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Original Article

A critical evaluation of the clinical value of high-dose rate brachytherapy in the treatment of prostate cancer

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Abstract

Prostate cancer has been treated with low-dose rate (LDR) brachytherapy for early localised disease in the form of permanent seed implants, with all its inherent problems in terms of dosimetry and seed migration. High-dose rate (HDR) brachytherapy has mainly been utilised as a boost to external beam radiotherapy (EBRT) in patients with locally advanced disease. However, limited studies investigating HDR as a monotherapy for early local disease are yielding promising results in terms of biochemical control and reduced toxicity. With the ability to optimise the plan and conform the dose, dose escalation can be achieved whilst sparing normal tissue. Recent studies to assess the α/β ratio of prostate cancer have shown this to be low, making this tumour sensitive to large fractions or hypofractionation. The HDR delivery and large fraction sizes may be advantageous in tumours sensitive to radiation fraction size making HDR brachytherapy the treatment of choice over LDR brachytherapy and EBRT.

Keywords

HDR; LDR; brachytherapy; α/β ratio; prostate cancer

INTRODUCTION

Prostate cancer is a disease which commonly occurs in ageing men, the peak incidence being in 70–80 years old. In old age, the benign enlargement of the prostate gland can present with the same signs and symptoms as early malignancy; these include increased frequency and difficulty in micturition. Since the wide availability of the prostate-specific antigen (PSA) test, the early detection of prostate cancer has risen in younger men (50–60 years old), where radical treatment is appropriate.

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The available treatment options for men diagnosed with early prostate cancers are as follows: active monitoring; surgery; hormone therapy and radiotherapy including brachytherapy. For younger men active monitoring or watch and wait may not be an appropriate strategy, and these patients are more likely to opt for active treatment options.[1] Radical prostatectomy is only a viable option for patients where the cancer is confined to the prostate and the patient would normally expect to live for 10 years in the absence of prostate cancer. Surgery, however carries the risk of impotence and incontinence. Hormone therapy is often used in combination with other treatments especially radiotherapy to reduce the size of the prostate gland, thus helping to reduce the toxicity experienced by patients undergoing external beam radiotherapy (EBRT). Downsizing using hormone therapy can also be of benefit in

brachytherapy making the volume of the prostate suitable for implantation and reducing pubic arch interference.

EBRT is the most common treatment option using either conformal radiotherapy (CRT) or intensity modulated radiation therapy (IMRT) techniques. These highly complex techniques aim to reduce the radiation dose to normal tissue as much as possible and attempt to minimise the dose to the base of the bladder and rectum in particular. However, it is impossible to avoid irradiating these structures and although the dose is minimised, the resulting complications are the limiting factor in EBRT, where tumour control has to be balanced against the patient's quality of life. Brachytherapy, however can irradiate a much smaller volume to a high dose. The rapid fall-off of dose reduces the toxicity to normal tissue and is well-tolerated. For this reason, brachytherapy as a treatment option in early prostate cancer is accepted.

Brachytherapy can be delivered by two methods: low-dose rate (LDR) using permanently implanted iodine-125 (I^{125}) or palladium-103 (Pd^{103}) seeds; or temporary implants using high-dose rate (HDR) stepping source afterloaders using a single iridium-192 (Ir^{192}) source. LDR permanent seed implants have commonly been used as a monotherapy, and sometimes as a boost to EBRT. HDR has mainly been used as a boost; however some centres are using it as a monotherapy, but results of these studies are limited at present.

The scope of this article is to compare LDR and HDR brachytherapy and the advantages and disadvantages associated with these modalities. To determine the clinical effectiveness of HDR brachytherapy and its role in the treatment of prostate cancer, a critical evaluation of the available literature concerning the radiobiology of prostate cancer, prognostic factors and treatment outcomes and toxicity resulting from brachytherapy will be attempted.

LOW-DOSE RATE

LDR brachytherapy in early prostate cancer involves the permanent implantation of radioactive seeds. The radio-isotopes commonly used are iodine-125 (I^{125}) and palladium-103 (Pd^{130}). I^{125} has a half-life of 60 days and Pd^{130} has a half-life of 17 days, they both emit a low-energy radiation (23–27 keV) so radiation protection is easily achievable, and the patient's level of radioactivity is not an issue. Delivery of the treatment dose takes a few months depending on the isotope used. Due to the LDR the prescription doses are much higher than for HDR. Typically for I^{125} the prescription dose to the periphery of the target volume is 145 and 125 Gy for Pd^{103} due to its higher dose rate for monotherapy. If the implant is used to boost EBRT prescribed to 50 Gy the prescription doses are 95–100 Gy for I^{125} and 90 Gy for Pd^{103}.

