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High and intermediate risk prostate cancer treated with three-dimensional computed tomography-guided brachytherapy: 2–8-year follow-up

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Abstract

Purpose: To report post-brachytherapy results in high and intermediate risk patients of prostatic adenocarcinoma.

Methods and materials: From June 1994 to June 2000, 356 consecutive high and intermediate risk patients were treated with three-dimensional computed tomography-guided stereotactic pararectal brachytherapy. The age was 42–90 years (median, 68 years), the initial prostate volume was 14–180 cm³ (median, 59 cm³), and initial PSA was 1.7–143 ng/ml (median, 10.5 ng/ml). Three hundred forty-eight patients were available for follow-up for 2–8 years (median, 4.5 years). Two hundred eighty patients had one or more high risk factors (PSA > 20 ng/ml, Gleason > 7, Stage T2b, T3a, or T3b). Sixty-eight patients had only one intermediate risk factor (PSA 10–20 ng/ml or Gleason = 7). Patients with both intermediate risks were considered high risk. The high-risk group was further stratified into subgroups with similar risk profile. A dose of 144 Gy with ¹²⁵I or 120 Gy with ¹⁰³Pd was achieved in 90–100% of the target. Thirty (30) patients (9%) had prior transurethral resection and 229 (64%) were treated with 3 months neoadjuvant androgen ablation.

Results: Biochemical disease-free survival was 92% of 280 high risk patients and 96% of 68 intermediate risk patients. Seven patients (2%) required catheterization during the first year for urinary retention, nine patients (3%) required TUR 1–3 years post-implant, three patients (1%) developed grade 1 or 2 incontinence after a second TUR, and four patients (1%) developed grade 3 rectal complications.

Conclusion: This method produces a high level of biochemical control 2–8 years (median 4.5 years). Morbidity is acceptable regardless of risk profile or initial prostate volume.

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Keywords: Prostate cancer; Brachytherapy; Stereotactic; Computed tomography-guidance; Pararectal

1. Introduction

We report 356 consecutive high and intermediate risk patients treated from June 1994 to June 2000 with three-dimensional CT-guided pararectal brachytherapy alone without or with short-term neoadjuvant androgen ablation. There are limited publications of high and intermediate risk prostate cancer treated with permanent radioactive seed implantation with or without short-term adjuvant androgen ablation [11,15,25]. High risk patients are those prostate cancer patients with one or more of the following risk factors: PSA > 20 ng/ml, Gleason > 7, stage T2b,T3a, or T3b. The stage T2b and T3a were stratified together because of the clinical overlapping of these two stages. The

intermediate group was those patients with only one risk factor (PSA 10–20 ng/ml or Gleason = 7). Patients with both intermediate risk factors are considered high risk patients. Patients with high risk prostate cancer are not ideal for radical prostatectomy and have often been referred for external beam radiation therapy (EBRT) with or without short- or long-term neoadjuvant androgen ablation [1,2,7,19,22,26]. Also, EBRT alone or additional pelvic irradiation has been reported [18]. Combine methods of treatment EBRT and booster with transperineal brachytherapy with or without hormone therapy has been performed [5,20]. Under the combined method of treatment, the dosage is 41 Gy with EBRT with field size to cover the prostate, seminal vesicles and pelvic lymph nodes and 80 Gy with ¹⁰³Pd, the isotope of choice for these high-risk patients, is prescribed [5,20]. Whether 41 Gy of EBRT will eradicate possible tumor cells

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outside the prostate treated with brachytherapy is subject to debate. Also, brachytherapy with temporary implant with high dose rate (HDR) of iridium-192 and external beam radiation therapy 2 weeks before or after implant is used [23].

2. Methods and materials

A total of 356 consecutive high and intermediate risk patients were treated from June 1994 to June 2000 with 3-D CT-guided posterior pararectal brachytherapy using ^{125}I or ^{103}Pd seeds. The characteristics of these patients are shown in Table 1. For staging, all patients underwent a digital rectal examination, transrectal ultra-sound-guided biopsy of the prostate as well as a CT of the abdomen and pelvis, and bone scan. Two hundred and forty-eight (248) patients (70%) out of 356 had 3-D CT-guided pararectal seminal vesicle (SV) biopsy prior to implant. Thirty-nine (39) patients (16%) of 248 had invasion in one or both seminal vesicles (T3b). Patients with Gleason scores of 8 or greater, and/or PSA levels of at least 20 ng/ml had a negative ProstaScint scan (Cytogen, Princeton, NJ) or laparoscopic pelvic lymphadenectomy. Routine lymphadenectomy is not performed prior to brachytherapy. No lymphadenectomy was performed in patient's who had a ProstaScint scan to compare the results.

