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CLINICAL INVESTIGATION **Prostate**

HYPOFRACTIONATED BOOST WITH HIGH-DOSE-RATE BRACHYTHERAPY AND OPEN MAGNETIC RESONANCE IMAGING–GUIDED IMPLANTS FOR LOCALLY AGGRESSIVE PROSTATE CANCER: A SEQUENTIAL DOSE-ESCALATION PILOT STUDY

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Purpose: To evaluate the feasibility, tolerance, and preliminary outcome of an open MRI-guided prostate partial-volume high-dose-rate brachytherapy (HDR-BT) schedule in a group of selected patients with nonmetastatic, locally aggressive prostatic tumors.

Methods and Materials: After conventional fractionated three-dimensional conformal external radiotherapy to 64–64.4 Gy, 77 patients with nonmetastatic, locally aggressive (*e.g.,* perineural invasion and/or Gleason score 8–10) prostate cancer were treated from June 2000 to August 2004, with HDR-BT using temporary open MRI-guided ^{192}Ir implants, to escalate the dose in the boost region. Nineteen, 21, and 37 patients were sequentially treated with 2 fractions of 6 Gy, 7 Gy, and 8 Gy each, respectively. Neoadjuvant androgen deprivation was given to 62 patients for 6–24 months. Acute and late toxicity were scored according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scoring system.

Results: All 77 patients completed treatment as planned. Only 2 patients presented with Grade ≥3 acute urinary toxicity. The 3-year probability of Grade ≥2 late urinary and low gastrointestinal toxicity–free survival was 91.4% ± 3.4% and 94.4% ± 2.7%, respectively. Rates of 3-year biochemical disease-free survival (bDFS) and disease-specific survival were 87.1% ± 4.1% and 100%, respectively.

Conclusions: Boosting a partial volume of the prostate with hypofractionated HDR-BT for aggressive prostate cancer was feasible and showed limited long-term toxicity, which compared favorably with other dose-escalation methods in the literature. Preliminary bDFS was encouraging if one considers the negatively selected population of high-risk patients in this study. © **2009 Elsevier Inc.**

Prostate cancer, Brachytherapy, Radiotherapy, High dose rate, Radiation toxicity.

INTRODUCTION

Radiotherapy (RT) for localized prostate cancer is a well-established treatment, competing with surgery with a similar curative potential but different side effects. The results of curative RT delivered in the 1970s and 1980s and assessed with sequential prostate-specific antigen (PSA) tests have shown a higher than previously expected treatment failure rate (40–50%) when delivering 65–70 Gy, the recommended dose at that time (1). Such failure rates have been frequently associated with the inability to control the disease locally, due to either inefficient dose delivery (inaccuracy in target definition, systematic and random treatment setup errors, and internal organ motion) or to a dose too low to sterilize the tumor in the irradiated region.

Strategies to improve local control in the past decade have included androgen suppression with RT, low-dose-rate implants with permanent seeds (^{125}I, ^{103}Pd), and dose escalation with either external-beam RT techniques (*i.e.,* three-dimensional [3D] conformal X-ray beams, intensity-modulated X-ray beams, and proton beams) or conformal high-dose-rate (HDR) brachytherapy (BT) with temporary implants (^{192}Ir). The goal of these strategies is to achieve

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higher cure rates but with a similar or lower incidence of late effects as compared with standard RT doses. Indeed, escalating the dose has already shown encouraging preliminary results in several Phase II–III trials, even though late effects have not always been improved accordingly (2–5). Zelefsky *et al.* (6) have reported long-term results after dose escalation, with an improved biochemical outcome and a simultaneous reduction in the incidence of distant metastases for doses above 81 Gy without an increased risk of late toxicity in those patients.

