Modern Prostate Brachytherapy

Prostate Specific Antigen Results in 219 Patients with up to 12 Years of Observed Follow-Up

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BACKGROUND. The purported lack of long term modern prostate brachytherapy outcome data continues to lead many physicians to recommend other, more traditional treatments. This concern for long term results has encouraged the authors to supplement their earlier 10-year follow-up of patients receiving brachytherapy; in the process, an additional 77 patients (> 50%) were added to the original cohort, and the follow-up time was increased by 2 years.

METHODS. Between January 1987 and September 1989, 229 patients with T1–T3 prostate carcinoma underwent transperineal prostate brachytherapy using iodine-125 (I-125). No patient received adjuvant hormone therapy. The median Gleason sum was 5 (range, 2–10). Of these patients, 147 were determined to have a high probability of organ-confined disease and were treated solely with an I-125 implant. The remaining 82 patients were determined to be at increased risk for extracapsular disease and received pelvic external beam radiation in addition to brachytherapy. All patients were followed continuously. Failure was defined as a positive biopsy, radiographic evidence of metastases, or three consecutive rises in prostate specific antigen (PSA) levels as defined by the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus article.

RESULTS. Excluding deaths from intercurrent disease, the median follow-up was 122 months (range, 18–144 months). Fourteen patients were excluded from analysis due to insufficient follow-up. Adopting the ASTRO definition of failure resulted in minimal change in survival when compared with the authors' previous study, which used a PSA level > 0.5 ng/mL as the failure point. Observed 10-year disease free survival (DFS) for the entire cohort was 70%. In the brachytherapy only group, the observed 10-year DFS was 66%, whereas those patients treated with the addition of external pelvic radiation achieved a DFS of 79%. None of the patients who were followed for the full 12 years failed between Years 10 and 12. Only 25% of the failures observed occurred > 5 years after treatment, thus confirming the durability of brachytherapy.

CONCLUSIONS. Prostate brachytherapy provides excellent long term disease control with few late failures reported in the authors' program. The addition of external beam radiation appears to confer survival advantages in selected patients. Using the ASTRO failure criteria for long term follow-up resulted in no significant difference compared with using a PSA failure point of 0.5 ng/mL. ***Cancer* 2000;89: 135–41.** © *2000 American Cancer Society.*

KEYWORDS: prostate carcinoma, brachytherapy, iodine-125, prostate specific antigen, disease free survival, results, external beam radiation, radical prostatectomy.

Over the last decade, prostate brachytherapy—a radiation treatment in which small, encapsulated, radioactive sources are implanted into the gland—has gained favor as an effective treatment for patients with clinically localized carcinoma. A recent American Uro-

logical Association policy briefing projects that prostate brachytherapy soon will surpass radical prostatectomies as the treatment of choice.[1]

The reasons for this notable attainment are several: Transrectal ultrasound imaging permits the radioactive metallic seeds to be inserted into the prostate in a precise and predictable way, delivering radiation that conforms to the gland at much higher doses than those achievable with external beam radiation. Optimal seed strength and locations for a particular gland are determined readily by using computer-based dosimetry planning systems. Implants can be performed in a cost-effective, outpatient setting at great convenience to patients. Finally, the morbidity of the procedure is markedly lower than that seen with radical surgery. However, most importantly, the growing popularity of brachytherapy is a result of the encouraging reports of long term disease free survival (DFS).[2–8] Those reports demonstrated an equal or better outcome compared with more traditional treatments for many men with clinically localized prostate carcinoma.

Almost 2 years ago, we reported on biochemical DFS of our initial, early population of 152 patients who were treated between January 1987 and June 1988 with iodine-125 (I-125) brachytherapy and observed for 10 years.[4] We concluded that report with an assurance that we would continue to update our series periodically. This report is the first of such articles, covering an additional 77 patients, adding fresh information to our previous paper, and following the original set of 152 patients for almost another 2 years.

MATERIALS AND METHODS

Patients

Modern prostate brachytherapy was started in this country by the senior author at Northwest Hospital in Seattle, Washington, in late 1985. However, in all of our data analyses to date, patients who were treated in the first 14 months have been excluded from the statistical analysis due to the requisite development phase of our brachytherapy program, which, at that time, was a completely new and untested procedure in this country. The accrual of patients who were used for analysis, hence, started in January of 1987, and patients were entered consecutively through the current analysis period until September 1989. Over one third of the patients accrued between June 1988 and September 1989 were seeded with Palladium-103 and excluded from this analysis.

