Ten-Year Disease Free Survival after Transperineal Sonography-Guided Iodine-125 Brachytherapy with or without 45-Gray External Beam Irradiation in the Treatment of Patients with Clinically Localized, Low to High Gleason Grade Prostate Carcinoma

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The authors would like to thank Hector Aldape, M.D., John Blasko, M.D., Gordon Grado, M.D., Peter Grimm, D.O., Kent Landin, R.D.M.S., and the nursing staff at Urology Resource Center and Northwest Hospital for their assistance in this study.

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Received May 7, 1998, revision received July 1, 1998; accepted July 2, 1998.

BACKGROUND. The authors report observed 10-year brachytherapy results in the treatment of 152 consecutive patients with clinically organ-confined prostate carcinoma.

METHODS. One hundred and fifty-two consecutive patients with T1–T3, low to high Gleason grade, prostate carcinoma were treated between January 1987 and June 1988 at Northwest Hospital in Seattle, Washington. Their median age was 70 years (range, 53–92 years). Of these 152 patients, 98 (64%) received an iodine-125 implant alone (Group 1), and the remaining 54 patients (36%), who were judged to have a higher risk of extraprostatic extension, also were treated with 45 gray (Gy) of external beam irradiation to the pelvis (Group 2). No patient underwent lymph node sampling, and none received androgen ablation therapy. Multivariate regression and the Mann–Whitney rank sum test were used for statistical analysis. Preoperative patient data with associated success or failure outcomes at 10 years after treatment were used for training and validating a back-propagation neural network prediction program.

RESULTS. The average preoperative prostate specific antigen (PSA) value, clinical stage, and Gleason grade were 11.0 ng/mL, T2, and 5, respectively. The median posttreatment follow-up was 119 months (range, 3–134 months). Overall survival 10 years after treatment was 65%. At last follow-up only 3 of the 152 patients (2%) had died of prostate carcinoma. Ninety-seven patients (64%) remained clinically and biochemically free of disease at 10 years of follow-up and had an average PSA value of 0.18 ng/mL (range, 0.01–0.5 ng/mL). In these patients a period of 42 months was required to reach the average PSA (0.5 ng/mL). The median to last PSA follow-up was 95 months (range, 3–134 months). Postoperative needle biopsies were negative in 56% of patients, positive in 15% of patients, and not available in 29% of patients. Only 6% of patients developed bone metastasis. At 10 years there was no statistically significant difference in treatment outcome between patients who received iodine-125 alone, and those who received iodine-125 with 45-Gy external beam irradiation ($P = 0.08$). Nevertheless, in these two groups preoperative PSA, stage, and Gleason grade were significantly different ($P < 0.01$). In the artificial neural network analysis, pretreatment serum PSA was the most accurate predictor of disease-free survival.

CONCLUSIONS. Percutaneous prostate brachytherapy is a valid and efficient option for treating patients with clinically organ-confined, low to high Gleason grade, prostate carcinoma. Observed 10-year follow-up documents serum PSA levels superior to those reported in several published external beam irradiation series, and comparable to those published in a number of published radical prostatectomy series. ***Cancer* 1998;83:989–1001.** © *1998 American Cancer Society.*

KEYWORDS: prostate carcinoma, brachytherapy, iodine-125, prostate specific antigen, disease free survival, radical prostatectomy, external beam irradiation, deferred treatment, neural network.

The use of serum prostate specific antigen (PSA) as a screening tool has led to the discovery of an increasing number of clinically localized prostate carcinomas.[1,2] Despite this, the optimal management of these patients remains undefined. Options for therapy include radical prostatectomy, external beam irradiation, and brachytherapy. In the U. S., radical prostatectomy and external beam irradiation have been the most common forms of treatment. In 1995, 34.1% of all patients diagnosed with clinically localized disease underwent radical prostatectomy, and 26.3% were treated with external beam irradiation. A mere 2.2% of the patients underwent brachytherapy.[3]

Although prostate brachytherapy was first described at the turn of the century (transperineal insertion of radium needles by digital rectal palpation) this novel treatment did not elicit significant professional interest until 1972, after Whitmore et al.'s description of their implant technique.[4] The procedure called for retropubic exposure of the prostate preceded by pelvic lymphadenectomy, and the implant needles were inserted into the gland freehand.[4] The procedure, initially sanctioned with cautious optimism, soon proved disappointing. Put to trial, the technique (avowed to deliver a higher dose to the prostate than could be administered safely by external beam irradiation and to improve theoretically local control) proved to be associated with unacceptable local control rates, attributed, at least in part, to inaccurate dose distribution by the freehand technique. The poor results led many to abandon brachytherapy as a treatment option for prostate carcinoma.[5–7]

Then, during the 1980s several technologic advances took place. Based on the description by Watanabe et al. of prostate ultrasound anatomy, Holm et al. used transrectal ultrasound (TRUS) to guide percutaneous delivery of radioisotopes, achieving uniform seed distribution in the prostate.[8, 9] Then came new and improved computerized algorithms for determining optimal seed configurations and biplanar ultrasound probes and an increasing familiarity with TRUS among urologists worldwide.[10–12] In addition, published 7-year and 8-year actuarial results of this treatment method provided biochemical (PSA) disease free results comparable to those achieved with external beam irradiation and radical prostatectomy, although with significantly lower morbidity.[13] The technical improvements occurred at a time when the escalated use of serum PSA as a screening tool had begun to discover increasing numbers of clinically organ-confined tumors, and routine serial posttreatment PSA determinations appeared to provide an unprecedented yardstick for judging treatment efficacy. At the same time, critics began to question the rationale for subjecting patients with prostate carcinoma– a "slow growing malignancy"–to treatments of unproven long term value, however they may influence quality-of-life. These combined events led to a resurgence of interest in the less invasive prostate brachytherapy.

Although intermediate follow-up reports have shown favorable biochemical disease free survival rates for brachytherapy, a lack of longer term data has limited full evaluation of the treatment method.[13–18] In this study we report the observed 10-year follow-up of 152 consecutive prostate carcinoma patients who underwent transperineal, sonographically guided brachytherapy a decade ago. These observed results expand on previously presented actuarial results.[13]

MATERIALS AND METHODS

Patients

A total of 162 implants were performed over the period of the study. Ten patients were excluded from the study because of higher clinical stage, palladium treatment, or prior hormonal or radiation failure. One hundred and fifty-two consecutive patients with International Union Against Cancer TNM stages T1-T3 biopsy proven prostate carcinoma were treated with TRUS-guided iodine-125 brachytherapy at Northwest Hospital in Seattle, Washington between January 1987 and June 1988. Ninety-eight patients (Group 1) were treated with iodine-125 to 160 gray (Gy) to a target volume including the prostate and a 2–3-mm margin added during treatment planning. Fifty-four patients (Group 2) initially received 45-Gy external beam irradiation followed by 120 Gy of iodine-125. The majority of patients were assigned to their treatment group based on clinical stage and biopsy Gleason grade. Group 1 patients were considered to be at low risk for extraprostatic disease, and Group 2 patients were deemed to have higher risk. No patient received androgen ablation therapy.

