

IMPROVING RADIOTHERAPY FOR PROSTATE CANCER

Considerable advances in radiotherapy have taken place over the last decade. Technological and computer developments have come together so that we have the ability to safely and accurately treat patients to higher doses with improved effectiveness whilst reducing side effects of treatment.



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Conformal radiotherapy (CFRT)

External beam radiotherapy (EBRT) is given by shaping high energy X-ray beams and pointing a number of these beams at a target - in this case the prostate. Usually three or more beams are used and where they overlap a high composite dose is given - outside the area of overlap the dose is considerably lower (see Figure 1A). This process is a little similar to pointing spotlights at an actor on a stage. The high energy X-rays used (6-20 million electron volts) are shaped by jaws called collimators inside the linear accelerator used to generate the X-ray beams. These collimators have to be several centimetres thick due to the high penetration of the beams. Previously square or rectangular fields were made which produced box-shape high dose volumes within the patient that did not necessarily match closely the more spherical or irregular shapes of the cancer. The development of multileaf collimators (MLC), where individual segments or leaves can be made to move independently, now enables us to conform or shape beams to match the cancer in steps from 10mm to as little as 2mm across (see Figure 1B). This is now known as conformal radiotherapy (CFRT).

Intensity modulated radiotherapy (IMRT)

The second major advance in radiotherapy has been the increase in power and speed of computer planning systems. Previously, the planning physicist added the dose contributions of three or more radiation beams together using their experience and skill to produce the dose distributions to treat the patient - a process called forward planning. It is now possible to tell the computer planning system to give a specified high dose to the target and a lower specified acceptable dose to the surrounding normal tissues. The computer algorithm works backwards from these instructions to produce a plan - a process

