What is the Role of Interstitial Brachytherapy?

Stephen W. Doggett, MD

In: Bowsher, W., editor. Challenges in Prostate Cancer.
1st ed. Blackwell Science, London 2000.

April 7, 2000

mailing address:
14642 Newport Ave #470
Tustin, California, USA
92780

telephone, fax and email:
714 669-4019
fax 714 669-4029
drdoggett@earthlink.net

What is the Role of Interstitial Brachytherapy?

Stephen W. Doggett, MD
April 7, 2000

Recent technological advances have permitted the widespread use in the U.S. and Europe of transperineally placed radioisotopes under ultrasound guidance into the prostate for treatment of gland confined cancer. This procedure is performed as a single outpatient minimally invasive procedure, has a low morbidity rate, a minimal impact on patient daily activities and a cure rate similar to other established forms of therapy.

In 1999, 179,300 American men were diagnosed with prostate cancer and 37,000 died of the disease. In 1998 there were an estimated 100,000 radical prostatectomies and 35,000 permanent radioisotope seedings performed in the U.S. Physician and public acceptance of the procedure is rapidly growing and industry estimates that 49,000 permanent seed procedures were performed in the US in 1999. Active centers in Italy, Germany, the UK, the Netherlands, Denmark and Australia have been performing prostate brachytherapy for several years. Since 1998, many new centers in these countries have established programs and worldwide interest in this procedure is increasing. Although there is enormous debate over the screening for and management of gland confined prostate cancer, many physicians believe that an aggressive approach can prolong life or cure. Recent studies suggest that screening programs or improved treatment modalities may now be responsible for stage reduction and declining prostate cancer mortality rates [1,2,3]. These falling mortality rates and increasing public awareness of prostate cancer are intensifying the interest in less morbid curative therapies for prostate cancer.

Previously, treatment of prostate cancer has consisted of surgical removal of the prostate gland or external beam radiation therapy. At 15 years follow-up, the published long-term results of surgery and external beam radiation therapy are similar [4]. However, there are significant side effects with these methods of treatment.

Radical prostatectomy can require a 3 to 4 day hospitalization and months of recovery time afterwards. It can be necessary to wear a catheter for several weeks after the surgery. 78% to 91% of patients who have surgery cannot sustain an erection sufficient for intercourse [5]. Urinary incontinence following the surgery is experienced by 18% to 50% of patients [5] Additionally, 25% of patients can have positive margins following radical prostatectomy and may require further therapy [6]. External beam radiation therapy generally requires 8 weeks of daily outpatient visits.
37% to 88% of all patients who have external beam radiation cannot sustain an erection sufficient for intercourse [5]. Urinary incontinence following external beam treatment occurs 5% to 26% of the

time [5].

Radiation oncologists have long sought a technique to accurately deliver a higher dose of radiations to the prostate than was feasible with external beam radiation therapy. The delivery of 7000-7500 cGy with conventional external beam radiations results in a 5 year local control rate of 80% with a 20% risk of rectal complications [7]. Attempts to increase the prostatic dose and decrease the rectal dose with three dimensional conformal radiation are underway. Although increasing the dose with three dimensional conformal radiation therapy has been shown to improve PSA control rates, an improvement in survival over that seen with conventional external beam radiation therapy has not been proven [8].
Three dimensional conformal radiation therapy has no long term data and may present a prohibitively high cost-benefit ratio [9].

Permanent seed brachytherapy is the ultimate in three dimensional conformal radiation therapy. Placement of multiple low activity radioisotope seeds directly into the prostate allows the delivery of twice the radiations (11500 cGy to 14500 cGy) possible with external beam radiation therapy. The low energy gamma radiations from palladium 103 and iodine 125 are minimally penetrating and therefore deliver a high dose of radiations to the target prostate tissue and an insignificant dose of radiations to rectum and bladder.

