NCRI
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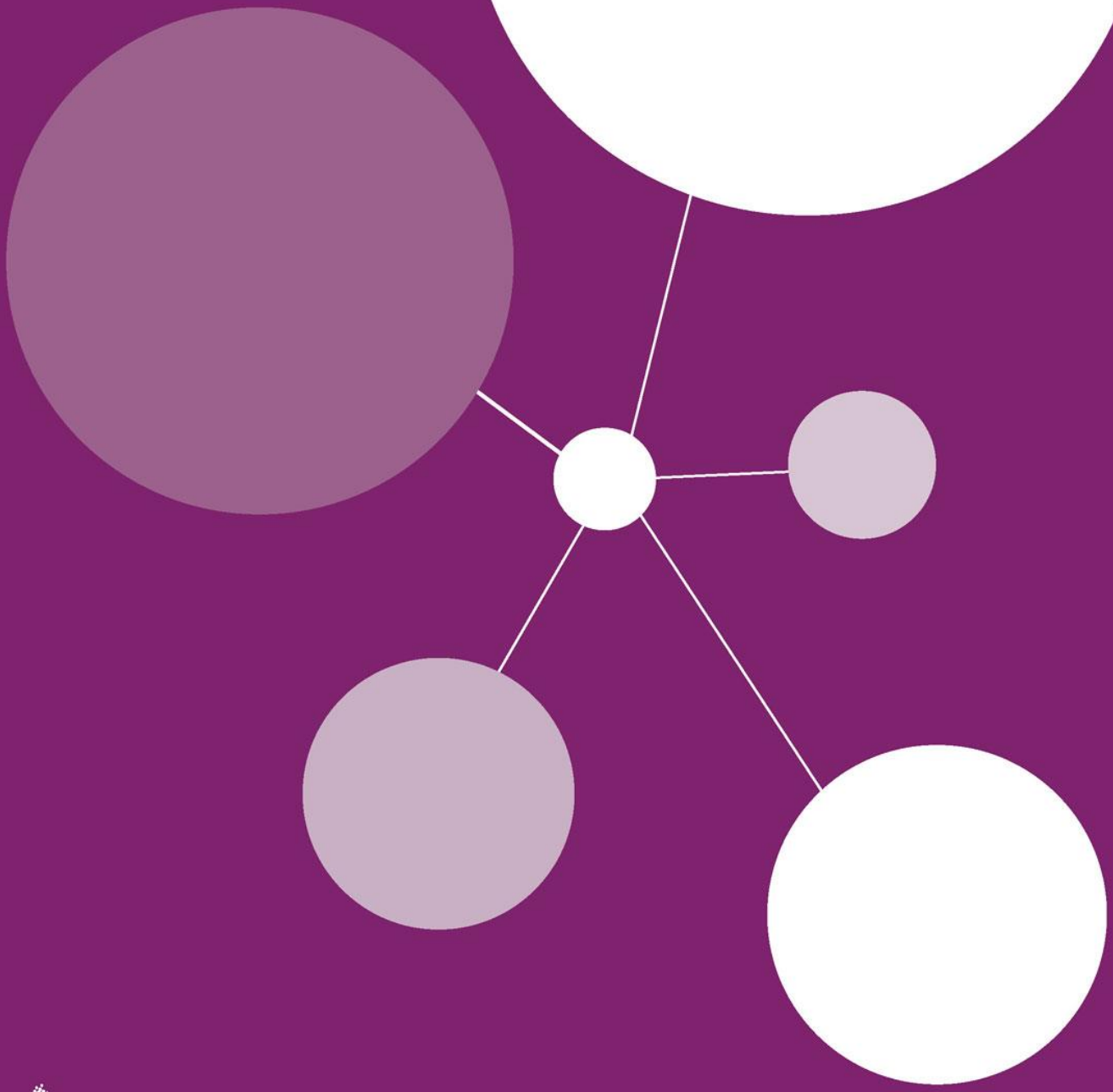
NCRI Imaging Advisory Group

