- Develop experimental models, which lend themselves to simple manipulations of factors important for clinical responses.
- Improve interaction with the clinic to facilitate the identification and investigation of new predictive measures.
- Develop appropriate models to understand additional complexity of structured tissues over and above that of isolated cells.
- Predicting clinical response to radiotherapy.

2.1.2. Radiosensitisation

This field encompasses the use of drugs to increase radiation effects, including those designed for targets referred to in Section 2.1.1, based on better understanding of radiation repair, cell cycle control and hypoxia. Currently there is also clinical trial work assessing combined chemotherapy and radiation. This appears to offer the possibility of large gains in local control, survival or both, achievable with current available treatment modalities. In combined modality therapy scheduling problems are complex as chemotherapy is generally given as a series of cycles over 4-6 months whereas radiotherapy is given as consecutive daily fractions over 4-6 weeks. Thus it is important to understand the mechanisms underlying the synergistic effects of the two modalities. We need to increase our understanding of the molecular mechanisms underlying concurrent chemoradiation, in order to optimise treatment schedules, and we need to understand the underlying biology of the radiation response of tumour and normal tissue in order to develop novel approaches.

It is important to distinguish between true sensitisation approaches and other current approaches for radio-chemotherapy, which are not necessarily based on a radiosensitistion effect. Clearly many sensitisers will be pharmaceuticals and so can come under the chemo-radiation heading but this heading is often used in a simple radiation+cytotoxic drug context.

Key Scientific Questions and Opportunities

1. **How do we choose the drug to use in combination with radiation, and in which tumour?**

- Is the chemotherapy target likely to be a component of radiation response? (e.g. DNA repair inhibition, signalling, apoptosis, cell cycle etc. or elimination of hypoxic cells).
- Investigate in pre-clinical models how the chemotherapy impacts on radiation cytotoxicity.

2. **How do we optimise the combination of chemotherapy and radiotherapy for maximum therapeutic gain?**

- Select drug doses and their scheduling, and investigate whether this is being done empirically or with underlying rationale.
- Investigate tumour versus normal tissue effects.
- Explore early versus late effects in normal tissue.
- Investigate the effect of drugs.

3. **Biological (molecular) validation of response of the combined treatment.**

- Profiling of tumours before and after drug/radiation treatment in order to define subjugate molecular endpoints for response.

2.1.3. Fractionation

As we enter the era of molecular targeted treatment, surgery and radiotherapy will remain important for management of gross disease with the potential for an increased role for organ preservation with minimal surgery and/or combined modality therapy. The results of radiotherapy can be improved either by increasing tumour control and/or by reducing unwanted side-effects in normal tissues. Laboratory and clinical research has already shown that manipulation of the programming of treatment (fractionation and overall time) and of dose elevation and distribution (conformal and intensity-modulated radiotherapy) can lead to benefit.

The variations encountered in tumour response to radiotherapy can be related to tumour bulk, inherent radiosensitivity, and cellular

repopulation during treatment and resistance due to hypoxia and other microenvironmental factors. The identification of the important factors related to any one individual tumour prior to the planning of treatment (Predictive Testing-Section 2.1.4) will lead to the optimal selection of radiation parameters appropriate to the case.

Radiation may be delivered as either a single large dose or as multiple exposures of smaller doses. This scheme of delivering radiation is referred to as fractionation. The way in which a given radiation dose is divided affects its biological efficacy alongside two other principal factors, total dose and the overall treatment time in which it is delivered. In general the higher the dose, the shorter the overall time and the larger the fraction size the greater the biological effect. Fraction size dependence is related to the tissue of interest; it is generally considered that most epithelial tumours and the cells responsible for acute radiation reactions are less fraction size dependent than time dependent, whilst the cells responsible for late radiation reactions are fraction size dependent. The overall effect of total dose and fraction size can be expressed as a single figure comparable across different fractionation schedules termed the biologically effective dose (BED). A simple mathematical model for this is quadratic, and characterises fraction size dependency in terms of the alpha beta ratio. A more complex model includes allowances for overall time and the rate of repair (using the repair half-time) of the tissue of interest. Research into altered fractionation has been driven largely by mathematical modelling from cell culture and animal experiments defining critical factors such as the radiation sensitivity, alpha beta ratio and potential tumour doubling time. Animal experiments into altered fractionation are complex and difficult requiring highly specialised radiobiology laboratories. Much of the work in developing fractionation schedules therefore has been as a result of clinical studies into the outcome of altered fractionation.

a) Conventional Radical Fractionation Schedules

The international standard is to deliver 2 Gy per day, 5 days per week giving a total of 10 Gy per week up to a total dose of 60 to 70 Gy for radical treatment of an epithelial tumour *in situ*. Variations on this have developed, and in the United Kingdom and Canada in particular there is a tradition for shorter fractionation schedules using larger doses per day, for example 55 Gy in 20 daily fractions of 2.75 Gy or 50 Gy in 15 daily fractions of 3.33 Gy being considered comparable to 66 Gy in 33 fractions.

In post-operative radiotherapy for breast cancer, perhaps the commonest use of radiotherapy in western societies and a major utilisation of radiotherapy resources the international standard is 50 Gy in 25 daily fractions. In the United Kingdom many centres have used 40 Gy in 15 daily fractions or 45 Gy in 20 daily fractions. Other alternatives include 39 Gy in 13 fractions treating 5 times per fortnight over 5 weeks or 41.6 Gy treating 5 times per fortnight. These schedules are the subject of a highly successful multi-centre U.K. trial recently completed, the START trial of breast radiotherapy.

b) Conventional Palliative Fractionation

Palliative radiotherapy is given to relieve symptoms, most commonly pain, neurological dysfunction, obstruction or bleeding, in patients with advanced disease in who cure is not expected and survival is likely to be measured in a matter of months. The United Kingdom has led the international community in evaluating the efficacy of hypofractionated radiotherapy for palliation, that is, using only one or two treatments instead of lengthy fractionated courses over 3 or 4 weeks. Examples include highly successful clinical trials in bone metastasis, brain metastasis and non-small cell lung cancer. There remain many other scenarios in palliative treatment where further investigation is needed of this type.

c) Altered Novel Fractionation Schedules

The standard fractionation schedule delivering 2 Gy per day can be modified in a number of ways in attempts to improve its efficacy based on biological hypotheses. These include:

- *Hyperfractionation* in which a smaller dose is given on each occasion but treatment is delivered two or three times per day with no change in overall time. The theoretical concept behind this approach is that smaller dose exposures reduce the extent of late normal tissue damage for any given total dose, and by treating two or three times a day an equivalent overall dose can be delivered in the same time. When multiple daily fractions are given the interfraction interval is crucial, requiring sufficient time to

enable normal tissue repair between fractions whilst being both practical and reducing the opportunity for tumour cell proliferation. Typically a minimum of 6 hours is defined.

- *Accelerated Fractionation* in which treatment is given in a shorter overall time. This aims to overcome repopulation and repair in the tumour cells. Acceleration can be achieved in a number of different ways:

  i. Treating with the same fraction size twice a day.
  ii. Treating 7 days per week instead of 5 days per week.
  iii. The concomitant boost model where for the latter part of the treatment more than one treatment is given per day, the second treatment being usually to a smaller area containing the macroscopic tumour.

- *Hypofractionation* is also being evaluated now in radical treatment at certain sites on the basis that some tumours, in particular prostate cancer, may have a low alpha:beta ratio and therefore be highly fraction size dependent. This means that larger fraction sizes would be relatively more effective than small fraction sizes.

- *Ultrafractionation:* Experimental work has suggested that at doses less than 1 Gy there is a relative increase in the efficacy of radiation in achieving residual DNA damage and cell kill, possibly because repair mechanisms are less efficient at this level of dose and damage. This has led to the hypothesis of low dose hypersensitivity or ultrafractionation in which multiple doses of less than 1 Gy are used, treating several times per day but over a prolonged period to much higher doses than would otherwise be achieved. Modelling suggests that relative gain will be greater than the absolute increase in dose because of the low dose hypersensitivity phenomenon. This is currently being evaluated in early clinical trials.

  The combination of hyperfractionation and accelerated fractionation has been applied in the CHART randomised clinical trials in head and neck cancer and in lung cancer. This lung cancer trial has been recognised as an "Evidence Based" advance in patient care.

Key Scientific Questions and Opportunities

1. **Optimise planned alterations in fractionation using modern treatments and imaging technology.**
2. **Can simpler technologies widen the patient treatment/research study base?**
3. **Evaluation of long term implications of normal tissue effects.**

2.1.4. Predictive Testing

Introduction

A group of cancer patients with seemingly identical tumours (i.e. same type and size) will differ in their response to radiotherapy. Additionally, while many patients will experience only minor side effects, a small minority will have an increased normal tissue reaction. Predictive assay research aims to find methods that can be used to determine the response of individual patients to radiotherapy and hence enable the treatment protocol to be individualised for the best benefit of each patient.

The current radiobiological factors that are known to determine how well a tumour responds to radiation are; its intrinsic sensitivity to radiation, how fast it proliferates and how much oxygen is present. We know that radiosensitivity can be measured but the assays studied so far are too inaccurate and complicated to be used on a routine clinical basis. Tumours can continue to grow during a protracted course (6 weeks) of radiotherapy and therefore long waiting times for radiotherapy and gaps in treatment will reduce the efficacy of treatment. Tumours that are growing rapidly may respond poorly to multi-fraction radiotherapy. There are methods for measuring tumour proliferation, but to date none have been sufficiently accurate to find a place in routine clinical use. It is also very well known that in the absence of oxygen (i.e. hypoxia) cells are resistant to radiation. There are several approaches currently under investigation for measuring tumour oxygenation in the clinic. There are also drugs that may have value in improving tumour oxygenation and others that preferentially kill or sensitise hypoxic tumour cells.

In addition to these tumour factors, individuals can differ in their intrinsic normal tissue sensitivity to radiation. Patients who are genetically sensitive to radiation have an increased risk of experiencing side-effects from radiotherapy compared to patients whose normal tissues are less radiosensitive. Some studies have shown that measurements of normal tissue radiosensitivity can predict reaction to radiotherapy. However, no assay has yet been found that is suitable for widespread clinical use. The evaluation of drugs that can reduce the level of normal tissue damage is also of interest.

Many of the ideas behind predictive assay work originated and/or were developed in the UK. The UK also has considerable experience in testing the ideas in the clinic, i.e. carrying out large predictive assay studies in cancer patients (e.g. Tpot, SF2). In the last decade technology has been developed that allows the simultaneous evaluation of the expression of thousands of gene products. It seems likely that the ability to obtain such a comprehensive genetic profile of tumour and normal tissue from individual patients should in the future provide the means of predicting patient response to radiotherapy. However, the loss in recent years of a number radiobiology groups experienced in predictive assay work compromises the ability of UK radiotherapy and related radiobiology to keep abreast of these exciting new developments in molecular biology and their potential in predictive assay research.

Tumour radiosensitivity
The UK has had considerable experience in carrying out large national predictive assay studies of tumour radiosensitivity where the biology is carried out in a single centre. However, this capability has diminished in recent years.

Tumour proliferation
The UK has considerable clinical experience of developing and evaluating methods to assess tumour phenotype. Microarray technology may be an improved means of predicting patient response to radiotherapy (of tumour and normal tissue.)

Key Scientific Questions and Opportunities

1. **Molecular profiling to improve/replace current approaches to predicting radiotherapy/radiochemotherapy outcome in tumour and normal tissue.**

- Evaluation of microarray technology to look at the expression of thousands, or specific families, of genes (including those involved in particular pathways such as the recognition and repair of radiation-induced damage to DNA, cell cycle regulatory proteins, hypoxia regulatory proteins) and their relationship to radiotherapy/ radiochemotherapy outcome.
- Use of predictive assays to target designer drugs to patients likely to respond e.g. repair inhibitors, cell cycle inhibitors, protein kinase inhibitor, apoptosis, signal pathway modifiers, anti-EGFR approaches and others.
- Carry out trials of hypoxia-modification approaches where tumour oxygenation is measured for all patients.
- Evaluation of new tests for predicting the risk of radiotherapy side-effects.
- Application of predictive testing to radiochemotherapy.
- Evaluating new tests and responses to prediction of the risk of radiotherapy side-effects, i.e. increase treatment if risk is low and converse if risk is high.
- Individualise treatment dose regimes to match the individual's tumour and normal tissue radiosensitivites.

2. **Identification of new/key targets that predict normal/tumour response to radiation.**

- Use of microarray technology in clinical studies to identify new/key targets that predict normal/tumour response to radiochemotherapy.
- Use molecular profiling to identify new/key targets within clinical studies.

2.1.5. Radiation Physics and Imaging

Effective radiotherapy depends upon precise localisation and on cytotoxicity, and advances in imaging, which can include functional measurements, offer considerable opportunities for applied research. Definition of the clinical target volume for planning purposes may be improved by multimodality

tumour imaging, such as adding to computer tomogarphy (CT) information from magnetic resonance (MRI), positron emission (PET) or single photon emission (SPECT) techniques. There is also scope for improving radiotherapy accuracy and verification, by imaging on the linac just prior to each treatment, exploiting in-line electronic devices and gantry-based kilovoltage CT. Techniques are now being developed to deal with the problem of intrafraction movement using gating or tracking. Finally, functional imaging of tumour physiology or response is a rapidly-advancing field, and includes techniques such as hypoxia and pH assessments with MR, response with FDG-PET, and blood flow measurements. These have research applications for radiotherapy predictive testing, and are likely to influence indications for treatment as well as dose, field size and use of sensitisers.

There are approximately 1500 medical physicists working in the UK and mostly NHS Trust employed. Off these, half work on aspects of radiotherapy physics. Their primary aim is to improve the physical basis of radiotherapy.

Radiotherapy comprises a chain of physics-based processes where its strengths depend on the weakest link. The links include (i) creating 3D medical images for determining the extent of disease, (ii) developing methods to determine the GTV (Gross Tumour Volume), CTV (Clinical Target Volume) and PTV (Planning Target Volume) from these images (iii) planning therapy, (iv) deciding between conformal therapy (CFRT) with geometric shaping only and intensity-modulated radiation therapy (IMRT), (v) developing tools to deliver CFRT and IMRT, (vi) verification of the patient location with respect to the developed high-dose volumes, (vii) quality assurance, (viii) mathematical prediction of outcome e.g. tumour control probability.

There is a well-understood progression of ideas from concept to practicality involving:

(a) fundamental development of concepts and proof-of-principle
(b) building prototype equipment
(c) studying the expected performance, delivery of radiation to phantoms and predictions of benefit
(d) introduction of limited one-off patient irradiation and extension to Phase1 trial with limited patient numbers to assess whether the concepts work with no damage
(e) Phase 2 and 3 trials to assess improvement consequent on new ideas

The UK strengths lie in the ability to invent new methodologies and concepts and orchestrate national and international organised trials. Another UK strength is the increasing awareness within EPSRC that physics as applied to medicine creates problems of equal challenge to more conventional physics fields.

UK weaknesses include the inability to persuade industry to collaborate and mass produce techniques. There is also little interest in start-up companies, leading to the USA dominating the commercial scene. There is under-funding and under-resourcing of research teams with research being concentrated in too few centres. The UK also lags behind in implementing clinically some of the newer technologies (e.g. IMRT).

The main barriers to progress are human resources with a chronic shortage of trained graduate and postgraduate physicists, an inability to recruit and retain specifically in the South-East, lack of a realistic career path for university research medical physicists, and current clinical burden overshadowing “time to think”.

The major research evidence required is the outcome of controlled randomised trials of CFRT and IMRT, which are the major fields of research activity in radiation therapy physics. There is a need to expand 3D medical imaging, link it to radiotherapy planning to refine judgement of the target volumes. The role of allied health professionals specifically radiographers is vital and therefore effort should be put into creating a wider research role for radiographers.

Alternative radiation modalities such as protons, light and heavy ions and neutron capture therapy are under development in many countries. The UK now lags behind many similar nations who now have more advanced facilities for proton, light-ion and binary high-LET therapies such as BNCT. The UK should participate in the development of these advanced health care technologies and is well

placed to make a significant contribution to the physics and engineering, the associated radiobiology and in the organisation of clinical trials. Currently, we have one proton therapy centre in the UK at Clatterbridge (which has a low energy such that deep-seated cancers cannot be treated). There is one advanced proposal for a major new facility (CASIM). Such high-energy facilities have the capability of reducing normal tissue dose beyond that achievable by conventional radiotherapy (including the use of IMRT etc.). Safe dose escalation can then be used to overcome the causes of radioresistance and in some instances (BNCT and light/heavy ions) the oxygen effect is reduced. There is also a well-established research programme on BNCT, which is yet to reach clinical application, although clinical trials of BNCT are underway in other countries although there is as yet no definite evidence of clinical benefit.

Mathematical methods will be increasingly used in future approaches to guide cancer treatment, in the same way as they are used in Engineering and Physics. All the separate aspects of radiotherapy (clinical, physical and biological) can be included within appropriate models. Simulation of clinical trials by computer can also be achieved in this way. Such exercises should enable a more rational scientific approach in the optimisation of outcomes, given the large number of permutations of therapeutic approaches.

Key Scientific Questions and Opportunities

1. **Will alternative radiation treatment modalities improve the outcome of cancer patients?**

- Research on new techniques of treatment delivery, e.g. protons, ultrasound, photodynamic therapy, neutron capture.
- Exploit our strengths in organising relevant randomised clinical trials of these technologies.
- In the comparison with IMRT, will the lower physical dose from proton therapy be a significant factor in normal tissue response?
- Will differences in radiation quality be a significant factor in tumour versus normal tissue responses?

2. **How do we improve the definition of volume and the delivery of dose to the tissues we treat?**

- If we know what needs to be treated we will be able to deliver tailored treatment (i.e. dose, sensitisers, exclusion of normal tissues), which will improve the therapeutic ratio and so increase cure.
- Improving the definition of volume: GTV (gross tumour volume) using functional imaging and multimodality image processing.
- Improving the definition of CTV (clinical tumour volume) with improved knowledge of biology/ phenotype.
- If we deliver the dose more accurately we will be able to improve the therapeutic ratio i.e. increase dose to tumour and decrease to normal tissue and so increase the cure.
- There are current scientific opportunities to do this by: i) using portal imaging/cone beam CT to accurately see the tumour in the treatment position and define the PTV (planning target volume) more accurately, ii) predict organ and tissue movement within the treatment delivery thereby adapting the PTV to individuals, iii) image-guided radiotherapy to on line track a moving tumour and normal tissue (e.g. intrathoracic).

