NOWOTWORY Journal of Oncology • 2003 • volume 53
Number 1 • 20–29

Low Dose Rate prostate brachytherapy with ^{125}Iodine & ^{103}Palladium

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Brachytherapy for cancer of the prostate can be performed using either low dose rate (LDR) or high dose rate (HDR) techniques. LDR implants used permanent seeds of ^{125}I or ^{103}Pd. Clinically there seemed to be no clear difference in treatment outcome between ^{103}Pd and ^{125}I. The American Brachytherapy Society (ABS) does not recommend one isotope in preference to the other. The recommended prescription doses for monotherapy are 145 Gy for ^{125}I and 125 Gy for ^{103}Pd. The corresponding boost doses, after 40 Gy to 50 Gy external beam radiotherapy, are respectively 110 Gy and 100 Gy. HDR, using 192Ir remote afterloading stepping sources, are not as popular as LDR brachytherapy. This review covers the physical and radiobiological basis of permanent implants. Prostate cancer is one of the slowest growing carcinomas with a mean doubling time of 577±68 days for those with a low Gleason score of <6, and 495±56 days for those with a high Gleason score of ≥6. T_{pot} varies from 16 to 67 days. The α/β ratio for localized prostatic carcinoma is close to 1.5 Gy. The techniques of brachytherapy have improved and currently the transperineal route is most commonly used. Traditionally pre-planning is performed before the procedure and after the positions of the sources are verified in the CT scan, the final planning process is made. However, intraoperative computer optimized conformal planning is now feasible. Patient selection is based on the combination of clinical stage, PSA level, and biopsy Gleason score. If the gland size is between 40 g and 60 g, one should perform a pubic arch study but avoid an implant if more than one-third of the prostate gland is blocked. Androgen ablation may improve the efficacy of radiation therapy. There is little published literature regarding the use of permanent seed implantation in the management of recurrent prostate cancer in patients who had been treated previously by radiotherapy of the true pelvis.

Leczenie raka prostaty brachyterapią z zastosowaniem niskiej mocy dawki (LDR) z wykorzystaniem izotopów jodu 125 lub palladu 103

Brachyterapia w raku prostaty może być prowadzona z zastosowaniem zarówno wysokiej (HDR), jak i niskiej mocy dawki (LDR). W przypadku stosowania techniki LDR wszczepia się albo izotop jodu 125 albo palladu 103. Obserwacje kliniczne nie dostarczyły danych dotyczących ewentualnej wyższej skuteczności jednego z tych izotopów. Amerykańskie Towarzystwo Brachyterapeutyczne (American Barachytherapy Society – ABS) nie poleca żadnego z tych dwóch izotopów jako lepszego. Dawki polecane w monoterapii sięgają 145 Gy dla jodu 125 i 125 Gy dla palladu 103. Dla "boostu" po uprzednim podaniu 40-50 Gy ze źródła zewnętrznego dawki te wynoszą, odpowiednio, 110 Gy i 100 Gy. Technika brachyterapii z zastosowaniem wysokiej mocy dawki (HDR), wykorzystująca izotop irydu 192, nie jest tak popularna, jak brachyterapia z zastosowaniem niskiej mocy dawki (LDR). Niniejsza praca poglądowa przedstawia fizyczne i radiologiczne tło leżące u podstawy stosowania trwałych implantów.

Rak prostaty jest jednym z najwolniej rosnących nowowtworów. Średni czas podwojenia guza sięga 577±68 dni dla guzów z niskim wskaźnikiem Gleasona (<6) i 495±56 dni dla guzów z wysokim wskaźnikiem Gleasona (≥6). W przypadku ograniczonych raków prostaty stosunek α/β jest zbliżony do 1,5 Gy. Techniki stosowane w brachyterapii uległy znacznej poprawie i obecnie najszerzej stosowana jest droga przezotrzewnowa. Tradycyjnie, przed rozpoczęciem leczenia wykonuje się tzw. przedplanowanie. Ostateczne planowanie wykonuje się po umieszczeniu źródeł promieniowania i potwierdzeniu ich położenia w obrazie tomografii komputerowej. Niemniej w chwili obecnej możliwe jest również komputerowe planowanie śródoperacyjne. Pacjenci są dobierani zależnie od stopnia zaawansowania klinicznego, poziomu PSA i wartości wskaźnika Gleasona. Jeżeli gruczoł krokowy osiąga masę 40-60 g, należy przeprowadzić ocenę łuków kości łonowych i unikać wprowadzania implantów, jeśli zajęte jest więcej niż 1/3 gruczołu. Ablacja androgenowa może przyczynić się do poprawy skuteczności radioterapii. Istnieje nie-

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wiele pubklikacji poświęconych stosowaniu permanentnych implantów izotopowych w leczeniu nawracających raków prostaty u chorych leczonych uprzednio radioterapią na obszar miednicy.

