

**JOE ARRINGTON CANCER CENTER  
PROSTATE CANCER BRACHYTHERAPY TRIAL  
JACC 004**

**PHASE II TRIAL OF TRANSRECTAL ULTRASOUND GUIDED TEMPORARY HIGH  
DOSE RATE (HDR) IMPLANTATION OF THE PROSTATE FOR DEFINITIVE  
MANAGEMENT OF LOCALIZED PROSTATE CANCER**

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**SCHEMA**

<b>S</b>	<b><u>PSA</u></b>	<b>R</b>	
	1. $\leq 4.0$		
<b>T</b>	2. 4 to 10	<b>E</b>	
	3. 10 to 20		
<b>R</b>		<b>G</b>	Patients will receive HDR
<b>A</b>	<b><u>Grade</u></b>	<b>I</b>	Temporary Implantation of the Prostate
	Gleason Score 2 to 10		45 Gy in 6 HDR fractions with 2 implants
<b>T</b>		<b>S</b>	
<b>I</b>	<b><u>T-Stage</u></b>	<b>T</b>	
	1. T1b, T1c		
<b>F</b>	2. T2a, T2b	<b>E</b>	
<b>Y</b>		<b>R</b>	

**Eligibility**

- Histologically confirmed, localized adenocarcinoma of the prostate
- Clinical Stage T1b – T2b
- $PSA \leq 20$
- No clinically or pathologically involved lymph nodes
- No distant metastases
- Karnofsky Score  $\geq 70$
- No prior chemotherapy, pelvic radiation therapy, or hormonal therapy
- Signed study-specific consent form prior to presentation

Required Sample Size: 100

JACC HDR Prostate 03-01 Eligibility Check

1. Is there histologically confirmed locally confined adenocarcinoma of the prostate? (Y)
2. What is the T-Stage? (T1b – T2b)
3. What is the N-Stage? (N-0)
4. What is the PSA ( $\leq 20$ )
5. What is the KPS? ( $\geq 70$ )
6. Has the patient had prior chemotherapy, pelvic radiation therapy, or hormonal therapy? (N)
7. Has the patient had prior radical surgery for prostate carcinoma? (N)
8. Are there any major medical or psychiatric illnesses that would prevent completion of treatment or interfere with follow-up? (N)
9. Has the patient had previous or concurrent cancer other than non-basal/squamous cell skin cancer? (Y/N)

If Yes, has the patient been disease free for at least 5 years (Y)

**The following questions will be asked at Registration:**

1. Has the eligibility checklist been completed? (Y)
2. Is the patient eligible (Y)
3. Date the study-specific Consent Form was signed?
4. Patient's Name:
5. Verifying Physician:
6. Patient ID Number:
7. T-Stage (T1b – T2b):
8. Gleason Score (2-10):
9. PSA ( $\leq 20$ ):
10. Birth date:
11. Race:
12. Social Security Number:
13. Zip Code:
14. Implant Date:
15. Completed by:
16. Date:

## **1.0 INTRODUCTION**

Adenocarcinoma of the prostate will affect over 184,500 U.S. males this year and approximately 39,200 males will die of the disease [1]. Prostate Specific Antigen (PSA) is a very useful tumor marker in early detection of this malignancy [2]. It also is a very reliable marker for control after definitive therapy with either surgery or radiation therapy [3, 4]. Unfortunately, the results with regard to permanent control or cure of localized prostate cancer after either definitive external beam radiation therapy or radical prostatectomy are not nearly as good as investigators once thought because post-treatment PSA levels have demonstrated recurrence or persistent disease at a much higher level than previously understood [5,6].

The use of brachytherapy or implantation of radioactive sources into the prostate for adenocarcinoma was first reported in 1911 by Pasteau [7]. He utilized radium as his brachytherapy source. This fell into disfavor as, over the next several years, many surgical developments occurred, as well as the understanding of the hormonal dependence of prostate carcinoma. Subsequently, megavoltage external beam radiation therapy began to be used in the management of localized prostatic carcinoma after it was 1<sup>st</sup> developed in 1956 [8]. Yet, some investigators still favored the use of implant, as it potentially could deliver a very high dose to the tumor and limit the doses to the surrounding normal tissue (i.e. bowel and bladder). I-125 as a permanent implantation source was utilized extensively at Memorial Sloan Kettering where patients were implanted at laparotomy with a free hand technique. Initially, the results looked favorable, but subsequently were found to be less favorable in regard to local control [9]. The main problem was that “ideal” geometry or an ideal implant with well-spaced radioactive seeds was very hard to achieve. Therefore, isodose “hot” and “cold” spots occurred. Presumably it was in the relative cold or under dosed areas that the prostate cancer was not controlled. Other investigators using similar techniques reported similar results [10, 11]. Therefore, open free hand implantation of the prostate fell out of favor.

