

An Overview of Prostate Brachytherapy

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Abstract: Prostate cancer is the most common male cancer in the European Union and United States of America. The incidence of prostate cancer had been rising before PSA screening and will continue to rise with PSA testing having become more widespread and an ageing population. Prostate brachytherapy is an effective treatment for early stage prostate cancer with some centres reporting 10 year biochemical control rates of up to 87% for low risk patients. However the outcome depends on the technical quality of the implant and careful patient selection i.e. a low prostate specific antigen (PSA) 10 or less, Gleason score of 6 or less and low International Prostate Symptom Score (IPSS)

Introduction

Prostate cancer is the most common male cancer in the European Union and United States of America. One in six new cases of male cancer are prostate, with a lifetime risk of one in fourteen in the U.K. The incidence of prostate cancer had been rising before PSA screening¹ and will continue to rise with PSA testing becoming more widespread and an ageing population.

The debate regarding prostate screening remains unresolved. At present the U.S. Preventive Services Task Force (USPSTF) does not recommend prostate screening for all men and it is not current U.K. practice. Currently there is no randomised clinical trial evidence that shows a difference between the number of prostate cancer related deaths in a screened and non-screened population. Hopefully the results from the Prostate, Lung, Colorectal and Ovary (PLCO) trial in the U.S.A., the Prostate testing for cancer and Treatment (ProtectT) trial in the U.K. and the European Randomized Screening for Prostate Cancer (ERSPC) trial in Europe will clarify the debate. However due to increased public awareness, despite the lack of evidence regarding any survival benefit from prostate cancer screening, the demand for PSA tests is increasing.

More early stage prostate cancers are being detected, often in asymptomatic patients, who are then presented with the dilemma regarding treatment options. Though active surveillance is an appropriate management for selected patients, patients with a projected life expectancy of greater than 10 years are usually offered radical treatment. The aim of a curative treatment for prostate cancer is to obtain local control with optimal preservation of bowel, bladder and sexual function².

In 1995, about 4 percent of men with localized disease received prostate brachytherapy and it is estimated in the U.S.A. that 40 to 50 percent of men will undergo this procedure by 2006 if current trends continue³.

History

Prostate brachytherapy was first described by Pasteau and Degrais in France in 1914 using radium needles⁴. In 1972 Hilaris and Whitmore at the Memorial Hospital, New York described their technique of iodine seed implantation using an open retro pubic approach⁵. Seeds were implanted manually according to a

nomogram and after dose finding studies a minimum peripheral dose of 160Gy# was decided upon. This technique was used in over 1000 patients and achieved good local control on digital rectal examination. However, once PSA testing became available it became clear that biochemical control was not often achieved, especially in those patients whose seed distribution was sub-optimal, and the technique was abandoned.

The technique of transrectal ultrasound (T.R.U.S.) and template guidance for prostate biopsies was developed in 1981 by Holm H. and in 1982 the same technique was used for percutaneous implantation of radioactive iodine seeds into the prostate under ultrasound control. From 1982-1987, 32 patients were treated using this technique⁶ but at ten years, 50% had died of metastatic disease and 14 patients had severe late complications and the technique was abandoned.

The T.R.U.S. and template technique was taken up in Seattle by Ragde and Blasko but modified so that a large number of low activity seeds were used. This modification obtained good results and the Seattle technique has been the basis for a number of other developments in trans-rectal ultrasound and template guided permanent seed implantation.

Remote afterloading brachytherapy became available in the early 1980's and was first used in Germany to treat prostate cancer with H.D.R. removable implants. The afterloading technique has been embraced by centres in the U.S.A. and elsewhere being further developed with the introduction of interactive real time dosimetry and optimisation of source position.

Image guided source placement with interactive real time dosimetry is now becoming possible for all techniques and allows consistent high quality implants to be performed in the vast majority of cases.

