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Technology Review

LOW DOSE RATE BRACHYTHERAPY FOR TREATMENT OF PROSTATE CANCER

HEALTH TECHNOLOGY ASSESSMENT UNIT
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH
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Author:
Ms Sin Lian Thye
Nursing Officer
Health Technology Assessment Unit
Medical Development Division
Ministry of Health Malaysia

Reviewed by
Datin Dr Rugayah Bakri
Head
Health Technology Assessment Unit
Medical Development Division
Ministry of Health Malaysia

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1. INTRODUCTION

Prostate cancer is one of the most common cancers in men. It tends to affect older men, as risk rises with age. It is not a single disease entity but may be indicated from an incidental biopsy finding to presentation with metastatic prostate cancer, which may or may not cause any symptoms or shorten life. Symptoms include urinary outflow obstruction and bone pain when metastases occurs （NICE 2005）.

Prognosis with prostate cancer is variable. It depends on the grade of the tumour and stage of the diagnosed cancer. The American Cancer Society estimated that 98% of men survive at least 5 years, 84% survive at least 10 years, and 56% survive at least 15 years. Comparative figures from the Cancer Research UK estimated the survival to be 80%, 61%, and 49% at 5, 10 and 15 years respectively. Treatment options depend on the stage of the cancer (NICE 2005).

Current treatment for localised prostate cancer include watchful waiting, radiotherapy, and radical prostatectomy. Metastatic prostate cancer is usually treated with hormone therapy (NICE 2005).

1. OBJECTIVE

To determine the safety and effectiveness of low dose rate brachytherapy in the treatment for localized prostate cancer.

3. METHODOLOGY

An electronic search on PUBMED, HTA databases, Guidelines databases, old MEDLINE, Cochrane library, DARE via OVID search engine, was carry out from October 2003 till Jan 2006, with the following keyword *brachytherapy, prostatic, prostate, cancer, neoplasm， permanent seed implant,* used either singly or in combination

4. TEHCNICAL FEATURES

Brachytherapy is the targeted delivery of radiation through implants directly to the prostate gland. This is through either permanent implants (low dose brachytherapy) of iodine-125 (I-125) or palladium-103 (Pd-103) seeds, or temporary implantation (high dose rate brachytherapy) with iridium-192 wires through hallow needles. Modern prostate brachytherapy is performed under trans-urethral ultrasound guidance and may be used as monotherapy, or as a boost to another primary therapy such as external beam radiotherapy (EBRT).It can also be used as a primary therapy with another treatment such as EBRT which act as a boost, with or without adjuvant or neoadjuvant deprivation therapy

5. RESULTS

5.1 Safety:

5.1.1 Urinary tract complication

A case series review found that when compared to surgery, brachytherapy has the advantage of having a lower percentage of immediate postoperative complications, lower incontinence rate, and a higher number of patients preserving erectile function (Prada et al, 2005, *level 8*).

Most studies found that manifestations of acute urinary morbidity, especially frequency and retention, are relatively common but acceptable events after I-125 prostate brachytherapy.

A study found that 111 patients (85.4%) developed some degree of urinary symptoms such as frequency, retention, dysuria, incontinence, or hematuria. Urinary frequency (73.1%) and retention (66.9%) was the most common, and showed no significant differences between the monotherapy group and combined therapy group. Six patients (4.6%) required catheterization for urinary obstruction; the median time onset was 1.5 days (range, 1-192 days) (Ohashi et al, 2005, *level 8*).

Another multicenter clinical trial found that the rate of urinary incontinence was increased to 14% at 6 months but had decreased to 1% at the 12-month follow-up. More than 60% of men reported decreased urinary function at 12 months compared with baseline. The rate of incontinence by 1 year after prostate brachytherapy is low, but many patients continued to have obstructive symptoms at 1 year (Feigenberg et al, 2005, *level 5*). It was also found that acute urinary retention occurred in 20 (9.3%) patients, with a further 26 (12.1%) patients using clean intermittent self-catheterisation to reduce voiding frequency associated with chronic retention (Henderson , Laing & Langley, 2004, *level 9*).

