

# Our Experience of Permanent Brachytherapy in Localized Prostate Cancer

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## Abstract

**Introduction:** In this study, we present the short-term results of our brachytherapy series in patients with localized prostate cancer administered by a team led by urologists.

**Methods:** Forty-one patients who underwent prostate brachytherapy between September 2003 and January 2007 were evaluated in this study. All patients had biopsy-proven adenocarcinoma. Low dose rate (LDR) Iodine-125 prostate brachytherapy was performed under general anesthesia according to intraoperative-interactive planning and peripheral loading technique. Preoperative and follow-up Prostate-Specific Antigen (PSA) levels, International Prostate Symptom Scores (IPSS) and International Index of Erectile Function-5 (IIEF-5) scores of all patients were determined.

**Results:** Preoperative mean PSA, Gleason score and prostate volume of the patients were 7.7±5 ng/ml (4-22.5), 5.8±0.9 (4-8) and 36.8±12.6 ml (15-58 ml), respectively. The mean age of the patients was 62.3±6.3 (52-76) years. The mean follow-up period was 36.5 (7-60) months. Mean PSA value at the third (1.4±1.3 ng/ml) and sixth months (1.0±0.7 ng/ml) was significantly lower than preoperative mean PSA value (p<0.05). There was no significant difference between preoperative mean IPSS score (12.1±5.3) and mean IPSS scores at the third and sixth postoperative months (13.5±6.5 and 11.7±7.5, respectively, p>0.05). There was no significant difference between the mean preoperative IIEF score (14.2±2.6) and mean IIEF scores at the third and sixth postoperative months (11.3±6.5 and 10.8±7.5, respectively, p>0.05). TURP was performed in two patients after brachytherapy because of chronic urinary retention in one patient and because of increased lower urinary tract symptoms in other patient. One patient was referred to radiotherapy due to inadequate radioactivity in the dosimetric control tomography.

**Discussion and Conclusion:** Brachytherapy is an effective method in the treatment of localized prostate cancer and it is recommended in current guidelines despite the recent decline in its use.

**Keywords:** Brachytherapy; iodine-125; prostate cancer

Prostate cancer is the fourth most common cancer among men in the world, with incidence and mortality rates varying from country to country<sup>[1]</sup>. There have been dramatic changes in incidence, stage of diagnosis and mortality, particularly after the introduction of PSA and the rate of the men with organ limited prostate cancer has in-

creased since the 1990s<sup>[2]</sup>. Quality of life is becoming more important due to long life expectancy for patients with localized prostate cancer and brachytherapy comes forward providing survival rates similar to radical prostatectomy and low complication rates in the treatment of prostate cancer<sup>[3, 4]</sup>. Brachytherapy is a form of radiotherapy per-

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**Submitted Date (Başvuru Tarihi):** 13.09.2018 **Accepted Date (Kabul Tarihi):** 06.10.2018

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formed by placing a radioactive source in the prostate. In our country, brachytherapy was introduced in the year 2000, but until now, its use is not widespread. The most important reasons for this are the high cost of the radioactive source and also its lack of coverage by health insurance systems. In this study, we present the short-term results of our brachytherapy series in patients with localized prostate cancer administered by a team led by urologists.

