Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 1, pp. 222–227, 2012

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.09.021

CLINICAL INVESTIGATION **Genitourinary Cancer**

HIGH-DOSE-RATE BRACHYTHERAPY BOOST FOR PROSTATE CANCER: COMPARISON OF TWO DIFFERENT FRACTIONATION SCHEMES

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Purpose: **This is a retrospective study comparing our experience with high-dose-rate (HDR) brachytherapy boost for prostate cancer, using two different fractionation schemes, 600 cGy × 3 fractions (patient group 1) and 950 cGy × 2 fractions (patient group 2).**

Methods and Materials: **A total of 165 patients were treated for prostate cancer using external beam radiation therapy up to a dose of 45 Gy, followed by an HDR brachytherapy prostate radiation boost. Between July 1997 and Nov 1999, 64 patients were treated with an HDR boost of 600 cGy × 3 fractions; and between June 2000 and Nov 2005, 101 patients were treated with an HDR boost of 950 cGy × 2 fractions. All but 9 patients had at least one of the following risk features: pretreatment prostate-specific antigen (PSA) level >10, a Gleason score ≥7, and/or clinical stage T3 disease.**

Results: **Median follow-up was 105 months for group 1 and 43 months for group 2. Patients in group 2 had a greater number of high-risk features than group 1 ($p = 0.02$). Adjusted for comparable follow-up, there was no difference in biochemical no-evidence-of-disease (bNED) rate between the two fractionation scheme approaches, with 5-year Kaplan-Meier estimates of 93.5% in group 1 and 87.3% in group 2 ($p = 0.19$). The 5-year estimates of progression-free survival were 86% for group 1 and 83% for group 2 ($p = 0.53$). Among high-risk patients, there were no differences in bNED or PFS rate due to fractionation.**

Conclusions: **Results were excellent for both groups. Adjusted for comparable follow-up, no differences were found between groups.** **© 2012 Elsevier Inc.**

Prostate cancer, High-dose-rate, Brachytherapy, Radiation therapy, Boost.

INTRODUCTION

Excellent local control rates for prostate cancer can be achieved using high doses of external beam radiation therapy (EBRT). Until recently, these outstanding outcomes with EBRT for the treatment of prostate cancer, including local control and survival, were seen primarily in patients with early-stage or low-risk prostate cancer. Patients with locally advanced disease had poor 5- and 10-year survival rates, 40% to 75% and 35% to 55%, respectively (1–4). To improve upon these rates, there have been an increasing number of dose escalation studies using various forms of radiation therapy that have included patients with intermediate- and high-risk disease. Several randomized trials have shown 10% to 20% improvement in biochemical progression-free survival (PFS) with dose escalation in the treatment of prostate cancer with radiation therapy (5–11). These dose escalation studies have included conventional four-field box radiation, three-dimensional conformal radiotherapy, intensity-modulated radiation therapy (IMRT), particle beam (proton) therapy, and interstitial brachytherapy.

There are prospective data from a phase I-II study using high-dose-rate (HDR) brachytherapy as a boost to EBRT for intermediate- and high-risk disease (12). That study showed that higher HDR doses improved 5-year biochemical control rates, clinical control rates, clinical event-free survival rates, as well as cause-specific survival, and overall survival (OS) rates. A randomized phase III trial from the United Kingdom evaluated patients with low-, intermediate-, and high-risk prostate cancer treated with EBRT alone and compared them to patients treated with EBRT with HDR brachytherapy boost. Patients treated with the combined approach, the higher-dose arm, had improved biochemical relapse-free survival and, importantly, less acute rectal toxicity and improved quality of life (10).

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Presented in poster form at the 50th Annual Meeting of the American Society for Radiation Oncology (ASTRO), Boston, MA, Sep 21–25, 2008.

Conflicts of interest: none.

Received June 2, 2010, and in revised form Sept 17, 2010. Accepted for publication Sept 24, 2010.

Advantages of using HDR brachytherapy technique to deliver the boost dose include conformal dose distribution, accurate dosimetry with lack of internal motion and setup errors, shorter treatment times, limited morbidity, lack of seed migration after the procedure, and elimination of radiation exposure to hospital staff and family members. We have previously reported our retrospective review of our initial set of patients with intermediate- and high-risk prostate cancer treated with HDR brachytherapy boost (13). We demonstrated that HDR brachytherapy is effective in the treatment of these patients for delivering conformal prostate radiation doses and can be used with whole-pelvis radiation therapy (WPRT) and hormone therapy (HT).

In this current retrospective analysis, we compare two different fractionation schemes used to deliver the HDR brachytherapy boost to determine whether we can further improve disease control. The prostate HDR brachytherapy program at the University of California, San Francisco, was started in 1997. In our initial patient series, the HDR fractionation scheme of 1,800 cGy in three fractions was given after administration of 4,500 cGy of conformal radiation therapy to the prostate and seminal vesicles for patients with ≤15% risk of lymph node involvement and to the whole pelvis for patients with >15% risk of lymph node involvement. The latter group also received combined HT with WPRT (14). In 2000, our fractionation regimen was changed to 1,900 cGy in 2 fractions. This fractionation allowed for a higher biologically effective dose than the initial regimen and decreased the treatment time. This analysis updates our experiences with HDR brachytherapy boost for prostate cancer treatment and compares the two fractionation schemes with regard to biochemical control, PFS rate, and toxicity.