Table 1
Patient characteristics of high and intermediate risk patients treated with 3-D CT brachytherapy June 1994–June 2000 ($n = 356$)

Characteristics	n	
Age: range: 42–90, median: 69, mean: 68 years		
Prostate volume < 50 cm ³	120	34
Prostate volume 50–59 cm ³	63	18
Prostate volume 60–79 cm ³	105	29
Prostate volume 80–100 cm ³	41	12
Prostate volume > 100 cm ³	27	7
Prostate volume: range: 14–180, median: 59, mean: 62 cm ³		
PSA < 10 ng/ml	160	45
PSA 10–20 ng/ml	133	37
PSA > 20 ng/ml	63	18
PSA > 10 ng/ml	196	55
PSA: range: 1.7–143, median: 10.5, mean: 15 ng/ml		
Gleason ≤ 6	193	54
Gleason = 7	129	37
Gleason > 8	34	9
Prior TOR ^a	34	10
HTxb ^b	229	64
Iodine125	124	35
Palladium ¹⁰³	232	65
Stage ^c		
T1a,T1b,T1c,T2a	97	27
T2b,T3a	219	62
T3b (biopsy-proven SV invasion)	39	11

^a Trans-urethral resection (1–3 years prior to implant).

^b Neoadjuvant androgen ablation (3 months prior to implant).

^c 1997 American Joint Committee on Cancer (AJCC) tumor staging.

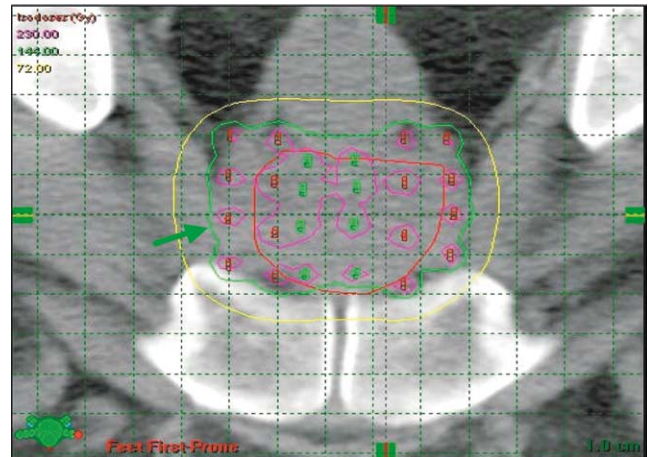


Fig. 1. Pre-implant computed-tomography planning. The prostate is outlined in red. The green isodose line represents 100 of the prescribed dose of 144 Gy of ^{125}I seeds. The green dots in the center represent lesser activity seeds (0.32 mCi/seed) to reduce dosage to the anterior rectal wall and urethra. The red dots represent the higher activity seeds at 0.38 mCi/seed in the periphery of the prostate.

All patients were treated at the Uro-Radiology Prostate Institute of Virginia. The senior author developed the posterior pararectal method of brachytherapy using 3-D stereotactic system and CT-guidance in 1994 [10]. In brief, CT is used for pre-treatment planning, the execution of the implant procedure in conjunction with the three-dimensional stereotactic system, and for post-implant dosimetry. 3-D CT-guided planning and dosimetry was performed with Varian BrachyVision (Fig. 1). Precise placement of the afterloading needles was achieved with the 3-D stereotactic system. The rectum was constricted with tannic acid prior to implant. The 3-D stereotactic template was adjusted as needed to avoid needle penetration through rectum or obstruction of insertion of the needles by the coccyx or sacrum. The correct position of the needles was verified with CT prior to implant. The stereotactic template (8 × 10 cm²) can cover a large target and has perforations that are 2.5 mm apart in either direction for fine needle correction if needed. The procedure was performed under epidural or spinal anesthesia. The patient was able to return home the same day. A Mick applicator was used for loose seeds. An attachment to the 3-D stereotactic template was used for instant loading and implant of seeds in rapid strand and/or loose seeds with spacers. Patients with seminal vesicle invasion (T3b) were treated with brachytherapy including the entire seminal vesicle. Our experience has previously been reported of brachytherapy of patients with seminal vesicle invasion, TURP defects, and large volume [10–14]. The treatment target includes 5–10 mm outside the capsule except the portion on the prostate adjacent to the anterior rectal wall (see Fig. 1). CT was performed during the implant to verify the seed coverage in each transverse row (Fig. 2). Post-implant CT dosimetry was performed immediately and 2 weeks after the implant if possible