## Materials and Methods

A total of 41 patients who underwent low dose rate prostate brachytherapy between September 2003 and January 2007 were evaluated in this study. Preoperative PSA levels, International Prostate Symptom Scores (IPSS) and International Index of Erectile Function-5 (IIEF-5) scores of all patients were determined. All patients had biopsy-proven adenocarcinoma. Low dose rate (LDR) Iodine-125 prostate brachytherapy was performed under general anesthesia according to intraoperative-interactive planning and peripheral loading technique. Intraoperative planning prevents the need for second anesthesia, and peripheral loading decreases urinary morbidity<sup>[5]</sup>. Patients were given oral magnesium citrate solution on the day before surgery and fleet enema two hours before surgery. Intravenous 1 gr cefazolin was administered one hour before surgery. After the patient was placed in the position of the exaggerated lithotomy under the general anesthesia, the rectum was irrigated with the isotonic solution until a completely clear fluid was obtained. Following skin cleansing with a povidone-iodine solution, a 16 F Foley urethral catheter was inserted to drain the bladder. Then, 100 mL saline was administered to the bladder, and the catheter was clamped. The length and volume of the prostate were measured using transrectal ultrasonography (Fig. 1). The required dose and the number of radioactive seeds to be implanted were calculated. First peripheral seeds, then, central seeds were placed with the help of a special device called the Mick Applicator™ (Fig. 2). After the procedure, direct urinary system x-ray and cystography were performed for all patients, and seed localizations were evaluated. Twenty-four hours after the operation, urethral catheters were removed and patients were discharged. To alleviate the symptoms of the lower urinary tract that may occur in the early period, alpha-blocker and anti-inflammatory treatment were administered to the patients. One month after the operation, pelvic computed tomography was taken and postimplant dosimetry was performed. Thus, it was decided whether the patient needed an additional treatment. From this point on, the patients were followed

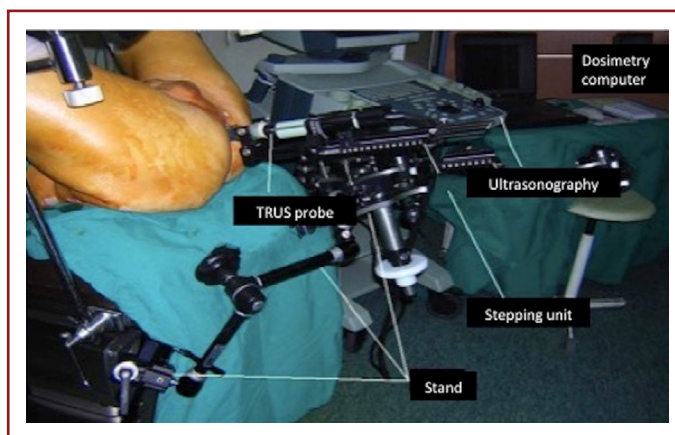


Figure 1. Implantation equipment.

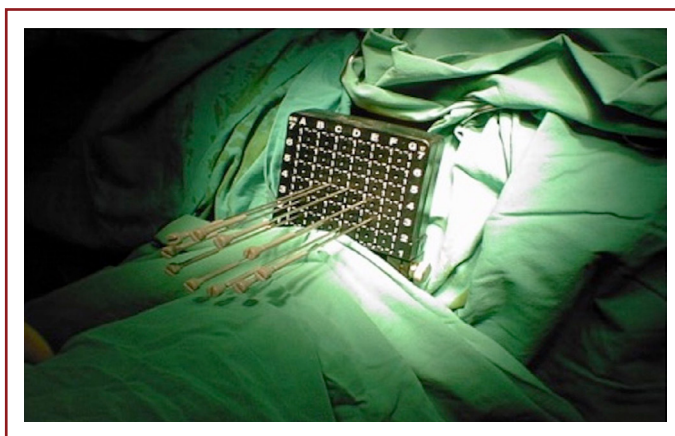


Figure 2. Peripheral needles placed.

up routinely for prostate cancer and PSA measurements were performed every three months for the first year and then every six months. In these follow-up examinations, IPSS and IIEF-5 scores of patients were also recorded.

Patient selection for brachytherapy was performed according to the criteria established by the European Society for Therapeutic Radiology and Oncology (ESTRO), European Association of Urology (EAU) and European Organization for Research and Treatment of Cancer (EORTC)<sup>[6]</sup>. After the patient was informed about cancer control and quality of life targets, we mainly chose our patients from group one, which has good outcomes or rarely from group two, which has intermediate outcomes except for one patient who refused all other treatment alternatives (Table 1). PSA recurrence was defined as three consecutive rises in PSA level according to the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus committee report<sup>[7]</sup>. Pre-treatment PSA value, Gleason score, prostate volume, age, IPSS and IIEF scores were noted. Prostate volume was measured using transrectal ultrasonography. A team of urologists, radiologist, medical physicist and radiation