As LDR brachytherapy is useful for the treatment of early prostate cancer confined to the gland, careful patient selection is essential. According to the ESTRO/EAU/EORTC recommendations[2] for permanent seed implantation patients should meet the following criteria: PSA < 10 ng/ml, Gleason score < 6, stages T1c–T2a. These patients fall into the low-risk category and are likely to respond well to LDR brachytherapy. Patients with higher PSA levels and Gleason scores have a higher risk of disease outside the prostate capsule therefore EBRT followed by a seed implant is indicated. Contraindications to brachytherapy are a recent transurethral resection of the prostate, which is associated with a higher risk of incontinence. Also the size of the cavity left after this procedure may make the satisfactory placement of the seeds difficult. Another contraindication is the volume of the prostate; ideally the gland should have a volume less than 50 cm^3. If the patient is otherwise suitable for implantation a course of hormone therapy may be indicated to reduce the size of the gland.

Implant procedure

Implantation is a two stage process; initially a volumetric study is carried out with the patient anaesthetised in the lithotomy position using a transrectal ultrasound probe in a stepper taking images at 5 mm intervals. The perineal template is positioned prior to the start of the study and superimposed over the images. From this study, the implant is pre-planned and the required seeds are ordered and prepared. The needles are inserted transperineally under ultrasound guidance according to the predetermined plan, the needles are

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withdrawn and the seeds are deposited.[3] On-line live planning and improved imaging may allow the procedure to be undertaken in a single stage; however the required number of seeds would be unknown. Post-implant dosimetry is checked after approximately 1 month using a CT scan. Bownes and Flynn[4] state that the calculation cannot influence the brachytherapy treatment for individual patients, but it is an important tool in the quality control procedure.

Problems associated with seeds

Seeds used for implantation are either loose seeds or seeds embedded in a suture such as Rapidstrand™ (Oncura, Amersham, Buckingham, England). Seeds can migrate into the bladder and surrounding tissues, causing cold spots in the dosimetry and unintended radiation doses to structure the seeds that migrate. Seeds may be passed in the urine and ejaculate, and patients are advised to use a condom for the first 2 months following the implant. Migration may also occur through the vascular system to the lungs. This is due to the rich venous plexus surrounding the prostate. Seeds implanted in or near to this plexus may migrate. Tapen et al.[5] conducted a study into this problem comparing the pulmonary migration for patients implanted with either loose or stranded seeds, by obtaining a chest X-ray the day after the procedure. They found that loose seeds are more likely to migrate than stranded seeds. They suggest that stranded seeds are used at the periphery of the implant to reduce the problem. They did not however follow-up these patients for the long-term and therefore late migration of the seeds was not taken into account. This is especially relevant when the suture material used in the stranded seeds dissolves and migration of the seeds is no longer prevented. Stone and Stock[6] investigated a method to reduce pulmonary migration by identifying the periprostatic venous anatomy and implanting the seeds individually inside the prostate capsule avoiding these structures. Some seed migration was detected, but they conclude that proper technique in the operating theatre can reduce the likelihood of seed migration. Most implants allow a margin round the prostate to ensure adequate dosage. This involves the placing of seeds outside the prostate capsule. By implanting only within the prostate capsule a question arises as to whether the gland is adequately treated. The migration of seeds to the lungs has had no adverse effects on pulmonary function; however there is a potential carcinogenic risk.

Radiation protection

Following implantation the patient is radioactive. Although these levels of radiation are low, the patient is advised to keep away from pregnant women and children for the first 2 months until the sources have decayed to a lower level of activity.