Clinical Evaluation

Evaluation was comprised of digital rectal examinations, bone scans, and PSA determinations. The clinical stages of the patients are listed in Table 1. Patients with positive biopsies and palpably negative prostates who had not undergone a previous transurethral prostatectomy were classified as T1c. Patients classified as

TABLE 1
Clinical Stages At Presentation Determined according to UICC TNM Classification (n = 151)

T Classification	No. of patients in Group 1	No. of patients in Group 2	Total no. of patients
T1a	4	0	4 (2.6%)
T1b	10	2	12 (7.9%)
T1c	6	4	10 (6.6%)
T2a	56	20	76 (50.3%)
T2b	22	14	36 (23.8%)
T2c	0	10	10 (6.6%)
T3a	0	3	3 (2%)

UICC: International Union Against Cancer.
One patient from Group 2 had no clinical stage assigned.
The difference in clinical stage between Group 1 and Group 2 was significant ($P = 0.001$), using the Mann–Whitney test.

TABLE 2
Preoperative Serum Prostate Specific Antigen Levels Determined in 147 Patients, Divided by Group

PSA level (ng/mL)	No. of patients in Group 1	No. of patients in Group 2	Total no. of patients
PSA < 4	46	10	56 (38.1%)
PSA 4–10	29	20	49 (33.3%)
PSA > 10	20	22	42 (28.6%)

PSA: prostate specific antigen.
Five patients (three in Group 1 and two in Group 2) had no preoperative prostate specific antigen level.
The difference in prostate specific antigen levels between Group 1 and Group 1 was significant ($P = 0.001$) using the Mann–Whitney test.

T2b and higher, and those with T1 lesions with a Gleason grade >6 generally were considered to be at risk for extraprostatic disease extension. All but five patients had pretreatment PSA determined (Table 2). Table 3 shows the pretreatment Gleason grades of the patients.

Pretreatment TRUS Planning

To plan local therapy, the size and volume of the prostate was measured by TRUS. The gland was mapped out in 5-mm steps, with each cross-sectional image carefully outlined with a light pen and overlaid with a grid that corresponded to apertures in a multichannel puncture attachment. The target circumference was delineated on each of these images and then entered into a computer algorithm from which a simulated three-dimensional image of the target volume was obtained, with seed arrangement and dose designation to provide a minimum dose of 160 Gy over the effective life of the radionuclide. This was verified by superimposing isodose distribution obtained from each cross-sectional image over the target outline of the respective image.

TABLE 3
Preoperative Tumor Biopsy Grade Determined by Gleason Grade in 150 Patients Divided By Group

Gleason Grade	No. of patients in Group 1	No. of patients in Group 2	Total no. of patients
Gleason Grade ≤ 4	44	2	46 (30.6%)
Gleason Grade 5–6	52	39	91 (60.7%)
Gleason Grade ≥ 7	0	13	13 (8.7%)

Two patients from Group 1 had no tumor grade assigned.
The difference in Gleason grade between Group 1 and Group 2 was significant ($P = 0.001$) using the Mann–Whitney test.

Group 2 patients initially received 45 Gy of external beam irradiation to the prostate and a limited pelvic field. Irradiation was delivered with conventional technique in 25 fractions of 1.8 Gy each in 4 fields (right, left, anterior, and posterior). The target volume was prescribed as the volume of tissue that included the prostate and periprostatic regions considered to be at risk of microscopic extension. The implant was performed 2 weeks after completion of the external beam irradiation course. The 160-Gy and 120-Gy dose specification of iodine-125 was installed before the International Commission on Radiological Units criteria.

Operative Implantations

All implantations were performed by the team of the senior author and a radiation oncologist in the surgical outpatient section of Northwest Hospital. The procedures were performed transperineally under TRUS guidance as described previously.[19]

Postimplant Follow-Up

The treatment protocol specified serum PSA evaluation every 3–6 months during the first year and then annually. All postbrachytherapy PSA measurements performed at Northwest Hospital were determined by the Tandem-E assay (Hybritech, Inc., San Diego, CA) until 1995, when it was changed to the Tosoh assay (Tosoh, Tokyo, Japan). Approximately 20% of the postimplant PSA determinations were ordered by referring physicians without our knowledge of the assay used. The treatment protocol further specified prostate needle biopsies annually for 5 years. Biopsies were TRUS-guided with an 18-gauge TruCut needle (MD-Tech Co., Gainesville, FL) and a Biopty gun™

(Radioplast AB, Uppsala, Sweden). Three to eight random and/or target-directed biopsies were obtained. Particular attention was paid to pretreatment positive biopsy site(s). The biopsies were classified as negative, positive, or indeterminate. The latter category characterized nests of radiation-damaged tumor cells whose recovery potential was uncertain. Such patients were followed with repeat biopsies until a positive or negative diagnosis was made. Negative biopsies portrayed radiation changes comprised of glandular atypia and stromal fibrosis. No malignant cells were identified. All biopsies were evaluated at Northwest Hospital by one of two staff senior pathologists. Bone scans, computed tomography scans, magnetic resonance imaging, or other tests were obtained as clinically indicated.

Definitions

Clinical recurrence included a positive biopsy, radiographic evidence of metastases, or both. The PSA values recorded in these patients were those measured at the time the clinical recurrence designation was made. Biochemical failure was defined as PSA $>$ 0.5 ng/mL, a threshold adopted to facilitate outcome comparisons with patients treated by radical prostatectomy. We also accepted a PSA threshold of $\leq$ 1.0 ng/mL for determinations performed 2 years after implantation for 3 patients prematurely lost to follow-up. In the biochemically disease free patients (PSA $\leq$ 0.5 ng/mL), the PSA value of record was that obtained at last follow-up.

