Permanent Low-dose-rate Prostate Brachytherapy

a report by
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Modern-day prostate brachytherapy using permanent implants was born in the 1980s following the development of transrectal ultrasound in Denmark. The use of transrectal ultrasound allows the accurate implantation of radioactive seeds into the prostate, which had previously been attempted at open operation but without clinical success.

Brachytherapy Procedure

There are a number of different techniques available to perform prostate brachytherapy, all of which, when performed in experienced hands, provide reproducible high-dose radiation targeted to the prostate. There does not appear to be any clinical difference between the isotopes of iodine-125 and palladium-103, and the latter is currently unavailable in the UK and much of Europe. The implant procedure as popularised in Seattle is a two-stage technique involving an initial planning transrectal ultrasound scan. The ultrasound images generated of the prostate are digitised to produce a three-dimensional (3-D) computerised model of the prostate, urethra and rectum. The precise number and position of the seeds required are then calculated to ensure coverage of the prostate with a suitable margin. The patient returns to the hospital two to four weeks later for the implantation of the radioactive sources. The patient is anaesthetised and placed in a similar extended lithotomy position as for the planning scan. The transrectal ultrasound is used to guide the needles, pre-loaded with radioactive seeds, into their predetermined positions within the prostate gland. The procedure takes 30–45minutes, after which the patient is catheterised. This catheter may then be removed later the same day, with the patient being discharge once they have voided or the following day.

Stranded iodine seeds (Rapid Strand™, Oncura, UK) allow a greater coverage of radiation just outside the gland and the risk of individual seed migration through the venous plexus around the prostate is avoided. In our audit of 40 patients who underwent a chest X-ray a minimum of three months after their Rapid Strand implant there were no cases of seed migration to the lungs. Implants are typically planned with a minimum margin of 5mm around the prostate, extending to 10mm at the base and apex in an attempt to treat any localised extra capsular spread of disease.

Some centres favour a one-stage technique where an estimate of the numbers of seeds required for a procedure is calculated from the prostate volume, which is assessed in clinic. The dosimetric calculations are then performed using computer software, whilst the patient is anaesthetised. This technique is more complex to learn and requires the use of loose rather than stranded seeds, with the risk of seed migration to the lungs reported in up to 20% of cases. Both techniques, when performed in experienced hands, however, may deliver high- quality implants.

A post-operative computer tomography (CT) performed either immediately for four weeks after the implant is used to calculate the post-implant dosimetry delivered to the prostate. It may be considered an indicator of the quality of the procedure.

The minimum prescribed dose to the prostate gland is 145Gy using iodine-125 implants, with approximately 50% of the gland receiving 150% of the dose, i.e. 217Gy (see *Figure 1*). The implants are arranged to allow relative sparing of the prostatic urethra to minimise urinary morbidity. In cases where there is an increased chance of local extension of the prostate cancer, a combined treatment using 45Gy external beam radiation to the whole pelvis, given as 1.8Gy/fraction, followed by a 110Gy brachytherapy implant, has been used to good effect and will be discussed below. In some series, the addition of three months of neo-adjuvant hormone therapy is also being utilised.

Brachytherapy Results

Long-term Results

The first 10-year results of transperineal ultrasound-guided prostate brachytherapy that derived from Seattle were reported in 1998. The 152 patients treated from 1986 to 1987 were the first ever to be treated by this technique and therefore include both the learning curve, as well as the curve of discovery for

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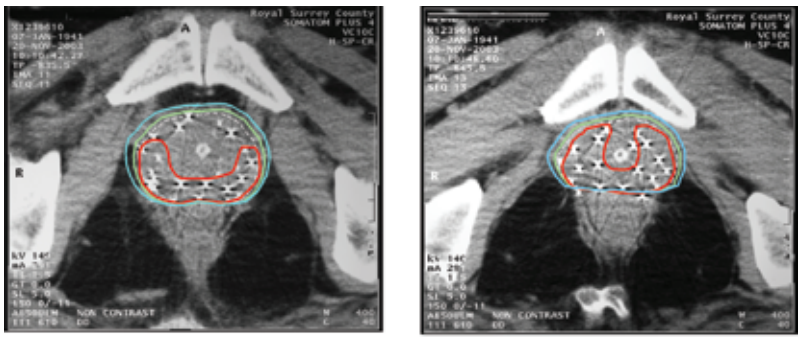
Since his training, he has developed an international reputation and expertise in prostate cancer – in particular, prostate brachytherapy – and has treated over 800 patients with this technique. He also has a keen interest in prostate cancer research at the Postgraduate Medical School of the University of Surrey and is co-lead of a large Multidisciplinary Research Unit investigating the molecular aspects of prostate cancer and novel therapies, including gene and vaccine therapies. Professor Langley has run numerous international courses for consultants across Europe in prostate brachytherapy and is currently establishing a British Urological Foundation Fellowship programme in brachytherapy in association with colleagues from Seattle, US. He trained to Medical School at St. Bartholomew's Hospital, London. He undertook a Masters of Surgery thesis at St. Thomas' Hospital, London, and was a Senior Urological Registrar in Bristol before being appointed a Consultant Urologist in Guildford in 1998.