The resultant 229 prostate carcinoma patients, all of whom underwent I-125 implantation treatment with curative intent, were staged clinically by digital rectal examination with T1–T3 disease. All but two patients had Gleason grading performed by one of three Northwest Hospital pathologists, and all but six patients had their pretreatment serum prostate specific antigen (PSA) levels determined (Hybritech, Inc., San Diego, CA; normal range, 0–4 ng/mL). No patient had clinical or radiographic evidence of distant metastases. No patient was staged surgically, and none was subjected to hormonal intervention, either before or after the implant, until there were signs of treatment failure.

Treatment

Based on their of risk of having extracapsular disease that not be treated adequately by using brachytherapy alone, patients were divided into two groups: a low risk population (Group 1) and a high risk population (Group 2). This risk assessment was based on two main factors: palpable clinical disease and Gleason score. For patients with a Gleason score $>$ 6 and/or a Stage $\geq$ T2b, the risk of extracapsular extension was considered high enough to warrant the addition of external beam radiation. The low risk patients (Group 1, which was comprised of patients with Gleason scores $<$ 7 and/or Stage $<$ T2b) were treated with brachytherapy alone using I-125 to a minimal peripheral dose (MPD) of 160 grays (Gy). Group 2 patients (the high risk patients) were treated initially with 45 Gy in 25 fractions of external beam radiation to a limited pelvic field followed by an I-125 implant delivering 120 Gy MPD. Note that the radiation doses used for this population appear to be higher than those now employed due to dosimetry constant changes for I-125 recommended and adopted by the American Association of Physicists in Medicine Task Group 43.[9] It also should be noted that, at the time of patient accrual, the significance of PSA as an indicator for extracapsular disease was not fully appreciated; therefore, the PSA level played no role in assigning patients to either the low risk group or the high risk group.

All volume studies and implants were performed with a Bruel and Kjaer transrectal ultrasound unit fitted with the appropriate accessories for volume determination and implantation. Brachytherapy at our institution has been accomplished primarily by using preloaded needles. Conformal seed-loading plans are computer derived for each individual patient from a separate office visit. Due to our concerns about the adequacy of dose distribution and other inherent problems with the intraoperative method of brachytherapy planning, we have never treated patients with intraoperative planning at Northwest Hospital. With the patient anesthetized in the dorsal lithotomy position, the ultrasound probe was inserted into the rectum. The probe was adjusted so that the transverse

images corresponded to the transverse volume study images obtained in the office. While continuously observing the real-time images, preloaded needles containing the preplanned number of seeds were inserted through the proper template apertures, and the needle tips were advanced into the prescribed image planes. Seeds were deposited from each needle by stabilizing the needle obturator, which held the seed column in a fixed position, while the needle was withdrawn slowly, depositing individual seeds into their preplanned positions in the prostate.

Beginning in 1988, axial computed tomography (CT) images of the prostate showing seed positions were obtained within 24–48 hours after the implant. The images were entered into a planning computer to generate isodose curves for quality assessment.

Evaluation

By using the implant date as time "zero," patients were followed with symptom assessment and PSA determinations every 3 months for the first year, every 3–6 months for the second year, and yearly thereafter. The outcome analysis employed three endpoints: evidence of metastatic disease, positive biopsy, and biochemical failure. Due to the slow response of prostate carcinoma to radiation, no patient was failed due to a positive biopsy or PSA within 18 months of treatment. Hence, patients who died within 18 months of treatment were excluded from the data analysis. In our previous paper, biochemical failure was defined as PSA level $>$ 0.5 ng/mL. For this paper, we adopted the American Society for Therapeutic Radiology and Oncology (ASTRO) definition[10] of biochemical failure of three consecutive rises in serum PSA level measured 6 months apart. We use the notation bNED for patients who biochemically (according to PSA level) had no evidence of disease. Observed survival was calculated for each year posttreatment, starting with Year 2, by subtracting from the number of initial patients who were available for evaluation those patients who met the failure criteria for that time period and then dividing by the number of initial patients who were available.