The development of Transrectal Ultrasound (TRUS) of the prostate with the ability to map the prostate in several planes, as well as the associated development of perineal implantation of the prostate has resurrected the concept of permanent implantation. With these techniques, the prostate can be implanted in a more dosimetrically reliable, as well as less invasive way. Blasko et al, have reported extensively on long-term results with this technique [12, 13, 14]. In this series, 197 patients with localized disease (T1a-T2c) have been treated with a 5 year PSA disease free survival of 93% [14]. These results compare favorably to external beam radiation therapy and surgery [5, 6].

A number of problems and questions persist with the use of permanent seed implants. With the permanent seed I-125 or Pd-103 procedures, the patient is permanently implanted with ~ 70 to 100 seeds. Therefore, the patient goes home radioactive, with radiation exposure to family members and others. Secondly, with the permanent seed techniques, seeds can migrate in the prostate after implant, resulting in dose inhomogeneity. In addition, seeds can leak out of the prostate into the bladder, or into the bloodstream. Seeds have been known to embolize to the lung and heart [15]. The permanent seed technique calls for a pre-plan, which is not always matched by the real implant; again, dose inhomogeneity is a common problem. Pubic arch interference and large prostate size ( $\geq 60 \text{ cm}^3$ ) create such technical difficulties with permanent seed implants that these patients are excluded. The ability to conform the radiation dose to the urethra is very limited with permanent seed technique. Therefore, patients who have undergone previous transurethral resection

of the prostate (TURP) are generally excluded from permanent seed implants because of the high risk of urinary incontinence. Lastly, the permanent seed technique does not permit treatment of peri-prostatic tissue or the seminal vesicles.

Regarding the last problem, review of prostate pathology specimens from the Mayo Clinic and Cleveland Clinic, led investigators to conclude, “treatment of the prostate with a 3-5 mm margin would encompass 96-99% of specimens with extraprostatic extension [16, 17].” Due to concerns of lack of radiation coverage of peri-prostatic extension and dose inhomogeneity, investigators postulated that adding external beam radiation to permanent seed implant might improve outcome. In addition, Blasko’s results noted above were achieved in a very favorable prostate cancer patient subset, i.e. patients with T1 and T2 tumors with Gleason Scores < 7, PSA < 10. Therefore, for all these reasons, external beam radiation therapy has been increasingly added to permanent seed implant. However, there is no conclusive evidence that the addition of peri-prostatic external beam radiation therapy (EBRT) improves outcome. Blasko et al, reviewed the results of 634 prostate cancer patients who underwent Implant +/- peri-prostatic EBRT treated in Seattle [18]. There was no significant difference in PSA survival. Patients were subdivided into low risk, intermediate risk, and high risk, based on T-Stage, Gleason Score, and PSA. No survival difference was found in any patient subgroup. Notably, there was increased rectal morbidity in the patients undergoing Implant + EBRT (8%) vs. Implant alone (2%). Blasko concluded, “Although the addition of EBRT to brachytherapy is conceptually appealing for patients with higher risk prostate carcinoma, we were unable to demonstrate a benefit.” Grado et al, also have reported no difference in PSA survival in a series of 490 patients treated with Implant, Implant + EBRT, or Implant + Hormonal Blockade [19].

Previous randomized trials conducted by the RTOG have demonstrated that there is no survival benefit to giving extended field external beam radiation to the prostate, either peri-aortic, or pelvic lymph nodes, vs. the prostate and peri-prostatic tissues alone [20, 21].

Starting about 15 years ago, investigators began using High Dose Rate (HDR) temporary implant technique in the management of prostate cancer. HDR offers many significant technical advantages over I-125, and other permanent seed (e.g. Pd-103) techniques. HDR is a temporary seed placement technique, while in the permanent seed I-125 or Pd-103 procedures; the patient is permanently implanted with ~ 100 seeds. Therefore, the patient is radioactive, and goes home radioactive, with radiation exposure to medical staff, family members, and other persons whom come in contact with the patient. With HDR, the patient goes home without active radiation sources, and does not expose any individuals to radiation. With the permanent seed techniques, seeds can migrate in the prostate during and after implantation, resulting in dose inhomogeneity. In addition, seeds can leak out of the prostate into the bladder, or into the bloodstream. Seeds have been reported to embolize to the lung, heart, and brain. HDR allows much more flexibility in tailoring conformal dose distributions to the bladder, rectum, and urethra. This has resulted in a much lower incidence of urethritis, urinary retention, and urethral stricture with HDR, than with permanent seeds. HDR can technically treat extraprostatic extension better than the permanent seed techniques. Pubic arch interference and large prostate size ( $\geq 60 \text{ cm}^3$ ) create insurmountable technical difficulties with permanent seed implants such that these patients are excluded as candidates for permanent seed therapy. The HDR temporary implant can be performed with high-quality; dosimetry in these patients with no essentially no volume limitations. Finally, the Permanent Seed