Annual Report 2016-17



Partners in cancer research

National Cancer Research Institute (NCRI)
Imaging Advisory Group

Annual Report 2016-17

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NCRI Imaging Advisory Group Annual Report 2016-17

Introduction

The Imaging Advisory Group (AG) was formed as a cross-cutting group to bring together imaging expertise across the Clinical Studies Groups (CSGs). The rationale for this was that many of the imaging issues recurring in the development and execution of clinical studies were common to the different tumour types. Although some of the CSGs have an imaging focused Subgroup, it was felt there was merit to try to bring some synergy and explore whether or not an overarching group could identify common themes that needed to be addressed and provide advice, particularly to those CSGs where there was not a radiologist on the CSG or where an imaging subgroup did not exist.

One of the aims of the Imaging AG was to try to ensure imaging was used appropriately in clinical trials either in the imaging investigations for entry phenotyping or as surrogate endpoints in the development of imaging biomarkers. To fulfil this aim, the Imaging Advisory Group provides a service to all CSGs irrespective of whether or not there is an imaging subgroup to provide advice on the type of imaging that might be helpful in a particular trial proposal.

1. Membership of the Advisory Group

The Imaging AG has now been in existence for over two years. The Group represents various tumour types, different imaging expertise and comes from different geographical areas, and to date has had one workshop and four conference calls. As a cross-cutting group, there is only funding for one face-to-face meeting. The NCRI Executive provides help to organise meetings and/or conference calls.

2. Progress towards delivery of remit

Provide ad hoc advice on imaging in late phase clinical trials to CSGs and others

During the reporting year, three proposals were received for advice from the Imaging Advisory Group which are listed in the table in Appendix 3.

An educational workshop for the imaging community has been organised at the Royal College of Radiologists for June 2017 where there will be presentations in the morning and an imaging sandpit in the afternoon. Ten trial proposals with a strong imaging component have been received. Proposals that had already been funded were not considered suitable as the imaging strategy had already been decided meaning five proposals will be discussed on the day with advice on imaging techniques given.

In response to the feedback from the Panel last year, the following actions have been taken:

1. The membership of the Expert Advisory Panel has been extended to include experts representing a wider range of cancers and imaging modalities.
2. Links have been developed with CTRad and the PET Core Lab.
3. A proactive approach to collaborations with other CSGs has been made by contacting the Chair of each CSG, having conference calls with representatives of several CSGs who did not have imaging members and attending those CSG meetings without imaging representation.

3. Links to other groups

NIHR CRN Imaging initiative

Professor Steven Smye leads this with Professor Gilbert as a member of the core group to ensure close working relations between NCRI and NIHR Imaging CRN. A document entitled “Delivering

Imaging research in the NHS" had been created which discussed the key challenges – addressing the imaging and radiology workforce shortage, strengthening industry partnerships, machine learning opportunities, supporting the spin out community and funding of technical innovations. A workshop was held on 7th February 2017 to develop a roadmap – A plan for Action. The following speakers contributed– Professors Alison Noble (Oxford), Paul Mathews (Imperial), Erica Denton (Norwich) with Professors Alan Jackson (Manchester) and Gina Brown (Marsden) to speak about multicentre clinical trials in which they are involved.

Improving interactions with the NCRI CSGs

A number of CSGs expressed an interest in having a member of the Imaging Advisory Group come and speak at their meetings. A list of CSGs with the radiology member was examined and it was felt that if an imaging person was already on the CSG then relatively little could be added in the way of advice.

- CTRad – Conference call in January and invitation to imaging workshop in June 2017. A follow up presentation will take place at the CTRad meeting in June 2017.
- Primary care – Richard Neal/Fiona Walter – emails, conference call to discuss low dose CT screening study and other potential studies and invitation to speak at workshop in June 2017.
- Skin CSG – email discussions have taken place but mutually agreeable time not found.
- Lung CSG – attendance at meeting in November 2017.