RESULTS

Patient Characteristics

The median age at treatment was 71 years (range, 48–92 years). Of the 229 total patients, 147 (64%) were classified as low risk for extracapsular disease and were treated with brachytherapy alone. These patients constituted Group 1. The remaining 82 patients (36%; Group 2), who had a higher risk of extraprostatic disease, were treated with pelvic radiotherapy followed by brachytherapy.

TABLE 1
Pretreatment Parameters of Individual Groups and Entire Cohort

Pre-tx parameter	Group 1 (%)	Group 2 (%)	All patients (%)
T1a	5 (3)	0	5 (2)
T1b	12 (8)	5 (6)	17 (7)
T1c	16 (11)	8 (10)	24 (10)
T2a	85 (58)	30 (37)	115 (50)
T2b	28 (19)	23 (28)	51 (22)
T2c	1 (1)	12 (15)	13 (6)
T3a	0	4 (5)	4 (2)
Gleason sum 2–4	65	9	74
Gleason sum 5–6	80	55	135
Gleason sum 7–10	0	18	18
Mean pre-tx PSA (s.d.)	8.8 (±10.5)	14.7 (±21.2)	10.9 (±15.1)
Mean age at tx (yrs)	70.5	70.4	70.5

tx: treatment; PSA: prostate specific antigen; s.d.: standard deviation.

The presence or absence of palpable disease, as discussed above, clinically determined all staging categories. Of the total 229 patients, 183 (80%) had palpable disease, possibly reflecting the absence of PSA as a widely used screening tool during that time period. The largest percentage of palpable lesions was in Group 2, the combination therapy arm.

The average pretreatment PSA level all patients was 11 ng/mL (range, 0.4–138 ng/mL). The median pretreatment PSA level in Group 1, 8.8 ng/mL (range, 0.4–75 ng/mL), was significantly lower than that in Group 2 (14.7 ng/mL; range, 0.4–138 ng/mL).

Seventy-four patients (32%) had a Gleason score of 2–4. The majority, 135 patients (59%), had Gleason scores 5 or 6, 16 patients (8%) had a Gleason score of 7, and 1 patient had a Gleason score 8, and 1 patient had a Gleason score of 10. Table 1 summarizes the pretreatment parameters of the patients.

Outcome

Fourteen patients (6%) were excluded from the survival analysis, seven from each treatment group. Seven patients had insufficient PSA follow-up, and 7 patients died of other illnesses within 18 months of the implant, leaving 215 patients for complete evaluation; however, all 14 patients who were lost to follow-up had low or decreasing PSA levels at their last contact. The median follow-up for the observed patient cohort was 93 months (range, 17–144 months); however, that included the 40% of men who died of intercurrent disease. The median follow-up of surviving patients was 122 months. The observed 10-year overall survival rate from all causes of death for the entire study population was 60%. Only 4 patients developed bone metastases.

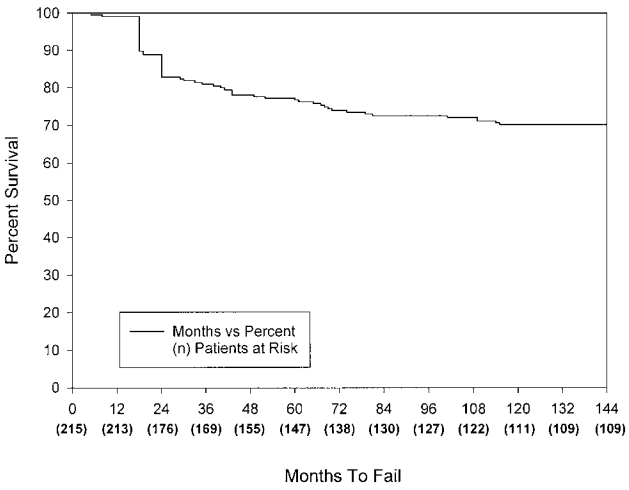

FIGURE 1. Disease free survival (DFS) versus years from implant for the entire cohort using the American Society for Therapeutic Radiation and Oncology (ASTRO) failure criteria (observed DFS) through Year 10 projected to Year 12). The numbers of patients who were available for evaluation (at risk) are shown in parenthesis (12-year DFS, 70%).