technique uses a pre-plan, which is infrequently matched by the final implant, resulting in dose inhomogeneity. HDR relies on real time treatment planning techniques, which delivers a homogenous treatment plan to the prostate and peri-prostatic tissues.

The published results with HDR Implant compare very favorably to radical prostatectomy, external beam radiation therapy and permanent seed implant, both in regard to PSA disease free survival and complications [22-28]. Eulau et al, reported a 78% 10 year PSA disease free survival [22]. These results were achieved in patients with Stage T1 thru T3 disease, with no Gleason Score, PSA, prostate volume, or pubic arch exclusions. Therefore, HDR has resulted in outcomes at least as good as permanent seed implants in a more complicated and unselected, patient population. Most of the published HDR data has utilized one HDR Implant in combination with peri-prostatic external beam radiation therapy.

In summary, pathologic data has shown that when extraprostatic extension occurs, it is within 3-5 mm of the capsule in 96-99% of the cases [16,17]. This cannot be adequately encompassed technically, with permanent seed implant alone. However, it can be adequately covered with a HDR implant alone. Since the addition of external beam radiation therapy to implant has been shown by Blasko et al, to increase rectal complications without improving survival, it is logical to treat localized prostate cancer with HDR implant alone. A number of centers in the United States, Europe, and Japan, are investigating the role of HDR implant alone. We have performed HDR alone in a series of 65 patients. With a median follow-up of 3 years, the PSA disease free survival was 92% with no long-term complications [29]. This phase II trial will analyze PSA measured disease free survival, survival, and complications with a uniform protocol of HDR implant alone. Results will be compared to historical controls of combined external beam radiation therapy and HDR implantation.

## **2.0 OBJECTIVES**

The aim of this study is to evaluate the effectiveness of TRUS HDR temporary implant of the prostate for organ confined adenocarcinoma of the prostate compared to historical data of radical prostatectomy or external beam radiation therapy. Our goal is to evaluate PSA survival, complications, and 3-dimensional dosimetry with HDR implant alone. Endpoints of the study will be:

- a. Freedom from PSA failure
- b. Overall survival
- c. Clinical relapse, local and/or distant
- d. Acute and chronic, GU and GI morbidity

### **3.0 PATIENT SELECTION**

#### **3.1 Conditions for Patient Eligibility:**

1. Histologically confirmed locally confined adenocarcinoma of the prostate.
2. T-Stage (T1b – T2b)
3. N-Stage (N-0)
4. PSA ( $\leq 20$ )
5. KPS ( $\geq 70$ )
6. No prior pelvic radiation therapy, chemotherapy, or hormonal therapy.

#### **3.2 Conditions for Patient In-Eligibility**

1. Stage T3 or T4 disease.
2. Lymph Node Involvement (N1)
3. Distant Metastases (M1)
4. Previous Radical Prostatectomy
5. KPS ( $\leq 70$ )
6. Previous or concurrent cancer other than non-basal/squamous cell skin cancer.
7. Presence of major medical or psychiatric illnesses that would prevent completion of treatment or interfere with follow-up.

### **4.0 PRE-TREATMENT EVALUATION**

1. History and Physical Examination with KPS.
2. Tumors must be Graded with Gleason Score.
3. PSA 30 days prior to implant.
4. Lymph node evaluation by CT, MRI, or lymph node sampling by exploratory laparotomy or laparoscopy.

