REVIEW

Prostate brachytherapy has come of age: a review of the technique and results

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Introduction

Prostate brachytherapy, using permanent radioactive implants, is increasingly becoming an accepted form of treatment for early-stage prostate cancer. Many patients are attracted to it because the treatment may be administered as a day-case procedure with a low long-term risk of urinary incontinence. Impotence also seems to be less likely than with some of the other conventional therapies, e.g. radical prostatectomy (RP) [1,2]. Brachytherapy may alter the balance in the risk of treating a non-lethal disease in a patient [3] against the success of the treatment and its morbidity. This review explores the development and techniques of prostate brachytherapy, together with the results in terms of disease control and quality of life.

History

Prostate brachytherapy was one of the first applications of ionizing radiation. In 1914, Pasteau and Degais used radium capsules inserted transurethrally into the prostate. Implants of ^{198}Au were later used in 1965 by Scardino and Carlton [4], combined with EBRT. In 1972, Whitmore *et al.* [5] described the technique of open retropubic insertion of iodine (^{125}I) seeds. The seeds were inserted 'free hand', in an anteroposterior direction, using a finger in the rectum of the patient to guide the delivery needles into position. The procedure was conducted without the benefit of a three-dimensional plan and resulted in a haphazard distribution of the implants. The 15-year data has now shown that this treatment did not provide an effective long-term control of the disease, with local recurrence and metastasis-free survival rates of 24% and 21%, respectively [6].

The use of a perineal template to provide the *x* and *y* co-ordinates for use in open retropubic transperineal temporary iridium implants [7], coupled with the development of TRUS of the prostate, which provides

the *z* co-ordinate, led to the concept of a closed/percutaneous transperineal permanent implant technique. First described in 1983 by Holm *et al.* [8], this technique has been further modified to allow sophisticated pre- and intraoperative planning, improved accuracy and postoperative dosimetry [9–14].

The rationale for brachytherapy

Brachytherapy is a method of accurately delivering a high dose of radiation to a target organ. Like all radiation techniques the aim is to maximize the dose to the target organ whilst sparing sensitive normal tissue. The dose to cure most solid tumours exceeds the tolerance of the surrounding normal tissue. Prostate [15], in common with other tumours such as those of the bronchus [16] and cervix [17], has a dose-response curve that requires doses of >75 Gy, delivered by fractionated radiotherapy, to achieve local control in most cases. Despite complex planning using conformally blocked, or intensity-modulated EBRT, doses of >80 Gy cannot be achieved without unacceptable toxicity. Prostate brachytherapy offers a technique that can deliver doses of >100 Gy (145 Gy delivered by ^{125}I is equivalent to >100 Gy in 2 Gy fractions [18,19]). This magnitude of dose offers the chance that all tumours irradiated by the prescribed dose will be controlled.

Techniques of modern prostate brachytherapy

To achieve a successful implant the choice of isotope, isodose distribution and dose delivered are critical. Currently, two isotopes are used as the radioactive seed source, ^{125}I and ^{103}Pd; they are similar in the energy imparted (E_{avg} of 27.4 keV vs 21 keV). The most significant radiobiological difference between the isotopes is their half-lives of 59.4 and 16.97 days, respectively, and their initial dose rate. ^{103}Pd has the higher dose rate and is biologically more active, therefore equivalent prescribed doses are lower (115 Gy vs 145 Gy). The radiobiological equivalent dose with EBRT depends on

the individual biology of each tumour and is 100–120 Gy [18,19].

Theoretically, the higher dose rate of [103]Pd should have more effect in killing tumours which have a faster doubling time, e.g. high-grade tumours, whereas ^{125}I would be suitable for those of a lower grade [20]. However, *in vitro* data on prostate cancer suggests the potential doubling time to be >15 days [21], which is relatively long and would favour [125]I. Clinical studies have also failed to show any significant difference between the isotopes in cancer control rates [22–24]. In reality, the choice may be made on availability and cost; ^{125}I, the only isotope readily obtainable in the UK, is available in both loose seeds and strands (Rapid Strand®, Nycomed Amersham, UK). Rapid Strand has the advantage of reducing migration to the lung of peripherally placed seeds.

