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Predictive factors of long-term rectal toxicity following permanent iodine-125 prostate brachytherapy with or without supplemental external beam radiation therapy in 2216 patients

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ABSTRACT

PURPOSE: We analyzed factors associated with rectal toxicity after iodine-125 prostate brachytherapy (BT) with or without external beam radiation therapy (EBRT).

METHODS AND MATERIALS: In total, 2216 prostate cancer patients underwent iodine-125 BT with or without EBRT between 2003 and 2013. The median followup was 6.9 years. Cox proportional hazards modeling was used for univariate and multivariate analyses to assess clinical and dosimetric factors associated with rectal toxicity. Dosimetric parameters from 1 day after implantation (Day 1) and 1 month after implantation (Day 30) were included in the analyses.

RESULTS: The 7-year cumulative incidence of Grade 2 or higher rectal toxicity was 5.7% in all patients. The multivariate analysis revealed that antiplatelet or anticoagulant therapy, neoadjuvant androgen deprivation therapy, treatment modality, Day 1 rectal volume receiving 100% of the prescribed dose (RV_{100}), and the Day 30 minimal percent of the prescribed dose delivered to 30% of the rectum (RD_{30}) were associated with rectal toxicity. Day 1 RV_{100} was a common predictor in both BT-alone and the BT + EBRT groups. The 5-year cumulative incidence of Grade 2 or higher rectal toxicity was 12.6%, 5.9%, and 1.7% for BT + 3-dimensional conformal radiation therapy, BT + intensity-modulated radiation therapy, and the BT-alone groups, respectively ($p < 0.001$).

CONCLUSIONS: Rectal dosimetric parameters in BT were associated with late rectal toxicity. Although the risk of rectal toxicity was higher when EBRT was combined with BT, with proper and achievable rectal dose constraints intensity-modulated radiation therapy yielded less toxicity than 3-dimensional conformal radiation therapy.

Keywords: Prostate cancer; Brachytherapy; Rectal toxicity; External beam radiation therapy; Intensity modulated radiation therapy

Introduction

Prostate brachytherapy (BT) has an essential role in the treatment of prostate cancer, in addition to radical prostatectomy and external beam radiation therapy (EBRT) (1). BT with or without supplemental EBRT has demonstrated excellent long-term outcome (2, 3). The results of the multicenter, randomized Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy trial, which compared low-dose-rate BT boost to dose-escalated EBRT boost for unfavorable-risk prostate cancer, showed that an iodine-125 (^{125}I) BT boost was more beneficial than an EBRT

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boost for both intermediate- and high-risk patients (4). However, the ^{125}I BT boost also increased the incidence of moderate-to-severe toxicity (5). In recent years, quality of life (QOL) after BT treatments has become a more important issue among patients and physicians for selecting the optimal treatment modality (6). Therefore, it is essential to make every effort to minimize treatment-related side effects to maintain high QOL after treatment, without impairing therapeutic benefit.

Rectal toxicity is one of the primary concerns after prostate BT. Among long-term prostate cancer survivors, bowel side effects had the strongest association with cancer-specific and general QOL (7). Although the incidence of late Grade 2 or higher (G2+) rectal toxicity following BT is typically on the order of 5−7% (8), this risk may be increased when BT is combined with EBRT (9, 10). To date, several groups have investigated predictors of rectal toxicity. As a result, the rectal volume receiving 100% of the prescribed dose (RV_{100}) has been established as a useful factor for the prediction of late rectal toxicity (8, 10−12). However, the timing of postimplant CT varies among these studies, and the most appropriate time to conduct postimplant dosimetry for predicting rectal toxicity remains unclear.

Here, we retrospectively analyzed the factors associated with rectal toxicity, including a comparison of values obtained from postimplant dosimetric analyses on the day after (Day 1) and 1 month after (Day 30) seed implantation. To our knowledge, only two studies have analyzed the association between postimplant dosimetric values on different days and the risk of rectal toxicity (13, 14). Our aim is to investigate how to minimize long-term rectal toxicity and to provide clinicians with valuable information for better clinical management.

