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Clinical Investigation: Genitourinary Cancer

Five-Year Outcomes from 3 Prospective Trials of Image-Guided Proton Therapy for Prostate Cancer

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Summary

Proton therapy (PT) for low-, intermediate-, and high-risk prostate cancer patients is highly effective, minimally toxic, and associated with excellent patient-reported outcomes. PT compares favorably with other contemporary radiation modalities used in treating prostate cancer.

Purpose: To report 5-year clinical outcomes of 3 prospective trials of image-guided proton therapy for prostate cancer.

Methods and Materials: A total of 211 prostate cancer patients (89 low-risk, 82 intermediate-risk, and 40 high-risk) were treated in institutional review board-approved trials of 78 cobalt gray equivalent (CGE) in 39 fractions for low-risk disease, 78 to 82 CGE for intermediate-risk disease, and 78 CGE with concomitant docetaxel therapy followed by androgen deprivation therapy for high-risk disease. Toxicities were graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Median follow-up was 5.2 years.

Results: Five-year rates of biochemical and clinical freedom from disease progression were 99%, 99%, and 76% in low-, intermediate-, and high-risk patients, respectively. Actuarial 5-year rates of late CTCAE, version 3.0 (or version 4.0) grade 3 gastrointestinal and urologic toxicity were 1.0% (0.5%) and 5.4% (1.0%), respectively. Median pretreatment scores and International Prostate Symptom Scores at >4 years posttreatment were 8 and 7, 6 and 6, and 9 and 8, respectively, among the low-, intermediate-, and high-risk patients. There were no significant changes between median pretreatment summary scores and Expanded Prostate Cancer Index Composite scores at >4 years for bowel, urinary irritative and/or obstructive, and urinary continence.

Conclusions: Five-year clinical outcomes with image-guided proton therapy included extremely high efficacy, minimal physician-assessed toxicity, and excellent patient-reported outcomes. Further follow-up and a larger patient experience are necessary to confirm these favorable outcomes. © 2014 Elsevier Inc.

Introduction

There is interest among patients, physicians, insurers, and government agencies in the relative effectiveness of various strategies for management of prostate cancer, the most common noncutaneous malignancy in men in the United States. One comparative study of patient-reported quality of life outcomes (PRQoLOs) among patients treated with surgery, brachytherapy, or external beam radiation therapy (EBRT) showed variation in

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toxicity profiles (1) but relatively favorable outcomes for EBRT. Most EBRT delivers x-rays using sophisticated techniques (2). There is growing interest in proton therapy (PT) as a radiation source because, compared with x-ray-based therapies, less radiation dose is deposited in normal nontargeted tissues, possibly resulting in less toxicity, better quality of life, and fewer second malignancies (3, 4). Reduction in dose to normal tissues might also make radiation dose escalation or intensification feasible, resulting in greater efficacy and shorter, less expensive treatment schedules. Despite reports of excellent outcomes in prostate cancer patients treated with PT alone (5) or in combination with x-ray therapy (6), many physicians consider the clinical evidence for PT to be insufficient (7, 8), and some investigators have relied on surrogate data from Medicare claims for comparative studies (9), leading to controversial findings.

To establish benchmark outcomes for PT, 3 prospective trials in low-, intermediate-, and high-risk prostate cancer patients were conducted at our institution. Five-year outcomes from these trials are reported below.

Methods and Materials

Patients

From August 2006 through September 2007, 211 patients were treated with institutional review board-approved protocols PR-01 (UFJ-2005-154), PR-02 (UFJ-2006-63), and PR-03 (UFJ-2006-94) to assess outcomes after undergoing PT for low-risk (n = 89), intermediate-risk (n = 82), and high-risk (n = 40) prostate cancer, respectively. Eligibility criteria and required staging were previously described (10). Patients were staged according to the seventh edition of the AJCC Staging Manual (11).

