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Comparative study of late rectal toxicity in prostate cancer patients treated with low-dose-rate brachytherapy: With or without supplemental external beam radiotherapy

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ABSTRACT

PURPOSE: Supplemental external beam radiation therapy (sEBRT) is often prescribed in men undergoing low-dose-rate (LDR) brachytherapy. A population of patients was analyzed to assess the effect of sEBRT on late rectal toxicity. It was hypothesized that sEBRT + LDR would be associated with a higher risk of late rectal toxicity.

METHODS AND MATERIALS: This retrospective cohort study examined LDR brachytherapy patients, treated with or without sEBRT, with a minimum of 5-year followup. Longitudinal assessments were evaluated using the computerized patient record system. The Kaplan−Meier method was used for analysis.

RESULTS: Median followup was 7.5 years for 245 patients from 2004 to 2007. sEBRT was administered to 33.5%. Followup beyond 5 years was available for 89%. Overall rates of Grade ≥2 and ≥3 rectal toxicities were 6.9% and 2.9%, respectively. The risk of Grade ≥2 rectal toxicity was 2.8-fold higher for patients receiving sEBRT (95% confidence interval: 1.1−7.2; $p = 0.02$). The risk of Grade ≥3 rectal toxicity was 11.9-fold higher for patients who received sEBRT (1.5−97.4, 95% confidence interval; $p = 0.003$). Six of seven patients with a Grade ≥3 rectal toxicity received sEBRT, including one who required an abdominoperineal resection. Median post-LDR D_{90}, V_{150}, V_{200}, and R_{100} values were 103.3%, 59.4%, 30.1%, and 0.5 cc.

CONCLUSIONS: In a cohort of LDR brachytherapy patients with high rates of followup, sEBRT + LDR was associated with significantly higher risk of Grade ≥2 and ≥3 late rectal toxicity. This analysis supports previous findings and maintains concern about the supplemental use of external beam radiation therapy with LDR brachytherapy while its benefit for tumor control has yet to be prospectively validated. Published by Elsevier Inc. on behalf of American Brachytherapy Society.

Keywords: LDR; Brachytherapy; Prostate; External beam radiation therapy; Rectal toxicity

Introduction

Low-dose-rate brachytherapy (LDR-BT) is a well-established treatment for prostate cancer (1−6). In an effort to improve tumor control rates for specific presentations, it may at times be supplemented with external beam radiotherapy (sEBRT) (7, 8). Early reports with this approach suggested the combination is well tolerated, although long-term followup was initially limited (9−14). This included the first report of RTOG 0019, a single-arm multi-institutional study of combination radiotherapy that had a median followup of 20 months and suggested an acceptable rate of toxicity when published by Lee *et al.* in 2006 (15, 16).

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When the RTOG 0019 study was updated by Lawton *et al.* in 2014, with a median followup of 8.2 years, the severe late Grade ≥3 rectal toxicity increased from <1% to 3% (17). This Phase II study did not have a comparator group of men treated with LDR-BT alone, and thus, the contribution of sEBRT in that study has since remained unknown. We are aware of only one other study with a median followup ≥5 years that reports on severe late rectal toxicities with combination radiotherapy. Published in 2013, the group at Mt Sinai reported a rectal fistula and ulceration rate of 0.11% and 0.22%, respectively, and their analysis suggested a negligible contribution by sEBRT (18). Although these data are encouraging, they may have been subject to underascertainment without access to each patient's entire medical history that would include visits to various specialists, or health care systems.

To seek a potentially more accurate estimate of the cumulative risk and better understand the hypothesis that sEBRT may contribute to an increased rate of late rectal toxicity, the authors investigated a cohort of patients treated in the veterans affairs (VAs) who are managed in a large integrated health care system with a uniform electronic medical record system. Such an infrastructure provides a robust opportunity to capture rectal toxicities that may present at nonradiation oncology followup visits many years after their implant. It was hypothesized that a query of their electronic medical records would identify a late severe Grade ≥3 toxicity rate closer to that reported in the prospective RTOG 0019 report and provide a robust opportunity to investigate the potential contribution of sEBRT to late rectal fistulas and ulcers. Because of the inability to adequately adjust for selection bias in treatment assignment, tumor control rates with or without sEBRT were not investigated.