Patient Selection

The key to providing good outcomes from prostate brachytherapy is careful patient selection. One needs to identify those patients who are likely to have a good disease free survival and have a good functional outcome. The most significant prognostic factors for disease free survival are initial P.S.A. Gleason score and stage. Regarding functional outcome the initial prostate volume and lower urinary tract symptoms best characterised by the IPSS provide the best guide to outcome⁷.

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Gy-Grey (a unit of radiation)

Essential pre-treatment investigations include P.S.A., transrectal ultrasound and biopsy. the pre-treatment P.S.A. is an important screening test, which not only correlates with outcome but also predicts for the presence of extra-capsular spread of the tumour⁸. Those patients with pre-treatment P.S.A. of less than 10 have very good outcome with some centres quoting up to an 87% 10-year biochemical and clinical control⁹. In contrast those patients with a P.S.A. of greater than 20 have a high rate of relapse within the first 2 years though still 30-50% may remain biochemically controlled. Similarly the lower the Gleason score the better the outcome. Patients with a Gleason score of 6 or less have very good outcomes from brachytherapy¹⁰. Those patients with a Gleason score of 7 have about a 50% probability of relapse in the first 5 years and those with predominantly grade 4 have a worse prognosis than those with predominantly grade 3 (Gleason combined score 7). Patients with a Gleason score of above 7 should not be considered for brachytherapy.

A clinical history and patient IPSS score provides key information regarding flow and irritable urinary symptoms. Urodynamic studies should be considered in patients with significant symptoms. M.R.I. is the most sensitive radiological technique to predict whether the patient has T3 disease but in good prognosis patients (P.S.A. <10, Gleason 6) it's role is less clear. Surgical lymph node staging is not routinely used and therefore the lymph node status is assessed radiologically. Lymph nodes are judged significant if greater than 1cm and in an appropriate anatomical site.

Other radiological investigations are not routinely used. C.T. scan is of little value in assessing the local extent of the disease and bone scintigraphy is not recommended unless the pre-treatment P.S.A. is >10.

The stage of the tumour also predicts for clinical outcome. Patients with stage T1c to T2b disease i.e. with a low risk of extra-capsular spread have good outcomes from brachytherapy. Further information can be gained from the amount of tumour present in each biopsy, the total amount of biopsies that contain tumour cells and the presence of perineural invasion. For T3a disease brachytherapy alone should not be considered though combinations of external beam and brachytherapy are used.

The Partin tables that were derived from radical prostatectomy samples can be used to predict the chance of extra-capsular spread, seminal vesicle and lymph node involvement. The Partin tables, although a good predictive guide for the presence of extra-capsular disease, can not predict for those patients who have extra-capsular disease within 2-3 mms of the capsule, which would be encompassed in the PTV.*

Urinary outflow as measured by the IPSS score is a sensitive predictor of urinary morbidity. Prostate volume also influences the incidence of acute retention and urinary morbidity. Patients with a prostate volume of greater than 36 grams and higher IPSS/American Urologic Association (AUA) score (>10) appear to be at higher risk of acute retention¹¹.

Patients with a prostate volume of greater than 50 grams should have neo-adjuvant hormonal therapy to reduce the gland, but despite this the patient's risk of urinary morbidity remains higher.

Contra-indications to permanent seed implants⁷

1. Life expectancy less than 5 year.
2. The presence of metastatic disease.
3. Recent transurethral resection of prostate (TURP) with persisting large prostatic defect. It is often difficult to achieve a satisfactory seed distribution and these patients have a high risk of incontinence after brachytherapy. If TURP was performed several years ago and the prostate has largely regrown patients can be considered for brachytherapy but steps should be taken to optimize the dose distribution in order to reduce urethral dose and patients should still be counselled that the risk of incontinence is higher than for non-TURP patients.
4. There should be no bleeding disorder and patients on regular aspirin or anticoagulants should stop it at least seven days before implantation.
5. Patients with a prostate gland of greater than 50cm³ have a high probability to pubic arch interference, this means that part of the prostate is situated behind the bone and does not allow a geometrically satisfactory implant to be performed. These patients also need a large number of seeds and are at increased risk of morbidity. If otherwise suitable these patients can be treated after several months of hormone therapy. This usually produces a 30% reduction in volume which will often bring the gland down to 50cm³ or less.