Statistical Analysis

The artificial neural network technology that mimics the brain's problem-solving process was used for analysis. A turboprop-variant training method was used in this study.[20] This is a back-propagation training algorithm that operates much faster than other methods and has the significant advantage of not being sensitive to learning rate and momentum factors. Training proceeded through an entire epoch of patient cases before network weights were updated. It added all the weight changes and the end of the epoch modified the weight. This method utilized an independent weight update size for each different weight, rather than the usual method of having a single learning rate and momentum that applies to all weights. This combination of learning properties has been found to yield acceptable accuracy for predicting prospective patient outcome.[20] In the database 16% of our patients were chosen randomly and withheld as a validation set. The remaining 84% were used to train the neural network. When training and architecture evolution (determination of the optimum number of hidden neurons) was complete, the network was presented with the validation set and asked to predict the success or failure of brachytherapy for each of these individuals. The network results then were compared with actual outcomes and a set of statistics generated. In addition, a multivariate regression analysis was developed for the training set and applied to the validation set. Multivariate regression and Mann–Whitney rank sum tests were used for conventional statistical analyses. The input variables used were age, clinical classification, pretreatment PSA, Gleason grade, and 45-Gy external beam irradiation. The neural network system always ran two cases for each patient; one case included preimplant external beam radiation and one did not. We then were able to decide whether brachytherapy alone was appropriate for a given patient, and whether a combination of radiation could increase the likelihood of success significantly.

Study Administration

Informed consent was obtained from all subjects. The Pacific Northwest Cancer Foundation was responsible for study administration and data management.

RESULTS

Patients Evaluated

The median age of the patients was 70 years (range, 53–92 years), and the median follow-up was 119 months (range, 3–134 months). The majority of patients (124 of 152; 82%) had palpable lesions. Table 1 shows their categories according to the International Union Against Cancer TNM classification.[21] Pretreatment PSA values, accessible in 147 of 152 patients (97%) ranged from 0.4–138 ng/mL, with an average value of 11.0 ng/mL (Table 2). The average pretreatment PSA for Group 1 was 8.5 ng/mL and was 15.6 ng/mL for Group 2. All patients had core needle biopsy-proven prostate adenocarcinoma scored by the Gleason grading system. The Gleason grade, ranging from 2–10, had a median of 5 (Table 3). Morbidity associated with brachytherapy has been described previously and was not included in this study.[13,22] In addition, a preliminary cross-sectional survey of patients treated with brachytherapy at Northwest Hospital has been completed and currently is undergoing analysis (Talcott JA, personal communication).

Five patients were lost to follow-up, leaving 147 patients for evaluation. Of these, 67 patients (46%) were alive with no evidence of disease (NED). Fifty-three patients died during the 10-year study period. Figure 1 shows a 65% overall survival, and Figure 2 shows a 71% survival for successfully treated patients. Thirty of the 53 deceased patients died with NED, and prostate carcinoma was the direct cause of death in only 3 of the patients, yielding a disease specific sur-

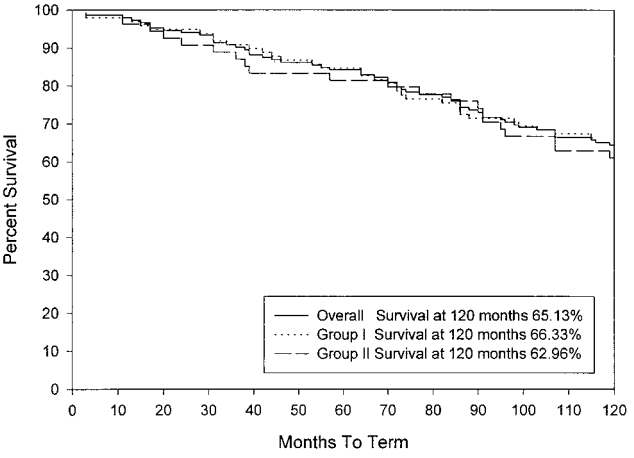


FIGURE 1. Observed 10-year overall survival by groups for the study population (n = 152). Group 1 was comprised of 98 patients treated with iodine-125 brachytherapy alone. Group 2 was comprised of 54 patients treated with a combination of 45-gray external beam irradiation and iodine-125 brachytherapy.

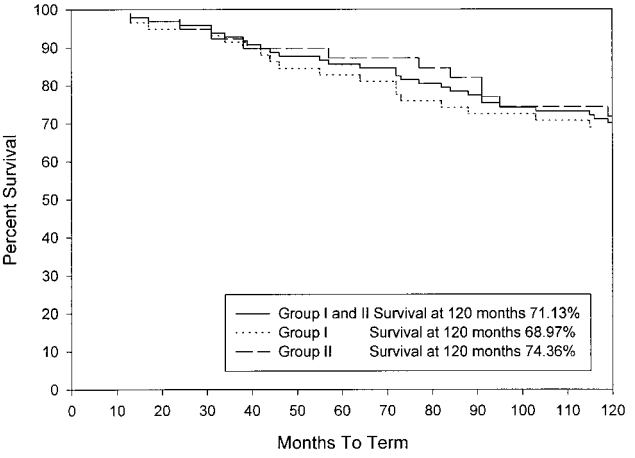


FIGURE 2. Observed 10-year survival, by group in all 97 patients who became free of disease. Group 1 was comprised of 98 patients treated with iodine-125 brachytherapy alone. Group 2 was comprised of 54 patients treated with a combination of 45-gray external beam irradiation and iodine-125 brachytherapy.

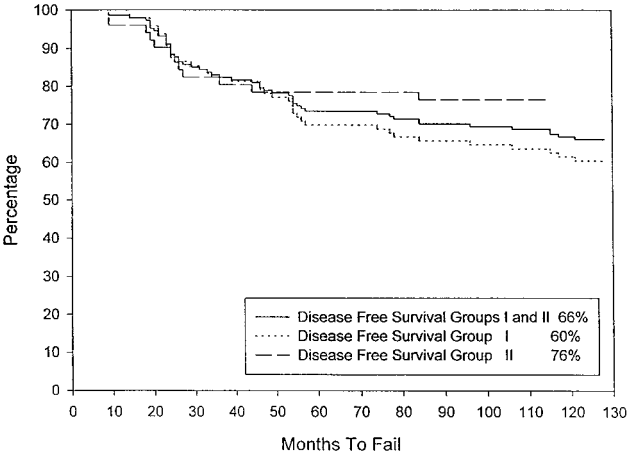


FIGURE 3. Observed 10-year disease free survival by groups (Prostate specific antigen (PSA) ≤ 0.5 ng/mL). The difference in outcome between Group 1 and Group 2 was not significant ($P = 0.09$). Positive bone scan, and/or positive biopsy, and/or PSA > 0.5 ng/mL signified treatment failure. Group 1 was comprised of 96 patients treated with iodine-125 brachytherapy alone. Group 2 was comprised of 51 patients who were treated with a combination of 45-gray external beam irradiation and iodine-125 brachytherapy. Five patients two in Group 1 and three in Group 2) were lost to follow-up.

vival of 98% (149 of 152). Twenty patients with recurrent disease died of other causes.

