Institution: The Institute of Cancer Research

Unit of Assessment: Clinical Medicine

Title of case study: Improved radiotherapy approaches for prostate cancer treatment

Period when the underpinning research was undertaken: 2004 to 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor David Dearnaley	ICR Team Leader	01/12/1987–31/08/2020
Professor Emma Hall	ICR Team Leader	05/04/1999–Present
Professor Alan Horwich	ICR Team Leader	01/10/1984–31/12/2015
Professor Robert Huddart	ICR Team Leader	29/03/1996–Present
Dr Vincent Khoo	ICR Honorary Faculty	01/07/2006–Present
Professor Chris Parker	ICR Team Leader and ICR Honorary Faculty	03/09/2001–30/09/2010; 01/02/2011–Present
Professor Steve Webb	ICR Team Leader	01/10/1974–30/09/2011
Dr Anna Wilkins	ICR Independent Researcher	01/09/2013–28/02/2019; 09/03/2020–Present

Period when the claimed impact occurred: 2009 onwards

Is this case study continued from a case study submitted in 2014? No.

1. Summary of the impact

The Institute of Cancer Research (ICR) led clinical radiotherapy fractionation research in prostate cancer that resulted in impact on:

- **Clinical practice.** Shorter standard curative radiotherapy regimens have been adopted internationally for patients with prostate cancers, the most common malignancy in men in the UK and other developed nations.
- **Patients.** Reduced side effects, less time off work, and savings in travel time and costs without any loss of very high levels of cancer control.
- **The economy.** Healthcare systems benefit from reduced treatment costs. Full implementation of the prostate cancer hypofractionation approach could save the NHS approximately GBP28,000,000, and USD360,000,000 in the US annually.

2. Underpinning research

Background. After surgery, radiation therapy remains the most effective way to treat cancer. In the past decades, significant developments have enabled advances in the delivery of radiotherapy to improve the targeting of the X-ray beam to the cancer while sparing the surrounding normal tissues. In the 1990s, Professor Steve Webb (ICR Team Leader) pioneered the technique of intensity modulated radiotherapy (IMRT) that adjusts the beam in both shape and intensity, leading to precise high intensity radiation of the tumour reducing irradiation of the surrounding healthy tissues. In 2000, Professor David Dearnaley (ICR Team Leader) led the first clinical research study to treat prostate cancer patients with complete IMRT treatments. He then went on to lead the UK national trial to establish the effectiveness high dose prostate radiotherapy **(Ref. 1)**. The clinical implementation of IMRT paved the way for the development of new radiotherapy fractionation practices with high dose hypofractionation, where a smaller number of large doses (called fractions) are delivered with the potential to improve efficacy and reduce side effects, and to improve the cost-effectiveness of radiation therapy to benefit both patients and the healthcare services.

Practice-changing IMRT hypofractionated radiotherapy trials. As a first step, the ICR alongside its hospital partner The Royal Marsden NHS Foundation Trust (RM) combined the developments in IMRT delivery with a hypofractionated treatment approach. Professor

Dearnaley, with Professor Emma Hall (ICR Team Leader) as the lead statistician, initiated a multicentre, randomised phase 1/2 trial (CHHiP) to assess the tolerance and effectiveness of hypofractionated IMRT in prostate cancer. The trial recruited 153 men at 11 UK centres who were assigned in a 1:1:1 ratio to receive conventional or two different hypofractionated high-dose IMRT schedules. The results published in 2012 established that the hypofractionated high-dose radiotherapy was equally well tolerated as the conventionally fractionated treatment **(Ref. 2)**.

Subsequently, the ICR led the phase 3 CHHiP trial (Chief Investigator: Professor Dearnaley; lead statistician: Professor Hall), the largest completed study undertaken in localised prostate cancer (3,216 patients) which showed non-inferior tumour control for 60Gy in 20 fractions (3Gy per day) compared to standard dose-fractionation (74Gy in 37 fractions, 2Gy per day). Hypofractionation gave the opportunity to develop shorter (20 hospital visits compared with 37), effective treatments benefitting both radiotherapy resource utilisation and patient convenience **(Ref. 3)**. Importantly, patient-reported outcomes were shown to be favourable across all treatment groups **(Ref. 4)** and improved compared with the previously developed high dose radiotherapy techniques in use in the UK. The trial data has been used to develop new dose constraints to improve patient safety **(Ref. 5)**. Two CHHiP trial sub-studies demonstrated the value of using image guide radiotherapy (IGRT) which has become the national standard of care **(Ref. 6)** and the lower dose of 57Gy in 20 fractions has been shown to be effective in more elderly patients over 75 years of age with improved tolerability and is recommended by NHS England as a standard of care **(Ref. 7)**.