## **5.0 IMPLANT PROCEDURE**

The patient will undergo conscious sedation. Three-way Foley catheter will then be inserted. Sigmoidoscopy will then be done to rule out rectal lesions, and remove residual stool from the rectum prior to interstitial needle implantation. Sterile Betadine prep will be performed over the perineal region in the usual fashion. The transrectal ultrasound probe will be positioned and the prostate gland measured. Local anesthetic will be administered using a mixture of Lidocaine, epinephrine, Marcaine, and neutralizing solution. Transperineal insertion of HDR interstitial needles will be done under ultrasound guidance. The needles will be placed ~ 1 cm apart, with attention to avoid the rectum, urethra, and bladder. The needles will be inserted to cover the seminal vesicles. Following completion of the implant, cystoscopy will be done to insure that no needles are in the urethra or bladder. A glidewire is then placed in the Foley catheter for future urethral dose calculations and adjustments at the time of HDR radiation treatment planning. Fluoroscopy will be done for further needle adjustments as needed. Rectal marker is then placed. The patient is then sent to the CT scanner to obtain images for future HDR radiation treatment planning. Final needle adjustments are made, as needed based on CT scan findings. Measurements are taken and recorded from the template to needle tips. Following completion of the CT scan, urethral glidewire and rectal marker are removed. The patient is then admitted to the oncology floor.

## **6.0 RADIATION THERAPY**

Following completion of CT Scanning, the images are sent by fiber optic link to the Nucletron Plato three dimensional computer treatment planning system. The Clinical Target Volume (CTV) includes the prostate + seminal vesicles, as defined by TRUS at the time of HDR Implant and subsequent CT scan for HDR radiation treatment planning. The expected activity for the HDR Ir-192 source is 3 to 10 Ci. The prescribed dose is 45 Gy in 6 HDR fractions delivered in 2 HDR implants 4 weeks apart. The goal for Isodose coverage of the CTV is 95%. Dose Volume Histograms (DVH) will be reported for the CTV, bladder, rectum, and urethra. The goal is to limit the urethra to 105% of the prescribed dose. Following completion of HDR radiation treatment planning, the patient is brought back down for treatment, and the 1<sup>st</sup> fraction administered. The following day, two more HDR fractions are administered. Before each HDR treatment, measurements are taken from the template to needle tips to make sure no movement has occurred. If movement is found, needles are readjusted as needed. The interval between HDR fractions is > 6 hours. After the 3<sup>rd</sup> HDR fraction, the implant and Foley catheter are removed, and the patient discharged home.

## **7.0 DRUG THERAPY**

Not applicable to this study.

## **8.0 PATHOLOGY**

Hematoxylin and Eosin (H & E) stained slides will be used for tumor grading and Gleason Score evaluation.

## **9.0 PATIENT ASSESSMENTS AND FOLLOW-UP**

PARAMATER	ON-STUDY	FOLLOW-UP
History and Physical	X	X
KPS	X	X
Sexual Status	X	X
T-Stage	X	X <sup>a</sup>
N-Stage	X	X <sup>a</sup>
M-Stage	X	X <sup>a</sup>
PSA	X	X
Gleason Score	X	
AUA Symptom Score	X	X
Sexual Function	X	X

a - At time of biochemical or clinical failure patients will be re-staged.

**9.1** The initial follow-up visit is within 1 month of implant. Subsequent follow-ups are at 3, 6, 9, and 12 months. After the 1<sup>st</sup> year, the patient will be followed at 6 month intervals for 2 years, and then annually for life. Measurement of tumor response will do as follows: be

- a. No Evidence of Disease (NED): No clinical evidence of disease by clinical examination or PSA level. The RTOG definition of PSA failure will be followed. Three consecutive rises in PSA must be documented. The rises must exceed 1 ng/ml above the nadir.
- b. Local Recurrence (LR): Must be biopsy proven. (Re-biopsy will be recommended for patients with PSA failures and negative Bone Scans and CT Scans.)
- c. Distant recurrence: positive bone scan or CT scan with absence of clinical local recurrence.
- d. Both local & distant recurrence: positive bone scan or CT scan with clinically positive DRE or biopsy.

**9.2** Disease Status

- a. Disease Free Survival (DFS): Measured from the date of accession to current biochemical no evidence of disease (NED) follow-up.
- b. Overall Survival (OS): Measured from the date of accession to death. Every effort will be made to establish cause of death.
- c. Toxicity: Toxicity will be measured according to RTOG criteria.

## **10.0 STATISTICAL CONSIDERATIONS**

The main objective of this study is to evaluate the effectiveness of TRUS HDR temporary implantation of the prostate. The primary hypothesis is to test whether HDR alone is as effective as HDR + External Beam Radiation Therapy. The study is designed in such a way that the treatment failure rate at 3 years since implantation is not 10% worse than that reported by the Blasko and Mate series with 95% confidence if the hypothesis is true. The primary endpoints are PSA DFS. Secondary endpoints are OS and Toxicity. The total sample size of the study is 100 patients. We expect to enroll this number in 2 years. Survival data will include analysis using the Kaplan Meier method [30,31]. Toxicity will be recorded according to the RTOG grading system.

