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Original article

Prostate brachytherapy: a review of current practice

Peter Bownes*, Anthony Flynn**

**Medical Physics Department, Mount Vernon Hospital, Middlesex; **Department of Medical Physics and Engineering, Cookridge Hospital, Leeds, UK*

Abstract

There is currently great interest in the treatment of prostate cancer due to its increasing profile in the older male population. In recent years brachytherapy has become a viable treatment option. Low dose rate implants using permanently implanted radioactive seeds and high dose rate treatments using afterloading machines are two methods regularly used for the treatment of this disease. Both techniques require close integration between imaging and the placement of the radioactive sources. Future developments in imaging will lead to improved targeting of the radiation to diseased areas of the prostate and interactive treatment planning. This review paper describes the current status of the treatment of prostate cancer by brachytherapy, references current published results and examines radiation protection issues.

Keywords

Prostate cancer; brachytherapy; LDR; HDR

INTRODUCTION

The purpose of this paper is to provide an overview of the practice of prostate brachytherapy (BT). It is intended as a general guide for health professionals who are not as yet directly involved but who may wish to know more about this form of treatment, which has expanded rapidly in the recent years. Specialists already in the field may also find it useful to have the current situation summarised, but the inclusion of detailed data is outside the intended scope of the review. The paper is written by two physicists who have been involved with prostate BT for a number of years. Any medical information is mentioned for background only and is not intended to be a definitive statement for direct clinical use. Also we have taken the unusual step of including web site addresses in the references as this is often the most convenient way of accessing the latest patient statistics.

Prostate cancer is the second most common cancer in men. According to the UK Office of National Statistics[1] there were 18,300 new cases in England and Wales in 1997 and the crude incidence rates are continuing to rise. The Institute of Health Science at Oxford University reported a rise in incidence in England and Wales of almost 40 percent in the 5 years from 1988 to 1993[2] and the Institute of Cancer Research[3] estimate that there are now (2003) about 22,000 new cases per year. However, a detailed study from the South East of England[4] suggests that the age-specific incidence rate and the age-specific death rate, that

Correspondence to: P. Bownes MSc, Medical Physics Department, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN, UK

is the crude rates corrected for demographic changes, have levelled off and may even be falling and that there is a higher proportion of localised cancers. These statistics seem to suggest that the general increase in incidence is due to an ageing population and the changing profile of the disease is perhaps due to the increased use of screening.

Options for treatment of prostate cancer include watchful waiting, radical prostatectomy, hormone therapy, external beam radiotherapy, prostate BT, and perhaps a combination of some of these. We do not propose to discuss the relative merits of each of these treatments, as that is a clinical decision based on the individual situation. However, prostate BT is being increasingly used for early stage prostate cancer. It is seen as a convenient treatment, which needs only one or two overnight stays in hospital, and patients are generally able to return to their normal activities within a few days of the procedure. Patients are selected for BT based on the stage of the disease, biochemical and histological factors and prostate volume. The American Brachytherapy Society (ABS) and The European Society for Therapeutic Radiology and Oncology (ESTRO) have produced guidelines for patient selection.[5,6] Reported results for tumour control are comparable with other methods of treatment with a tendency for reduced morbidity.[7–9] A recent systematic review of the literature by Norderhaug et al.[10] concluded that the results and morbidity are comparable with other forms of treatment. Typically bNED (biological no evidence of disease) at 5 years are about 70% for prostate BT, external beam radiotherapy and radical prostatectomy.

HISTORY OF PROSTATE BRACHYTHERAPY

Holm[11] has written an excellent early account of the history of prostate BT, including his own contribution to the modern-day development of the technique. Early attempts at prostate BT were made by Barringer[12] in 1917 who used radium needles inserted transperineally and up to the 1960s various radioactive materials were tried including colloidal gold. Whitmore reported the first major attempt at BT with iodine-125 seeds from the Memorial Hospital in New York in 1972.[13] The seeds were implanted via a mid-line lower abdominal incision (the so-called retropubic approach) following a lymph node dissection. In 1987 Battermann in Utrecht reported using a retropubic approach from 1981.[14] However long term results with this approach were not promising and this was considered to be due to the poor geometrical arrangement that ensued from the implantation method.[15] In the early 1970s, Holm and his group in Copenhagen developed transrectal ultrasound for use in prostate biopsies and extended this expertise to the implantation of iodine seeds. At the same time, improvements in transrectal ultrasound imaging led to improved visualisation of the prostate and surrounding structures and soon the basis of the current method of insertion using a combination ultrasound probe and perineal template was developed. Holm[11] treated cases in the 1980s and was visited by Ragde from Seattle in 1986. Ragde and his colleagues[7] further refined the method and from Seattle it was taken up across North America. At about the same time Battermann[16] used the ultrasound guided transperineal approach from 1989 in Utrecht. In 1994 BT specialists from the Cookridge Hospital Leeds visited Seattle to study the technique and treated their first patient in Leeds in 1995. There are now several centres in the UK that provide this method of treatment using either iodine-125 or palladium-103 seeds. The use of high dose rate (HDR) afterloading for prostate implants has also developed, combining the recent developments of transrectal ultrasound[11] and HDR remote afterloading units. Kiel in 1986,[17] Seattle in 1989[18] and Michigan in 1991[19] were some of the early centres to adopt the technique of external beam and a HDR BT boost. Mount Vernon implanted their first patient in 1997. We will describe both methods.

DOSE RATE CONSIDERATIONS

Treatments using iodine-125 or palladium-103 seeds are examples of low dose rate permanent implants. The seeds are not removed and remain in the prostate. The treatment is given continuously and the dose rate falls exponentially with time. Although the dose rate never reaches exactly zero, in practical terms the treatment is complete after a period of a few months, depending on which radionuclide is used. In contrast HDR afterloading gives a high dose rate (at about

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1 Gy/min) and the treatment has to be divided into a number of fractions. The consequence is that the radiation dose prescriptions are different for the two types of BT, being higher for the low dose rate method. More details of the radiation doses used are given in the paragraphs that follow.

PATIENT SELECTION

The standard pre-treatment investigations detailed in the ESTRO/EAU/EORTC recommendations for permanent seed implantation[6] should be followed for the staging of the patient and determination of the treatment options available. The probability of spread outside the gland can be predicted with some accuracy using the Partin Tables.[20] The Partin tables use a combination of T-stage, prostate specific antigen (PSA) level and Gleason score to estimate the percentage probability of disease being organ confined, capsular penetration, seminal vesicle involvement and lymph node involvement.

Prostate BT with implanted seeds without external beam therapy ("monotherapy") is normally considered for early stage disease in which the disease has not spread beyond the prostate itself, as confirmed by transrectal ultrasound and/or MR scanning. Suitable patients are those that have a life expectancy of 10 years, no evidence of metastases, no previous TURP, clinical stage lower than T_{2b}, Gleason score less than 6, PSA less than 10 $ng.ml^{-1}$ and a prostate volume of less than 50 cc.[21] Currently some centres will consider implanting up to PSA of 50 $ng.ml^{-1}$ but in practice the upper limit rarely exceeds 20 $ng.ml^{-1}$. For patients who have a good prognosis it is recognised that permanent implant BT alone may be optimal, exploiting the biological advantages of low dose rate permanent implants.

Patients with intermediate risk also have a higher probability of microscopic spread (>50%), clinical T-stage T_{2b} to $T_{3a,}$ PSA between 10 and 20 ng/ml and Gleason score of 7 or above may be best treated with a combination of external beam radiotherapy and either HDR or LDR (permanent implant) BT boost.