Dose planning

Currently there are two widely used techniques for delivering permanent implants, although there are numerous minor modifications that can be used. However, regardless of the technique used, both have the same aim in providing a high dose of irradiation to the prostate in a distribution that contours the shape of the gland, whilst minimizing the radiation delivered to adjacent structures.

The technique popularized by Grimm *et al.* [25] from Seattle, for which the longest follow-up is available, is the most commonly used in the UK. This is a two-stage technique; the initial stage requires a pre-planning TRUS examination with the patient in the lithotomy position, undertaken as either an outpatient procedure or as a day-case under general anaesthesia. It involves recording a series of transverse images 5 mm apart from the base to the apex of the prostate. A urinary catheter and/or aerated jelly is instilled into the urethra to allow its identification on the ultrasonograms. These pictures are digitized to produce a three-dimensional model of the prostate on the planning computer. Using this information the position and number of the seeds required are determined (Fig. 1). A modified uniform distribution of the seeds is typically used. This loading pattern increases the seed density to the periphery of the gland and reduces the density around the urethra. The technique is designed to reduce the total radiation dose to the urethra, and therefore the potential for urethral toxicity and urinary retention afterwards.

The single-stage technique advocated by Stock *et al.* [14] aims to calculate seed placement at the time of the implant. Before the implant, the prostate volume is determined by TRUS and a nomogram used to calculate approximately how many seeds will be
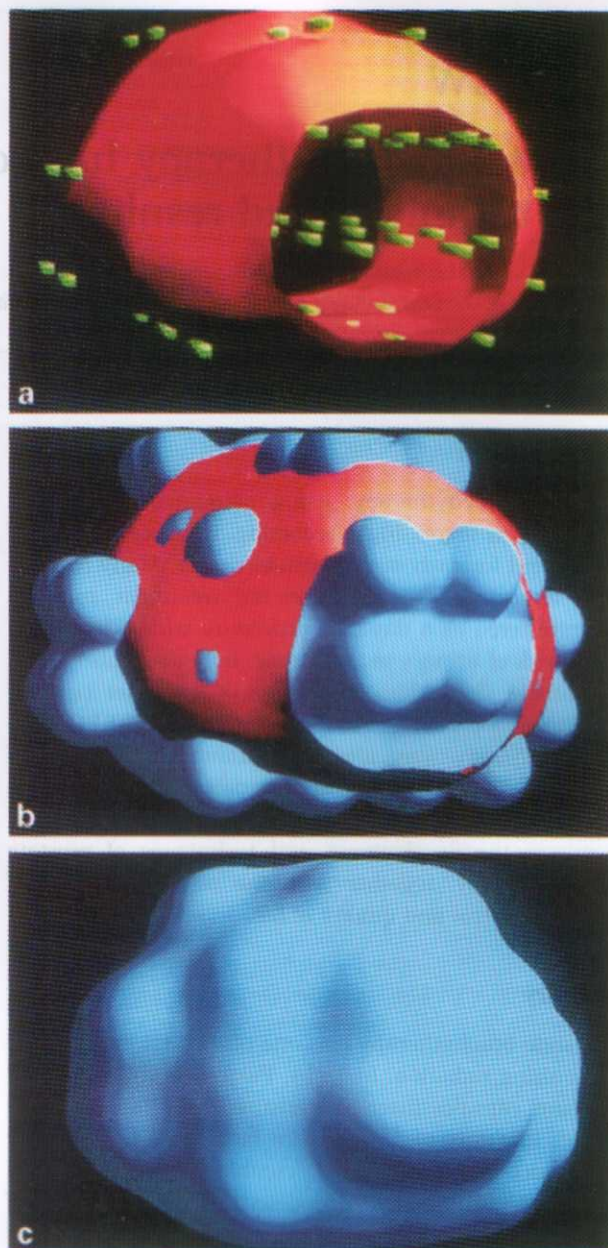

Fig. 1. a, Three-dimensional reconstruction of an outer surface of the prostate with the urethra in green, showing the simulated seed position. b, The effective radiation dose delivered by each seed illustrated in blue. c, Reconfigured seed placement ensuring complete coverage of the gland by the prescribed radiation dose.

required. The planning dosimetry calculations with this technique are performed peroperatively.