**Table 1.** Criteria established by the European Society for Therapeutic Radiology and Oncology (ESTRO), European Association of Urology (EAU) and European Organization for Research and Treatment of Cancer (EORTC)

	Brachytherapy Recommended (Good outcomes)	Optional (Intermediate outcomes)	Research Purposes (Poor outcomes)
PSA (ng/dl)	<10	10-20	>20
Gleason Score	5-6	7	8-10
Stage	T1c-T2a	T2b-T2c	T3
IPSS	0-8	9-19	>20
Prostate Volume (ml)	<40	40-60	>60
Qmax (ml/sn)	>15	10-15	<10
Residual Urine	-	-	>200
TUR-P±	-	-	+

PSA: Prostate-Specific Antigen; IPSS: International Prostate Symptom Score; Qmax: Maximum Flow Rate; TUR-P: Transurethral Resection of Prostate.

oncologist performed the brachytherapy procedure. This study was approved by the Ethics Committee.

### Statistical Analysis

SPSS for Windows version 18.0 software package (SPSS, Chicago, USA) was used for the statistical analysis. Mann-Whitney U test was used to evaluate the data. The statistical significance was defined as  $p < 0.05$ .

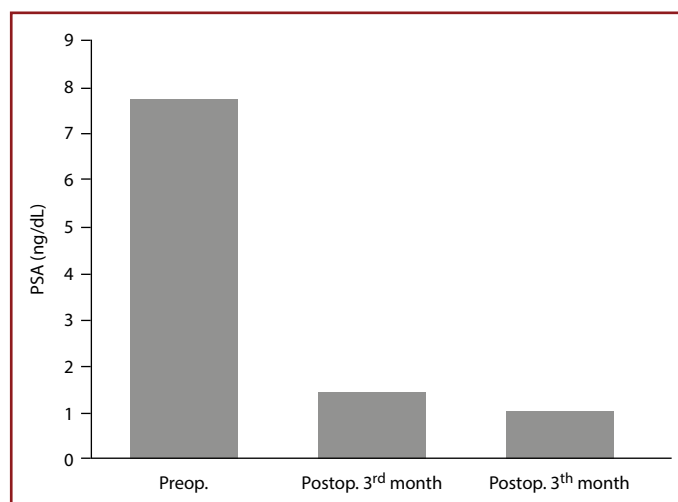
### Results

Preoperative mean PSA, Gleason score and prostate volume of the patients were  $7.7 \pm 5$  ng/ml (4-22.5),  $5.8 \pm 0.9$  (4-8) and  $36.8 \pm 12.6$  ml (15-58 ml), respectively. The mean age of the patients was  $62.3 \pm 6.3$  (52-76) years (Table 2). The mean follow-up period was 36.5 (7-60) months. The mean PSA value at the third ( $1.4 \pm 1.3$  ng/ml) and sixth months ( $1.0 \pm 0.7$  ng/ml) was significantly lower than the preoperative value ( $p < 0.05$ ) (Fig. 3). There was no statistically significant difference between the mean preoperative IPSS score ( $12.1 \pm 5.3$ ) and mean IPSS scores in the third and sixth postoperative months ( $13.5 \pm 6.5$  and  $11.7 \pm 7.5$ , respectively,  $p > 0.05$ ). Also, there was no statistically significant difference between the mean preoperative IIEF score ( $14.2 \pm 2.6$ ) and mean IIEF scores in the third and sixth postoperative months ( $11.3 \pm 6.5$  and  $10.8 \pm 7.5$  respectively,  $p > 0.05$ ) (Table 3). A total of 23 patients completed the 2-year follow-up period.