Technique

Prior to the implantation the prostate volume must be measured to assess the amount and distribution of seeds. This has been traditionally done in our centre with a formal prostate volume study under general anaesthesia approximately 4 weeks prior to the procedure. The patient is aligned in the lithotomy treatment position using a grid system and moving stepwise every 5mm from base to the apex. a 3-Dimensional image is obtained. A target volume is defined. The urethra is avoided and careful margins around the rectum are defined. These images are then used for calculating the amount and distribution of the seed implants (according to TG-43#)²¹. In some centres this is performed under local anaesthesia¹⁶ but other centres including Cookridge find that a general anaesthesia provides better reproduction of the patient's position.

At Cookridge, to speed up the procedure, reduce waiting time and amount of general anaesthetics, suitable patients are assessed in the first clinic visit. A trans-rectal ultrasound is performed with no sedation or preparation. This gives an accurate prostate volume and an estimate of the number of seeds required can be obtained. The patient then returns for planning and brachytherapy as a "one-stop" procedure. This has many advantages:

Early assessment of the prostate volume identifies those patients who will require neo-adjuvant hormone therapy to reduce the prostate volume prior to implantation; reduces the amount of visits and in-patient stay; requires only one general anaesthesia.

The implantation procedure can be carried out under general or spinal anaesthesia. The patient is placed in the lithotomy position with a transrectal ultrasound and grid template in position. A perineal approach is used and the seeds, either single or in strands

*PTV - Planning target volume

are inserted using the co-ordinates on the grid and under direct ultrasound and fluoroscopy control.

Commonly used isotopes are iodine 125 and palladium 103. Iodine 125 has a half life of 60 days and an energy of 27KeV. In comparison, palladium has a half life of 17 days and an energy of 25KeV. Whilst iodine 125 is the most commonly used isotope, palladium, theoretically may have an advantage in more aggressive, rapidly dividing cancers due to its higher dose rate. However, there is no clinical evidence to suggest a difference between the two sources. The most commonly prescribed dose of Iodine 131 is 145Gy to the margin of the planned target volume according to the TG-43 guidelines. The total dose of Palladium 103 is reduced to 110Gy to account for the higher dose rate and give an equivalent biological dose.

High dose rate (HDR) brachytherapy is also used in some centres using afterloading techniques with iridium-192. HDR-brachytherapy has been used both as boost to external beam radiotherapy and alone in localised prostate cancer. HDR-brachytherapy alone has been given for good prognosis localised prostate cancer in phase II trials and have proved feasible and well tolerated¹⁴ though we await long term outcome data. HDR-brachytherapy has an advantage of being feasible in patients who have had a trans urethral resection of prostate and can treat extracapsular disease.

However, HDR-brachytherapy has to be given in multiple fractions, perineal catheters must remain in place during the treatment period and substantial movement of catheters between treatments means that verification films and adjustments are needed prior to each fraction¹³.

Side Effects and Follow Up

All patients are discharged from our centre with oral ciprofloxacin to prevent/treat infective prostatitis and alpha-blockers given to maximise urinary flow. Despite this all patients will develop a varying degree of urethritis. Anti-inflammatory drugs can be added if symptoms are severe. Approximately 15% of patients need a catheter due to temporary urinary retention. Altered bowel habit is relatively common and some patients can develop radiation proctitis. Most patients do not report deterioration in bowel function and symptoms improve with time¹⁵.