Observed Disease Free Survival

Figure 3 shows the treatment outcome of the 147 patients at 5 and 10 years. The observed disease free survival of Group 1 patients at 5 years was 71% (68 of 96 patients); Group 2 patients, it was 80% (41 of 51 patients), and for the 2 groups combined it was 74% (109 of 147 patients). The average PSA level of the latter group was 0.2 ng/mL (range, 0.1–1.7 ng/mL). At 10 years, the observed disease free survival of Group 1 patients was 60% (58 of 96 patients); for Group 2 patients it was 76% (39 of 51 patients); and for the 2 groups combined it was 66% (97 of 147 patients). The average PSA level of the latter group was 0.18 ng/mL (range, 0.01–0.5 ng/mL). Figures 4 and 5 show the 10-year disease free survival curves for PSA levels ≤ 0.4 ng/mL and PSA levels ≤ 0.2 ng/mL. The 10-year disease free survival stratified by clinical stage, pretreatment PSA, and Gleason grade is illustrated in Figures 6, 7, and 8, respectively.

PSA Follow-Up

Overall, there were 1780 PSA measurements obtained during the postoperative follow-up period of the study. Of these, 376 PSA measurements were performed within the first year for 150 patients. This included 134 patients checked within 6 months and 123 patients who had at least another PSA determination within 7–12 months. Five patients were considered lost follow-up because of no PSA determination (two patients) or only a single PSA determination (3 patients). Reliable posttreatment PSA values were accessible in 147 patients. After implantation, the PSA declined from pretreatment values in all patients. It reached levels of PSA ≤ 1.0 ng/mL within 24 months in 74 of 109 successfully treated patients (68%) and continued on a downward slope to levels of PSA ≤ 0.5

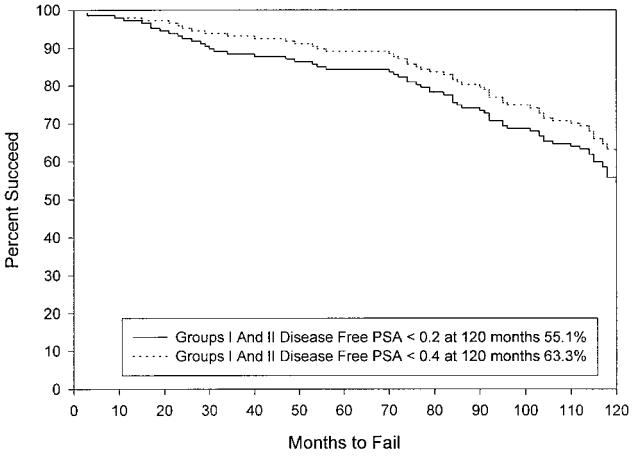


FIGURE 4. Observed 10-year disease free survival (groups 1 and 2 combined) for prostate specific antigen (PSA) level $\leq$ 0.2 and $\leq$ 0.4 ng/mL. Groups 1 and 2 combined were comprised of 147 patients treated with iodine-125 brachytherapy, with or without 45-gray external beam irradiation. Five patients (two in Group 1 and three in Group 2) were lost to follow-up. Two patients with a PSA level $>$ 0.2 ng/mL and 3 patients with a PSA level $>$ 0.4 ng/mL were designated as treatment failures at 120 months.

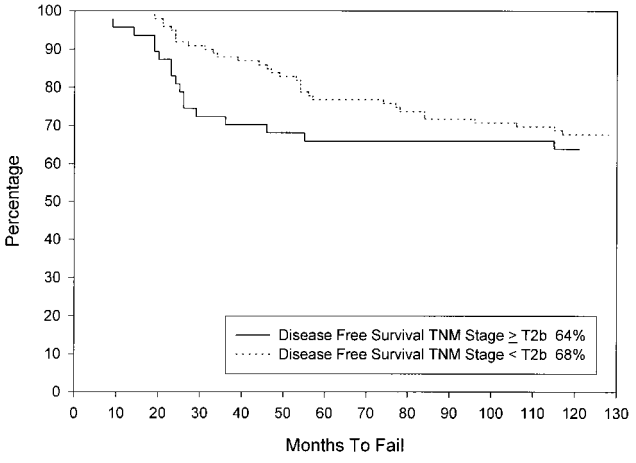


FIGURE 6. Observed 10-year disease free survival by clinical stage (available in 151 patients). Sixty-eight percent (67 of 99) of patients with clinical tumors less than T2b were free of disease (prostate specific antigen (PSA) levels $\leq$ 0.5 ng/ml), whereas 3 were lost to follow-up. Sixty-four percent (30 of 47) of patients with clinical tumors of T2b or lower were free of disease, whereas 2 were lost to follow-up. There was no significant difference in treatment outcomes.

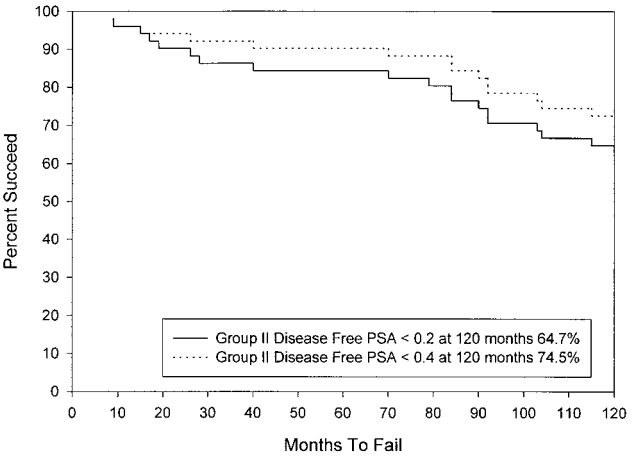


FIGURE 5. Observed 10-year disease free survival in group 2 patients for a prostate specific antigen (PSA) level of $\leq$ 0.2 ng/mL and a PSA level $\leq$ 0.4 ng/mL. One patient, whose PSA at 10 years was 0.2 ng/mL, was subsequently designated a treatment failure by rising PSA values.