HDR monotherapy can be offered to patients who are good prognosis but have a volume greater than 50 cc but have no significant pubic arch interference. It may also be the approach adopted for those who fall between the two categories i.e. PSA greater than 10 and Gleason less than 6 or PSA less than 10 and Gleason = 7 and thus may exceed the good prognosis level so their general risk falls between the two groups.

Contraindications for BT procedures include: not organ-confined disease, prostate volume greater than 50 cc, pubic arch interference, previous TURP, unfit for general anaesthetic and distant metastases.

LOW DOSE RATE BRACHYTHERAPY

Types of seed

There are several suppliers of iodine-125 and palladium-103 seeds. They differ in detail in their internal construction leading to small differences in the dosimetry but are similar in overall size. Figure 1 shows an iodine-125 seed (Type 6711, Oncura), which is the seed most commonly used in the UK. This type of seed is 4.5 mm long, 0.8 mm diameter and consists of a titanium casing containing a silver rod on which is absorbed the radioactive iodine-125. It is available with a range of source activities. As well as in loose format, seeds are available in strands of ten, spaced 10 mm apart in an absorbable suture material (Rapidstrand™, Oncura). These can be cut into shorter strands, as required (Fig. 2).

Figure 1. Iodine-125 seed (Type 6711) compared with a 5p piece. (Picture courtesy of Oncura)

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Figure 2. Rapidstrand, containing type 6711 seeds. (Picture courtesy of Oncura)

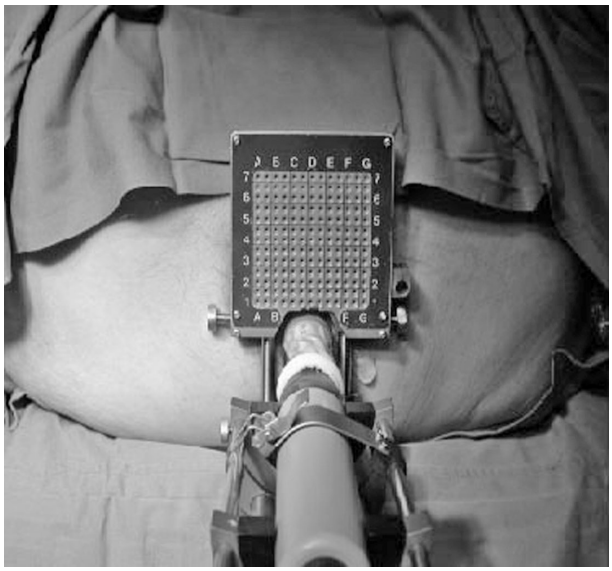

Figure 3. Patient set-up for volume study, showing ultrasound probe and template

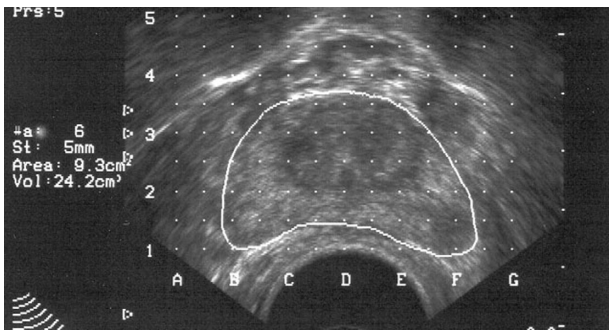

Figure 4. One image from the sequence taken for the volume study. The dots indicating possible needle positions can be seen. The white line shows the prostate as contoured by the radiologist

Iodine-125 has a half-life of 59.4 days and decays by electron capture to tellurium-125. It emits a complex photon spectrum in the range 27.4 keV to 35.5 keV. Palladium-103 has a half-life of 16.97 days and decays by electron capture to rhenium-103. Its emission spectrum is in the range 20.1 keV to 23.0 keV.[22] The low energy of these emissions requires minimal radiation protection requirements.

The cylindrical nature of the seeds and the low photon energy lead to the radiation dose distribution around an individual seed that is anisotropic, the dose rate being less along the long axis of the source compared with the transverse axis. This is due to the extra attenuation by greater length of material on the long axis. This effect is accounted for in the treatment planning process. It has been shown that variations in seed orientation in implants have little effect on the overall dose distribution.[23]

Treatment planning

The first stage in the treatment planning process is to perform a prostate volume study. This is normally done a few weeks before the scheduled implant date (though this is starting to change as procedures develop and will be referred to later). The patient is placed in lithotomy position under anaesthesia or sedation. A transrectal ultrasound probe is used to acquire cross-sectional images of the prostate at 5 mm intervals. Figure 3 shows set-up, and also shows the template that will be used subsequently to assist in seed placement. The first image of the sequence is just above the base of the prostate (superior) and the final image is below the apex (inferior) ensuring that the whole prostate has been covered. The software controlling the image collection superimposes a series of dots on the image; these correspond to holes in the template, which are subsequently used to guide needles, which will deposit the seeds. An example of one image from such a sequence is shown in Fig. 4. The radiologist or urologist contours the prostate on all the images and the treatment pre-plan is based on these contours. The aim of the pre-plan is to calculate the seed positions required,

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in three dimensions throughout the prostate, which will give the specified dose envelope. The dose normally prescribed is 145 Gy for I-125 seeds and 125 Gy for Pd-103 seeds monotherapy; these are reduced to 110 Gy and 100 Gy respectively when combined with external beam radiation.[24]

The criteria for the pre-plan are illustrated in Fig. 5, which represents a sample cross-section of the prostate. The intention is to enclose the prostate within the prescription dose contour (in this case 145 Gy) with about a 3-mm margin, though this margin may be much less close to the rectum. The dose to the urethra within the prostate is kept as low as possible, in this case less than 125%. The dots on the cross-section represent the seed positions on that plane, though of course in general there are seeds on planes above and below this example plane, which contribute to the dose. Seeds are generally spaced 10 mm apart 'centre to centre' in the cranio-caudal direction and more than 5 mm apart in the other two directions. A prostate implant will use between about 60 and 110 seeds depending on the volume and a common arrangement is to have a bias towards placing seeds around the periphery of the volume with a reduced seed density towards the middle of the prostate. The seeds are ordered from the supplier and are delivered a few days before the implant.

Implant procedure

For a two-step procedure the implantation session normally takes place a few weeks after the volume study. The seeds are unpacked in the theatre and the seeds activity is checked in a calibrator. This has to be done under sterile conditions. The seeds specified in the pre-plan are loaded into implant needles under sterile conditions. A stylet is placed in each needle behind the train of seeds. Each needle is destined to go into a specified hole in the template and will contain the sequence of seeds needed along its track through the prostate. The loaded needles are stored in a shielded loading box while the patient is being prepared. An implant will use up to about thirty needles. Meanwhile the patient is anaesthetised/sedated and placed in the lithotomy position. The rectal ultrasound probe and template are positioned and the radiologist or urologist re-creates the images of the volume study, ensuring everything is in the same place. Each needle is taken in turn and inserted through its assigned hole in the template to its assigned depth. Its positioning is checked by ultrasound imaging. When it is in its correct place the needle is pulled back over the stylet, depositing the train of seeds in its assigned position in the prostate. The needle and stylet are discarded. This process is repeated for all the needles until all the seeds are in place (Fig. 6). Some hospitals use a different insertion technique in which the seeds are inserted one by one. Finally the seed positioning is checked by radiography.