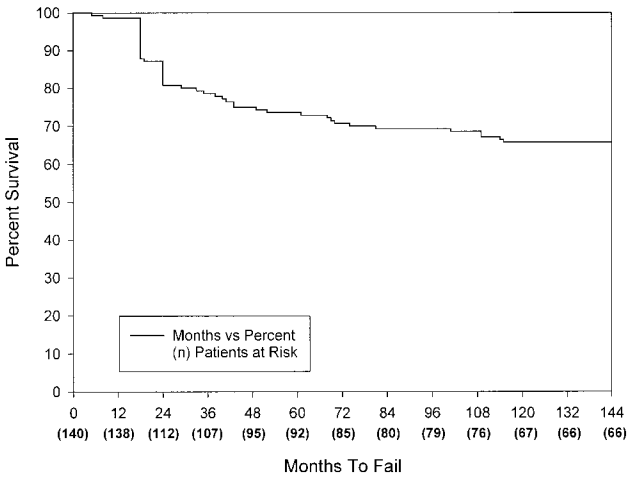

FIGURE 2. Disease free survival (DFS) versus years from implant for Group 1 (monotherapy) using the American Society for Therapeutic Radiation and Oncology (ASTRO) failure criteria (observed DFS through Year 10 projected to Year 12). The numbers of patients who were available for evaluation (at risk) are shown in parenthesis (12-year DFS, 66%).

Death from prostate carcinoma occurred in only 4 of the 215, patients yielding a disease specific 10-year survival rate of 98%.

At the 10-year evaluation point, 151 patients, or 70% of the original 215 patients, had developed no clinical or biochemical evidence of disease. The average value of the last PSA level of this group was 0.16 ng/mL (range, 0.01–0.8 ng/mL).

The observed 10-year bNED control rate for the 140 patients who were treated with monotherapy (Group 1) was 66%. For the 75 patients who were treated with combination therapy (Group 2), the rate was 79%. Figure 1 shows the DFS for the total population, and Figures 2 and 3 document the outcome of the two individual treatment groups. Note that only 2 fewer patients (109 patients vs. 111 patients) were available for evaluation at 12 years versus 10 years and that there were no failures after 115 months; hence, we found that the 12-year survival rates essentially were identical to the 10-year survival rates.

A comparison applied to the 152 patients who were evaluated in our earlier paper between the prior failure criterion of PSA level $>$ 0.5 ng/mL and the ASTRO failure criteria used in the current paper demonstrated a 3–6% survival improvement for that same population with the ASTRO criteria. There was no statistical significance to this difference in survival between the two failure criteria. Treatment-associated morbidity was not examined specifically in this cohort.

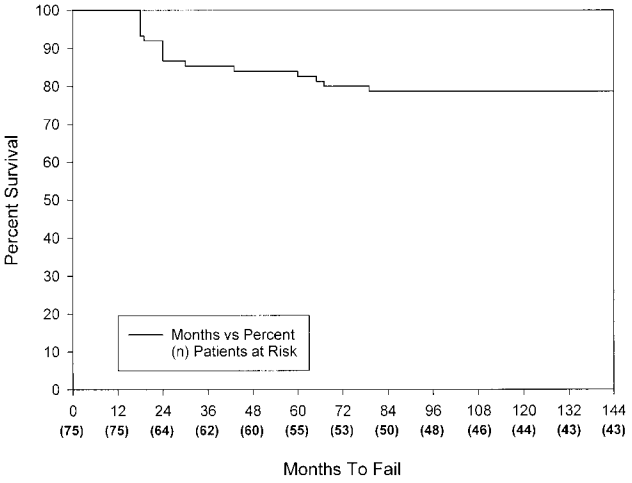

FIGURE 3. Disease free survival (DFS) versus years from implant for Group 2 (combination therapy) using the American Society for Therapeutic Radiation and Oncology (ASTRO) failure criteria (observed DFS through Year 10 projected to Year 12). The numbers of patients who were available for evaluation (at risk) are shown in parenthesis (12-year DFS, 79%).

Patterns of Failure

By 10 years, 86 patients (40%) of the original 215 had died. However, only 4 patients died as a direct consequence of their prostate carcinoma, yielding a disease specific survival rate of 98%. Four patients were failed for positive bone scans, 5 for positive prostate biopsies, and 55 for consecutive PSA elevations according to the ASTRO criteria. The monotherapy group contained all of the positive biopsies, 2 of the positive

bone scans, and 41 of the PSA failures. The majority of recurrences (75%) occurred within the first 5 years after treatment. The failure rate after that time period averaged only 1.5% per year. The latest treatment failure occurred at 115 months, and there were no failures between month 116 and month 144 in the 109 men who were followed for 12 years.