Ongoing research in this area. The new hypofractionated regimen (60Gy in 20 fractions) has been further developed to incorporate magnetic resonance imaging (MRI)-directed tumour dose boosts combining IMRT and IGRT in the single institutional DELINEATE study (ISRCTN04483921), and is now being assessed in the ICR-led PIVOTALboost national phase 3 trial (ISRCTN80146950). Professor Hall is the scientific lead on the international, multicente phase 3 PACE study aiming at determining if ultra-hypofractionated stereotactic body radiotherapy (SBRT) offers therapeutic benefit over prostatectomy or conventional fractionated or moderate hypofractionated radiotherapy.

3. References to the research

Key: **ICR employed staff** at the time of publication, **ICR Team Leaders and independent researchers (including Honorary Faculty)** at the time of publication.

1. **Dearnaley DP**, Jovic G, Syndikus I, **Khoo V**, Cowan RA, Graham JD, Aird EG, Bottomley D, **Huddart RA**, Jose CC, Matthews JHL, Millar JL, Murphy C, Russell JM, Scrase CD, Parmar MKB, Sydes MR. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. Lancet Oncol. 2014 Apr;15(4):464-73 (http://dx.doi.org/10.1016/S1470-2045(14)70040-3). *Times cited: 245 (WOS).*

2. **Dearnaley D**, Syndikus I, **Sumo G**, **Bidmead M**, Bloomfield D, **Clark C**, **Gao A, Hassan S, Horwich A, Huddart R, Khoo V**, Kirkbride P, Mayles H, Mayles P, Naismith O, Parker C, Patterson H, Russell M, Scrase C, South C, Staffurth J, **Hall E**. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial, Lancet Oncol. 2012, 13, 43-54 (http://dx.doi.org/10.1016/S1470-2045(11)70293-5). *Times cited: 218 (WOS).*

3. **Dearnaley D**, Syndikus I, **Mossop H**, **Khoo V**, Birtle A, Bloomfield D, Graham J, Kirkbride P, Logue J, Malik Z, Money-Kyrle J, O'Sullivan JM, Panades M, **Parker C**, Patterson H, Scrase C, Staffurth J, Stockdale A, Tremlett J, Bidmead M, Mayles H, Naismith O, South C, **Gao A**, **Cruickshank C**, **Hassan S**, **Pugh J**, **Griffin C**, **Hall E**; CHHiP Investigators. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-

inferiority, phase 3 CHHiP trial. Lancet Oncol. 2016 Aug;17(8):1047-1060. (http://dx.doi.org/10.1016/S1470-2045(16)30102-4). *Times cited: 443 (WOS).*

4. **Wilkins A**, **Mossop H**, Syndikus I, **Khoo V**, Bloomfield D, **Parker C**, Logue J, Scrase C, Patterson H, Birtle A, Staffurth J, Malik Z, Panades M, Eswar C, Graham J, **Russell M, Kirkbride P, O'Sullivan JM, Gao A, Cruickshank C, Griffin C, Dearnaley D, Hall E**. Hypofractionated radiotherapy versus conventionally fractionated radiotherapy for patients with intermediate-risk localised prostate cancer: 2-year patient-reported outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol. 2015 Dec;16(16):1605-16. (http://dx.doi.org/10.1016/S1470-2045(15)00280-6). *Times cited: 83 (WOS).*

5. **Wilkins A**, Naismith O, **Brand D**, Fernandez K, **Hall E**, **Dearnaley D**, **Gulliford S**; CHHiP Trial Management Group. Derivation of Dose/Volume Constraints for the Anorectum from Clinician and Patient-Reported Outcomes in the CHHiP Trial of Radiation Therapy Fractionation. Int J Radiat Oncol Biol Phys. 2020 Apr 1;106(5):928-938. (http://dx.doi.org/10.1016/j.ijrobp.2020.01.003). *Times cited: 4 (WOS).*

6. **Murray J**, **Griffin C**, **Gulliford S**, Syndikus I, Staffurth J, Panades M, Scrase C, **Parker C**, **Khoo V**, **Dean J**, Mayles H, Mayles P, Thomas S, Naismith O, Baker A, **Mossop H**, **Cruickshank C**, **Hall E**, **Dearnaley D**; CHHiP Investigators. A randomised assessment of image guided radiotherapy within a phase 3 trial of conventional or hypofractionated high dose intensity modulated radiotherapy for prostate cancer. Radiother Oncol. 2020 Jan;142:62-71. (http://dx.doi.org/10.1016/j.radonc.2019.10.017). *Times cited: 5 (WOS).*