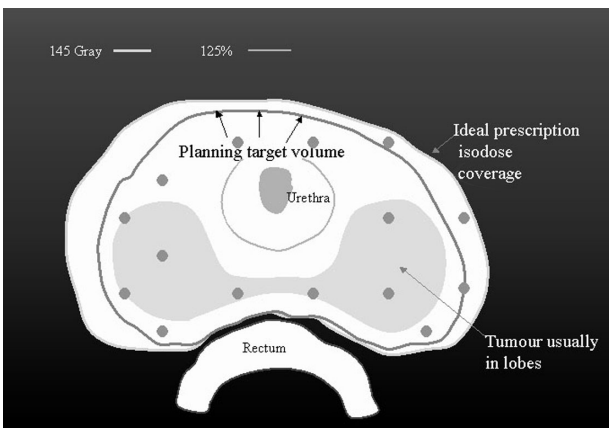

Figure 5. Diagrammatic representation of 145 Gy and 125% isodose curves superimposed on prostate contour

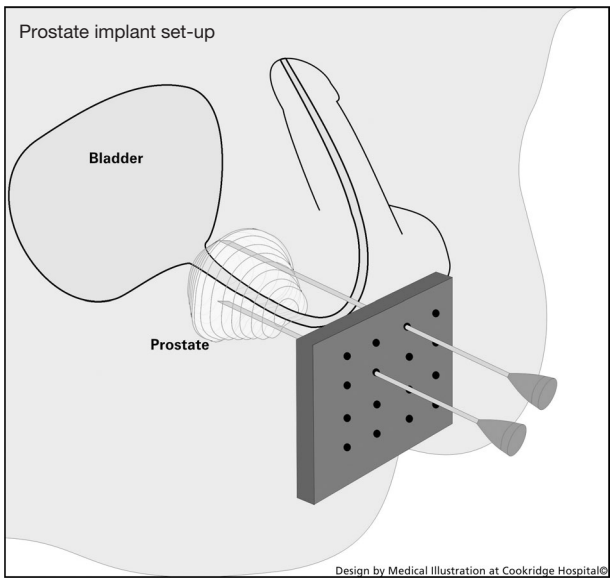

Figure 6. Diagrammatic representation of the template and needles. Although two needles are shown here to illustrate the different penetration depths, in practice only one needle is inserted at a time

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A single-step procedure is being used now for some patients. In this the volume study and implant are performed at the same visit. This has the advantage for the patient that only one anaesthetic is required but it requires the treatment planning team to be in the theatre and there is a tendency to waste more seeds as the precise number required is not known in advance.

After recovery the patient returns to the ward and it is a common practice to accommodate him in a single room. The radiation protection requirements are minimal (see below) due to the low radiation energy emitted by the seeds, but a single room is convenient as it delineates the area to be monitored for stray seeds (which are unlikely) when the patient leaves. The patient usually returns home the day following the implant and returns to normal activities within a few days.

Post-implant dosimetry

The dose distribution achieved for each patient is checked. At some interval after the implant the patient is recalled for a CT scan and dosimetry is based on these. This calculation cannot influence the BT treatment of the individual but post-implant dosimetry is an important tool in the quality control of the procedure. Results from the post-implant analysis can be fed back into the technique thereby improving the clinical service. There is increasing evidence that the dosimetry results show correlation with the biochemical progress of the disease. Stock et al.[25] report an increased freedom from biochemical failure with increasing radiation dose. More recently Potters et al.[26] suggest that a D90 (dose to 90 percent of the prostate volume) of greater than 90 percent of the prescribed dose can be used as a predictor for PSA relapse-free survival.

There has been much discussion in the literature regarding the optimum interval between implantation and the post-implant dosimetry CT scans. The implanting of the seeds causes oedema in the prostate and this has largely dissipated within a month, so there is a strong argument for waiting. Should the scans be done too early the prostate will be larger than at the time of implantation giving an incorrect dosimetry analysis, but an early scan might, in theory at least, permit re-implantation if an unintended low dose region was observed. The ABS recommendations for post-implant dosimetry[27] note the lack of consensus on this but state that scanning after one month will give the most reproducible results and that each centre should perform the post-implant scanning at a consistent interval. In Leeds the scanning and dosimetry analysis is performed after about a month. Results are fed back to the individual's oncologist, and to the whole team of oncologists, radiologist, physicists and nursing staff in order to continually improve and develop the technique. Patients are followed up in the usual way with regular clinic visits. In particular repeat PSA tests are done at regular intervals.

RESULTS

A search of the literature reveals no prospective clinical trials comparing prostate BT and other treatments for early prostate cancer. Indeed prostate cancer is generally a slowly developing disease and it would take many years to collect meaningful data from such a study. There are however reports from individual treatment centres.[7–10,16,21] Ragde et al.[7] report on a series of 769 consecutive patients treated with either iodine-125 or palladium-103 implants between 1987 and 1997. Biochemical disease-free survival rates of the 619 patients available for follow-up were 85% at 3 years and 77% at 13 years and they conclude that BT is an effective treatment for organ-confined prostate cancer. A recent review by Blasko et al.[8] reports that, although short-term morbidity after BT can be significant, most current series report low long-term urinary and rectal complications and that treatment results appear to be equivalent or superior to other treatment modalities.

RADIATION PROTECTION CONSIDERATIONS

There is little external radiation hazard due to the low energy emitted by the seeds. The seeds are delivered pre-sterilised in steel tubes (Fig. 2) and the external dose rate from these is minimal. The seeds must be handled with forceps for reasons of sterility and radiation protection but finger dose monitoring has shown that no extra radiation protection is required when calibrating and

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loading the seeds into the needles, provided that an experienced person does it quickly. A new starter, who will work more slowly, might need extra protection until speed and skill have developed. The loaded needles are stored in a shielded box pending their insertion into the patient.

The external dose rate is low once the seeds are implanted as the surrounding tissues absorb most of the radiation. There are few published figures for this; Smathers et al.[28] report surface doses of around 50 μSv.hr^{-1} and our own measurements are consistent with this on the surface; however, they fall to almost background levels at 1 metre from the patient. As a consequence there is practically no external radiation hazard whilst the patient is in hospital and the main issue is the containment of seeds. There is a small risk that the patient might pass a seed in urine so this is filtered before disposal and the patient's room and linen are monitored when the patient is discharged. Patients are asked to observe some restrictions on contact with small children and pregnant women for two months, but this is really for their 'peace of mind' as our risk assessment shows that there is no significant risk of a family member receiving a radiation dose of any consequence. It is recommended that patients abstain from sexual intercourse for two weeks post implant and thereafter to use condoms for a period of two months to avoid the risk of passing a seed in the ejaculate. Michalski et al.[29] report on a survey of family members, pets and the home environment following 44 prostate seed implants with iodine-125 or palladium-103 seeds in the United States. They concluded that the radiation exposure was very low and certainly below the US Nuclear Regulatory Commission dose limits for members of the public. There are restrictions on cremation should the patient die within three years of the implant due to the radioactivity contained in the body and there may be restrictions on further abdominal surgery should that be required for any reason within the three-year period. Also it has been reported from the US that patients have triggered radiation detectors installed for security purposes at airports. Patients are advised of all the radiation protection issues before the implant and each is given an information card to carry with contact phone numbers in case of any queries.

HIGH DOSE RATE BRACHYTHERAPY

Introduction

Modern techniques of implantation using transrectal ultrasound-guided insertion of applicators in conjunction with HDR afterloading enables customised conformal BT to be delivered accurately and safely to the prostate gland, while sparing surrounding critical normal tissues. The inherent conformality of BT approaches and the rapid fall-off dose outside the implanted area is superior to external beam treatment, even with sophisticated conformal techniques.

HDR BT can be used as both monotherapy[30,31] and as a boost within a combined external beam schedule.[17–19,32–38] A combination of external beam and BT enables a moderate external beam dose to be given to a volume encompassing any potential sites of microscopic spread followed by a localised high dose boost to the site of the macroscopic tumour within the prostate gland using HDR BT.