The Colorectal, Lymphoma and Breast CSGs all have good imaging representation already on their main group and, following discussion, it was felt that additional input from the Imaging Advisory Group was not required.

4. Additional outcomes of the Advisory Group

Imaging repository

A strategic initiative was presented to the subcommittee. The CRUK Cancer Imaging Centres are piloting an XNAT database similar to the method used by UKDP. Support for both this and an expanded piece of work are required to involve the wider community of imagers and oncologists (research and NHS) and Industry (PACS providers and software companies) to explore a more pragmatic affordable approach. If nothing changes, most trials will not be fulfilling the requirement of the concordat to share imaging data. Action is timely as most images are now digital which facilitates storage and mining of the data, where there is huge interest in deep learning, and commercial companies are very keen to acquire curated datasets (GE, Siemens, Google, Microsoft, etc). The opportunity to link genomic data with phenotypic features is desirable to improve understanding of disease processes. A National Cancer Imaging Repository linked to trial meta data would allow valuable datasets to be reused and is timely due to the opportunities presented by machine learning.

Personalised stratified screening

A joint meeting will be held in May 2017 with the aim of identifying the research gaps and developing research proposals – the topic is screening for germline mutations in breast, ovarian, lung, colorectal and skin cancer. There will be attendance from multiple disciplines and it is hoped there will be productive discussion on future steps. The Imaging AG will be represented by Professor Gilbert.

5. Future plans for the Advisory Group

Strategy

- Work closely with CRN to support development and increase in capacity of imaging research community.
- Develop a strategy for a national imaging repository.
- Develop an MRI core lab for QA purposes to support imaging trials.
- Promote imaging standardisation to facilitate individual patient data meta-analysis.
- Run Imaging workshop in June 2017.

Appendix 1

Membership of the Imaging Advisory Group

Name	Specialism	Location
Professor Fiona Gilbert (Chair)	Radiologist	Cambridge
Professor Alan Jackson	Neuroradiologist	Manchester
Professor Iain Lyburn	Radiologist	Gloucestershire
Dr Gina Brown	Oncology Radiologist	London
Professor Edwin Van Beek	Radiologist	Edinburgh
Dr Kevin Bradley	Radiologist	Oxford
Professor David Buckley	Professor of Medical Physics	Leeds
Professor Nandita de Souza	Oncology Radiologist	Surrey
Professor Adam Waldman	Neuroradiologist	Edinburgh
Dr Lucy Pike	Medical Physicist, PET Core Lab	London
Mrs Christine Allmark	Consumer	Yorkshire

Membership of the Expert Panel

Imaging Expert Advisory Panel		
Name	**Tumour types**	**Imaging Modality**
Dr David Landau	Lung	Radiotherapy, planning, novel imaging techniques (e.g. heterogeneity, fMRI, MRE, novel PET tracers)
Professor Harish Poptani	Brain & Head and Neck	MRI and MR spectroscopy
Professor Luc Bidaut	Imaging (all modalities and analysis)	
Dr Samantha Mills	Brain and CNS	MRI (T1 & T2 perfusion, DTI and spectroscopy, oxygen enhanced MRI). CT perfusion
Professor Phil White	Brain & spine	CT, MRI
Dr Anthony Maxwell	Breast	Mammography, DBT. ultrasound, MRI interventional and therapeutic
Dr Christina Messiou	Soft Tissue Sarcoma, Myeloma and Melanoma	MRI, CT
Dr Tristan Barrett	Prostate, kidney, bladder	MRI, CT
Dr Stavros Stivaros	Paediatric brain	MRI, CT
Professor Margaret Hall-Craggs	Sarcomas and gynaecological	MRI
Dr Kieran McHugh	Paediatric oncology	
Dr Richard O'Connor	Ovary, Uterus, Cervix, Lymphoma, Breast, Colorectal, Melanoma, Thyroid, Testes, Lung	CT, U/S, MRI, Nuclear Medicine Interventional radiology
Dr James O'Connor	Lung , Ovarian and Colorectal	MRI, Preclinical imaging
Dr Ferdia Gallagher	Prostate, ovary, breast	MRI, Hyperpolarised and molecular
Dr Dow-Mu Koh	Gastrointestinal, hepatobiliary, pancreatic, lung and metastatic prostate	Body MRI, DWI, fMRI
Dr Gabriella Baio	Breast, haematological and prostate	MRI, PET/CT and CT, molecular (PET and MRI compounds).
Dr Steve Gwyther		CT, MRI and ultrasound
Dr Jai Patel	Liver	
Dr Thomas Booth	Brain	All imaging modalities

