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Rectal dose constraints for salvage iodine-125 prostate brachytherapy

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ABSTRACT

PURPOSE: Organ-confined prostate cancer recurrences after primary radiotherapy can be treated with salvage iodine-125 brachytherapy. Options include total salvage (TS) or focal salvage (FS). TS often leads to severe late gastrointestinal (GI) toxicity. Differences in rectal dosimetry between TS and FS are presented and dose constraints proposed to reduce late severe GI toxicity (>90 days).

METHODS AND MATERIALS: Intraoperative dosimetry and 30-day CT-dosimetry of 20 FS and 28 TS patients were evaluated. GI toxicity was evaluated using the common terminology criteria for adverse events-4. With receiver operating characteristic analysis, dosimetry cutoff values to prevent severe late GI toxicity were assessed.

RESULTS: FS reduces rectal dose significantly. Median $D_{0.1cc}$, D_{1cc}, D_{2cc}, and V_{100} reductions were 38 Gy ($p = 0.002$), 46 Gy ($p < 0.0001$), 46 Gy ($p < 0.0001$), and 0.41 cc ($p = 0.0001$), respectively, compared with TS. FS patients had no late severe GI toxicity. TS patients with severe GI toxicity (41%, n = 11) showed significantly higher rectal doses than TS patients without GI toxicity (59%, n = 16). Median $D_{0.1cc}$, D_{1cc}, D_{2cc}, and V_{100} differences were 29 Gy ($p < 0.001$), 17 Gy ($p = 0.001$), 28 Gy ($p < 0.001$), and 0.45 cc ($p = 0.001$). With receiver operating characteristic analysis, restrictions for the $D_{0.1cc}$, D_{1cc}, D_{2cc}, and V_{100} are <160 Gy (area under the curve [AUC], 0.88; 95% confidence interval [CI] 0.76–1.00), <119 Gy (AUC, 0.87; 95% CI, 0.74–1.00), <102 Gy (AUC, 0.89; 95% CI, 0.77–1.00), and <0.38 cc (AUC, 0.88; 95% CI, 0.75–1.00), respectively. Thirty-day CT dosimetry showed minor overestimation of intraoperative D_{2cc} (median, 10 Gy [$p = 0.02$]).

CONCLUSIONS: FS reduces rectal dose compared with TS. $D_{0.1cc}$, D_{1cc}, D_{2cc}, and V_{100} restrictions were 160 Gy, 120 Gy, 100 Gy, and 0.35 cc. Taking correlation into account, the $D_{2cc} <$ 100 Gy might be sufficient for clinical practice. Larger series and multivariable models are necessary to further assess the found restrictions.

Keywords: Focal salvage; Total salvage; Prostate cancer; I-125 brachytherapy; Dose constraints; Rectum; Toxicity

Introduction

Patients with organ-confined recurrent prostate cancer after primary radiotherapy can be treated with total salvage iodine-125 brachytherapy (TS I-125 BT), thereby possibly postponing the use of androgen deprivation therapy (ADT) in a subset of patients. TS targets the entire prostatic volume, leading to increased cumulative dose to the previously irradiated rectum, with often severe gastrointestinal (GI) toxicity. TS I-125 BT series report 0–25% (average 5.6%) Grade 3–4 GI toxicity (1). The only prospective salvage BT study reports a 25% severe GI toxicity rate (2). Comparable GI toxicity frequencies are found for other salvage modalities (1, 3–6). These patients subsequently require elective (Grade 3) or emergency (Grade 4) surgical intervention.

Advancements in diagnostic modalities (e.g., MRI) have made a focal salvage iodine-125 brachytherapy (FS I-125

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BT) approach feasible, targeting only the recurrent lesion. Small series in the last years have shown promising toxicity results (7–10). The only three FS I-125 BT series performed so far have shown no ≥ Grade 2 GI toxicity in a total of 42 patients (9–11).

Owing to cumulative radiation dose and possible reduced repair capacity of the rectum in salvage I-125 BT patients, more stringent dose constraints might be necessary. Currently, there are no salvage rectal dose recommendations. Recommendations for primary BT are available from the American Brachytherapy Society (ABS) and the European Society for Radiotherapy and Oncology (ESTRO) (12–14). In the present study, we analyze the difference between rectal dosimetry parameters for TS and FS I-125 BT and propose constraints to reduce late severe GI toxicity.