HDR afterloading: equipment advances

The recent developments of transrectal ultrasound incorporating a perineal template have allowed bi-planar real time image guided transperineal implants. This has enabled accurate source placement, which was a major criticism of earlier techniques.[15] The second major technological advance was the introduction of HDR afterloading, which has the advantage of a small, high activity iridium-192 source, availability of both flexible and rigid catheters and short exposure times.

Iridium-192 has a half-life of 73.83 days and decays to the stable isotope platinum-192. It emits a complex photon spectrum in the range of 0.2 to 1.06 MeV, with a mean energy of 0.37 MeV. There are a variety of types of these HDR sources, ranging from 0.2 to 1.3 mm diameter and 1 to 20 mm active length, with activity typically up to 370 GBq (air kerma rate 42 mGy/hr at 1 metre). Different manufacturers source design vary slightly in dimension and construction, but result in similar dose distributions.

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The source is permanently attached to a cable drive. The active source is encapsulated within a stainless steel pellet, which also absorbs any unwanted beta radiation. HDR afterloading units offer greater flexibility in dose distribution than low dose rate implants by customising the dwell positions used and the amount of time the source remains in each dwell position.

The other recent technological advance that has occurred is the development of 3D image-based treatment planning systems. The more advanced systems on the market allow full image-based manipulation (including image fusion), contouring tools and automated catheter reconstruction. Computer-based dose optimisation both volumetric and geometric are available along with interactive graphical dose shaping.

HDR afterloading: radiobiological considerations

The dose rate of a modern HDR afterloading unit, at about 1 Gy/min is similar to that of a linear accelerator and does not have the same biological advantages as iodine-125 seed implants. Therefore radical radiotherapy doses can only be delivered safely by using multiple small fraction sizes to achieve biological sparing of normal tissues. Alternatively a hypofractionated schedule employing large fraction sizes with a lower total dose to remain within the normal tissue tolerance can be used.

For these biological reasons HDR afterloading was considered mainly for boost treatments in combination with external beam radiotherapy. Over recent years understanding of radiobiology of the prostate cancer have changed and increasing published evidence suggests that it is a tumour with a low alpha beta ratio in its radiation dose response characteristics.[39,40] The new understanding of the radiobiology of prostate cancer suggests a small number of large fraction treatments may be the optimal approach for treatment delivery to the prostate and radiobiological modelling undertaken in this department supports this hypothesis.[41] This recent clinical data has allowed HDR monotherapy to be developed as a treatment schedule.[30,31]

Current protocols

The protocol used at Mount Vernon Hospital delivers a conformal external beam dose of 35.75 Gy in 13 daily fractions, following the RTO1 guidelines for volume definition.[42] This is then followed by a HDR boost of 17 Gy in two daily fractions, (approximate time between fractions is 18 hours), within 1 week of completion of external beam treatment. This protocol was developed as part of a prospective, randomised controlled trial comparing it to our standard external beam alone schedule of 55 Gy in 20 daily fractions.

At Mount Vernon treatment is planned using Brachyvision (Varian) planning software and delivered using the Gammamed 12i HDR unit (Varian). The active source dimensions of the Gammamed 12i are 3.5 mm long and 0.6 mm in diameter, encapsulated in a stainless steel pellet of dimensions 5.1 mm long and 1.1 mm in diameter.

The combination of external beam and HDR boost for radical prostate treatment is not unique and has been adopted in many centres across Europe and US. However reviewing the protocols for various centres, the external beam component is very similar (40–45 Gy in 4 to 5 weeks or its appropriate equivalent dose schedule) but there is considerable variation in the dose schedules for the HDR component. Table 1 shows this variation. This variation may be partly explained by examining the actual dose definition of the implant itself. For example some centres may prescribe to cover the peripheral zone to one dose level and the prostate capsule to another.

Table 1. Dose fraction schedules for HDR boost treatments of the prostate reported at different centres

Centre	Total dose	Number of fractions
Mount Vernon Hospital	17 Gy	2
Seattle [18]	16.5 Gy	3
Kiel [17]	30 Gy	2
Michigan [19]	18 Gy	3
Offenbach [34]	28 Gy	4
Oakland CA [35]	16.5 Gy	3
Berlin [36]	18 Gy	2
Goteborg [37]	20 Gy	2

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Implant procedure

Applicators may be rigid needles or flexible plastic catheters. They are placed into the prostate through the transperineal route using transrectal ultrasound guidance. All implants are performed with the patient under general or spinal anaesthesia. The patient is placed in the lithotomy position with a urethral catheter inserted until the end of the treatment. The ultrasound probe sits in a stepping unit, which controls the probe movement. A 7 × 7 cm rectilinear grid template with 1 cm spacing between grid positions is attached to the stepping unit and the grid positions are superimposed onto the transverse ultrasound image.

The ultrasound probe is aligned to ensure the prostate gland is covered by the grid positions with the bottom row no more than 5 mm inside the posterior border of the gland and the urethra is aligned with the central column of template grid positions throughout the implant. The geometrical position of the applicators within the implant is the primary factor that governs how good the dose coverage will be.

Prior to inserting applicators two fixation needles are inserted into the prostate gland to minimise movement of the gland during the procedure. Using the transverse ultrasound image the afterloading applicators are inserted using a metal stylet, working from anterior to posterior to minimise echo interference, and ensuring good peripheral coverage. Grid positions around the urethra are left empty: see Fig. 7a. The sagittal image is used to check the depth of the insertion and that the applicator is inserted parallel and straight: see Fig. 7b. It is our standard practice to over-insert needles in the superior direction to account for any catheter movement between fractions.

The applicators will be left in-situ between treatment fractions; therefore, a second template is required to be attached to the patient's perineum to hold the applicators in position. An alternative approach used at Mount Vernon is a flexible silicon rubber template, which mimics the rigid ultrasound template. It comprises of 'O-rings', which the applicators pass through and then they grip and hold the needle. The template is aligned to the ultrasound template and then glued and sutured to the patient (Fig. 8).

Once all the applicators have been inserted the ultrasound template is pulled over the applicators and taken away, leaving the applicators held in place by the silicon template (Fig. 9). The applicators are capped, labelled and their lengths measured to provide a quality assurance baseline.

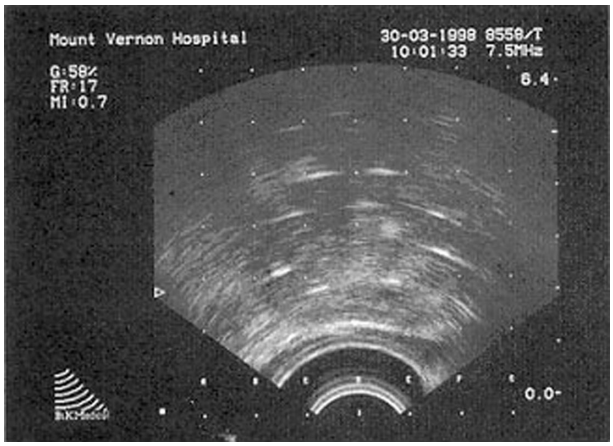

Figure 7a. Transverse ultrasound image

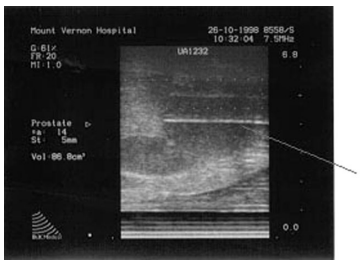

Figure 7b. Sagittal ultrasound image

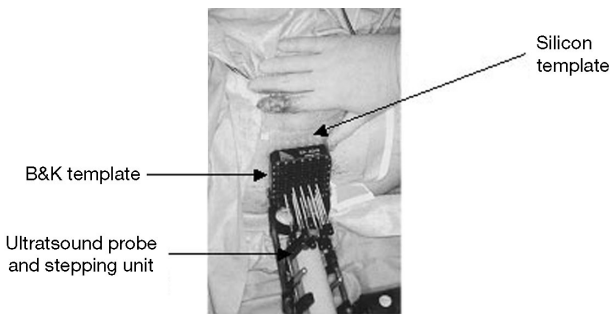

Figure 8. Transrectal ultrasound unit and grid, with the perineal silicon fixation grid