3. **How can we link genetics, imaging and other patient measurements in mathematical models of response to improve outcome?**

- Sophisticated functional imaging may be capable of monitoring physiological changes during radiotherapy.
- Extended mathematical models that incorporate the above biological parameters can be evaluated within the radiotherapy planning process and optimised by graphical, numerical or calculated methods to predict improved outcomes.

2.1.6. Targeted Radiation

Targeted radiotherapy has been used successfully for many years in the treatment of thyroid carcinoma with sodium iodide (I-131). The efficacy and safety of this approach are well established. More recently the number of new targeted radiotherapy therapies that are being used or are under clinical investigation has increased substantially. These types of

therapies fall broadly into two types of approach that consist of either using small molecular weight vehicles or monoclonal antibodies (mAB) to deliver the targeted radiotherapy. The use of radiolabelled tumour-seeking agents, has the additional potential advantage of the “crossfire” or "bystander" effect of radiation, which refers to the fact that not every tumour cell has to be targeted to sustain radiation-induced damage.

Iodine-131 metaiodobenzylguanidine (MibG) has been used successfully in the treatment of neural crest derived tumours and currently plays an important role in the salvage of chemotherapy refractory patients. A variety of different radioisotopes have been used particularly in the treatment of disseminated metastatic prostate bone cancer including Strontium-89, Samarium-153 and Rhenium-186. Encouraging results are also emerging from early clinical investigations using Yttrium-90 labelled octreotide in the treatment of neuroendocrine tumours and antibody in the treatment of lymphoma.

mAB have emerged as new therapeutic choices for patients with haematological and solid malignancies both as unconjugated antibody and as vectors to target radioisotopes in radioimmunotherapy (RIT). Over the last few years a number of different mAB have been granted US FDA approval for the treatment of cancer, including Rituximab (anti-CD20), Traztuzumab (anti-Her 2/neu), Alemtuzumab (anti-CD52, Campath-1H). Thus, radioisotope emissions may extend up to several hundred cell diameters, depending on the physical properties of the radioisotope and may impinge on antigen-negative cells from surrounding antigen-positive tumour cells coated with radiolabelled antibodies. In addition many mAb are therapeutically active in their own right, via a number of different mechanisms that may include direct cell surface signalling, mAb dependent cytoxicity [ADCC] or complement dependent cytotoxicity [CDC].

RIT has delivered some of the most compelling clinical data in the treatment of lymphoma and haematological malignancies and has emerged as an effective treatment option for “low grade” non-Hodgkin Lymphoma (NHL). Recently Yttrium-9 tiuxetan ibritumomab (Zevalin TM) was granted approval for the treatment of relapsed “low grade” NHL and Iodine-131 labelled Tositumomab (BexxarTM) is likely to follow suit in the near future. Successful RIT in NHL appears to depend not only on targeted irradiation but also the host immune effector mechanisms. RIT is also likely to play an increasing role in the treatment of preconditioning bone marrow prior to transplantation in acute myeloid leukaemia and many clinical investigations are ongoing in a variety of other haematological malignancies, including chronic lymphocytic leukaemia and multiple myeloma. Results in solid tumours are improving, however considerable progress remains to be made before RIT becomes a component of standard practice in the treatment of solid cancers.

In contrast mAB used in combination with external beam irradiation is producing some promising data in the treatment of solid cancers. Here mAB have the potential to trigger selective tumour cell death via cell surface signalling or to trigger inherent immune effector mechanisms. For the tumour-associated antigens these target antigens may not be tumour specific, but rather normal cellular macromolecules expressed at increased density or in atypical context on the cancer cells. This type of approach is being used against anti-epidermal growth factor receptor (Cetuximab, IMC C225) which is currently undergoing Phase 3 studies in a number of different solid tumours sites including head and neck cancer, colorectal cancer and lung cancer. The possibility of immunoregulation with mAB or biological response modifiers concurrently with irradiation also holds great promise for the treatment of cancer in the future but is currently limited to pre-clinical investigation.

Radioimmunotherapy (RIT) has emerged as a new effective treatment option for patients with a variety of B cell lymphomas and is likely to play an increasing role in a variety of other haematological cancers and possibly solid cancers as well. RIT is however unlikely to be curative as a single treatment modality and therefore the future for RIT is likely to involve integration into chemotherapy/radiotherapy schedules. Further pre-clinical and clinical research is required to understand the underlying mechanisms of action of RIT and increase our knowledge as to how best to integrate RIT into standard treatment schedules to improve tumour response rates.

The basic research in biological targeting, radioisotopes and related radiobiology although of a good quality, is very limited, when compared to the US and other EU countries. There are limited numbers of dedicated controlled rooms in the UK for the delivery of radioisotope therapy, (1 per 667,000 per head of population, 1 per 40,000 in Germany), gamma camera and PET facilities. There are very few posts funded nationally (Cancer charity/NHS) that are either involved or allow time to pursue the development of radioisotope based therapies.

Several opportunities exist for taking interesting new therapies into large-scale clinical trials, using targeted radioisotope therapies researched in the UK or in collaboration with non-UK based institutions. There is also access to government (NTRAC), charity (CR UK) and private sector funding sources.

There are barriers, because of the absence of local production of reactor isotopes and limited cyclotron capacity. There is also a negative public perception of radiation. Clinical and radioprotection regulations are more onerous than in some other countries.

While tumours which are confined to their site of origin may often be cured by local treatment such as surgery or conventional external beam irradiation, cancer that has spread to locations distant from the primary tumour requires a treatment which is applied to the whole body of the patient. Total body irradiation is effective in the management of leukaemia but normal tissue intolerance restricts the radiation dose which can be given, so that it cannot be used against less radiosensitive neoplasia. Biologically targeted radionuclide therapy is an alternative method of systemic irradiation treatment, which circumvents the two problems of widespread distribution of disease and the intolerance of normal tissues. Targeted radiotherapy uses a molecular vehicle, which either localises on the surface of malignant cells or is preferentially accumulated within them. For many tumours, monoclonal antibodies or their fragments represent the only targeting agents. With the notable exception of B-cell lymphoma, clinical applications of these radiolabelled macromolecules have generally been unsatisfactory due to low tumour-specificity of targeted epitopes, limited penetration into tumours and the provocation of anti-mouse immunoglobulin responses. These considerations favour the use of non-immunogenic small molecules with higher uptake in tumours. These criteria are fulfilled by peptides, meta-iodobenzylguanidine (MIBG) and sodium iodide (NaI), which are readily available in radioiodinated form. MIBG and NaI have been used extensively for the treatment of neural crest-derived tumours (neuroblastoma and phaeochromocytoma) and thyroid carcinoma respectively.

The new challenge is to enhance targeted radiotherapy by combining it with the transfer into tumour cells of genes encoding specific transporters. The success of this approach has been demonstrated in model systems. Efforts are now underway to optimise tumour to normal tissue uptake ratios; to limit the expression of transporter genes to malignant sites; and to compare the therapeutic potential of and emitting radionuclides conjugated to tumour-seeking agents. These investigations will determine optimal promoter/transgene/ radionuclide combinations for effective human anti-cancer gene therapy.

Key Scientific Questions and Opportunities

1. **Modelling & investigating efficacy of radioisotopes in tumour cell kill and normal tissue toxicity**.

- Analysis of the relative efficacy and effect on normal tissue of isotope therapy.
- Methods for improving therapeutic ratio of kill: normal tissue e.g. pharmacodynamic, receptor-mediated.
- Novel mechanisms to assess targeting and dosimetry *in vivo* e.g. MRI, PET.
- Exploitation of the tranfectant mosaic spheroid model for the critical appraisal of targeted radiotherapy strategies used in combination with gene transfer.
- Experimental therapy using alpha particle emitters.

2. **How should radioimmunotherapy be combined with conventional treatments?**

- Radioimmunotherapy has established efficacy in treatment of lymphomas and other haematological malignancies such as AML. It is unknown how to schedule with conventional treatments especially chemotherapy.
- Develop new antibodies to be combined with irradiation (radioisotopes and external beam radiation) to be used in combination.
- Develop strategies to reduce dose to protect critical normal tissue (e.g. kidney, lung or bone marrow).

3. **Can we optimise the uptake of radiopharmaceuticals in cancer?**

- Increase the dose to tumour cells by enhancing the targeting efficacy.
- Optimise the methods of delivery- aiming to deliver the dose locally and therefore reduce the systemic dose.
- Can current agents enhance inherent uptake by cells i.e. Iodine Receptor and/or chemotherapy up-regulate at genetic level to enhance transporter or immunogenicity.
- Development of good *in vitro* models to assess uptake and efficacy and the dependence of these upon proliferation status, oxygen supply etc.
- Evaluation of the expression of radiopharmaceutical transporters for the rapid selection of patients for radiotherapy.
- Applications of gene transfer to targeted radiotherapy.

2.2. Key Scientific Questions/Issues for Patient and Health Service Need

Radiotherapy is an effective treatment for local disease and will remain so for the foreseeable future. In many cases, however, the effectiveness of radiotherapy could be enhanced by a wide variety of adjuvant therapies and other interventions. Over the past decade pre-clinical studies have generated positive data for a number of approaches, but few of these have reached clinical trial. One reason may be that the data available, however scientifically convincing, do not specifically address issues of concern to clinicians. What is needed, is a framework for the evaluation of new approaches, with a view to providing the evidence that clinicians will need to be convinced there is merit in initiating a clinical trial. Issues such as efficacy in a clinically relevant tumour model, acceptable toxicity in appropriate normal tissue models and practical applicability in a clinical setting will be important. Radiation Oncologists need to be involved at a fairly early stage in determining what are the most appropriate experiments to provide the crucial evidence. An appropriate collaborative framework for the evaluation of new ideas and how to develop them for consideration by clinical trials committees could enhance the progression of the science into clinical reality.

2.2.1. Defining the Target

Imaging techniques which enable accurate staging and the physical location of tumours would dramatically improve the effectiveness of both interventional and drug therapies. Improvements in surgical techniques, external beam radiotherapy and targeted chemotherapeutics have outstripped our ability to locate malignant tissue and assess its status.

Key Scientific Questions and Opportunities

1. **Does imaging the tumour phenotype improve patient experience/selection of patient/individualisation of therapy and outcome?**

- New imaging technologies such as PET are being introduced but from the patient and health service point of view do they improve the patient experience?
- Can invasive procedures be avoided?
- Are treatment side-effects reduced?

2. Can we define and set minimum standards of definition of volume/imaging for patients (e.g. by patterns of care studies)?

- Provide from clinical research the evidence underpinning critical standards of care for particular tumours, such as technology to be used to define target volumes.

2.2.2. Treatment Planning Techniques

There has been considerable change in planning RT over the last two decades, stimulated by improved imaging and now involving 3-D planning and therapy. There is the potential for avoidance of adjacent normal tissues, but this may compromise cure. Direct use of Magnetic Resonance Images (MRI) in planning requires distortion correction. The more precise the treatment the more accurate must be the planning and issues of day-to-day reproducibility and organ movement need technical innovation.

Key Scientific Questions and Opportunities

1. Develop optimum planning techniques for IMRT for common tumour sites.

- How do you introduce change into the clinical environment?
- Retraining needed for new techniques e.g. 3D planning.
- Research to evaluate smarter training methods.
- Evaluation of virtual simulations should improve accuracy and efficiency.

2.2.3. Technology of Delivering Treatment

One of the barriers to radiotherapy progress is currently the lack of research access to linear accelerators. If the time required administering the radiotherapy could be reduced, linear accelerator capacity could be increased. This would be of benefit for reducing waiting lists and releasing capacity for research. Simplifying standard radiotherapy delivery techniques could decrease treatment times and enable more centres to accrue patients into national studies. Additionally, the routine use of new technologies such as portal imaging, multi-leaf collimators and auto-assisted set-up could simplify treatment delivery further, allowing additional time reductions. It is therefore proposed that these methods should be investigated to decrease radiotherapy treatment times and widen the patient study base available.

Studies have shown local tumour control or reduced toxicity benefits when using more complex treatment solutions such as conformal radiotherapy, however many centres are reluctant to implement these due to the additional treatment times required. The use of new technologies such as portal imaging, multi-leaf collimators and auto-assisted set-up could offset the additional time required for these complex techniques, allowing more centres to utilise these techniques and thus increasing the patient study base. Simplifying techniques would accrue a larger study base as more centres could afford the entry level requirements. However, the evidence supporting the use of more complex techniques is well established.

Key Scientific Questions and Opportunities

1. How can we provide a framework for evaluating the efficacy of new treatments involving radiotherapy?

- Radiotherapy is already an effective form of cancer treatment. In terms of patient benefit these changes are very important. We need to structure clinical trials such that sufficient numbers can be entered in trials allowing benefit to be demonstrated.

2. Can new technologies or simpler techniques widen the patient treatment/research study base?

- Most R&D is hindered in the clinical radiotherapy setting due to high demand of the clinical service and long waiting lists. It is challenging to implement complex radiotherapy treatments or conduct clinical trials which are often time/resource consuming, at the possible cost of delaying treatment to others.
- Can the development and use of advanced technological features such as assisted set-up, partial imaging, MMLC and stereoscopy, reduce patient treatment times? Alternatively, using simpler techniques and hypofractionation could also reduce treatment times. Both could then enable more capacity on linear accelerators.

2.2.4. Fractionation

There are potential benefits to either hyper- or to hypo-fractionation and to accelerating the overall treatment time. Predictive testing may allow a rational choice. Hypofractionation is very resource-efficient and is being evaluated now in radical treatment at certain sites (breast and prostate cancers) on the basis that some tumours may have a low alpha beta ratio and therefore be highly fraction size dependent. This means that larger fraction sizes would be relatively more effective than small fraction sizes.

Key Scientific Questions and Opportunities

1. **Improvement of the selection of dose escalation or treatment acceleration or both policies on the basis of hypoxia, re-population, radiosensitivity in the context of more focused forms of radiotherapy.**

- What is the time course of hypoxia during fractionated course of therapy?
- 25% of tumours do not re-oxygenate efficiently. Can dose escalation can overcome hypoxia?
- It is not known if 2 Gy is the optimum dose. Trials comparing long v short fractionation schedules will address the question of resources. Most economical is whichever treatment is successful. A shorter radical treatment may be optimal because dose is reduced.
- It is possible to use a bigger fraction size for subclinical disease because you do not need to use a big dose.
- Do we escalate because of severe hypoxia or radioresistant tumours?
- Acceleration of RT in treatment combination with sensitisers.

2. **Extended comparisons (in clinical trials) of hypofractionation with conventional schedules for radical radiotherapy.**

- Exploration of the optimum fraction dose.

2.2.5. Short term effects (acute toxicity and symptom relief)

Effects within a month or so of RT include acute side-effects such as mucositis and erythema, as well as the desired rapid relief of symptoms after palliative treatment. Mechanisms of symptom are poorly understood e.g. pain relief.

Key Scientific Questions and Opportunities

1. **Evaluation of existing new methods, using current toxicity criteria, to improve the management of side effects.**

- Published toxicity classifications are underused.
- There are very few symptomatic measures proven by randomised trial.
- Very little short-term toxicity data is available outside clinical therapy trials.
- Added value through working in partnership with psychosocial oncologists and palliative care in other areas.

2.2.6. Long Term Side Effects & Outcomes

The depletion of tumour and tissue stem cells is the basis not only of successful anti-cancer therapy, but also the potential for long term tissue damage. Treatment comparisons need accurate and reliable quantification of effects, both objective and subjective. The therapeutic ratio can be improved by addressing mechanisms and treatment of dose-limiting toxicities, as well as by dose escalation/enhancement.

Late side effects of curative radiotherapy are chronic and progressive, limiting the dose of radiotherapy that can be safely delivered. Fibrosis is a prominent feature, long considered to represent a passive stromal remnant responsible for strictures and/or loss of tissue compliance. Current research findings suggest that fibrotic states represent a genetically regulated response to chronic physical, chemical or biological injury, potentially amenable to interventions that modify key molecular processes. It is hypothesised that components of the late normal tissue response to ionising radiation, including fibrosis, represent active responses that can be modified with benefit to patients. A modest amount of level I and II clinical evidence based on the use of hyperbaric oxygen therapy and high dose antioxidants is consistent with this hypothesis.

Key Scientific Questions and Opportunities

1. **Identify and evaluate methods for modifying long term side effects.**

- Chronic and progressive normal tissue injuries affect a significant proportion of cancer survivors in terms of functional disabilities and quality of life.
- Normal tissue injuries developing years after RT represent an active response to treatment capable of modulation by a range of drug interventions.
- Empirical data suggest that hyperbaric oxygen therapy or antioxidants may reverse some of the adverse consequences of radiotherapy. These and other approaches merit prospective evaluation in well-designed clinical trials.
- NHS does not know the scope, size, and cost of long term side effects and sub-optimal outcomes. Patients assume side-effects are inevitable and irreversible. They are rarely consulted over treatment options. Doctors underestimate side effects and fail to ask specific questions.
- Quality of life studies/health economics evaluations should be integrated with treatment interventions.
- Side effects may not necessarily be reduced by improved planning and treatment techniques because the dose is often increased.

2. **Through a cancer survivorship study can we better quantify the risks and benefits associated with radiation therapy?**

- Improve the understanding of the hazards and the ability to inform patients.
- Provide utilities for cost-effectiveness analysis.
- Provide a focus for preventative treatment strategies.

3. **Modifying long-term complications.**

2.3. Voting Results

Introduction
Participants at the Roundtable Meeting were asked to vote on the top research opportunities identified in the different breakout sessions. Details of these have been given above. Each member was given up to three votes to cast and any of the questions that appeared to overlap significantly were merged during the plenary session in order to prevent duplication.

When considering the results of this voting exercise it is important to consider what they do and do not represent. Given the limited number of people present and risk of selection bias, the results cannot be considered to represent an agreed national priority list of research questions in radiotherapy/radiobiology. However, these questions emerged from the questionnaire survey and Roundtable discussions, as the key issues that need to be tackled for the future, so they can all be considered as important in the field. The Roundtable meeting brought together Key Opinion Leaders for the field from across the UK. The results of the voting can be seen as a majority view of those present on the relative importance of the different questions. Results have been presented in the table below in three groupings: top cluster, middle cluster and bottom cluster.

Top Cluster
- Molecular array profiling, and other high-throughput techniques, to improve current approaches to predicting radiotherapy/radiochemotherapy outcomes in either tumour or normal tissue.
- Identify and evaluate methods for modifying long term complications.
- Improve the definition of volume and the delivery of dose to the tissues we treat.
- Exploit physiological differences between normal & tumour tissues and investigate to search for new molecular targets.
- Understand and exploit the genetic differences between tumour and normal tissues in DNA damage responses to RT and to combined treatments.