Figure 1: Post-implant CT Scan Taken with the Patient Catheterised at Mid Gland and Apical Levels of the Prostate



Mid gland Apex of gland

The Iodine-125 sources are clearly seen within the prostate tissue. The dashed white line shows the peripehery of the prostate. The green isodose line is a simulation showing coverage of the prescribed radiation dose, 145Gy. The red isodose line simulates that portion of the prostate receiving 150% of the prescirption dose, 217Gy. The blue isodoseline simulates the 72Gy isodose showing the rapid fall off in radition to the surrounding structures

Table 1: Risk Group Classification of Prostate Cancer Patients

Seattle Risk Groups	PSA	Stage	Gleason Grade
Low	≤10	T1a–T2b	2–6
Intermediate: 1 factor	>10	≥T2c	≥7
High: 2 or more factors	>10	≥T2c	≥7

Stage is based on the 1992 American Joint Committee on Cancer staging where T2b involves more than 50% on one side of the gland and T2c involves both sides as assessed by a digital rectal exam (DRE).

the procedure. Sixty-four per cent of patients were treated by implant alone (either iodine-125 or palladium-103) and the remaining 36% of patients, judged to be at higher risk of extra-prostatic extension, underwent combined external beam radiation therapy (EBRT) to 45Gy, followed by brachytherapy. Five and 10-year prostate-specific antigen (PSA), biochemical-free survival as defined with a PSA of <0.5µg/l revealed results of 74% and 66%, respectively. This learning curve was demonstrated in a more contemporary series of similar low-risk patients (defined in *Table 1*) treated in Seattle from 1988 to 1999. Improvements in the technique revealed an increased 10-year biochemical-free survival rate from 65% to 87% for this group of patients.

A further cohort of 125 patients treated by iodine-125 monotherapy, with an average follow-up of 77 months, revealed 100% cancer-specific survival and an 85% progression-free survival at 10 years.[8,9] The overall Seattle published series of 634 patients – 402 treated with an implant alone (iodine-125/palladium-103) and 232 treated by an implant and external beam radiation – revealed a progression-free survival rate of 77%. No patients underwent lymph node sampling or androgen ablation, and biochemical survival was determined by two successive PSA rises rather than the American Society for Therapeutic Radiology and Oncology (ASTRO) criteria of three. When stratified by risk factors (see *Table 1*), low-, intermediate- and high-risk disease had progression-free survival rates of 87%, 74% and 45%, respectively. Similar 10-year results have been recently reported by others with PSA-free survival rates of 79% from a cohort of 883 patients, and results on 619 patients at 13 years continue to show a PSA-free survival of 77%.

Ten-year disease-specific survival rates for 1,561 men treated by brachytherapy, with or without EBRT and hormone therapy, have recently been published with a 96% survival, suggesting that the excellent results obtained using PSA as a surrogate marker appear to translate to actual clinical outcomes.

Reproducibility of Brachytherapy Results

Several centres across America have reported similar results for low risk patients, as indicated in *Table 2*. In centres with demonstrable high-quality implants and that are regularly performing brachytherapy, excellent results have also been seen in intermediate-risk patients with biochemical-free survival of this group of patients matching those obtained from Seattle.

