

Advances in external beam radiotherapy for prostate cancer

REENA DAVDA, ALHASSAN AL-ABDULLAH AND KATE RICKETTS

This article describes some of the advances that have been made in external beam radiotherapy techniques over recent years. These developments mean that modern radiotherapy to the prostate is now highly accurate, maximising the dose to the prostate target whilst minimising radiation to adjacent normal tissues.

Radiotherapy is an important treatment modality in both localised and metastatic prostate cancer. For men with early or locally advanced disease, radiotherapy can be used radically with curative intent. For those with metastatic or advanced disease, radiotherapy can be used for palliation, helping to control symptoms such as pain.

Radiotherapy is the therapeutic use of ionising radiation. There are two types of electromagnetic radiation used in radiotherapy, X-rays and gamma rays, which are physically identical but known by different names to distinguish their means of production. Gamma rays are produced from the nuclear decay of radioactive isotopes, while X-rays are produced by interactions that occur outside the nucleus. Both types of radiation have short wavelengths, high frequencies and carry high energies that enable them to break chemical bonds,

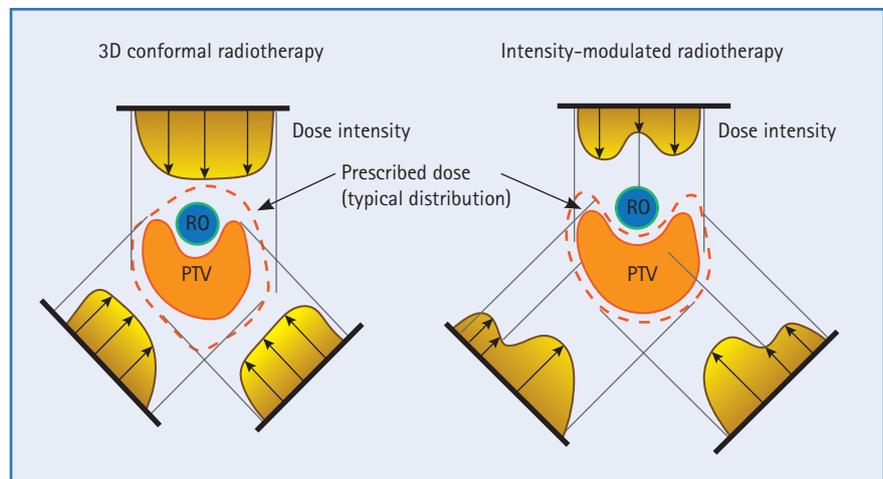


Figure 1. Intensity-modulated radiotherapy improves the conformity of the total dose delivered to the planning target volume (prostate and seminal vesicles, PTV) while reducing the dose to the risk organ (rectum, RO) compared to conformal radiotherapy. The dotted line represents the applied dose delivered to the prostate and seminal vesicles

resulting in DNA damage and subsequent cell death if damage is unrepaired.

In the 1980s, the position of the prostate and its surrounding structures was determined using two-dimensional X-ray films. Unshaped radiotherapy beams were delivered to the prostate, resulting in exposure to radiation of the surrounding tissues (bladder and rectum), which were included in the treatment field.

The results of early prostate cancer radiotherapy were disappointing. In a large series of nearly 5000 men treated in nine US institutions as part of a Mayo Clinic collaborative study between 1973 and 1987, the PSA disease-free survival rates were 59% at five years and 53% at eight years for men with localised prostate cancer.¹ The authors noted that similar studies in the future utilising

Reena Davda, Consultant Oncologist, University College London Hospitals NHS Trust; Alhassan Al-Abdullah, Specialist Registrar in Clinical Oncology, University College London Hospitals NHS Trust; Kate Ricketts, Senior Lecturer, Division of Surgery and Interventional Sciences, University College London

higher doses of radiotherapy and more contemporary techniques would be necessary to fully explore the potential of this treatment modality.

Recent technological advances have dramatically improved outcomes for those treated with radiotherapy, in terms of both efficacy and tolerability.

THE THERAPEUTIC RATIO

There is evidence that increased radiation dose is associated with increased prostate cancer cell kill. However, each tissue type has differing sensitivity to radiation. The radiotherapy dose that can be safely delivered is limited by the tolerance of the surrounding normal structures (bladder, rectum and bowel) to radiation. Radiotherapy treatments therefore require a careful balance between doses that are adequate to treat the tumour but not cause irreparable damage to normal tissues. Known as the 'therapeutic ratio', ongoing technological advances and research continue to investigate techniques to maximise this balance.

EXTERNAL BEAM RADIOTHERAPY (EBRT)

External beam radiotherapy (EBRT) involves the therapeutic use of ionising radiation created in a linear accelerator. Radiation beams are targeted to a defined tumour volume and applied from a number of directions in order to optimise dose distribution, overlapping to give a higher dose at the tumour. The radiotherapy treatment is usually divided into a number of doses (fractions) delivered daily over five to six weeks to allow for sufficient repair of normal tissue between each fraction; cancer cells repair less readily.