This review is limited to permanent seed brachytherapy because of the long follow up of ultrasound guided series reported in the literature and because of the long history of the use of permanent seed implants by retropubic placement. Temporary after loading of iridium can also be accomplished with ultrasound guided needle placement. Compared to the single procedure outpatient permanent seed brachytherapy, temporary iridium after loading is a more costly and labor intensive procedure requiring several hospitalizations. Iridium after loading is currently more popular in Europe than the U.S. It commonly requires two implants and two anesthesias, and the addition of external beam radiation therapy. In the U.S the iridium afterloading procedure generally requires an overnight stay in the hospital with 24-40 hours patient immobilization. In Europe most centers perform the procedure as an outpatient. Reported results have been favorable [10] although follow up data is short and scanty and the cost benefit ratio may be excessively high. Because the emitted energy of the iridium 192 gamma rays are fifteen times more energetic than for the gamma rays of the permanent seeds (330kv for iridium192 vs 21-28 kv for palladium 103 and iodine 125), long term complication rates may be higher for after loading iridium therapy than for permanent seed implants with palladium or iodine [11]. There are also major differences in the radio biologic effects of the radiations from low activity iridium, high activity iridium, the permanent seeds (palladium and iodine) and from external beam therapy. These differences are the subject of much study and are beyond the scope of this chapter.

History of Prostate Brachytherapy

The first reported use of interstitial prostate brachytherapy was with transperineal radium needles in 1917 [12]. With the atomic age development of new, safer isotopes came renewed interest in the

treatment of prostate cancer with interstitial implantation. Permanent radioisotope seeding through the open retropubic technique was performed in the US in the 1970's [13]. The procedural intent was to place a series of radioactive sources directly into the cancerous prostate thus delivering a cancericidal dose of radiations while minimizing the dose to surrounding sensitive structure such as the bladder and rectum. Seeds were placed free hand via laparotomy into the gland via parallel placed trocars with the operators finger in the rectum guiding the needle tips. Heterogenous seed positioning with this technique resulted in areas of radiation overdosage and underdosage. In many series, poor surgical exposure, inability to intra operatively monitor seed placement and lack of postoperative dosimetric analysis led to complications and poor tumor control. However, the local failure rate at Memorial Sloan-Kettering was reported at 20% for B1 lesions and 40% for B2, B3 and C lesions indicating promise for interstitial brachytherapy [14]. The open laparotomy freehand technique was abandoned in the US as practitioners searched for techniques providing a more uniform seed placement.

The development of interventional imaging and introduction of transrectal ultrasound in Denmark led to the development of ultrasound guided perineal template needle and seed placement [15]. This procedure allows the radioisotopes to be transperineally placed into the prostate under precise ultrasound guidance in a single outpatient operation (Figure 1). This technique was introduced to the US and refined and taught by Drs Ragde, Blasko and Grimm in Seattle from the mid 1980's on and now enjoys increasing popularity throughout Europe and the US. In 1995, the American Urological Association recommended that patients with clinically localized prostate cancer be informed of the option of radioisotope seed implants [16].

Patient Selection

Patient selection is broader than for radical prostatectomy. There are no data that patient age is a contraindication to brachytherapy. Ideal candidates for seeding as monotherapy are T1b, T1c, T2a and T2b tumors with Gleason sum less than 7 and PSA less than 10. Patients with greater than 10 year longevity, clinically gland confined disease, the ability to tolerate spinal or general anesthesia, and prostatic size small enough [<60 cc] to avoid obstruction of needle passage by pelvic skeleton are candidates for seeding alone without external beam radiation therapy boost. Patients with large volume T2 or minimal T3 disease require a 4500 to 5000 cGy external beam radiation therapy boost to cover potential extra capsular extension. Patients who present with glands larger than 60cc are treated with several months of downsizing hormonal therapy prior to implant.

External Beam Boost Criteria

Seed radiations are minimally penetrating and are cancerocidal at only a few millimeters distance from their placement. External beam radiations (5 weeks, 4500-5040cGy) are therefore added pre or post implant to patients at high risk for capsular extension, seminal vesicle invasion, or first echelon lymph node involvement. Current recommendations for the addition of external beam radiations to the implant include PSA greater than 10, Gleason greater than 6 and stage greater than T2A [17]. External beam radiations delivered with small fields with blocking of sensitive structures ensures

acute and chronic toxicities distinctly lower than those seen with primary treatment of prostate cancer by large pelvic fields and higher doses (8 weeks, 6600-7600cGy)

Hormonal Therapy and Prostate Brachytherapy

The addition of adjuvant hormonal blockade has been shown to improve progression-free survival in patients with advanced prostate cancer treated with external beam radiation therapy [18,19]. Hormonal deprivation can induce prostate cell death via apoptosis but the clinical significance of this remains unclear. Hormonal deprivation prior to brachytherapy likely decreases the cancer cell burden and may cause an increase in local cancer control. Hormonal deprivation increases radiation induced cell death in animal models although definitive survival benefit in human brachytherapy subjects remains to be proven [20].