### **References:**

1. Cancer Statistics 1998. CA: A Cancer Journal for Clinicians, American Cancer Society, 1998.
2. Stamey TA, Tang N, Hay AR, McNeal JE, Freiha FS, and Redwine E. Prostate Specific Antigen as a serum marker for adenocarcinoma of the prostate. NEJM, 1987; 317: 909-916.
3. Zagars GK, Sherman NE, Babaian RJ. Prostate-specific antigen and external beam radiation therapy in prostate cancer. Cancer, 1991; 67: 412-420.
4. Lange PH, Ercole CJ, Lightner DJ, et al. The value of serum prostate-specific antigen determinations before and after radical prostatectomy. J Urol, 1989; 141: 873.
5. Zagars GK and Von Eschenbach AC. Prostate specific antigen: An important marker for prostate cancer treated by external beam radiation. Cancer, 1993; 72: 538.
6. Partin AW, Poend CR, Clemmes JQ, and Walsh PC. Serum PSA with anatomic radical prostatectomy. The Johns Hopkins experience after 10 years. Urol Clin N America, 1993; 20: 713-725.
7. Pasteau O. Traitment du cancer de la prostate par le Radium. Rev Mal Nutr, 1911; 363-7.
8. Bagshaw MA, Kaplan HS, and Sagerman RH. Linear accelerator supervoltage radiotherapy: Carcinoma of the prostate. Radiology, 1965; 85: 121-129.
9. Fuks Z, Leibel SA, Wallner KE, Begg CB, Fair WR, Anderson LL, et al. The effect of local control on metastatic carcinoma of the prostate: Long-term results in patients treated with I-125. Int J Radiat Oncol Biol Phys, 1991; 21: 537 – 547.
10. Kuban DA, El-Mahdi AM, Schellhammer PF. I-125 interstitial implantation for prostate cancer. What have we learned 10 years later? Cancer, 1989; 63: 2415-2420.
11. Koprowski CD, Berkenstock KG, Borofski AM, Ziegler JC, Lightfoot DA, Brady LW: External beam radiation therapy versus I-125 implant in the definitive treatment of prostate carcinoma. Int J Radiat Oncol Biol Phys, 1991; 21: 955-960.

12. Blasko JC, Grimm PD, Ragde H: Brachytherapy and organ preservation in the management of carcinoma of the prostate. Seminars in Rad Onc, 1993; 3: 240-249.
13. Blasko JC, Ragde H, Grimm PD: Transperineal vs. guided implantation of the prostate: Morbidity and complications. Scand J Urol Nephrol, 1991; 137: 113-118.
14. Blasko JC, Walker K, Grimm PD, Ragde H: Prostate specific antigen based disease control following ultrasound guided I-125 implantation for Stage T1/T2 prostatic carcinoma. J Urol, 1995; 154: 1096 – 1099.
15. Older RA, Synder B, Krupski TL, Glembocki DJ, Gillenwater JY. Radioactive implant migration in patients treated for localized prostate cancer with interstitial brachytherapy. Journal of Urology, 2001; 165[5]: 1590-2
16. Davis BJ, Pisansky TM, Myers RP, Rothenberg HJ, Pacelli A, Hillman DW, Sargent DJ, Bostwick DG. The radial distance of extraprostatic extension of prostatic adenocarcinoma: implications for prostate brachytherapy. Int J Radiat Oncol Biol Phys, 1998; 42[1]: 132.
17. Pisansky TM, Blute ML, Hillman DW, Davis BJ, Haddock MG, Suman VJ, Wilson TM, Zincke H. The relevance of prostatectomy findings for brachytherapy selection in patients with localized prostate carcinoma. Cancer, 2002; 95 [3]: 513.
18. Blasko JC, Grimm PD, Sylvester JE, Cavanagh W. The role of external beam radiotherapy with I-125/Pd-103 brachytherapy for prostate carcinoma. Radiother Oncol, 2000; 57: 273-8.
19. Grado GL, Larson TR, Balch CS et al. Actuarial disease-free survival after prostate cancer brachytherapy using interactive techniques with biplane ultrasound and fluoroscopic guidance. Int J Radiat Oncol Biol Phys, 1998; 42: 289-98.
20. Pilepich MV, Krall JM, Johnson RJ, Sause WJ, Perez CA, Zininger M, Martz K. Extended field (periaortic) irradiation in carcinoma of the prostate – analysis of RTOG 75-06. Int J Radiat Oncol Biol Phys, 1986; 12 [3]: 345-51.
21. Asbell SO, Krall JM, Pilepich MV, Baerwald H, Sause WT, Hanks GE, Perez CA. Elective pelvic irradiation in Stage A2, B carcinoma of the prostate: analysis of RTOG 77-06. Int J Radiat Oncol Biol Phys, 1988; 15 [6]: 1307-16.
22. Eulau SM, Van Hollebeke L, Cavanagh, Gottesman JE, Mate TP. High dose rate 192-Iridium brachytherapy in localized prostate cancer: Results and toxicity with maximum follow-up of 10 years. Int J Radiat Oncol, Biol Phys, 2000; 48[3]: 149.