A matched pair analysis to compare biochemical control of patients treated with EBRT plus low dose rate (LDR) to patients treated with EBRT alone found that both treatments were associated with comparable incidences of late genitourinary (GU) side effects of 18-19% (Singh et al, 2005, *level 6)*. A prospective comparison study found that both therapies either with permanent 125I-seed brachytherapy or radical prostatectomy showed typical acute and late morbidity; the most bothersome late symptoms were urinary incontinence for patients after radical prostatectomy and fecal soiling after brachytherapy (Borchers et al, 2004, *level 9*).

A randomized controlled trial (RCT) found that dysuria is common after brachytherapy but is typically mild. The use of prophylactic alpha-blockers gave significantly lower maximum dysuria scores but did not affect the time to the resolution of dysuria (Merrick et al, 2005, *level 4).*

5.1.2 Rectal complication

Colonoscopy with or without fulguration for rectal bleeding was performed in 37 of 158 patients (97 in the brachytherapy group and 61 in the combination therapy group) at a median of 17 months (range, 4-45 months), including 15 patients (15.5%) after brachytherapy and 22 patients (36%) after combination therapy. It was found that combination therapy resulted in fecal diversion in 6.6% of patients, urinary diversion in 3.2% of patients, and clean intermittent self-catheterization for recurrent stricture after multiple Transurethral resection of the prostate (TURP) in 4.9% of patients. None however occurred after brachytherapy. Overall, 20.6% of patients underwent TURP or colonoscopy after brachytherapy, whereas 44.2% underwent those or more extensive unplanned procedures after combination therapy (Sarosdy, 2004, *level 9*). However, late rectal toxicity was decreased by 15% in patients treated with EBRT plus LDR brachytherapy (Singh et al, 2005, *level 6*).

5.1.3 Sexual problem

A study found that age is an indicator of sexual function after brachytherapy, with younger patients experiencing less sexual dysfunction than older patients. Other aspects of sexual function are like pain on orgasm and hematospermia are also significant side effects of brachytherapy and must be considered in the treatment decision for low-risk prostate cancer (Finney et al, 2005, *level 8*). A multicentre clinical trial found that the percentage of men who reported the ability to have an erection decreased from 73% at baseline (65% unassisted, 8% assisted) to 57% at 1 year (36% unassisted, 21% assisted). At 1 year after prostate brachytherapy, 80% of men reported decreased sexual functioning according to SAQ scores. Although 78% of 1-year respondents stated that they can achieve an erection with or without assistance, almost 50% reported a decrease in sexual function (Feigenberg et al, 2005, *level 5*). Another study on the effect of 103-palladium implantation for localized prostate cancer found that 24 (31%) had mild/moderate erectile dysfunction (ED) and 27 (35%) had severe ED. Overall, 52 men (67%, including those with severe ED at baseline) remained in the same ED category at 30 months after therapy as before, 12 (15%) deteriorated by one category, 14 (18%) by two or more, and no patient had improved. Of the 27 patients fully potent (score 26-30) at baseline, 37% remained so after 30 months, 19% developed mild and the remaining 44% moderate/severe ED (Ponholzer et al, 2005, *level 9*). Sexual function was impaired significantly in patients who were potent before radical prostatectomy (RP) with unilateral nerve-sparing (RP plus NS), whereas after brachytherapy men reported only a minor change in sexual performance at 1 year (Borchers et al, 2004, *level 9*).

5.1.4 Seed migration

A study of 238 patients who underwent implantation with either iodine-125 (I-125) or palladium-103 (Pd-103) found that seed embolism to the lungs was a rare event when patients undergo implantation using the real-time method (Stone & Stock, 2005, *level 8*). Another study found that there was no evidence of seed embolization observed with the use of stranded I-125 seeds as used for prostate brachytherapy (Al-Qaisieh et al, 2004, *level 8*).

However, a review found that migrated seeds in the lungs were reported to reach mainly the pulmonary artery and caused embolization without clinical symptoms (Fukada et al,

