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CLINICAL INVESTIGATION **Prostate**

PROGNOSTIC SIGNIFICANCE OF 5-YEAR PSA VALUE FOR PREDICTING PROSTATE CANCER RECURRENCE AFTER BRACHYTHERAPY ALONE AND COMBINED WITH HORMONAL THERAPY AND/OR EXTERNAL BEAM RADIOTHERAPY

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Purpose: To analyze the prognosis and outcomes of patients who remain free of biochemical failure during the first 5 years after treatment.

Methods and Materials: Between 1991 and 2002, 742 patients with prostate cancer were treated with brachytherapy alone ($n = 306$), brachytherapy and hormonal therapy ($n = 212$), or combined implantation and external beam radiotherapy (with or without hormonal therapy; $n = 224$). These patients were free of biochemical failure (American Society for Therapeutic Radiology and Oncology [ASTRO] definition) during the first 5 post-treatment years and had a documented 5-year prostate-specific antigen (PSA) value. The median follow-up was 6.93 years.

Results: The actuarial 10-year freedom from PSA failure rate was 97% using the ASTRO definition and 95% using the Phoenix definition. The median 5-year PSA level was 0.03 ng/mL (range, 0–3.6). The 5-year PSA value was ≤0.01 in 47.7%, >0.01–0.10 in 31.1%, >0.10–0.2 in 10.2%, >0.2–0.5 in 7.82%, and >0.5 in 3.10%. The 5-year PSA value had prognostic significance, with a PSA value of ≤0.2 ng/mL ($n = 661$) corresponding to a 10-year freedom from PSA failure rate of 99% with the ASTRO definition and 98% with the Phoenix definition vs. 86% (ASTRO definition) and 81% (Phoenix definition) for a PSA value ≥0.2 ng/mL ($n = 81$; $p < .0001$). The treatment regimen had no effect on biochemical failure. None of the 742 patients in this study developed metastatic disease or died of prostate cancer.

Conclusion: The results of this study have shown that the prognosis for patients treated with brachytherapy and who remain biochemically free of disease for ≥5 years is excellent and none developed metastatic disease during the first 10 years after treatment. The 5-year PSA value is prognostic, and patients with a PSA value <0.2 ng/mL are unlikely to develop subsequent biochemical relapse.

Prostate cancer, Brachytherapy, 5-year PSA level, Biochemical failure, Outcomes.

INTRODUCTION

Newly diagnosed patients with prostate cancer are often presented with three National Cancer Care Network recommended primary therapeutic approaches: brachytherapy, external beam radiotherapy (EBRT), or surgery. The likelihood of success (biochemical control) as measured by prostate-specific antigen (PSA) follow-up for each treatment modality is considered to be equal within a few percentage points of uncertainty.

The PSA kinetics after prostate brachytherapy are often very difficult to interpret and can be a source of anxiety for both clinicians and patients. Unlike prostatectomy, in which a PSA level >0.2 ng/mL is considered failure, brachytherapy results in a gradual decline in the PSA level, with occasional increases in some individuals (1, 2).

It is, therefore, important to inform patients at what point they would be considered cured after brachytherapy. To address this issue, we analyzed the prognosis and outcomes for patients without a documented failure in the first 5 years after treatment. In particular, we were interested in the incidence of late biochemical failure and the prognostic significance of the 5-year PSA value for predicting future disease recurrence.

METHODS AND MATERIALS

Between July 1991 and February 2002, a total of 742 patients with Stage T1-T3 prostate cancer were treated with brachytherapy at Mount Sinai Hospital (New York, NY) and had a minimum of 5 years of follow-up with no evidence of PSA failure using the American Society for Therapeutic Radiology and Oncology

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(ASTRO) definition during their first 5 post-treatment years (3). Although a new definition for PSA failure has been recommended (the Phoenix definition), the ASTRO definition is still considered valid, provided sufficient follow-up is available (4). The ASTRO definition was chosen because all the patients in the study had sufficient follow-up (5-year minimum), and because it backdates the failure to the beginning of the increasing PSA profile. We believe this date signifies the start of the biochemical failure and is thus more reflective of the actual timing of the failure. Because the focus of this analysis was on the incidence of late failure, the use of the ASTRO definition would exclude patients who had an indication of an increasing PSA level during the first 5 years of follow-up. All patients underwent disease staging using the 1992 American Joint Committee on Cancer staging system, and no patient had radiographic or pathologic evidence of metastatic disease at presentation (5). The clinical presentation of all patients by Gleason score, PSA level, stage, and risk groups is given in Table 1.