Middle Cluster
- Evaluate long term implications to patients of normal tissue effects.
- Through a cancer survivorship study can we better quantify the risks and benefits associated with radiation therapy?
- Define and set minimum standards for definition of planning volume in imaging patients e.g. by patterns of care studies.
- Optimise the combination of chemotherapy and radiotherapy for maximum therapeutic gain.
- Identify new/key targets that predict normal/tumour response to radiation.
- Investigate and construct models to improve efficacy of radioisotopes in tumour cell kill and normal tissue toxicity.
- Develop optimum planning techniques for IMRT for common tumour sites.
- Selection of new drugs to use in combination with radiation, and choice of tumour.

Bottom cluster
- How should radioimmunotherapy be combined with conventional treatments?
- Does imaging the tumour phenotype (e.g. PET) improve patient experience?
- How can we provide a framework for evaluating the efficacy of new treatments involving radiotherapy?
- Extended comparisons (in clinical trials) of hypofractionation with conventional schedules for radical radiotherapy.
- Can simpler technologies release resources to widen the patient research study base?
- Will alternative radiation treatment modalities improve the outcome of cancer patients (protons, light or heavy ions, BNCT)?
- Evaluation of existing and new methods, using current toxicity criteria, to improve the management of side effects.
- Optimise planned alterations in fractionation.
- How can we link genetic, imaging and other patient measurements to mathematical models of response to improve outcome?
- To develop appropriate models to relate molecular and cellular events to clinical outcomes (cell:cell interactions, tissue responses).

2.4. Implications for the organisation of radiotherapy/radiobiology research in the UK

In the final breakout session, Roundtable participants were asked to consider what the implications of all that had been discussed during the day were for the organisation of radiotherapy and related radiobiology research in the UK. They were asked to think against the background of the key scientific questions that they had identified and they were also asked to think, not only in terms of the funding streams on offer, but also about how the RT/RB research community organised itself.

The Roundtable discussions and plenary discussions identified a large number of organisational and funding issues that the participants felt needed addressing. The majority of the issues recorded below were identified by all of the Breakout groups independently. For the purposes of this report we have organised them into five main areas:

a. Encouraging multidisciplinary collaboration
b. Amount and type of funding
c. Training, career structure and workforce capacity
d. Communication and networking
e. Improving the profile of radiotherapy research

a. Encouraging multidisciplinary collaboration

A major theme emerging from the scientific breakout sessions was the importance of the interface between RT/RB research and other areas of cancer research, in particular molecular biology. The PRG meeting provided a unique opportunity for scientists from different disciplines to meet and discuss the field. A central issue that emerged from these discussions was the need to create a research environment that encouraged communication and which could lead to interdisciplinary collaborations. Key collaborations were identified between molecular biologists, physicists, chemists and clinicians. The need to facilitate translation of basic research towards the development of new combined therapeutic approaches was highlighted by a number of groups. Specific needs and suggestions emerging from the breakout session include:

- Foster inter-disciplinary research environments.
- Facilitate collaborations among different disciplines by encouraging interdisciplinary grant applications in RT/RB research, providing greater access to reagents, specialised facilities and shared expertise.
- Multidisciplinary teams should be established to deliver translational radiotherapy research.
- Fund meetings and workshops to encourage networking between cancer biologists and the RT community.
- Create developments for translational research and provide support for taking basic research to the clinic.
- Develop and fund centres of excellence focusing on translational research and training without losing existing centres.

b. Amount and type of research funding

There is a strong perception that RT/RB research has suffered from progressive reductions in funding over the past 15 years and that key researchers have often been lost to the subject due to an inability to provide stable research environments. A current threat is the uncertain future of the Gray laboratories, due to departures/retirements and to NHS changes. It is perceived that grant funding for radiation research is harder to obtain than that for other areas of cancer research. A number of reasons were put forward for this including a lack of appropriate representation on key peer-review committees. Members also identified funding opportunities of which the RT/RB research community had not taken full advantage, such as EU and EPSRC funding. Specific needs and suggestions emerging from the breakout session include:

- Achieve representation on peer-review committees.
- Establish a separate specialist institution for radiation studies in the UK.
- Create a new separate funding stream for RT/RB research, which currently falls between disciplines.
- Establish a dialogue on research funding with the Royal Colleges.
- Take steps to provide stability for existing groups.
- Provide access to MRC/HEFCE funding for key institutes.
- Encourage the development of joint initiatives between Research Councils and take greater advantage of EPSRC funding

opportunities to enhance interdisciplinary research.
- Initiate collaborative studies with the US and Europe to maximise funding options and take advantage of resources and expertise.
- Take better advantage of future EU funding opportunities to develop strategic translational research (e.g. Framework 6 and 7).

c. Training, career structure and workforce capacity

A strong message emerged from the Breakout Groups that, if the UK is to answer any of the key questions identified earlier in this document, then there is a need to build up an adequately sized and well-trained scientific and clinical work force specialising in RT/RB research. Only three Academic RT Units in the UK have Programme Grant support; ICR, Mt Vernon, Christie. Specifically, there are insufficient numbers of medical physicists and adequately qualified clinicians working in academic medicine. Reasons for this include lack of training, lack of job stability, inadequate remuneration as well as short-term research contracts. Lack of recognition of the importance of research within training by the Royal College of Radiologists was considered a handicap. Specific needs and suggestions emerging from the breakout session include:

- Dedicated time for training of staff in multidisciplinary environment.
- Increase the number of medical physicists UK wide, providing a robust training programme at undergraduate and postgraduate level.
- Consider importing high calibre scientists into UK and keep them.
- Need long-term support to maintain existing research groups.
- Use research to retain radiographers.
- Need dedicated clinical research time. NHS staff has limited spare time for research. Few opportunities to train radiotherapists in research.
- Recruit new talent and sustain proven talent in the field of RT/RB research by ensuring career opportunities in both training grades and beyond. Counteract the current trend of decreasing pool of expertise in RT/RB-translational research in the UK and lack of University training opportunities to attract new talent.

d. Communication and networking

A number of issues relating to communication and networking were raised. These ranged from the suggestion that a strategic oversight mechanism should be established, perhaps similar to the NCI Study Group model, that would develop an overall strategy for research in the area, to better communication between individuals working in the field nationally. The need to establish networks of appropriately well-founded centres that could provide a quality base for RT trials was raised. The lack of an appropriate forum for co-ordination of RT research activity and dissemination and implementation of the results of research was highlighted. Better co-ordination within the community to ensure that effort was not expended in re-inventing the wheel both nationally and internationally emerged as an issue. Specific needs and suggestions emerging from the breakout sessions included:

- The need to establish a national consortium/network looking into RT/RB research preferably led by prominent individual.
- Follow the NCI model encompassing Research Councils, training, translational research and NHS.
- Establish international collaboration on guidelines in order to avoid duplication.

Other key recommendations

- Create national database and accessible tissue banks with coordinated national administration.

e. Improving the profile of radiotherapy research in the UK

There was a general and strong feeling that radiotherapy research in the UK had a low profile. It wasn't considered exciting by the research community compared with other areas of cancer research such as molecular biology. In addition, within the NHS administration there pervaded the unjustified view that there were few questions left to answer in radiotherapy research. The general view held amongst participants was that, despite a strong tradition in the UK for evidence-based medicine, radiotherapy remains a predominantly service driven discipline compared with medical oncology. Problems deriving from this included recruitment of first-class scientists, development of academic careers and winning of competitive research grants.

Specific needs and suggestions emerging from the breakout session included:

- Address image problem of RT research by increasing profile of RT/RB research in conferences/meetings.
- Radiotherapy in the UK is driven exclusively by service; there is a need to have protected academic time both in the lab and in the clinic.

3. DISCUSSION OF KEY ISSUES & OPTIONS EMERGING FROM REVIEW PROCESS

In this section Co-Chairmen explore the key issues emerging from the review process in the light of comments from the PRG members and suggest a number of options relating to the organisation of RT/RB research in the UK for consideration by the NCRI partner organisations.

The current situation in the UK

Currently RT/RB research in the UK is in a state of decline and this has been the trend over the last decade. Although old and new scientific questions are there, (see below) and new opportunities exist to address them, the critical mass of people active in the field is heading towards the point where it will no longer be sustainable as an academic discipline.

The major RB (for radiotherapy) groups in the Gray Laboratories, the Institute of Cancer Research (ICR), and recently in Manchester, have either retired, departed or moved to other research fields. The focus at the ICR is on applied physics and clinical trials, although there is some genetics research and gene therapy. At Mt Vernon the focus is on radiobiology; at Manchester it is Applied Imaging, especially PET. There are also few Academic (i.e. university) Radiotherapy consultant appointments; current estimates put these at 8 at ICR, 3 at Mt Vernon, 2 in Manchester, Edinburgh and Glasgow, and 1 each at Birmingham, Cardiff, Southampton, Guildford, Dundee, Maidstone, Norwich, Cambridge and Sheffield (26 in total). Some of these appointments, especially in Scotland, are funded by the NHS and have substantial service responsibilities greatly limiting research time. This is also limited for NHS Consultants due to service pressures.

Academic radiotherapists with radiobiological research knowledge are no longer being produced in any numbers and with very few exceptions, this has been the case for at least a decade. Part of the problem is that there are now few scientists in radiobiology. Whilst academic radiotherapists are still coming through, their science training is not in radiobiology any more because of a lack of scientific supervisors. In addition there are now not many academic posts dedicated to radiobiology.

Funding for radiotherapy and radiobiological research has continued to be in open competition with other areas of cancer research and, has in general, not competed well. In part this may be because in the mid 1990s a major funding body produced a strategic plan in which "classical radiobiology" was categorised as being of low priority for radiotherapy. In addition, there is a perception in the research community that an under-representation of appropriate specialists in these areas on peer-review committees has contributed to a reduction in funding in this area as have impressions of research impact by others on the committees.

This decline has corresponded with an increasing emphasis on molecular biology and genetics in cancer research. Many RT/RB groups have not been in a position to recruit or collaborate with molecular biologists and clinicians developing associated therapeutic modalities. This means that the UK RT/RB research community is not best placed to capitalise on advances in other areas of cancer research.

Future Directions of RT/RB Research

The last decade of research in this area has provided an increasing baseline of knowledge showing that the topic now provides a wealth of opportunities for improving the therapeutic ratio as detailed in section 1 of this report e.g. growth factors for ameliorating early and consequential late toxicity, vascular modifiers of late toxicity, radiation-activated molecular switches to activate pro-drugs selectively, bio-reductive cytotoxins etc. So there is no shortage of ideas and potential in the area.

The nature of these new opportunities reflects a clear message emerging from this consultation process. This is the importance of studying radiobiology and radiotherapy in the context of an improved understanding of molecular and genetic behaviour of tumours and normal tissues and individual variability. Similarly, the integration of conventional or novel radiation treatments into multi-modality protocols rather than as a stand alone therapeutic option is likely to be increasingly important as there needs to recognition of advances in associated therapeutics. These two issues combine in a way that now places the study of radiobiology and radiotherapy firmly at the interface with other major strands of cancer research. This does not mean to say that there are no more challenges in ‘pure’ medical physics or

radiobiology, but the implication is that the 'centre of gravity' of the field has shifted. This has major implications for the way funding is organised in this area and how we train the next generation of researchers in this area.

Should Radiotherapy and Radiobiology research in the UK be rescued and can it be done?

The answer to both these questions is clearly yes! The scientific and therapeutic opportunities in this field are potentially very exciting. They are of a slightly different nature to those that have gone before, but no less powerful for that. However, to put this area back on a competitive footing and re-establish a sustainable research community in this area, will require a coherent approach from key stake holders. These include, not only the NCRI funding bodies, but also the Royal Colleges, the radiotherapy/radiobiology community itself and the wider research community. The key elements required include:

- Promoting multidisciplinary working
- Establishing critical mass and stability of funding in a number of research groups
- Major change in the approach to training in the area
- Improved communication and networking within the research community
- A change in culture and a raising of the profile of radiotherapy research

Each of these issues is addressed in more detail below and each section ends with a series of practical options to be considered by the stakeholders.

1. Encouraging multidisciplinary collaboration

This issue is key to the future of radiotherapy research in the UK. It is striking that many of the key scientific questions facing this field of research and particularly those that received the highest number of votes, were intrinsically linked to other areas of cancer research and require interdisciplinary working. In particular, the interface between RT/RB and molecular and tumour biology emerged as increasingly important as did translational RT/RB research.

The challenge for the funders is to strike a balance between maintaining a critical mass of specialist radiotherapy/radiobiology research groups and nurturing radiotherapy/radiobiology research groups within multidisciplinary cancer research environments. There is clearly a need to create a new generation of research leaders in this field that can confidently cross the boundaries between RT/RB and cancer biology in general. This would require support for RT/RB research groupings in an environment where they work closely with their colleagues from other disciplines. Establishing this sort of environment is probably key to recruiting and keeping the next generation of researchers in this field.

In creating a new interdisciplinary approach and cadre of researchers it will be important not to lose a critical mass of radiotherapy/radiobiology researchers who have a secure background in the established principles of the subject. An obvious way of doing this is to support large stand-alone RT/RB institutes and/or departments. However, given the benefits of multidisciplinary working and the changing face of cancer research it may only be possible to achieve critical mass within existing comprehensive cancer research centres.

The message that we need to facilitate translational research in this area came through strongly. Once again lessons from other areas of cancer research suggest that this is best achieved by avoiding separation and creating critical mass within multidisciplinary research environments. The establishment of NTRAC also offers an opportunity to promote the RT translational research agenda.

The need to promote multi-disciplinary working pervades all the other issues in this area. However, there are a number of key options that should be considered by the NCRI partner organisations.

Options for action:

- Fund high quality RT/RB research groups within existing multi-disciplinary cancer research centres
- Encourage interdisciplinary research collaborations by offering funding incentives – this could be done through partnerships between different funders (MRC, EPSRC, BBSRC, CCLRC, DoH, CR UK)
- Build up a small number of multidisciplinary centres of excellence alongside clinical centres, which would address the problems of critical mass and links with more basic biology, and would promote multidisciplinary and translational research

- Organise a series of cross-disciplinary research conferences/workshops that promote interdisciplinary working

2. *Amount and type of funding*

The perception is that RT/RB research has suffered from progressive reductions in funding over the past 15 years. This low base is now a substantial impediment to the field's ability to exploit the many new research opportunities that have opened up, and to build up strong links with high profile academic institutions and with leading departments carrying out relevant related research in genetics, molecular biology and cancer. Support for RT/RB research is fragmented amongst the cancer charities, research councils and the NHS; there should be benefit in identifying lead responsibilities and in funding co-ordinated joint initiatives that would reflect both the continuing major role of radiotherapy in treating patients, and the many opportunities that now exist for advancement by research for the future further benefit of large numbers of patients.

Funding stability is essential to retain key researchers, to build strong teams and to reduce the wastage of valuable research time by the few remaining senior staff in the field as they struggle to maintain funding for research staff. A suitable mix of dedicated research posts together with competitive short-term funding is required, to reflect the importance of the field and its research opportunities and to attract clinical oncologists to RT/RB (including as a counterbalance to the comparatively more available funding for clinical trials in other areas of oncology, such as chemotherapy with commercial support). The funding process needs to take account of the special needs of long-term translational research and the strategic imperative to re-activate RT/RB research from the current reduced pool of expertise in the UK.

The challenge for the funding bodies will be to strike a balance between providing the long-term stable funding in the right environments and short-term funding aimed at attracting new people to the field and encouraging multi-disciplinary working.

There were two main issues relating to infrastructure provision that emerged. The first of these is related to the need to ensure that there is a viable network of centres with the appropriate configuration of expertise, personnel, equipment and available time on equipment to underpin multi-centre clinical trials in radiotherapy. There is some variation as to whether the issue here is one of equipment, equipment time or an organisational issue. This may be something that should be considered in the light of NHS infrastructural developments such as NCRN and NTRAC. An appropriate forum to consider this issue further and develop the necessary network might be the newly established NCRI Radiotherapy Clinical Study Group.

The second infrastructure issue that emerged both in the questionnaire survey and from the breakout groups was the proposed CASIM component of SIRIUS based at Daresbury. The scientific driver that emerged from the Roundtable meeting was the need to evaluate alternative treatment modalities such as protons, light or heavy ion beams and BCNT. This issue was not considered in detail, however, the need to evaluate these treatment modalities, whilst desirable, only received 2 out of a possible 126 priority votes from the Roundtable participants.

The NCI model for funding radiotherapy/radiobiology research was considered to be a good one, key elements of which are a separate funding stream for RT/RB and strategic leadership to allow ongoing priority setting.

Options for action:

- Consider strategic/targeted funding initiatives in key RT/RB areas
- Consider NCI model of separate funding stream for RT/RB research and ongoing strategic leadership
- Provide stable funding for a number of centres in appropriately multi-disciplinary environments
- Explore joint funding between different agencies, in particular MRC/EPSRC/BBSRC/CCLRC/CRUK
- Examine the representation of RT/RB on key peer-review panels
- Further examine the infrastructure issues underpinning radiotherapy clinical trials

3. *Training, career structure and workforce capacity*

The severe shortage of staff and staff time committed to RT/RB research extends across all categories of staff, including academic clinical oncologists, radiobiologists, post-

doctoral scientists, medical physicists and therapy radiographers. This shortage has reduced the opportunities for training the next generation in research, and it acts as a disincentive for recruitment and career advancement. Strategic action is required to reverse this downward spiral.

Academic Radiotherapists with Clinical Radiobiological research knowledge are no longer being produced because the scientific groups have virtually all disappeared. Up until now, there has been no concerted strategic action to prevent this happening or to restock this category of specialists. There used to be a RCR regulation that centres could only be recognised for training if there was a resident radiobiologist on site. This is the current situation in US, but no longer holds true in the UK. One of the reasons why so many surgeons seek formal research training is that trainee surgeons need higher degrees for career advancement, and radiation oncologists do not. This could be rectified only by a radical change in the career structure specified by the Royal College (RCR) and approved by the new Postgraduate Education Standards Board, and by reorganisation of the Academic and Service Units in Radiotherapy in the UK to foster applied research, which is an integral part of medical oncology and surgical policies. In addition, there needs to be a greater requirement and attraction for trainees to be involved in applied research work in their speciality topics, and a greater realisation of the benefits of integration of conventional or novel radiation treatments into multi-modality protocols. However there is pressure against any lengthening of oncology training from the national shortage, so it may be that any curricular change would be of balance rather than the creation of additional requirements.