23. Stromberg JS, Martinez AA, Horwitz EM, Gustafson GS, Gonzalez JA, Spencer WF, Brabbins DS, Dmuchowski CF, Hollander JB, Vicini FA. Conformal high dose iridium-192 boost brachytherapy in locally advanced prostate cancer: superior prostate-specific antigen response compared with external beam treatment. Cancer Journal of Scientific American, 1997; 3 [6]: 346-52.
24. Kovacs G, Galalae R, Toch T, Rzehak P, Wilhelm R, Bertermann H, Nurnberg N, Kohr P, Kimmig B. High dosage brachytherapy and external irradiation of localized prostate carcinoma – results at the Kiel University Clinic. Schweiz Rundsch Med Prax, 2001; 90 [38]: 1617-22.
25. Borghede G, Hedelin H, Holmang S, Johansson KA, Aldenborg F, Pettersson S, Sernbo G, Wallgren A, Mercke C. Combined treatment with temporary short-term high dose rate iridium-192 brachytherapy and external beam radiotherapy for irradiation of localized prostate carcinoma. Radiotherapy and Oncology, 1997; 44 [3]: 237-44.
26. Deger S, Dinges S, Roigas J, Schnorr D, Turk I, Bucach V, Hinkelbein W, Loening SA. High-dose rate iridium-192 afterloading therapy in combination with external beam radiation for localized prostate cancer. Tech Urol, 1997; Winter; 3[4]: 190-4.
27. Curran MJ, Healey GA, Bihrlle W, Goodman N, Roth RA. Treatment of high-grade low-stage prostate cancer by high-dose-rate brachytherapy. Journal of Endourology, 2000; 14 [4]: 351-6.
28. Syed AM, Puthawala A, Sharma A, Gamie S, Londrc A, Cherlow JM, Damore SJ, Nazmy N, Sheikh KM, KO SJ. High-Dose-Rate brachytherapy in the treatment of carcinoma of the prostate. Cancer Control, 2001; 8 [6]: 511-21.
29. Mark R, Anderson P, Neumann T, Nair M, White D, Gurley S. Interstitial high dose rate (HDR) brachytherapy for Stage T1 and T2 prostate cancer. Abstract submitted to American Society of Therapeutic Radiology and Oncology Annual Meeting, 2003.
30. Gray RJ: A Class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat, 1988; 16: 1141-1154.
31. Kaplan EL and Meier P. Nonparametric estimation from incomplete observations. J Amer Statist Assoc, 1958; 53: 457-481.

**APPENDIX I: Patient Consent Form**

**JOE ARRINGTON CANCER CENTER  
PROSTATE CANCER BRACHYTHERAPY TRIAL  
JACC 004**

**PHASE II TRIAL OF TRANSRECTAL ULTRASOUND GUIDED TEMPORARY HIGH DOSE RATE (HDR) IMPLANTATION OF THE PROSTATE FOR DEFINITIVE MANAGEMENT OF LOCALIZED PROSTATE CANCER**

- I. Research Study:** This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. You are being asked to take part in this study because you have prostate cancer.

Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, *Taking Part in Clinical Trials: What Cancer Patients Need to Know*, is available from your doctor

- II. Purpose of the Study:** It has been explained to me that I have prostate cancer. My doctor feels that a prostate implant may be an appropriate treatment option. This study uses a temporary radioactive seed implanted in the prostate through hollow needles inserted through the area between the anus and scrotum. The procedure is done under conscious sedation and local anesthesia. The purpose of the study is to determine whether a prostate temporary implant is as good as the usual treatments for this disease, which, are surgery, or external radiation treatments. The other objective of this study is to analyze the risk of complications of this procedure compared to surgery or radiation treatments.