Methods

Study design and patient population

The investigation was designed as a retrospective cohort comparison of all prostate cancer patients treated with LDR-BT, with or without sEBRT, between January 2004 and December 2007 at a single institution. This period was selected to evaluate all patients with available postimplant CT-based dosimetry and a minimum of 5-year followup. All patients underwent treatment at the Hunter-Holmes McGuire Veterans Affairs Medical Center (Richmond, Virginia) which is a teaching hospital staffed by radiation oncologists and medical physicists from Virginia Commonwealth University. The prostate brachytherapy program is credentialed by the Nuclear Regulatory Commission and VA National Health Physics Program. It is also credentialed by the RTOG and NRG Oncology and was a leading enrollment site (n = 33 patients) for the RTOG 0232 study. Although this medical center currently offers LDR-BT to veterans from across the country, all patients treated during the study period resided locally and were referred from urologists within Veterans Integrated Service Network 6.

Data on patient, tumor, and treatment characteristics were retrospectively collected via individual electronic chart review using the VA computerized patient record system (CPRS). Clinical risk stratification (low, intermediate, or high) was based on the 2015 National Comprehensive Cancer Network guidelines. All patients had biopsy-confirmed prostate adenocarcinoma and were typically evaluated with pretreatment CT and Technetium^{99m} bone scintigraphy to complete their staging. The institutional review board has determined the unidentifiable results in this report that were analyzed as a quality improvement project did not meet the definition of human subjects research as defined in Code of Federal Regulations.

Treatment

Throughout the study period, transperineal LDR-BT was performed using iodine-125 (^{125}I) or palladium-103 (^{103}Pd) under spinal or general anesthesia by two radiation oncologists who dedicated a significant percentage of their practice to prostate brachytherapy; urologists were typically not present during the procedures. A treatment plan was generated preoperatively, and brachytherapy seeds were implanted under direct ultrasound guidance without the use of intraoperative treatment planning. The prescribed minimal peripheral dose for LDR-BT monotherapy was 145 Gy for ^{125}I and 124 Gy for ^{103}Pd, respectively. All patients who received sEBRT were subsequently implanted 2−6 weeks afterward with a minimal peripheral dose of 110 Gy and 80−90 Gy, respectively. All patients underwent postimplant CT-based dosimetry evaluations on Day 30 as described below. Patients receiving sEBRT were treated to 45−46 Gy to the prostate and seminal vesicles with elective coverage of the pelvic lymph nodes up to the caudal aspect of the sacroiliac joint. The decision to deliver sEBRT was left to the discretion of the treating physician. Before 2006, 3D-conformal therapy (3D-CRT) with a four-field box technique was the predominant method for delivering sEBRT. The institution transitioned to intensity-modulated radiation therapy (IMRT) for sEBRT delivery during 2006. External beam radiation therapy prescriptions were uniformly planned to cover the planning treatment volume which consisted of expanding the prostate by 6−10 mm, except 5 mm posteriorly. Planning goals aimed to achieve a minimum coverage of 95%. Treatment was administered in daily fractions of 1.8−2 Gy. Image guidance radiation therapy (IGRT) was performed using bony anatomy in all patients receiving 3D-CRT sEBRT, and fiducial markers were used for IMRT sEBRT delivery; cone beam CT was not routinely used during this period.

When indicated, adjuvant androgen deprivation therapy (ADT) was offered and typically consisted of a luteinizing hormone−releasing hormone agonist preceded by a short course of peripheral androgen blockade. When ADT was