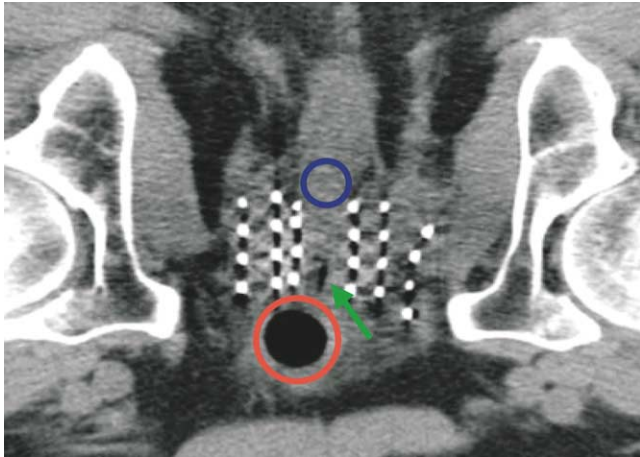


Fig. 2. Computed-tomography during implant. The empty urinary bladder with the balloon of the catheter in place is outlined in the red circle, the rectum is outlined in the blue circle, and the urethra is referenced by the green arrow. There is excellent coverage of the target with seeds and sparing the urethra.

(Figs. 3 and 4). Dosage to the prostate and seminal vesicles, if involved, under this method was 120 Gy with ^{103}Pd or 144 Gy with ^{125}I . CT dosimetric analysis including dose volume histogram has been performed for the last 4 years. The first 4 years of using our CT-guided computed dosimetry technique was performed with orthogonal radiographs.

Disease-free survival was based on a modified American Society for Therapeutic Radiology and Oncology definition as not two consecutive rises in PSA, with a minimal rise of 1.5 ng/ml above the nadir. The Kaplan–Meier product-limit method was used to calculate the disease-free survival rate [3,8]. The log-rank test was used to compare the survival curves.

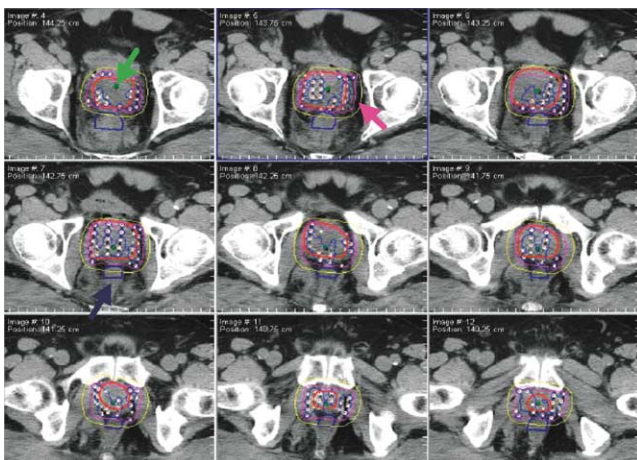


Fig. 3. Computed-tomography dosimetry immediately after implant of high risk patient with prostate cancer. Nine consecutive 5-mm tomographic slices were taken through the prostate. The prostate is outlined in red, the urethra is referenced by the green arrow, and the purple isodose line represents 100% of the prescribed dose of 144 Gy with ^{125}I seeds. Note the constricted rectum outlined in blue and referenced by the arrow.

3. Results

Follow-up, including PSA data, was determined by office visits every 3 months during the first year, every 6 months during the second year, and yearly thereafter. In addition, data were collected from direct telephone contact and patient responses to written annual questionnaires.

Follow-up PSA results were available 2–8 years (median, 4.5 years) in 348 patients treated with CT-guided posterior pararectal brachytherapy.