Methods and materials

Patient selection

Institutional review board approval was obtained. In the University Medical Center Utrecht (UMCU, the Netherlands), 20 patients underwent FS I-125 BT from March 2009 to October 2012. Agreement was necessary between systematic biopsy results and visible unifocal peripheral tumor on multiparametric (mp)-MRI (T1 and T2-weighted, dynamic contrast enhanced, and diffusion weighted imaging sequences). The recurrent lesion, termed the gross tumor volume (GTV), was prescribed ≥145 Gy (D_{90}). MR-images were imported into the planning system and (prostate, GTV) delineations were transferred and fused with the intraoperative transrectal ultrasound. The 100% isodose line was expanded up to half of the prostate, to account for uncertainties in GTV definition and delineation. No specific margins for this expansion were applied. The technical aspects, quality of life, toxicity, and biochemical outcomes have been described recently for this group (10).

In addition, 62 patients from the UMCU and the Radiotherapeutic Institute RISO, Deventer (the Netherlands) were treated with TS from December 2001 to April 2010. Intraoperative ultrasound (US) images with the dose distribution were available for 28 patients. The prescription dose (D_{90}) for the entire prostatic volume (clinical target volume [CTV]) was ≥145 Gy. Available CT-based rectal dosimetry for 12 FS and 10 TS patients was analyzed after 30 days (CT_{30}) and compared with intraoperative dosimetry.

In the UMCU, images were analyzed in Sonographic Planning of Oncology Treatment (SPOT, n = 28) or Oncentra Prostate (OCP, n = 2; Nucletron BV, Veenendaal, the Netherlands). Patients from Deventer (n = 18) were analyzed using VariSeed version 8 (Varian Medical Systems, Palo Alto, CA). Patients from Deventer were implanted with stranded seeds (Amersham Health model 6711 or IBt model 1251L) and patients from the UMCU with Isotron model 130.002 loose seeds (^{125}I selectSeed).

Delineations and dosimetry

Delineations of the prostate/CTV, GTV, and rectum were analyzed. Dosimetric parameters were adopted from guidelines for primary prostate brachytherapy from the ABS and ESTRO (12–14), supplemented with parameters from the literature and institutional preferences (15–19). Rectal $D_{0.1cc}$, D_{1cc}, and D_{2cc} (minimum dose in maximum irradiated 0.1, 1, and 2 cc) and the V_{100}, V_{150}, and V_{200} (volume of the rectum receiving 100%, 150%, and 200% dose) were obtained. For the prostate and GTV, the D_{90}, V_{100}, and V_{150} were analyzed on intraoperative US.

All contours were re-evaluated by two independent radiation-oncologists (CH, JVZ), blinded for the patient's clinical profile. Structures were delineated every 2.5 mm (SPOT, OCP) and 5 mm (VariSeed) on US and every 2 mm on CT_{30}. The prostate was delineated from the base at the bladder neck to as far as the apex could be continued. The outer rectal wall was delineated on every available US-image and CT_{30} image. An example of an FS and TS implant on US is shown in Fig. 1.

Toxicity

Subsequently, toxicity was scored with the common terminology criteria for adverse events (CTCAE), version 4.0 (20). Toxicity was scored by the primary researcher (MP) and separately re-evaluated by the two independent radiation oncologists (CH and JVZ). Late toxicity was defined as occurring >3 months after TS.

Grade 2 radiation proctitis is defined by the CTCAE as moderate symptoms (such as rectal discomfort, passing blood, or mucus), with or without requiring medical intervention or limiting instrumental activities of daily living. Patients with symptoms of radiation proctitis severe enough to undergo colonoscopy with biopsies and/or argon plasma coagulation (APC) were classified as Grade 2 because the CTCAE classification did not specify the required intervention for Grade 3. Fistulas (rectourethral and rectovesical) were defined as either Grade 3 or Grade 4 when requiring elective or emergency surgical intervention/ICU hospitalization, respectively.

Statistical analysis

Dosimetric parameters are presented as medians with ranges because of their non-Gaussian distribution. Normally distributed data are presented as mean (±standard deviation). TS patients were grouped corresponding to the presence (n = 11) or absence (n = 16) of late ≥ Grade 2 GI toxicity. A Mann–Whitney U test was performed to assess differences in skewed data. An independent samples t test was used for differences in normally distributed data. A Wilcoxon signed-rank test was used to assess differences (between US and CT-based dosimetry) within the same patients. Pearson's χ^2 test