3D CONFORMAL RADIOTHERAPY (CRT)

Radiotherapy has undergone a technological revolution in the last decade, whereby three-dimensional anatomical models of the patient through use of CT imaging, often complemented by MRI scans, are used for treatment planning.

A mathematical algorithm is applied to the anatomical model of the patient to calculate and optimise radiation dose. CT-planned, three-dimensional conformal radiotherapy (3D-CRT) has improved EBRT by shaping beams more accurately to the target volume while reducing radiation to dose-limiting structures, such as the adjacent healthy rectum.

In comparison to unshaped treatments, this technique has demonstrated significant reductions in rectal toxicity.² As a result, higher and potentially more effective doses of radiation have been investigated to establish the optimal dose that can be safely delivered to the prostate. The UK Medical Research Council RT01 trial included 843 men with localised prostate cancer, who were randomly assigned to receive either 64Gy or 74Gy of CRT. The trial demonstrated that higher doses of radiotherapy were possible and acceptable and, as a consequence, NICE recommended routine delivery of the higher dose in 2008.³ At 10 years' follow-up, although no significant difference in overall survival was observed, men who had received the higher dose had improved biochemical progression-free survival (55% versus 43%).⁴

INTENSITY-MODULATED RADIOTHERAPY (IMRT)

The next development for prostate cancer radiotherapy was the introduction of intensity-modulated radiotherapy (IMRT). This technique uses multiple beams of varying intensity to achieve complex shaping of the radiation dose around a target volume. As shown in Figure 1, many small 'beamlets' from various angles contribute to the total dose administered. Data from several studies of prostate IMRT have demonstrated improvements in PSA relapse-free survival rates with increased dose delivered. The greatest advantage has been seen for men with localised high-risk (PSA \geq 20, Gleason Grade \geq 8) or locally advanced prostate cancer. Results have confirmed the advantage of dose-escalated

radiotherapy with doses of over 80Gy.⁵ IMRT also has the potential to reduce significant late rectal toxicity at three years' follow-up.⁶

VOLUMETRIC ARCING TREATMENT (VMAT)

EBRT with CRT or IMRT involves the head of the linear accelerator moving around the patient and then delivering therapy from fixed positions that are determined during the planning process. Volumetric arcing treatment (VMAT) is a novel form of EBRT, which involves treatment of the whole target volume using one or two arcs of beams from a machine that rotates around the patient continuously while delivering therapy. This form of EBRT simultaneously adjusts for both the shape of the beam as it rotates around and the dose intensity delivered from any particular angle. The resulting highly conformal dose distribution has the potential to reduce the time for delivery of each fraction compared with static field IMRT.⁷

HYPOFRACTIONATION

Hypofractionation, the delivery of more than the standard 2Gy at each fraction, is another promising strategy under investigation. The alpha/beta ratio is a mathematical term derived from cell survival curves and indicates the sensitivity to change in fractionation. Radiobiology studies have indicated that the alpha/beta ratio for prostate cancer is lower than for most other tumour types – alpha/beta ratios for tumours are usually higher than those for surrounding normal tissue. Tissues with a lower alpha/beta ratio will undergo greater cell killing by larger doses per fraction of radiotherapy than tissues with a higher ratio (Figure 2). Hypofractionation may therefore improve control of prostate cancer for the same level of radiotherapy.

The UK CHHiP (Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer) study recently presented results

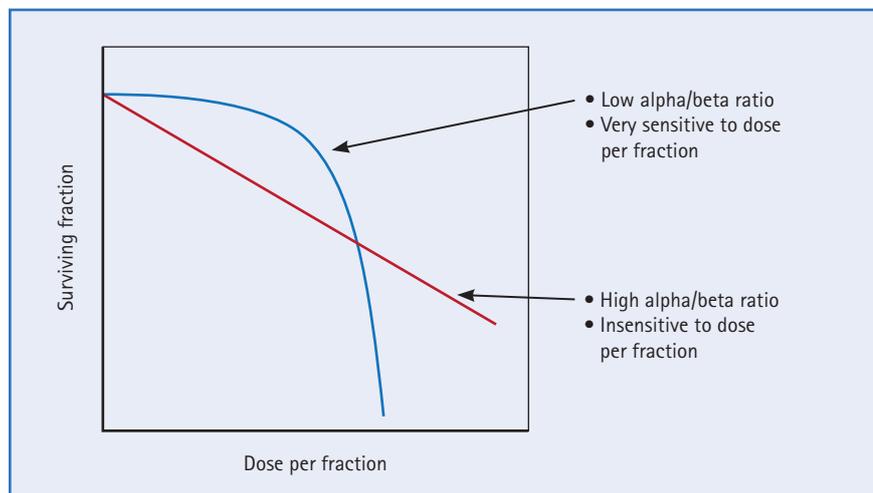


Figure 2. Cell survival curves for low and high alpha/beta ratio tissue. The surviving fraction describes the proportion of cells treated with a radiation dose that survive. Prostate cancer cells are sensitive to larger dose of radiotherapy per fraction, therefore fewer but larger doses of radiotherapy (hypofractionation) may give better results

showing that 60Gy delivered over four weeks is non-inferior to 74Gy over seven-and-a-half weeks in terms of prostate cancer progression and is not associated with significant differences in bladder and bowel toxicity.^{8,9} This is likely to become the new standard of care for many men with low- or intermediate-risk prostate cancer and will allow considerable savings in resources as well as being more convenient for patients.

