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Clinical Investigation

Rectal Toxicity After Proton Therapy For Prostate Cancer: An Analysis of Outcomes of Prospective Studies Conducted at the University of Florida Proton Therapy Institute☆

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Summary

Proton therapy was associated with a low rate of grade 2 or higher gastrointestinal toxicity in patients undergoing both investigational and outcome tracking protocols, predominantly transient rectal bleeding, which was highly correlated with aspirin, anticoagulation, and rectal dose-volume histogram parameters.

Purpose: Study goals were to characterize gastrointestinal effects of proton therapy (PT) in a large cohort of patients treated for prostate cancer, identify factors associated with rectal bleeding (RB), and compare RB between patients receiving investigational protocols versus those in outcome-tracking protocols.

Methods and Materials: A total of 1285 consecutive patients were treated with PT between August 2006 and May 2010. Potential pre-existing clinical and treatment-related risk factors for rectal toxicity were recorded. Common Terminology Criteria for Adverse Events version 3.0 was used to score toxicity.

Results: Transient RB was the predominant grade 2 or higher (GR2+) toxicity after PT, accounting for 95% of gastrointestinal events. GR1 RB occurred in 217 patients (16.9%), GR2 RB in 187 patients (14.5%), and GR3 in 11 (0.9%) patients. There were no GR4 or GR5 events. Univariate analyses showed correlations between GR2+ RB and anticoagulation therapy ($P = .008$) and rectal and rectal wall dose-volume histogram (DVH) parameters ($P < .001$). On multivariate analysis, anticoagulation therapy ($P = .0034$), relative volume of rectum receiving 75 Gy (V75; $P = .0102$), and relative rectal wall V75 ($P = .0017$) were significant predictors for G2+ RB. Patients treated with investigational protocols had toxicity rates similar to those receiving outcome-tracking protocols.

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Conclusions: PT was associated with a low rate of GR2+ gastrointestinal toxicity, predominantly transient RB, which was highly correlated with anticoagulation and rectal DVH parameters. Techniques that limit rectal exposure should be used when possible.

Introduction

External beam radiation treatment (EBRT) is commonly used to treat localized prostate cancer. The most common source for EBRT has been x-rays. With sophisticated x-ray delivery techniques, such as intensity modulated radiation therapy (IMRT), which permit delivery of high doses of radiation to the prostate and low to moderate doses to normal tissues, patients have experienced a reduction in radiation toxicity (1). This reduction in toxicity has permitted dose escalation, resulting in increased efficacy (2, 3). The use of protons in lieu of x-rays as the source for EBRT may offer further reduction in toxicity and improvement in efficacy by reducing the incidental radiation dose to normal tissues. Reports from Loma Linda University Medical Center (LLUMC; Loma Linda, CA) in which proton therapy (PT) alone has been used to treat prostate cancer (4, 5) and studies of PT in combination with x-ray therapy (6) have shown grade 3 (GR3) rectal toxicity rates of $<1\%$.

Recent studies using the Medicare database, however, have implied higher rates of rectal toxicity (7-9) in patients receiving PT than previously reported and, in some instances, higher than in patients receiving IMRT. These studies have been criticized for dependence on correlative data (eg Medicare claims codes) rather than physician-assessed toxicity or patient-reported outcomes (10).

Early toxicity and 5-year results from 3 prospective PT protocols conducted at our institution showed low rates of gastrointestinal (GI) and genitourinary (GU) toxicity (11-13), mirroring the LLUMC reports. The purposes of the present study was to confirm our early findings with a larger population of patients and to identify clinical and treatment factors associated with rectal toxicity.

Methods and Materials

The medical records of 1538 consecutive patients with localized prostate cancer treated with PT at our institution between August 2006 and May 2010 were reviewed under institutional review board approval. Patients were excluded from analysis if they had hypofractionation protocols (n = 141), PT for salvage therapy (n = 14), or pelvic IMRT (n = 60) or had non-hemorrhoidal rectal bleeding (RB; n = 1) or colostomy (n = 2) prior to PT. Thirty-five additional patients were excluded for inadequate data contribution, including 19 who refused follow-up, 8 who refused to complete questionnaires, 3 who died of non−treatment-related causes, and 5 who discontinued treatment for non-GI toxicity. A previous report included 211 patients enrolled in early investigational protocols (IP) (11) (the primary purpose of which was to establish benchmarked outcomes for patients receiving PT for localized prostate cancer), including 2 excluded from this analysis because of death from non−treatment-related causes during or within a month of PT. The analysis thus consists of 1285 patients with baseline characteristics shown in Table 1, of whom 209 were undergoing IP. An additional 1076 patients were enrolled in an outcome-tracking protocol (OTP) in which data were collected prospectively at the same regular follow-up intervals as IP patients, with additional data collected between follow-up visits if toxicity, disease recurrence, or other serious adverse events developed. The primary difference between the IP and OTP was in exclusion criteria; the IP did not enroll patients whose medical history included a factor that could confound interpretation of outcomes, such as a previous malignancy, whereas all treated patients were eligible for the OTP.

All patients had outside pathology reviewed at our institution to ensure consistency of diagnosis and Gleason grading. All patients had pretreatment serum prostate-specific antigen (PSA) and complete blood count and blood chemistry tests, pelvic computed tomography (CT), and magnetic resonance imaging (MRI), unless contraindicated. Patients with intermediate- and high-risk disease had bone scans. After May 2009, screening colonoscopies were required before PT to lessen concerns about potential malignant sources of post-treatment RB.

Treatment simulation and planning

The treatment simulation and planning processes have been described in detail previously (11). All patients underwent intraprostatic fiducial marker placement followed by CT simulation in a vacuum-locked body mold with 100 to 200 cm^3 saline instilled in the rectum. After May 2008, all patients had rectal balloons inflated with 80 to 100 cm^3 of saline for prostate stabilization. A planning MRI was also obtained with a Panorama model 0.23-T open MRI system (Philips, Amsterdam, the Netherlands) in patients able to tolerate MRI scanning, which was then fused with the CT for target and critical organ delineation. The rectum was manually contoured by dosimetrists, from the ischial tuberosity inferiorly to the sigmoid flexure superiorly. The rectal wall was constructed as 3-mm thick wall structures within the volume of the rectum.

The clinical target volume (CTV) included only the prostate in low-risk patients or the prostate and proximal 2 cm of seminal vesicles in intermediate- and high-risk