Neoadjuvant hormonal downsizing prior to radiation therapy has also shown a 30% reduction in prostate volume [21]. Hormonal induced prostate downsizing prior to brachytherapy reduces the number of seeds required, reduces the chance of pelvic skeletal needle obstruction, and may reduce the incidence of post implant urinary obstruction. Pre-radical prostatectomy hormonal deprivation significantly reduces the incidence of margin positivity in T1 and T2 cancers although an improvement in survival has yet to be demonstrated [22]. Preimplant hormonal deprivation increases fat deposition at Denonvilliers fascia, increasing the distance between the radioisotopes and the rectum which may decrease rectal symptoms. Optimal timing and duration of hormonal blockade remains to be determined.

Implant Design and Planning

Traditionally**,** the implant design starts with a planning volumetric transrectal ultrasound one or two weeks prior to the surgery date. This is performed with the unanesthetized patient in the dorsal lithotomy position and with the same ultrasound device, probe and stepper as will be used in the operating room. Biplanar ultrasonography is essential to the performance of a quality implant. The probe is locked in the same position as anticipated for the implant. With the implant template electronically superimposed, transverse images are obtained at 5 millimeter increments from the base of the prostate to the apex with one additional image above and below the gland. The exterior contour of the prostate is marked with a 2 mm to 5 mm margin (Figure 2). These images and the treatment prescription are sent to medical radiation physics where the images are digitized into a treatment planning computer and the treatment plan generated. This plan specifies the template needle insertion coordinates, the number and spacing of seeds per needle and the activity of radioisotope per seed. The seeds for each case contain the same amount of radioactivity and there are commonly 20 to 30 needles and 60 to 100 seeds per case.

Advances in intraoperative treatment planning now permit the planning ultrasound and the treatment plan generation to be performed in the operating room with far greater precision (vide infra). Intraoperative planning allows greater seed placement precision than with the planning performed in

the clinic**.**

Surgical Technique

Patients are prepared with a cleansing enema the morning of the procedure. The implant is performed under spinal or general anesthesia in the dorsal lithotomy position in a 90 minute outpatient procedure. The physics dosimetry plan is reviewed and approved. The bladder is catheterized and drained at the beginning of the procedure to place contrast and to localize the urethra on ultrasound. Transrectal ultrasound probe is placed and manipulated until the real time images obtained are identical to those obtained during the pre implant planning ultrasound. Care is taken to ensure that the patient position in the operating room is as close as possible to the patient position when the planning ultrasound was performed. Perineal template is attached to the transrectal ultrasound probe and mounted on the OR table. Prostatic motion during the implant is common and is decreased through the use of stabilizer needles. Prostatic swelling during the procedure is common and frequent reevaluations of the plan and ultrasound determined prostatic position are needed. 18 gauge stainless steel hypodermic needles are parallel placed through the template into the prostate following the computer generated treatment plan. The needles are placed a single row at a time moving anterior to posterior in order to minimize ultrasound generated artifact. Positioning of the needles is constantly monitored by biplanar ultrasound as well as fluoroscopy (Figure 3). The use of sagittal ultrasound permits positioning of the needle tip at the prostato-cystic interface while avoiding bladder or urethral puncture. Seeds are deposited singly by the use of a mechanical injector or in groups by preloaded needles.

Cystoscopy with foreign body extraction can be performed at the conclusion of the implant if there is concern that seeds may have been misplaced into the bladder or urethra. The catheter is removed at the onset of needle placement and replaced following cystoscopy. Intra operative antibiotics and corticosteroids are given at the physicians= discretion. Catheter is removed in the recovery area and patient discharged home after voiding. Patients return home the same day and do not require oral narcotics. The majority of patients return to work or full activity in one to three days. Sexual intercourse can be resumed at the patients= discretion.