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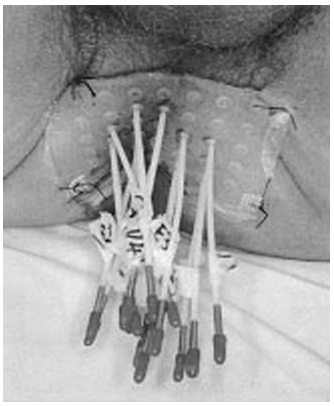

Figure 9a. Needle labelling

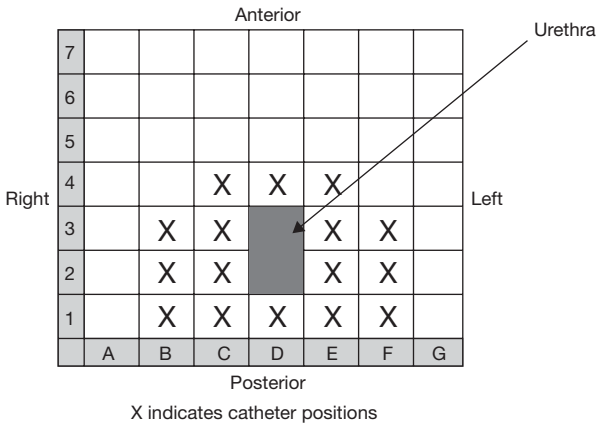

Figure 9b. Needle placement summary

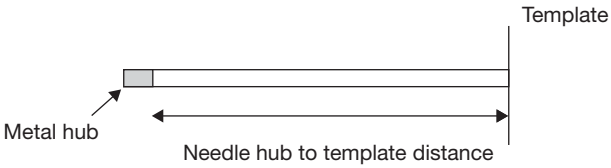

Figure 9c. Quality assurance measurements of needle distance

TREATMENT PLANNING AND DOSE PRESCRIPTION

Following recovery from the anaesthetic the patient is taken to have a CT scan (3-mm slice separation and 3-mm slice thickness), with the patient in the treatment position (legs down), to reconstruct the implant. The CT data is transferred onto the treatment planning system and the clinician will contour the clinical target volume (CTV), which is the entire prostate gland and surrounding critical structures (rectum, bladder and urethra). The PTV is defined as the CTV with a 3-mm margin and the rectum set as a limiting structure to the expansion.

The applicator positions are reconstructed and the dwell positions (HDR source stopping positions) are defined to be within the PTV with a 5-mm separation between dwell positions. Dose constraints are set for each volume defined and volumetric optimisation is used to obtain a 'first pass' dose distribution (Fig. 10). Dose distributions can then be modified using graphical interaction or by changing the dwell time of the dwell positions manually. The final plan tends to show differential loading between the periphery and the core of the implant. The aim of the plan is to encompass the prostate within the prescription isodose (in Mount Vernon's case this is 8.5 Gy per fraction). The dose to the urethra within the prostate is kept as low as possible, at Mount Vernon less than 125%, while the dose to the rectal wall should be less than 100%. Full evaluation of the plan includes looking at the distribution in 3D and using dose volume histograms (Fig. 11).

Treatment delivery

Before each fraction the distance from the template to the front of the metal cap at the end of the needle is measured. This allows the assessment of any external needle movement between fractions relative to the baseline measurement in theatre, see Fig. 9c, and adjust if required.

The first treatment is then delivered with an HDR afterloading unit as defined by the generated plan. At completion of the treatment the applicators are capped and the patient returns to the ward where he stays overnight.

Quality assurance for the second fraction

The radiobiological features of HDR/BT demand fractionated treatment as discussed earlier. For fractionated treatments the most important issues are related to reproducibility of the implant geometry and dosimetry for each fraction. If a single implant is used for multiple fractions then some form of assessment is required of the implant geometry to ensure that the quality of the implant dosimetry remains high for all fractions. Our

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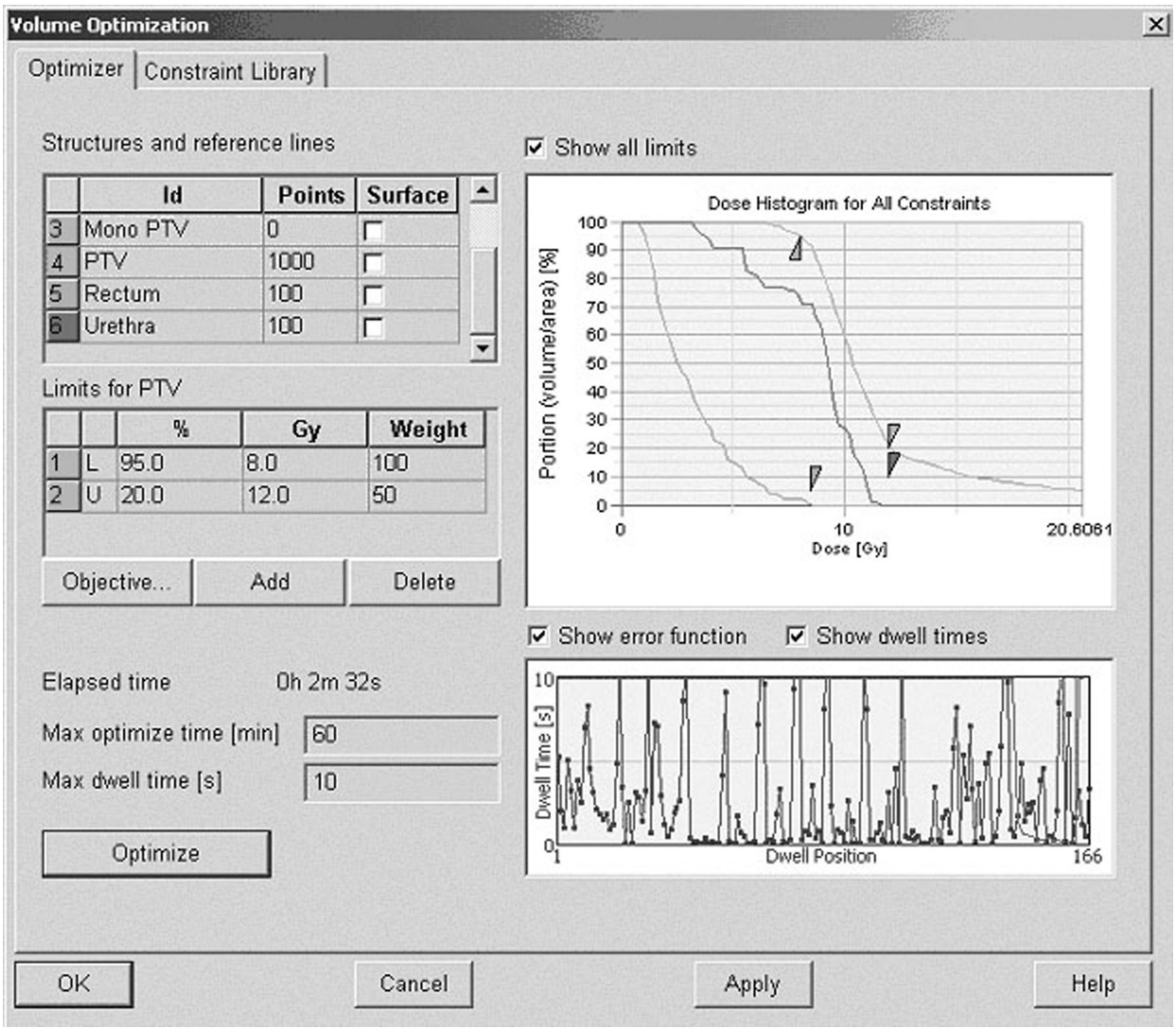