Appendix 2

Group remit

Following the restructure of the Biomarkers & Imaging Clinical Studies Groups (CSG) two new advisory groups were formed:

- Molecular Biomarkers Advisory Group
- Imaging Advisory Group

This paper outlines the role of the Advisory Groups, how it will function and expectations of the Group members.

Role of the Advisory Groups

The role of the Advisory Group will be to:

- Provide ad hoc advice on biomarkers/imaging in late phase clinical trials to CSGs and others. Specifically, members of the advisory group will provide advice for trials involving biomarkers/imaging and conduct peer-reviews of the biomarker/imaging component of trials.
- Run an annual educational workshop (max capacity: 80) for the biomarker/imaging community.

Advice on Trials/Peer review

Trialists will be required to complete a trials registration form, which will be available on the NCRI website. The NCRI CSGs Administrator will forward the completed form to the Chair, who will essentially act as a "filter" and send the trial query to a relevant member of the Advisory Group. The NCRI restricts advisory group members to 10, but to enable the advisory group to function effectively, the Chair may hold an extended list of experts and redirect queries as necessary.

Format of the workshop

The format and content of the workshop will be planned and decided by advisory group members, and they may wish to include a short closed meeting for the advisory group.

What is expected of advisory group members?

Chair

- Maintain general oversight of the group's advisory activities, redirecting any queries where necessary.
- Take minutes and record attendance at teleconferences and annual closed meeting and send to NCRI CSG Administrator.
- Provide specialist advice to trialists when requested either directly or through advisory group members.
- Prepare and submit annual report.
- Plan annual workshop structure and provide details of speakers/extra guests to the Research Project Officer.

Members

- Provide specialist advice to trialists when requested.
- Assist chair in preparation of annual report.
- Assist chair in planning annual workshop format, suggesting topics/speakers/extra guests as necessary.

Members will be asked to step down from the advisory group if:

- They do not provide timely advice to trialists when requested.

- They are unavailable for three consecutive meetings (teleconference or annual meeting).

How will success of the advisory group be measured?
A CSG is evaluated yearly using the annual reporting procedure, with more thorough quin-quennial review. The Advisory Group will be required to report on activities in these same timescales, although a more relevant set of metrics as a marker of success will be developed. The metrics for success will be based around:

- The number of trialists seeking and gaining advice from the Advisory Group.
- Involvement of biomarker experts in the trials going forwards – was a one-off piece of advice given or has the involvement been longer-term?
- Others to be agreed following discussion with the advisory groups.

Membership rotation and appointment of Members
Rotation
Members are appointed in their own right for three years in the first instance and for a further two years if re-appointed. If all members of a Group are appointed at the same time the Chair should determine in discussion with Group members and the Head of the Clinical Studies Groups, the phasing of membership to ensure continuity within the Group.

Adverts for rotating and new members are placed on the NCRI and NIHR websites, in the winter and summer of each year and circulated to all networks. In addition, adverts may be placed in other journals, newspapers and websites subject to the agreement of the Head of the Clinical Studies Groups and availability of funds.