If the prostate is large (>60 mL) the pubic rami may shield part of the gland, making it impossible to implant seeds into the anterolateral portion of the gland. Such a situation can be anticipated if a planning scan is taken in which the position of the pubic rami in relation to the prostate gland can be determined. For glands of <45 mL, pubic arch interference is rarely a problem. If the prostate

is large and of arch interference is anticipated, the gland may be reduced using an LHRH analogue for at least 3 months and continued until the time of implantation. However, we have found that the antiandrogen bicalutamide is not as effective as monotherapy in producing a reliable reduction in gland size.

Implant technique

The Seattle technique requires the patient to be placed in an identical lithotomy position to that used for the planning scan, under general or regional anaesthesia. The position of the TRUS probe is adjusted to the provide similar radial images of the prostate as obtained from the planning scan. Then 18 G needles are inserted percutaneously into the prostate, passing through the perineal (x/y) template to a pre-calculated depth (z), which is determined by the position of the ultrasound probe within the rectum.

The needles may either be pre-loaded with the appropriate number of seeds, as calculated by the planning software, or the seeds can be inserted individually from a cartridge via a Mick applicator (Bronx, NY, USA). A catheter or aerated jelly is again used to delineate the urethra within the prostate gland to ensure that seeds are not deposited within its lumen. The seeds most anterior in the prostate are implanted first, to avoid obscuring the view of those more posterior.

At the end of the procedure cystoscopy may be used to ensure that there are no seeds in the urethra or bladder, and a catheter inserted whilst the patient recovers. This is removed shortly afterwards and the patient discharged once they have voided.

With the technique of Stock et al. [14], a predetermined number of 18 G needles are inserted into the periphery of the gland. Their exact position within the prostate is detected by TRUS and the images transferred directly to the dose-planning computer. About 75% of the seeds are inserted through these peripheral needles with the remaining 25% inserted into the centre of the gland. The dose-planning computer calculates where these central needles must be placed and how many seeds each must deliver, to ensure that the whole of the gland is adequately treated.

The advantage of this technique is that it is effectively a one-stage procedure and does not require the patient, and more importantly their prostate, to be replaced in an identical position to that used for the preplanning scan. However, the procedure is more complex and lengthy, with the dose being planned whilst the patient is under anaesthesia. The planning computer also bases the intraoperative dose plan on where the peripheral needles are situated rather than where the actual seeds are deposited, which may not be identical. Each

technique has its protagonists, although the outcome data for both appears to be equivalent.

Dosimetry after implantation

It is widely recommended that all patients should undergo dosimetry after implantation; this allows a comparison between where the seeds were actually placed and the original plan. CT is used to identify each seed and the prostate outline; this is transferred to the planning computer and the dose that 90% of the prostate receives (D_{90}), the volume that receives 100% and 150% of the prescribed dose (V_{100} and V_{150}) are calculated. These results give an indication of the quality of an individual implant, and of the implants at a particular institution. Such information allows the identification of systematic under-dosing errors that may need correction for future implants.

The difficulty with this assessment arises from the identification of the prostate outline on CT; CT has been shown to overestimate the volume when compared with MRI or ultrasonography by 30%, and is made more inaccurate by the artefact caused by the seeds. Various solutions have been sought to improve accuracy, e.g. MRI fusion [26], but this is time-consuming and expensive. Possibilities for the future are the better identification of the seeds on TRUS and the use of three-dimensional ultrasonographic mapping to allow the dosimetry to be calculated at the end of the implant procedure.

The doses prescribed are similar whichever technique is used. Patients with a low risk of extracapsular disease are treated with brachytherapy alone. Typical doses are 145 Gy with ^{125}I and 110 Gy with [103]Pd. Some centres, including the authors', advocate EBRT in conjunction with brachytherapy for intermediate- and high-risk patients, i.e. with one or more of the following risk factors: stage >T2b, PSA >10 ng/mL, and a Gleason score of >6. Typically prescribed doses are 45 Gy by EBRT given in 25 fractions, followed by 110 Gy via an ^{125}I-brachytherapy implant.

Results

As with all other locally curative modalities, there are no prospective randomized trials to compare the results of brachytherapy with those of RP or EBRT; furthermore, if such a trial could be designed and recruit sufficient patients, it would be many years before the results would be available. Therefore, the only results available for scrutiny tend to be single-institution experiences reporting retrospective series.