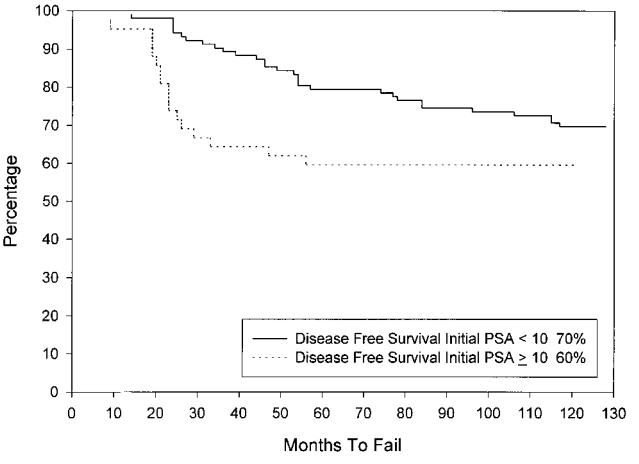


FIGURE 7. Observed 10-year disease free survival by preoperative prostate specific antigen (PSA) levels (available in 147 patients). Seventy percent (71 of 102) of patients with a PSA level $<$ 10 ng/mL were free of disease (PSA $\leq$ 0.5 ng/mL), whereas 2 were lost to follow-up. Sixty percent (25 of 142) of patients with a PSA level $\geq$ 10 ng/mL were free of disease, whereas 1 was lost to follow-up.

ng/mL. It is noteworthy that the time required to reach an average PSA level $\leq$ 0.5 ng/mL extended to nearly 4 years (Fig. 9). Regular PSA measurements were available in 123 and 119 patients at 3 and 4 years, respectively. In 4 patients the PSA declined to 0.6–0.9 ng/mL in the 2–5 years after implantation. No further PSA measurements were performed. Another patient whose PSA was 1.7 ng/mL at 5 years, had his next PSA determination at 8 years that gave a PSA value of 0.2 ng/mL, which was maintained beyond 10 years. These five patients were included in the disease free category. At 8–10 years, regular PSA determinations continued and were obtainable in 71 of the patients, (42 patients in Group 1 and 29 patients in Group 2).

Biopsy Follow-Up

A minimum of one set of negative postimplantation biopsies was available in 85 patients (56%), implying local cure. The average time lapse between implant

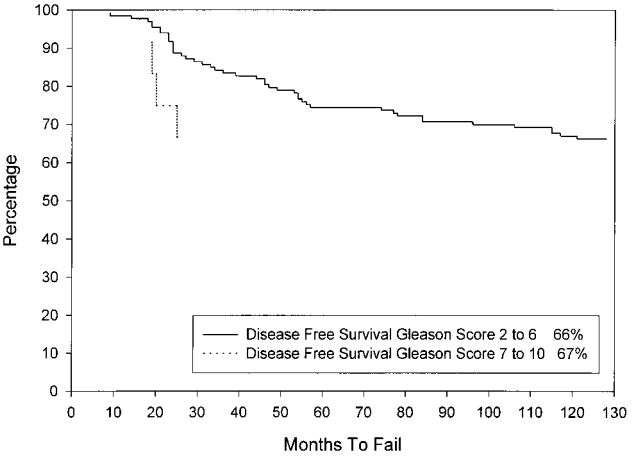


FIGURE 8. Observed 10-year disease free survival by preoperative Gleason score (available in 150 patients). Sixty-six percent (88 of 133) of patients with a Gleason grade < 7 were free of disease (prostate specific antigen (PSA) level ≤ 0.5 ng/mL), whereas 4 were lost to follow-up. Sixty-seven percent (8 of 12) of patients with a Gleason grade ≥ 7 were free of disease, whereas 1 was lost to follow-up. There was no significant difference in treatment outcomes.

and biopsy was 55 months (range, 12–128 months). Positive biopsies were obtained in 23 patients (15%), and they were classified as local failure. The median PSA level in these 23 patients was 2.7 ng/mL (range, 0.3–28.9 ng/mL). Although positive biopsies generally correlated with PSA values > 1.0 ng/mL, it is noteworthy that 3 of these 23 patients had PSA levels ranging from 0.3–0.6 ng/mL, and in another 3 patients the positive biopsies were obtained 115–128 months after implantation. Biopsies on 15 patients, obtained <18 months after implantation, were classified as indeterminate. On repeat biopsies, 11 reverted to negative and 4 to positive. Posttreatment biopsies were not available for 44 patients (29%). Nine patients (6%) developed bone metastases 19–128 months after implantation. All had elevated PSA levels and positive biopsies.

Statistical Analyses

There was significantly statistical difference between Group 1 and Group 2 with regard to preoperative stage, PSA, and Gleason grade ($P < 0.01$). There was no significant difference in the disease free survival rates between the 2 groups at 10 years ($P = 0.08$) (Fig. 3).

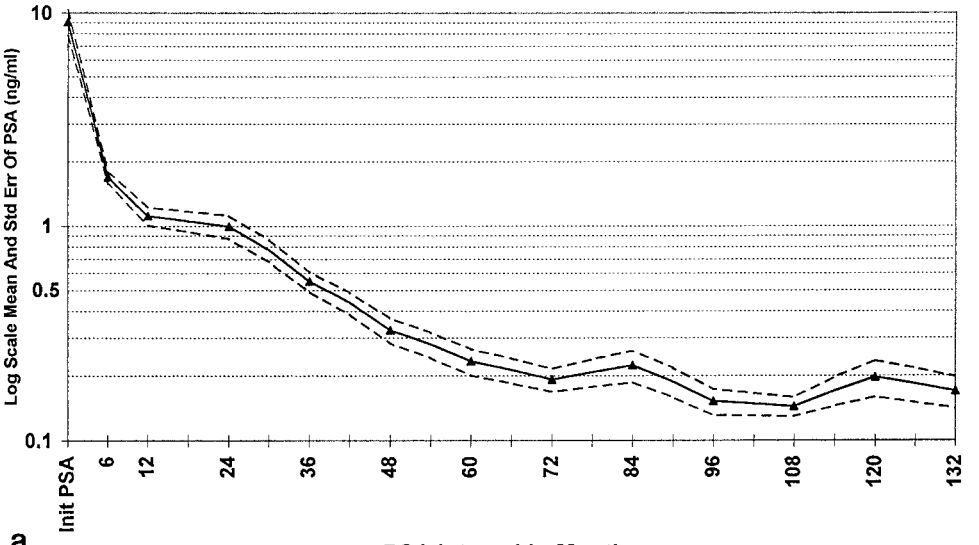
The nonrandom distribution of the variables in the database called for the Mann–Whitney rank sum test to evaluate correlation between the variables. When the variables were considered as isolated entities, the only prognostically important variable was the pretreatment PSA level ($P = 0.005$).