Key words: prostate cancer, brachytherapy, implants
Słowa kluczowe: rak prostaty, brachyterapia, implanty

Brachytherapy for cancer of the prostate can be performed using either low dose rate (LDR) or high dose rate (HDR) techniques. As early as the 1920s radium needles were implanted with in some cases, because of low activity needles, the sources remaining *in situ* for 18-20 days and a typical dosage being 7000 milligram-hours. Radon seeds of typical dimensions 7.5 mm length by 1 mm diameter were an improvement on the use of radium, but still far from ideal from the viewpoints of radiation safety, implantation technique, and size. Typically, ^{125}I and ^{103}Pd seeds are now 4.5 mm x 0.8 mm [1]. The LDR temporary implants with ^{226}Ra and ^{222}Rn have now been totally replaced by the modern permanent seed implants using ^{125}I or ^{103}Pd. The use of permanently implanted gold grains, the radionuclide ^{198}Au, was essentially a transitional stage and is now seldom used.

In this modern era, high dose rate (HDR) techniques are also available, using ^{192}Ir remote afterloading stepping sources but they are not as popular as LDR brachytherapy, in part, in the USA, due to cost considerations in terms of reimbursement. However, brachytherapy, either LDR or HDR, with its rapid dose fall-off offers, when compared to external beam radiotherapy, a potential advantage for reducing dose to nomal structures, such as, bladder, rectum, small bowel and neurovascular bundle at the periphery of the prostate gland. It will continue to be an integral part of prostate cancer available treatment technology for many years to come.

^{125}Iodine & ^{103}Palladium sources

Physical considerations

^{125}I has been widely used for permanent implants in prostate cancer and has, for example, an advantage over ^{198}Au because of its long half-life of 60 days, see Table I, which makes it convenient for storage. Also, because of its low photon energy these sources require less shielding. However, because of the presence of titanium end welds, the dose distribution around ^{125}I seeds is highly anisotropic and this can pose problems by creating *cold spots* near the source ends. The users of ^{125}I implants either ignore this problem or try to minimise the extent of *cold spots* by creating a random seed distribution. ^{103}Pd sources have recently become available for use and have a shorter half-life, 17 days, than that of ^{125}I. The philosophy underlying the development of ^{103}Pd brachytherapy sources was a possible biological advantage in permanent implants as the dose is delivered at a much faster rate.

Radiobiological considerations

Dicker has compared the radiobiological and treatment planning effectiveness of ^{103}Pd and ^{125}I implants by using the linear-quadratic model with recently published data regarding: prostate tumour cell doubling times, T_{pot}, alpha and alpha/beta ratio [2]. The tumour potential doubling times (T_{pot}) were determined based on recently published proliferation constants: fraction of cells proliferating per day, Kp, i.e. $1/T_{pot}$. The initial slope of the cell radiation dose survival curve, α, the terminal slope β and the α/β ratio were taken from recent published clinical and cellular results.

The total dose delivered from each isotope was the dose used clinically, that is, 120 Gy for ^{103}Pd and 145 Gy for ^{125}I. Dale's modified linear-quadratic equation was used to estimate the biological effective dose, the cell surviving fraction, the effective treatment time, and the wasted radiation dose for different values of T_{pot}. Treatment plans for peripherally loaded implants were compared. The T_{pot} reported for organ-confined prostate carcinomas varied between 16 and 67 days. At short T_{pot} both radionuclides were less effective, but ^{103}Pd had much less dependence on T_{pot} than ^{125}I. However, at long T_{pot} both radionuclides produced similar effects. The minimum surviving fraction for exposure to ^{103}Pd decreased from 1.40×10^{-4} to 1.31×10^{-5} as the T_{pot} increased from 16 to 67 days. In contrast, for exposure to ^{125}I, the minimum surviving fraction decreased from 3.98×10^{-3} to 1.98×10^{-5} over the same range of T_{pot}.

A comparison of treatment plans revealed that ^{103}Pd plans required more needles and seeds. This was a func-

Table I. Physical characteristics of radionuclides used in prostate LDR brachytherapy [1].
Notation: *unfiltered source in equilibrium with daughter products

Radionuclide	Half-life	Photon energy (MeV)	Half-value layer (mm lead)	Exposure rate constant (Rcm^2/mCi-h)
^{222}Rn	3.83 days	0.047-2.45 (0.83 mean)	8.0	10.15*´
^{198}Au	2.7 days	0.412	2.5	2.38*
^{125}I	60.2 days	0.028 mean	0.025	1.46*
^{103}Pd	17.0 days	0.021 mean	0.008	1.48*

tion of seed strength. Both radionuclides had similar dose-volume histograms (DVH) for prostate, urethra, and rectum. The greatest benefit of ^{103}Pd was shown to be with tumours with a short T_{pot}. Although the regrowth delay would be longer with ^{125}I, the benefit was inconsequential compared with the very slow doubling times of localised prostate cancer. Treatment planning with either radionuclide revealed no significant differences. These findings may explain why clinically there seemed to be no clear difference in treatment outcome between ^{103}Pd and ^{125}I.

The American Brachytherapy Society (ABS) does not recommend one isotope in preference to the other [3]. This is despite the fact that implantation with ^{103}Pd resulted in lower radiation doses to the rectum, the choice of radionuclide was not predictive of bowel function scores in a patient survey [4]. The ^{103}Pd implants were more greatly affected by fixed amounts of oedema than were ^{125}I implants, and the slopes of the DVH curves indicate less homogeneity from ^{103}Pd implants [5].

