Institution: The Institute of Cancer Research

Unit of Assessment: UoA1

Title of case study: Developing and disseminating conformal radiotherapy and intensity modulated radiotherapy

1. Summary of the impact

The Institute of Cancer Research (ICR) has made seminal contributions to the development and dissemination of conformal radiotherapy and intensity modulated radiotherapy (IMRT), leading to changes in clinical practice, reduced treatment complications and improved cure rates. ICR researchers developed conformal radiotherapy, which allowed better shaping of the high-dose radiation volume around a tumour, and they then refined this technique to create IMRT, which makes possible the definition of a high dose volume with a concave border allowing further sparing of critical normal tissue. IMRT is now the approved treatment regime for many cancers such as prostate, breast and head and neck in the USA, the UK and many European countries.

2. Underpinning research

Radiation therapy has been revolutionised by the ability to delineate tumours and adjacent normal structures in three dimensions using specialised scanners and planning software. ICR researchers have played a key role in this field through the research-based development of conformal radiotherapy and then IMRT. In the 1980s, Professor Steve Webb (ICR Faculty) pioneered the application of the mathematical technique, simulated annealing to solve optimisation problems in radiotherapy treatment planning, and then developed new ways to deliver beam modulation. These are the underpinning technologies behind conformal radiotherapy and IMRT. Conformal radiotherapy was further refined by Webb to optimise beam modulation for IMRT delivery (Ref 1).

During the early development of conformal radiotherapy in the UKonly the ICR (with its clinical partner the Royal Marsden NHS Foundation Trust, RM) and a few other centres had equipment capable of delivering this treatment, but the objective was to make the technology widely available. Between 1994 and 2000, the Webb team worked with an industrial partner, Elekta AB, and carried out research to develop techniques using a commercial accelerator that could accurately and reproducibly deliver conformal radiotherapy.

In September 2000, the ICR/RM team was the first internationally to treat patients with full-course-fractions of IMRT (Ref 2); this clinical research study was led by radiation oncologist Professor David Dearnaley (ICR Faculty).

In the 2000s, Webb continued his research to more precisely define the conformal shaping of the high-dose level radiotherapy volume of the tumour and to variably modulate the dose-delivery across the tumour volume. This led to significant advances in what became known as IMRT delivery. This had a major benefit in avoiding normal tissue irradiation and also enabled motion-compensation to be introduced into treatment delivery (Ref 3). The clinical advantages of IMRT are that side effects are reduced, higher radiation doses are concentrated on the tumour and therefore improved cancer cure rates can be achieved. Because of the reduced irradiation to healthy tissue, IMRT permits hypofractionation of radiation dose delivery (a smaller number of large dose fractions), improving the cost-effectiveness of radiotherapy (Ref 4). These advantages have been the subject of research trials in the clinic by the ICR/RM, which have confirmed the expected benefits.

An early ICR/RM prospective randomised trial of conformal versus standard radiotherapy in prostate cancer demonstrated a reduction in toxicity. This was followed by a further prospective trial to explore radiation dose-escalation to 74Gy compared with the “standard” 64Gy dose. The trial demonstrated treatment benefits (Ref 5) and led on to a large national MRC trial under the leadership of Dearnaley and Professor Alan Horwich (ICR Faculty), which confirmed these results.

Other important clinical research trials of IMRT initiated by the ICR/RM include the demonstration of tolerance and efficacy of hypofractionated IMRT in prostate cancer (Ref 4), which was then confirmed in a national multicentre trial. The ICR/RM also led the world's first IMRT Phase III clinical trial in head and neck cancer with Professor Chris Nutting (ICR Honorary Faculty) as the Chief Investigator (Ref 6), which showed a significant improvement in quality of life and a reduction in debilitating side effects of treatment. Nutting and his team have also demonstrated that IMRT can improve local tumour control in head and neck cancers (Ref 7), and this is currently being tested in a head and neck IMRT trial run in conjunction with Professor Judith Bliss (ICR Faculty) in the ICR's Clinical Trials & Statistics Unit (Cancer Research UK trial number CRUK/10/018).