The neural network evaluated prognostic efficacy of combinations of variables in a nonlinear fashion. Table 4 shows the statistical results of the predictive ability of the neural network compared with a multivariate regression analysis. The positive predictive value refers to 10-year brachytherapy failure, and the negative predictive value to 10-year treatment success. The neural network was able to predict 10-year success with 82% accuracy and failure with 76% accuracy, a 10% increase over that attained with regression analysis. Furthermore, the 45-Gy preimplantation external beam irradiation was used as an input variable to the neural network and was an important parameter in outcome (i.e., success or failure of brachytherapy). Only 16% of the patients were held back randomly for validation because the more patients held back from the analysis the higher the likelihood that important information would be lost to the neural network. In a database such as the one presented in the current study, experience indicates that randomly holding back approximately 20% of the database for validation purposes significantly increases the chances the neural network will not learn the underlying patterns in the database properly.

DISCUSSION

Determination of optimal therapy for clinically organ-confined prostate carcinoma must await results of well controlled prospective studies. In the interim retrospective comparisons must suffice. In the past this was difficult due to disparities in data inclusion and endpoint stratification. However, pretreatment and serial follow-up PSA determination, has facilitated outcome reporting greatly and allowed for more objective evaluation of different treatments. In surgical patients, the failure of serum PSA to approach undetectable levels after removal of the prostate gland or a rising PSA level indicates treatment failure. Given that the prostate remains in situ after irradiation, the serum PSA cannot be used to detect failures as readily as after radical prostatectomy. Based on long term follow-up of patients treated with external beam irradiation or brachytherapy, it appears that those who achieve a serum PSA < 1.0 ng/mL and maintain that level are likely to become long term disease free survivors.[23,24] Stratifying disease manifestation in this manner allows a more precise assessment of the effects of a given treatment on prostate carcinoma.

The current study reports 10-year observed efficacy results of clinically organ-confined prostate carcinoma treated with TRUS-guided iodine-125 brachytherapy with and without 45-Gy external beam irradiation. The patients underwent pretreatment and serial posttreatment PSA determination, and by set-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PSA Interval In Months

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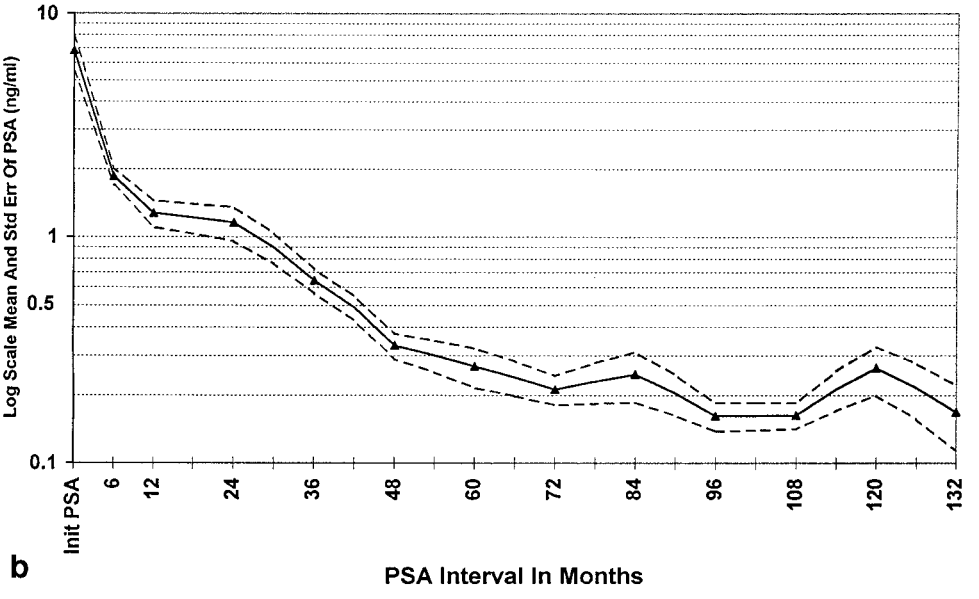
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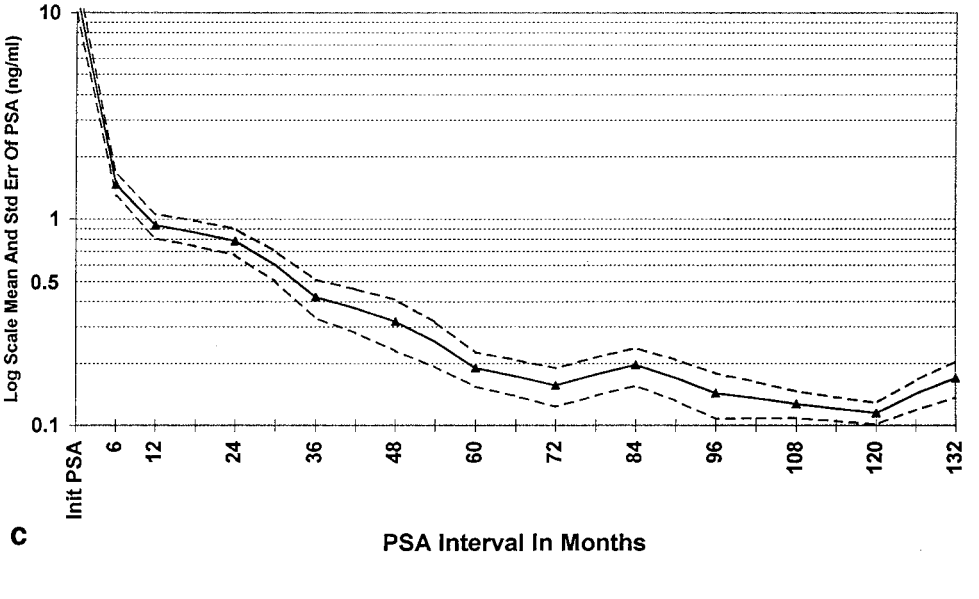
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PSA Interval In Months

c

TABLE 4
Comparative Analysis between the Neural Network Predictive Ability and the Multivariate Regression Analysis

Statistical results	Neural network	Regression analysis
Sensitivity	55%	15%
Specificity	90%	94%
Positive predictive value	76%	59%
Negative predictive value	82%	64%
Overall accuracy	76%	66%

Positive predictive value refers to brachytherapy failure and negative predictive value refers to success of brachytherapy.

ting the endpoint of PSA as $\leq$ 0.5 ng/mL, the study outcome reasonably may be compared with similar outcomes from radical surgery and external beam irradiation series. Figure 3 shows the 5-year and 10-year disease free survival of these patients.