Perspective on technique

Retropubic versus transperineal approach

In the 1970s, prostate implant was initially started *via* a retropubic approach. The 15-year outcome of the historical series of retropubic implantation from the Memorial Sloan-Kettering Cancer Center has served as the framework for the current transperineal implant approaches used in the treatment of localised prostatic cancer [6].

Between March 1970 and December 1987 a total of 1078 patients with biopsy proven *adenocarcinoma* of the prostate were treated with permanent implantation of ^{125}I seeds *via* a retropubic approach. In addition, all patients underwent bilateral pelvic lymphadenectomy before implantation. The clinical stages of disease were B1 in 234 patients (22%), B2 in 472 (44%), B3 in 145 (14%) and C in 227 (20%). Of these patients 733 (68%) had pathologically negative lymph nodes, whereas 345 (32%) had positive lymph nodes at lymph node dissection. Median follow-up was 11 years.

Multivariate analysis identified nodal involvement, high-grade disease, clinical stage B3/C and implant doses less than 140 Gy, as independent predictors of local relapse. The local recurrence-free survival rates for patients with negative nodes at five, 10 and 15 years were respectively 69%, 44% and 24%. The distant metastases-free survival rates at five, 10 and 15 years for patients with negative lymph nodes were respectively 59%, 36% and 21%. Therefore these results showed that ^{125}I implantation of the prostate via the retropubic approach was associated with a greater than expected incidence of local relapse at 15 years. Technical limitations of the retropubic technique resulting in suboptimal distribution of the ^{125}I seeds within the prostate are believed to be the explanation for the inferior local control outcome [6]. Later transperineal interstitial permanent prostate brachytherapy has become an increasingly popular treatment for early stage, favourable risk adenocarcinoma of the prostate.

High strength versus low strength seeds

Two common dosimetric philosophies for prostate implants are the use of many low activity seeds versus relatively fewer seeds of higher activity [7-9]. When fewer seeds of higher strength are used, individual seeds at the periphery of the gland rely on the higher activity of the seeds and proper placement to deliver sufficient doses to the central portion of the gland. The theoretical advantage of this technique is avoidance of high central doses, particularly to the urethra and the reduced number of needles/catheters required for the positioning of the sources for the implant. However, the theoretical disadvantage is that high doses may subsequently be delivered to the periphery: that is, to the rectum and neurovascular bundle.

Modern uniform seed loading requires more seeds (of lower activity) than peripheral loading, with generally, uniform 1 cm spacing of the seeds throughout the prostate. The advantage of this approach is that the dose delivered to any point is less dependent on the nearest seed and therefore this may be more *forgiving* than the peripheral technique. However, strict adherence to uniform spacing can lead to high doses to the urethra, particularly in large glands. In practice, a combination of philosophies is frequently used to optimise each patient's implant. ^{125}I has been called a more *forgiving* radionuclide because the higher energy, 28 keV, has a slightly greater penetration distance than the 21 keV photons of ^{103}Pd.

Intraoperative ultrasound guidance

Intraoperative real-time ultrasound guided technique is nowadays most commonly used and after completion of the implant a series of CT scans is then performed to document the source positions. Recent studies have demonstrated that magnetic resonance spectroscopic imaging (MRSI) of the prostate may effectively distinguish between regions of cancer and regions of normal prostatic epithelium [10]. This diagnostic imaging tool takes advantage of the increased choline and creatine *versus* citrate ratio found in malignant, compared with normal, prostate tissue.

Computer optimised conformal planning

Traditionally pre-planning is performed before the procedure and after the positions of the sources are verified in the CT scan, the final planning process is made. However, intraoperative computer optimised conformal planning is now feasible [11-13] and is not too time-consuming so as to delay the operation time. The average time for the intraoperative procedure is 1.74 hours [12].

Treatment decisions

Organ-confined disease, stages T1a-c & T2a-c

For clinically organ-confined prostate cancer stages T1a-c and T2a, Gleason score <7 and PSA <10 ng/ml, implant alone is adequate. Otherwise add 45 Gy external beam radiotherapy. The *rule of thumb* is that whenever the risk for extracapsular disease is high, the patient should receive pelvic external beam radiation [14].

Interstitial prostate brachytherapy for patients with a PSA level of <10 ng/ml yields at least a 87% rate of freedom from biochemical relapse at three years, which is numerically equivalent to results achieved with external beam radiotherapy or radical prostatectomy [15]. The combination of clinical stage, PSA level, and biopsy Gleason score allows for the selection of patients with the highest probability of having all of the prostate cancer encompassed by the high dose implant volume, while simultaneously respecting the normal tissue tolerance doses of the rectum and bladder. In particular, patients with non-palpable, T1c, lesions, a biopsy Gleason score of ≤6, or ideally ≤4, and a PSA level of <10 ng/ml represent the optimal implant candidates.

Prior TURP

For patients with a previous transurethral resection of the prostate (TURP) the optimum strategy is to avoid an implant if there is a large defect due to excessive urethral toxicity. If there is only a small defect, explain the risks to the patient and proceed with an implant if he consents.