After brachytherapy PSA is still detectable and may take many years to reach its nadir [27]. The criteria

used to determine the success or failure of a treatment therefore frequently differs among surgical series and those using radiation. The former report a treatment failure when the level of PSA typically rises above 0.1–0.4 ng/mL, whereas radiation oncologists more commonly use the ASTRO consensus definition of biochemical failure as determined by three consecutively rising PSA levels after the nadir is reached [28]. Reporting results from prostate brachytherapy using an absolute PSA value as the criterion for failure may overestimate failures if the outcome is analysed before the nadir is reached. However, reporting progression-free survival may underestimate failure in patients with stable but elevated PSA levels who will subsequently fail if series are reported with insufficient follow-up. A further complicating factor is the phenomenon of 'PSA bounce', where transient rises in PSA may occur before the nadir is reached. The magnitude of such rises is usually 0.2–3 ng/mL occurring during the first 3 years after implantation [29].

The PSA-free survival results for RP usually emerging from a few centres of excellence in the USA have been well reported [30,31], although their reproducibility in less specialized units remains unconfirmed. Similarly, excellent biochemical-free survival rates have been reported in centres using conformal EBRT, where dose-escalation studies have shown the importance of giving <70 Gy to the prostate [32], although unfortunately such treatment is frequently unavailable in the UK.

Instead of contriving to compare the results of different surgical and EBRT series with those from brachytherapy in an attempt to draw meaningful conclusions,

a format practised by advocates of both surgery [33,34] and brachytherapy [35], this review will concentrate on the data for brachytherapy alone.

Numerous reports have shown good biochemical (PSA), control at 5 years after treatment (Table 1) [19,27,35–41], although the advent of 7- [19], 9- [27], 10- [35,40] and 12-year data [41] has led to a greater acceptability for prostate brachytherapy.

The initial 10-year results for brachytherapy reported on the first 152 patients treated encompassed both the discovery and development of the new technique [35]; a 66% biochemical disease-free survival was achieved, which has been maintained in the 12-year follow-up results [41]. Further long-term data from the Seattle group, based on an unselected group of 634 patients with localized disease treated with both monotherapy ^{125}I or ^{103}Pd (403 patients) and combination therapy (231 patients), shows an 85% PSA progression-free survival rate at 10 years [42]. When the results are stratified according to risk groups they reveal a 92%, 84% and 60% PSA progression-free survival for the favourable, intermediate and unfavourable groups [43].

The value of neoadjuvant hormone treatment coupled with 40–45 Gy EBRT in combination with a brachytherapy boost (110 Gy with ^{125}I) to the prostate has been suggested in patients with unfavourable disease [35,44]. The results in such patients (Gleason >6, PSA >10 ng/mL, stage T2b/c) treated by implant alone may be inferior to those of surgery [45,46]. However, Blasko et al. [42] recently failed to show a benefit with the addition of EBRT to high-risk group patients, with good biochemical-free survival rates of ≈60% at 5 years.

Table 1 The actuarial results of prostate brachytherapy using both a combination of implant alone or with EBRT

Series	Median follow-up, months	Isotope, ±EBRT	Disease severity	No. of patients	PSA progression-free survival, % (years)
[19]	55	^{125}I or ^{103}Pd alone	All patients	320	80 (7)
[36]	47	^{125}I or ^{103}Pd alone or +EBRT	All patients	490	79
[37]	41	^{125}I or ^{103}Pd alone or +EBRT	All patients	717	82 (5)
		^{125}I or ^{103}Pd alone	Favourable*	334	92 (5)
		^{125}I or ^{103}Pd alone	Intermediate†	261	74 (5)
		^{125}I or ^{103}Pd alone	Unfavourable‡	122	55 (5)
[38]	48	^{125}I alone	All patients	248	71 (5)
			Favourable*	146	88 (5)
			Intermediate†	85	77 (5)
			Unfavourable‡	17	38 (5)
[39]	51.3	^{125}I or ^{103}Pd alone	All patients	695	71 (5)
[27]	41.5	^{103}Pd alone	All patients	230	83.5 (9)
[35]	119	^{125}I and/or EBRT	All patients	152	66 (10) PSA <0.5
[40]	52	^{125}I alone	All patients	125	87 (10)
[41]	122	^{125}I and EBRT	All patients	219	66 (12)

*PSA <10 ng/mL, Gleason score <6; †PSA >10 ng/mL or Gleason score >6; ‡PSA >10 ng/mL, Gleason score >6.