Currently it would be difficult to obtain post-doctoral training in RT radiobiology in the UK. Most opportunities arise in the USA. Attractive career structures are required also for non-clinical scientists to remain in the field in the UK, to form stable research partnerships with the clinicians and to contribute to training in the field. Opportunities and career rewards for research should be widened also for medical physicists and radiographers.

Clearly the right environment is crucial to encouraging quality training. Establishing a number of centres of critical mass will undoubtedly help in this area. In order to attract high quality applicants; these radiotherapy/radiobiology training environments need to be integrated into comprehensive cancer research centres offering wide exposure to ongoing developments in cancer related biology and other disciplines.

Options for action:

- Review training and career structure for radiotherapists specified by the Royal College of Radiologists
- Open up a formal dialogue between NCRI funders and the Royal College to ensure a coherent approach
- Review the career structure for scientists in Radiotherapy /Radiobiology Research
- Fund protected research time for NHS clinicians and other categories of staff
- Consider how to create more attractive academic consultant posts involved in RT/RB research
- Create appropriate training environments in large multidisciplinary centres
- Extend support of core Clinical Research Fellowships to departments with training capacity
- Develop opportunities and career rewards for research involvement of medical physicists and radiographers
- Create a significant number of five-year Fellowships for laboratory research workers and of clinicians prepared to devote their carers to translational research.
- Create a mechanism so that those successful in their Fellowships can expect long-term employment in the field

4. *Communication and networking*

This section contains a number of similar but not necessarily related issues surrounding communication and networking within the field.

Strategy setting and leadership – one of the elements of the NCI approach that was considered beneficial to the research community in the US was that there was an ongoing focus for strategy setting and leadership within the field. This may be important to ensure that the community evolves appropriately with the rest of mainstream oncology research. It is not clear whether this strategic leadership should come from the funders or from within the community itself.

Dissemination and implementation of research results – there was a generally held view that it has been difficult to translate the results of research in radiotherapy into clinical practice on anything more than a local scale where additional resources are required (e.g. CHART). This issue may be related the competition with service needs and emphasises the need for raising the profile and benefit of research in this area. It may also gain from the establishment of a dialogue with the NHS.

Better interface with industry – there was a general perception that 'industry' were reluctant to invest or collaborate in radiotherapy/radiobiology research where there was no clear commercial gain through patents or for marketing. There was no clear consensus on this issue but it may warrant following up. Further discussions between leaders in the field and appropriate companies in the medical devices and pharmaceutical industry may be beneficial.

Networking in general – collecting together members of the radiotherapy and radiobiology research communities under the auspices of the NCRI raised many issues and stimulated much debate. The issue of how these communities communicate and work together on a day to day basis arose. One view is that a new forum for the community to get together is needed. Perhaps, organisation of the RT/RB research community into a discrete network or into consortia may not be desirable in view of the opportunities for interdisciplinary research discussed above. The other side of the coin is that some examples of these already exist and we need to re-examine their roles and profiles within the community. In particular, the NCRI Radiotherapy Clinical Study Group is relatively new but would provide an obvious focal point for clinical research. The NCRN plays a key role in clinical oncology in general. There was much emphasis on the translational nature of much of the research now needed and the challenges this posed. The potential for NTRAC to play a facilitatory role here should be explored.

Options for action:

- Explore models for providing ongoing strategic direction for the field
- Discuss dissemination and implementation of results with key stakeholders (radiotherapy community, Royal Colleges, NHS)
- Run workshops with industry to explore closer interactions (NTRAC?)
- Consider the need for establishing further networks and consortia
- Consider the role of existing networks (NTRAC, NCRN, NCRI CSG)

5. *Improving the profile of radiotherapy research*

The NCRI partners' decision to hold a PRG in this area has already helped in raising the profile of radiotherapy/radiobiology research. If the key funders were to recognise the field as a strategic priority this would also help. If action is taken on the issues outlined above, this will have a further major effect on the research profile of the discipline. The difficulty of reversing the current trend is recognised, but there is considerable motivation within the field to develop translational initiatives and their clinical evaluation, within a broader integrated cancer research framework. There may be an opportunity to raise the status of clinical research in both medical training and consultant practice through the Royal College of Radiologists and, as a direct consequence of the Review, a Meeting has been organised by the College to seek to define its role in this regard.

Options for action:

- Organise a high profile conference on 'Radiotherapy Research in the NHS'
- Establish an initiative within the Royal College to promote research, perhaps building on the model developed by the Royal College of Surgeons
- Increase interaction of the UK with Europe and the USA

APPENDIX A

Questionnaire analysis 1

In your opinion, what are likely to be the most important scientific opportunities in radiotherapy/ radiobiology research over the next ten years?

Cellular & Molecular Radiobiology

- Progress in molecular biology, in particular the cloning of the human genome and the development of high-throughput biological assays will allow a dramatic refinement in the indication for and prescription of radiotherapy. By using high-throughput assays and functional imaging, the delivery of radiation dose may be modulated in time and space to phenotypic variations among patients and even within a single solid tumour.

- Prospective collection of robust clinical data along side molecular profiling of tumours, normal tissue genotyping, will allow assessment of treatment response to radiotherapy and new drug treatments.

- The human genome project has provided the opportunity for a quantum leap in our understanding of the genes that regulate cellular sensitivity. Studies designed to identify the genes involved in pathways affecting radiosensitivity and how these genes are regulated have the potential to enhance the specificity and effectiveness of radiotherapy within the ten year time scale. The most likely means of exploiting that information will be through the development of small molecules.

- Identification of most of proteins involved in DNA repair and damage response mechanism and understanding of the pathways involved.

- The ability to target specific cells for radiotherapy coupled with use of dominant negative constructs such as RNAi techniques to inhibit the most important repair processes, represents the ability to exploit basic knowledge of damage responses for targeting coupled with ability to target specific cells or tissues (or tumour cells).

- To apply the technology of molecular biology to those areas in radiobiology applied to radiotherapy where past and present work has shown that real margins of improved tumour control may be achieved but where advance has been limited or marginal to this time. For example, tumour cellular proliferation and its pattern during the course of treatment, radioresistance due to hypoxia and its pattern during the course of treatment, inherent radiosensitivity of tumours, develop chemical and biological response modifiers using reductive delivery and tumour specific delivery, identification of particularly radiosensitive patients prior to treatment, radiosensitisation using radiation activated and hypoxia directed gene therapy, identification and prediction of the pattern of the response to treatment.

- To identify targets for modifying radiotherapy response i.e. reduce morbidity and increase efficacy.

- Molecular markers of sensitivity to treatment (includes sensitivity to other treatments such as chemotherapy as well).

- Use of proteomics and expression profiling to understand the stress response genes involved – this can particularly be used to identify rapidly the response of individuals to radiation exposure.

- Identifying better key biological prognostic factors for cancer control and morbidity, including patient/tumour microarrays. The aim would be to try to identify a small number of key unrelated and seminal parameters measurable in specimens obtainable from average patients in a general oncology department.

- Exploration of the potential of microarray technology as a tool to understand the heterogeneity of tumour and normal tissue biology and how this influences patient response to radiotherapy.

- Imaging analysis of molecular genetic markers determining outcome of treatment. (1) Using tissue/gene arrays developing predictive markers to rationalise trial strategy. (2) Develop ligands for visualisation by PET. (3) Develop strategies to modify the function of molecular and genetic determinants of outcome.

- From studies of tumour physiology and gene expression during radiotherapy, to determine which tumours require dose escalation, which require hypoxic cell elimination by either chemical means or by highly focussed high LET radiation, e.g. heavy ions, and which require acceleration of therapy. Some may require all approaches for there to be reasonably improved efficacy.

- Development of repair inhibitors of radiation-induced DNA damage. Understand the mechanism(s) of processing of radiation induced complex DNA damage in cells, which if not repaired may cause cell death. Develop strategies to target DNA damage-repair inhibitors to tumour cells using chemical and molecular approaches possibly in conjunction with radioprotectors of normal tissue to provide differential effects.

- Improved understanding of short-term and long-term radiation responses by studies of inter- and intra-signalling pathways in normal and tumour cells and tissues and the role of genetic factors in modifying responses. This broad area of fundamental research, covering a number of scientific opportunities, has the potential to contribute to the prediction of radiation responses and to improved understanding of variations in radiosensitivities and radiogenic tumour susceptibilities. Microarray and proteomic high throughput approaches would be highly relevant. As cellular and molecular processes are defined it should be possible to identify new therapeutic targets and agents for normal tissue protection in both pre- and post-therapy settings.

- Identify & manipulate molecular pathways that contribute to radioresistance in tumour cells (both targeted and non-targeted effects).

- Research into the basic mechanisms of cell, tissue and tumour responses to gain better understanding of the roles of intra and inter-cellular signalling in radiation response. The aim to develop mechanistic models of response that can be used to indicate new strategies to improve the therapeutic index, including combined modality and gene therapy approaches.

- Molecular assays of expected efficacy and adverse effects.

- To extend knowledge of radiobiological parameters (α/β), re-population factors, vascular dynamics} for a wider variety of cancers and correlate tumour genetic characterisation with the known radiobiological parameters. Use of such knowledge should provide enhanced mathematical optimisation of therapy with gains that should far exceed the marginal gains found in conventional clinical trials.

- To safely determine normal tissue tolerance levels by feedback of cytokine responses during radiotherapy. To adapt existing radiation effect models to include the factors that may adversely influence tolerance.

- Investigating specifically the impact on cell killing and mutagenesis of the spatial distribution, and energy/ LET distribution of the radiation dose.

- Thorough appreciation of radiological bystander effects and how to manipulate these for the enhancement of therapeutic ratios.

- Decreasing emphasis on *in vitro* systems in which cells are considered as autonomous units responding to damage and increasing emphasis on tissues being highly integrated systems in which cell: cell interactions and microenvironmental factors play major functional roles in physiological ad pathological conditions will substantially improve our understanding of radiation responses.

- Radiation induced mutagenesis as it is applied to second tumours arising from normal tissue in the radiation exposure field and individuals susceptible to radiation induced mutation due to genetic

susceptibility i.e. AT families, BRCA families.

- Investigate cellular mechanisms of late toxicity from radiation including carcinogenesis and thereby improve therapeutic ratio.

- Scientific evaluation of methods for reducing normal tissue toxicity.

- Chemical modifiers of radiation damage. Four main approaches:
  1. Mechanism-led drug design to develop targeted radiosensitisers, building on experience with hypoxic cell radiosensitisers, perhaps targeting sequence-specific radiation 'hotspots' at the DNA level. Need to integrate radiation chemistry with drug development.
  2. Exploit tumour characteristics such as hypoxia or tumour-specific p450s for selective delivery to tumours of pro-drugs of chemical modifiers, e.g. nitric oxide.
  3. Inhibitors of DNA damage repair, possibly targeted using methods developed in (2) above.
  4. Develop chemical modifiers of normal tissue early and late damage, possibly modifiers of oxidative stress such as superoxide dismutase.

- Research into chemical and biological modifiers of tumour and normal tissue attempting to increase the effect of radiation on tumours and minimising it on normal tissues.

- Develop chemical modifiers of normal tissue early and late damage, possibly modifiers of oxidative stress such as superoxide dismutase.

- Mechanistically driven strategies based on free radical (bio) chemistry in the cell. Increase the relative efficiency of killing hypoxic tumour population, which is an important factor-limiting outcome of radiotherapy. Use mechanistically driven strategies based on the biochemistry of the hypoxic cell to activate pro-drugs to generate cytotoxins. Utilise the differential between tumour and normal cells in the metabolic oxidative/reductive pathways perturbed by radiation, to oxidatively activate pro-drugs to cytotoxic agents.

- Drugs that specifically target tumour characteristics have great promise. In particular hypoxic cells are increasingly implicated in negative outcomes for all aspects of cancer treatment including radiotherapy and their elimination must be a top priority. The current available compounds are promising, but developments of new classes of agent should be encouraged.

- The rational combination of radiotherapy with cytotoxic drug treatment.

Radiotherapy and Chemotherapy

- Combining radiotherapy with drugs in order to enhance efficacy or ameliorate side effects appears to have big gains in local control. These may be biological response modifiers, cytostatic drugs, or drugs targeted at modification of the induction or processing of radiation damage at the cellular or tissue level. Progress in basic radiation research may identify new targets for modulation of radiation effects.

- Combining appropriate chemotherapy modalities with radiotherapy, will require the initial validation of the combination's superior (additive/synergistic) effect and tumour specific response *in vitro*. Recently, the combining of CT & RT has led to dramatic improvements in tumour cure for certain tumour types.

- Bio-effect modelling combining the effects of radiotherapy and chemotherapeutic interventions in an organ / tissue specific manner. These modelling techniques need to incorporate functional information, (e.g. from PET and MRS) along with spatial information from CT and MRI together with tissue response assays based on gene expression.

- Combination of systemic therapy (established and novel) and radiotherapy.

- Improved understanding of mechanisms of chemoradiation to allow optimum scheduling.

- How to add to the tumour cidal effect, by the addition of chemotherapy or surgery etc?

- Rational integration of radiotherapy with chemotherapy based on (for example) improved knowledge of proliferation kinetics, sensitivity indicators, and apoptotic pathways. 'Chemoradiation' is a rather non-descriptive label and is probably to be discouraged: need to distinguish clearly between drugs that modify radiation response by direct interaction with radiation damage, and drugs acting independently but used in a rational way to improve overall therapeutic response.

- Establish mechanisms of synergy between radiation and chemotherapy/ novel agents and therefore how to exploit this fully.

- Drug interactions and the use of radiation to activate pro-drugs in the context of improving therapeutic ratio and normal tissue protection.

- Combination of chemo-radiation to overcome the effects of mutated genes in tumour cells which regulate cell division and survival (e.g. switch off apoptosis) Develop strategies to:
  I. turn on the apoptotic response in tumour cells, using chemical and molecular approaches, in combination with radiation to provide the apoptotic signal(s) and
  II. inhibit anti-apoptotic genes, based on knowledge of radiation-induced changes in regulation of 'DNA damage-sensing' and 'survival' genes.

Fractionation

- Dose fractionation in dealing with unscheduled treatment interruptions and new technologies. How to maintain treatment efficacy in the face of treatment 'gaps'. What it the optimal total dose and fractionation schedule to optimise treatment delivery in the emerging area of IMRT?

- New fractionation schemes based on radiobiological evidence to be deployed in the latest IMRT treatments involving dose escalation to enhance tumour control.

- Establishing the best fractionation regimens for each type of cancer (that is responsive to radiotherapy.
- To make radiotherapy treatment more sophisticated, e.g. conformal radiotherapy; combined chemotherapy and radiotherapy (provided this is safe); giving one (large) dose of radiotherapy during an operation to remove a cancerous tumour.

- Better co-ordination of clinical information from different departments. For example in Germany there is national co-ordination of treatment and outcome data on a site-by-site basis. In the UK, there is no such widespread co-ordination. This could really help to bring the debate on different fractionation regimes to an end.

- To gear fractionation regimens to the individual patient - (e.g. individuals who are (very) sensitive to radiotherapy would be treated with a lower dose and those who are much less sensitive could be treated with a higher than average radiotherapy dose).

Predictive Testing

- The evaluation and establishing of valid predictive tests of radiotherapy outcome; exploiting validated cellular/tumour end-point measures and genomic technology (i.e. micro-array) to predict the likelihood of tumour cure by radiotherapy and/or normal tissue complications. Success in this arena will ultimately allow for the individualisation of patient treatment by RT (or otherwise).

- Optimisation of radiotherapy treatment using genetic information to determine the radiosensitivity of tissue – both tumour and normal.

- Prediction of radiation response (tumour and normal tissue response).

- Continued research into the factors governing individual sensitivity to radiation including the genetic determinants of response as they relate to early and late damage and treatment-induced tumours. The aim is to identify patients at high or low risks of toxicity and tailor treatments accordingly, including selective use of preventive therapies. Research should aim

to produce robust genomic/proteomic assays that can be applied routinely.

- How do we select patients for optimal therapy, either selecting them for more or less dose or the addition of therapy e.g. sensitisors?

- Imaging analysis of molecular genetic markers determining outcome of treatment. (1) Using tissue/gene arrays developing predictive markers to rationalise trial strategy. (2) Develop ligands for visualisation by PET. (3) Develop strategies to modify the function of molecular and genetic determinants of outcome.

- Exploration of the potential of microarray technology as a tool to understand the heterogeneity of tumour and normal tissue biology and how this influences patient response to radiotherapy. Evaluation of the potential of pharmacogenomics to individualise patient treatment.

- To translate promising results from the studies described above to the clinic finally performing high standard randomised controlled clinical trials. This requires a network of laboratory and clinical research groups to work together to go through phase 2 and phase 3 testing in a collaborative fashion. There must be careful observation of tumour response and that of the normal tissues. Data generated needs handling and analysis by those experienced in this field and familiar with all aspects of radiobiology and radiotherapy.

Radiation Physics & Imaging

- Providing the biological and clinical knowledge base that will allow the current advances in radiotherapy planning and delivery to be converted into improved cancer therapy. This requires a major effort in translational and clinical research. Improved methodology for early clinical trials in radiotherapy and the development of surrogate markers for radiotherapy outcome would be most valuable in screening a large number of novel treatment strategies involving radiation therapy.

- Functional imaging.

- To target radio-resistant areas within the tumour due to hypoxia, cellular re-population and tumour bulk using the methods of imaging now available particularly using molecules which can be visualised using PET. This will be best achieved using animal tumour models followed by phase one study in patients guided by the findings of the animal tumour models.

- Improved dose distributions e.g. IMRT.

- Applied research based around major facilities such as CASIM, Proton Beam Therapy.

- Intensity Modulated RT

- Improved delivery techniques (IMRT, CRT, etc) and defining their clinical roles and utility.

- An important development will be the increased use of imaging to allow better tumour definition. This can be from functional imaging or at the most advanced level molecular imaging.

- It will be important to fully explore the role of IMRT over the next 10 years. To evaluate its advantages and limitations and to explore areas of dose escalation.

- Imaging and tracking internal organ motion; employing tacking signals to adjust radiation therapy fields in real time to optimise dose to the planning target and minimise dose to organs at risk, meanwhile updating treatment planning data including dose calculations also in real time.

- Application of engineering and physics technology to improve treatment delivery. In particular the use of IMRT and Image guided radiotherapy to optimise radiation effect.

- The development of novel radiolabelled agents for imaging tumour location, gene transfer and the effectiveness of therapy.