7. Wilson JM, **Dearnaley DP**, Syndikus I, **Khoo V**, Birtle A, Bloomfield D, Choudhury A, Graham J, Ferguson C, Malik Z, Money-Kyrle J, O'Sullivan JM, Panades M, **Parker C**, Rimmer Y, Scrase C, Staffurth J, Stockdale A, **Cruickshank C**, **Griffin C**, **Hall E**; CHHiP Investigators. The Efficacy and Safety of Conventional and Hypofractionated High-Dose Radiation Therapy for Prostate Cancer in an Elderly Population: A Subgroup Analysis of the CHHiP Trial. Int J Radiat Oncol Biol Phys. 2018 Apr 1;100(5):1179-1189. (http://dx.doi.org/10.1016/j.ijrobp.2018.01.016). *Times cited: 15 (WOS).*

Additional Quality Indicators

Selected peer reviewed research grant support:

- Cancer Research UK Clinical Trial Award, 2006 to 2016, GBP990,253: "CHHIP: a randomised phase III multicentre trial of conventional or hypofractionated high dose intensity modulated radiotherapy for prostate cancer."

Prizes:

- Award for Excellence in Radiation Oncology 2011, EMUC (European Multidisciplinary Meeting on Urological Cancers), 2011: David Dearnaley

4. Details of the impact

There are approximately 48,500 new prostate cancer cases in the UK annually and since the early 1990s incidence has increased by 41%. UK incidence rates for prostate cancer are expected to rise by 12% between 2014 and 2035 **[A]**. Therefore it is a growing healthcare burden, both in the UK and globally. 30% of patients diagnosed with prostate cancer have radiotherapy as part of their primary cancer treatment. Radiotherapy is the most commonly used curative form of therapy in the UK, and development of more effective radiotherapy techniques provides huge opportunities for clinical benefit by increasing survival rates and reducing treatment-related toxicities. This latter consideration is increasingly important as cancer patients survive longer and live with the long-term consequences of treatment.

International guidelines/recommendation and international uptake of the improved radiotherapy techniques. The commissioning policy in 2014 recommended a dose of 74Gy in 37 fractions which was based on the UK national phase 3 dose-escalation radiotherapy trial

(Ref. 1) led by Professor Dearnaley **[B]**. In 2017 the results from the ICR-led CHHiP phase 3 trial **(Ref. 2-7)** led to the new recommendation by the NHS England Clinical Commissioning Policy that high dose intensity modulated hypofractionated radiotherapy is both safe and effective when delivered giving 60Gy in 20 fractions over a 4-week period for prostate cancer **[C]**. The guidance states that:

> *"Radiotherapy providers must submit their activity to the national Radiotherapy Dataset (RTDS) on a monthly basis. For reporting purposes, it is expected that 70% of prostate cancer patients requiring radical external beam radiotherapy should receive hypofractionated radiotherapy (i.e., ≤20 fractions of treatment)."*

In addition this guidance mandated the use of IMRT and recommended that IGRT should be used to reduce side effects of high dose radiotherapy based on data from the CHHiP trial.

In the UK, the National Cancer Registration and Analysis Service (NCRAS) has recorded prostate cancer fractionation in the National Radiotherapy Dataset (RTDS). There has been an increase in the use of the 60Gy treatment in 20 fractions from 8% in 2012/13 rising to 49% in 2016/17, with a corresponding decrease in the previous standard treatment (74–78Gy in 37–39 fractions) from 77% to 26% **[D]**. Moreover, the National Prostate Cancer Audits reported that 91% rising to 96% of people in 2019 and 2020, respectively, receiving radical radiotherapy for intermediate-risk disease had the 60Gy treatment in 20 fractions in combination with androgen deprivation therapy **[E, F]**. These data show the increased uptake of this schedule across the UK following the publication of results of the CHHiP trial.

In addition, there have been international recommendations of the 60Gy treatment in 20 fractions protocol based on data from the CHHiP trial. The American Society for Radiation Oncology (ASTRO), American Society of Clinical Oncology (ASCO), and American Urological Association (AUA) Evidence-Based Guideline concluded that the accumulated data are sufficiently robust to justify routine use of 60Gy treatment in 20 fractions protocol in clinical practice. This guideline is endorsed by the Society of Urologic Oncology, the European Society for Radiotherapy & Oncology (ESTRO), and the Royal Australian and New Zealand College of Radiologists **[G]**. In 2019, the National Institute for Health and Care Excellence (NICE) reviewed the evidence as part of a larger update of their prostate cancer guideline and the committee agreed with the recommendations made by NHS England (see **[C]**) that 60Gy in 20 fractions was the optimal dose for patients having radiotherapy for localized prostate cancer **[H]**.