METHODS AND MATERIALS

A total of 195 consecutively accrued patients were treated for newly diagnosed localized prostate cancer, using EBRT to a dose of 4,500 cGy, followed by an HDR brachytherapy boost. This analysis is limited to the 165 patients treated with two commonly used fractionation regimens, 600 cGy × 3 and 950 cGy × 2; 26 patients treated with other fractionation regimens were excluded. Two additional patients with node-positive disease and 2 patients with no follow-up were excluded. Patients' clinical records were retrospectively reviewed after obtaining the approval of the committee of human research. All but 9 of the patients in this analysis had at least one of the following risk features and were thus referred to receive HDR brachytherapy boost: pretreatment prostate-specific antigen (PSA) level >10, Gleason score (GS) ≥7, or clinical stage T3 disease. The HDR was administered with a single implant, and all fractions were given within 24 hours.

Radiation technique and treatment characteristics

Patients whose risk of positive lymph nodes exceeded 15%, calculated using the formula, risk (%) = 2/3 (pretreatment PSA [pPSA]) + 10 [(GS − 6)], received WPRT to a dose of 4,500 cGy (15). Patients with <15% risk of lymph node involvement were treated with 4,500 cGy to the prostate and seminal vesicles. Three-dimensional treatment planning or IMRT was used for dose calculation. Daily fractions of 180 cGy were delivered.

Standard HT was administered to 86 patients (52%), most commonly as 2 months of neoadjuvant HT followed by concurrent HT with EBRT. HT consisted of total androgen blockade, using both a peripheral androgen blockade and a luteinizing hormone-releasing hormone agonist. One patient received only neoadjuvant HT. For patients with high-risk disease (PSA >20, GS >7, or T3 disease), 2 additional years of HT was recommended (luteinizing hormone-releasing hormone agonist alone) after completion of radiotherapy; 56 patients received adjuvant HT.

Patients received a transrectal ultrasound (TRUS)-guided HDR implant approximately 1 week after completing EBRT. Our implant technique and practice changed over time. Between July 1997 and November 1999, 12 catheters were inserted transperineally near the prostate capsule, and 6 catheters were inserted periurethrally, based on the disposable Syed-Neblett prostate template. Our technique has been described in detail previously (13). Since June 2000 16 catheters were inserted transperineally and periurethrally near the prostate capsule, using image guidance but without the template. Similar to our initial technique, the catheters were adjusted to cover any TRUS-identified extracapsular extension or seminal vesicle involvement. The time gap between November 1999 and June 2000 was due to the exclusion of patients treated with different fractionation schemes between December 1999 and May 2000.

Patients who did not have gold marker seeds placed prior to EBRT had gold marker seeds placed at the prostatic base and apex at the start of the implant procedure. These marker seeds were used in the determination of the treatment volume. A Foley catheter was placed during the implant procedure, allowing better visualization of the bladder and urethra. All patients underwent flexible cystoscopy during and after the implant to ensure that no catheters remained in the urethra or bladder. Patients underwent a computed tomography (CT) scan after the implant for planning purposes. Planning for patients treated with 600 cGy × 3 used geometric optimization and manual adaptation. Beginning in June 2000, all patients were treated with 950 cGy × 2, using a three-dimensional inverse planning system algorithm called inverse planning simulated annealing (IPSA), described in detail previously (16). With regard to catheter migration, the patients are not routinely rescanned prior to the second or third fraction. Our implantation and treatment planning techniques have been adapted to minimize this problem (17,18).

Between July 1997 and November 1999, 64 patients were treated with an HDR boost of 600 cGy × 3. The first fraction was given on the day of the implant, and two additional fractions were given on the following day, with a minimum of 6 h between treatments. Between June 2000 and November 2005, 101 patients were treated with an HDR boost of 950 cGy × 2. The first fraction was given on the day of the implant, and the additional fraction was given on the following day. Patients were followed for at 1 month postimplant and then after every 3 to 6 months, until 5 years after treatment. After 5 years, patients were followed yearly.

Statistical analysis

Two sequentially accrued groups of patients newly diagnosed with localized prostate cancer were treated with an HDR boost of either 600 cGy × 3 or 950 cGy × 2. Comparability of baseline patient and disease features as well as EBRT and HT treatment was analyzed using Fisher's exact test for categorical variables (*e.g.*, GS) and the Mann-Whitney test for distributions (*e.g.*, PSA).

The Kaplan-Meier product limit method was used to estimate the probability of biochemical control, PFS, and OS, all measured from the end of HDR therapy. Biochemical failure was defined using the