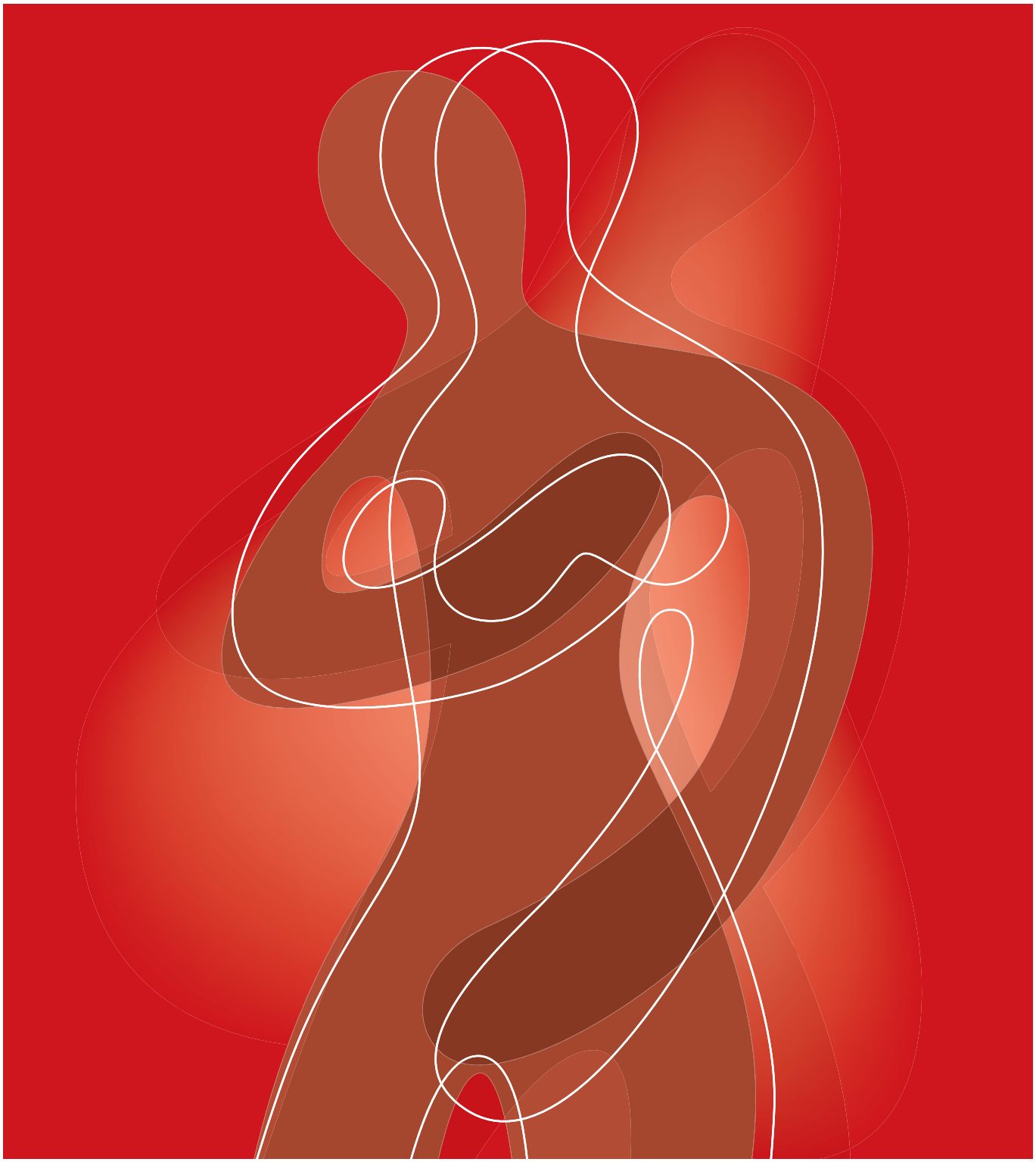
The benefit of treating patients with intermittent risk factor disease by brachytherapy alone or in combination with EBRT has yet to be clarified and there are proponents of each technique. A current Radiation Therapy Oncology Group (RTOG) study randomising intermediate risk patients to brachytherapy alone or combination therapy should answer the question as to the necessity of EBRT.

The results achieved in the US appear exportable to the UK. We have treated over 800 patients and prospectively assessed outcomes of both PSA-free survival using the ASTRO criteria as well as continence, potency and quality-of-life parameters using validated questionnaires.

The demographics and results of the first 300 patients treated with median follow-up of 45 months (range 33–82) shows an overall actuarial PSA-free survival of 93% at five years.