Our study documented that interstitial prostate irradiation can achieve a PSA level comparable to the standard PSA disease free survival after radical prostatectomy. At 10 years, 66% of the patients had disease free survival with a PSA level $\leq$ 0.5 (Fig. 3). In addition, 58.5% (86 of 147) of these patients were free of disease and had achieved a PSA level $\leq$ 0.4 ng/ml. In addition 48.3% of the patients (71 of 147) had a PSA level $\leq$ 0.2 ng/mL. In Group 2, the disease free survival after treatment was impressive (Fig. 5). Of the 51 patients initially diagnosed with a more aggressive disease, 74.5% had no evidence of disease after treatment, and achieved a PSA level $\leq$ 0.4 ng/mL. Another 64.7% had a PSA level $\leq$ 0.2 ng/mL. The apparent finding that patients in the less favorable Group 2 had a better 10-year disease free survival than Group 1 patients (76% vs. 60%) was not statistically significant (P = 0.08). However, if a more stringent endpoint of PSA $\leq$ 0.4 ng/mL was applied, resulting in a 10-year disease free survival of 63%, the outcome difference between the two groups became statistically significant (P = 0.046). One may speculate that the reason for the improved results in Group 2 was the addition of 45-Gy external beam irradiation.

The large number and longer term of follow-up biopsies is another source of strength in this study. Seventy-one percent of our patients underwent at least 2 posttreatment biopsies to document local tumor response after brachytherapy. We have reported a relatively high incidence of negative biopsy after brachytherapy compared with that reported after previous brachytherapy or external beam irradiation.[25,26] However, a sampling error was conceivable with any of the 85 patients (56%) with a negative biopsy in the current study. However, in these cases the consistent PSA follow-up results confirmed the disease free survival status. The evidence of tumor disappearance on biopsy supported by a decline in the PSA level led us to believe that brachytherapy could control prostate carcinoma better than external beam irradiation. In some cases a repeat biopsy was essential to determine disease status. Any confirmed positive biopsy 2 years after treatment was considered as treatment failure, regardless of PSA level. Actually, only three patients had positive biopsy results earlier than biochemical recurrence. This infrequent incidence was not different from that reported after external beam irradiation or radical prostatectomy.[26,27] We believe that biochemically disease free status might be more reliable than biopsy results after brachytherapy.

Neural networks are computer-based statistical models that can be used to imitate biologic neural processes. These networks learn from experience by learning to improve their guesses by incorporating feedback from each success and failure. The learning process used in this study was a modified form of back-propagation of errors, a training algorithm that operates much faster than other methods. In this study 84% of randomly chosen patient data were used for training the network, and 16% for validating it. The trained neural network was able to predict therapy success in this series of patients with an accuracy of 82% and a failure prediction accuracy of 76% using clinical information available prior to therapy. Of significance was the network's ability to identify individual patients who would benefit from 45-Gy external beam irradiation prior to brachytherapy.

A significant number of patients diagnosed with clinically localized prostate carcinoma elect to be managed by deferred treatment. This long has been an accepted strategy for older patients with significant comorbidity. Whether it is a reasonable option for healthy patients with a longer life expectancy remains uncertain. Proponents of deferred treatment justify

FIGURE 9. (a) Mean and standard error (Std Err) of prostate specific antigen (PSA) for all 97 successfully treated patients (Groups 1 and 2). Note the slow decline from the initial PSA level (Init PSA) to 0.2 ng/mL within the 10-year follow-up. (b) Mean and Std Err of PSA for 58 successfully treated patients in Group 1. Note the slow decline from init PSA to 0.2 ng/mL within the 10-year follow-up. (c) Mean and Std Err of PSA for 39 successfully treated patients in Group 2. Note the slow decline from Init PSA to 0.2 ng/mL within the 10-year follow-up.

TABLE 5
Disease Free Survival for Patients Undergoing Prostate Brachytherapy with or without 45-Gray External Beam Irradiation Compared with External Beam Irradiation Alone for Clinically Localized Prostate Carcinoma with No Evidence of Disease At 5-Year and 10-Year Follow-Up

References and Institutions	No. of cases	Definition of PSA Failure or PSA cutoff	NED% at 5-Year FU	NED% at 10-Year FU	Average FU	Treatment radiation	Notes/clinical stage
Hancock et al.[36]	110	> 4.0	NA	38% (at 12.4-yr FU)	12.4 yrs	XRT	T1–T4
Stanford University					XRT		Observed data, at 12.4-yr FU
Hanks et al.[37]	502	> 1.5	44%	NA	50 mos	Conventional/ Conformal irradiation	T1–T3
Fox Chase CC					Median FU		Projected, ⇓to 41% at 7-yr FU
Kuban et al.[33]	652	< 4.0	60%	20%	14–17 yrs	XRT	T1–T4
E. Virginia Medical School						XRT	Observed data, long term FU
Rosenzweig et al.[38]	285	> 4.0	NA	33%	NA	XRT	T1–T2
Yale Univ. Medical School							Projected data, ⇓ to 22% in T3
Schellhammer et al.[39]	434	> 4.0	NA	21.7%	10-yr	123 patients I-125/311 XRT	Stage A,B,C (i.e, T1–T4)
E. Virginia Medical School		> 0.5	NA	13%	Minimum FU		Different results for PSA cutoffs
Stamey et al.[40]	113	≥ 1.0	20%	NA	6 yrs	XRT	Stage A,B,C (Jewett staging) (i.e., T1–T4)
Stanford University			25.4%			XRT	Projected data, ⇑ to 25% in T1–T2
Zagars[41]	269	> 1.0	64%	NA	33 mos	XRT	T1–T2
M. D. Anderson CC							Projected (actuarial) data
Zietman et al.[42]	85	> 1.0	41%	NA	> 2 yrs	XRT	T1–T2
Massachusetts General Hospital						Radical XRT	Projected data, ⇓ to 15% in T3–T4
Ragde et al.[22]	126	> 1.0	87%	NA	69 mos	Brachytherapy	T1–T2
Northwest Hospital					Median FU	I-125 solely	Projected data at 7-yrs FU
Current study	98	> 0.5	71%	60%	10-yr	Brachytherapy	T1–T2
Group 1 alone					Median FU	I-125 alone	Observed data, 10-yr FU
Current study	152	> 0.5	74%	66%	10-yr	Brachytherapy I-125/XRT-45 Gy	T1–T3
Groups 1 and 2					Median FU		Observed data, 10-yr FU

PSA: Prostate specific antigen; NED: no evidence of disease; FU: follow-up; CC: cancer center; NA: not available. I-125: iodine-125; Gy: gray; XRT: external beam irradiation.
Note the difference between projected and objected results, and the varying prostate specific antigen endpoints used. As observed in the current study, the actuarial results previously reported (prostate specific antigen level ≤ 1.0 ng/mL) were more optimistic than the observed result.

their preference by citing the significant morbidity associated with radical prostatectomy and external beam irradiation, and question whether the early detection and treatment of prostate carcinoma while it is still organ-confined would reduce mortality. Therefore it would be of interest to compare a deferred treatment series with a less intrusive, cost-effective, lower morbidity, brachytherapy series.