- Optimisation of radiotherapy using protocols for non-uniform irradiation of the clinical target volume. Up to now, the emphasis

has been on uniform doses. With the development of better (functional) imaging (PET, MRI), it should be possible, using IMRT, to target specific parts of the CTV for escalated dose.

- Improved imaging of the target volume during treatment, with capability of adjusting treatment on-line.
- Improvements in understanding normal tissue and tumour responses that will allow full advantages to be gained from improved imaging (PET, PET-CT, CT and MRI) coupled with improved treatment methods (IMRT, conformal RT, charged-particle RT (CASIM/SIRIUS?).
- How do we improve treatment delivery, by improving definition of the volume, delivering the dose more accurately, or reducing the dose bath?
- Technological advances in functional imaging and radiotherapy delivery.
- Improving precision of delivery to increase therapeutic index.
- IMRT development. Image guided radiotherapy. Treatment robotics.
- Scientific evaluation of methods for reducing normal tissue toxicity.

Targeted Radiation

- Molecular targets.
- Gene therapy combined with radiotherapy; in particular the utilisation of targeted radiotherapy with gene transfer strategies. Novel radiopharmaceuticals with short path lengths and high LET; such as radioastatine will be the optimum choice for radiolabelling.
- Optimisation of targeted radiotherapy by utilisation of the maximal effects of radiation mediated physical and biological bystander effects.
- To establish the benefits of targeting radiotherapy to a more localised area.
- Targeted (Monoclonal Antibody etc). Radioimmunotherapies.
- Gene transfer in combination with targeted therapy using radionuclides of high and low LET and of short and long range of emissions.
- Radiation directed gene therapy: Introducing a suicide gene into a tumour. The expression of the gene is controlled by radiation allowing temporal and spatial control of suicide vector gene activation combined with the proven effect of radiotherapy.

APPENDIX B

Questionnaire analysis 2

"What radiotherapy/radiobiology research evidence would have the most impact in improving services for cancer patients?"

Defining the target (imaging)

- Functional imaging

Treatment Planning Techniques

- The use of radiobiological parameters within complex treatment planning processes coupled to IMRT/ proton beam/ion therapy with a demonstration of improved outcomes defined as true therapeutic ratios {tumour control / toxicity}.
- Improved planning and treatment delivery – IMRT, tumour boundary definition etc.
- Animal studies relating functional images (PET, MRI) to biopsied tumour tissue to determine correlation between image and microscopic disease.
- Cell survival curves related to genetic information and clinical trials using the above results.
- Evidence that tumour resistance can be both identified and overcome, e.g. by combined treatments, improved delivery techniques or modified scheduling.
- Development of biomarkers (e.g. hypoxia, pre-disposition genes, DNA repair defects, guardian genes) to optimise the predictivity of treatment success. Early diagnosis of cancer with rapid intervention.
- Basic research into intrinsic sensitivity of normal and tumour tissue, proliferation of tumours and hypoxia could dramatically improve service to cancer patients because dose fractionation schedules could be altered either to give the same dose with greater cure or reduce overall time for the same cure.
- Factors influencing responses to radiation and radiation: drug interactions.

Individualisation of treatment

- Increased knowledge of both tumour and normal genotype would have the ultimate aim of individualising all aspects of cancer treatment.
- Stratifying/selecting patients according to key prognostic indicators should become easier with advances made e.g. in quantifying hypoxia and proliferation kinetics. 'Data mining' with gene arrays will identify new prognostic indicators.
- Means to identify the response of individuals to radiotherapy
- Evidence that patients could be selected for different therapeutic approaches in a way that ensures maximum efficiency-efficacy for the individual. Evidence of benefit form studies/trials of the above compared to current standard treatment.
- Optimisation of chemoradiation schedules.
- Evidence that individual sensitivity can be predicted and/or treatment modified to minimise treatment-related morbidity. This evidence would be expected to come from a combination of laboratory research, pre-clinical and clinical trials.

Technology of Delivering Treatment

- Increase the use of conformal radiotherapy and where appropriate IMRT.
- The Adoption of 'Translational Research' theme – whereby specific clinical problems are addressed by targeted laboratory research.
- Randomised controlled trials comparing high resolution dose escalated IMRT with conventional techniques.

- Are there more optimal ways of increasing the “effective” dose to increase tumour cure?
- Evidence from b) including novel molecular targeting/vascular acting agents.

- Outcomes of phase3 trials of IMRT.

- We require demonstrations of the effectiveness of novel therapeutic strategies. This must be shown in simple cell culture systems and then usually in animal models before proceeding to clinical evaluation.

Fractionation

- Fractionation Trials.

- Whether we really need to give 2 Gy fraction for radical RT – half the country uses 15-20 fractions for radical courses. If the latter group is right the manpower and machine crisis disappears overnight.

- Establishing methods of treatment and fractionation regimes that are most effective in eradicating (wherever possible) the cancer; reducing the risk of local recurrence; and causing the least damage to normal tissue.

- Simple trials comparing practice variations in radiotherapy e.g. START. Where results are positive they must be implemented.

- Data on the effect of patient waiting times as a function of clinical site, on optimum fractionation regimes and on national recommended best practice for each site. Better understanding at the fundamental level of the synergies of combined modality treatment.

- Reducing resource demand without reducing efficacy.

- There is enough radiobiological evidence that delaying the start of radiotherapy reduces the chances of patient survival. Ensuring that Clinical Oncology departments have the resources to treat all patients soon after they are referred for treatment would have the greatest impact. Standardising radiotherapy across the UK would have an impact. Updating treatment-planning resources across the UK would have an impact.

Side Effects and Outcomes (short-term and long term)

- Positive outcome as a result of treatment with minimal side-effects.

- Improved prediction of RT outcome and complications (inc. secondary cancers).

- Evidence from controlled clinical trials will be required for the ultimate documentation of a gain in therapeutic ratio. One bottleneck in current radiobiology/radiotherapy translational research is the transition from pre-clinical to early clinical testing. The methodology established for cytostatic drug development is not particularly useful in radiation oncology. At the same time, the proportion of patients receiving radiotherapy who actually contribute useful knowledge in a clinical research setting is disappointingly low, and we need new models for improving the synergy between routine care and clinical research. That such a positive interaction is indeed feasible is illustrated by the ongoing START trial.

- Demonstration and fast transposition to the clinic of novel effective therapies.

- Evidence Based Medicine of improved tumour control which can reasonably be expected to translate into improved survival without increase in treatment related morbidity. The new approaches should have or preferably require resources likely to be available in UK Cancer Centres in the foreseeable future.

- Above all, cancer patients need treatments that eliminate cancer as a factor in their lives whether that is through cure or long term control of their disease. Radiotherapy, when using best available practice, is an extremely effective form of treatment. Combination with any of the above developments (a-c) plus other developments in IMR and fractionation is likely to lead to very high levels of local control over the next 10 years. These developments are also likely to lead to

better approaches to dealing with disseminated disease.

- Positive health economic data supporting radiotherapy procedures. Mortality/ morbidity comparisons between radiotherapy and chemotherapy in specific tumours.

- National frameworks to apply existing evidence-based knowledge to current treatments.

APPENDIX C

Questionnaire analysis 3

What are the barriers (e.g. organisational, cultural, financial, institutional) to conducting research in these areas?

Financial

- Key researchers are often lost from teams due to inability to provide funding stability. In radiation biology, groups with novel approaches often waste senior staff in maintaining the current staff levels rather than in investigation.
- Grant funding for radiation research is harder to obtain that for chemotherapeutic approaches.
- The difficulty of securing anything other than short-term funding from the Charities and Government Bodies.
- NHS staff has limited spare time for research - emphasis is on meeting waiting list and financial targets only. Therefore, need funded research time or dedicated research posts with strong linkage to both University and Hospital environments.
- The surviving units for radiobiology/radiotherapy research having no long-term security.
- Financial, staff shortages within radiotherapy and equipment/machines.
- Radiobiology/radiotherapy research has suffered from progressive reductions in funding over the past 15 years. This has resulted, in part, from a perception on the part of those controlling the purse strings (overwhelmingly, non radiobiologists/ radiotherapists) that the scientific approaches in the research area were outmoded, and also a belief that the development of small molecules is the only way to cure cancer. True, radiobiology could have embraced the new molecular technologies more effectively in the past, but that is certainly not true today. We are also realising that an understanding of cancer biology at the tissue and whole animal level will be necessary to exploit new molecular developments and these skills have barely survived over the past 10 years, and mainly in the radiobiology research community.
- Support for research in this area is fragmented among the cancer charities, research councils, the NHS etc. In general, each agency perceives it as a relatively low priority in relation to, for example, the latest research in genomics or proteomics.
- Lack of support from funding bodies for radiation research. Diffuse nature of radiobiology research community, lack of strong links to high profile academic institutions or to departments carrying out related research outside immediate radiobiology community.
- The key funding bodies with their lack of recognition of the importance of radiotherapy in curing patients have contributed to the poor survival figures for UK cancer patients.
- Lack of funding for radiotherapy studies: in addition comparative ease of funding from commercial sources for chemotherapy studies divert many Clinical oncologists away from radiation based studies.

Organisational/Institutional

- It is very difficult to attract top researches to this field and in particular there is a desperate shortage of experienced radiation orientated Post Doctoral scientists.
- Lack of lab-based RT research. Few opportunities to train radiotherapists in research. Shortage of NHS research resources.
- Most radiotherapy trials can only be undertaken within the cancer centres and currently within the SWLCRN we are identifying clinical trials which can be undertaken within the DGHs, however clinicians and research staff can identify eligible patients within the DGHs for referral to the centre if they were more radiotherapy trials within common cancers.

- Stability must be achieved for key personnel in order to continue research. Senior staff spends most of their time attempting to obtain funding to maintain employment of research and technical staff as well as themselves - wasting valuable research time. Key staff members with knowledge and skills vital to continued research programmes often must leave due to the uncertain nature of grant funding. More experienced and valuable senior research staff becomes too expensive to maintain resulting in their departure to industry or the service sector, bleeding the academic department of valuable human resources.

- Low academic base.

- There is a major problem with lack of IT support to allow clinical data to be used with research data. Radiotherapy research has a very low profile. Undertaking radiotherapy research is hampered by the current waiting times and machine burden.

- Insufficient contemporary equipment in routine clinical use. No national focal point for research / development.

- Shortage of appropriately trained physicians, physicists and radiographers; lack of incentives to learn new ways of working and work longer hours.

- There are so few academic researchers left in radiation research in the UK. This applies to clinicians, scientists and those at the clinical-scientific interface. Each "University" cancer centre should ideally have an academic division of radiation oncology, with a professor of Clinical Oncology and Medical Physics.

- Insufficient treatment machines and chemotherapy machines (for planning); and insufficient staff, especially therapeutic radiographers and physicists. There is a lack of knowledge, understanding and hence commitment to radiotherapy services amongst the general population and amongst those with the purse strings. It is really only when you have personal or professional experience of cancer and radiotherapy that you understand its importance and the lack of resources.

- There is a lack of satisfactory scientific support, and little educational support, for this type of key activity. The lab techniques do not translate easily or directly into the clinic. The clinical staff are always driven by clinical demands and a lack of "research" sessions in NHS contracts.

- Shortage of key staff in radiography and medical physics and clinical oncology. Consultants are generally too busy to spend enough time doing interesting research and therapy radiographers are difficult to recruit.

- The scientific knowledge base in radiotherapy in the UK has decreased over the last 10 years. As a consequence the number of clinicians with sound knowledge of radiobiology has also decreased.

- Too few academic clinical oncologists – partly due to exams, emphasis on large service commitments.

- Clinical oncologists wanting to do research drawn to molecular biology, chemotherapy questions rather than radiation research.

- There has been a lack of co-ordination in the UK of laboratory and clinical research in the radiotherapy/radiobiology area, even though: radiotherapy continues to be a major treatment modality, there is plainly much room to improve its efficacy, there are scientifically promising avenues to improve it.

- Essential to provide training of researchers and radiation oncologists to ensure availability of the essential expertise for the future to made significant advances.

- To be pro-active in advancing cancer treatments through active, inter-disciplinary interactions between the clinic and the laboratory. A good balance between fundamental research & translational research.

- Lack of ambitious self-generating academic clinicians that are trained in research.

- Lack of critical mass generally on the clinical medical physics and biology side.

- Lack of an organised UK strategy, which makes the most of the resources and

assures that the sum is greater than the parts.

- Too much reliance in radiotherapy on using a NHS resource.
- There will be ZERO radiotherapy based academics in this country in 10 years if this pattern continues.

- Translation of pre-clinical to clinical research and subsequently clinical research to clinical practice: in drug development this is facilitated very successfully by drug companies.

- Lack of infrastructure and career pathway for academic clinicians, many potential candidates feeling that an academic career is hopeless.

- Too few researchers in translational radiobiology.

- Junior staff shortages, particularly radiographers.

- Main problem is organisational: lack of career structure for young/mid-career scientists, exacerbated by retirements, career changes and emigration of skilled specialists in short supply. Closely linked are the effects of these losses on the ability to teach and train a new generation, even if funds were freely available. To some extent these problems could be described as 'cultural' since effective multidisciplinary work is essential.

- Deprivation of the resources required for cancer treatment in Cancer Centres presently make it difficult to deliver long-established treatments and this discourages interest in the application of advances in practice translated from the laboratory.

- Radiotherapy is under-resourced. There should be more clinical trials so that many more radiotherapy patients are entered into clinical trials. Radiobiological data should be obtained as part of these trials. Radiotherapy departments throughout the UK are overstretched with a much higher service load than for Medical Oncology departments.

Cultural

- Despite a very strong tradition in the UK for evidence-based medicine, it is unfortunately true that radiotherapy is less research driven than medical oncology as illustrated by the slow acceptance in routine practice of therapeutic advances supported by Level I evidence. The historical evolution of conflicting schools of radiotherapy in this country is a major impairment for development of national and international radiotherapy trials. This has probably also weakened the political impact of radiotherapy and the whole field seems to be lacking a voice in many political or organisational contexts. 'Classical radiobiology' has been very strong in the UK but is now undergoing a difficult, but necessary transition. Unfortunately, many radiobiologists have been too reluctant to integrate new biological concepts in their research programmes. The UK has many very strong basic research groups, but these are largely detached from clinical therapy. In the case of new drug development, the road from pre-clinical to clinical research is paved with money from the pharmaceutical industry.

- Misconception, particularly in the late 1980s and early 1990s, that anything with radiation in it was 'bad'. The attitude failed to recognise the advances made by the field and its integration with new biological concepts. The impact of radiation science on basic and applied biology has been substantive (as described, for example, in the recent article by Bedford and Dewey (Radia Res 158, 251-259, 2002). In the USA, radiation science, radiation biology and radiation oncology have continued to be well supported.

- Neglect of Academic Radiation Oncology progressively over the past 20 years.

- A culture of scepticism concerning scientific research among practising radiation oncologists in the United Kingdom.

- To conduct fractionation trials would require a major change in culture in the South of England and would present resource problems elsewhere as a trial would increase the mean number of fractions per patient in already stretched departments.

Nonetheless it should be done as a matter of urgency. Chemo RT studies are ongoing and more participation should be encouraged via NCRN etc. Molecular marker studies are again ongoing. Major obstacles include funding and also ethics of tissue collection (esp. post Alder Hey as we are prevented from studying surplus stored tissue without consent from patients who may in fact be long dead).

- Culture that radiobiology research is unexciting/difficult to fund (lack of drug company support in comparison to chemotherapy).
- Impression that much radiobiology is mathematical modelling and of little clinical relevance.
- Lack of research/academic ethos in clinical oncology (especially in comparison to medical oncology).
- Lack of culture or prioritisation of research in radiotherapy.
- Radiobiology related to radiotherapy research has become so unfashionable and seemingly under-valued that it is hard to attract good scientists into the area, and many radiobiologist trained in England have left the country.

Apart from more funding, or ring-fenced funding, how can we overcome these barriers?

- Better links between scientists and clinicians must also be forged to allow transposition of novel therapies to the clinic. Our experience suggests that the clinical logistics of treating patients with targeted radiotherapy often preclude its investigation.
- Because of the large scale required for the clinical trials, consideration should be given to international (EORTC) trials.

