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CLINICAL INVESTIGATION **Prostate**

HIGH-DOSE-RATE INTENSITY-MODULATED BRACHYTHERAPY WITH EXTERNAL BEAM RADIOTHERAPY FOR PROSTATE CANCER: CALIFORNIA ENDOCURIETHERAPY'S 10-YEAR RESULTS

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Purpose: To present the long-term outcome and morbidity of high-dose-rate brachytherapy (HDR-BT) combined with external beam radiotherapy (EBRT) for localized prostate cancer.

Methods and Materials: Between September 1991 and December 1998, 209 consecutive patients with no prior androgen suppression were treated with HDR-BT plus EBRT. The median follow-up was 7.25 years (range, 5–12 years). The patients were stratified into three risk groups: low (Stage T2a or less, Gleason score ≤6, and prostate-specific antigen [PSA] level ≤10 ng/mL), intermediate (Stage T2b,c, Gleason score 7, and PSA level 10–20 ng/mL), and high (Stage T3, Gleason score 8–10, and PSA level >20). Four definitions of PSA progression were compared with the general clinical failure outcome: the American Society for Therapeutic Radiology and Oncology (ASTRO) definition, nadir plus 2.0 ng/mL, two consecutive rises ≥0.5 ng/mL, and PSA level >0.2 ng/mL. Morbidity was scored using Radiation Therapy Oncology Group criteria.

Results: The general clinical control rate was 90% (188 of 209), and the general clinical failure rate was 10% (21 of 209). The overall survival rate was 79%, and the cause-specific survival rate was 97%. The PSA progression-free survival (ASTRO definition) rate was 90%, 87%, and 69% for the low-, intermediate-, and high-risk groups, respectively. The nadir plus 2 ng/mL and two rises ≥0.5 definitions correlated better with the actual clinical outcome than did the ASTRO and PSA >0.2 ng/mL definitions. The rate of Grade 3 and 4 late urinary morbidity was 6.7% and 1%, respectively, mostly occurring in patients who had undergone post-RT transurethral prostate resection. No late Grade 3 or 4 rectal morbidity developed. The sexual potency preservation rate was 67%.

Conclusion: Our 10-year results have demonstrated HDR-BT plus EBRT is a proven treatment for all stages of localized prostate cancer. The morbidity was low, but post-RT transurethral resection should be avoided.

HDR, Prostate, Long-term outcome, External beam radiotherapy.

INTRODUCTION

High-dose-rate brachytherapy (HDR-BT) applies advanced technology to the delivery of ^{192}Ir. It allows the user to modulate the intensity of the radiation by varying the time the source spends at each location (dwell position) within the implant. The California Endocurietherapy Center (CET) HDR prostate BT method was derived from our experience with the temporary afterloading technique described by Syed *et al.* (1). The main differences are the high dose rate and the fractionation. We designed and applied a fractionated dose protocol from linear-quadratic calculations that we believed was comparable to continuous low-dose-rate BT (2, 3).

The California Endocurietherapy Center is a clinical practice dedicated exclusively to HDR-BT. We report our 10-year results (7.25-year median follow-up) of a prospective study of HDR-BT and external beam radiotherapy (EBRT), without the use of androgen suppression, for prostate cancer.

METHODS AND MATERIALS

Case material, selection, and exclusions

A total of 209 consecutive patients with Stage T1-T3, NX-N0, M0 prostate cancer, prostate-specific antigen (PSA) level <50 ng/mL, who had not undergone prior EBRT or androgen suppression, received combined HDR-BT and EBRT between September 1, 1991 and December 31, 1998. The clinical characteristics and risk group stratifications are shown in Table 1. The median age was 69 years (range, 44–87 years). Ten patients who declined or delayed completion of treatment against medical advice (n = 5),

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Table 1. Presenting characteristics (n = 209)

Characteristic	n (%)
T stage	
T1a,b	7 (3)
T1c	78 (37)
T2a	57 (27)
T2b	27 (13)
T2c	27 (13)
T3	13 (6)
Pretreatment PSA (ng/mL)	
<10	139 (67)
10–20	51 (24)
>20	19 (9)
Gleason score	
2–6	134 (64)
7	51 (24)
8–10	24 (12)
Positive cores (%)	
≤25	65 (31)
25–50	108 (52)
>50	36 (17)
Risk group	
Low	70 (33.5)
Intermediate	92 (44)
High	47 (22.5)

Abbreviation: PSA = prostate-specific antigen.

did not complete treatment for medical reasons (n = 1), or died without disease in <2 years (n = 4) were excluded from the analysis.