These conflicting results may be attributable to the quality of the implant, but unfortunately there are no randomized prospective studies to confirm or refute this treatment strategy, although such a project should be feasible.

Biopsy data after treatment are limited and the tissue is often difficult to interpret (Table 2) [26,35,47–49]. If the tissue is obtained too soon after implantation, cells may show characteristics of radiation damage but their viability remains uncertain. Frequently such equivocal biopsies are found to be negative if the prostate is re-biopsied a year or more later [47].

As with all techniques, considerable training and experience is required when embarking on brachytherapy [50]. The quality of the implant, as assessed by CT dosimetry, is an essential factor required to assess reported results; it is important that the D_{90} is >140 Gy, to provide effective PSA-free survival [51].

Complications and management

The management of patients after brachytherapy highlights the importance of urologists being closely involved in any brachytherapy programme used to treat patients using this technique. Urinary incontinence, which has been reported as high as 34% in UK series of RP [2], is uncommon in patients treated by brachytherapy, occurring in ≈1% of those who have not undergone TURP [20,52–55]. This is reflected in our experience, in which none of our first 120 patients were incontinent. In patients who require a TURP, the stress incontinence rate may reach 40% [20,24,48,52,56]. The mechanism for incontinence in this subgroup is unclear; it may be caused by damage and necrosis of the prostatic urethra [53] but a more likely explanation is that the external urinary sphincter is weakened by irradiation, which can be compensated by a functioning bladder neck/internal sphincter together with the prostatic bulk to allow continence. However, when the last two factors are also affected by surgery, stress incontinence may result.

All patients develop a significant deterioration in their urinary symptoms after implantation. Typically, the IPSS

doubles in the first few weeks before returning to mean baseline levels by ≈3 months [57,58] (Fig. 2). Patients are routinely prescribed an α-blocker for several months after seed implantation, to help relieve their obstructive symptoms [59]. Urinary retention is not uncommon after brachytherapy, at ≈5%, and becomes more likely the greater the pretreatment IPSS [52]. Patients with an IPSS of <10 have a 2% chance of retention after implantation, rising to 29% with an IPSS of >20. Patients in retention are best treated by intermittent catheterization and in most the retention resolves within a few weeks. Urethral stricture formation has been reported, with rates of 0–12% [59,60]. Zelefesky et al. [38] reported a 5-year incidence rate of 10% with the median time to occurrence of 18 months.
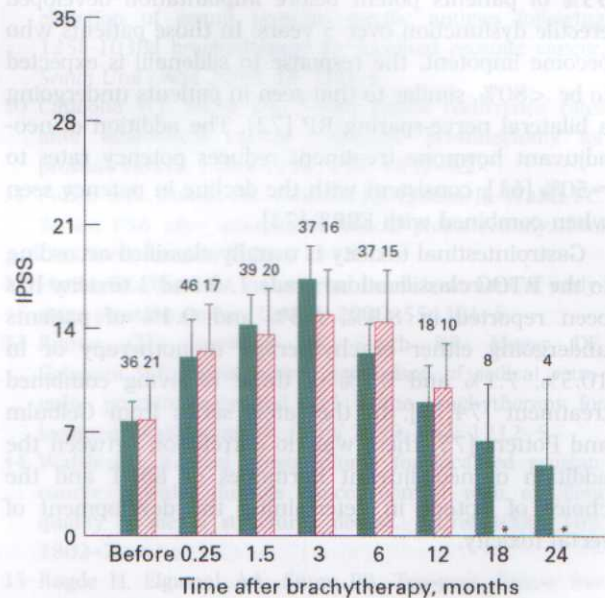

Fig. 2. The mean (SD) IPSS of the first 97 brachytherapy patients, before and after treatment with an ^{125}I implant; 71 were treated by 145-Gy brachytherapy implant alone (green bars) and 26 were treated initially with 40 Gy EBRT, then by a 110-Gy brachytherapy boost (red hatched bars). The numbers on bars are the number of patients in each group. * insufficient data.