APPENDIX D

NCRI RADIOTHERAPY/RADIOBIOLOGY PROGRESS REVIEW GROUP

Name	Position	Organisation
Dr C Norman Coleman	Director	National Cancer Institute
Professor Stanley Dische	Director	Gray Cancer Institute
Professor Dudley Goodhead	Director	MRC Radiation and Genome Stability Unit
Professor David Hirst	Professor of Radiation Science	School of Biomedical Sciences, University of Ulster
Professor Alan Horwich	Chairman, Section of Radiotherapy	Royal Marsden NHS Trust/ICR
Dr Peter Hoskin	Consultant in Clinical Oncology	Marie Curie Research Wing, Mount Vernon Hospital
Dr Tim Illidge	Senior Clinical Lecturer, Cancer Sciences	School of Medicine, University of Southampton
Dr Nicholas James	Reader in Clinical Oncology	Cancer Research UK Institute for Cancer Studies, University of Birmingham
Mr John Jeans	President - Therapy Products	Department of Radiation Oncology, Amersham Health
Dr Rob Mairs	Group Leader	Department of Radiation Oncology CRC, Beatson Laboratories
Professor Trevor McMillan	Professor of Cancer Biology	Department of Biological Sciences, Lancaster University
Professor Allan Price	Professor of Radiation Oncology	Clinical Oncology Department; University of Edinburgh
Professor Pat Price	Professor of Radiation Oncology	Academic Department of Clinical Oncology, Christie Hospital NHS Trust
Mr Derek Stewart	Chairman	Gedling Primary Care Trust
Professor Ian Stratford	Professor of Pharmacy	School of Pharmacy & Pharmaceutical Sciences, University of Manchester
Professor Steve Webb	Professor of Radiological Physics	Institute for Cancer Research and Royal Marsden NHS Trust
Dr Cathy West	Experimental Radiation Oncology Group	Paterson Institute for Cancer Research, Christie Hospital

List of Delegates

WORKSHOP – Friday 28th June 2002

Name	Organisation
Mrs Helen Bailey	Department of Health
Mrs Angela Ball	Christie Hospital, Manchester
Dr Jim Barber	Velindre Hospital, Cardiff
Professor Søren Bentzen	Gray Cancer Institute, Middlesex
Mr George Binney	Ashridge Consulting Ltd
Dr Marie Boyd	Beatson Laboratories, Glasgow
Dr Helen Campbell	National Cancer Research Institute
Dr Dai Chaplin	Oxigene Inc
Dr C Norman Coleman	National Cancer Institute, USA
Dr Lynne Davies	National Cancer Research Institute
Professor Stanley Dische	Gray Cancer Institute, Middlesex
Dr Angela Galpine	Cancer Research UK
Miss Ethna Glean	Society of Radiographers
Professor Dudley Goodhead	MRC Radiation & Genome Stability Unit, Harwell
Dr Stuart Green	Queen Elizabeth Hospital, Birmingham
Ms Rachel Gresty-Bayes	South West London Cancer Research Network
Ms Julie Hearn	National Cancer Research Network Co-ordinating Centre
Professor David Hirst	University of Ulster
Professor Alan Horwich	Royal Marsden Hospital, Surrey
Dr Peter Hoskin	Mount Vernon Hospital, Middlesex
Dr Tim Illidge	University of Southampton
Dr Nick James	University of Birmingham
Mr John Jeans	Amersham Health, Buckinghamshire
Dr Sarah Jefferies	Addenbrookes Hospital, Middlesex
Dr Penny Jeggo	Sussex Centre for Genome Damage & Stability
Dr Bleddyn Jones	Imperial College, London
Dr George 'Don' Jones	University of Leicester
Mrs Margaret King	NCRI Patient Liaison Group
Dr David Landau	St Thomas' Hospital, London
Dr Rob Mairs	University of Glasgow
Mrs Samia Majid	National Cancer Research Institute
Professor W Gillies McKenna	University of Pennsylvania, USA
Dr Alan Melcher	St James' Hospital, Leeds
Dr Barry Michael	Gray Cancer Institute, Middlesex
Professor Alastair Munro	Ninewells Hospital & Medical School, Dundee
Dr Peter O'Neill	MRC Radiation & Geonome Stability Unit, Harwell
Dr Liam O'Toole	National Cancer Research Institute
Dr Jens Overgaard	Danish Cancer Society, Denmark
Professor Allan Price	University of Edinburgh

Name	Organisation
Professor Pat Price	Chrisitie Hospital, Manchester
Professor Roy Rampling	University of Glasgow
Dr Martin Robinson	Weston Park Hospital, Sheffield
Dr Gill Ross	South West London Cancer Research Network
Mrs Donna Routsis	Society of Radiographers
Dr Magdalena Sara	National Cancer Research Institute
Dr George Sarna	Medical Research Council
Professor Michelle Saunders	Mount Vernon Cancer Centre, Middlesex
Dr Susan Short	Gray Cancer Institute, Middlesex
Mr Derek Stewart	NCRI Patient Liaison Group
Professor Ian Stratford	University of Manchester
Dr John Toy	Cancer Research UK
Dr Janet Valentine	National Cancer Research Institute
Mrs Linda Ward	National Translational Cancer Research Network
Dr Peter Wardman	Gray Cancer Institute, Middlesex
Professor Steve Webb	Royal Marsden Hospital, Surrey
Dr Cathy West	Paterson Institute, Christie Hospital, Manchester
Professor Eric Wright	Ninewells Hospital & Medical School, Dundee
Dr John Yarnold	Royal Marsden Hospital, Middlesex

NCRI Radiotherapy and Related Radiobiology Progress Review Group Response from NCRI Partner Organisations

July 2003

NCRI Radiotherapy and Related Radiobiology Progress Review Group
Response from NCRI Partner Organisations

Contents

1 PURPOSE OF THIS DOCUMENT

The PRG Report has been discussed by NCRI Partner organisations and this document represents a response to the issues raised. This document will be published as the formal response from the NCRI Partners.

2 REASONS FOR SETTING UP A PROGRESS REVIEW GROUP IN RADIOTHERAPY/ RADIOBIOLOGY

The NCRI Partners agreed that whilst Radiotherapy remained a major treatment modality it was characterised by a relatively small number of research groups with long term funding. The funders faced key decisions on the future of a number of these groups and the field in general faced difficulties in bringing in new people. The NCRI Partners agreed that it was important to get an overview of the field to inform their long-term strategic planning.

3 RESULTS OF NCRI ANALYSIS OF RADIOTHERAPY / RADIOBIOLOGY RESEARCH

3.1 Scope of the analysis

In order to get a feel for the state of the research base in radiotherapy and radiobiology research, an analysis was done of the NCRI Cancer Research Database (CRD).

The NCRI CRD contains the complete up-to-date research portfolios of the 15 largest Government and Charity funders of cancer research in the UK.

The database only includes entries where funding can be directly attributed to a set of clearly defined research objectives. Each of the 1864 records on the database includes details of the researcher(s) carrying out the work and an abstract or brief description of the funded research. This means that the CRD only contains information on all direct research funding (project, programme, fellowship, unit and institute) currently financed by an NCRI Member organisation.

Research included on the CRD is classified on the basis of an abstract detailing the research objectives at the time of award. Analysis of the database therefore gives an indication of the broad trends in different types of cancer research but should not be taken as an exact measure of the total research activity in any one area. The coding should therefore be regarded as a useful indicator of the 'centre of gravity' of a particular piece of research rather than a comprehensive description of all the aims and possible outcomes of that study. Further details on how and why the database was developed can be found in the NCRI Strategic Analysis 2002 (www.ncri.org.uk).

Developing a search strategy for radiotherapy research is relatively straightforward, identifying a strategy that will pick up all radiobiology research 'directly relevant to radiotherapy' is more challenging and will inevitably involve a degree of subjectivity and include some basic radiobiology unrelated to cancer therapy and also some radiobiology underpinning other fields such as carcinogenesis and radiation risk. In this case, a search filter was designed to identify research that captures all radiotherapy research and most underpinning radiobiology research that studies the effects of radiation exposure in the cell. It is acknowledged that not all of this research will be directly applicable to radiotherapy.

Using this definition, a combined analysis of RT/RB research and a more detailed separate analysis have been conducted.
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3.2 NCRI Partners Organisational spend

The NCRI spend of £15 million on RT/RB research constitutes 6% of the total Partners research spend of £257 million on the NCRI CRD (April 2002). This represents, £12 million spent on Radiotherapy and £4 million spent on underpinning radiobiology research that studies the effects of radiation exposure

in the cell. Figure 1 shows RT/RB spend by NCRI Member organisations. Three organisations, CRUK, DOH, and the MRC make up 96% of the total spend. The same three organisations fund the majority of the Radiotherapy research (Figure 2). Underpinning radiobiology research that studies the effects of radiation exposure in the cell research is funded mainly by the MRC and CRUK (Figure 3).

3.3 Duration of funding

The duration of funding is a useful descriptor of the health of a research area or field. Analysis shows that most of the annualised spend in both the combined RT/RB research and in the separate radiobiology and radiotherapy fields (about 80%) is in the form of long-term support (i.e. grants ≥ 3 years) (Figure 4 a,b,c).

3.4 Analysis of RT research into different cancers

Cancer research has been divided into two modes of study; research that is focused on specific tumour types (Site Specific Research) and research that is generic and may be applied to all types of cancer. Over half of radiotherapy research is site specific. Prostate and breast cancer RT research currently receive the most site specific funding (Figure 5). It must be noted that the majority of the Prostate spend is attributed to the ProtecT Trial (evaluating the effectiveness of treatment for clinically localised prostate cancer).

3.5 Distribution of RT/RB funding

Figure 6 shows current distribution of funding for RT research by NCRI Partners mapped across the UK. Two cities, London (74%) and Manchester (13%) have the majority of the NCRI Partners RT research spend. Further analysis of the distribution of RT funding within the UK is shown in Figure 7; there is significant variation in investment between the different institutions receiving funding. The highest proportion is currently attributed to a single research site (Gray Cancer Institute) funded predominantly by CR-UK. High levels of funding and research activity are also concentrated at the Institute of Cancer Research, MRC Clinical Trials Unit, the Royal Free/UCL and the Paterson Institute in Manchester.

Underpinning radiobiology research that studies the effects of radiation exposure in the cell, on the other hand is concentrated in four main centres Harwell, London, Dundee, and Manchester (Figure 8).

4 NATURE OF NCRI RESPONSE

The NCRI is a partnership that brings together cancer research funding bodies from the Government, Charity and industrial sectors. The role of the NCRI is to:

- Take a strategic oversight of cancer research in the UK
- Identify gaps in current research and opportunities
- Plan and co-ordinating approaches between funding bodies to fill gaps and take advantage of opportunities
- Monitor progress in implementing agreed plans and in achieving agreed objectives

As an umbrella body, the NCRI focuses its efforts on activities that:

- Clearly add-value
- Could not be accomplished by a single member organisation
- Have the potential to benefit patients and the research community

The NCRI Partnership can respond to strategic needs and opportunities in a number of ways:

Joint action by member organisations

A number of NCRI partners, in particular MRC, Cancer Research UK and DH are currently considering the future of some of their major investments in this area. The recommendations in this report will be critical

in informing each organisation's strategic discussions. In particular members recognise the need to build up a small number of multidisciplinary centres of excellence alongside clinical centres with links with basic biology. The intention would be to promote multidisciplinary and translational research. These organisations have undertaken to work closely together to ensure that they develop a coherent and complementary approach to the area.

Examples of action might include:

- Co-funded initiatives
- NCRI Position Statement
- Negotiation with a third party organisation on behalf of the NCRI
- NCRI Workshop
- NCRI Report or Analysis
- Action through NCRN or NTRAC
- Focussed collaboration between research units funded by different partner organisations
- Agreement to co-ordinate specific ongoing activities

Action taken by an individual member organisation

All NCRI Partner organisations are research funding bodies and have their own mechanisms for funding research and responding to strategic imperatives. Strategic discussions within the forum provided by the NCRI allow partner organisations to individually respond to a strategic or scientific driver identified in an NCRI review by using its existing mechanisms or developing new approaches. By working closely within the NCRI partnership these organisations can ensure that individual actions they take are part of a coherent national approach to the issue.

5 RESPONSE FROM NCRI PARTNERS

The NCRI Partners welcome the PRG Report and the options for action suggested by PRG members. They accept that in order to ensure the health of the field the following is needed:

- Promoting multidisciplinary working
- Establishing critical mass and stability of funding in a number of research groups
- Major change in the approach to training in the area
- Improved communication and networking and profile within the research community

The NCRI Partners response is focused on achieving these key aims.

Proposed Joint Actions

- A number of NCRI partners, currently have significant investments in this area and have agreed to work closely to ensure that their future funding develops in a coherent manner. The recommendations from this report will inform decisions taken by organisations on current investment. These organisations are also willing to consider (individually or collectively) approaches from any HEI's with locally developed strategies to develop RT/RB research groups.

  The NCRI will approach the Royal College of Radiologists to discuss a number of issues:

  a. Review of research training and career structure for radiotherapists. In particular, an aim will be to encourage more widespread adoption of a years research training during the statutory five years professional training period.
  b. Explore the possibility of joint Fellowship schemes between the Royal College and NCRI member organisations.

c. An initiative within the Royal College of Radiologists to promote research, perhaps building on the model developed by the Royal College of Surgeons.

- The NCRI Partners will encourage applications for clinical and basic science in this area. The aim will be to increase the numbers of people coming through and to ensure that there is appropriate joint supervision from radiation biologists and clinical oncologists in order to ensure an appropriate translational training environment.

- All NCRI Partner organisations will consider the issue of representation on peer-review committees

- NCRI Partners will explore the feasibility of joint funding approaches with non-NCRI partners such as EPSRC

- NCRI will consider running workshops with representatives from appropriate industries to explore closer interactions through NTRAC

- NCRI Partners will consider the need for establishing further networks and consortia in radiation research

- The NCRI will review the role of existing networks (NTRAC, NCRN, NCRI CSG) in relation to RT/RB research

- The NCRI Partners will use existing funds left over from the UKCCCR Radiation Programme to establish a National Quality Assurance Program to underpin ongoing radiotherapy trials

Specific actions proposed by individual member organisations

MEDICAL RESEARCH COUNCIL

As a result of the NCRI PRG the MRC has highlighted multidisciplinary research that links RT/RB research and cancer biology as one of its **new research funding and training priorities for 2003/04.**

i. Encouraging multidisciplinary collaboration:

The progress review group acknowledged that there is a need for RT/RB research groups to exploit approaches already successfully harnessed in other areas of cancer research, in particular genomic approaches. The MRC would be keen to receive high quality proposals that cross the boundary between RT/RB and cancer biology. MRC would also be keen to work with groupings able to prepare such proposals to identify the best way to support intellectually stimulating and well-resourced environments that provide high quality training opportunities.

MRC would be pleased to develop links between centres such as the MRC Radiation and Genome Stability Unit, Harwell, the MRC/University of Sussex Centre Development in Genome Damage and Stability, and other centres of excellence, particularly to maximise the potential and impact of the UK expertise in this important field and its translation to radiotherapy. MRC is interested in further collaborative links with other funding agencies and organisations such as NTRAC to take this area forward.

Specifically MRC recognises that the search for a new Director for RAGSU presents opportunities to develop the remit and research at this Unit in new directions. **MRC will conduct a search for a new Director with expertise in radiation biology and cancer. It will explore the feasibility of making this a joint post with Oxford University and will discuss with other NCRI Partners the possibility of joint funding**

programmes to develop radiation/biology and cancer in Oxford.

ii. Training, Career structure and workforce capacity.

MRC welcomes the recommendations to address training and career structure for radiotherapists. Council expects, following the 2002 spending review settlement, to seek to expand the number of MRC fellowships in all areas of biomedical research**.** MRC has made multidisciplinary research that links RT/RB research and cancer biology a strategic priority for its fellowships in this area and would welcome high quality applications.

The MRC Discipline Hopping Awards are short term grants aimed at encouraging imaginative ways to use physical science techniques or expertise to tackle biological, medical or medically related problems. **MRC would therefore welcome Discipline Hopping applications from physical scientists wishing to work in radiotherapy research.**

iii. Communication and Networking

MRC has placed particular emphasis on providing long-term funding for multidisciplinary groupings, through its co-operative, development and centre grant schemes. These schemes provide a route to building up a critical mass of research effort within a field and the opportunity to bid for funding for infrastructure, in partnership with other funding agencies and HEIs. **MRC would be happy to discuss with researchers the case for funding for the networking of groups, with a view to preparing applications for research funding.**

DEPARTMENT OF HEALTH

DH welcomes the PRG's report. The report **is already influencing DH investments** in RT/RB research.

For example DH is making £900K available through the NCRN to enable NHS patients to enter the National Institute of Canada/American College of Surgeons Oncology Group trial of **brachytherapy for prostate cancer**. The NCRI Prostate Cancer Clinical Studies Group and the NCRN are working closely together to take this trial forward in the NHS.

DH has also agreed to provide £300k through the NCRI South of England Prostate Collaborative to support the evaluation of the safety and effectiveness of **IMRT for prostate cancer.**

With regard to **promoting multidisciplinary working** the new NTRAC centres involve over 2000 cancer researchers from many disciplines. As a result of the PRG report NTRAC is actively looking to foster multidisciplinary working on RT/RB research across relevant NTRAC centres. Multidisciplinary working has always been a key criterion in DH/NHS R&D funding decisions.

With regard to **critical mass and stability of funding** NHS R&D Funding is currently being modernised to form Support for Science and NHS Priorities and Needs Funding (PNF). PNF takes the form of a research programme lead by an NHS/Academic grouping. This form of funding will provide much more stability. A number of PNF Programmes include radiotherapy/ radiobiology research.

DH has recently established NTRAC in partnership with NCRI funding partners. NTRAC involves the top ten comprehensive cancer centres in England. Funding is long-term and associated with flexibility in terms of unblocking barriers to the rapid development of new treatments and diagnostics. **A number of NTRAC centres are active in RT/RB research.**
DH has also recently established the NCRN to provide major NHS infrastructure for cancer trials. **The NCRN trials portfolio includes a number of RT/RB trials.**

With regard to **research capacity and training**, the NHS Research Capacity Development Programme is currently

reviewing provision for personal award schemes following DH restructuring in line with Shifting the Balance of Power. The PRG's report will clearly be of interest in this respect.

It is acknowledged that research-active NHS staff research time sometimes suffers as a result of service pressures. However various actions set out in the NHS Cancer Plan, such as extra cancer consultants, more radiographers, and new ways of working may help to protect dedicated research time.

With regard to **improving communication and networking**, these are key features of the new NCRN and NTRAC. With regard to improving the profile of RT/RB research, NTRAC has agreed to host a workshop on translational RT/RB research later this year.

CANCER RESEARCH UK

Cancer Research UK is in the process of developing its scientific strategy for the future and in the area of radiation science will seek to take note of the important points raised in the PRG report.

CR-UK welcomes the review group's recognition that RT/RB research needs to interact more with other areas of cancer biology and apply techniques which are providing important information for other aspects of cancer treatment. For instance there will be opportunities to understand the basic biology underpinning the selective killing of cancer cells by ionising radiation arising from the biology of DNA repair and the cell death response to DNA damage. **Through its response-mode project and programme grant funding CR-UK would seek to support high quality proposals which embraced this approach.**
The success of the CHART studies indicates that there are still important therapeutic questions to be answered concerning radiation fractionation and delivery, and the use of radiation in combination with other treatment modalities. It is expected that the Radiotherapy CSG will develop protocols in these areas and put forward for funding via the CTAAC route.

CR-UK notes the emphasis placed on multidisciplinary approaches to RT/RB research and the potential benefits from maintaining centres of excellence in radiation science which are interactive/integrated with the wider academic cancer research community. In particular, CR-UK recognises that the Gray Cancer Institute is at a critical phase in its development and the comments of the PRG will be helpful in considering approaches towards its future evolution.

Cancer Research UK has recognised that problems exist in the development and maintenance of a clinical research career across all cancer-related specialities, and is seeking to address this through appropriate fellowship schemes. It recognises that the situation is exacerbated in relation to clinical oncology (radiotherapy) by the very few academic departments in UK universities.

Cancer Research UK appreciates that there are currently real difficulties in RT/RB research in the UK and will, where and when appropriate, work with other agencies to promote and support a strong research base relevant to radiation science.

6 NEXT STEPS

The NCRI Board have agreed to establish a Strategic Planning Group (SPG) made up of senior representatives from the major NCRI funding bodies, to oversee the implementation of their responses to the PRG Report.

The role of the SPG will be to implement the joint actions agreed in this response document and ensure that NCRI partners develop a coherent national approach to the field of radiobiology/radiotherapy research.

Implementation is intended to be an ongoing process where the NCRI Partners will continue to discuss and work with the community in addressing the key issues. Part of this process will be for the SPG to meet

with PRG members to discuss their response to the PRG Report.

