High Dose Brachytherapy as Monotherapy for Intermediate Risk Prostate Cancer

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Purpose: We evaluated our retrospective, single institution experience with high dose rate brachytherapy as monotherapy for intermediate risk prostate cancer.

Materials and Methods: Our cohort included 284 patients with intermediate risk prostate cancer, defined as clinical stage T2b/T2c, Gleason score 7 and/or prostate specific antigen 10 to 20 ng/ml, and 1-year minimum followup. Treatment was 2 high dose rate brachytherapy sessions at 3 fractions of 6.5 Gy each for a mean of 19 days. Prostate specific antigen failure was defined as nadir +2 ng/ml.

Results: Mean followup was 35.1 months (median 31.9). Actuarial 5-year cause specific survival and clinical local control were 100%, distant-metastasis-free survival 98.8% and biochemical disease-free survival 94.4%. Clinical stage predicted biochemical disease-free survival. For stage T2a or less 5-year biochemical disease-free survival was 95.1% vs 100% for stage T2b and 77.4% for T2c ($p = 0.012$). Percent positive biopsy cores and prostate specific antigen nadir were also predictive. International Prostate Symptom Score results remained stable and potency was maintained in 82.6% of patients at 2 years. Pads were used for the first time after brachytherapy in 22 patients (7.7%), mostly for grade 1 incontinence (occasionally or less per week). Excluding patients with prior transurethral prostatectomy, stroke or tremor 2.5% used pads for the first time after treatment. No patient had urethral stricture. Radiation Therapy Oncology Group grade 1 rectal toxicity developed in 12 patients (4.2%) but not beyond grade 1.

Conclusions: High dose rate brachytherapy as monotherapy is safe and effective for patients with intermediate risk prostate cancer. We recommend caution for percent positive biopsy cores exceeding 75% or clinical stage T2c. Excluding such patients the 5-year biochemical disease-free survival rate was 97.5%.

Key Words: prostate, prostatic neoplasms, brachytherapy, neoplasm staging, mortality

Abbreviations and Acronyms

bDFS = biochemical disease-free survival

bRFS = biochemical recurrence-free survival

EBRT = external beam radiation therapy

HDR = high dose rate

HDR-MT = HDR monotherapy

IIEF-5 = International Index of Erectile Function

I-PSS = International Prostate Symptom Score

PBC = positive biopsy core

PSA = prostate specific antigen

PSB = permanent seed brachytherapy

RP = radical prostatectomy

RTOG = Radiation Therapy Oncology Group

SPIRIT = Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial

TRUS = transrectal ultrasound

FOR patients with organ confined prostate cancer the best care option is far from straightforward. A paucity of randomized evidence and similarity in outcomes among studies has resulted in various approaches. For low risk prostate cancer active surveillance may be suitable. Definitive approaches include RP,[1] EBRT[2] and brachytherapy,[3,4] for which comparable outcomes have been reported.[5,6]

For most patients at high risk there is broad agreement on definitive treatment. Nonetheless, optimal ther-

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Study received institutional review board approval.

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apy is open to debate. Available evidence supports radiation therapy with hormonal therapy[7,8] or RP with adjuvant EBRT as indicated.[9]

Patients at intermediate risk occupy a challenging middle ground. Recommendations include RP,[1,9] EBRT with maximum androgen ablation,[10] EBRT with a brachytherapy boost[11] and brachytherapy alone.[12–15] Some groups failed to identify differences in biochemical outcome among these approaches.[5,16] However, 3 recent publications revealed superior results for an HDR boost.[17–19]

At the inception of our practice 12 years ago we treated patients with EBRT and an HDR boost. Given publications suggesting skepticism about the need for EBRT in patients treated with brachytherapy,[12,13,15,20] we shifted toward HDR-MT for patients at low and intermediate risk.

MATERIALS AND METHODS

Since 2001, we have treated more than 1,400 patients with HDR-MT. By limiting analysis to intermediate risk disease (clinical stage T2b or T2c, Gleason score 7 and/or PSA 10 to 20 ng/ml) and at least 1-year followup we established a cohort of 284 patients. Institutional review board approval was obtained.