Figure 10. An example of the dose constraints set for volumetric optimisation

recommendation is to perform routine CT imaging before each fraction of HDR BT to assess the implant geometry in relation to the target volume.[43]

From our experience[43] the skin fixation template used appears highly efficient. However significant internal movement has been observed between fractions. The caudal migration of the applicators relative to the bony landmarks and prostate gland observed is attributed to peri-prostatic oedema in the perineal region between the prostate apex and skin surface. Similar caudal migration has been observed in other studies.[44–46]

In summary to avoid any significant reduction in implant quality, both in terms of under-dosage to the base of the prostate and overdosage to the critical structures, then caudal displacement of the applicators relative to their planned positions and internal anatomy must be quantified and appropriate adjustment of the origin to the first dwell position made or re-insertion of each applicator performed.

When all adjustments have been made and the final fraction of treatment has been delivered then the applicators are removed and the template taken off the skin. This process does not require

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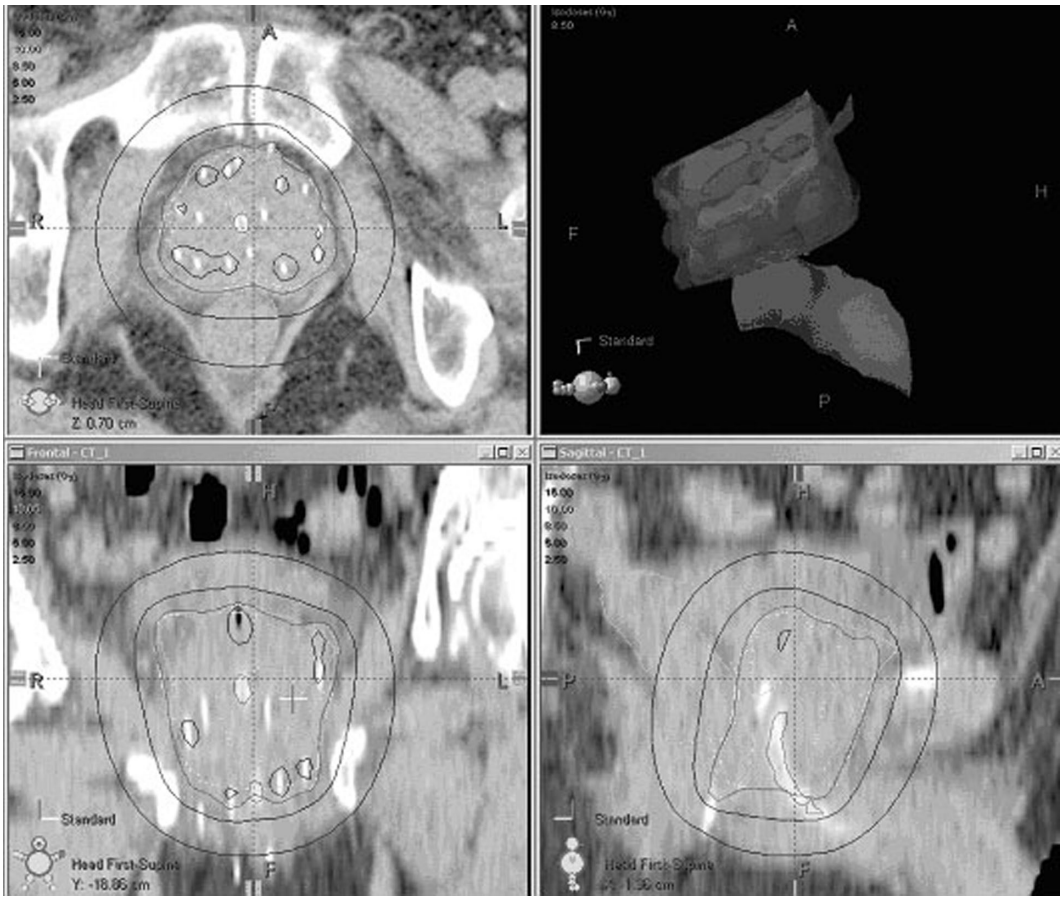

Figure 11. Plan evaluation of the implant using 3-dimensional dose distributions and dose volume histograms

anaesthetic and leaves the perineum intact with minimal bruising afterwards. The urinary catheter is also removed at this point.

RESULTS

Results reported in the literature for this technique are still relatively immature. A summary of the published data is shown in Table 2. PSA-free survival results are shown, with biochemical failure being defined according to American Society for Therapeutic Radiology and Oncology (ASTRO).[47] Three consecutive rises in PSA after reaching nadir, (lowest PSA reading achieved after treatment), constitutes biochemical failure. The main conclusions drawn from the literature is that the technique of combining external beam radiotherapy with HDR BT boost is an effective form of treatment with high control rates from locally advanced disease as well as early prostate cancer.

This technique is generally well tolerated with toxicity similar to those experienced from high dose pelvic external beam radiotherapy. During the implant there may be minor discomfort, usually controlled with moderate analgesia. Haematuria is common but rarely of great consequence. Bowel function maybe disturbed and may take up to one or two weeks to return to normal. Urinary symptoms of mild dysuria and haematuria may be observed in the first couple of weeks after the catheter has been removed.

Late rectal and urinary complications are rare. Kiel, as reported by Kovacs[17] has the most mature data and suggests that incidence of the order of 3% for grade 3/4 rectal complications and a similar or slightly higher incidence of grade 3/4 urinary complications.

There are few published results from HDR monotherapy. Preliminary results[30,31] reveal

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Table 2. Clinical results and complications for HDR boost treatments of the prostate reported at different centres

Centre	Number of patients	Stage	PSA DFS	Grade 3/4 toxicity
Mount Vernon Hospital	50		91.5%	Bowel 4% Urinary 0%
Seattle [18]	104	T1: 31% T2: 59% T3: 11%	84%	Bowel 1% Urinary 8%
Kiel [17]	171	T2: 110 T3: 59	T2: 89% T3: 85%	Bowel 3% Bladder 7%
Michigan [19]	207	T1c: 36 T2: 152 T3: 19	74%	Bowel 1% Urinary 8%
Oakland CA [35]	110		85%	Rectal 1% Urinary 4%
Berlin [36]	82	T2: 21 T3: 61	All: 53%	Bowel 3.6%

no excess toxicity and tumour control data is awaited.

There is no randomised data comparing the HDR and external beam technique with LDR iodine-125 implantation discussed earlier and external beam radiotherapy. At Mount Vernon Hospital a randomised trial is currently underway comparing our standard external beam schedule of 55 Gy in 20 daily fractions with the HDR schedule described previously.