Members due to rotate receive a letter from the Secretariat prior to the advert being placed. Group members receive details of who is due to rotate and when, as part of their meeting papers. Current members due to rotate who have neither submitted an application nor indicated their intention to reapply/not reapply are followed up by the Secretariat.

Appointment
A panel consisting of the following will review applications and appoint accordingly:

- NCRI Clinical Director or nominated Associate Director or ex-Member of NCRI CSG >3 years or ex-CSG Chair of >5 years (to Chair the panel).
- Chair of NCRI Advisory Group.
- Head of the NCRI Clinical Studies Groups Secretariat.

The selection panel meets via teleconference. Applicants are informed of the outcome in writing and successful applicants invited to the next Advisory Group Teleconference.

Attendance of members
The Secretariat keeps records of attendance of all members. Details of attendance at the last three meetings will be routinely presented as part of each set of meeting papers. Members who have failed to attend three consecutive meetings will have their continued membership considered and be asked to leave the Group. The Secretariat will write to such non-attendees. Members who fail to attend two consecutive meetings may be written to by the Secretariat at the discretion of the Chair.

What role will consumers play in the advisory groups?
The role of consumers will be discussed with the advisory groups once they have been established.

Appendix 3

Requests for imaging advice

Name of lead proposer	Working title	Brief summary of study design
Konstantinos Georgiadis	Addition of chemotherapy to EGFR inhibitor Afatnib on rising tumour cell free DNA (ctDNA)	Patient population: Stage IIIb/IV lung adenocarcinoma, EGFR mutation positive (exon19del or L838R) in the tumour tissue, ECOG PS 0-1 Primary endpoint: Progression free survival Secondary endpoints: Overall survival, Safety and Tolerability, QoL, Rate of patients receiving platinum based chemotherapy beyond progression, correlation between ctDNA and tissue biopsy at disease progression. Brief summary: Phase II study where eligible patients (n=60-80) will be started on Afatinb 40mgs daily. ctDNA, harbouring the EGFR sensitizing mutation, will be measured by Droplet Digital PCR, 4 times weekly. Upon increase in ctDNA, patients will be randomised either to Afatinib+chemotherapy (single agent Gemcitabine)(experimental arm) or Afatinib alone (control arm) until RECIST disease progression, at which stage a second biopsy will be performed to correlate findings with ctDNA. Tested Hypotheses: 1) Increase in ctDNA precedes RECIST defined disease progression, and is the result of evolving resistant clones (those clones harbour mutations that confering resistance to Afatinib but continue to have the sensitizing mutation, which can be measured as rising ctDNA in the circulation) 2) Catching the evolving clones earlier, in the micrometastatic stage and treating with chemotherapy at this stage is more effective than chemotherapy at the stage of RECIST visible disease progression 3) Treatment with chemotherapy is more effective, targeting a heterogeneous population of resistant clones, as compared to the addition of a second TKI at the stage of ctDNA progression. The trial could be conducted as a two-phase study. During the first stage (exploratory/feasibility) the hypothesis that increase in ctDNA precedes RECIST defined disease progression will be tested. Also