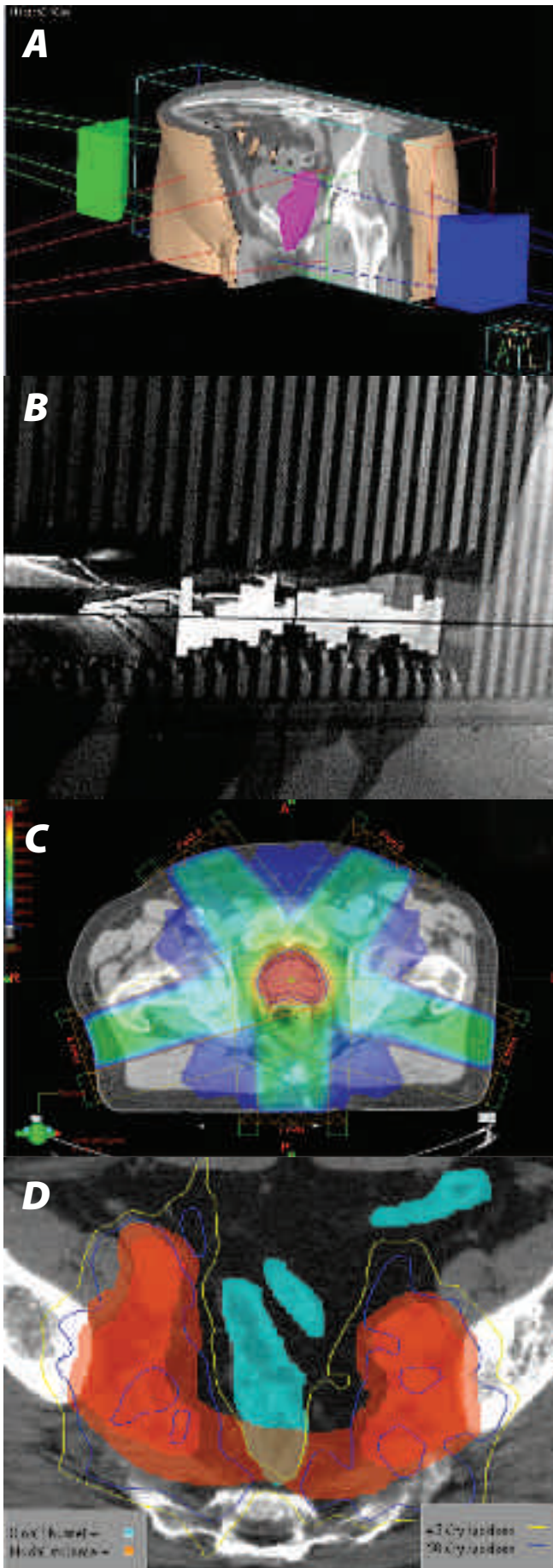


Figure 1: Conformal radiotherapy (CFRT) and intensity modulated radiotherapy (IMRT) in prostate cancer (A) CT reconstruction showing 3 field CFRT beam arrangement to treat the prostate (pink). (B) Multileaf collimator used to shape radiotherapy fields. (C) IMRT plan shaping high dose volume to prostate (red) reducing dose to rectum. (D) Complex IMRT distribution using 5-fields to pelvic lymph node areas (red) reducing dose to bowel (blue).

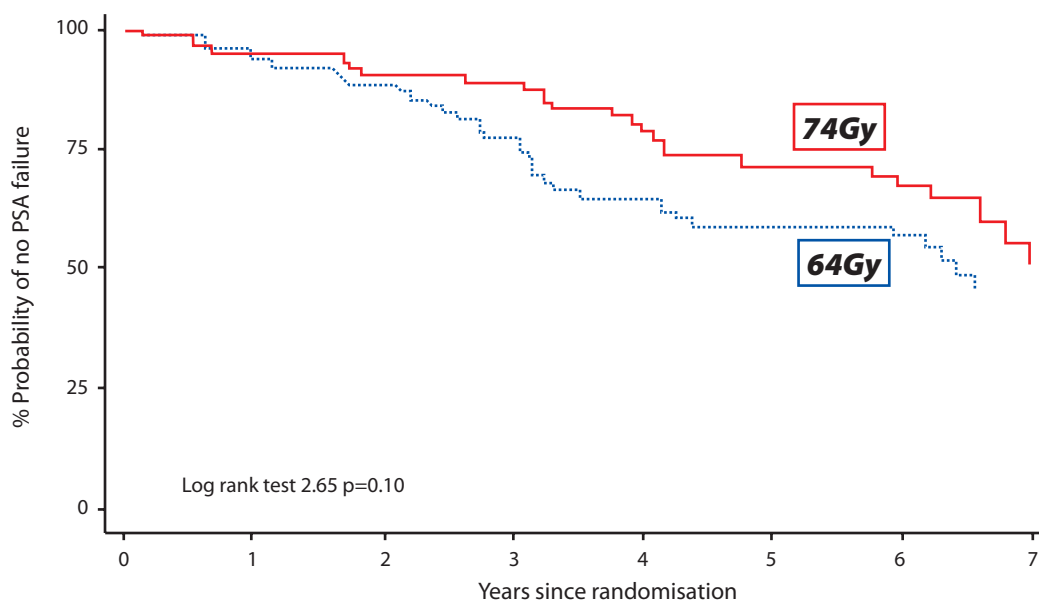
called inverse planning. Combining the MLC and inverse planning process, with the added innovation of adjusting and moving individual MLC leaves during the radiotherapy, produces what we call intensity modulated radiotherapy (IMRT). IMRT can produce very complex target shapes, 'shrink wrapping' the high dose region around the cancer, substantially avoiding sensitive surrounding normal tissues (see Figures 1C and 1D). This gives opportunities both to increase the dose to the cancer (dose escalation) - improving control rates, as well as reducing the dose to surrounding normal tissues (conformal avoidance) - limiting the side effects which determine the dose that can be safely given.

▣ The much improved dose distributions highlight the importance of two other aspects of radiotherapy: accurate definition of the cancer and accurate delivery of treatment. ▣

Image guided radiotherapy (IGRT)

Imaging techniques have markedly improved localisation of cancer over the last decade using faster and more accurate computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET). These advances in tumour localisation are now being incorporated in the radiotherapy planning process. As cancer localisation, treatment planning and treatment delivery become ever more precise, it becomes crucial to ensure very high levels of treatment accuracy. Accuracy is limited by patient movement and this includes breathing, heart motion, and bowel, bladder and prostate movement. New methods to standardise patient positioning and to locate the treatment more precisely on a daily basis using portal imaging, CT using the linear accelerator, and implantation of visible fiducial markers, for example, are being explored to make treatment ever more accurate; these processes are termed image guided radiotherapy (IGRT).