Gland sizes > 60 g, or 40-60 g

If the prostate gland size is more than 60 g, consider using a hormonal blockade but avoid an implant. If the gland size is between 40 g and 60 g, perform a pubic arch study but avoid an implant if more than one-third of the prostate gland is blocked. Androgen ablation may improve the efficacy of radiation therapy [16].

A total of 296 patients who had either ^{125}I (206/296) or ^{103}Pd (90/296) transperineal prostate brachytherapy without any external beam radiation therapy, had a routine Transrectal Ultrasound TRUS guided needle biopsy with a minimum of six cores, at two years post-treatment without regard to disease status. It was shown that prostate brachytherapy yields a high negative biopsy rate of 90% at two years after treatment. Neoadjuvant hormonal therapy (NHT: leuprolide acetate and flutamide) was used in 115/296 patients for three months prior to and three months after the implant. Of the 296 patients only a total of 30 had positive prostate biopsies. Biopsies were respectively positive in 4/115 *versus* 26/181 of those who received or had not received NHT, P = 0.002 [16].

Neoadjuvant hormonal therapy & gland size reduction

When patients were separated into low risk (PSA ≤10 ng/ml, stage ≤T2a and Gleason score ≤6) and high risk groups (PSA >10 ng/ml, stage >T2a and Gleason score >6), it was seen that low risk patients did not benefit from NHT (3.8% *versus* 7.7% positive biopsy rate: P = 0.5) whereas high risk patients did benefit from NHT (3.4% *versus* 21.1%: P = 0.003). With neoadjuvant hormonal therapy, the prostate gland sizes were reduced and this facilitated brachytherapy. The mean prostate volume (PV) after NHT was 31 cm^3 (range 11.7-73.7 cm^3) [17]. The mean PV reduction was 35% (range 2-62%). Volume reduction was compared in those 51 patients who presented with a PV <40 cm^3 and those 56 with a PV ≥40. The mean reduction for the smaller glands was 29% (range 2-54%) compared with 41% (range 7-62%) for the larger glands, P <0.05.

Aspirin & anticoagulants

There should be no bleeding disorder and patients on regular aspirin or anticoagulants should stop at least seven days before implantation [18].

Prior radiotherapy of the true pelvis

There is little published literature regarding the use of permanent seed implantation in the management of primary and recurrent prostate cancer in patients who had been treated previously by radiotherapy of the true pelvis. Battermann has reported on a total of 21 patients who received an ^{125}I implant after radiotherapy for bladder cancer (2/21), anal cancer (1/21), seminoma (2/21) and prostate cancer (16/21) [19]. Two seminoma and 10 prostate cancer patients were treated after previous definitive external beam radiation therapy, while the bladder and anal cancer were initially treated with external beam radiotherapy plus a ^{192}Ir implant. Six of the prostate cancer patients were initially treated by brachytherapy alone. After previous external beam radiotherapy, no serious late toxicity was observed with permanent seed implants.

However, one of the six patients who had two ^{125}I seed implants experienced serious complications which resulted in a vesico-rectal fistula. The permanent seed implantation with ^{125}I is feasible after previous radiotherapy in the prostate area but experience is very preliminary and the efficacy of treatment remains to be proven by further series from other centres. A second implant is also possible but may result in severe complications, depending on the initial dose and the interval between the two treatments [19].

Grado has published results of 49 patients with previous external beam radiation and three with ^{125}I seed implants as primary radiotherapy [20]. Salvage brachytherapy achieved a high rate of local control and a 34% actuarial rate of biochemical disease-free survival at five years. The incidence of major complications after salvage

brachytherapy appears to be lower than that after other potentially curative salvage procedures, such as radical prostatectomy and cryoablation.

Treatment planning

In the Seattle technique for an ^{125}I implant, the treated volume is calculated as the volume encompassed by the 144 Gy isodose distribution [21]. A post-implant computed tomography scan is obtained the following day, using 5 mm slices for the images. The prostate margin is taken to be the gross tumour volume (GTV). This group is currently using 5 mm treatment margins around the GTV, as identified on pre-implant TRUS images or on CT scans. However, the poor correlation between planned and actual post-implant treatment margins calls into question any attempt to make a rational recommendation regarding optimal treatment margins.

The recent American Brachytherapy Society recommendations for permanent prostate brachytherapy [3] recommends treating patients with a high probability of organ-confined disease with brachytherapy alone. Brachytherapy candidates with a significant risk of extraprostatic extension should be treated with supplemental external beam radiotherapy.

The recommended prescription doses for monotherapy are 145 Gy for ^{125}I and 125 Gy for ^{103}Pd. The corresponding boost doses, after 40 Gy to 50 Gy external beam radiotherapy, are respectively 110 Gy and 100 Gy. The ABS also recommends that post-implant dosimetry should be performed on all patients undergoing permanent prostate brachytherapy for optimal patient care. A DVH of the prostate should be performed and the dose to 90% of the prostate gland, D(90), be reported by all centres. Additionally, the D(80) D(100), the fractional V(80), V(90), V(100), V(150), V(200), that is, the percentage of the prostate volume receiving respectively 80%, 90%, 100%, 150%, and 200% of the prescribed dose, and the rectal and urethral doses should also be reported. The detailed reports of the American Association of Physicists in Medicine (AAPM) recommendations for ^{125}I by the AAPM Task Group 43 [22] and for ^{103}Pd [23] should be consulted.