Stratified by risk group, the actuarial survival were 96%, 89% and 93% for low-, intermediate- and high-risk disease. There was no statistical difference in survival between hormone-naïve patients and those treated with three months of neo-adjuvant therapy (95% versus 93%, p=0.3, respectively).

The Leeds group, UK, have also recently presented their seven-year PSA-free survival results, showing similar outcomes to those from America with rates of 84%, 72% and 54% for low-, intermediate- and high-risk disease from a cohort of 669 patients.



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The Role of Hormone Therapy in Brachytherapy

Hormone therapy may be used to reduce gland size to allow patients with larger prostates(55–75cc) to be treated by brachytherapy without incurring pubic arch interference at the time of implantation. It has also been used in a neo-adjuvant setting in higher-risk patients in an analogous situation to patients treated by EBRT. However, the excellent results demonstrated in patients treated with low-risk prostate cancer implies that neo-adjuvant therapy in this group is unwarranted. When volume reduction is the goal, goserelin has been shown to provide a significantly greater reduction in prostate size than bicalutimide, mean volume reduction 26% versus 8%, respectively.

The value of neo-adjuvant hormone therapy in a therapeutic role is more contentious. Following the work of Pilepich et al., where an improved survival was demonstrated in patients treated with four months of combined androgen blockade with EBRT, many patients in the UK are treated in a similar way when undergoing such therapy. Further studies have suggested that high-grade tumours require longer adjuvant treatment. There are no randomised studies evaluating the benefit of neo-adjuvant hormones in brachytherapy. To date, some studies have shown an advantage for intermediate- and high-risk patients at five years, whereas others have failed to identify a benefit in case-matched series. Furthermore, any such advantages must be balanced by the side effects of hormone therapy, which, in our experience, can adversely affect erectile function up to one year after implantation.

Comparison Results

There are currently no randomised studies comparing brachytherapy to either radical prostatectomy or EBRT available. In a study of over 6,500 patients treated with either brachytherapy, radiotherapy or radical prostatectomy, who were stratified according to a PSA and Gleason score, there would appear to be no significant difference between any of the primary treatment options in PSA-free survivals. The only consistent finding was that conformal beam T, but no individual treatment had overall superiority. A further retrospective comparison of 1,305 patients treated for stage T1-2 prostate cancer by either radical prostatectomy or brachytherapy failed to demonstrate any clear superiority of one treatment over the other.

Kupelian reported data from a large cohort of 2,991 patients treated with either brachytherapy with or without EBRT, conformal beam radiotherapy to >72Gy or <72Gy and radical prostatectomy. EBRT given to <72Gy appeared less effective than the other modalities, all of which appeared indistinguishable when assessed at five years by biochemical-free survival.

It appears highly unlikely, given the size of these cohorts, that one will be able to determine a significant difference between treatment groups until randomised studies are available, and at present brachytherapy, radical prostatectomy and conformal beam radiotherapy would appear to hold similar chances of cure for patients. The durability of brachytherapy has been demonstrated in 10- and 13-year results from Seattle. No further recurrences were identified in patients who were deemed biochemically free at 10 years compared to 12 or 13 years of follow-up.

Complications

Incontinence is rare, occurring in <1% in our work and most contemporary series. The primary complication of prostate brachytherapy is a temporary deterioration of urinary function with increased irritative and obstructive symptoms. Patients are routinely treated with α-blockers. We have found that such urinary symptoms assessed by the International Prostate Symptom Score (IPSS) are improved at three months and return to baseline by nine months. Urinary retention can occur in 2–27% of patients, although with improved case selection the risk can be minimised. This side effect is best managed by intermittent self-catheterisation and is usually resolves within four weeks. A transurethral resection of the prostate (TURP) should be avoided for at least nine months as symptom will often resolve and we have a <2% incidence of our patients requiring any outflow tract surgery. Although urinary obstruction can often be readily relieved at operation, a 26% rate of stress incontinence has been reported. Urethral strictures may develop in ~5% following brachytherapy typically at the membranous urethra. They respond well to simple dilatation followed by weekly intermittent self-catheterisation. A similar incidence of strictures has been reported in patients treated by both radical prostatectomy and EBRT.

Proctitis is relatively uncommon, occurring in approximately 5% of cases and, in our experience, has always resolved with conservative medication alone. It is more troublesome in patients with combined EBRT and brachytherapy as the rectal dose is increased. Patient-administered questionnaires have shown that there is relatively little long-term bowel dysfunction.