IMAGE-GUIDED RADIOTHERAPY (IGRT)

Image-guided radiotherapy (IGRT) is a technique whereby regular imaging of the tumour or a marker associated with the tumour is used to ensure accuracy of treatment delivery, confirming that the target and surrounding organs are truly in a position appropriate for the radiotherapy to be given, thus ensuring that the treatment-day patient geometry and delivered dose matches the planned geometry and intended dose. This helps to compensate for variations in the position of the target volume, for example internal organ movement due to bladder filling or bowel gas and small errors in daily set-up.

In prostate cancer, IGRT can be achieved by implanting small inert seeds (fiducial

markers) into the prostate itself prior to treatment (Figure 3). Once a patient is set up in the treatment position, a simple X-ray can easily visualise the location of these markers and the patient can be moved by millimetres to the most optimal position prior to delivery of the radiotherapy treatment. This can be repeated prior to every fraction during a course of treatment. In addition, or alternatively, a cone beam CT scan can be taken once the patient is in the treatment position and target and other organ positions can be compared to the original CT planning scan. Shifts in the position of the patient can then be made prior to the delivery of treatment.

SYSTEMIC THERAPY WITH HORMONES

Men with high-risk localised (PSA ≥ 20 , Gleason grade ≥ 8) or locally advanced prostate cancer may have microscopic metastases at the time of presentation, which may be the limiting factor for progression or survival benefits as radiotherapy continues to improve. Such men in particular benefit from systemic therapy, which aims to treat sites of micrometastases in combination with radical radiotherapy to treat the known primary cancer aggressively.

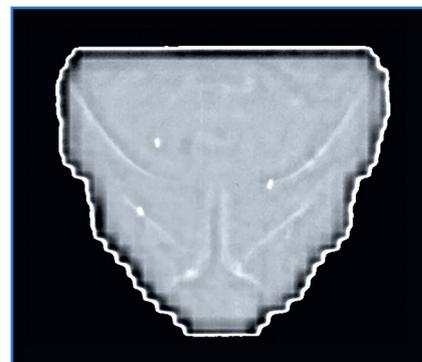


Figure 3. X-ray showing position of three fiducial markers that have been inserted into the prostate prior to radiotherapy planning and treatment. These are used to confirm the position of the prostate prior to EBRT delivery

Hormonal androgen deprivation therapy (ADT) is standard systemic therapy used in conjunction with radiotherapy. Hormone therapy may have an additive or synergistic effect with radiotherapy on local prostate tumour cell kill due to improved tumour oxygenation and entry of cells into a resting phase, reducing tumour repopulation. There is strong clinical evidence to support this neoadjuvant approach.^{10,11} Neoadjuvant ADT prior to radiotherapy also reduces the size of the prostate between 25–40% and potentially allows smaller radiation fields and sparing of normal tissues. ADT for up to three years after radical EBRT has been shown to significantly increase overall survival at 10 years in a number of studies, including the EORTC 228631, which reported that, in patients with locally advanced prostate cancer, the addition of the ADT initiated at the start of radiotherapy (dose of 70Gy) and continued for three years significantly improved survival compared with radiotherapy alone and ADT given for later disease progression.¹² The 10-year overall survival increased from 39.8% to 58.1% ($p < 0.0004$) with the addition of immediate adjuvant ADT. There were similar significant improvements demonstrated for other endpoints, including progression-free survival and clinical or PSA relapse.

Other randomised phase 3 studies of adjuvant ADT have demonstrated similar, very positive results and it is now standard practice to continue with hormone therapy for two to three years after radiotherapy for men presenting with high-risk localised disease.

CONCLUSION

Prostate cancer can be effectively treated with a course of radical radiotherapy. Radiotherapy to the prostate is a balance between escalating dose to the prostate target volume and minimising the dose to adjacent normal tissues, such as the rectum. Advances in technology have enabled more accurate conformity of dose around the target, which allows dose escalation while not exposing normal tissues to excessive doses. This has led to improvements in clinical outcomes with better rates of progression-free survival. The long-term effects of hypofractionation and the use of particle therapy such as protons are awaited. The field is likely to see further improvements in the coming years.

Declarations of interest: none declared.

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