- III. Description of Procedures:** Before I undergo the implant procedure a physical examination will be done by my physician. My PSA will be measured. My lymph nodes will be assessed by CT or MRI Scan, or lymph node sampling by exploratory laparotomy or laparoscopy.

After all of these tests have been completed, I will be scheduled for my implant. The implant is done under conscious sedation and local anesthesia. The procedure includes sigmoidoscopy, transrectal ultrasound, interstitial needle placement, and possibly cystoscopy. The procedure takes about 1 hour. I will stay overnight in the hospital with the implant in place. I will have three HDR treatments during my stay.

After my implant, my doctor will see me at the following time intervals: within one month of my implant, then every 3 months for the 1<sup>st</sup> year, then every 6 months for 2 years, and then annually. During these visits I will undergo a physical examination and have a PSA test.

- IV. Risks and Discomforts:** Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Implant: The possibility exists for infection, but this should be controlled with antibiotics should infection occur. There will be soreness in the implant area. The implant itself has the possible side effects of temporary fatigue, diarrhea, abdominal cramps, bladder irritation, bleeding into the bladder, urine incontinence, and, in some patient's an inability to have an erection. There is also a chance of permanent injury to the bladder, urethra, bowel, and other tissues in the pelvis. The side effects related to bladder, urethra, and bowel, may not manifest for months to years after treatment.

Transrectal Ultrasound: Other than discomfort, and sometimes local irritation, there are no significant risks from ultrasound.

CT Scan with Contrast: An allergic reaction due to the contrast dye is possible, there is a small amount of radiation exposure with the CT scan, otherwise CT carries no significant risk.

Anesthesia: There is the slight possibility of blood pressure problems usually a drop in blood pressure, heart rhythm problems, breathing problems, drug reactions, nausea, vomiting, seizures, stroke, and death.

- V. Benefits:** If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with prostate cancer in the future. The information obtained from this study will be used scientifically. It may possible be helpful to others. The possible benefits of this treatment program are greater control of my tumor with decreased side effects.
- VI. Alternatives:** Alternatives that could be considered in my case include watchful waiting, hormonal blockade, surgery or external radiation therapy with or without hormonal blockade, permanent seed implant with or without external radiation therapy, and temporary HDR implant with external radiation therapy.

My doctor can provide detailed information about my disease and the benefits of the various treatments available. I should feel free to discuss my disease and my prognosis with the doctor. The physicians involved in my care will be available to answer any questions I have concerning this program. I am free to ask my physician any questions concerning this program that I wish in the future.

- VII. Voluntary Participation:** Participation in this study is voluntary. I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. If I do not take part in or withdraw from the study, I will continue to receive care. I am free to seek care from a physician of my choice at any time.

**VII. Confidentiality:** I understand that records of my progress while on the study will be kept confidential form at this institution and in a computer file. However, no information by which I can be identified by name will be released or published. Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution. Your personal information may be disclosed if required by law. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*), or organizations that have a role in this study, including the Covenant Health System Institutional Review Board (IRB).

**VIII. WHAT ARE THE COSTS?**

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. You or your insurance company will be charged for continuing medical care and/or hospitalization. You will receive no payment for taking part in this study.

**IX. WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?**

For information about your disease and research-related injury, you may contact:

Rufus J. Mark, M.D.  
 Joe Arrington Cancer Center  
 4101 22<sup>nd</sup> Place  
 Lubbock, TX 79410  
 806-725-7942 (W)

For information about your rights as a research subject, you may contact:

Covenant Health System IRB Office  
 (806) 725-7980

**I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion. I willingly give my consent to participate in this program. Upon signing this form I will receive a copy.**

---

Patient signature

---

Date

**Appendix II: Karnofsky Performance Scale**

100	Normal; No complaints; No evidence of disease
90	Minor signs or symptoms of disease; Able to perform normal activity
80	Some signs or symptoms of disease; Normal activity with effort
70	Cares for self; Unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; Requires special care and assistance
30	Severely disabled; Hospitalization is indicated, though death not imminent
20	Very sick; Hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

### Appendix III: AJCC STAGING SYSTEM PROSTATE CANCER

#### Primary Tumor

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically in apparent tumor, not palpable or visible by imaging
T1a	Tumor incidental finding in 5% or less of resected tissue
T1b	Tumor incidental finding in more than 5% of resected tissue
T1c	Tumor identified by needle biopsy because of elevated PSA
T2	Tumor confined to the prostate
T2a	Tumor involves one lobe
T2b	Tumor involves both lobes
T3	Tumor extends through the prostate capsule
T3a	Extra capsular extension
T3b	Tumor involves the seminal vesicle
T4	Tumor extends to bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