Evidence of the quality of the ICR's research in the field of IMRT and its key contribution is the recent award of the EFOMP Medal to Professor Webb by the European Federation of Organisations for Medical Physics at the SFPM-EFOMP conference in Strasbourg, France (http://www.efomp.org/index.php/efomp-medal-awardees).

3. References to the research

All ICR authors are in bold and ICR team leaders/Faculty are in bold and underlined.

1. **Webb S.** 1994, Optimizing the planning of intensity-modulated radiotherapy, Phys Med Biol. 39, 2229-2246 (http://dx.doi.org/10.1088/0031-9155/39/12/007)
2. **Adams EJ, Convery DJ, Cosgrove VP, McNair HA, Staffurth JN, Vaarkamp J, Nutting CM, Warrington AP, Webb S, Balyckyi J, Dearnaley DP**. 2004, Clinical implementation of dynamic and step-and-shoot IMRT to treat prostate cancer with high risk of pelvic lymph node involvement, Radiother Oncol. 70, 1-10. (http://dx.doi.org/10.1016/j.radonc.2003.09.004)
3. **Webb S**. 2005, The effect on IMRT conformality of elastic tissue movement and a practical suggestion for movement compensation via the modified dynamic multileaf collimator (dMLC) technique, Phys Med Biol. 50 (6), 1163-1190. (http://dx.doi.org/10.1088/0031-9155/50/6/009)
4. **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**. 2012, Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial, Lancet Oncol. 13, 43-54 (http://dx.doi.org/10.1016/S1470-2045(11)70293-5)
5. **Dearnaley DP**, **Hall E**, **Lawrence D**, **Huddart RA, Eeles R, Nutting CM**, **Gadd J**, **Warrington A**, **Bidmead M, Horwich A.** 2005, , Phase III pilot study of dose escalation using conformal radiotherapy in prostate cancer: PSA control and side effects, Br J Cancer. 92, 488-98. (http://dx.doi.org/10.1038/sj.bjc.6602301)
6. **Nutting CM**, **Morden JP**, **Harrington KJ**, Urbano TG, **Bhide SA**, Clark C, Miles EA, **Miah AB**, **Newbold K**, **Tanay M**, Adab F, Jefferies SJ, Scrase C, Yap BK, **A'Hern RP**, **Sydenham MA**, **Emson M**, **Hall E**; PARSPORT trial management group. 2011, Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial, Lancet Oncol. 12,127-36. (http://dx.doi.org/10.1016/S1470-2045(10)70290-4)
7. **Miah AB, Bhide SA, Guerrero-Urbano MT, Clark C, Bidmead AM, St Rose S, Barbachano Y, A'hern R, Tanay M, Hickey J, Nicol R, Newbold KL, Harrington KJ, Nutting CM**. 2012, Dose-escalated intensity-modulated radiotherapy is feasible and may improve locoregional control and laryngeal preservation in laryngo-hypopharyngeal cancers, Int J Radiat Oncol Biol Phys. 82, 539-47. (http://dx.doi.org/10.1016/j.ijrobp.2010.09.055)

Selected Research Grants:

1. Webb S – 'Development of polymer gel dosimetry and application to conformal (including intensity modulated) radiotherapy', EPSRC, 2000-2003, £152,975

2. Dearnaley D – 'Modulated Radiotherapy (IMRT) for Prostate Cancer', MRC, 2003-2006, £300,000

4. Details of the impact

Impact on health

The development by ICR researchers of conformal radiotherapy and then the refinement of that technique to create effective and deliverable IMRT has revolutionised radiation therapy. The impact has been seen both in terms of more effective disease control and improvements in patient wellbeing by decreasing the side-effects of healthy tissue irradiation. Tumours can be precisely targeted within a high intensity radiation volume, while adjacent normal structures can be spared, leading to reduced side effects. Because of reduced irradiation of adjacent tissues, higher doses can be delivered to the tumour - resulting in improved cure rates. In addition, cost-effective hypofractionation can be employed, providing economic benefit to the NHS (Research Ref 4 above).