HIGH-DOSE RATE

HDR brachytherapy uses a single iridium-192 (Ir^{192}) afterloaded stepping source. Ir^{192} has a half-life of 74 days and energy of 380 keV. Due to this, the HDR treatment has to be fractionated. There are also radiation protection issues necessitating the need for treatment to be undertaken in a specially-shielded room designed for the purpose. However unlike seed implants, the patient is not radioactive after the procedure as the source is withdrawn into the afterloader unit. Typical doses and fractionation for HDR used as a boost to EBRT (45–54 Gy given in 6–7 weeks) is 12–20 Gy in 2–4 fractions.[7] Used as a monotherapy, the number of implants and size of the fraction varies. From the literature the range of implants is 1–2, and the fraction size has a range of 6–9.5 Gy given in 4–9 fractions giving a total dose of 38–54 Gy in 2–7 days.[8]

Patient selection for HDR monotherapy is the same as for LDR, i.e. PSA $<$ 10 ng/ml, Gleason score $<$ 6, stages T1c–T2a. However, GEC/ESTRO-EAU[7] recommends patients with localised or locally advanced disease for HDR boost in combination with EBRT. This group of intermediate high-risk patients ($>$T2a, PSA $>$ 10 ng/ml, Gleason score $>$ 6) respond well to EBRT with HDR boost.

Implant procedure

The implantation technique for HDR is similar to LDR, except there is no pre-planning stage. A template is sutured to the patient's skin and the needles or flexible plastic catheters are inserted transperineally under ultrasound guidance using a stepper. The template holds the catheters in place

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between fractions. Due to the dose rate fewer needles or catheters are required to cover the prostate volume. The patient is imaged and planned and the catheters attached to the afterloader. The source is driven to the different dwell positions until the dose has been delivered according to the plan, this can take approximately 10 min. After treatment, the catheters are capped and the patient is sent to the ward between fractions.

Catheter movement between fractions

The biological effects of radiation are dependent on the rate of dose delivery. Radiobiologically HDR brachytherapy is similar to fractionated external beam radiation therapy, therefore to reduce the effects on normal tissues HDR has to be fractionated. The most important factor is the reproducibility of the implant geometry and dosimetry for each fraction.[4] Some centres use multiple implants for each fraction, but this necessitates the patient going through the procedure again. This method, however may be more accurate if the geometry of the implant is matched with the previous one, as there is no risk of the catheters moving. If a single implant is used for multiple fractions then assessment of the implant must be made prior to each fraction to check the geometry and ensure the catheters have not moved. Hoskins et al.[9] studied this phenomenon and found that catheters moved in a predominantly caudal direction relative to the prostate and bony anatomy leading to under dosage at the base of the prostate if not corrected. The reason for this is periprostatic oedema which develops predominantly in the perineal region between the apex of the prostate and the skin displacing the template and catheters. Despite, over-insertion of the catheters movement can still be a problem and they recommend repeat imaging prior to each fraction to check the degree of movement and adjust accordingly. The ability of the template to prevent slippage of the catheters is not an issue as shown by Martinez et al.[10] Damore et al.[11] noticed that the needles all moved in the same direction, which is consistent with template movement rather than catheter slippage. Mullokandov and Gejerman[12] demonstrated through serial CT scans that the template and catheters moved as a unit and that the degree of movement was time dependent.

HDR techniques and results

HDR is commonly used as a boost to EBRT in the intermediate to high-risk patients. The treatment is well-tolerated and the level of toxicity is acceptable. The use of real-time on-line planning removes the need for the clinician to decide on the best needle placement as this is achieved interactively. As the needles are implanted into the target volume the margins can be tightened reducing toxicity to normal tissue compared to EBRT. Optimisation of the plan makes HDR brachytherapy a truly conformal therapy leading to dose escalation in this group of patients.[13] Results for tumour control, although relatively immature are promising with biochemically no evidence of disease (bNED) rates of 74% at 5 years reported by Martinez et al.,[14] 72% at 5 years and 64% at 8 years reported by Galalae et al.[15] with acceptable levels of gastrointestinal (GI) and genitourinary (GU) toxicity of = grade 3 according to the RTOG/EORTC[16] scoring scheme. Astrom et al.[17] report a 5-year bNED of 82% for all stages of disease and conclude that dose escalation with HDR brachytherapy is safe and effective.