Symptoms of urethritis usually persist for the first 6 weeks and in the majority of patients settle by 3 months. However, a minority have ongoing symptoms for 6-12 months and in a series of 581 patients, although dysuria was a common event and peaked at 1 month (52%), at approximately 45 months all patients were free of dysuria¹⁸. Incontinence is very rare (<1%) following brachytherapy in comparison with radical prostatectomy. Impotence does occur after brachytherapy in 30-60% of patients and may be under-reported. Co-morbid factors such as hypertension, smoking, diabetes, hormonal manipulation and age are thought to reduce post-treatment potency. Multi-variate analysis has shown that only pre-treatment potency, diabetes mellitus and supplemental external beam radiotherapy have a statistical significant effect on potency. In a study of 425 patients 39% of patients (52% with brachytherapy alone) maintain potency at 6 years. Sildenafil is an effective treatment and 92% of patients maintained potency with

pharmalogical support¹⁷.

Patients are seen at 4-6 weeks post implant and then placed on 3 monthly follow-up. At this first visit a C.T. scan is performed to establish post-implant dosimetry. This is valuable for quality control as there is good evidence that the probability of achieving good biochemical control is related to the quality of the implant¹⁸.

Outcome

With improved patient selection and implantation techniques some centres report 10 year biochemical control rates of up to 87% for low risk patients i.e. pre-treatment P.S.A. < 10, Gleason 6 or less and T1-T2b disease⁹. In higher risk patients (Gleason 8-10) with T1-2a disease, external beam radiotherapy was associated with a significantly better 5-year biochemical relapse free rates (52%) vs. 28% for brachytherapy alone. However, in lower risk patients the 5-year rates were similar¹⁹. In a systematic overview of brachytherapy compared with radical prostatectomy in low risk patients (T1-2, Gleason 6 or less, pre-treatment P.S.A.<10) the outcome was comparable²⁰.

Salvage Therapy

To establish whether salvage therapy is indicated we need a definition of recurrence. The definition of a recurrence adopted by the ASTRO* after external beam radiotherapy is also applied to brachytherapy i.e. 3 consecutive rises in P.S.A. after the nadir level has been reached.

*ASTRO - American Society of Therapeutic Radiation Oncology.

The nadir P.S.A. is reached later in both forms of radiotherapy compared with radical prostatectomy and is further complicated by the P.S.A. "bounce" which can occur in approximately a third of patients in the first 2 years post-implant. If a *recurrence* is confirmed biochemically, treatment will depend on whether the recurrence is local or distant. local recurrence raises the possibility of salvage surgery, either radical prostatectomy or cryotherapy. There is very little published data, but both are feasible though a high complication rate has been reported. In post-brachytherapy radical prostatectomy the rate of positive margins is - 50%, incontinence 40-50%, and rectal injury 15%. Salvage cryotherapy after brachytherapy is feasible but also with significant morbidity with high risks of impotence and incontinence. Nodal or distant recurrence is managed with anti-androgen therapy.

Conclusion

Prostate brachytherapy is an effective treatment for early stage, T1-2, low pre-treatment P.S.A. and with low I.P.S.S. score. It has lower rates of impotence and incontinence compared with radical prostatectomy and much lower operative risk. In comparison with external beam radiotherapy it requires only one treatment, has less rectal morbidity but higher rates of short-term urethritis. The comparative rates of biochemical relapse free interval is similar for all three modalities in good prognosis patients though this is based on case-control and cohort studies. Randomised control trials allocating patients to either radical prostatectomy or brachytherapy would give clearer evidence but recruitment would be very difficult. Despite the lack of randomised trials there is abundant evidence that high quality brachytherapy with selected patients provides a safe, well tolerated and effective treatment for early prostate cancer.

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Drug Profile

TACROLIMUS

Tacrolimus is a macrolide lactone with potent immuno suppressive activity, isolated from streptomyces tsukubaensis. In contrast to all other US food & Drug Administration (FDA) approved immuno-suppressive agents developed to date, the clinical development of tacrolimus was conducted primarily in liver transplantation in 1994. It was used in Renal transplant recipients in 1996. It is viewed widely as preferable to cyclosporine for maintenance immuno suppression in high-immunological risk renal allograft recipients (Repeat renal transplant recipients, high panel reactive antibody renal transplant recipients, & combined kidney-pancreas transplant recipients). More recent experiences indicated that tacrolimus may have additional properties, including steroid-sparing properties, that may be superior to cyclosporine.