Radiation Safety

The use of palladium or iodine seeds in the operating room poses no health risk to hospital personnel.
The gamma radiations from the sealed palladium or iodine sources are minimally penetrating; 50% are blocked by only 0.02 mm of lead. There is far more exposure to operating room personnel from scattered fluoroscope radiations than from seed radiations. The use of leaded gowns during any procedure requiring fluoroscopy is customary. Further precautions for the operating room personnel due to the use of palladium or iodine are unnecessary. Geiger counters are used to survey the operating room after the procedure to ensure no seeds have been washed out in the bladder irrigant. Implanted patients are asked not to hold nursing infants in their lap for 2 months after seeding. Condom use is recommended for the first intercourse in the event a seed is ejaculated from the

seminal vesicle.

Follow Up

Follow up consists of periodic PSA and DRE testing. Frequently noted is the PSA Abounce≅ wherein PSA transiently elevates and then recedes, most commonly during the first two years post radiation therapy. PSA failure is defined by the American Society for Therapeutic Radiology and Oncology as three consecutive rises of PSA over a 6 month period without regard for the specific PSA level [23]. PSA may take up to 4 years to reach nadir and post implant biopsy should be performed judiciously during this time [24].

Isotope Selection

Palladium 103 and Iodine 125 are the two commonly used gamma emitters for permanent implantation. Commercially available isotopes are identically sized (0.8 mm in diameter and 4.5 mm in length) and are sealed inside bioinert titanium capsules. Palladium has an energy of 21 KeV and a half life of 17 days. Iodine has an energy of 28 KeV and a half life of 60 days. Theoretical radio biological advantages can be attributed to the use of a faster decaying isotope although there is no clinical evidence that either isotope is superior regarding cell kill or measurable survival advantage[42]. However, palladium has been shown to have a dramatically lower overall complication rate as compared to iodine (0% vs 13%) [43].

Outcomes

PSA based outcomes from permanent ultrasound guided implant series without external beam radiation therapy have been excellent (Table 1). As of 1998, seed implants alone have demonstrated a 60% disease free survival rate at 10 years (defined as PSA less than or equal to 0.5 ng/mL), which remains comparable to surgery [24] The addition of an external beam radiation therapy boost resulted in a 76% disease free survival at 10 years [24]. The addition of external beam radiation therapy to all seed implants is advocated by other authors, with a reported 72% 10 year disease free survival (defined as PSA less than or equal to 0.5 ng/mL)[30]. These reported 10 year disease free survival rates compare favorably to the 47%-73% rates reported with contemporary radical prostatectomy series, all of which report a PSA nadir of less than or equal to 0.6 ng/mL [31,32,33,34].

There are significant difficulties in comparing the results of prostate cancer treatment series. In the past, disease free survival, overall survival, cause specific survival, distant metastasis free survival and biopsy evaluated local control have all been used as end points. PSA levels as a surrogate marker for tumor activity are now the most commonly reported end point reported post treatment. Series comparisons continue to be hampered by lack of consensus of the optimal nadir PSA. Recent literature reviews show inconsistencies exist in the use of pretreatment PSA to group patients for

subsequent analysis [35]. These studies underscore the need for standard definitions of disease stage and outcomes for prostate cancer treatment series. Acceptance is growing in the US of the concept that a lower post treatment PSA nadir presages a higher local control rate and that PSA nadir of 0.5 ng/mL or lower is essential [30]. PSA failure is currently defined by the American Society for Therapeutic Radiology and Oncology as three consecutive rises of PSA over a 6 month period without regard for the specific PSA level [23]. The results of controlled, prospective and randomized clinical trials are awaited to determine optimal treatments for early stage prostate cancer [36].

Complications

Acute and chronic complications from seeding are significantly less than those seen with radical prostatectomy or external beam radiation therapy. Palladium induced complications are distinctly lower than those induced by iodine[43]. Urinary incontinence occurs in 0% of palladium treated patients without prior TURP [37,43]. 0% of palladium treated patients develop fistula or require surgical intervention for proctitis [37,43]. Impotency rates are age dependent, varying from 15% in the under age 70 group to 50% in the over age 70 group [38]. Most implant patients experience symptoms of acute radiation prostatitis which can be minimized through isotope selection, judicious seed placement and the short term use of alpha blockers and corticosteroids. 3%-7% of patients experience post implant urinary obstruction significant enough to require surgical intervention. Seed migration is rare and does not pose any clinical significance. 0.2% of implanted seeds were found to have embolized to the lungs without clinical symptoms in one series (7 of 3213 seeds implanted in 30 patients) [39]. Prior TURP is not a contraindication to seeding but does increase the risk of post seeding incontinence. This risk is minimized by careful preoperative planning and intra operative seed placement to ensure that seeds are not placed immediately adjacent to the TURP defect. An increased incidence of radiation induced malignancies following laparotomy placed seeds has not been reported.