**Table 2.** Preoperative characteristics of the patients

Mean Age (years)	$62.3 \pm 6.3$ (52-76)
Mean PSA (ng/ml)	$7.7 \pm 5$ (4-22.5)
Mean Gleason Score	$5.8 \pm 0.9$ (4-8)
Mean Prostate Volume (ml)	$36.8 \pm 12.6$ ml (15-58)

PSA: Prostate-Specific Antigen.

**Figure 3.** Change of the mean PSA value at the postoperative 3<sup>rd</sup> and 6<sup>th</sup> months compared with preoperative value ( $p < 0.05$ ).

PSA: Prostate Specific Antigen; Preop: Preoperative; Postop: Postoperative.

The mean PSA value of these patients at the postoperative 24<sup>th</sup>-month was  $0.8 \pm 0.3$  ng/ml, and it was statistically significantly lower than their mean preoperative PSA value ( $7.4 \pm 3.2$  ng/ml,  $p > 0.05$ ). There was no statistically significant difference between the preoperative Mean IPSS and IIEF scores ( $13.5 \pm 4.6$  and  $14.7 \pm 3.2$ , respectively) and the mean IPSS and IIEF scores in the postoperative 24<sup>th</sup> month ( $12.0 \pm 5.2$  and  $12.8 \pm 4.7$ , respectively) of the patients who completed the 2-year follow up period ( $p > 0.05$ ) (Table 4).

**Table 3.** Mean IPSS and IIEF scores in the postoperative 3<sup>rd</sup> and 6<sup>th</sup> months compared with preoperative value ( $p > 0.05$ )

	Preop.	Postop. 3 <sup>rd</sup> month	Postop. 6 <sup>th</sup> month
Mean IIEF	$14.2 \pm 2.6$	$11.3 \pm 6.5$	$10.8 \pm 7.5$
Mean IPSS	$12.1 \pm 5.3$	$13.5 \pm 6.5$	$11.7 \pm 7.5$

IIEF: International Index of Erectile Function; IPSS: International Prostate Symptom Score; Preop: Preoperative; Postop: Postoperative.

In 27% of the patients, there was frequent urination, and 14% had dysuria in the postoperative 3<sup>rd</sup> month. There were no patients who had incontinence after brachytherapy. TURP was performed in two patients after brachytherapy because of chronic urinary retention in one patient and because of increased lower urinary tract symptoms in another patient. One patient had total urinary incontinence after TURP, and this patient became continent after artificial urinary sphincter implantation. One patient was referred to radiotherapy due to inadequate radioactivity observed in postimplant dosimetry performed one month after brachytherapy. Four of our patients (20% of those who completed the 24-month follow-up) had a transient PSA elevation with a median time to occurrence of 14 months. Their PSA levels declined afterwards. Only one patient had PSA recurrence that developed in the postoperative 12<sup>th</sup> month.

### Discussion

After brachytherapy has become a viable method for localized prostate cancer, many questions have been raised about appropriate patient selection, hormone use, and the reliability of the results<sup>[8]</sup>. According to the results obtained from clinical trials, ESTRO, EAU and EORTC formed three categories for prostate cancer patients suitable for brachytherapy depending on cancer control and quality of life as patients with good results, patients with intermediate results and patients with poor results<sup>[6]</sup>. In our clinic, we considered these categories while choosing appropriate patients for brachytherapy and we obtained all of the patients from two groups that were eligible for brachytherapy except one patient who refused all other treatment alternatives.

Brachytherapy has high biochemical control rates when used as monotherapy in patients with low-risk localized prostate cancer. Biochemical recurrence-free survival rates of 87-96% have been reported for follow-up periods of up to 10 years<sup>[4, 9, 10]</sup>. Stone et al.<sup>[8]</sup> reported a 10-year biochemical recurrence-free survival rate as 78% for 279 patients with stage T1-T2. Blasko et al.<sup>[11]</sup> stated that they had an 82% 9-year biochemical recurrence-free survival rate