Figure 2: Improved control of prostate cancer using prostate specific antigen (PSA) as a marker of treatment effect.



Conformal radiotherapy trials

How have we used and tested these radiotherapy advances in prostate cancer? Firstly, we have performed the only randomised trial to compare conventional and conformal radiotherapy at any tumour site. The study, which was completed in the late 1990s and treated 215 men, showed a three-fold reduction in important radiation side effects but no reduction in cancer control. As a result, CFRT became the recommended national standard of care endorsed by the National Institute for Health and Clinical Excellence (NICE). The next trial at The Institute and The Royal Marsden compared a standard dose of radiotherapy (64Gy) with a high dose (74Gy) both using CFRT techniques. After a pilot study, the trial was developed into a national protocol with the Medical Research Council (MRC). Together, the studies recruited almost 1,000 men and provided a vehicle for introducing quality assured CFRT into over 20 centres in the UK. Results showed an 11% improvement in cancer control (see Figure 2) and we expect the higher dose to become the new standard of care. However, a note of caution was that side effects, whilst remaining at a low and acceptable level, also increased. This emphasises the importance of continually testing the new technologies to improve dose distributions and treatment accuracy.

Intensity modulated radiotherapy trials

We have now introduced IMRT into prostate cancer clinical trials. Firstly, in low- and intermediate-risk localised disease, we are using simple or more complex IMRT with hypofractionated radiotherapy which involves giving a smaller number of larger radiotherapy treatments (see Figure 1C). In this study (called CHHiP), we are comparing 20 treatments of 3Gy with the standard 37 treatments of 2Gy. Why are we doing this? Modelling studies from clinical data suggest that prostate cancer,

unlike the majority of other cancers, responds more favourably to larger doses of radiation. As the total dose of treatment can be reduced we also hope that side effects may be moderated. If the hypofractionated treatment is as, or more, effective than standard treatment and side effects are unaltered or reduced, then the shorter treatment schedule would not only be convenient for patients but would also make better use of radiotherapy resources. As in our other studies, an initial pilot study (including 150 men) has been performed at The Institute and The Royal Marsden in collaboration with partners at The Clatterbridge Centre for Oncology in Liverpool. The Department of Health funded expansion to Part 2 (450 men) and allowed us to implement quality-assured IMRT in 12 radiotherapy centres. Funding has now been granted by Cancer Research UK to expand the trial to 20-30 centres nationally and internationally. The study, to be co-ordinated by The Institute's Clinical Trials and Statistics Unit (ICR-CTSU), is the only trial bringing together these aspects of physical and biological optimisation in prostate cancer.

■ We aim to treat over 2,100 men, making the CHHiP study one of the largest prostate and radiotherapy international trials ever performed. ■

For more advanced localised prostate cancer, there is evidence that giving additional treatment to the draining pelvic lymph nodes may also improve cancer control. However, these lymph nodes have a complex horseshoe-shaped distribution surrounding pelvic bowel and bladder (see Figure 1D). In the past, we have been cautious