FUTURE DEVELOPMENTS FOR SEED AND HDR IMPLANTS

The following developments are speculative but it seems likely that the future of prostate BT might include:

Intraoperative treatment planning: The method for seed implants as described requires two sessions of transrectal ultrasound, usually a few weeks apart, with the consequent two anaesthetics. This is to permit time for the treatment planning and the ordering of the correct number of seeds. Seed wastage has to be kept to a minimum both for reasons of cost and also to minimise the number of unused sources that have to be disposed of. However from a patient perspective the two-step procedure is inconvenient, carries an increased anaesthetic risk, and relies on the skill of the oncologist/urologist to reproduce accurately the position of the patient and the prostate on the second attendance. As previously mentioned, in Leeds we now do most patients as a one-step procedure with the planning and implant being performed in one theatre session. This method still has discrete planning and implantation phases but the patient is not moved between the two. The next step is to consider interactive planning and dynamic dose calculation in which the plan is refined in real time based on imaging and feedback of the needles and seeds positions as they are implanted, with real time updating of the dose distribution as the implant progresses. The ABS[48] investigated the possibilities of this in 2001 and concluded that intraoperative planning would be advantageous over the traditional approach but the main current difficulty is in the identification of the seed positions by ultrasound during the procedure.

Seed visualisation: This can be difficult during the procedure due to shadowing of seeds by others closer to the probe and the diffuse nature of the seed images in the prostate. Intraoperative planning will become a realistic option if this can be improved. In Leeds we are investigating the seed parameters that influence the images and some seed manufacturers are changing the seed design in an attempt to improve the visualisation, for example Echoseed™ (Oncura).

Imaging for post-implant dosimetry: Post-implant dosimetry for seed implants is normally based on a CT scan of the prostate about a month after implantation. Despite being the generally accepted "gold standard" there are difficulties associated with this, in particular the prostate surface is not well defined by CT, although the seeds are well visualised. Errors in defining the prostate will inevitably lead to errors in the calculated dosimetry parameters.[49,50] MR imaging offers a way to improve this as the prostate is well defined, but the seeds are not. In the future image fusion of CT and MR might improve the consistency of post-implant dosimetry for seed implants. Also, possible improvements in ultrasound imaging of the seeds would permit post implant dosimetry to be performed directly from the "operative" ultrasound images, perhaps removing the need for further imaging. The advances in biological imaging,

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image fusion and computer technology with particular relevance to treatment planning and treatment delivery have been discussed for general BT[51,52] and these will also apply to prostate BT.

Most centres base their HDR dosimetry on post-implant CT imaging, but some centres plan using ultrasound imaging only. As already mentioned, errors in defining the prostate on CT are well known[49,50] and these errors propagate through to dosimetry errors. As for seeds, MR imaging offers the HDR method improved volume definition of the prostate and if used in conjunction with CT imaging using image fusion then improved accuracy in treatment planning will result. Most commercial treatment planning systems can incorporate image fusion in their systems, along with full 3D image reconstruction. In the UK the major limitation is routine access to MR imaging and how this would fit into the HDR planning pathway. The development of MR compatible applicators from the manufacturers is a further advance in the use of MR imaging.

Functional imaging: Considerable research in the area of functional biological imaging, using magnetic resonance spectroscopy (MRS) or positron emission tomography (PET) is being undertaken and could allow the clinician to identify where the tumour cells exist by monitoring blood flow and oxygen consumption. This will allow the clinician to define two target volumes, a biological tumour target volume and a physical target volume defined on conventional sectional imaging. Treatment planning, for either seeds or HDR, can then be designed to deliver an intensity-modulated map with a higher dose level conformed to the biological target volume and a lower dose level to the physical target volume.

Intensity-modulated brachytherapy: HDR BT offers the possibility of exploring intensity-modulated therapy without the same level of extensive and labour intensive quality assurance of external beam IMRT. Organ motion problems associated with external beam IMRT are also minimised with HDR BT as the applicators are fixed within the target volume.

Dosimetry: Intraoperative planning is also being developed for HDR implants but localisation of multiple catheters on ultrasound images remains problematic and fully real time optimisation for volume implants is still being refined along with automated tools for segmenting soft tissue structures.

Bio-effect dose modelling is of considerable interest and has generally been used for research purposes. Further work is required before it can be incorporated into clinical planning, but could have an impact in prostate BT.

Three dimensional dose algorithms that include corrections for tissue inhomogeneities and shielding materials on dose distributions are just emerging. The current standard for 3D dose calculations is Monte Carlo calculations. However current clinical treatment planning systems do not have the computer power/speed to support Monte Carlo.

CONCLUSION

Permanent seed implants and HDR afterloading implants provide viable options for the treatment of prostate cancer. The required radiation dose to the prostate gland can be achieved with sparing of adjacent normal tissues. The use of HDR afterloading enables the delivery of customised conformal high dose distribution to the prostate gland and the seminal vesicles if necessary. Doses to the normal tissues, rectal and urinary, can be limited to remain within tolerance.

Combined with external beam radiotherapy a high conformal dose can be delivered to the gross tumour volume and potential paths of microscopic spread are treated using external beam component. This treatment schedule offers both conformal and intensity-modulated treatment and although results are immature they suggest it is a highly effective treatment option in the management of localised prostate cancer.

References

1. Office of National Statistics (www.statistics.gov.uk).
2. Institute of Health Science (www.ihs.ox.ac.uk).
3. Institute of Cancer Research (www.icr.ac.uk).