2005. *level 8*). Another study also showed that among 12,179 implanted seeds, 44 were found to have migrated (0.36%). Most of the migrating seeds (32/44; 73%), were found in the lungs. Overall, one or several seed migrations were observed in 35 patients (21% of the total number of patients). In the majority of cases (77%), only one seed migrated. It was also found that there was a significant relationship between the number of migrating seeds and the number of implanted ones. More specifically, a significant relationship could be demonstrated between the number of seeds implanted at the periphery of the prostate and the number of seeds migrating to the lungs (Chauveinc et al, 2004, *level 9*). It was also found that one or more seeds were identified on the chest X-rays of 55 (55%) of 100 patients. The mean number of intrathoracic seeds in patients with migration was 2.2 (range, 1-10), and the proportion of seeds that migrated to the thorax was 0.98%. The rate of extraprostatic seeds planned was 43.9%, and post-implant CT identified 37.9% in such a location (Eshleman et al, 2004, *level 8*). A case report found that seed embolization to the intracardiac region was rarely reported. The true rate may be higher, but has not been adequately documented owing to the limitation of diagnostic quality of chest radiographs to detect seed migration to the intracardiac region. The seed migration detector, on the other hand, demonstrated its efficacy in the detection of seed migration, particularly in the detection of a seed located in the intracardiac region (Blair, Porter & Chen, 2004, *level 9*).

5.1.5 Radiation exposure

An evaluation study found that the exposure risks related to brachytherapy with I-125 to operators and public were limited. However, alternative operators should be considered to minimize exposure. Patient-related measurements should verify the dose rate around the patient to evaluate the need for shielding and to define appropriate radiation protection recommendations (Anglesio et al, 2005, *level 9*)

A study found that personnel radiation exposure (RE) per case, fluoroscopy time (FT), operation room time (OT), and anesthesia time (AT) were decreased as the case number increased. It was shown that the whole body badge dose per case decreased from a mean of 0.15+/-0.01 mSv (15+/-1 mrem) in 1998 to 0.074+/-0.011 mSv (7+/-1 mrem) in 2000. Average FT per case decreased from a mean of 17:27 min (range, 10:40-28:23) in 1998 to 12:08 min (range, 6:40-31:00) in 2000. Resident participation was associated with increased FT. Mean whole body and ring badge doses for the treating radiation oncologist were 0.0076 mSv/min (0.76 mrem/min) and 0.05 mSv/min (5.26 mrem/min) of FT, respectively. It was concluded that FT was the predominant factor that related to RE during trans-perineal interstitial permanent prostate brachytherapy (TIPPB). Treating radiation oncologists were exposed to less than 20 mSv per 100 cases, significantly less than other fluoroscopically guided procedures. Nonetheless, appropriate radiation exposure precautions during TIPPB should continue to be adhered (Schwartz et al, 2003, *level 9*).

5.2 Effectiveness

5.2.1 Survival rate

a) LDR brachytherapy (monotherapy)

An evaluation study found that the actuarial biochemical relapse-free survival at 4 years was 86.8%. There was no significant difference in biochemical relapse-free survival noted between patients treated with I-125 and Pd-103 (Potters et al, 2003, *level 8*).

A case series review found that the 5 year survival rate was 96%, with a 97% disease-free survival and a 99% biochemical failure-free survival (Prada et al, 2005, *level 8*). Another study of 272 patients with prostate cancer who were treated with ultrasound-guided transperineal implantation incorporating I-125 or Pd-103 found that the 5-year biochemical disease-free survival rates for those in the favorable group (clinical stage T1c or T2, prostate-specific antigen (PSA) level <10, Gleason score <7) were 92% for the I-125 group and 92% for the patients treated with Pd-103. The 5-year disease-free survival rates for those in the intermediate and poor prognostic groups, which were combined, was 72% and 74%, for I-125 and Pd-103 respectively (Peschel et al, 2004, *level 9*). It was also found in a clinical trial of 63 men treated with low dose rate prostate brachytherapy that the 5-year estimate of biochemical relapse-free survival was 85%. It was also reported the most men who had pre-treatment PSA level of 6.68 ng/ml had non-palpable disease, gleason score was less than 7 in 84% of men, and nine men developed evidence of biochemical relapse at a median of 19 months (McMullen et al, 2004, *level 8*)

Another evaluation study demonstrated that the actuarial 7-year biochemical progression-free survival rate was 96.1% and 98.3% for a PSA with cut-off-point of 0.4 ng/mL or less and for the American Society for Therapeutic Radiology and Oncology consensus definition, respectively. The median post-treatment PSA level for the biochemically disease-free group was less than 0.1 ng/mL. In the multivariate analysis, it was found that only the pretreatment PSA level predicted the biochemical outcome. It was shown that hormone-naive patients 62 years of age or younger have a high probability of 7-year biochemical progression-free survival after permanent interstitial brachytherapy with or without supplemental external beam radiotherapy (Merrick et al, 2004, *level 8*)