If EBRT is given then the HDR brachytherapy dose has to be reduced to prevent adverse effects, which reduces the ability of brachytherapy to deliver an increased dose to the tumour.[18] HDR as a monotherapy is still in its infancy and data is diverse in terms of dose and fractionation. As this modality is not yet widely used there is insufficient data to recommend it. With the phasing out of LDR afterloaders, oncologists are looking to other solutions as a replacement, and pulsed dose rate (PDR) and HDR afterloaders fill the gap. The radiobiological effect of PDR is not well-known, whereas HDR is, making this the preferred choice in many institutions. Widespread use of HDR may encourage further investigation into its use as a monotherapy in prostate cancer. The early results of HDR monotherapy are promising with low rates of GI and GU toxicity reported (often lower than for LDR); however urethral stricture was more common in HDR. This can be reduced with improved imaging and planning systems where the urethral dose can be further minimised.[17] Biochemical control rates are similar in HDR and LDR treatment groups.[10,18,19] Kestin et al.[20] conclude that patients with locally advanced prostate cancer treated with EBRT and HDR demonstrate improved biochemical

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control compared with those treated with conventional doses of EBRT alone.

Plan optimisation

Optimisation of the plan allows the isodoses to be contoured around structures such as the rectum, urethra and base of bladder to reduce the dose, leading to a lower toxicity rate compared with LDR and EBRT. An important point to remember is that the plan shows the 'actual' dose the prostate will receive, and not the 'estimated' dose as in LDR due to seed migration altering the dosimetry. The radiation from permanent seeds cannot reach more than 2–3 mm outside of the prostate capsule. To overcome this seeds have been implanted outside the prostate in the surrounding tissue, but this carries a high-risk of seed migration. With HDR the dose can be conformed to cover the prostate capsule and any possible extension whilst still avoiding normal tissues making HDR more versatile and effective.[21]

α/β Ratio in prostate cancer

Cell survival for different tissues is expressed radiobiologically by α/β ratios. 'Early reacting normal tissues and tumour have a lower sensitivity to the dose per fraction and a higher α/β ratio than late responding normal tissues. Biological effects increase faster with increasing dose per fraction in late responding tissues than in early reacting tissues and tumour, and small doses per fraction are associated with a lower risk of complications and a better therapeutic ratio.'[22] Recent studies[23–25] into the radiobiological response of prostate cancer shows that the α/β ratio is lower than previously thought around 1.2–3.1 Gy compared with the average of 10 α/β ratio assumed for most tumours. A low α/β ratio implies that prostate cancers possess higher fractionation sensitivity similar to those of late responding normal tissues.[23] If this is the case then hypofractionation or HDR regimens for prostate cancer with the appropriate doses should produce tumour control and late sequelae which are as good as or better than currently, with the possibility that early sequelae may be reduced.[24] Therefore, the RBE effect in permanent implantation may not be clinically significant for prostate cancer.[25] With this in mind HDR brachytherapy may be the better treatment option delivering large fractions to the tumour and hence dose escalation, whilst minimising the toxicity to the patient.[26]

CONCLUSION

Although still in its infancy in comparison to LDR brachytherapy, HDR has a lot of potential in the treatment of prostate cancer. Normally, HDR is used as a boost to EBRT for patients in the intermediate to high-risk group leading to dose escalation. It is well-tolerated and carries reduced toxicity compared to EBRT and LDR. Limited studies using HDR as a monotherapy in early localised disease are yielding promising results in terms of biochemical control and toxicity leading to an improvement in the quality of life for these patients. Real-time on-line planning facilitates the placement of the needles to attain the best dose distribution. Plan optimisation reduces the dose to vital structures whilst delivering a high-dose to the tumour. HDR is a truly conformal therapy and dose escalation can be easily and safely achieved without the limitations of increased toxicity as experienced in CRT and IMRT. Extra-capsular spread can be safely treated with HDR through optimisation of the plan to irradiate a margin around the prostate without unduly increasing the toxicity experienced by the patient.

Fractionation of HDR brachytherapy presents problems in terms of reproducing the geometry of the implant for each fraction. Some centres use a new implant for each fraction, which is the most accurate method. Other centres use a single implant for multiple fractions. However, catheter movement needs to be assessed prior to each fraction and appropriate adjustments made either to the position of the catheters or to the plan to compensate. Even so, unlike LDR the dose can be delivered to the prescribed plan.

Recently, research to assess the α/β ratio of prostate cancer has implications for HDR brachytherapy. The low α/β ratio of prostate cancers would suggest that these tumours are sensitive to hypofractionation and HDR regimes. The RBE effect of LDR may not be clinically significant. HDR has the ability to deliver high-dose fractions conformally and its radiobiological effectiveness would make it the treatment of choice over LDR.

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