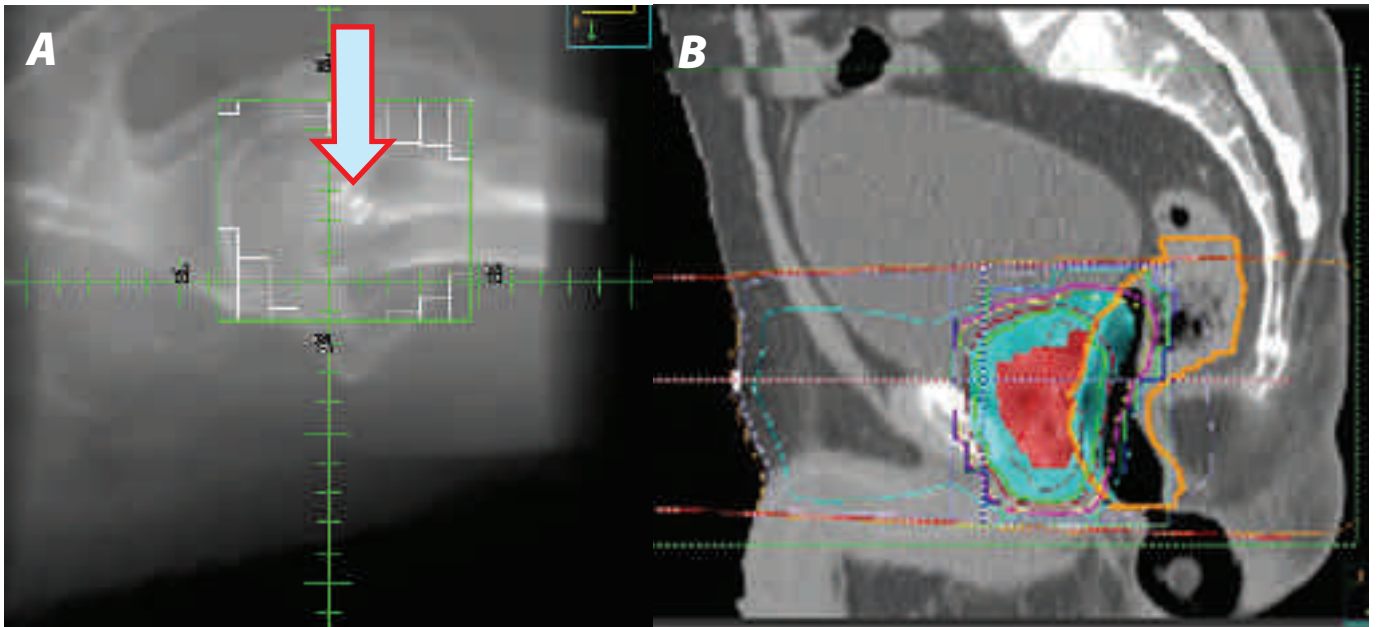


Figure 3: Treatment accuracy and image guided radiotherapy (IGRT)
 (A) Gold grain fiducial markers implanted in prostate surrounded by radiotherapy field shaped by multileaf collimator (MLC).
 (B) Novel localising obturator "ProSpare" (patent pending).

about giving pelvic lymph node irradiation and concerned about causing excessive bowel side effects. Our modelling studies showed that IMRT very significantly reduced the volume of bowel treated. We shall shortly complete a Phase I dose escalation study in over 100 patients using complex IMRT methods. Preliminary results are favourable showing a low side effect profile. We next plan to test a hypofractionated technique in a similar way to the CHHIP study.

Improved imaging

Whilst these clinical trials have progressed, we have developed new approaches to prostate cancer localisation with colleagues within The Institute and The Royal Marsden. In particular, magnetic resonance imaging and spectroscopy are being developed to identify discrete cancer nodules within the prostate, and paramagnetic iron oxide contrast agents have been assessed to aid the localisation of pelvic lymph nodes (collaborations with Dr Nandita deSouza (Cancer Research UK Clinical Magnetic Resonance Research Group at The Institute) and Dr Aslam Sohaib (Department of Diagnostic Radiology at The Royal Marsden)).

Treatment accuracy and image guided radiotherapy (IGRT)

The final all important step in the radiotherapy technology chain is to take full advantage of our other developments. Exciting new opportunities include the introduction of cone beam CT on The Royal Marsden's new linear accelerators, use of gold grain fiducial markers and development of a novel prostate localising obturator (ProSpare) (see Figure 3). Shortly, tracking technology will

be introduced to enable MLC leaves to follow the movement of prostate markers.

■ The challenge is to establish such IGRT methods for the routine daily treatment of patients. ■

Translational research

Prostate cancer has a long natural history and many years of clinical follow-up are needed to work out the true value of changes in treatment approach; our clinical trials give us such databases. How do we elucidate which patients benefit most from radiotherapy and dose escalation, and also identify those patients most at risk of treatment side effects? Tissue microarrays developed at The Institute (in collaboration with Professor Colin Cooper from the Section of Molecular Carcinogenesis) will allow us to dissect prostate cancer treatment response pathways to help answer these questions. Additionally, in collaboration with colleagues in Manchester and Cambridge, the ongoing RAPPER study is evaluating the radio genomics of normal tissue effects and we hope to link these results to detailed analysis of the dose distributions used to treat individual patients - thereby linking the biology and physics of treatment.