A third evaluation study involving of 668 consecutive patients who underwent brachytherapy using either Pd-103or I-125 for clinical Stage T1b-T3aNxM0 (2002 - American Joint Committee on Cancer) adenocarcinoma of the prostate gland, without undergoing seminal vesicle biopsy or pathologic lymph node staging. The study showed that the actuarial 8-year biochemical progression-free survival rate was 98.2%, 98.4%, and 88.2% for low-, intermediate-, and high-risk patients, respectively. Although the role of supplemental EBRT could not be adequately evaluated in the high-risk patients, it did not improve the biochemical outcome in the low- and intermediate-risk patients. However, androgen deprivation therapy (ADT) resulted in a statistically significant improvement in progression-free survival for the high-risk patients (Merrick et al, 2005, *level 9*)

b) Combination with other therapy

The addition of external radiation, with or without luteinizing hormone-releasing hormone therapy, improved the biochemical control rates in intermediate and high-risk brachytherapy groups (Sharkey et al, 2005, *level 9*). A matched pair analysis to compare biochemical control of patients treated with EBRT plus low dose rate (LDR) brachytherapy to patients treated with EBRT alone found that the 5-year biochemical failure free survival (BFFS) was 86% for patients treated with EBRT plus LDR and 72% for patients treated with EBRT. These results supported EBRT followed by brachytherapy boost as a safe and effective method for dose escalation in the treatment of prostate cancer (Singh et al, 2005, *level 6*). However, a large cohort study comparing 2991 patients who underwent brachytherapy either using monotherapy or combined with ERBT, external beam radiotherapy at less than 72Gy, or radical prostatectomy found that there was no difference between biochemical replase-free survival at 5 or 7 years post-treatment (Kupelian et al, 2004, *level 5*)

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A review showed that an addition of androgen deprivation and external beam radiotherapy (EBRT) to LDR brachytherapy may increase urinary, bowel and sexual complication (Henderson, Laing & Langley, 2004, *level 9*). However, another study found that the overall relapse-free survival for all patients was 75%; the initial PSA, Gleason score and risk group were significant factors predicting the outcome. Increasing clinical experience was associated with a better outcome but neo-adjuvant hormone therapy had no effect (Joseph et al, 2004, *level 9)*

c. Comparison with other treatment modalities

A review showed that brachytherapy with Pd-103 exclusively and radical retropubic prostatectomy (RRPP) were found to provide equivalent control (<0.4 ng/mL for prostatectomy and <3ng/ml successive rise in PSA as defined by the American Society for Therapeutic Radiology and Oncology [ASTRO]) in the low-risk groups. While in intermediate and high-risk groups, it was also found that brachytherapy patients had better control rates than RRRP (Sharkey et al, 2005, *level 9*).

Another study found that the overall survival median of 58 months in patients with T1-T2 cancer who underwent brachytherapy was found to be 93%, radical prostatectomy 96% and EBRT 96%. Physical function scores in 92 patients treated with brachytherapy and 327 by radical prostatectomy showed no significant changes in either group from baseline to 24 months (Downs et al, 2003).

5.2.2 PSA level

A study found that the median post-treatment PSA for biochemical disease free group was < 0.1 ng/ml (Merrick et al, 2005, *level 9*).

Henderson et al (2004, *level 9*) reported that the median PSA at 1, 2 and 3 years was 0.5, 0.4 and 0.1 ng/ml, respectively. Ninety-five per cent of patients experienced temporary deterioration in their urinary symptoms, which persisted at clinically significant levels (International Prostate symptom score (IPSS) increase >3 points) for 9 months after

implant. The severity of urinary symptoms (IPSS) after implant was most closely related to IPSS at presentation.