DISCUSSION

The group of patients described in this paper represent some of the earliest work with transperineal ultrasound-guided brachytherapy. At the inception of this study, only Dr. Hans Holm of Denmark had treated patients as we did, and his work formed the foundation for our treatment approach.[11] In our work at Northwest Hospital, the exclusion of the first 14 month's patients, although it shortened the follow-up time, allowed us to overlook our earliest trials and tribulations when our method of implantation was being developed and when equipment and dosimetry were being standardized. Indeed, it was not until 1987 that the procedure was standardized to the extent that we could start offering brachytherapy courses to other physicians.

Even though PSA was widely available in the middle to late 1980s, its utility as both a screening tool and an indicator of disease extent was not appreciated completely in those early years with this population (evidence both the large percentage of men with palpable tumors and the high levels of PSA in the brachytherapy-alone group). Our current criteria for monotherapy limit PSA to < 10 ng/mL, clinical stage to no greater than T2a, and Gleason score < 7. These cut-off values form the basis for treatment decisions in most of our present day patients. It has been confirmed recently by others[12] that brachytherapy alone is inappropriate for some patients, a fact that we have long taught at our seed-implantation courses.

Many of the methods we adopted in the mid-1980s are still in our protocol. The actual brachytherapy radiation doses have not changed, although the prescription dose used has been reduced by 10% due to physical constant changes for I-125 imposed by the American Association of Physicists in Medicine Task Group 43.[9] The dosimetry is now run on dedicated computer software, although dose distribution throughout the gland remains similar to that of the earlier days. Our needles are still preloaded before surgery according to this plan; hence, expensive operating room time is used solely for the implant, not the time-consuming volume studies and treatment planning required by those sites using an intraoperative planning method.[13,14] In our planning stage, seeds are placed in locations determined by the radiation oncologist to be most appropriate for the size and shape of the gland, with the computer software instantaneously showing the resultant isodose curves throughout the gland. We find that, with reasonable attention to the details of patient and probe positioning during both the office volume study and the actual implant, the often reiterated concerns about changes in the size and shape of the gland do not occur. This means that the prostate volume used for the preloaded plan matches exactly the gland implanted. Rather than ordering 10% more seeds like some for intraoperative planning, we order at most two or three extra seeds. Dosimetry from postoperative CT scans confirms excellent seed position and dose coverage for almost every patient. The cost saved the patient from the combination of shortened operating room time and fewer seeds easily can exceed several hundred dollars.

It is now accepted almost universally that sequentially monitored PSA level currently is the best method for classifying a patient as either potentially cured or failed. Sequential PSA values also are verified and validated most easily by independent observers. In our previous report of 10-year results,[4] we compared the total treatment group, monotherapy group, and combination therapy group with different surgical and external beam radiation series. For the previous study, the criterion for biochemical failure was PSA level > 0.5 ng/mL. In a move toward standardization of reporting prostate brachytherapy results, we considered adopting the ASTRO Consensus Conference definition[10] of PSA failure after radiation of three consecutive rise in the PSA level. However, before converting to this new definition for the current study, we attempted to validate the ASTRO failure criteria by returning to the previous study population and repeating the pass/fail analysis from that cohort with the new ASTRO criteria instead of the old PSA level threshold of 0.5 ng/mL. A very small number of patients who had passed with the old criteria now failed, and vice versa. This resulted in a negligible improvement in the prior results with no statistical significance, confirming the validity of both methods when used for long term analysis.