		feasibility of recruitment will be assessed. During the second stage the primary and secondary endpoints will be the main outcome. Finally, with regards to chemotherapy, platinum and Pemetrexed should be spared at the stage of ctDNA increase, as they will be used as second line treatment at RECIST disease progression. Gemcitabine is chosen based on the evidence of its efficacy in lung cancer and the acceptable safety profile.
Hashim Ahmed	A phase I/II 3-way, open label randomised controlled trial assessing the role of ablation of the primary prostate cancer, with or without an immune-modulatory vaccine, compared to standard-of-care to treat men with oligo-metastatic prostate cancer	Hypothesis: In men with oligo-metastatic prostate cancer, local prostate ablation either alone or in conjunction with intradermal IMM-101 (heat-killed Mycobacterium Obuense) with standard androgen deprivation therapy compared to standard-of-care alone (androgen deprivation therapy alone) leads to improved medium-term disease-control (biochemical progression-free survival, radiological progression-free survival), time to castrate-resistant disease and long-term disease-control (cancer-specific survival and overall survival). Aims: Aim for pilot: To assess the feasibility of a 3-way randomisation and assess the toxicity profiles in each randomised intervention arm Aim for main phase: to determine whether the ablation of the primary prostate cancer, with or without vaccine, compared to standard androgen deprivation therapy alone can lead to improved disease control as measured by time to castrate resistant prostate cancer Objectives: Primary objective for pilot To determine feasibility of randomisation Secondary objectives for pilot: - To describe and obtain point estimates for rate of adverse events, side-effect profile and health-related quality-of-life outcomes in patients undergoing intervention compared to standard care If feasibility of randomisation and safety can be demonstrated, then we will determine whether we should seek funding for a separate main phase II randomised controlled trial in which we aim to determine medium-term cancer-control outcomes or consider this intervention within STAMPEDE, following discussions with the CSG and the STAMPEDE team. The primary outcomes

		for our main phase II RCT will be time to castrate-resistance (biochemical progression despite androgen deprivation therapy). We will secondarily measure time to progression of metastases on imaging (radiological progression) as well as cancer-specific and overall survival. Study type and design: Interventional, prospective, randomised, open-label, phase II trial with internal pilot. Stratified randomisation will occur on a 1:1:1 ratio using random permuted blocks (strata will include PSA, number of metastases, Gleason grade of primary tumour, stage of primary tumour). Patient population: Men with prostate cancer who are treatment-naïve and present with oligo-metastatic disease. Outcomes: In our internal pilot study, the following outcomes will be measured up to 12 months follow-up after randomisation: Primary outcome for pilot: - Randomisation of 60 participants within a 12-month period (competitive recruitment between sites) Secondary outcomes for pilot: - A description of and point estimate for adverse events - A description of and point estimate for genito-urinary side-effect profile (incontinence, rectal toxicity, potency)
James Powell	Observational study of neurocognitive function (NCF) in patients undergoing Stereotactic Radiosurgery (SRS) at Velindre Cancer Centre (VCC)	Stereotactic radiosurgery (SRS) and whole brain radiotherapy (WBRT) has demonstrated a survival benefit over WBRT alone, establishing SRS treatment for 1-3 brain metastases. This improved outcome has put greater emphasis on quality of life (QoL) following treatment and particularly on the deleterious effect on neurocognitive function (NCF) of WBRT. Consequently, SRS is increasingly delivered without WBRT, in favour of close surveillance, as a strategy to preserve NCF in patients with brain metastases. Nevertheless, even in patients treated with SRS alone a sizeable proportion of patients (20 – 25% of patients reported in randomised trials) suffer reduced NCF, with memory the most commonly affected neurocognitive domain. The effect of radiation on neurogenesis in the hippocampus has been implicated in the