Post Implant Dosimetry Evaluation

Measurements of implant quality are mandatory and are currently based on dosimetric measurements of post implant CT or US images obtained four weeks post operative (Figure 4). These computerized measurements calculate the radiation contribution of each implanted seed in an additive fashion so the total dose to any point in the area of interest can be obtained. This information allows the brachytherapist to identify under dosed and over dosed areas in the target region and teaches the operator how to improve accuracy of seed placement. Current guidelines from the American Brachytherapy Society recommend that at a minimum 90% of the prostate gland receive the prescribed dose of radiations.

Brachytherapy Technology Advances

Image registered intra-operative real-time treatment planning (IRIRTP) for permanent seed prostate brachytherapy is the first significant technological advance in prostate permanent seed

brachytherapy in 15 years. IRIRTP is designed to substantially reduce human operator input during the treatment planning process with its= attendant error rate. Inaccuracies due to prostatic motion and size changes in the time between planning and surgery are mitigated. Increased accuracy of seed placement can produce a shorter operator learning curve, lower complications and higher local control rates.

Until now, treatment plans have been computer generated days or weeks prior to the implant based on a clinic generated ultrasound or CT scan of the unanesthetized patient in the treatment position. Size and position of the prostate at a later date in the OR with the anesthetized patient in an even slightly different position and with the pelvic musculature relaxed leads to increased uncertainty of seed placement. New developments in treatment planning software and hardware have led to the introduction of ultrasound based IRIRTP [Interplant(tm), Burdette Medical Systems, Champaigne-Urbana, Illinois] allowing the computerized plan to be calculated in a few minutes in the operating room with the anesthetized patient in the treatment position. Spatial image registration allows the isodose plan to be overlaid on the real-time US prostate image so the operator can see precisely how much radiation is delivered to any point in the prostate, bladder, rectum or neurovascular bundles. Operator selected alterations in the planned placement of seeds and needles can be made in seconds, an option not possible with off line planning. Electronic position monitoring of the probe in relationship to the template and stepper allow accurate realtime ultrasound image acquisition eliminating many of the uncertainties plaguing the older planning techniques. IRIRTP is designed to sharply reduce the long learning curve for quality implants seen with off line planning and to permit high quality implants to be achieved in centers performing limited numbers of implants.

Real time intra operative ultrasound images can now be used to locate seeds with volume detection software permitting instantaneous intra operative assessment of seed placement [Interplant(tm), Burdette Medical Systems, Champaigne-Urbana, Illinois]. Additional seeds can be implanted as needed resulting in a higher quality implant without the need for a second procedure. Image fusion of preoperative MRI with the realtime intra operative ultrasound images is under development and by more accurate intra operative localization of treatment volumes and radiosensitive structures (neurovascular bundles and urethra) may further increase local control rates and reduce impotency and urinary complication rates. Future advances in needle and seed design and in robotic needle and seed placement systems will allow even more precise seed positioning.

Summary

Long term results for ultrasound guided transperineal radioisotope prostate cancer seeding exist and based on PSA measurements appear to be equivalent to the results of comparable radical prostatectomy series and superior to the results of external beam radiotherapy series. Impotency and incontinency rates from brachytherapy are lower than for radical prostatectomy or external beam radiotherapy. Advances in intraoperative treatment planning will continue to decrease complication rates, shorten operator learning curves and likely increase local control rates. Published scientific literature, increasing physician and public awareness of prostate cancer and associated treatment

morbidities continue to increase the role of prostate permanent seed brachytherapy internationally.

Continued technological improvements in brachytherapy are making this procedure increasingly competitive with surgery and external beam radiotherapy. Based on historical growth trends, estimates indicate by the year 2001 that 45% of all primary prostate cancer in the US will be treated by permanent seed brachytherapy [41]. With rare exceptions, patients who are candidates for radical prostatectomy or external beam radiotherapy are candidates for permanent seed brachytherapy and should be considered for this option.

.