Table 2 Biopsy results after prostate brachytherapy

Series	No. of patients	Isotope ± EBRT	% negative for malignancy	% equivocal for malignancy	% positive for malignancy
[48]	41	^{125}I	51	32	17
[49]	95	^{125}I or ^{103}Pd alone or +EBRT	80	–	20
[47]	201	^{125}I or ^{103}Pd	80	17	3
[35]	123	^{125}I alone or +EBRT	69	12*	19
[26]	117	^{103}Pd alone	93	–	7

*On subsequent biopsy of these 15 patients, 11 reverted to negative and four to positive.

Patients with prostates of >50 mL appear to have an increased tendency to develop urinary retention after implantation [24,61]. Larger glands are also technically more difficult to implant, as described earlier. Neo-adjuvant hormone treatment using a LHRH analogue for 3 months can lead to a reduction in prostate volume by 30–60% [62–64] to overcome this problem, and may have a synergistic effect with brachytherapy in improving disease control rates, as it has with EBRT [14,65,66] although confirmatory studies are awaited.

Brachytherapy, like EBRT but unlike surgery, preserves ejaculation; potency rates also appear to be relatively high after brachytherapy, at 50–85% [48,61,67–70], and for most patients sexual quality and function are preserved [70]. Unfortunately there are no studies that have rigorously evaluated long-term potency, although Zelefsky et al. [71] reported that 53% of patients potent before implantation developed erectile dysfunction over 5 years. In those patients who become impotent, the response to sildenafil is expected to be <80%, similar to that seen in patients undergoing a bilateral nerve-sparing RP [72]. The addition of neo-adjuvant hormone treatment reduces potency rates to ≈50% [61], consistent with the decline in potency seen when combined with EBRT [73].

Gastrointestinal toxicity is usually classified according to the RTOG classification; grade 1, 2 and 3 toxicity has been reported in 8.9%, 6.5% and 0.4% of patients undergoing either brachytherapy monotherapy or in 10.5%, 7.1% and 0.7% of those receiving combined treatment [74,75]. In the latest series from Gelbulm and Potters [75] there was no correlation between the addition of neoadjuvant hormones or EBRT and the choice of isotope in determining the development of rectal toxicity.

Quality of life

To date, most quality-of-life assessments for patients undergoing brachytherapy have been retrospective and usually comparative with patients attending differing institutions undergoing RP or EBRT [76–79]. Lee et al. showed that the deterioration in urinary symptoms, as shown by at least a doubling of the IPSS during the first few weeks after ^{125}I implant [80], had a detrimental effect on the patients' quality of life, as determined by the 'Functional Assessment of Cancer Therapy-Prostate' instrument, before scores returned to near baseline levels at 3 months. Patients undergoing EBRT combined with brachytherapy tend to have the greatest deterioration in their quality of life, whereas the findings for patients treated by RP and brachytherapy alone are similar [78].

Surgery will produce a rapid decrease in the PSA level that, together with confirmatory evidence that the resection margins are clear, may provide early reassurance to the patient. Such confidence may allow patients to be more accepting of the side-effects associated with surgery than are patients undergoing brachytherapy, whose PSA level may decline slowly over several months and who frequently have a significant temporary deterioration in urinary symptoms after implantation. Patients treated with brachytherapy must also be fully informed before consent about the likely side-effects and their duration, rather than being under the impression that the treatment is a 'soft option' and free of side-effects.

Summary

Brachytherapy for early prostate cancer provides an effective treatment, with good long-term results now available to support its use. It offers a low risk of urinary incontinence, with potency and sexual function frequently preserved. Brachytherapy is administered as a day-case or overnight-stay procedure and is sought by increasing numbers of patients. The technique appears to have an acceptable morbidity when balanced against the risk of mortality from the underlying disease. For example, Albertsen et al. [3] showed that a 62-year-old man with a Gleason 5 cancer has a <10% chance of dying from his disease in the subsequent 15 years. However, prostate brachytherapy is not free of side-effects and patient selection, as in all medicine, is critical in avoiding prolonged urinary symptoms.

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Abbreviations: RP, radical prostatectomy.
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