Treatment results & dose-response relationship

New York Mount Sinai School of Medicine have reported excellent treatment results with brachytherapy [24]. Implants were performed using a real-time ultrasound guided technique with ^{125}I in 186 patients and ^{103}Pd in 82 patients. The implant dose was defined as the D(90) dose delivered to 90% of the gland from the DVH generated using one-month post-implant CT based dosimetry. Overall, 89% of patients (238/268) had negative biopsies and therefore a positive biopsy could be considered to be a good predictor of biochemical failure. Patients with a positive biopsy had a five-year freedom from biochemical failure of 40% *versus* 76% for patients with a negative biopsy, P=0.0003. Univariate and multivariate analyses found that risk group, hormonal therapy and implant dose significantly affected biopsy outcome.

A total of 104 patients with low risk features (PSA ≤10 ng/ml; Gleason score ≤6; and stage T2a or lower) had a negative biopsy rate of 95% *versus* 85% when compared with 168 patients with high risk features (PSA >10 ng/ml, Gleason score ≥7 or stage ≥T2b), P=0.008.

The 174 patients receiving a high implant dose, defined as D(90) ≥140 Gy for ^{125}I or ≥100 Gy for ^{103}Pd, had a negative biopsy rate of 95% *versus* 77% compared with those 87 patients receiving a low dose, defined as D(90) <140 Gy for ^{125}I or <100 Gy for ^{103}Pd, P<0.001.

Memorial Sloan-Kettering Cancer Centre results for five-year biochemical outcome with transperineal CT planned permanent ^{125}I prostate implants [25] were as follows. A total of 38 (15%) patients developed a PSA relapse and the overall five-year PSA relapse-free survival (PRFS) rate was 71%. The five-year PRFS rates for the favourable risk group of 146 patients, the 85 cases in the intermediate risk group and the 17 in the unfavourable risk group were respectively 88%, 77%, and 38%, P<0.0001. The five-year PRFS rates among patients treated with a two month course of neoadjuvant androgen deprivation prior to transperineal implant (TPI) compared to patients treated with TPI only were respectively 100% and 77%, P=0.03. Multivariate analysis identified pretreatment PSA >10 ng/ml and Gleason score >6 as independent predictors for biochemical relapse after TPI.

Transient elevation of serum PSA after brachytherapy

It is important to emphasise that serum PSA sometimes exhibits a transient elevation. This causes a lot of anxiety for both the patient and physician. In patients judged biochemical successes at their last follow-up, serum PSA ≤1.0 ng/ml, 35.8% exhibited a temporary increase of 0.2 ng/ml or more [26]. 75% of these patients exhibited a temporary increase between 0.3 ng/ml and 3.4 ng/ml. The average time of the temporary increases was 24.8 months after implant. *Spiking* was not associated with a higher risk of clinical failure in this data set. The aetiology of PSA *bounce* is probably due to late developing radiation prostatitis [27].

Men often experience urinary symptoms during radiation treatment followed by a resolution of symptoms within a few months of treatment. Between 12 and 24 months after treatment recurrent urinary symptoms may develop, indicating delayed radiation prostatitis. This time frame corresponds to the time that PSA *bounce* is most frequently observed. A further support of this association is that the PSA *bounce* was uncommon when a PSA nadir 0.2 ng/ml or less was achieved, a level that reflects little or no existing benign epithelium that could become inflamed.

Complications

Acute complications which can occur before six months has elapsed following treatment are given in Table II and the chronic complications which can occur later than six months post-treatment are given in Table III. The complication percentage incidence figures are taken from the Teaching Course of the Seattle Prostate Institute where many physicians have been trained before starting their own brachytherapy programme.

Table II.
Acute complications which can occur <6 month post-treatment

1. Dysuria occurs in almost all cases. Can start immediately after the implant or about a week post-implant.
2. Hematuria is common for first 24 hours. Protracted hematuria occurs in 5-7%.
3. Perineal hematoma as a minor complication is common. In only fewer than 3% is this a significant complication.
4. Obstruction occurs in 5-12% but is more of a problem in the acute post-implant phase.
5. Perineal pain/orchalgia occurs in fewer than 5%.
6. Diarrhoea/rectal urgency occurs in fewer than 10%.
7. Musculoskeletal aches and pains occur in fewer than 2%.
8. Constipation occurs in more than 20%.
9. Prostatitis is very common.
10. Ejaculatory pain/hematospermia is common.
11. Acute proctitis occurs in fewer than 2%.

Table III.
Chronic complications which can occur at >6 months post-treatment

1. Chronic cystitis occurs in 3-7%.
2. Incontinence occurs in fewer than 1%.
3. Rectal ulceration occurs in fewer than 1%.
4. Obstruction/urinary retention occurs in fewer than 3%.
5. Urethral necrosis occurs in fewer than 1%.
6. Complete erectile dysfunction occurs in 20-25% and partial erectile dysfunction in 20-25%.