References:

1. Meyer F, Moore L, Bairati I, Fradet Y, Downward Trend in Prostate Cancer Mortality in Quebec and Canada. J Urol 1999;161: 1189-1191.
2. Roberts R, Bergstralh E, Katusic S, Lieber M, Jacobsen S, Decline in Prostate Cancer Mortality From 1980 to 1997, and Update on Incidence Trends in Olmsted County, Minnesota. J Urol 1999;161:529-533.
3. Rietbergen J, Hoedemaeker R, Kruger A, Kirkels W, Schroder F, The Changing Pattern of Prostate Cancer At The Time Of Diagnosis: Characteristics Of Screen Detected Prostate Cancer In A Population Based Screening Study. J Urol 1999;161:1192-1198.
4. Oesterling J, Fuks Z, Lee C, Scher H, Cancer of the Prostate. In: DeVita, Jr. V, Hellman S, Rosenberg S, eds. Cancer Principles and Practice of Oncology, 5th edition, 1997:1356
5. Herr H. Quality of Life in Prostate Cancer Patients. Ca Cancer J Clin 1997;47:207-217
6. Wasson J, Cushman C, Bruskewitz R, et al. A Structured Literature Review of Treatment for Localized Prostate Cancer. Arch Fam Med 1993;2:487-493.
7. Sander HM, McShan DL, Lichter, AS. Potential improvement in the results of irradiation for prostate carcinoma using improved dose distribution. Int J Rad Oncol Biol Phys 1991;22:361-367
8.Peschel RE. Three Dimensional Conformal Radiation Therapy for Early Prostate Cancer. Cancer J Sci Am 1999;5:145-146.
9. Wilson L. Three Dimensional Conformal External Beam Radiation Therapy for Prostate Cancer. Ernstoff M, Heaney J, Peschel R, eds. Prostate Cancer. MA USA: Blackwell Science, 1998:156-159]
10. Vicini F, Kestin L, Stromberg, J Martinez A. Brachytherapy Boost Techniques for Locally Advanced Prostate Cancer. Oncology 1999;13:491-504.
11.Wallner K, Blasko J, Dattoli M. Prostate Brachytherapy Made Complicated, 1st edn. Seattle Washington: Smart Medicine Press ,1997. 2.4
12. Barringer B. Radium in the Treatment of Carcinoma of the Bladder and Prostate. JAMA 1917;68;1227-1230
13. Whitmore W, Hilaris, B, Grabstald H. Retropubic implantation of iodine 125 in the treatment of prostate cancer. J Urol 1972;108:918.
14. Hilaris B, Nori D, Anderson L. An Atlas of Brachytherapy, New York: Macmillan Publishing,

1988 p 228.
15. Holm H, Juul N, Pederson J, Hansen H, Stroyer I. Transperineal 125 Iodine Seed Implantation in Prostatic Cancer Guided By Transrectal Ultrasonography. J Urol 1983;130:283-286.
16. Middleton J, Thompson I, Austenfeld M, et. al. Prostate Cancer Clinical Guidelines Panel Summary report On the Management Of Clinically Localized Prostate Cancer. J Urol 1995;154:2144-2148.
17. Wallner K, Blasko J, Dattoli M. Prostate Brachytherapy Made Complicated, 1st edn. Seattle Washington: Smart Medicine Press ,1997. 12.23-12.24.
18. Bolla M, Gonzalez D, Warde P, et. al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997;337:295-300.
19. Lawton C, Winter K, Byhardt R, Sause W, et. al. Androgen Suppression Plus Radiation Versus Radiation Alone For Patients With D1 (pN+) Adenocarcinoma of the Prostate (Results Based On A National Prospective Randomized Trial, RTOG 85-31). Int J Rad Oncol Biol Phys. 1997;38:931-939.
20. Zeitman A, Nakfoor B, Prince E Gerweck L. The effect of androgen deprivation and radiation therapy on an androgen sensitive murine tumor: an in vitro and in vivo study. Ca J 1997;3:31-36.
21. Forman J. Neoadjuvant hormonal downsizing of localized carcinoma of the prostate: effects on the volume of normal tissue irradiation. Ca Invest 1995;13:8-15.
22. Garnick M, Fair W. First International Conference on Neo-adjuvant Hormonal Therapy of Prostate Cancer: Overview Consensus Statement. Urology 1997;49(suppl):1-4.
23. American Society for Therapeutic Radiology and Oncology Consensus Panel, Consensus Statement: Guidelines for PSA following radiation therapy. Int J Rad Oncol Biol Phys 1997;37:1035-1041.
24. Ragde H, Elgamal AA, Snow PB. Ten year disease free survival after transperineal sonographically guided iodine 125 brachytherapy with or without 45 Gy external beam irradiation in the treatment of patients with clinically localized, low to high Gleason grade prostate carcinoma. Cancer 1998;83:989-1001.
25. Wallner K, Roy J, Harrison L, Tumor Control and Morbidity Following Transperineal Iodine 125 Implantation For Stage T1/T2 Prostatic Carcinoma. J Clin Oncol 1996;14:449-453
26. Blasko J, Wallner K, Grimm P, et al., Prostate Specific Antigen Based Disease Control Following Ultrasound Guided 125 I Implantation For Stage T1c/T2 Prostatic Carcinoma. J Urol 1995;154:1096-1099.
27. Stock R, Stone N, DeWynegaert J, et. al., Prostate Specific Antigen Findings And Biopsy Results Following Interactive Ultrasound Guided Transperineal Brachytherapy for Early Stage Prostate Carcinoma. Cancer 1996;77:2386-2392.
28. Stokes S, Real J, Adams P, et. al., Transperineal Ultrasound-Guided Radioactive Seed Implantation for Organ-Confined Carcinoma of the Prostate. Int J Radiat Oncol Biol Phys 1997;37:337-341.
29. Beyer D, Priestley J, Biochemical Disease Free Survival Following 125 I Prostate Implantation. Int J Radiat Oncol Biol Phys 1997;37:559-563.
30. Critz F, Levinson A, Williams W, et. al. Simultaneous Radiotherapy for Prostate Cancer: 125 I Prostate Implant Followed by External Beam Radiation. Cancer J Sci Am 1998; 4:359-363.
31. Pound C, Partin, Epstein, J. Prostate-Specific Antigen After Anatomic Radical retropubic