Pretreatment evaluation and clinical staging

The pretreatment evaluation included history and physical examination, digital rectal examination (DRE), transrectal ultrasonography (TRUS), prostate biopsies with Gleason score, and PSA determination. Staging procedures, such as bone scan, CT of the abdomen and pelvis, and surgical lymph node sampling, were performed in some cases. T stage was based exclusively on the DRE. Prostate anatomy, volume, and transurethral resection of the prostate (TURP) defects were determined by TRUS. The pathologic finding was recorded as unilateral or bilateral, and the percentage of positive cores was calculated.

CET prostate BT method

The CET implant method has been described previously (4). In brief, it consists of transperineal interstitial implantation of 17 flexiguides, directed by TRUS, cystoscopy, and fluoroscopy. The ultrasound probe and the template were hand-held rather than mounted on a stabilization unit. Manual angulations of the template and redirection of the flexiguides made the technique applicable to a wide range of clinical circumstances, including large prostates, prior TURP, asymmetric glands, large median lobes, extracapsular extension, and seminal vesicle involvement. Simulation radiography was based on available plain film simulator technology, and dosimetry was computed using Nucletron, versions 10 through 11.4, NPS brachytherapy treatment planning system (Nucletron Corporation B.V., Veenendaal, The Netherlands).

The 100% isodose (planning treatment volume) was normalized to a 5–6-mm margin anterior and lateral to the prostatic capsule to include local disease extensions and a 2–3-mm margin posterior to the prostatic capsule to prevent rectal injury. The dose to the prostatic capsule was at least 110% of the nominal prescription dose. The dwell times were adjusted to limit the maximal anterior rectal wall dose to 75% and the maximal bladder neck dose to 80%. Two implants were performed 1 week apart. During each implant, two HDR fractions were given, ≥6 h apart. Fluoroscopy was used to verify the flexiguide positions before each subsequent treatment fraction. The total HDR-BT dose was 22–24 Gy (four fractions of 5.5–6.0 Gy), and the total EBRT dose was 36 Gy given in 20 fractions. A 2-week interval was given between HDR-BT and EBRT. Implant quality was assessed by graphic isodose line clinical target volume coverage and the dose delivered to 90% of the prostate volume (D_{90}), prostate volume receiving 100% of prescribed dose (V_{100}), and prostate volume receiving 150% of prescribed dose (V_{150}) analysis.

Definitions of disease control

Many years of observation are needed to assess the efficacy after treatment of prostate cancer, a disease with a long natural history. We selected the same criteria for general clinical failure (GCF) used in the multi-institutional validation study by Thames *et al.* (5) of 4839 patients treated with EBRT alone for prostate cancer. The endpoints were local failure (determined by DRE or positive biopsy >2 years after treatment associated with PSA progression), distant failure, hormonal therapy, or a posttreatment PSA level >25 ng/mL. Our results are presented in terms of GCF and PSA progression-free survival (PSA-PFS).

Radiotherapy, unlike surgery, does not eliminate all prostatic tissue, so some level of residual PSA after treatment is expected. Much has been said and written about the use of serial PSA determinations to predict disease control. PSA elevations observed during a shorter period can be used to predict subsequent general clinical progression of disease. An important problem for clinical practice is that the utility of serial PSA testing is limited by the frequent occurrence of benign transient elevations after RT (6–8). Although most authors have used the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus conference recommendation (9), subsequent validation studies have shown other methods to be both more sensitive and more specific (5, 10). We applied four definitions of PSA progression to our cohort: the ASTRO definition (three consecutive rises, backdated); two consecutive rises of ≥0.5 ng/mL, backdated; current nadir plus 2 ng/mL, not backdated; and PSA level >0.2 ng/mL. The middle two definitions were selected for comparison because the analysis of 102 definitions of failure by Thames *et al.* (5) found them to be both more sensitive and more specific than the ASTRO definition. We also included the PSA >0.2 ng/mL definition because it has also been proposed to be a better predictor of outcome than the ASTRO definition (11).

Prostate-specific antigen-PFS signified that no clinical, pathologic, or biochemical evidence of disease progression was present. Local control was assessed by DRE. Prostatic tissue specimens were available after RT in 16 cases. Diagnostic radiologic studies were used to identify distant metastasis.

Morbidity scoring

Late GU and lower GI morbidity was evaluated using the Radiation Therapy Oncology Group scoring system (12). Preexisting conditions such as urethral strictures and prior TURP were identified as baseline conditions. New or worsening signs and