An evaluation study found that there was a significant difference in time to reach a PSA threshold of ≤ 1.0 ng/ml between I-125 and Pd-103. There were 10.2 weeks for Pd-103 and 22 weeks for I-125 respectively. However, the percentage of delivered dose relative to the time to reach the threshold were the same between I-125 and Pd-103 (Potters et al, 2003, *level 8*)

A study found that a high biochemical and local control in men with T1-T2 prostate cancer treated with I brachytherapy. The delivered radiation dose and risk category are important predictors of success. Patients who received a dose of at least 140 Gy have a 90% chance of biochemical freedom from failure and a 95.2% likelihood of local control (Stone, Stock & Unger, 2005, *level 8*)

5.2.3 Health related quality of life

A review showed that low dose rate brachytherapy (BXT) offered a high probability of maintaining continence, potency and normal rectal function though both storage and voiding urinary symptoms have been reported. Thus, quality of life outcome following brachytherapy compared favourably with other radical treatment options for the management of early prostate cancer (Henderson, Laing & Langley, 2004, *level 9*)

Another study suggested that prostate brachytherapy is associated with minimal long-term urinary morbidity. The sub-group of patients who presented with marked urinary symptoms before implantation had improvement in symptoms and quality of life (QOL) after implantation. These data substantiate the favorable long-term QOL outcomes associated with modern brachytherapy techniques (Stone & Stock, 2003, *level 8*)

6. CONCLUSION

There is sufficient evidence to indicate that brachytherapy is safe with regards to acceptable occurrence of complications such as urinary tract complications, rectal complications and sexual problem and seed migration. There is also good evidence of effectiveness for brachytherapy in term of improving the post-treatment PSA threshold particularly for low risk prostate cancer and good survival rate. It was also found that the combination with other modalities like EBRT or neo-adjuvant hormone therapy had no significant difference in improving survival rate

REFENRCES

Al-Qaisieh B, Carey B, Ash D, Bottomley D. (2004) .The use of linked seeds eliminates lung embolization following permanent seed implantation for prostate cancer. *Int J Radiat Oncol Biol Phys.* Jun 1;59(2):397-9.

Anglesio S, Calamia E, Fiandra C, Giglioli FR, Ragona R, Ricardi U, Ropolo R. (2005) Prostate brachytherapy with iodine-125 seeds: radiation protection issues. *Tumori.* Jul-Aug; 91(4):335-8.

Blair HF, Porter A, Chen QS. (2004). In vivo detection of an 125I seed located in the intracardiac region after Prostate permanent brachytherapy. *Int J Radiat Oncol Biol Phys.* Mar 1;58(3):888-91.

Borchers H, Kirschner-Hermanns R, Brehmer B, Tietze L, Reineke T, Pinkawa M, Eble MJ, Jakse G. (2004) Permanent 125I-seed brachytherapy or radical prostatectomy: a prospective comparison considering oncological and quality of life results. *BJU Int*. Oct;94(6):805-11.

Chauveinc L, Osseili A, Flam T, Thiounn N, Rosenwald JC, Savignoni A, Cosset JM (2004 ） [Iodin 125 seed migration after prostate brachytherapy: a study of 170 patients]，*Cancer Radiother.* Aug; 8(4):211-6.

Eshleman JS, Davis BJ, Pisansky TM, Wilson TM, Haddock MG, King BF, Darby CH, Lajoie WN, Oberg AL. (2004). Radioactive seed migration to the chest after transperineal interstitial prostate brachytherapy: extraprostatic seed placement correlates with migration. *Int J Radiat Oncol Biol Phys.* Jun 1;59(2):419-25.

Finney G, Haynes AM, Cross P, Brenner P, Boyn A, Stricker P. (2005) Cross-sectional analysis of sexual function after prostate brachytherapy. *Urology.* 2005 Aug; 66(2):377-81.

Fukada J, Yorozu A, Toya K, Ohashi T, Sugawara A, Dokiya T. (2005) [Pulmonary embolization of permanently implanted radioactive iodine-125 seeds for carcinoma of the prostate] *Nippon Igaku Hoshasen Gakkai Zasshi*. Apr; 65(2):121-3.

Henderson A, Laing RW, Langley SE. (2004). Quality of life following treatment for early prostate cancer: does low dose rate (LDR) brachytherapy offer a better outcome? A review. *Eur Urol*. Feb;45(2):134-41.

Joseph J, Al-Qaisieh B, Ash D, Bottomley D, Carey B. (2004). Prostate-specific antigen relapse-free survival in patients with localized prostate cancer treated by brachytherapy. *BJU Int.* Dec; 94(9):1235-8.