Methods and materials

Patients

Between September 2003 and December 2013, 2216 consecutive patients with nonmetastatic prostate cancer underwent ^{125}I BT with or without supplemental EBRT at the Tokyo Medical Center, National Hospital Organization. The median age was 68 years (interquartile range [IQR], 63−73 years), and the median followup duration was 6.9 years (IQR, 4.7−9.4 years). The clinical characteristics of these patients are summarized in Table 1. Patients were classified into risk groups according to the National Comprehensive Cancer Network guidelines (1). Low risk was defined as T1−2a, Gleason score (GS) ≤ 6, and prostate-specific antigen (PSA) < 10.0 ng/mL. High risk was defined as T3, GS ≥ 8, or PSA >20 ng/mL. The others were classified as intermediate risk. In intermediate-risk patients, PSA <10 ng/mL and GS 3 + 3 or PSA <10 ng/mL and GS 3 + 4 with a biopsy positive core rate of <34% was classified as low-tier intermediate risk.

Neoadjuvant androgen deprivation therapy (ADT) was administered to 860 patients (39%). The median duration of neoadjuvant ADT was 6 months (IQR, 3−10 months). Neoadjuvant ADT consisted of a luteinizing hormone−releasing hormone agonist alone, or in combination with an antiandrogen. None of the study patients received adjuvant hormonal therapy.

Written informed consent was obtained from all patients before BT was performed, and this study was approved by the institutional review board of our hospital (approval no. R16-165).

Seed implantation and supplemental EBRT

At our institution, low-risk and low-tier intermediate-risk patients typically received BT as a monotherapy. In total, 1261 patients (56.9%) were treated with BT as a monotherapy (BT-alone group), and another 955 patients (43.1%) were treated with BT combined with EBRT (BT + EBRT group).

Our implant procedure has been previously described (15). The preplanning technique was initially used for the first 233 patients (10.5%), and from December 2004, the procedure has been shifted to a real-time intraoperative planning technique. The prescribed dose in the BT-alone group was 145 Gy for 326 patients (25.9%) treated through 2006, and 160 Gy for 935 patients (74.1%) after 2007. In the BT + EBRT group, the prescribed dose was 100 Gy for 614 patients (64.3%) treated through 2009, and 110 Gy for 341 patients (35.7%) after 2010. The planning target volume (PTV) was the prostate with a 3-mm margin only in the lateral directions in the preplanning technique era, and then the entire prostate in the intraoperative planning technique era. During intraoperative planning, the planning goals aimed to achieve a prostate volume receiving 100% of the prescribed dose (V_{100}) to be >99%, the minimal dose received by 90% of the prostate (D_{90}) to be 110−130% of the prescribed dose, an RV_{100} <0.1 cc, the urethral volume receiving 150% of the prescribed dose (UV_{150}) to be <0.1 cc, and the minimal percent of the prescribed dose delivered to 30% of the urethra (UD_{30}) to be <130%. A VariSeed planning system version 7.1−7.2 (Varian Medical Systems, Inc., Palo Alto, CA) was used for treatment planning.

For the BT + EBRT group, supplemental EBRT was started 1−2 months after BT, with a prescribed dose of 45 Gy in 25 fractions in 5 weeks. Between September 2003 and December 2009, EBRT was delivered using a 4-field box, 3-dimensional conformal radiation therapy (3D-CRT) technique to the prostate and seminal vesicles, with a margin of ≤1 cm on the rectal side and a 1.5-cm margin on the other sides. After January 2010, the EBRT technique was changed to intensity-modulated radiation therapy (IMRT). We used the Day 30 postimplant CT for target volume delineation and dose calculation. The PTV was defined by expanding the prostate and seminal vesicles by 9 mm in all directions, except for 6 mm posteriorly. The prescribed dose to cover 50% of the PTV was 45 Gy in 25 fractions over the course of 5 weeks. The rectum was