Prostatectomy. Urol Clin North Am 1997;24:395-406.
32. Trapasso J, deKernion J, Smith R, et. al. The Incidence and Significance of Detectable Levels of Serum PSA After Radical Prostatectomy. J Urol 1994;52:1821-1825.
33. Ohori M, Goad J, Wheeler T, et. al. Can Radical Prostatectomy Alter The Progression of Poorly Differentiated Prostate Cancer? J Urol 1995;154:1818-1824.
34. Catalona W, Smith D. Five Year Tumor Recurrence Rates After Anatomic Radical Retropubic Prostatectomy For Prostate Cancer. J Urol 1994;152:1833-1842.
35. Vicini F, Horwitz E, Gonzalez J, et. al. Treatment Options For Localized Prostate Cancer Based On Pretreatment Serum Prostate Specific Antigen Levels. J Urol 1997;158:319-325.
36. Wilt T, Brawer M. The Prostate Cancer Versus Observation Trial: A Randomized Trial Comparing Radical Prostatectomy Versus Expectant Management For The Treatment of Clinically Localized Prostate Cancer. J Urol 1994; part 2 152;1910.
37. Blasko J, Grimm P, Ragde H, Schumacher D, Implant Therapy for Localized Prostate Cancer. In: Ernstoff M, Heaney J, Peschel R, eds. Prostate Cancer. MA USA: Blackwell Science, 1998:137-155.
38. Blasko J, Grimm P, Ragde H. Brachytherapy and organ preservation in the management of carcinoma of the prostate. Semin Radiat Oncol 1993;3:240-249.
39. Nag S, Scaperoth D, Badalament R, Hall S, Burgers J. Transperineal Palladium 103 Prostate Brachytherapy: Analysis of Morbidity and Seed Migration. Urology 1995;45:87-92.
40. Prestidge B. Radioisotopic Implantation for Carcinoma of the Prostate: Does It Work Better Than It Used To? Semin Radiat Oncol 1998;8:124-131.
41. Snitkin E. Investing in Urology May 1998 p 17 Health Care Industry Overview. NationsBanc Montgomery Securities
42. Cha, C.M., Potters, L., Ashley, R., et. al. Isotope Selection for Patients Undergoing Prostate Brachytherapy. Int J Rad Onc Biol Phys 45:2 391-395 1999
43. Peschel, R. E., Chen, Z., Roberts, K. Long Term Complications with Prostate Implants: Iodine-125 vs Palladium-103. Rad Onc Invest 7:278-288 1999