4. Evans S, Møller H. Recent trends in prostate cancer incidence and mortality in southeast England. Eur Urol 2003; 43: 337–341.
5. Nag S, Beyer D, Friedland J, Grimm P, Nath R. American Brachytherapy Society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer. Int J Radiol Oncol Biol Phys 1999; 44(4): 789–799.
6. Ash D, Flynn A, Battermann J, de Reijke T, Lavagnini P, Blank L, ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer. Radiother Oncol 2000; 57: 315–321.
7. Ragde H, Grado GL, Nadir BS. Brachytherapy for clinically localized prostate cancer: thirteen-year disease-free survival of 769 consecutive prostate cancer patients treated with permanent implants alone. Arch Esp Urol 2001; 54(7): 739–747.
8. Blasko JC, Mate T, Sylvester JE, Grimm PD, Cavanagh W. Brachytherapy for carcinoma of the prostate: techniques, patient selection, and clinical outcomes. Semin Radiat Oncol 2002; 12(1): 81–94.
9. Stone NN, Stock RG. Complications following permanent prostate brachytherapy. Eur Urol 2002; 41(4): 427–433.
10. Norderhaug I, Dahl O, Hoisaeter PA, *et al*. Brachytherapy for prostate cancer: a systematic review of clinical and cost effectiveness. Eur Urol 2003; 44(1): 40–46.
11. Holm HH. The history of interstitial brachytherapy of prostatic cancer. Semin Surg Oncol 1997; 13: 431–437.
12. Barringer BS. Radium in the treatment of cancer of the bladder and prostate. JAMA 1917; 68: 1227–1230.
13. Whitmore WF Jr, Hilaris B, Grabstald H. Retropubic implantation to iodine 125 in the treatment of prostatic cancer. J Urol 1972; 108(6): 918–920.
14. Battermann JJ, Boon TA, de Voogt HJ. Preliminary results with iodine-125 seeds for permanent implantation in patients with localized prostatic cancer. Radiother Oncol 1987; 10(2): 91–95.
15. Zelefsky MJ, Whitmore WF Jr. Long-term results of retropubic permanent 125-iodine implantation of the prostate for clinically localized prostatic cancer. J Urol 1997; 158(1): 23–29.
16. Battermann JJ. I-125 implantation for localized prostate cancer: the Utrecht University experience. Radiother Oncol 2000; 57(3): 269–272.
17. Kovacs G, Wirth B, Bertermann, H, *et al*. Prostate preservation by combined external beam and HDR brachytherapy at nodal negative prostate cancer patients – an intermediate analysis after ten years experience. Int J Radiat Oncol Biol Phys 1996; 36(suppl): S80,198.
18. Mate T, Gottesman J, Hatton J, *et al*. High dose rate afterloading iridium-192 prostate brachytherapy. Feasibility Report. Int J Rad Oncol Biol Phys 1998; 41(3): 525–533.
19. Stromberg J, Martinez A, Gonzalez J, et al. Ultrasound-guided high dose rate conformal brachytherapy boost in prostate cancer: treatment description and preliminary results of a Phase 1/11 Clinical Trial. Int J Radiat Oncol Biol Phys 1995; 33: 161–171.
20. Partin AW, Subong ENP, Walsh PC, *et al*. Clinical stage and Gleason score to predict pathological stage of localised prostate cancer. J Am Med Assoc 1997; 17: 1191–1197.
21. Ash D, Bottomley D, Carey BM. Prostate brachytherapy (Review). Prostate Cancer and Prostatic Diseases. Stockton Press, 1998: 185–188.
22. Nath R, Anderson LL, Luxton G, Weaver KA, Williamson JF, Meigooni AS. Dosimetry of interstitial brachytherapy sources. Report of AAPM Radiation Therapy Committee Task Group 43. Med Phys 1995; 22(2): 209–233.
23. Corbett JF, Jezioranski JJ, Crook J, Tran T, Yeung IW. The effect of seed orientation deviations on the quality of 125I prostate implants. Phys Med Biol 2001; 46(11): 2785–2800.
24. Nag S. Brachytherapy for prostate cancer: summary of American Brachytherapy Society recommendations. Semin Urol Oncol 2000; 18(2): 133–136.
25. Stock RG, Stone NN, Tabert A, Ianuzzi C, DeWyngaert JK. A dose–response study for I-125 prostate implants. Int J Radiat Oncol Biol Phys 1998; 41(1): 101–108.
26. Potters L, Cao Y, Calugaru E, Torre T, Fearn P, Wang X. A comprehensive review of CT-based dosimetry parameters and biochemical control in patients treated with permanent prostate brachytherapy. Int J Radiat Oncol Biol Phys 2001; 50(3): 605–614.
27. Nag S, Bice W, Dewyngaert K, Prestidge B, Stock R, Yu Y. The American Brachytherapy Society recommendations for permanent prostate brachytherapy post implant dosimetric analysis. Int J Radiat Oncol Biol Phys 2000; 46(1): 221–230.
28. Smathers S, Wallner K, Korssjoen T, *et al*. Radiation safety parameters following prostate brachytherapy. Int J Radiat Oncol Biol Phys 1999; 45(2): 397–399.
29. Michalski J, Mutic S, Eichling J, Ahmed SN. Radiation exposure to family and household members after prostate brachytherapy. Int J Radiat Oncol Biol Phys 2003; 56(3): 764–768.
30. Martinez A, Pataki I, Edmundson G, *et al*. Phase II prospective study of the use of conformal high-dose rate brachytherapy as monotherapy for the treatment of favourable stage prostate cancer. Int J Radiat Oncol Biol Phys 2001; 50: 61–69.
31. Yoshioka Y, Nose T, Yoshida K, *et al*. High-dose-rate brachytherapy as monotherapy for localised prostate cancer: a retrospective analysis with special focus on tolerance and chronic toxicity. Int J Radiat Oncol Biol Phys 2001; 50(3): 605–614.
32. Hoskin PJ. High dose rate brachytherapy boost treatment in radical radiotherapy for prostate cancer. Radiother Oncol 2000; 57: 285–288.
33. Hoskin PJ. High dose rate afterloading for brachytherapy for prostate cancer. In: Principles and Practice of Brachytherapy (eds: CAF Joslin, A Flynn and EJ Hall) London: Arnold, 2001.

34. Martin T, Kolotas C, Dannenberg T, *et al*. New interstitial HDR brachytherapy technique for prostate cancer: CT based 3D planning after transrectal implantation. Radiother and Oncol 1999; 52: 257–260.

35. Rodrigues R, Demanes DJ. HDR brachytherapy: ultimate in conformal radiotherapy for the treatment of prostate cancer. In: New developments in Interstitial Remote Controlled Brachytherapy (ed: Zambogolou). Munich: W Zuckschwerd und Verlag, 1997; 119–125.

36. Dinges S, Deger S, Koswig S, *et al*. High dose rate interstitial with external beam irradiation for localised prostate cancer – results of a prospective trial. Radiother Oncol 1998; 48: 197–202.

37. Borghede G, Hedelin H, Holmang S, *et al*. Irradiation of localised prostatic carcinoma with a combination of high dose rate iridium-192 brachytherapy and external beam radiotherapy with three target definitions and dose levels inside the prostate gland. Radiother Oncol 1997; 44: 245–250.

38. Martinez A, Gustafson G, Gonzalez J, *et al*. Dose escalation using conformal high-dose-rate brachytherapy improves outcome in unfavourable prostate cancer. Int J Radiat Oncol Biol Phys 2002; 53: 316–327.

39. Brenner DJ, Hall EJ. Fractionation for radiotherapy of prostate cancer. Int J Radiat Oncol Biol Phys 1999; 43: 1095–1101.

40. Fowler J, Chappell R, Ritter M. Is alpha/beta for prostate tumours really low? Int J Radiat Oncol Biol Phys 2001; 50: 1021–1031.

41. Diez P, Bownes PJ, Hoskin PJ, Ostler PJ, Aird EGA. Optimising of prostate cancer radiotherapy using high dose brachytherapy: a radiobiological analysis. Clin Oncol 2003; 15 (suppl 2): S11.

42. MRC Radiotherapy working Group. RTO1 A randomised trial of high dose therapy in localised cancer of the prostate using conformal radiotherapy techniques. May 2000, version 2.

43. Hoskin PJ, Bownes PJ, Ostler PJ, Bryant L. The effect of catheter movement on implant quality for fractionated high dose rate afterloading brachytherapy of prostate cancer. Radiother Oncol 2003; 68: 285–288.

44. Martinez A, Gonzalez J, Stromberg J, *et al*. Conformal prostate brachytherapy: initial experience of a phase I/II dose escalating trial. Int J Radiat Oncol Biol Phys 1995; 33: 1019–1027.

45. Damore SJ, Syed N, Puthawala, *et al*. Needle displacement during HDR brachytherapy in the treatment of prostate cancer. Int J Radiat Oncol Biol Phys 2000; 41: 1205–1211.

46. Mullokandov E, Gejerman G. Analysis of serial CT scans to assess template and catheter movement in prostate HDR brachytherapy. Int J Radiat Oncol Biol Phys 2004; 58: 1063–1071.

47. ASTRO Consensus Statement: Guidelines for PSA following radiation treatment. Int J Rad Oncol Biol Phys 1997; 37: 1035–1041.

48. Nag S, Ciezki JP, Cormack R, *et al*. Intraoperative planning and evaluation of permanent prostate brachytherapy: Report of the American Brachytherapy Society. Int J Radiat Oncol Biol Phys 2001; 51(5): 1422–1430.

49. Al-Qaisieh B, Ash D, Bottomley DM, Carey BM. Impact of prostate volume evaluation by different observers on CT-based post-implant dosimetry. Radiother Oncol 2002; 62(3): 267–273.

50. Al-Qaisieh B. Pre- and post-implant dosimetry: an intercomparison between UK prostate brachytherapy centres. Radiother Oncol 2003; 66(2): 181–183.

51. Cumberlin RL, Coleman CN. New directions in brachytherapy. Int J Radiat Oncol Biol Phys 2002; 53: 6–11.

52. Van Der Laarse, Luthmann RW. Computers in Brachytherapy Dosimetry. In: Principles and Practice of Brachytherapy (ed: CAF Joslin, A Flynn and EJ Hall). London: Arnold, 2001.