Adolfsson et al. recently reported on 122 patients with low grade prostate carcinoma managed by deferred treatment.[28] The median age at diagnosis was 68 years, and 64 of 122 patients (52%) required antitumor medication during follow-up. Overall and disease specific 10-year survival in these patients were 52% and 90%, respectively; 30 patients required transurethral resection and skeletal metastases were detected in 32 of 122 patients (26%). In contrast, the median age of patients in our brachytherapy series was 70 years; they had a higher grade tumor, and only 50 of 147 (34%) required antitumor medication. The 10-year overall and disease specific survival rates in this brachytherapy series were 65% and 98%, respectively, and metastases occurred in only 9 of 147 (6%). At 10 years, 69 of our 97 successfully treated patients (71%) were alive and disease free, whereas no patient in the deferred treatment series was alive and free of disease. Prostate carcinoma may grow quickly or it may grow slowly; nevertheless, it will continue to grow. One may speculate that "watch-and-wait" management of clinically organ-confined prostate carcinoma soon may be replaced by an effective low morbidity treatment, such as brachytherapy.

External beam irradiation long has been regarded as the archetype for radiation treatment of localized prostate carcinoma. Based on digital rectal examination, the local control rate after external beam irradi-

TABLE 6
Disease Free Survival for Patients undergoing Brachytherapy with or without 45-Gray External Beam Irradiation Compared with Radical Prostatectomy for Clinically Localized Prostate Carcinoma - No Evidence of Disease at 5-Year and 10-Year Follow-Up

References - Institutions	Average age (yrs)	Peroperative PSA (ng/mL)	Average FU	No. of Cases	Definition of PSA Failure or PSA Cutoff	NED% at 5-Yr FU	NED% at 10-Yr FU	Notes/clinical stage
Catalona and Smith [43]	63.9 ± 7	67% < 10.0	27 mo	925	> 0.6	78%	NA	T1–T2
Washington University		33% ≥ 10.0				± 4%		Projected (actuarial) data
Ohori et al.[44]	63	68% ≤ 10.0	36 mo	500	> 0.4	76%	73%	T1–T3
Baylor College	range 43–79	32% > 10.0				± 5%	± 6%	Projected (actuarial) data
Partin et al.[45]	59 ± 64	78% ≤ 10.0	4.1 ys	955	> 0.2	83%	70%	T1-T2
Johns Hopkins		22% > 10.0						Actual (observed) data
Paulson[46]	65	NA	13.5 yrs	613	≥ 0.5	75%	NA	Localized (i.e., T1–T2)
Duke University	Median age							Actual data
Trapasso et al.[47]	NA	Average 11.9	34 mo	601	≥ 0.4	69%	47%	T1–T2
UCLA		range 0.3–96.0	Median FU			± 2%	± 3%	Projected (actuarial) data
Zincke et al.[48]	65.3 ± 6.4	NA	5 ys	3170	> 0.4	77%	54%	T1–T2
Mayo Clinic								Actual data, ⇓to 40% at 15-yrs FU
Current study	70	Average, 11.0	10 yrs	152	> 0.5	74%	66%	T1–T3
Groups 1 and 2	Range 53–92	Range 0.4–138.0	Median FU					Observed data, 10 yr FU
Current study	70	Average, 15.6	10 yrs	54	> 0.5	80%	76%	T1–T3
Group 2 alone	Range 53–87	Range 0.4–138.0	Median FU					Observed data, 10 yr FU

PSA: Prostate specific antigen; FU: follow-up; NED: no evidence of disease; UCLA: University of California-Los Angeles; NA: not available.
Group 1 was comprised of 98 patients treated with brachytherapy with iodine-125 alone.
Group 2 was comprised of 54 patients treated with a combination of iodine-125 brachytherapy and 45-gray external beam irradiation.

ation was approximately 85%.[29,30] However, with the advent of more sophisticated follow-up evaluations, notably serial PSA determinations and repeat biopsies, the local failure rates were found to be much higher than once thought.[26,29–35] Table 5 shows 5-year and 10-year outcome comparisons between the brachytherapy study and several external beam irradiation series.[33,36–42] These data suggest that patients treated with brachytherapy with or without 45-Gy external beam radiation supplement fare better than patients treated with external beam irradiation as monotherapy. Furthermore, authors believe that the combination of 45-Gy external beam irradiation and 120-Gy brachytherapy could be the ultimate conformal radiation therapy for the treatment of clinically localized prostate carcinoma patients with unfavorable prognosis.

Over the last decade, radical prostatectomy has emerged as the preferred treatment for clinically localized prostate carcinoma, as verified by the number performed annually in the U. S. (e.g., 32,857 in 1992). Table 6 shows 5-year and 10-year outcome comparisons between brachytherapy with or without a 45-Gy external beam irradiation and radical prostatectomy.[43–48] A close examination of this table demonstrates that radical prostatectomy and brachytherapy have comparable outcomes, although brachytherapy patients are older in age with potentially more aggressive disease than their younger counterparts treated by surgery.[49] Moreover, authors believe that they have provided evidence that a combination of 45-Gy external beam irradiation and 120-Gy brachytherapy could be the treatment of choice for patients with clinically localized prostate carcinoma and an unfavorable prognosis. In this group of patients, the combination of external beam irradiation and brachytherapy allowed precise delivery of higher radiation doses to the prostate. Thus, patients did better than with conventional radiation and radical prostatectomy (comparing the outcome of Group 2 alone with the studies presented in Tables 5 and 6). Figure 5 shows observed 10-year disease free survival in Group 2 patients with a PSA level ≤ 0.4 ng/mL and a PSA level ≤ 0.2 ng/mL. In this group, 74.5% of patients were disease free at 10 years with a PSA level ≤ 0.4 ng/mL.

CONCLUSIONS

Brachytherapy is an effective and valid treatment for patients with clinically organ-confined prostate carcinoma. Observed 10-year follow-up results in the current study document better biochemical disease free survival than several reported conventional external beam irradiation series, and appears comparable to disease free results from several surgical series. The trained neural network may enable the clinician to forecast treatment outcome prior to commencement

of any therapy. Follow-up of the large number of prostate carcinoma patients at Northwest Hospital in Seattle who were treated with brachytherapy is continuing, and treatment results will be upgraded on an annual basis.

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