Stage, PSA and Pathological Evaluation

Stage was determined by digital rectal examination. Pathological assessments were reviewed by parent institution pathologists at each hospital in our state, or several neighboring or distant states, or at recognized national laboratories. Each pathologist assigned Gleason grades and most of them described biopsied sites, number of cores and percent tumor involvement in each specimen. Most biopsies were sextant or modified sextant with 6 to 12 biopsied sites and a total of 6 to 24 cores. We determined percent PBCs by dividing the number of tumor bearing cores by the total number of cores.

Prostate Volume

Volume was initially measured by TRUS guided biopsy. A total of 46 patients (16.2%) had large volume glands, typically exceeding 80 cc, and were treated with androgen deprivation plus antiandrogen for a median of 4 months (range 3 to 36), of whom 80% were treated for 4 months. Two patients (0.7%) had a prostate of less than 10 cc at initial HDR brachytherapy, of whom 1 underwent TURP before brachytherapy and each had received hormonal therapy. Pretreatment volume was assigned by TRUS at initial brachytherapy.

Planning and Treatment

Treatment consisted of 2 brachytherapy procedures, each with 3 fractions of 6.5 Gy during a 1-night hospitalization for a total of 39.0 Gy in 6 fractions for a mean of 19 days (range 7 to 35). At the first procedure 4 nonradioactive gold marker seeds were placed in the prostate at the right base, left base, right apex and left apex. At each procedure 15 gauge plastic brachytherapy needles with metal stylets were placed under TRUS and fluoroscopic guidance. Treatment planning was based on computerized tomography with the stylets removed. Anteroposterior x-rays with stylets were taken as a reference for needle position.

Target volume was defined as the prostate on planning computerized tomography, considering ultrasound findings and marker seed positioning, with no additional expansion. Treatment was planned so that the 100% prescription isodose encompassed the entire prostate and the 120% isodose encompassed the peripheral zone. The 110% isodose was not allowed to touch the urethral catheter surface, limiting urethral central points to less than 105% of the prescription dose. Anterior rectal mucosa, which was defined by luminal contrast medium, was limited to less than 60%. No portion of the rectum was permitted to receive greater than 100%. Bladder wall doses were limited to 100%. Mean prostate, planning target and treatment volumes were 38.1 (range 3.5 to 98.8), 68.7 (range 7.5 to 142.7) and 95.2 cc (range 7.9 to 191.1), respectively.

Brachytherapy was administered using a microSelectron® with a ^{192}iridium source of 4.5 to 9.9 Ci. One brachytherapy fraction was given on the afternoon of day 1, the second on the morning of day 2 and third on the afternoon of day 2. The minimum interfraction interval on day 2 was 5 hours (mean 5.5). Needle positions were evaluated relative to 4 gold fiducials placed at initial brachytherapy. In case of movement the needles were adjusted within 1 mm of the reference x-ray. Adjustments, commonly in the range of 2 to 3 mm, were needed in about a third of patients.

Followup and Outcome Evaluation

Followup was scheduled at 3-month intervals for 1 year and every 6 months thereafter. PSA failure was defined as nadir +2 ng/ml.[21] Patients recorded I-PSS before treatment and at each followup. Continence was evaluated by pad use according to a modified Subjective, Objective, Management, Analytic scale, including grade 0—no pads, grade 1—occasionally (weekly or less), grade 2—intermittent (less than daily), grade 3—persistent (2 or fewer pads daily/self-catheterization and grade 4—refractory (greater than 2 pads daily, permanent catheter or urinary diversion).[22] Erectile function was scored by each patient using the IIEF-5 questionnaire.[23,24] Rectal side effects were scored by RTOG criteria.[25]

Statistics

Statistical analysis was done with PASW® Statistics and STATA/IC™ 11.1. Standard statistics were used to summarize patients and treatment characteristics. The Kaplan-Meier method was used for survival analysis and with log rank post hoc analysis was used for comparisons among patient groups. Longitudinal analysis of I-PSS was done with a generalized least squares random effects model.

RESULTS

The table 1 lists patient characteristics and treatment parameters. Mean ± SD followup was 35.1 ± 16.2 months (median 31.9, range 12.13 to 96.1).

Survival and Biochemical Outcome

Four patients (1.4%) died, of whom none had recurrent prostate cancer. Actuarial 5-year overall sur-