for patients in the intermediate-risk group. Dattoli et al.<sup>[12]</sup>, who combined brachytherapy with EBRT in 243 high-risk patients, reported a biochemical recurrence-free survival of 81% with a median follow up 8.5 (1-12.5) years. These rates are comparable with the rates of radical prostatectomy and EBRT. In our study, we found that mean PSA value at the third (1.4±1.3 ng/ml) and sixth months (1.0±0.7 ng/ml) were significantly lower than the preoperative value (p<0.05). The mean PSA value of the patients who completed two years of follow up at the postoperative 24<sup>th</sup> month was 0.8±0.3 ng/ml, and it was statistically significantly lower than their mean preoperative PSA value (7.4±3.2 ng/ml, p>0.05). In the mean follow up 36.5 (7-60) months, only one patient had PSA recurrence that developed in the postoperative 12<sup>th</sup> month. No metastasis was detected in the bone scan, abdomen and thorax tomography.

Radical prostatectomy (RP) has long been the preferred method of treatment for men with localized prostate cancer, whose life expectancy is more than 10 years<sup>[13]</sup>. Long-term cancer control results are excellent, and the development of anatomic nerve-sparing radical prostatectomy significantly decreased the complications<sup>[14, 15]</sup>. However, publications showing that intermediate and long-term results of brachytherapy are comparable to RP have led to various debates about the choice of treatment in localized prostate cancer<sup>[16]</sup>. Ramos et al.<sup>[17]</sup> compared 299 patients who had radical prostatectomy with 122 brachytherapy patients of Radge who had similar preoperative characteristics concerning Gleason score, clinical stage and PSA values. PSA >0.3 ng/ml was accepted as recurrence. The 7-year recurrence-free survival rate was 84% for the RP group and 79% for the brachytherapy group. Although the results seemed to be slightly in favor of radical prostatectomy, no statistically significant difference was detected. Potters et al.<sup>[18]</sup> compared RP, EBRT and Brachytherapy and reported that 7-year biochemical recurrence-free survival rates were 74%, 77% and 79%, respectively.

Although acute urethral irritation and urinary obstruction are well-documented short-term complications of modern brachytherapy technique, these complaints gradually decrease in the long term. Desai et al.<sup>[19]</sup> investigated urinary morbidity in 117 patients who had Iodine-125 brachytherapy and stated that IPSS scores reached the highest level at the end of the first month and decreased to preoperative values at the postoperative 24<sup>th</sup> month. In our study, there was no statistically significant difference between mean preoperative IPSS score (12.1±5.3) and mean IPSS scores in the postoperative 3<sup>rd</sup> (13.5±6.5) and 6<sup>th</sup> (11.7±7.5) months (p>0.05). Also, there was no statistically significant differ-

**Table 4.** Mean PSA, IPSS and IIEF values preoperative and at the 24<sup>th</sup> month for the patients who completed 2-year follow up period

	Preop.	24 <sup>th</sup> -month	p
PSA (ng/dl)	7.4±3.2	0.8±0.3	p<0.05
IPSS	13.5±4.6	12.0±5.2	p>0.05
IIEF	14.7±3.2	12.8±4.7	p>0.05

PSA: Prostate-Specific Antigen; IPSS: International Prostate Symptom Score; IIEF: International Index of Erectile Function; Preop: Preoperative.

ence between the preoperative mean IPSS score ( $13.5\pm 4.6$ ) and mean IPSS score in the postoperative 24<sup>th</sup> month ( $12.0\pm 5.2$ ) of the patients who completed the 2-year follow up period ( $p>0.05$ ).

It is reported that transurethral resection of the prostate (TURP) is required in 0-8.3% of the cases after brachytherapy and TURP after brachytherapy is also associated with increased risk of incontinence<sup>[20]</sup>. If TURP is required, minimal resection and cauterization should be performed. We performed TURP in two patients because of chronic urinary retention in one patient and because of increased lower urinary system symptoms in other patient. One patient had total urinary incontinence after TURP, and this patient became continent after artificial urinary sphincter implantation.