As a result of the outcome of the ICR/RM clinical research trials programme, IMRT is now the approved treatment technique for many cancers in the UK and elsewhere, with changes made in clinical guidelines to implement this. For example, IMRT is standard treatment for early prostate cancer, benefiting about 8,500 men per year in the UK [1]. This treatment modality is now recommended in guideline publications from the European Association of Urology (EAU), the European Society for Medical Oncology (ESMO) [2] and from the US [3]. The dose and fractions that are recommended in these guidelines are based on the ICR/RM trials, which are referenced as evidence in the guidelines.

IMRT is also being used in the treatment of breast cancer (NICE guideline CG80 [4]), lung cancer (NICE guideline QS17 [5]) and metastatic spinal cord compression (NICE guideline CG75 [6]). The patient benefit that is attributable to IMRT, which stems from the changes in clinical guidelines in the UK, has recently been positively assessed by Cancer Research UK [7].

IMRT is in widespread use for head and neck cancers to reduce parotid gland dose and avoid the complication of "dry mouth". The ICR and the RM led the national PARSPORT trial of parotid-sparing radiotherapy and from that demonstrated the dose constraints to be applied (Research Ref 6 above). The national implementation of IMRT for head and neck cancer has been led by a number of different levers, for example, the National Cancer Action Team recommended that it should be made available in all centres for head and neck cases following the PARSPORT trial.

The ICR has had a significant impact on healthcare practice through its important role in the implementation of the proper and effective delivery of IMRT throughout the UK, leading to gains in efficiency and productivity in the NHS. Using test cases, ICR medical physicists train staff in other UK hospitals to use this technique, thus driving the modernisation of radiotherapy throughout the NHS. The ICR runs a national IMRT course each year involving around 70 trainee radiography practitioners. All new radiotherapy equipment can deliver IMRT but without the training provided by the ICR/RM not all the hospitals would have the capability to use it. Thanks to the UK Governments Radiotherapy Innovation Fund (£23m), 22% of patients receiving radiotherapy were given IMRT in April 2013, up from around 14% in Aug 2012 [8]. The fund's primary objective is to extend NHS capacity to deliver IMRT, and as such this initiative has also funded a nationwide IMRT fundamentals course under the leadership of Professor Nutting, in collaboration with the Royal College of Radiologists, to increase clinician involvement in and awareness of IMRT.

Impact on commerce

In addition to the clinical impact of the ICR research on the development and implementation of conformal radiotherapy and IMRT, the research has also had a commercial impact. The ICR worked with the company Elekta AB to develop techniques for its accelerators to enable them to effectively deliver conformal radiotherapy and subsequently IMRT. Elekta formed an international IMRT research consortium from 1994 to 2001 to help to develop IMRT delivery technology. Professor Webb was Chair from 1998-2000 and played an active role throughout. Elekta continues

to market accelerators with IMRT capability, based on this research, to this day. This has added considerable shareholder value to Elekta [9].

ICR's collaboration with Elekta was never exclusive and many other companies developing IMRT technology were helped by the ICR's publications and expertise (for example, Varian, BrainLab and Calypso).

Professor Webb also worked with DKFZ, through a Visiting Professorship, helping their spinoff company MRC Systems (later part of Siemens) to develop IMRT technology.

5. Sources to corroborate the impact

[1] Hounsome et al National Cancer Intelligence Network Report 2012

[2] Horwich A, Parker C, Bangma C, Kataja V, On behalf of the ESMO Guidelines Working Group. (2010) Ann. Onc. 21 (suppl 5), v129-v133. (http://dx.doi.org/10.1093/annonc/mdq174)

[3] NCCN (2011 Pros-4) - http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

[4] NICE guideline CG80 - http://www.nice.org.uk/nicemedia/live/12132/43312/43312.pdf

[5] NICE guideline QS17 - http://publications.nice.org.uk/quality-standard-for-lung-cancer-qs17/quality-statement-11-optimal-radiotherapy

[6] NICE guideline CG75 - http://publications.nice.org.uk/metastatic-spinal-cord-compression-cg75/research-recommendations

[7] CRUK Radiotherapy report p6-8, Aug 2013

[8] http://www.cancerresearchuk.org/cancer-info/news/archive/pressrelease/2013-07-11-radiotherapy-innovation-fund

[9] VP Scientific Research, Eleckta, Redhill, UK (identifier 1)