The SPG will prepare a progress report within a year of publication of the response.

Annex 1 Executive Summary of the PRG Report

1. The NCRI secretariat was asked to set up a review with the following remit:

    - To review the current state of radiotherapy/radiobiology (RT/RB) research in the UK.
    - To identify: UK's strengths and weaknesses; scientific opportunities for the UK; barriers to progress; recommendations for overcoming these barriers.
    - To identify: what research evidence is required to underpin the advancement of services in the UK.
    - To report to the NCRI Board.

2. The review was designed to cover all clinical radiotherapy research plus underpinning medical physics research and underpinning radiobiology research that was directly relevant to clinical application. The review was not designed to include very basic radiobiology, unrelated to cancer therapy such as certain aspects of DNA damage/ repair, carcinogenesis, radiation chemistry etc, nor radiobiology underpinning other fields.

3. A review process built around the Progress Review Group (PRG) model used by the NIH NCI was developed. This was the first such review carried out by the NCRI and the process was designed to act as a pilot exercise for PRG methodology. The PRG process was carried out in three stages: an initial meeting, a questionnaire survey and a larger Roundtable discussion.

4. The PRG and Roundtable discussion groups identified important therapeutic research opportunities for RT/RB in the fields of molecular radiosensitivity; predictive testing; radiosensitisation; imaging; applied physics; targeting of systemic isotopes. The dual training of UK clinical oncologists in both chemotherapy and radiotherapy creates particular potential for clinical research.

5. RT/RB research in the UK has declined over the last decade. Although important and relevant scientific questions are there, the critical mass of people active in RB is heading towards the point where it will no longer be sustainable as an academic discipline. The major clinically applied RB groups in the Gray Laboratories, the Institute of Cancer Research (ICR), and recently in Manchester, have either retired, departed or moved to other research fields. There are also few Academic (i.e. university) Radiotherapy consultant appointments in the UK, an estimate of 26 in total. Some of these appointments, especially in Scotland, are funded by the NHS and have substantial service responsibilities greatly limiting research time. This is also limited for NHS Consultants due to service pressures.

6. There is a threat that the lack of RB research will be self-perpetuating as neither academic clinicians nor scientists can enter a UK laboratory for appropriate training.

7. Funding for radiotherapy and radiobiological research in open competition with other areas of cancer research has in general not competed well. In part this may be because "classical radiobiology" was categorised as low priority by one funding body in the mid 1990s. There is a perception in the RT/RB research community that an under-representation on peer-review committees has contributed to a reduction in funding.

8. Many RT/RB groups have not collaborated with molecular biologists and clinicians developing associated therapeutic modalities. This means that the UK RT/RB research community has not been well placed to capitalise on advances in other areas of cancer research.

9. A range of modern cancer research topics have relevant applications in RT/RB. An inability to exploit these would be to the detriment of both the public and of the scientific community. These include: DNA repair; angiogenesis; apoptosis; hypoxia and other stress responses; cell cycle control; stem cell research; growth factors and receptors. At the same time there is the opportunity to gain a more sophisticated

understanding of RT problems, such as cellular radiosensitivity and mechanisms of normal tissue injury.

10. RT/RB research needs to be developed as an integrated component of more broad-based biological research. This has major implications for the way funding is organised and how we train the next generation of researchers.

11. Re-growth of RT/RB research in the UK would be valuable but will require a coherent approach from key stakeholders to effect a change in the culture and profile of the subject. These include, not only the NCRI funding bodies, but also the Royal Colleges, the radiotherapy/radiobiology community itself and the wider research community. Particular issues are:

- Promoting multidisciplinary working
- Establishing critical mass and stability of funding in a number of research groups
- Major change in the approach to training in the area
- Improved communication and networking and profile within the research community

12. Multidisciplinary collaborations are key to the future of radiotherapy research in the UK. The challenge is to encourage integration while maintaining a skill base in cellular and animal models for RB.

Options for action:

- Fund high quality RT/RB research groups within existing multi-disciplinary cancer research centres
- Encourage interdisciplinary research collaborations by offering funding incentives – this could be done through partnerships between different funders (MRC/EPSRC/ BBSRC/CCLRC/ DoH, CR UK)
- Build up a small number of multidisciplinary centres of excellence alongside clinical centres, which would address the problems of critical mass and links with more basic biology, and would promote multidisciplinary and translational research
- Organise a series of cross-disciplinary research conferences/workshops that promote interdisciplinary working

13. Funding is an influential lever to attract and retain key researchers, and the funding process needs to take account of the special needs of long-term translational research. Clinical research in RT/RB has less recourse to commercial funding than chemotherapeutics. There is a need to ensure a viable network of centres with the appropriate configuration of expertise, personnel, equipment and equipment time to underpin multi-centre clinical trials.

Options for action:

- Strategic/targeted funding initiatives in key RT/RB areas
- NCI model of separate funding stream for RT/RB research with strategic leadership
- Provide core funding for a number of Centres for RT/RB Research in appropriately multi-disciplinary environments
- Coordinate joint funding between different agencies, in particular MRC/EPSRC/BBSRC/CCLRC/CRUK
- Review the representation of RT/RB on key peer-review panels
- Examine the infrastructure issues underpinning RT/RB clinical trials

14. Flexibility of clinical training in RT is an issue for the Royal College of Radiologists though additionally laboratory-based research training fellowships need funding support. Overseas fellowships for clinicians and scientists may be optimal in the short term for subjects not available in the UK.

Options for action:

- Review training and career structure for radiotherapists specified by the Royal College of Radiologists and ensure dialogue with NCRI
- Review the career structure for scientists in Radiotherapy /Radiobiology Research

- Protect research time for NHS clinicians and other research-active NHS staff such as physicists and radiographers
- Consider how to improve attractiveness of academic consultant posts in RT/RB research
- Create appropriate training environments in large multidisciplinary centres
- Extend support of core Clinical Research Fellowships to departments with training capacity
- Create a number of five-year Fellowships for laboratory research workers and of clinicians preparing to devote their careers to translational RT/RB research and consider their long term career structure

15. RT/RB communication, networking and profile would gain from strategic leadership with the responsibility to report on progress to the NCRI. The US model within the NCI is seen as effective. This has bearing on collaboration with industry and new structures such as NTRAC, as well as on problems of applying research findings in the NHS.

Options for action:

- Explore models for providing ongoing strategic direction for the field
- Discuss dissemination and implementation of results with key stakeholders (radiotherapy community, Royal Colleges, NHS)
- Run workshops with industry to explore closer interactions (NTRAC?)
- Consider the need for establishing further networks and consortia
- Review the role of existing networks (NTRAC, NCRN, NCRI CSG)

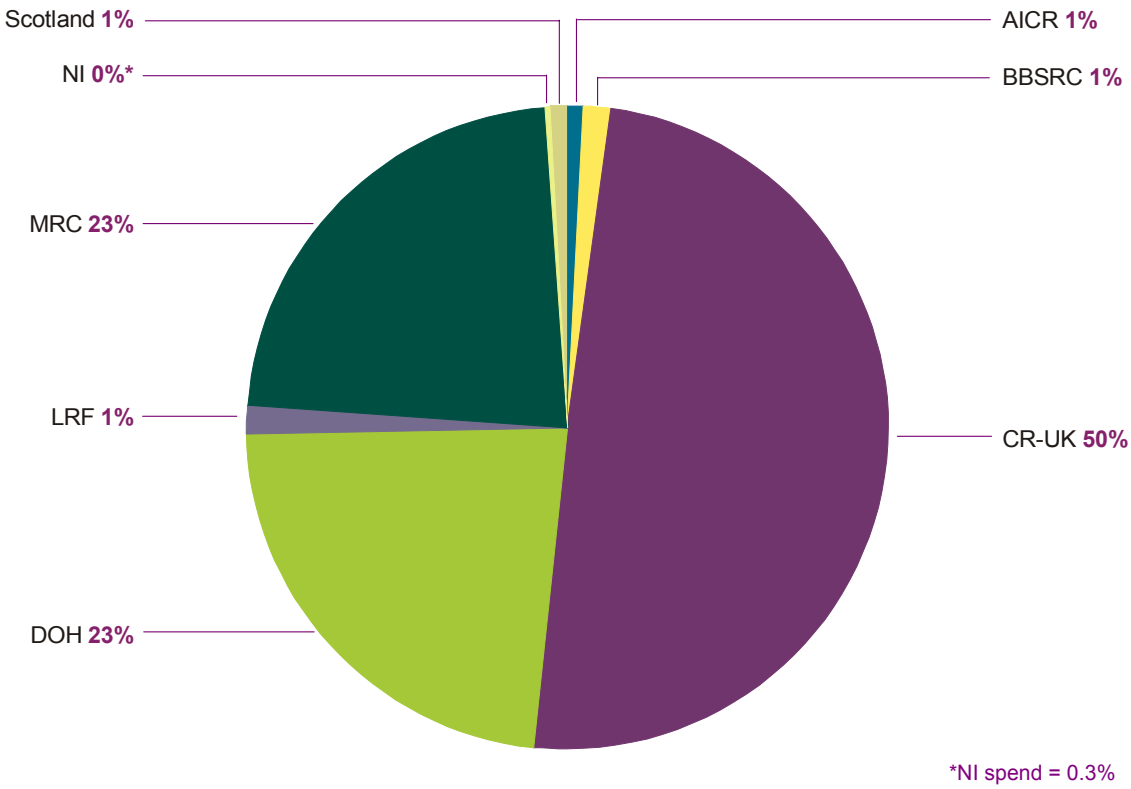
16. The profile of RT/RB research has been raised by the PRG process and will gain further from a declared strategic prioritisation by NCRI.

Options for action:

- Organise a high profile conference on 'Radiotherapy Research in the NHS'
- Establish an initiative within the Royal College of Radiologists to promote research, perhaps building on the model developed by the Royal College of Surgeons

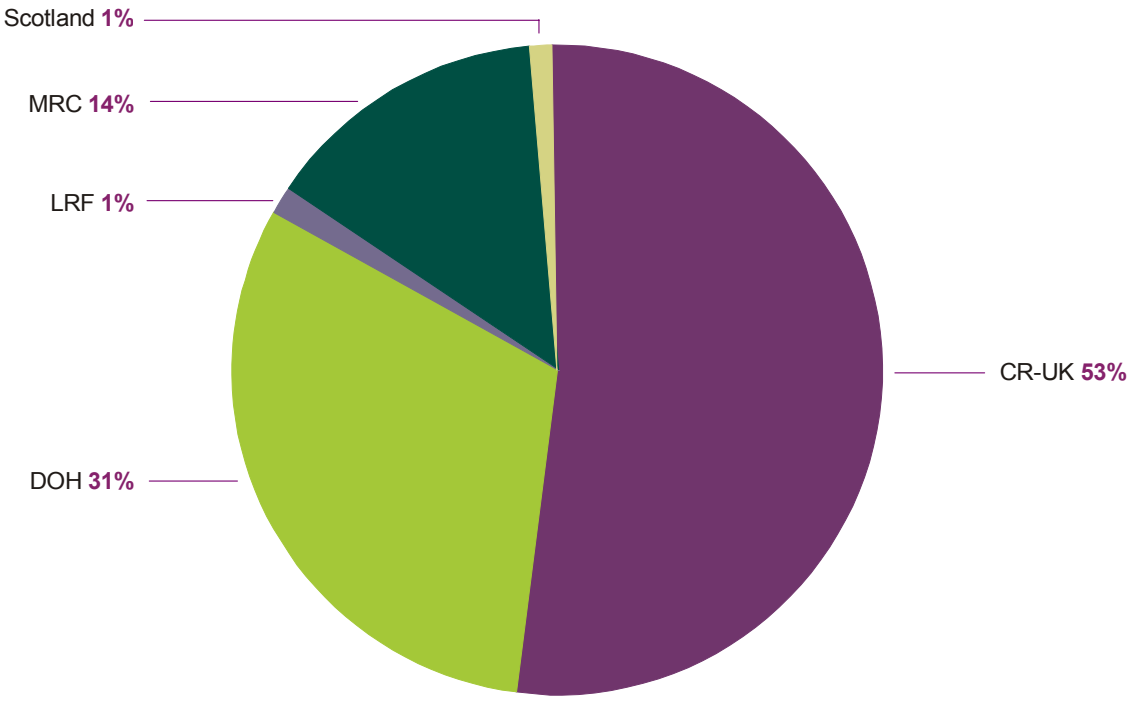
Annex 2 CRD analysis of Radiotherapy/Radiobiology research in the UK