Patient benefit of the improved radiotherapy techniques. The CHHiP trial found that long-term side effects were similar in the hypofractionated groups compared with the conventional group. There were no significant differences in either the proportion or cumulative incidence of side effects 5 years after treatment using clinician-reported and patient-reported outcome measures **(Ref. 4)**. However, the 60Gy treatment in 20 fractions approach has further benefits for patients as it leads to an average of 17 less hospital visits per patients, reducing time spent attending appointments and reducing patients' travel costs. It is estimated that 238,906 hours per year are saved for all patients. The benefits of 60Gy treatment in 20 fractions was perhaps best highlighted by a prostate cancer patient himself, whose treatment was influenced by the CHHiP trial:

> *"I found the 20 sessions of radiotherapy sessions extremely manageable. It was so much better psychologically to 'get it over and done with', and in terms of less disruption to my daily life, to have the sessions condensed was great. […] I have been lucky in a way. I haven't had any particularly serious side effects from the treatment, and now live a normal life. This is a huge step forward in the development of radiotherapy treatment, it will save the NHS money and cause less disruption for the patient. It would be great if things continue to develop in this way."* **[I]**

Cost saving for the NHS and global healthcare as a result of improved radiotherapy techniques. Full UK implementation of the CHHiP regimen (60Gy treatment in 20 fractions) in

prostate cancer is estimated to reduce total treatment fractions and attendances by approximately 200,000 per year with an annual NHS cost saving of GBP28,000,000. The regimen saves 17 hospital trips and complex radiotherapy treatments for each patient, leading to a national reduction of more than 150,000 visits per year **[D]**. Prostate cancer radiotherapy accounts for 28% of the workload of radiotherapy departments and the use of hypofractionation is expected to release approximately 13% of capacity, resulting in shorter waiting times and greater availability of radiotherapy resource for other uses.

The cost of standard fractionation (45 or 39 fractions) in the US is USD26,782 and USD23,625 per patient, respectively. With 60Gy treatment in 20 fractions, the cost is reduced to USD13,402 per patient. Therefore the use of 60Gy treatment in 20 fractions may have the potential to save approximately USD360,000,000 in the US annually without impacting survival or tolerability **[J]**.

5. Sources to corroborate the impact

A. Prostate cancer statistics: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Zero

B. NICE-accredited National Collaborating Centre for Cancer clinical guideline (2014) for prostate cancer radiotherapy: https://www.nice.org.uk/guidance/ng131/evidence/full-guideline-pdf-6781033550

C. NHS Commissioning guidance (2017) for prostate cancer radiotherapy: https://www.england.nhs.uk/wp-content/uploads/2017/10/clinical-policy-hypofractionated-external-beam-radiotherapy.pdf

D. Increased uptake of hypofractionation in prostate cancer: Dearnaley D, Hall E. How will the CHHiP trial affect the future of prostate radiotherapy?, Expert Review of Anticancer Therapy, 18:7, 607-609. https://doi.org/10.1080/14737140.2018.1477595

E. NICE Impact prostate cancer: https://www.nice.org.uk/Media/Default/About/what-we-do/Into-practice/measuring-uptake/prostate-cancer/nice-impact-prostate-cancer.pdf

F. National Prostate Cancer Audit Annual Report 2020: https://www.npca.org.uk/content/uploads/2021/01/NPCA-Annual-Report-2020_Final_140121.pdf

G. ASTRO, ASCO, and AUA Evidence-Based Guideline: Morgan SC, Hoffman K, Loblaw DA, Buyyounouski MK, Patton C, Barocas D, Bentzen S, Chang M, Efstathiou J, Greany P, Halvorsen P, Koontz BF, Lawton C, Leyrer CM, Lin D, Ray M, Sandler H. Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline. Pract Radiat Oncol. 2018 Nov - Dec;8(6):354-360. https://doi.org/10.1016/j.prro.2018.08.002.

H. NICE review: https://www.nice.org.uk/guidance/ng131/evidence/c-radical-radiotherapy-pdf-6779081776

I. Patient benefit testimonial: https://www.icr.ac.uk/blogs/science-talk/page-details/how-will-a-clinical-trial-called-chhip-affect-the-future-of-prostate-radiotherapy

J. Cost saving in the United States: Moore A, Stav I, Den RB, Gordon N, Sarfaty M, Neiman V, Rosenbaum E, Goldstein DA. The Financial Impact of Hypofractionated Radiation for Localized Prostate Cancer in the United States. J Oncol. 2019 Jan 2;2019:8170428. https://doi.org/10.1155/2019/8170428.