Influence of Pretreatment and Treatment Factors on Intermediate to Long-Term Outcome After Prostate Brachytherapy

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Purpose: We describe how treatment factors influence biochemical freedom from failure, local control, freedom from metastasis and cause specific survival in patients treated with prostate brachytherapy.

Materials and Methods: We followed 2,111 men who underwent brachytherapy a median of 6 years (range 2 to 17). Median prostate specific antigen was 7 ng/ml. Of the men 1,455 (68.9%) had clinical stage T2a or less and 1,428 (67.6%) had Gleason score less than 7. A total of 1,171 patients (55.5%) received ^{125}I, 221 (10.4%) received ^{103}Pd and 719 (34.1%) received supplemental external beam irradiation combined with ^{103}Pd. Post-implant dosimetry was done 30 days after implantation with doses converted to the biologically effective dose. Prostate biopsy was done 2 years after permanent prostate brachytherapy in 586 men (27.8%). Survival functions were determined by the Kaplan-Meier method and Cox regression with proportions tested by the log rank test.

Results: The 12-year biochemical freedom from failure rate was 78.6%, and stage, Gleason score, prostate specific antigen and biologically effective dose were significant predictors ($p = 0.007$, <0.001, 0.005 and <0.001, respectively). In 964 patients at low risk the biochemical freedom from failure rate was 88.1% and significant predictors were hormonal therapy ($p = 0.030$), prostate specific antigen ($p = 0.026$) and biologically effective dose ($p = 0.003$). In 499 patients at intermediate risk the biochemical freedom from failure rate was 79.2% with biologically effective dose a significant predictor ($p <0.001$). In 648 men at high risk the biochemical freedom from failure rate was 67% and significant predictors were hormonal therapy, Gleason score and biologically effective dose ($p = 0.036$, <0.001 and 0.012, respectively). The local failure rate was 7.3% with biologically effective dose a significant predictor ($p <0.001$). Prostate biopsy was positive in 21 of 121 cases (21.5%) for a biologically effective dose of 150 Gy2 or less, in 14 of 248 (5.6%) for greater than 150 to 200 Gy2 and in 3 of 193 (1.6%) for greater than 200 Gy2 ($p <0.001$). The 12-year freedom from metastasis rate was 95.2% with Gleason score a significant predictor ($p <0.001$). Cause specific survival at 12 years was 94.5% with Gleason score and biologically effective dose significant predictors ($p <0.001$ and 0.027, respectively).

Conclusions: Permanent prostate brachytherapy yields excellent long-term oncologic outcomes. High biologically effective dose may need to be delivered to achieve successful biochemical freedom from failure, local control and cause specific survival.

Key Words: prostate; prostatic neoplasms; brachytherapy; dose-response relationship, radiation; mortality

Abbreviations and Acronyms

BED = biologically effective dose

BFFF = biochemical freedom from failure

D90 = dose to 90% of prostate

EBRT = external beam radiotherapy

HT = hormonal therapy

LPLND = laparoscopic pelvic lymph node dissection

PSA = prostate specific antigen

SVB = seminal vesicle biopsy

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BRACHYTHERAPY has become a popular treatment for localized prostate cancer but long-term data have only recently started to emerge.[1] Several groups identified radiation dose as an important contributor to biochemical and local control.[2–4] Stock et al initially reported a dose response for ^{125}I brachytherapy and found that prostate D90 was the best predictor of biochemical control.[5] Others also described different D90 variations when relating delivered dose to freedom from PSA failure.[6,7]

While these studies underscore the importance of determining and reporting the delivered dose, they also created difficulty when trying to compare results from different centers using different forms of radiation. The prescription dose is usually 145 Gy for ^{125}I, 125 Gy for ^{103}Pd and 72 to 80 Gy for intensity modulated radiation therapy.[8,9] Rather than rely only on the physical dose Stock et al reported a dose response study using BED in patients treated with brachytherapy alone or combined with EBRT.[10] Biochemical and local control were improved with increasing BED.

We investigated long-term biochemical and local control, freedom from metastases and cause specific survival outcomes in different radiation BED groups in a cohort of more than 2,000 patients treated at our center since its brachytherapy program inception in 1990.