Mechanism of action : It exerts potent inhibitory effect on T-Lymphocyte activation. It binds to immunophilins FK 506 binding proteins (FKBP-12) and a complex of FKBP-12, Calcium, calmodulin & Calcineurin is formed, inhibiting phosphatase activity of calcineurin. This prevents dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT) and inhibits transcription of early T-cell activation gene, interleukin-2, Tumor necrosis factor (TNF- α) and proto-oncogenes; suppressing expression of IL-2 and IL-7 receptor. This results in inhibition of T-Lymphocyte activation. Tacrolimus also inhibits the mixed lymphocyte reaction, generation of cytotoxic T-cells dependent B-Cell activation.

Pharmacokinetics : Absorption of Tacrolimus after oral administration is incomplete & variable with oral bioavailability of 4-93% and mean bioavailability of 25%. Food appears to reduce the absorption & relative bioavailability of tacrolimus. In most cases, CMax is achieved after 0.5 to 1 hour. It is mainly metabolized (799%) in liver by a cytochrome isoenzyme (P450 CYP3A) to at least 15 compounds. The main route of elimination of tacrolimus metabolites is biliary & less than it is excreted unchanged in urine. Fecal elimination is around 92%.

Indication & Usage : It is used in liver & kidney transplant cases as immuno suppressive drug.

Warning: Administration of tacrolimus may cause diabetes mellitus. Neurotoxicity & nephrotoxicity. Mild to moderate hyper kalemia may occur with it. Patients receiving tacrolimus are at high risk of lymphomas, malignancies & infections due to oversuppression of immune system. Mild to moderate hyper-

tension is common with the drug.

Precautions : Patients with hepatic & renal impairment, lower dosage should be used.

Hypertrophic cardiomyopathy - It is observed in infant & children. Dosage reduction or discontinuation of therapy is required.

Pregnancy - No well controlled trials. It should be used only if the benefits outweigh potential risk to fetus.

Nursing mothers - Since it is excreted in human milk, should be avoided in nursing mothers.

Drug Interaction: As tacrolimus is metabolized by cytochrome P450 CYP3A enzyme, potential drug interactions are -

(a) increased tacrolimus blood concentration - Calcium channel blockers antifungal agents, macrolide antibiotics, corticosteroids, cyclosporine, prokinetic drugs, omeprazole & bromocriptine. (b) Decreased Tacrolimus blood concentration - Anticonvulsant, anticoagulants antacids & rifampicin. Vaccines - Drug may reduce the efficacy of vaccines & recipients of tacrolimus should not receive live attenuated vaccines.

Adverse Reactions : Tacrolimus shows adverse events common to other immuno suppressive therapies viz, neurotoxicity, nephrotoxicity, increased risk of infections & malignancy, diabetes mellitus & a lymphoproliferative disorder, related to Epstein Barr Virus common adverse events are - Nervous System - Tremor, headache, paresthesia, dizziness, insomnia, seizures, GI Tract - Diarrhoea, constipation, Nausea, vomiting, dyspepsia. CUS - hypertension chest pain.

Metabolic Disturbance - Hyperkalemia, hyper chloremic acidosis, hypomagnesemia - diabetes mellitus, hypercholesterolemia. Hypertension, Nephrotoxicity- Reduced Renal blood flow, glomerular perfusion, tubular & vascular toxicity.

Dosage & Administration - dosage 0.2mg/kg/day in 2 divided doses. The target trough blood levels of tacrolimus is 12-15 ng/ml in 1st month post transplant period, 1-3 months after transplant 10-12 ng/ml, 5-10ng/ml 3-6 month after transplant.