With a minimum median follow-up time of 24 months, 81% to 85% two-year actuarial and three-year crude potency rates have been reported concomitantly with two-year actuarial rates of 12% for ≥ grade 2 rectal complications and 10% for ≥ grade 3 urethral complications [15]. Differential loading of the implant away from the geometrical centre and not accepting as implant candidates those patients with large prostate glands, defined as ≥ 60 cm^3, or a history of transurethral resection of the prostate, may reduce urethral toxicity.

In a patient survey, a trend toward increased rectal symptoms was noted for older patients, and a non-significant improvement in rectal survey scores was noted with elapsed time from implantation [4]. Only 19.2% (40/208) of the treatment group reported a worsening of bowel function following implantation. To date, no severe changes in late bowel function have been noted following prostate brachytherapy. Although the survey scores indicate bowel function is worse after an implant, the minor changes are not significant enough to cause any real problem to most individuals. Less than 20% of patients reported that their bowel function was worse following prostate brachytherapy.

In another report, serious rectal injury was again shown to be very rare [28]. Only seven prostatourethral-rectal fistula (PRF) developed in 754 patients between nine and 12 months after treatment [29]. One PRF occurred in a patient who was treated with brachytherapy alone. PRFs occurred in 2/69 patients who were treated with combination brachytherapy and external beam therapy and in 4/43 patients who underwent salvage brachytherapy. All six patients who developed fistulas in the context of combination brachytherapy and external beam therapy or salvage brachytherapy had biopsies of an anterior rectal lesion overlying the prostate noted on physical examination during routine follow-up.

Gastrointestinal endoscopic evaluation alone was not associated with any PRF. 5/7 PRFs resolved with either surgical repair, 3/5, or conservative management, 2/5. Because all patients who developed PRF did so subsequent to prior rectal biopsies, the authors currently are strongly discouraging such practices if the rectal lesion is consistent with radiation-induced effects.

Development of erectile dysfunction following radical therapy is a particular concern, and occurs in perhaps one-third of patients treated by radiotherapy and 30-70% of patients treated by radical prostatectomy [30]. Although it is assumed that the erectile dysfunction relates to damage to the nerves subserving erection, this view has been questioned recently and in at least a proportion of patients the cause appears to be vascular. Despite the likely cause of their erectile dysfunction, all patients presenting with erectile dysfunction after treatment for prostate cancer should undergo assessment by history and examination to ensure that there are no other correctable risk factors. Patients can then be considered for a number of treatment options, and currently sildenafil (Viagra, Pfizer) is usually used as first-line therapy assuming there are no contraindications, such as severe ischaemic heart disease or nitrate therapy.

Sildenafil improves erectile function in 70% of patients with erectile dysfunction post-radiotherapy, but appears less effective in men after radical prostate surgery when there is a response rate of 40-50%. Other treatment options include self-injection or intra-urethral administration of alprostadil, and some patients are happy to use a vacuum erection device. Finally, if all else fails, patients may be suitable for penile implant surgery.

Advantages & limitations of LDR compared with HDR

For prostate brachytherapy LDR is more convenient than HDR. It requires *six* hours in hospital *versus* 24 hours for HDR. LDR is also simpler for a department to start up a prostate brachytherapy programme if they do not have an HDR unit or interstitial HDR experience.

LDR requires a long initial learning curve. Permanent seeds must be placed exactly as intended, or *cold* and *hot spots* will occur. If a cluster of seeds is placed near the rectum this *hot spot* can cause a fistula and a *cold spot* cannot easily be corrected. With HDR, catheters can be removed or adjusted under CT guidance and variable HDR catheter spacing is corrected by geometric optimisation. An HDR implant can be aborted if dosimetry is not ideal, however, the only way to abort an LDR implant is to perform a prostatectomy. Figure 1 shows an ultrasound scan performed for estimation of the prostate gland volume, which can be measured by the physicist or technologist easily. Figure 2 shows a HDR implant with relatively good distribution of catheters. Further adjustment by loading the source for different time periods can achieve good dosimetry. On the other hand, HDR also has its own problems: such as guide movement between the CT scan and treatment and also between the treatment sessions [31]. Also, since the treatment can be completed in a shorter time for HDR, the effect of edema is less than for LDR.

Volume studies are used in advance with LDR seed implants because it is difficult and expensive to undertake real-time dosimetry during the seed implant and the number of seeds to be ordered can be determined by the volume study. However, it is difficult to position the pro-