The patients were divided into low-, intermediate-, and high-risk groups. Low risk was defined as a PSA level of ≤10 ng/mL, Gleason score of ≤6, and Stage T2a or less. Intermediate risk was defined as possessing only one of the following features: PSA level >10–20 ng/mL, Gleason score of 7, or Stage T2b. High risk included those with two or more intermediate-risk features or one or more of the following features: PSA >20 ng/mL, Gleason score of ≥8, Stage T2c-T3, or positive seminal vesicle biopsy findings. Seminal vesicle biopsy and laparoscopic pelvic lymph node dissection were done at the discretion of the urologist. A total of 337 patients underwent seminal vesicle biopsy, and 19 had positive findings; and 106 patients underwent laparoscopic pelvic lymph node dissection, and 2 had positive nodes.

Treatment

All patients were treated with brachytherapy using a real-time ultrasound-guided technique. The technique has been previously described (6). The treatment regimens were developed over time and were divided into three categories: brachytherapy alone (n = 306), brachytherapy and hormonal therapy (n = 212), and combined implantation and EBRT (with or without hormonal therapy; n = 224) (7).

Brachytherapy without EBRT (with or without hormonal therapy) was performed using both ^{125}I (prescription dose, 160 Gy, Task Group 43; 414 patients) and ^{103}Pd (prescription dose, 124 Gy, National Institute of Standards and Technology 1999 primary calibration standard; 328 patients). In general, ^{125}I was used for patients with a Gleason score of ≤6 and ^{103}Pd for those with a Gleason score of ≥7. Most patients treated with brachytherapy alone were low risk, although during the early years of the study period both intermediate- and high-risk patients received implantation alone.

Table 1. Disease characteristics

Factor	Patients (%)
PSA (ng/mL)	
≤10	528 (71)
>10–20	159 (21)
>20	55 (8)
Gleason score	
≤6	537 (72)
7	139 (19)
8–10	66 (9)
Clinical stage	
T2a or less	491 (66)
T2b	164 (22)
T2c or greater	85 (12)
Risk group	
Low	328 (44)
Intermediate	181 (24)
High	231 (32)

Abbreviation: PSA = prostate-specific antigen.

Hormonal therapy was used with brachytherapy for two main reasons. The first use of hormonal therapy was for downsizing in patients with large prostates (gland size, >50 cm^3). It was given for 3 months before implantation and usually for 2–3 months after implantation. The second use was as adjuvant therapy with brachytherapy for patients with intermediate- or high-risk features. In this case, hormonal therapy was given for 3 months before and 3 months after implantation (8).

Trimodality therapy usually involved 3 months of hormonal therapy followed by ^{103}Pd brachytherapy implantation (198 patients; prescription dose, 100 Gy, National Institute of Standards and Technology 1999 primary calibration standard) or ^{125}I (1 patient; prescription dose, 120 Gy) and 2 months later, EBRT to a dose of 45 Gy. The seminal vesicles were implanted in patients with biopsy-positive seminal vesicle disease. The total duration of hormonal therapy was 3–9 months (median, 9). In the earlier years of the study, lower implant doses were used with greater EBRT doses. The EBRT dose range was 39.6–61.2 Gy (median, 45). The details of this regimen have been previously described (9). The EBRT fields were conformal and treated the prostate and seminal vesicles using 1.5–2-cm margins. Overall, when hormonal therapy was used, it involved a luteinizing hormone-releasing hormone with or without an antiandrogen.

Dose equations

The dose delivered to the prostate was calculated with a 1-month postimplant computed tomography-based dosimetric analysis. All patients were asked to return 1 month after implantation for computed tomography scanning. Dosimetry was performed in 723 patients. The reasons for not performing dosimetry were poor visualization due to hip prostheses or patient noncompliance. The implant dose was defined as the dose delivered to 90% of the gland from the dose–volume histogram) (10). To compare the doses between the different isotopes and between implantation alone and combined implantation and EBRT, biologically effective dose (BED) equations were used. The BED values were obtained for both low-dose-rate permanent implants and the EBRT portions of the treatment. An α/β ratio of 2 was used in these equations. The details of these equations have been previously described (11). Patients treated with combined implantation and EBRT had their BED values for both methods combined to determine the total BED. The BED values for all treatments were 48–282 Gy2 (median, 195 Gy2).

Follow-up

All patients were asked to return every 6 months after treatment completion. Follow-up information was obtained from the clinical visits, telephone calls to referring physicians and patients, and mailed questionnaires. The follow-up blood tests included serum PSA and testosterone levels. Follow-up was calculated from treatment completion to the last available follow-up date or date of death. The follow-up period for the entire population was 5–14.4 years (median, 6.93). Survival curves were determined using the Kaplan-Meier methods. The freedom from biochemical failure rates were calculated using both the ASTRO and the Phoenix definitions. Distant metastasis was defined as radiographic or pathologically