The patients were stratified into groups of high and intermediate risk. The high risk group, 280 patients, were those with one or more high risk factors (PSA > 20 ng/ml, Gleason > 7, stage T2b, T3a or biopsy-proven seminal vesicle invasion, T3b). The stage of T2b and T3a were stratified together because of the clinical overlapping of these two stages. The intermediate risk group, 68 patients, were those with only one intermediate risk factor (PSA 10–20 or Gleason = 7). Patients with both intermediate risks were considered high risk.

In addition, the high risk group was stratified into three groups according to the number of risk factors. These three high risk groups were also subdivided into subgroups with similar risk profile (Table 2).

As can be seen from Table 2, in high risk patients with PSA > 20 ng/ml (groups 3b, 2d, 2g) the biochemical results were less favorable. Patients with seminal vesicle invasion and PSA < 20 (groups 3a, 3c, 2a, 2b, 1a) had excellent biochemical results.

In 2–8 years (median, 4.5 years), the disease-free biochemical results of high risk groups were achieved in 55 patients (90%) out of 61 with three risk factors, 124 patients (91%) out of 136 with two risk factors, and 250 patients (92%) out of 280 with one risk factor. In intermediate risk patients, disease-free results were achieved in 65 patients (96%) out of 68. Overall, disease-

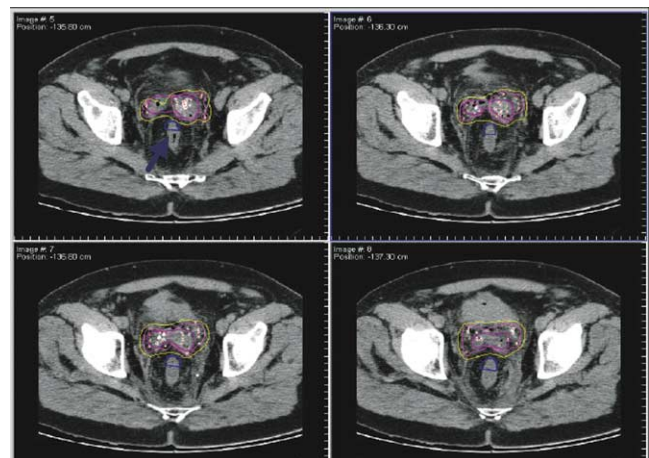


Fig. 4. Computed-tomography dosimetry immediately after implant of high risk prostate cancer patient with seminal vesicle invasion. The seminal vesicles are outlined in purple and the pink isodose line represents 100% dose of 144 Gy with ^{125}I seeds. Note the constricted rectum outlined in blue.

Table 2

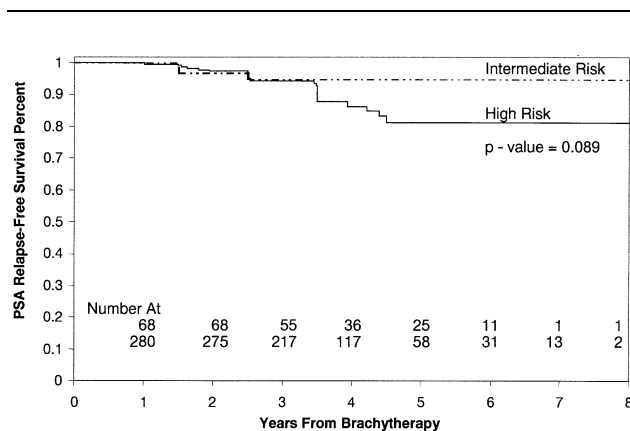
Risk profile and biochemical results of high risk patients treated with 3-D CT-guided brachytherapy [8 years follow-up (median 4.5 years) $n = 348$]