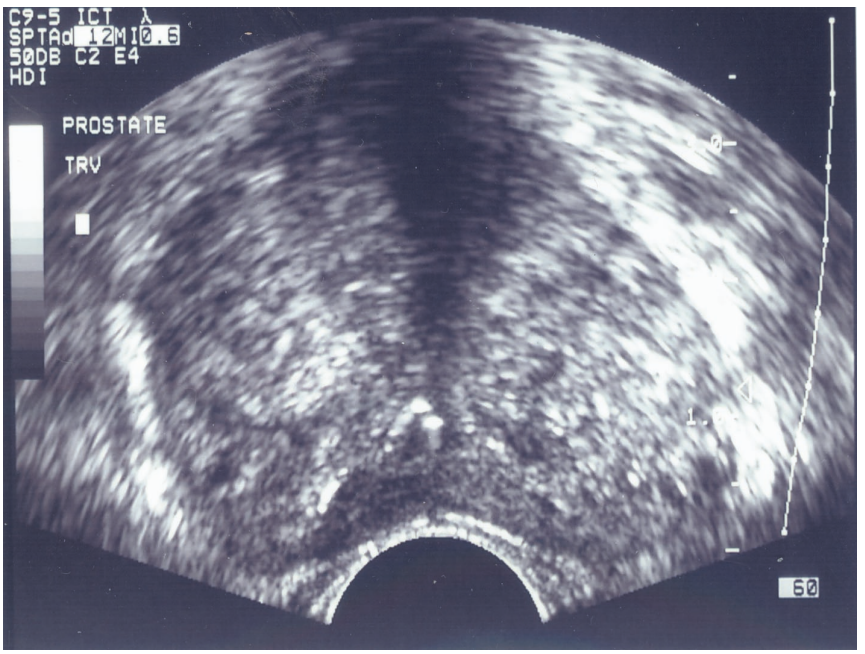

Figure 1. Shows an ultrasound scan performed for estimation of the prostate gland volume, which can be measured by the physicist or technologist easily

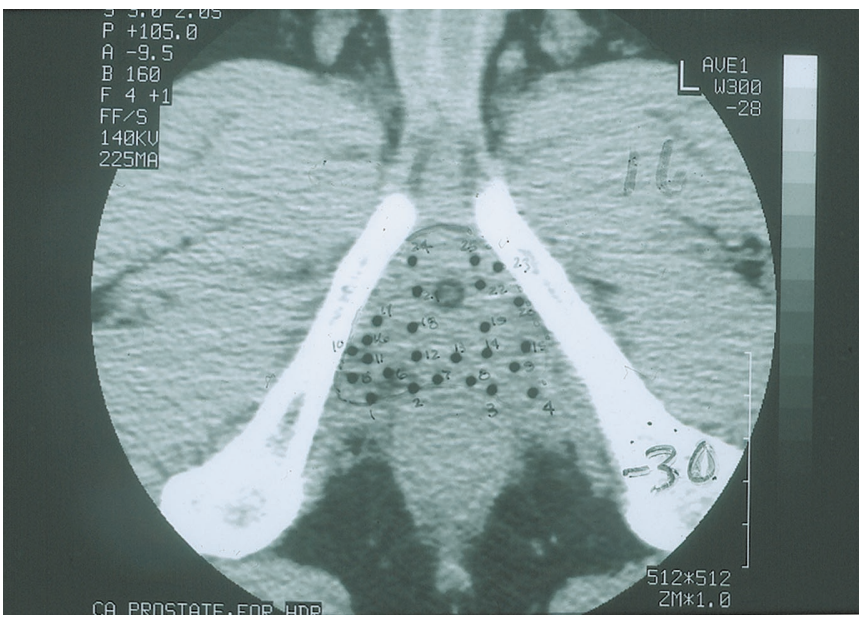

Figure 2. Shows a HDR implant with relatively good distribution of catheters. Further adjustment by loading the source for different time periods can achieve good dosimetry

state in exactly the same way during the actual seed implant procedure.

Seeds can migrate to the lung or spine, or can be urinated out of the patient. Patients may be concerned about this possibility. Loss of seeds may cause a *cold spot* in the prostate and the prostatic base may not be well covered by the seeds. During an HDR implant procedure, cystoscopy is performed to ensure that the catheters are pushed in as far as possible. HDR dwell times can be adjusted to allow a ballooning of the isodose at base to give the full prescribed dose.

Permanent seeds cost US$ 5,000 or more per patient, versus a HDR cost of US$ 30,000 per year to maintain. However, a HDR machine can be used for other purposes such as bronchus, oesophagus, etc.

Permanent implants take into consideration cell inactivation by protracted irradiation, repair of sublethal radiation damage during the radiation delivery, tumour cell repopulation, and the exponentially decreasing radiation dose rate. Prostate cancer is one of the slowest growing carcinomas with a mean doubling time of 577±68 days for those with a low Gleason score of <6, and 495±56 days for those with a high Gleason score of ≥6 [32]. T_{pot} varied from 16 to 67 days [33]. The α/β ratio for localised prostatic carcinoma is close to 1.5 Gy [34]. ^{125}I requires six months to give 87% of its dose at an average dose rate of 3.7 cGy/hour. HDR gives 550 cGy in five minutes. Finally, it is noted that Duchesne's editorial in the *Int J Radiat Oncol Biol Phys* favours HDR afterloading brachytherapy over permanent seed implants [35].