MATERIALS AND METHODS

A total of 2,111 men with a median age of 67 years (range 39 to 88, IQR 61–71) were treated from 1990 to 2006 with a median followup of 6 years (range 2 to 17). Followup was censored at the last PSA recorded or at the time of death. Of the 2,111 men 210 (10%) died, including 34 (1.6%) of prostate cancer. Patients not seen at our clinic for more than 1 year were contacted by telephone or mail. National databases were searched to determine whether patients who could not be contacted had died. This study had institutional review board approval.

Median PSA was 7 ng/ml (mean 9.8, range 0.55 to 300). Of the men 1,455 (68.9%) had clinical stage T2a or less and 1,428 (67.6%) had Gleason score less than 7 (table 1). Cases were staged using the 1992 American Joint Committee on Cancer system and in those with initial PSA greater than 10 ng/ml or Gleason score greater than 6 bone scan and computerized tomography were done. Also, most patients with PSA greater than 10 ng/ml, Gleason score 7 or greater, or stage T2b or greater underwent SVB.[11] Those with positive SVB, Gleason score 7 or greater with perineural invasion, or PSA greater than 30 ng/ml also underwent LPLND. Those with positive LPLND were excluded from analysis.

Patients at low risk, defined as PSA less than 10 ng/ml, Gleason score 6 or less, stage T2a or less and prostate volume less 50 cc, received an ^{125}I implant to a prescription dose of 160 Gy (BED 169 Gy2) according to Task Group 43. From 1990 to 2002 patients at low risk with a prostate of 50 cc or less were usually placed on 3 months of neoadjuvant HT before implantation. About 50% of these men also continued on HT for an additional 2 to 3 months. After 2002 due to patient complaints of impotence and hot flashes HT was discontinued unless the prostate was greater than 70 cc or the American Urological Association symptom score was 15 or greater.[12] Those at intermediate risk, defined as PSA 10 to 20 ng/ml, Gleason score 7 or stage T2b, were offered 6 months of HT, including 3 months before implantation, and ^{125}I or ^{103}Pd to a dose of 124 Gy (BED 143 Gy2 according to the 1999 National Institute of Standards and Technology) or a ^{103}Pd implant (100 Gy). This was followed 2 months later by 45 Gy external beam irradiation as combination therapy (BED 198 Gy2). Men at high risk, defined as PSA greater than 20 ng/ml, Gleason score 8–10, stage T2c–T3, positive SVB with negative LPLND or 2 intermediate risk features, were treated with 9 months of HT and combination therapy. The 61 patients with positive SVB underwent implantation of the vesicles, in addition to the prostate.[13] Short course hormonal therapy (median 6.5 months, range 2 to 28) was done in 1,170 patients (55.5%), including luteinizing hormone-releasing hormone analogue plus an antiandrogen in 52% and luteinizing hormone-releasing hormone analogue alone in 565. Of the patients 1,171 (55.5%) received ^{125}I, 221 (10.4%) received ^{103}Pd and 719 (34.1%) received supplemental external beam irradiation combined with ^{103}Pd.

Combination therapy began in 1994 with EBRT delivered using 3-dimensional conformal techniques and 16 MV photons. Rectal, prostate and seminal vesicle margins were 1.0, 1.5 and 1.5 cm, respectively. Dose was prescribed to the isodose line covering the planning target volume and was delivered using 1.8 Gy fractions during 25 days. In 2003 image guided radiation therapy was implemented

Table 1. *Treatment characteristics in 2,111 patients with brachytherapy*

Characteristics	No. Pts (%)
PSA (ng/ml):	
0–10	1,575 (74.6)
Greater than 10–20	386 (18.3)
Greater than 20	150 (7.1)
Gleason score:	
2–6	1,428 (67.6)
7	474 (22.5)
8–10	209 (9.9)
Stage:	
T1c–T2a	1,455 (68.9)
T2b–c	609 (28.9)
T3	47 (2.2)
Risk group:	
Low	964 (45.9)
Intermediate	499 (23.6)
High	648 (30.5)
BED groups (Gy2):*	
150 or Less	182 (9.0)
Greater than 150–200	895 (43.6)
Greater than 200	974 (47.4)

* Available in 2,052 patients (97.2%).