One of the reasons for preferring brachytherapy to radical prostatectomy is the thought that erectile function is less likely to be affected<sup>[20]</sup>. Pre-treatment erectile function quality is reported to be the strongest predictor of erectile dysfunction due to brachytherapy<sup>[21]</sup>. The etiology of erectile dysfunction after brachytherapy is not fully known, but it is thought to be due to fibrosis developing over time, just like EBRT related erectile dysfunction<sup>[22]</sup>. Stock et al.<sup>[23]</sup> investigated the erectile function and affecting factors after brachytherapy on 416 patients. They found that for the patients who had erectile function sufficient for coitus, the rate of potency was 79.6% in the postoperative 3<sup>rd</sup> year and 59% in the postoperative 6<sup>th</sup> year. In our study, there was no statistically significant difference between mean preoperative IIEF scores ( $14.2\pm 2.6$ ) and mean IIEF scores in the postoperative 3<sup>rd</sup> and 6<sup>th</sup> months ( $11.3\pm 6.5$ ,  $10.8\pm 7.5$ , respectively,  $p>0.05$ ). Also, there was no statistically significant difference between the mean preoperative IIEF score ( $14.7\pm 3.2$ ) and the mean IIEF score at the postoperative 24<sup>th</sup> month ( $12.8\pm 4.7$ ) of the patients who completed the 2-year follow up period ( $p>0.05$ ). These results support the hypothesis that erectile function is minimally affected after brachytherapy.

Recently, the use of brachytherapy in locally advanced prostate cancer has significantly declined. In a study conducted by Martin et al.<sup>[24]</sup>, it was seen that the percentage of patients treated using brachytherapy for localized prostate cancer was 16.9% in 2002, and then, it decreased to 8.2% in 2010. We think that the introduction of robotic surgery and active surveillance for low-risk prostate cancer is effective on this decrease.

Radiation-induced secondary cancers are defined as tumors arising five years or more after radiation from tissue

within the irradiated field and have different histopathologic features from the primary tumor<sup>[25]</sup>. In our series, small cell cancer of prostate was detected in two patients. One patient had Cushing Syndrome 59 months after brachytherapy, and PET-CT showed suspicious activity in the prostate. Prostate biopsy was performed and the result came as small cell cancer of prostate. In the other patient, TUR-P was performed due to increased lower urinary tract symptoms 55 months after brachytherapy; pathology of the specimen was reported as small cell cancer of prostate. Both patients were referred to the oncology department. Small cell cancer of the prostate after brachytherapy is very rare. In the literature, there is only one case report about a patient who had small cell cancer of prostate after high dose rate brachytherapy for low-risk prostate cancer<sup>[26]</sup>.

The major obstacle to the widespread use of brachytherapy in our country is the relatively high cost and the failure of social security coverage. In developed countries, the cost of brachytherapy is more favorable than other treatment options<sup>[27]</sup>. Our study has several limitations. First of all, we present the preliminary results for a small number of patients. We mainly present the first six months' results of PSA, IPSS and IIEF scores and also the results of a small group who completed a two-year follow-up period. Studies with a larger number of patients and longer follow-up periods will provide clearer information on the advantages and disadvantages of brachytherapy.

## Conclusion

Despite the recent decline in its use, brachytherapy is an effective modality with limited effects on quality of life and it is recommended in current guidelines in the treatment of localized prostate cancer. Brachytherapy patients, like all cancer patients treated with other modalities, should be monitored closely after treatment.

**Ethics Committee Approval:** Ethics committee approval was received for this study from Ethics Committee of Bezmialem University of Medicine (Approval number: 11/99 - Date: 8.05.2018).

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions:** Concept: M.I.K., M.I.O.; Design: M.I.K., A.I.; Data Collection or Processing: S.K., S.C., A.I., O.K.; Analysis or Interpretation: M.I.K., M.I.O, A.I., S.K., O.K.; Literature Search: A.I., S.K., O.K., S.C.; Writing: A.I., S.C., M.I.O, M.I.K.

**Conflict of Interest:** None declared.

**Financial Disclosure:** The authors declared that this study received no financial support.

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