Figure 1 Organisation spend in Radiobiology & Radiotherapy Research



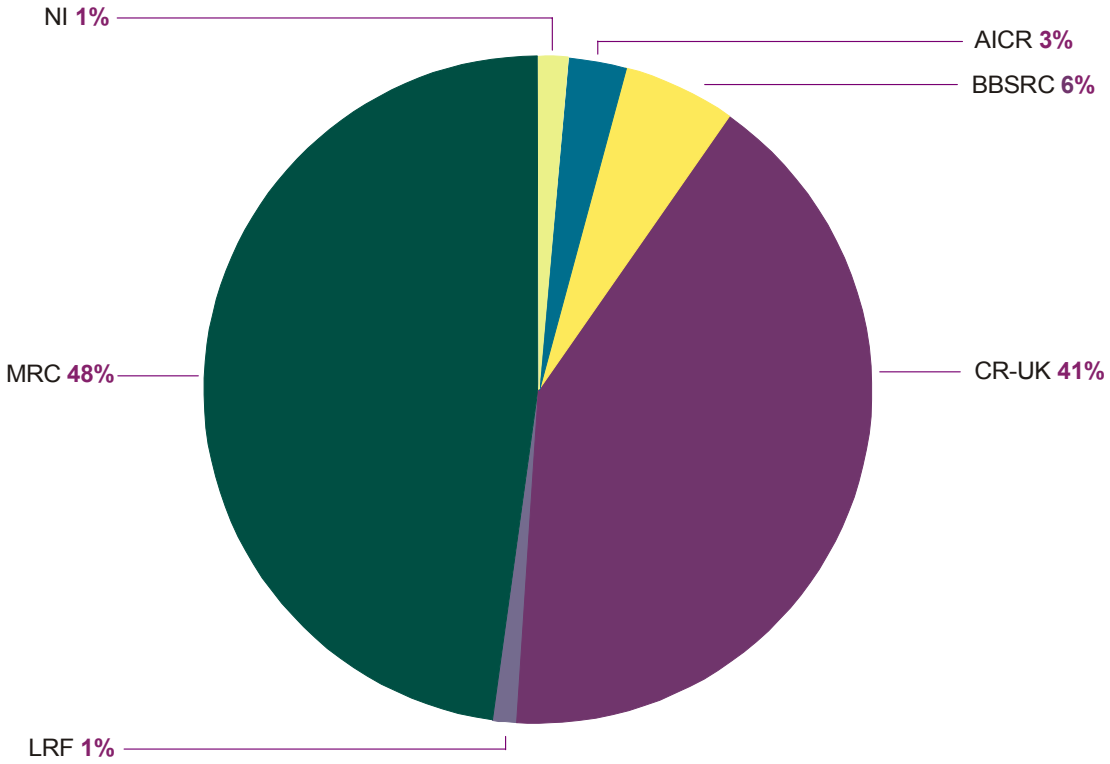
Total spend = £15.8million

Figure 2 Organisation spend in Radiotherapy Research



Total spend = £11.7million

Figure 3 Organisation spend in Radiobiology Research



Total spend = £4.1million

Figure 4a Duration of funding in Radiobiology & Radiotherapy Research

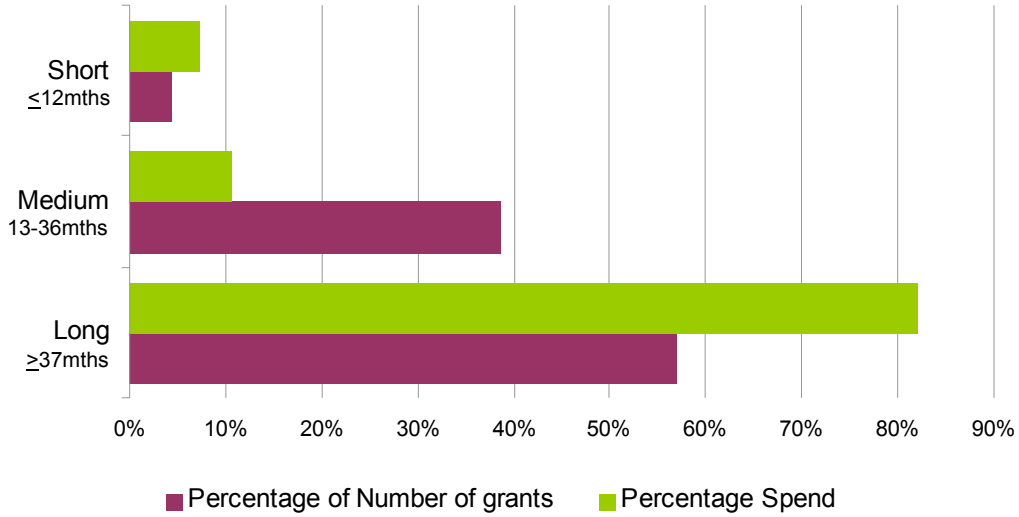


Figure 4b Duration of funding in Radiotherapy Research

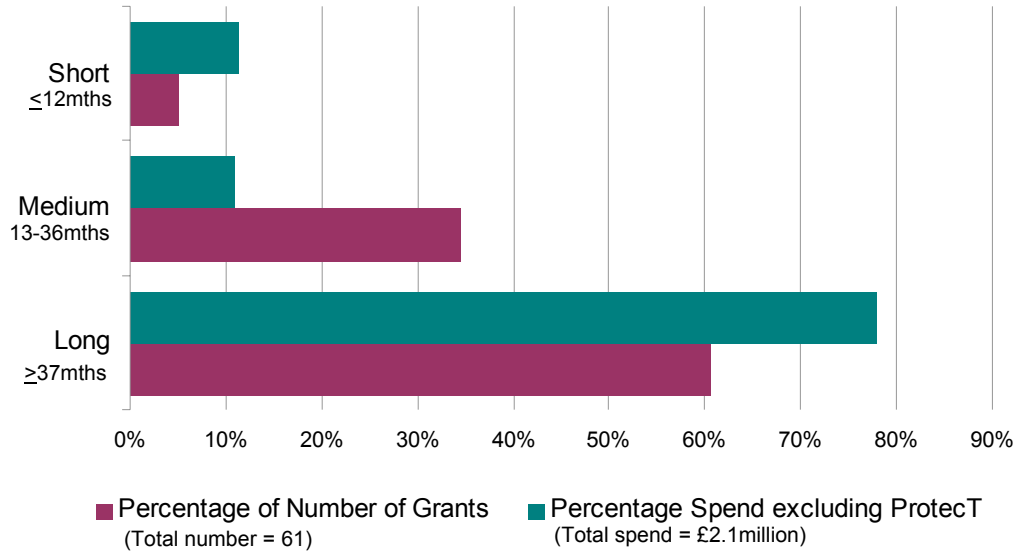


Figure 4c Duration of funding in Radiobiology Research

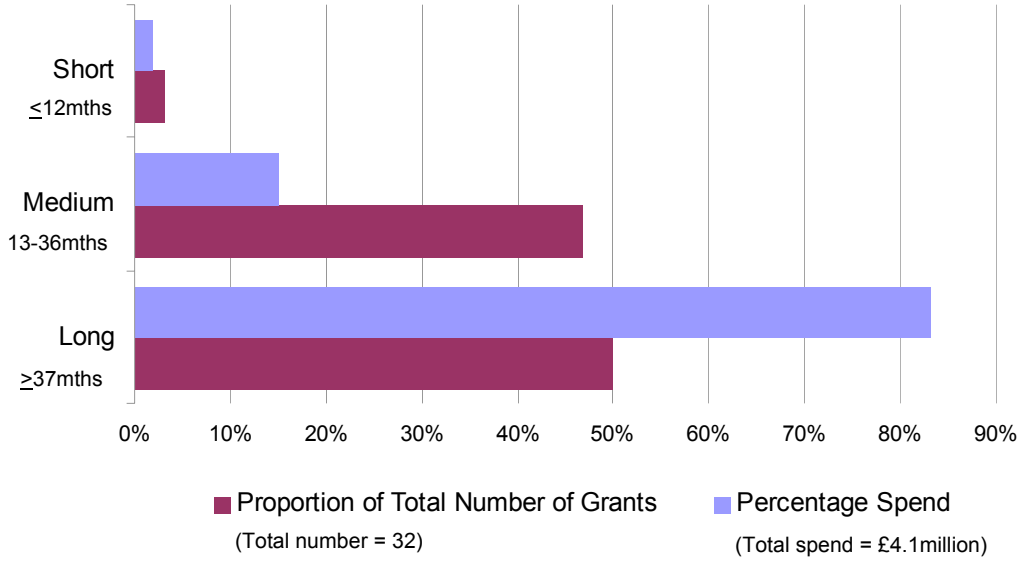
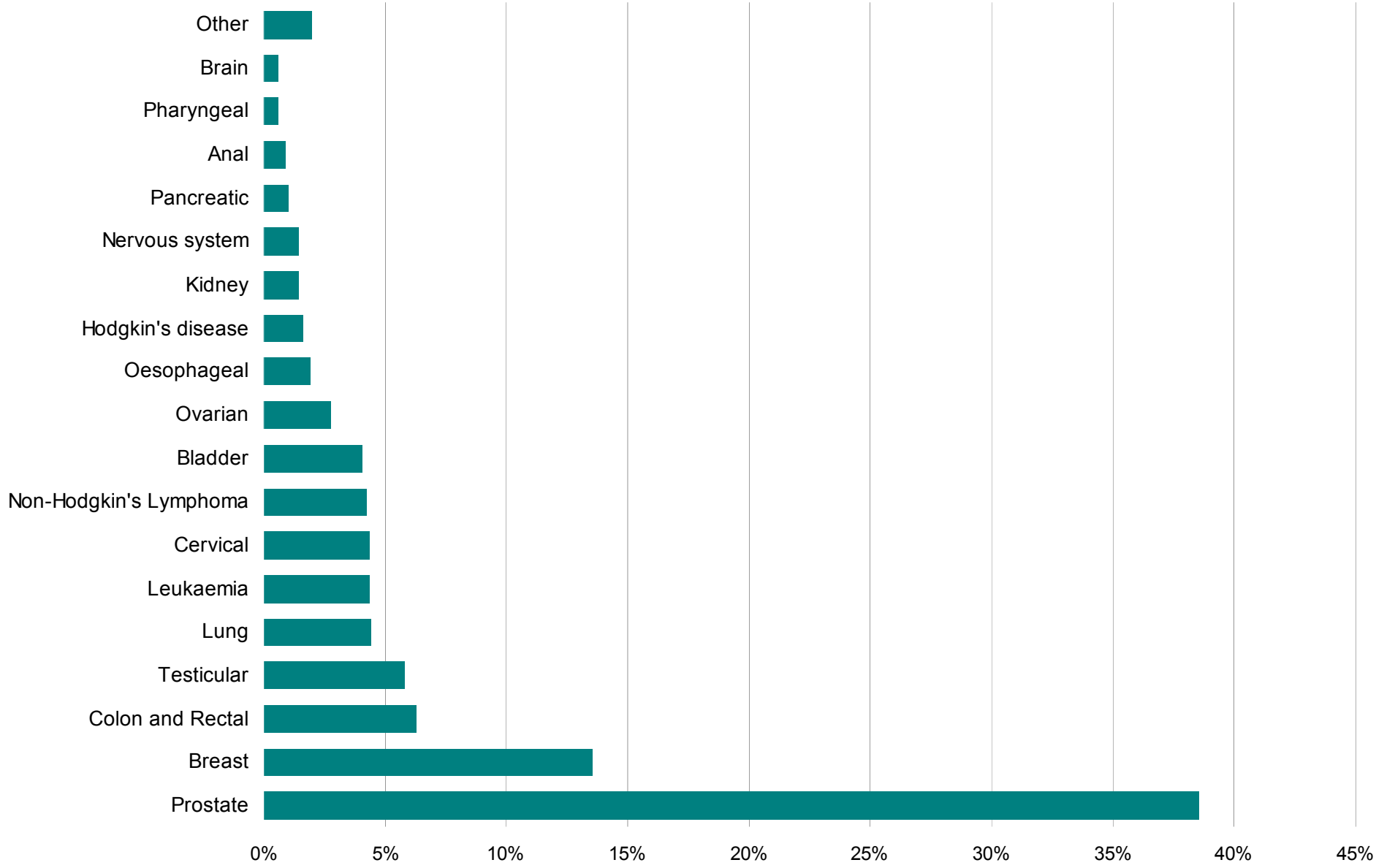
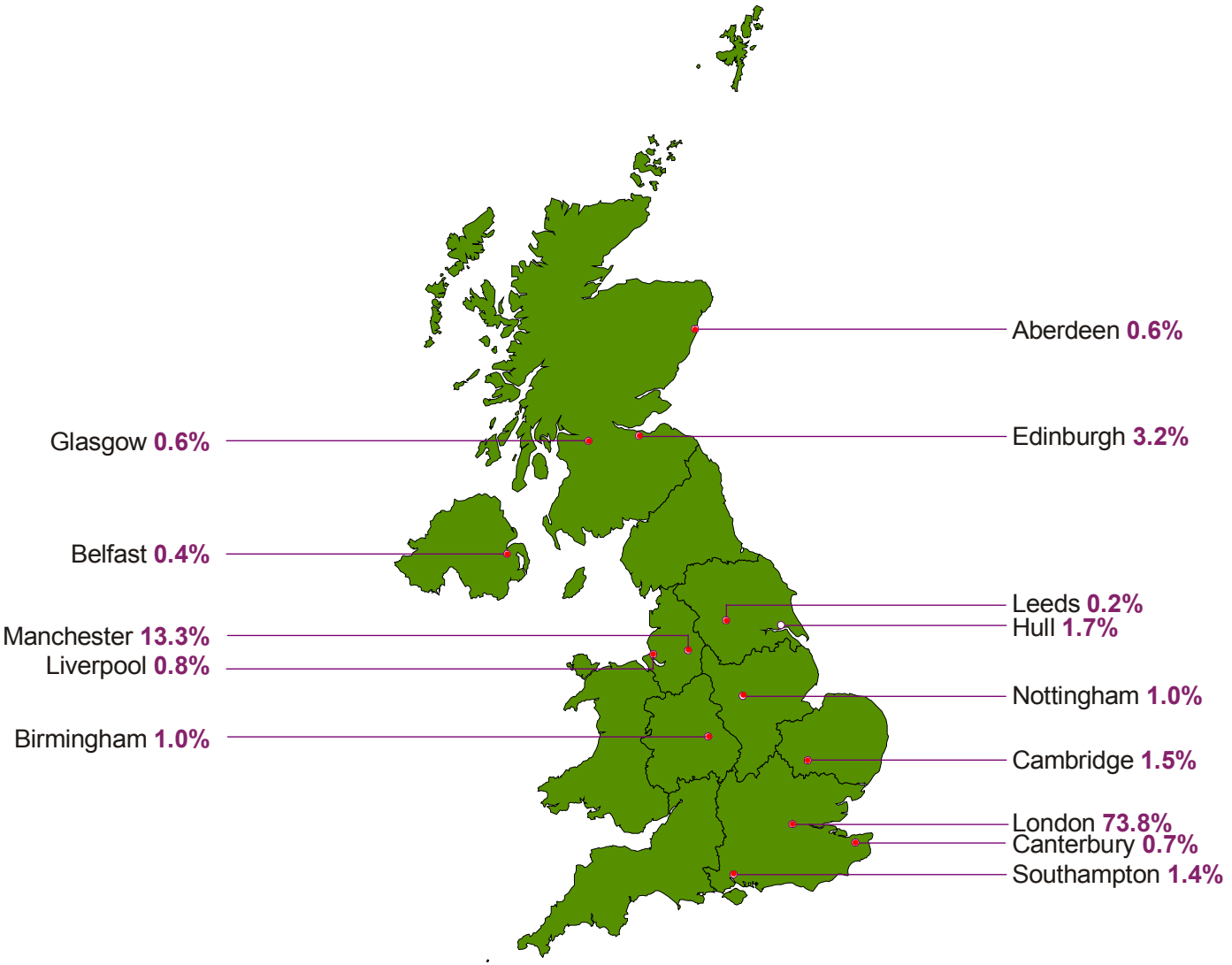


Figure 5 Percentage of Total NCRI Partners' Radiotherapy Spend on Specific Tumour types



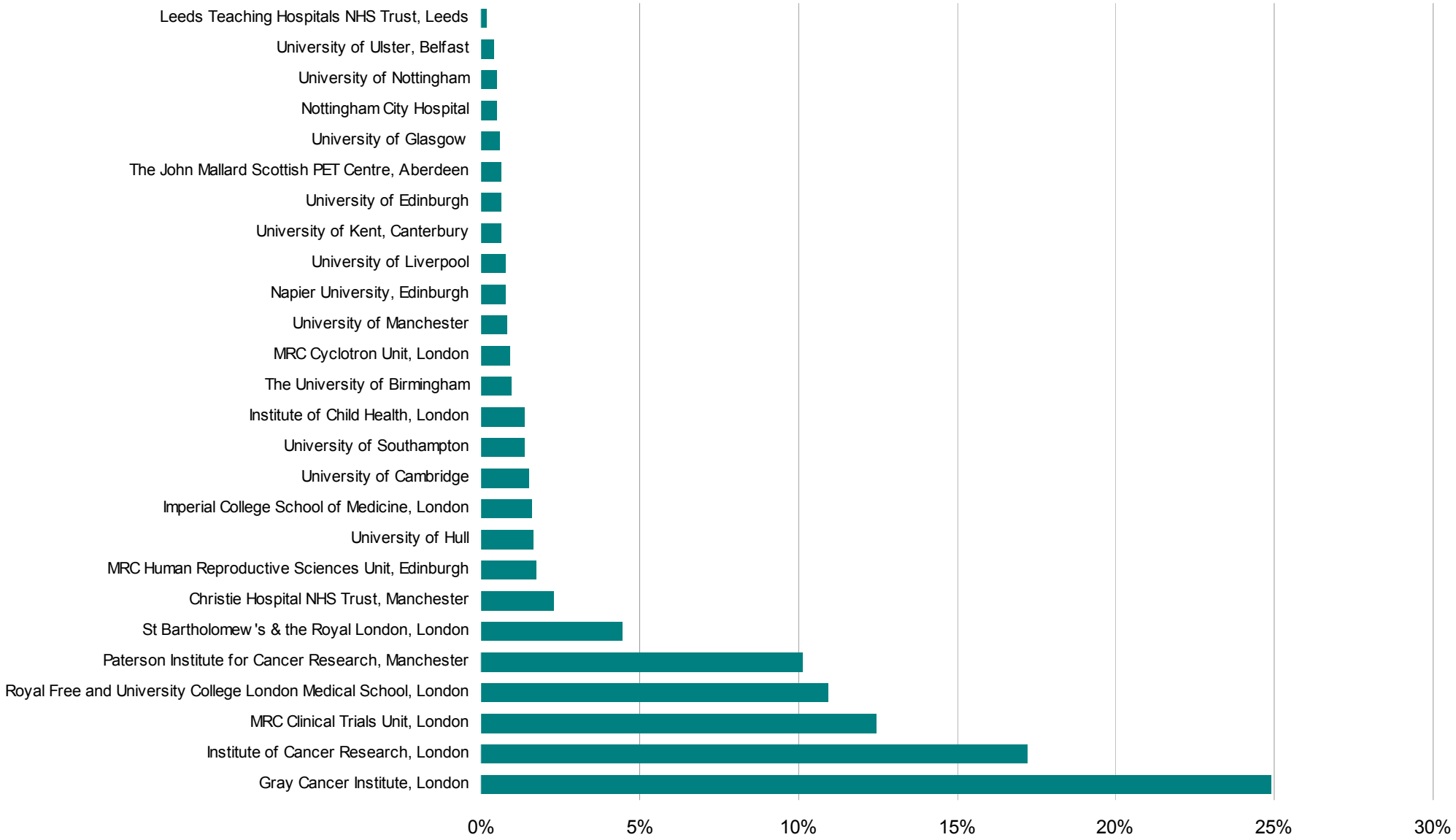
Note: 85% of Prostate spend is ProtecT

Figure 6 Distribution of NCRI Partners' Radiotherapy Research spend



NOTE: Figure excludes 18% (2.1million) spend on ProtecT (DOH) trial in Sheffield & 9% (1m) spend on Radiological Protection Research Program (DOH)

Figure 7 Percentage of Total NCRI Partners' spend on Radiotherapy Research by Institution



NOTE: Figure excludes 18% (2.1million) spend on ProtecT (DOH) trial in Sheffield & 9% (1m) spend on Radiological Protection Research Program (DOH)

Figure 8 Distribution of NCRI Partners' Radiobiology Research spend

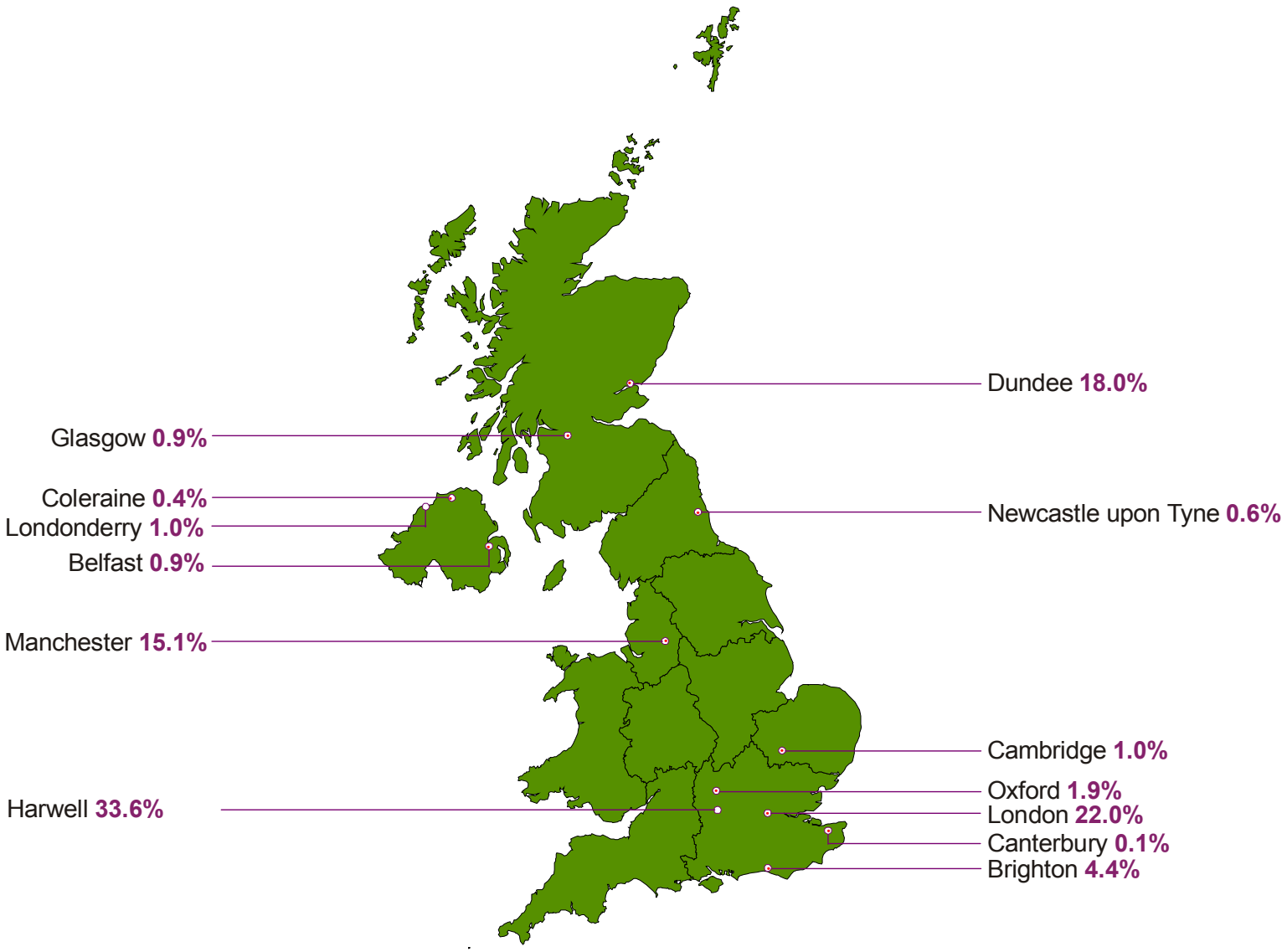


Figure 9 Percentage of Total NCRI Partners' spend on Radiobiology Research by Institution