Groups	Risk factor(s)	# Patients	bNED ^a (%)
High risk			
3 Risks			
3a	T3b, GL > 7, PSA 10–20 ng/ml	5	5 (100)
3b	T3b, GL > 7, PSA > 20 ng/ml	14	11 (79)
3c	T2b,3a, GL > 7, PSA 10–20 ng/ml	22	21 (96)
3d	T2b,3a, GL > 7, PSA > 20 ng/ml	20	18 (90)
	Subtotal	61	55 (90)
2 Risks			
2a	T3b, GL > 7, PSA < 10 ng/ml	12	11 (92)
2b	T3b, PSA 10–20 ng/ml, GL < 7	3	3 (100)
2c	GL > 7, PSA 10–20 ng/ml, T1a,b,c,T2a	14	13 (93)
2d	GL > 7, PSA > 20 ng/ml, T1a,b,c,T2a	2	1 (50)
2e	T2b,3a, GL > 7, PSA < 10	53	50 (94)
2f	T2b3a, PSA 10–20 ng/ml, GL < 7	37	33 (89)
2g	T2b,3a, PSA > 20 ng/ml, GL < 7	15	13 (87)
	Subtotal	136	124 (91)
1 Risk			
1a	T3b, PSA < 10 ng/ml, GL < 7	5	5 (100)
1b	T2b3a, PSA < 10 ng/ml, GL < 7	66	63 (94)
1c	PSA > 20 ng/ml, GL < 7, T1a,b,c,T2a	11	10 (90)
1d	GL > 7, PSA < 10 ng/ml, T1a,b,c,T2a	1	1 (100)
	Subtotal	83	79 (95)
	High risk total	280	250 (92)
Intermediate risk			
1a	GL = 7, PSA < 10 ng/ml, T1,a,b,c,T2a	19	19 (100)
1b	PSA 10–20 ng/ml, GL < 7, T1a,b,c,T2a	49	46 (94)
	Intermediate risk total	68	65 (96)
	High and intermediate total	348	323 (93)

^a Biochemical disease-free survival.

free result was achieved in 323 high and intermediate patients (93%) out of 348.

The 5-year disease-free survival rate for the high and intermediate groups was 81% and 95%, respectively (Table 3). There was borderline significance between the high and intermediate risk groups ($P = 0.089$). The 5-year disease-

Table 3
Risk Groups

free survival rate for patients with or without pre-implant hormone therapy were both 84%, and there was no significant difference found between these two groups ($P = 0.893$). However, our most unfavorable patients were treated with neoadjuvant androgen ablation.

Twenty percent (20%) of patients treated with brachytherapy experienced grade I GU complications with frequency of urination, dysuria and nocturia lasting 2–4 weeks and were treated with alpha-blockers and pyridium and/or steroids. Seven (7) patients had grade II GU complications (2%) requiring catheterization during the first year for urinary retention. Nine (9) patients had grade III GU complications (3%) requiring TUR 1–3 years after implant. Three (3) patients (1%) developed grade 1 or 2 incontinence after a second TUR. Four (4) patients (1%) had grade III GI complications. The average percent reduction of prostate gland volume in 123 patients from 6 months to 1 year was 56%.

4. Discussion

We performed 3-D CT-guided stereotactic posterior pararectal brachytherapy alone with radioactive ¹⁰³Pd or ¹²⁵I seeds in 280 high-risk and 68 intermediate risk prostate

cancer patients without EBRT and with or without short-term neoadjuvant androgen ablation. We found that this method produces a high level of clinical and biochemical control 2–8 years (median, 4.5 years) with 93% of patient disease free survival. In our method, the treatment target with 3-D CT-guided brachytherapy of all patients includes 5–10 mm outside the capsule except the portion of the prostate adjacent to anterior rectal wall. There were 39 patients with 3-D CT-guided pararectal biopsy proven seminal vesicle invasion, and the entire seminal vesicle was included in the treatment target. Extracapsular extension in localized prostate cancer has been reported in 35% of patients after radical prostatectomy by Sohayda et al. [24]. Epstein et al. reported 33.4% established capsular penetration [6]. The progression-free risk at 4 years for positive margins was 74%, and 54.9% for 10 years after radical prostatectomy [6]. We achieved 90–100% coverage of the target with the prescribed dose (144 Gy for ^{125}I and 120 Gy for ^{103}Pd). We perform CT evaluation of the coverage of the target prior to termination of the CT-guided pararectal brachytherapy. CT for the coverage of the target with seeds is performed during the implant (see Fig. 2) and CT dosimetric analysis the same day and 2 weeks post-implant. The American Brachytherapy Society recommends post-implant CT dosimetry analysis for all patients treated with permanent radioactive implant for prostate cancer [17]. The CT based dosimetric analysis was performed after the termination of the transperineal ultrasound-guided brachytherapy. The significance of relapse-free survival with coverage $D_{90} > 90\%$ versus $D_{90} < 90\%$ has been reported by Potters et al. [21].