		reduced NCF evident following WBRT and techniques such as hippocampal–sparing radiotherapy have been evaluated to limit hippocampal radiation dose during WBRT. However, limited information exists to define appropriate radiation dose tolerance constraints for the hippocampus either for standard radiotherapy fractionation or for hypofractionated radiotherapy regimens used in SRS. Equally, other structures within the brain important for NCF exist, including the amygdala, striatum, mamillary body and prefrontal cortex, which haven't been as extensively evaluated for the effect of radiation on NCF and limited studies have correlated neurocognitive outcomes with radiation dose and neurophysiological change in these structures. Mechanistic understanding of neurocognitive decline following radiotherapy is also limited although different hypotheses exist including vascular injury, white matter injury, loss of brain plasticity and functional network disruption. We propose conducting a prospective observational study evaluating NCF in 50 patients treated with SRS at Velinder Cancer Centre (VCC) over 2 years. We will correlate clinical changes in NCF with radiation dosimetry to the hippocampus, wider limbic system and prefrontal cortex. Additionally, in a collaborative, translational study, serial MRI scans will be performed by the Cardiff University Brain Research Imaging Centre (CUBRIC) where functional, physiological and structural change using latest 7 Tesla, functional and spectroscopic MRI techniques will be evaluated in these different structures. Specific neurocognitive and spectroscopic assessments sensitive for detecting changes in hippocampal neurogenesis will also be performed at CUBRIC. NCF will be assessed by performing a formal neurocognitive test battery assessing different cognitive domains including memory, processing, executive function, verbal fluency and motor dexterity. QoL will be assessed using standardized EORTC assessment of physical, emotional and social wellbeing. Each patient will undergo neurocognitive testing at VCC pre-treatment and at 1, 4, 8 and 12 months following SRS treatment and have MRI brain scans at the same timepoints performed at CUBRIC. Changes in NCF will be correlated with radiation dose measurements and changes on MRI scans. Our hypothesis is that radiation dose to the cognitive structures will correlate with worsening

		NCF and with changes in functional MRI markers such as hippocampal blood flow and the primary outcome measure of this study will be NCF at 4 months. This study will help define radiation tolerance doses for the cognitive structures described using SRS and may identify radiation induced MRI markers of neurcognitive deterioration offering mechanistic and predictive insights that can evaluated prospectively in a randomized trial.

Appendix 4

Radiologists on NCRI CSGs

CSG	CSG member	Specialism	Location
Brain	Dr Samantha Mills	Radiologist	Liverpool
Brain	Dr Adam Waldman	Radiologist	London
Breast	Dr Emma Harris	Radiologist	London
Breast	Professor Iain Lyburn	Radiologist	Cheltanham
Colorectal	Professor Gina Brown	Radiologist	London
Colorectal	Dr Rohit Kochhar	Radiologist	Manchester
Bladder & Renal	Dr Jane Belfield	Radiologist	Liverpool
Bladder & Renal	Professor Vicky Goh	Radiologist	London
Head & Neck	Dr Wai Lup Wong	Radiologist	Middlesex
Prostate	Dr Tristan Barrett	Radiologist	Cambridge
Prostate	Professor Gary Cook	Radiologist	London
Prostate	Dr Suniel Jain	Radiologist	Belfast
Sarcoma	Dr Rajesh Botchu	Radiologist	Birmingham
Lymphoma	Dr Victoria Warbey	Radiologist/Nuclear Medicine specialist	KCL, London

Radiologists on NCRI Subgroups

CSG	Subgroup	Subgroup member	Specialism	Location
Brain	Imaging & Technology	Dr Alan Jackson	Radiologist	Manchester
Brain	Imaging & Technology	Dr Rolf Jager	Radiologist	London
Brain	Imaging & Technology	Dr Adam Waldman (Chair)	Radiologist	London
Brain	Imaging & Technology	Dr Chris Clark	Reader in Imaging and Biophysics	London
Brain	Imaging & Technology	Professor Franklyn Howe	Reader in MRI Physics	London
Breast	Translational & Imaging	Professor Iain Lyburn	Radiologist	Cheltenham
Colorecal	Anorectal	Professor Gina Brown	Radiologist	London
Lung	LOcoRegional Disease	Dr Anand Devaraj	Radiologist	London
Lung	Screening/Early Diagnosis	Professor Fergus Gleeson	Radiologist	Oxford
Upper GI	Neuroendocrine	Dr Prakash Manoharan	Radiologist	Manchester
Bladder & Renal	Penile	Dr Mark Callaway	Radiologist	Bristol
Gynae	Cervix/Vulva	Dr Tara Barwick	Radiologist	London
Prostate	Localised Disease	Dr Shonit Punwani	Radiologist	London
Sarcoma	Young onset soft tissue sarcoma	Dr Kieran Hugh	Radiologist	London