Comparison of brachytherapy with other treatment modalities

A study from the Joint Centre for Radiation Therapy at Harvard [36] on 194 men treated with radical prostatectomy for clinically localised prostate cancer between 1995-1996 examined if the anterior prostatic base needs to be treated by brachytherapy. Of 269 foci of prostate cancer found in 39 low risk prostate cancer patients (PSA <10 ng/ml, biopsy Gleason score ≤6, and 1992 AJCC clinical stage T1c, 2a), only a single focus, representing 0.37% of this patient series, was noted in the anterior base. Conversely, 20/355 (5.6%) and 18/251 (7.2%) tumour foci were noted in the anterior base in 43 patients with intermediate risk and in 24 patients with high-risk disease, respectively. Therefore for intermediate and high risk disease, external beam radiotherapy should be able to provide a better target volume coverage.

This is also reflected in another publication [37]. This retrospective cohort study consisted of a total of 1872 men treated between January 1989 and October 1997 with a radical prostatectomy (888/1872) or implant with or without neoadjuvant androgen deprivation therapy (218/1872) at the Hospital of the University of Pennsylvania, or external beam radiotherapy (766/1872) at the Joint Centre for Radiation Therapy, Boston. The relative risks (RR) of PSA failure in low risk patients (stage T1c, T2a, PSA ≤10 ng/ml and Gleason score ≤6) treated using radiotherapy, implant plus androgen deprivation therapy, or implant therapy alone were respectively RR=1.1 (95% CI of 0.5-2.7), RR=0.5 (95% CI of 0.1-1.9), and RR=1.1 (95% CI of 0.3-3.6), compared with those patients treated with RP.

The relative risks of PSA failure in the intermediate risk patients (stage T2b, Gleason score = 7, PSA >10 and ≤20 ng/ml) and high risk patients (stage T2c, PSA >20 ng/ml, Gleason score ≥8) treated with implant compared with radical prostatectomy were respectively RR=3.1 (95% CI of 1.5-6.1) and RR=3.0 (95% CI of 1.8-5.0).

Therefore low risk patients had estimates of five-year PSA outcome after treatment with radical prostatectomy, external beam radiotherapy, or implant with or without neoadjuvant androgen deprivation that were not statistically different, whereas intermediate risk and high risk patients treated with radical prostatectomy or radiotherapy had a better outcome then those treated by implant.

Although prospective randomised trials are needed to verify these findings, the implication appears to be that brachytherapy alone is inferior in intermediate risk and high risk disease since coverage of the anterior base and extracapsular spread is inadequate. Implant brachytherapy therefore has to be combined with external beam radiotherapy.

Seed implants are associated with greater morbidity than external beam radiotherapy. For example, Zelefsky has published the results of a study comparing the 3D conformal radiotherapy (3DCRT) with transperineal prostate ^{125}I seed implant (TPI) [38]. A total of 11 patients (8%) in the 3DCRT group and 12 patients (8%) in the TPI group developed a biochemical relapse. The five-year PSA relapse-free survival rates for the 3DCRT and the TPI groups were respectively 88% and 82%, P =.09. Protracted grade 2 urinary symptoms were more prevalent among patients treated with TPI compared with those in the 3DCRT group. Grade 2 urinary toxicity, which manifested after the implant and persisted for more than one year after this procedure, was observed in 45 patients (31%) in the TPI group. In these 45 patients, the median duration of grade 2 urinary symptoms was 23 months, range 12-70 months.

On the other hand, acute grade 2 urinary symptoms resolved within 4-6 weeks after completion of 3DCRT, and the five-year actuarial rate of late grade 2 urinary toxicity for the 3DCRT group was only 8%. The five-year actuarial rate of developing a urethral stricture, classified as a grade 3 urinary toxicity, for the 3DCRT and TPI groups were respectively 2% and 12%, P<.0002. Of 45 patients who developed grade 2 or higher urinary toxicity after TPI, the likelihood of a resolution or significant improvement of these symptoms at 36 months from onset was 59%. The five-year likelihood of grade 2 late rectal toxicity for the 3DCRT and TPI patients was similar: 6% and 11% respectively, P=.97.

No patient in either group developed any grade 3 or higher late rectal toxicity. The five-year likelihood of post-

treatment erectile dysfunction among patients who were initially potent before therapy was 43% for the 3DCRT group and 53% for the TPI group, P=.52. In conclusion, both 3DCRT and TPI are associated with an excellent PSA outcome for patients with early stage prostate cancer. Urinary toxicities are more prevalent for the TPI group but subsequently resolve or improve in most patients.

Conclusions

This review has raised various issues. For low risk patients, both brachytherapy and 3DCRT produce similar treatment results in different series. One could argue that the outcome for these patients is in any event good with such a short follow-up period no matter what treatment modality is chosen. Brachytherapy has more morbidity and is more invasive, labour-intensive, and expensive than 3DCRT.

For intermediate-risk and high-risk patients, target coverage with brachytherapy may not be as good as with 3DCRT since the anterior base and any extracapsular spread are not adequately covered. However, theoretically, brachytherapy has a higher tissue dose surrounding the radioactive sources than does 3DCRT, provided that it can be shown that the dose-response is important for prostate cancer. We are waiting for the result of the RTOG 3DCRT dose escalation studies.

In the future, a randomised trial of the most optimal dose of 3DCRT as a sole modality *versus* brachytherapy combined with 3DCRT for intermediate risk and high-risk patients may be able to resolve the issue for these risk groups.

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Paper received and accepted: 28 August 2002