The durability of brachytherapy to control prostate carcinoma is confirmed again by this study. With an average PSA level of only 0.16 ng/mL in the controlled group at both 10 years and 12 years, we were able to demonstrate that prostate carcinoma remaining in vivo indeed can be cured with brachytherapy. Even patients at the top end of the range with relatively high PSA levels (e.g., 0.8 ng/mL) have shown no evidence of disease progression when they were followed for up to 12 years. Thus, it is possible for an intact gland to continue to produce small amounts of

TABLE 2
Ten-Year Observed Results Comparing Our Previous Study Using Failure Criteria of Prostate Specific Antigen > 0.5 ng/mL, the Same Previous Study Using the American Society for Therapeutic Radiology and Oncology Failure Definition, and the Current Study Using the American Society Therapeutic Radiology and Oncology Failure Definition

	Previous study PSA < 0.5		Previous study ASTRO failure criteria		Current study ASTRO failure criteria	
Group	No.	10-yr DF survival (%)	No.	10-yr DF survival (%)	No.	10-yr DF survival (%)
All groups	147	66	147	70	215	70
Group 1	96	60	96	66	140	66
Group 2	51	76	51	79	75	79

PSA: prostate specific antigen; ASTRO: American Society for Therapeutic Radiology and Oncology; DF: disease free.

PSA through "normal" mechanisms and yet be cleared of all malignant cells. This phenomenon has demonstrated in many other human adenocarcinomas, such as salivary gland carcinomas in which cured patients retain salivary function, albeit at reduced levels.

The addition of 77 more patients to the earlier study increased that population by 51%, an increase that was divided proportionately between the two treatment arms of the previous study. Because there have never been any failures after 115 months, the addition of another year of follow-up to the original study did not change the control rates from our prior publication. The comparisons between the different study results as well as between the old PSA criteria and the ASTRO criteria are shown in Table 2.

The apparent benefit of adding external beam radiation to brachytherapy in selected high risk patients is demonstrated by the excellent results achieved in this group. However, we do not yet feel that the data support the addition of external beam radiation to every brachytherapy patient. Some consider that external beam therapy is a necessary treatment component for patients with any stage or grade of prostate carcinoma who are treated with brachytherapy.[15,16] Although the published results from those studies were good, the follow-up was relatively short, and survival was projected by using actuarial methods rather than observation, which was used in our study. Conversely, Grado et al.,[2] reporting 5-year actuarial results on a series of 490 patients who were treated with brachytherapy and brachytherapy combined with external beam radiation therapy, found no significant benefit by adding external beam radiation. Certainly, the expense in terms of both monetary means and side effects involved with indiscriminately treating every prostate brachytherapy patient with external beam radiation will be a consideration in this age of limited health care dollars.

Our current view is that we do not yet have sufficient evidence to support the addition of external beam radiation therapy to every prostate brachytherapy patient. Our practice as this is written is to offer external beam radiation therapy to our higher risk patients only. We continue to evaluate our data and feel that the current recommendations for the judicious addition of external beam radiation therapy are sound. However, as the data mature, these recommendations may change.

No definitive evaluation of the relative merits of different treatment approaches can be made without carefully planned and well-controlled, prospective, randomized trials. However, it can be argued reasonably that this may not occur in the near term. Even if such controlled studies were started today, definitive answers likely would not be available for many years. Meanwhile, in the absence of such enabling standards, physicians must provide the best possible care for their patients, acting on the most valid information available, and treatment decisions must be made on the balance of probabilities instead of waiting for absolute proof that may never even materialize. Increasingly, patients are seeking (even demanding) estimates of their prognosis, which, in many cases, have long been available in the lay press and medical literature.

Finally, it is interesting to compare our current work to the often-referenced Swedish article by Johansson et al.[17] purporting high 10-year survival rates in a group of 223 men with early stage, untreated prostate carcinoma. Both the current study and Swedish studies had similar populations and follow-up. However, 19 (8.5%) of the men who went untreated in Sweden died of prostate carcinoma, whereas did only 4 of our patients (2%) died of their disease. Only 86 of our patients died from any cause versus 124 deaths reported by Johansson et al. Even comparing their "progression free" survival rate (53%) with our DFS rate (70%) shows the potential benefit of treating patients with early stage prostate carcinoma with brachytherapy.

CONCLUSIONS

The addition of 77 more patients to our ongoing analysis of prostate brachytherapy with up to 12-years of follow-up confirms the previously documented excellent results for men with localized prostate carcinoma. There appears to be little risk of late failures, with 75% of this population's failures occurring within 5 years of

the treatment, and no patient failing after 115 months. The appropriate addition of external beam radiation allows even patients with high grade, high stage disease to select brachytherapy as a very effective therapy (79% 10-year DFS rate). The adoption of the ASTRO recommendations for PSA failure resulted in no significant survival changes when applied to our previously reported series.

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