Prostate-specific antigen (PSA) concentration was assessed before and after treatment and then at 3-month intervals; the Phoenix definition for PSA progression (nadir + 2 ng/mL) was used (12). In all patients with PSA progression, a bone scan and positron emission tomography-computed tomography (CT) and/or magnetic resonance imaging (MRI) of the pelvis were performed to determine patterns of failure. Physician-determined toxicities were assessed weekly throughout treatment and at 6-month intervals, using Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0) (13). Serious adverse events were also classified retrospectively according to the 2010 edition of CTCAE v4.0 (14), which is based on instrumental and self-care activities of daily living (ADLs). The Expanded Prostate Cancer Index Composite (EPIC; version 2.2002) score and the International Prostate Symptom Score (IPSS) were used to assess PRQoLOs before and at 6-month intervals after PT. Ninety-six percent of patients were seen in follow-up, were deceased, or were contacted within 12 months of this analysis. Minimum potential and median actual follow-up intervals were 5 and 5.2 years, respectively.

Prognostic information is provided in Table 1. Forty-two patients with low-risk disease and prostate volumes <60 cm^3 were brachytherapy candidates. Twenty low-risk patients (22%) were "very low-risk" per National Comprehensive Cancer Network guidelines (15). Twenty-eight intermediate-risk patients (34%) were considered "unfavorable" (having a dominant Gleason pattern of 4, a PSA of $\geq$15 and $<$20, and/or clinical stage (CS) T2 C disease).

Protocol treatment

PR-01 for low-risk patients delivered 78 cobalt gray equivalent (CGE). PR-02 delivered 78 to 82 CGE for intermediate-risk prostate cancer. PR-03 for high-risk patients delivered 78 CGE with weekly concomitant docetaxel (Taxotere, Sanofi-Aventis U.S. LLC, Bridgewater, NJ) (20 mg/m^2) therapy, followed by 6 months of androgen deprivation therapy (ADT). The daily dose was 2 CGE. Two PR-03 patients refused ADT after completing PT with Taxotere. Ten low-risk and 7 intermediate-risk patients received neoadjuvant ADT prior to referral (Table 1). No pelvic node irradiation was delivered.

Treatment simulation and planning

Previously reported planning details (10) include customized vacuum-locked body bags, bladder filling, and rectal instillation of saline to reduce intrafractional prostate motion. Fused CT and MRI simulation images were used to define both the clinical target volume (CTV) and organs at risk (OARs). The CTV for PR-01 was the prostate only but the proximal 2 cm of the seminal vesicles were included in PR-02 and PR-03. The planning target volume (PTV) included an expansion beyond the CTV of 8 mm in the superior–inferior axis and 5 mm in the axial plane; beam angles were selected to optimize both target coverage and avoidance of OARs. Brass apertures included the PTV plus 1 cm in all directions except posterior, which was 7 mm. Compensators for distal conformity of target coverage used a smearing value of 1.9 cm and 1.0-cm border smoothing (subsequently reduced to 0 cm following experimental validation). Proton beam stopping power was calculated from the CT Hounsfield unit value (16). Distal and proximal beam margins from the PTV were 0.5 cm.

Target and normal tissue dosimetric specifications

When all dosimetric specifications for target coverage and avoidance of OARs (10) could be met with a single field, only 1 of the 2 fields was treated each day. Both fields were treated each day in only 23 cases (11%).

The intermediate-risk protocol, PR-02, permitted dose escalation to 82 CGE if OAR constraint goals were met; 57 patients (69%) received 82 CGE, 13 (16%) received 80 CGE, and 12 (15%) received 78 CGE.

Image guided treatment delivery

Daily targeting was based on intraprostatic fiducial markers identified by orthogonal orthovoltage imaging. Rectal balloons were added in 8 patients (3.7%) whose daily intrafractional motion exceeded 5 mm.

Statistical analysis

Maximum genitourinary (GU) and gastrointestinal (GI) toxicity scores were assessed at 6-month intervals; cumulative incidence, prevalence, and actuarial rates were calculated.

All statistical computations were performed with SAS and JMP software (SAS Institute, Cary, NC). The Wilcoxon signed rank sum test was used for paired comparisons of baseline and posttreatment