#### Regional Lymph Nodes (N):

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph nodes

#### Distant Metastasis (M):

Mx	Presence of distant metastases cannot be assessed
M0	No distant metastases
M1	Distant Metastases
M1a	Non-regional lymph node
M1b	Bone
M1c	Other sites

#### Histopathologic Grade (G):

Gx	Grade cannot be assessed
G1	Well-differentiated
G2	Moderately well differentiated
G3	Poorly differentiated

Stage Grouping:

I	T1a, G1
II	T1a, G2-4, T1b, T1c, T2a, T2b
III	T3
IV	T4 Any T, N1 Any T, M1

### **Appendix IV: RTOG Toxicity Grading for GI and GU:**

#### **RTOG Late Toxicity Grading for GI and GU**

<u>Organ</u>	<u>0</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>
Rectum	None	Diarrhea Bowel Movement x 5 qd Slight rectal Bleeding	Diarrhea Bowel Movement > 5 qd Intermittent rectal bleeding	Obstruction or bleeding requiring surgery	Necrosis Perforation or fistula	Death
Bladder	None	Microscopic Hematuria Asymptomatic	Moderate Frequency Intermittent Gross Hematuria	Severe Frequency & Dysuria Frequent Gross Hematuria	Necrosis Contracted Bladder Capacity Severe Hemorrhagic Cystitis	Death

### **Appendix V: Gleason Scoring System [1]**

<u>Pattern</u>	<u>Margins Tumor</u>	<u>Gland Pattern</u>	<u>Gland Size</u>	<u>Gland Distribution</u>	<u>Stromal Invasion</u>
1	Well Defined	Single Separate Round	Medium	Closely Packed	Minimal Expansile
2	Less Defined	Single Separate Round	Medium	Spaced up to one gland diameter	Mild invasion in larger stromal planes
3	Poorly Defined	Single Separate Irregular	Small to Large	Spaced more than one gland diameter Rarely packed	Moderate invasion
<b><u>Or</u></b> 3	Poorly Defined	Rounded masses of Cribriform or Papillary Epithelium	Medium to Large	Rounded masses with smooth sharp edges	Expansile masses
4	Ragged Infiltrating	Fused glandular Masses or Hypernephroid	Small	Fused in ragged masses	Marked thru smaller planes
5	Ragged Infiltrating	Almost absent, few Tiny glands	Small	Ragged anaplastic masses of epithelium	Severe

**Or**

5	Poorly Defined	Few small lumina in Rounded Masses of Solid epithelium Central necrosis	Small	Rounded masses and cords with smooth sharp edges	Expansile masses
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The Gleason Scoring System is a system of histologic grading based on over-all pattern of tumor growth at relatively low-magnification (40 to 100x). Five patterns of growth are recognized and numbered in order of increasing malignancy. Because of histologic variation in tumor, two patterns are recorded for each case, a primary pattern, and a secondary pattern. The Gleason Score is the sum of the primary and secondary pattern. If only one pattern is present, the primary and secondary pattern receive the same designation.

1. Gleason, D.F. et al: Prediction of prognosis for prostatic carcinoma by combined histologic grading and clinical staging. J Urol, 1974; 111: 58.

**Appendix VI: American Urologic America Symptom Score**

Patient Name:

Please fill out this short questionnaire to help us find out more about any urinary problems you might have. Circle a number in each column that best describes your situation.

<u>Question</u>	<u>None</u>	<u>&lt; 1 time in 5</u>	<u>Less than ½ the time</u>	<u>½ the time</u>	<u>More than ½ the time</u>	<u>Almost always</u>
	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?						
2. Over the past month, how often have you had to urinate again, less than 2 hours after you finished urinating?	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
3. Over the past month, how often have you found you stopped and started again several times when you urinated?	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
4. How often do you find it difficult to post-pone urination?	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
5. Over the past month, how often have you had a weak urinary stream?	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>

**Appendix VII: Sexual Function Score**

PATIENT NAME: \_\_\_\_\_ DATE: \_\_\_\_\_

Please fill out this short questionnaire to help us find out more about your sexual function.  
Circle a number in each column that best describes your situation.

No erection (Impotent)	Unsatis- Factory Erection & Orgasm ; Able to get penetration	Unsatis- factor Erection, but able to have orgasm with Medical Assistance	Satisfactory Erection & have orgasm with Medical Assistance	Satisfactory Erection & have orgasm without Medical Assistance
_____	_____	_____	_____	_____
<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>