Radiotherapy for localised prostate cancer

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Introduction

Prostate cancer is now the commonest malignancy in men in the UK, with 41,000 men being diagnosed in 2010.1 An increase in the use of prostate specific antigen (PSA) testing is thought to account for the rise in prostate cancer incidence and a shift to earlier diagnosis. The majority of men are now diagnosed with asymptomatic localised disease, rather than presenting with locally advanced or metastatic disease. However, it remains the second commonest cause of male cancer death in the UK, with more than 10,000 patients dying from the disease every year.1 Radiotherapy plays an important role in the management of prostate cancer, for both cure and palliation. Herein is provided an overview of the radical use of radiotherapy, focusing on external beam radiotherapy (EBRT) and highlighting some new developments in the area.

Prostate cancer staging and management options

Treatment options are dependent on the TNM stage of disease at diagnosis (referring to Tumour, Node, Metastasis staging system using the UICC classification system), together with other prognostic factors such as PSA level and histological Gleason grade of the tumour. These are used to stratify patients into risk categories that guide potential treatment options (figure 1 and table 1 adapted from MDT Guidance for Prostate Cancer).

Radiotherapy for localised disease

In patients with localised disease, all treatment modalities including surgery, brachytherapy and EBRT are suitable. While there are no direct randomised studies comparing these treatment options, they are generally regarded as having broadly similar efficacy but differ in their side-effect profiles. The most appropriate treatment option for an individual patient will need to take into account the disease extent as well age, co-morbidities, symptoms and preferences.

Radiotherapy also has a role in the post operative setting. It can be given as adjuvant treatment following surgery to patients with positive margins or high risk factors for recurrence on pathology.5 The current UK RADICALS trial is investigating the optimal timing of radiotherapy (immediately or at the time of PSA confirmed relapse), as well as the value of hormone therapy and its duration (none, six months or two years) in this setting.

Radical treatment options involving radiotherapy

Brachytherapy

In low dose rate (LDR) brachytherapy, tiny seeds of a radioactive isotope are inserted directly into the prostate using a grid-template under transrectal ultrasound guidance. As the isotope decays, high doses of radiation are emitted to the immediate area. Iodine125 is the commonest isotope used, with a half-life of 59 days. The prescribed dose is 145Gy to the whole prostate. Brachytherapy is commonly performed as a one-stop procedure under general anaesthetic, with real-time planning and adaptation of the needle positions followed immediately by seed delivery. Seed delivery can be via an automated robotic system (figure 2).

There is increasing interest in the use of high-dose rate (HDR) brachytherapy which may have radiobiological advantages over LDR, if the α/β ratio of prostate cancer is as low as suspected (see below). HDR brachytherapy involves the temporary insertion of a catheter device into the prostate under general anaesthetic, followed by remote after loading of an HDR source such as iridium192. It can be used as a means of delivering a ‘boost’ dose to the tumour following EBRT, but can also be used on its own as monotherapy, and occasionally for salvage.

External beam radiotherapy

EBRT is the commonest method of delivering radiotherapy for localised prostate cancer. Over the past two decades, there have been substantial improvements in prostate radiotherapy. These include advances in imaging for target delineation using MRI, more sophisticated techniques for treatment delivery such as conformal radiotherapy (CFRT) and intensity modulated radiotherapy (IMRT), as well as the evolution of image guided radiation therapy (IGRT) and dose painting.

Conformal radiotherapy versus conventional radiotherapy

CFRT describes the process of using computed tomography (CT) imaging to acquire detailed three-dimensional anatomical information about the prostate and its spatial proximity to nearby pelvic organs at risk (OAR). The radiotherapy treatment fields can then be shaped in the beams-eye-view to the profile of the prostate (and/or seminal vesicles and pelvic nodes), while minimising the dose delivered to the rectum, bowel and bladder. The CT data set can be used to calculate and optimise the dose received by the prostate and OAR, using dose volume histogram (DVH) data or alternative models to predict normal tissue complication probability. CFRT has now entirely replaced conventional RT as the minimum standard for prostate radiotherapy delivery within the UK.

The benefit of using CFRT over traditional techniques has been proven in a randomised study where men with prostate cancer were randomised to receive radiotherapy with unshaped treatment fields or CFRT. CFRT was shown to significantly reduce the incidence of clinically relevant...
late rectal toxicity by 50% without any reduction in PSA-assessed local control rates. Subsequently CFRT has permitted the assessment of dose escalation, moving from treating with doses of 64-68Gy to 74-78Gy. The efficacy of dose escalation has been confirmed in a meta-analysis of 2,812 patients, demonstrating a significant reduction in the incidence of biochemical failure in those treated with higher doses. However, while dose escalation is an effective means for improving local control, it may come at the expense of increased toxicity unless OARs such as the rectum can be adequately protected from also receiving higher doses. The same meta-analysis confirmed the limitations of using CFRT for dose escalation, with patients receiving high dose CFRT being 1.58 times more likely to develop aG2 late GI toxicity than patients who had received conventional doses. In CFRT there is limited scope to physically conform the dose around concave shaped structures, such as the prostate-rectum interface but this can be overcome by newer techniques such as IMRT.