Patients with poorly differentiated tumors (*i.e.,* Gleason scores 8–10) and/or perineural invasion in the biopsy specimen may be at a higher-than-average risk for local failure and may benefit most from dose escalation to the tumor (7–10). The largest tumor burden (the dominant intraprostatic tumor nodule[s]) is predominantly located in the peripheral or in the central zone (base) of the prostate, especially in locally advanced tumors and/or in those with high Gleason scores (*i.e.,* 7–10) (11). Thus, a heterogeneous density in the distribution of tumor cells within the prostate supports the notion of an intentionally inhomogeneous dose distribution to deliver a relatively higher dose to the high-density tumor-bearing regions and relatively lower doses to areas with smaller tumor foci (*e.g.,* transitional zone). Progress in imaging (*e.g.,* endorectal spectroscopic magnetic resonance, ^{11}C- or ^{18}F-marked tracers such as choline or acetate positron emission tomography [PET]) may help to further improve definition of local tumor extent within the prostate, thus optimizing tumor dose ''painting'' (12–16).

Prostate cancer cells may have relatively long doubling times and may repair sublethal radiation damage effectively at low doses per fraction (low α/β ratio, 1.2–1.7 Gy). Thus, prostate cancer may be very sensitive to changes in fractionation. Dose escalation via hypofractionation (fewer fractions but with a larger dose per fraction) may be biologically advantageous because of the comparatively lower sensitivity to fractionation changes of surrounding critical organs, such as the bladder and the rectum (α/β ratio = 3–5 Gy) (17–19). Thus, hypofractionation may increase the tumor cell killing effect. Several investigators have reported their respective experiences with doses per fraction above 2 Gy (2.5–10 Gy) in prostate cancer. They all found the treatment to be efficient and well tolerated (20–28).

Clinical data suggest that 64 Gy delivered in 32 daily ''standard'' 2-Gy fractions can cure residual or relapsing microscopic local disease after postprostatectomy biochemical failure (29). Thus, it is reasonable to approach the curative treatment of gross disease by prescribing a similar dose level (*i.e.,* 64 Gy) to areas of potentially microscopic foci in the transitional zone while boosting the dominant intraprostatic tumor nodule(s)-bearing region(s) (i.e., peripheral and/or central zones and/or seminal vesicles) up to 80 Gy and above to improve local cure.

In the present sequential dose-escalation pilot study we aimed to evaluate the feasibility, tolerance, and preliminary outcome of an open MRI-guided prostate partial volume HDR-BT schedule in a group of selected patients with nonmetastatic, locally aggressive prostatic tumors.

METHODS AND MATERIALS

From June 2000 through August 2004, 77 consecutive patients with nonmetastatic, locally aggressive prostate cancer (either perineural invasion or Gleason scores 8–10 in the pathology report of the biopsy specimen) were eligible and consented to participate in this study. Sextant biopsies from both sides of the prostate (six cores, minimum) were performed in all patients. All patients underwent an endorectal MRI (erMRI) study of the prostate to assess the site and extension of the disease inside the prostatic gland and to rule out any infiltration of the seminal vesicles; patients with disease above the root of the seminal vesicles were ineligible for the brachytherapy boost. All erMRI studies were performed no earlier than 4–6 weeks after biopsy of the prostate and before the start of RT or androgen deprivation. Endorectal MRI with spectroscopy was only performed starting in January 2004.

The mean age at presentation was 65 years (range, 49–79 years). The distribution of patients according to clinical stage, Gleason score, blood PSA level at diagnosis, and risk group is presented in Table 1. Patients were seen on follow-up visit 6 weeks after treatment completion, 3 months later, and every 6 months subsequently. Patients have been followed for a median of 41.2 months. Acute low-gastrointestinal (GI) and genitourinary toxicities were assessed once per week during treatment and 6 weeks to 3 months after treatment completion. Late toxicity was assessed thereafter and reported after each follow-up visit (every 6 months). Genitourinary and GI

Table 1. Patient characteristics

Characteristic	*n*	%
Clinical stage		
T1c	14	18.2
T2a	10	13.0
T2b	8	10.4
T2c	1	1.3
T3a	40	51.9
T3b	4	5.2
Gleason score		
2–6	25	32.5
7	21	27.3
8–10	31	40.3
PSA at diagnosis (ng/mL)		
<10	17	22.1
10–20	32	41.6
>20	28	36.4
Risk group		
Low	6	7.8
Intermediate	25	32.5
High	46	59.8
Perineural infiltration		
No	20	26.0
Yes	52	67.5
Unknown	5	6.5
Pelvis irradiation		
No	28	36.4
Yes	49	63.6
Androgen deprivation		
No	15	19.5
Yes	62	80.5

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