There are limited publications of transperineal brachytherapy alone of prostate for high and intermediate risk patients. Young et al. reported 5-year disease-free survival rate for 33 intermediate and 28 unfavorable patients at 63% and 24%, respectively, for 10-year follow-up (median, 7 years) [25]. Brachytherapy alone with or without short-term hormone therapy in 201 high risk patients was reported by Lee et al. [15]. The 5-year disease-free survival was 79% with combined method (brachytherapy and short-term neoadjuvant androgen ablation) and 54% without neoadjuvant androgen ablation [15].

Advanced EBRT and high-dose (81 Gy and 86.4 Gy) intensity modulated therapy has recently been reported by Zelefsky et al. [27]. The 3-year actuarial PSA disease-free survival was 81% for 175 high risk and 86% for 322 intermediate risk with 6–60 months follow-up time (median, 24 months) [27]. However, 425 patients (55%) out of 772 patients received neoadjuvant androgen deprivation 3 months prior to implants and 2 months during the radiotherapy [27]. Longer data are needed for long-term biochemical and clinical results. The use of androgen ablation did not produce significant impact on the biochemical outcome [27]. In 309 high risk patients treated with EBRT of the prostate and additional pelvic irradiation did not benefit from the additional pelvic irradiation [18].

Pan et al. reported the 5-year disease-free survival was 45.7% for those without additional pelvic irradiation and 45.3% with additional pelvic irradiation [18].

Dattoli et al. reported biochemical disease-free survival for combination EBRT and brachytherapy for 102 high risk patient with 79% disease-free survival for 4-year follow-up [5]. When an implant provides inadequate dose coverage to the target volume, inferior tumor control rates have resulted [21].

The 5-year disease-free survival rate for intermediate and high risk patients was reported at 60% and 15%, respectively, by D'Amico et al. for men receiving EBRT alone [4]. Radical prostatectomy alone has shown 5-year disease-free survival for intermediate and high risk patients at 42–60% and 27–30%, respectively, by Moul et al. [16].

Biochemical disease-free survival was increased with long-term hormone therapy up to 3 years. Bolla et al. reported EBRT and long-term hormone therapy for 36 months starting the day of EBRT for 415 high risk patients [2]. The 5-year estimated biochemical results for high risk patients were 78% in the combined group and 48% in the group with EBRT alone [2]. Horwitz et al. reported improvement in outcomes with EBRT and adjuvant long-term over short-term hormone therapy [7]. The use of hormone therapy with EBRT or brachytherapy is still unclear as other studies do not show advantage with hormone therapy. A large number of patients with similar risk profile (see Table 2) should be compared with 5–10 years follow-up. The quality of life and disease-free long-term survival should be a priority for managing patients with prostate cancer. Innovative techniques should be adapted.

King et al. report increased biochemical disease free survival in high risk patients with dose escalation with EBRT, including 3D-CRT, intensity modulated radiotherapy (IMRT), and permanent transperineal brachytherapy. [9]. We report a higher disease free survival rate with low morbidity in 280 high-risk patients treated with 3-D CT-guided posterior brachytherapy with permanent implant of ^{125}I seeds or ^{103}Pd seeds. We have included 39 patients with biopsy-proven seminal vesicle invasion in this high risk group. Coverage of the entire seminal vesicle is not reported with the transperineal brachytherapy approach. However, under the posterior lateral approach with the three-dimensional system and CT guidance, coverage of the entire seminal vesicles is possible. The fat tissue adjacent to the seminal vesicles is sufficient to spare the bowel. Furthermore, the fat pad between the prostate and the anterior rectal wall is much less than the fat surrounding the seminal vesicles. Insertion of needles through the stereotactic template avoids obstruction of the coccyx and bowel penetration. Also, placement of seeds in strand in the seminal vesicles minimizes the risk of local or distant seed migration.

5. Conclusion

The three-dimensional CT-guided pararectal permanent implant method produces a high level of biochemical control 2–8 years (median 4.5 years) of high risk patients. Morbidity is acceptable regardless of risk profile or initial prostate volume.

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