Intensity modulated radiotherapy
IMRT is an advanced radiotherapy technique that provides improved dose conformity, allowing high dose regions to be shaped around concave targets such as the prostate-rectum interface, therefore avoiding excessive dose delivery to the rectum (figure 3). This is achieved by varying the intensity of the beam fluence across each treatment field via dynamically varying the multi-leaf collimators during dose delivery or on-line set-up correction. This can be used to treat different parts of the planning target volume (PTV) to different dose levels, a technique often referred to as dose painting. One potential application is delivering a higher simultaneous integrated ‘boost’ dose to regions of the prostate thought to contain high risk tumour cells. The feasibility of using novel imaging techniques, such as choline-PET and diffusion weighted MRI, to identify high risk areas of the tumour to be treated with a dose painting technique is currently being investigated. The clinical benefits of using IMRT have been shown in two series reported from the Memorial Sloane Kettering Cancer Centre. In a series of 1,571 patients with a median follow-up of 10 years, they demonstrated that IMRT significantly reduced the risk of GI toxicity over CFRT (13% vs 5%, p<0.001), despite treating with doses up to 81Gy. A recent update of 1,002 patients has confirmed that IMRT appears to be a safe tool for dose escalation, reporting acceptable rates of late GI toxicity (aG2 4.4%) with excellent rates of local control using an escalated dose of 86.4Gy.

Image guided radiotherapy
IGRT describes the process of acquiring imaging data to help reduce some of the spatial uncertainties associated with accurately delivering radiotherapy treatment on a day-to-day basis, over a treatment period of up to four to eight weeks. The prostate is a relatively mobile structure within the pelvis, being susceptible to displacement as a result of filling and emptying of both the rectum and bladder. During the period of a course of radiotherapy the prostate and seminal vesicles may also undergo deformation changes as a response to treatment. The radiotherapy planning CT, often performed a few weeks prior to treatment commencing, only provides a one-off snapshot of the position of the prostate and its relationship to nearby pelvic organs. Using daily image guidance to correct for changes in the prostate position, IGRT aims to reduce the risk of a geographical miss and allow margins to be reduced safely.

Several methods of IGRT for prostate cancer have been developed. The commonest involves inserting radio-opaque markers or fiducials into the prostate gland, using them as surrogates for the position of the prostate. Daily imaging and on-line set-up correction can then be performed, reducing set-up inaccuracies prior to treatment. IGRT imaging may be 2D, using the position of the fiducials relative to bony landmarks (figure 4), or 3D, such as with kv cone beam, which provides additional cross-sectional information on the prostate position and any gland deformation that has occurred. The use of IGRT in prostate cancer has been shown to improve clinical outcomes. In a retrospective matched cohort analysis, a significant improvement in biochemical tumour control was observed in high risk patients treated with IGRT compared with those who received non-IGRT treatment. Areas of focus in IGRT research at present include using fiducial markers to enable intra-fraction tracking of tumour motion (for example using CyberKnife).

New advances in prostate radiotherapy
Improved radiobiological understanding has led to the suggestion that the α/β ratio of prostate cancer may be much lower than previously thought. While most cancers have an α/β ratio on average close to 10Gy, it is estimated that prostate cancer may have an α/β ratio as low as 1.2-1.5Gy, similar to that of late responding normal tissues. This is clinically important as it suggests that the use of hypofractionated radiotherapy (ie using fewer fractions each of a higher size) may improve the therapeutic ratio by delivering a larger biological-equivalent dose to the tumour, while maintaining a similar or lower incidence of late side effects. Hypofractionated regimes have the added convenience of fewer treatment visits for the patient, with the associated reduction in treatment costs. The potential radiobiological advantages of hypofractionation are being explored in brachytherapy, using HDR, and EBRT. The completed UK CHHiP trial of over 3,000 patients, aims to answer the question of whether a hypofractionated approach (60Gy in 20 fractions or 57Gy in 19 fractions) may result in equivalent or improved outcomes for similar toxicity rates, compared to the standard dose regimen of 74Gy in 37 fractions. The results of this potentially practice-changing trial are eagerly awaited.

The introduction of stereotactic body radiation therapy (SBRT) has prompted investigation into the use of more extreme hypofractionation schedules for localised prostate cancer based on the low α/β ratio. The CyberKnife is an example of a specialised SBRT delivery platform, using a robotic radiosurgery system featuring real-time tumour tracking with sub-millimetre accuracy to enable small CTV to PTV margins to be used. The use of multiple non isocentric, non coplanar beams allows highly conformal dose distributions to be produced with rapid dose fall off outside of the PTV (figure 5). The current international trial (PACE) is evaluating the role of a four or five fraction CyberKnife delivered SBRT regimen, randomising against laparoscopic prostatectomy or conventionally fractionated IMRT in early stage prostate cancer.

Conclusion
Technological advances in imaging and radiotherapy have dramatically changed the treatment of prostate cancer with radiotherapy. Research continues into the optimal volume to be treated in locally advanced cases (ie prostate versus prostate and pelvic nodes) and the value of hypofractionated regimens. The evolution of advanced radiotherapy techniques are permitting research into sub-prostate volume boosting, prostate gland re-irradiation, and treating isolated pelvic nodal recurrences with ablative doses. It is important that the outcomes are evaluated and assessed, where permissible in comparative studies, so that the potential beneficial outcomes can be quantified.
References

Possible treatment options

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TABLE 1
Summary of potential treatment options dependent on stage (adapted from').
Figure 2
Showing Nucletron brachytherapy needle and template grid for LDR seed insertion.

Figure 3
Five-field prostate IMRT plan showing concave dose shaping at prostate/rectum interface.

Figure 4
Lateral and AP kv images showing prostate fiducial marker position for IGRT.

Figure 5
CyberKnife prostate plan showing (A) typical multiple beam arrangement and (B) axial CT slice showing highly conformal dosimetry with rapid dose fall off.