Kupelian PA, Potters L,Khuntia D, Ciezki JP, Reddy CA, Reuther AM et al (2004). Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy > or = 72Gy , permanent seed implantation or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. I*nt J of Radiation Oncology, Biology, Physics* , 58(1), 25-33

McMullen KP, deGuzman AF, McCullough DL, Lee WR. (2004) Cancer control after low-dose-rate prostate brachytherapy performed by a multidisciplinary team with no previous prostate brachytherapy experience. *Urology*. Jun;63(6):1128-31

Merrick GS, Butler WM, Wallner KE, Allen Z, Galbreath RW, Lief JH. (2005) Brachytherapy-related dysuria. *BJU Int.* Mar; 95(4):597-602.

Merrick GS, Butler WM, Wallner KE, Galbreath RW, Adamovich E. (2005). Monotherapeutic brachytherapy for clinically organ-confined prostate cancer. *W V Med J*., Jul-Aug; 101(4):168-71.

Merrick GS, Butler WM, Wallner KE, Galbreath RW, Adamovich E. (2004). Permanent interstitial brachytherapy in younger patients with clinically organ-confined prostate cancer. *Urology*. 2004 Oct;64(4):754-9

Merrick GS, Butler WM, Wallner KE, Galbreath RW, Lief JH, Allen Z, Adamovich E. (2005). Impact of supplemental external beam radiotherapy and/or androgen deprivation therapy on biochemical outcome after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys.* Jan 1;61(1):32-43.

Morton G, Baikadi M, Sandler H. (2005), Health-related quality of life in men receiving prostate brachytherapy on RTOG98-05. *Int J Radiat Oncol Biol Phys*. Jul 15; 62(4):956-64.

National Institute for Clinical Excellence (NICE) (2005) Low dose rate brachytherapy for localized prostate cancer IP Guidance Number: IPG132

Ohashi T, Yorozu A, Toya K, Saito S, Momma T. (2005) Acute urinary morbidity following I-125 prostate brachytherapy. *Int J Clin Oncol.* Aug; 10(4):262-8.

Ponholzer A, Oismuller R, Somay C, Buchler F, Maier U, Hawliczek R, Rauchenwald M, Madersbacher S.(2005) The effect on erectile function of 103palladium implantation for localized prostate cancer. *BJU Int.* Apr; 95(6):847-50.

Potters L, Huang D, Fearn P, Kattan MW. (2003). The effect of isotope selection on the prostate-specific antigen response in patients treated with permanent prostate .brachytherapy.*Brachytherapy*; 2(1):26-31.

Prada PJ, Hevia M, Juan G, Abascal JM, de la Rua A, Abascal R, Fernandez J, Rodriguez R. (2005) [I125 low dose rate brachytherapy in localized prostate cancer. Preliminaryresults after 5 years] *Arch Esp Urol.* Apr;58(3):213-26

Sarosdy MF. (2004) Urinary and rectal complications of contemporary permanent transperineal Brachytherapy for prostate carcinoma with or without external beam radiation therapy. *Cancer*. Aug 15; 101(4):754-60.

Schwartz DJ, Davis BJ, Vetter RJ, Pisansky TM, Herman MG, Wilson TM, LaJoie WN,Oberg AL. (2003). Radiation exposure to operating room personnel during transperineal interstitial permanent prostate brachytherapy. *Brachytherapy*. 2(2):98-102.

Sharkey J, Cantor A, Solc Z, Huff W, Chovnick SD, Behar RJ, Perez R, Otheguy J, Rabinowitz R. (2005) 103Pd brachytherapy versus radical prostatectomy in patients with clinically localized prostate cancer: a 12-year experience from a single group practice. *Brachytherapy*.;4(1):34-44

Singh AM, Gagnon G, Collins B, Niroomand-Rad A, McRae D, Zhang Y, Regan J, Lynch J, Dritschilo A. (2005) Combined external beam radiotherapy and Pd-103 brachytherapy boost improves biochemical failure free survival in patients with clinically localized prostate cancer: results of a matched pair analysis. *Prostate*. Jan 1; 62(1):54-60.

Stone NN, Stock RG, Unger P. (2005). Intermediate term biochemical-free progression and local control following 125iodine brachytherapy for prostate cancer. *J Urol.* Mar; 173(3):803-7.

Stone NN, Stock RG. (2003) Prospective assessment of patient-reported long-term urinary morbidity and associated quality of life changes after 125I prostate brachytherapy. *Brachytherapy*.;2(1):32-9

Stone NN, Stock RG. (2005) Reduction of pulmonary migration of permanent interstitial sources in patients undergoing prostate brachytherapy. *Urology*. Jul; 66(1):119-23.