Erectile dysfunction (ED) seems significantly less common than with radical prostatectomy, where impotence from UK and European studies is as high as 86% despite utilising nerve sparing techniques.

Potters reported on the potency of 482 patients potent pre-treatment and revealed a potency rate as high as 90% in men younger than 60 treated with an implant alone. The potency rates gradually worsened with increasing age of the patient, the addition of EBRT and the use of neo-adjuvant androgen depravation therapy. In those patients that do experience impotence, a >80% response to sildenafil can be expected. Pre-implant erectile status is a strong predictor of brachytherapy-induced impotence. At six years post-implant, 70% of patients remained potent enjoying normal erectile function pre-treatment compared with only 34% of patients whose pre-treatment erectile function were sufficient for intercourse but considered sub-optimal.[54] In our prospective study at Guildford, we have a 67% potency rate at one year in patients with International Index of Erectile Function (IIEF) score of greater than ≥11/25, who were potent pre-treatment.

The literature lacks any randomised studies comparing side effect profiles with EBRT, radical prostatectomy or brachytherapy. A recent review article in the *Lancet*, discussing the clinical decision-making aspects of the treatment of early prostate cancer, highlighted the relatively low risk of urinary incontinence, rectal complications and sexual dysfunction following brachytherapy compared with radical prostatectomy or external beam radiotherapy. However, the risk of retention following brachytherapy is appreciable and highlights the importance of careful case selection to minimise this significant, although temporary, deterioration in urinary symptoms. A meta-analysis comparing erectile function outcomes of men with prostate cancer treated with curative intent suggests that, of the different radical treatments, brachytherapy offers the higher risk of remaining potent at 76% (reducing to 60% with combination therapy). Quality-of-life studies suggest that the greatest deterioration in urinary continence and sexual function occurs in patients treated by radical prostatectomy compared with brachytherapy, although, often, more global quality-of-life measures remain similar.

Patient Selection Issues for Brachytherapy

Patient selection for prostate brachytherapy involves both cancer issues and more general urological issues. In accordance with the recommendations of the American Brachytherapy Society and the European Association of Urology/European Organisation for Research and Treatment of Cancer (EAU/E ORTC), patients with low-risk prostate cancers may be treated effectively with a brachytherapy implant alone. Those with intermediate-risk prostate cancer pose a more difficult question, and the current RTOG study randomising patients to a brachytherapy implant alone or combination treatment with EBRT will help to determine which is the optimal treatment strategy. Factors such as patient age, competing co-morbidities, the percentage of cores positive for cancer and the presence of perineural invasion can influence the decision as whether to offer combination treatment.

For patients with high-risk cancers, the role of brachytherapy is less certain. If there is evidence of seminal vesicle invasion, combination treatment of brachytherapy and EBRT does not provide as high a dose to the vesicles as conformal beam radiotherapy, which would be considered the optimum treatment. However, if the seminal vesicles appear clear, combination therapy has been used with good effect, as demonstrated in a number of series with up to 50% biochemical-free survival at 10 years.

The urological issues surrounding prostate brachytherapy are important in selecting patients who are likely to have minimal post-implant symptoms. Patients should ideally have glands less than 60cc in size to avoid pubic arch interference, although this can occur with smaller glands and needs to be assessed at the time of the planning scan. In patients whose glands are between 60cc and 75cc, a three-month course of hormone deprivation via an luteinising hormone releasing hormone (LHRH) analogue will usually allow sufficient volume reduction to permit an adequate implant. Such patients, however, tend to have an increased risk of temporary retention and urinary morbidity. Patients must be able to flex their hips to 90°, have few pre-treatment lower urinary tract symptoms, (IPSS <15) and should be urodynamically unobstructed.

Summary

Brachytherapy appears highly effective in the treatment of localised prostate cancer and these results have been reproduced across America as well as within Europe. A number of quality of life surveys have suggested that optimum quality of life is obtained with brachytherapy both in terms of urinary and sexual parameters. With many patients treated by brachytherapy in a day-case setting and being able to return to work within a few days, the advantages of brachytherapy are readily apparent. As with every treatment in medicine, however, case selection is critical in brachytherapy to ensure satisfied patients with a low morbidity and high chance of cure. ■

A version of this article containing references and additional tables can be found in the Reference Section on the website supporting this briefing (www.touchoncologicaldisease.com).