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Prostate

Avoidance of late rectal toxicity after high-dose-rate brachytherapy boost treatment for prostate cancer

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ABSTRACT

PURPOSE: To elucidate potential risk factors important for the appearance of late rectal toxicity (LRT) after high-dose-rate boost treatment (HDRBT) of prostate cancer and to validate the predictive value of the minimal dose to the most exposed 2 cc of rectum received with HDRBT ($D2cc_{rect}$).
METHODS AND MATERIALS: The study of LRT, defined as relative deterioration of defecation problems (RDDP) (stool frequency, pain, rectal bleeding, fecal urgency, and incontinence) during follow-up period, was carried out on 88 patients, consecutively treated from October 2006 through April 2011 with HDRBT of 3 × 6–7 Gy to 50–50.4 Gy of EBRT. The impact of patients and treatment characteristics on third year prevalence of RDDP was analyzed by using binary logistic regression method.
RESULTS: At third year of follow-up, RDDP was evidenced in 30 of 77 (39.0%) patients. More important as $D2cc_{rect}$ (OR, 1.15; 95% CI, 0.99–1.34; $p = .059$) was minimal dose to the most exposed 1 cc of the rectum ($D1cc_{rect}$; OR, 1.15; 95% CI, 1.01–1.31; $p = .032$), whereas the sum of $D1cc_{rect}$ and EBRT mean rectal dose ($EDmean_{rect}$) was the only significant parameter in multivariate analysis (OR, 1.12; 95% CI, 1.04–1.22; $p = .004$). Based on a multivariate model, the safe compound 2 Gy equivalent dose was estimated at 44.4 Gy with the average ratio of $D1cc_{rect}$:$EDmean_{rect}$ = 1:3.1 (95% CI ± 1.8) and negative predictive value of 0.828.
CONCLUSIONS: The study confirms the value of composite dose parameter and the importance of rectal high-dose and low-dose regions for LRT. Taking account of suggested dose constraints and CT/MRI-based HDRBT, the incidence of LRT can be reduced by a half. © 2016 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords: Late rectal toxicity; High-dose-rate brachytherapy; Prostate cancer D2cc; Prostate cancer D1cc

Introduction

The combination of high-dose-rate brachytherapy boost treatment (HDRBT) and external-beam radiation (EBRT) is highly effective treatment of localized or locally advanced prostate cancer. In most reports, 5-year relapse-free survival rates are in excess of 90% for low-risk and intermediate-risk, and 80% for high-risk patients (1). Micturition problems are the predominant long-term toxicity after HDRBT + EBRT (2–7). However, identification of risk structures together with appropriate dose-volume constraints and identification of patients' derived risk factors, it is possible to reduce long-term urinary toxicity (8).

In comparison to urinary, late rectal toxicity (LRT) after HDRBT + EBRT is less frequent and only exceptionally of high grade (1–5,7,9) but still excessive when compared to exclusive brachytherapy treatment (7) and radical prostatectomy (10, 11). Rectum, or merely anterior rectal wall (12) as defined by its external and mucosal surface (13), is universally accepted as the organ at risk crucial for the development of LRT after HDRBT + EBRT of prostate. Dose and volume dependency of LRT is well evidenced for radical prostate EBRT (14); however, data for HDRBT + EBRT are rare (2, 15, 16). Furthermore, there is no study based on dose-volume histogram (DVH) data of prostate HDRBT + EBRT that would allow proposing of the dose-volume constraints for the rectum. American Brachytherapy Society consensus guidelines therefore suggest that normal tissue constraints used by experienced HDR centers should be used as a reference (13).

According to GEC/ESTRO recommendations, the minimal dose received by the most exposed 2 cc of rectum

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($D2cc_{rect}$) is suggested as a surrogate predictor of LRT of HDRBT + EBRT (12), most probably with analogy to the combination of EBRT and brachytherapy treatment of gynecological tumors (17–20). Also, the concept of adding the dose, received by the anterior rectal wall along EBRT to $D2cc_{rect}$ and received along brachytherapy treatment, originates in the treatment of uterine cervical carcinoma (19). Neither the predictive value of $D2cc_{rect}$ nor the concept of dose summation has been validated in prostate HDRBT + EBRT yet.

Aiming at proposing solutions for the reduction of LRT with HDRBT + EBRT, the objective of the study was to evaluate the predictive role of $D2cc_{rect}$.

Methods and materials

Patients

In the follow-up study, initially 88 patients with intermediate or high risk clinically localized or locally advanced prostate cancer (21), and low-risk patients that refused to get radical prostatectomy, consecutively treated by the first author with HDRBT + EBRT at the Institute of Oncology Ljubljana (IOL) in the period 2006–2011, were included.

Treatment characteristics

In short, brachytherapy was based on transperineal TRUS-guided needle insertion and computed tomography (CT)–based or magnetic resonance imaging (MRI)–based planning. Initially, prescribed dose was 21 Gy to prostate ± 3 mm (planning target volume 1 [PTV1]) and 22.5 Gy to prostate periphery ± gross tumor volume (PTV2), with 7 Gy and 7.5 Gy per fraction, respectively. Later, to reduce problems with acute urinary retention, the dose was reduced to 18 Gy to PTV1 and 19.5 Gy to PTV2, also given in three fractions with 6-to-8-hour interfraction interval and in selected patients also into the proximal part of seminal vesicles (if infiltrated with cancer, and the infiltrate, as seen on MRI, was reachable with needles). Rectum was defined by the outer surface of rectum/internal anal sphincter with craniocaudal margin exceeding planning target volume (PTV) for 0.5–1 cm. The recommended constraint was to keep the maximal dose received by the most exposed 2 cc of rectum <4.5 Gy and 1 cc <4.7 Gy.

EBRT was delivered as 3D conformal radiation. Clinical target volume included prostate, proximal 1/3–2/3 of seminal vesicles with lymph nodes along external, internal, and common iliac vessels if the risk of positive lymph nodes exceeded 15% according to the equation of Roach *et al.* (22). Prescribed dose was 50–50.4 Gy in 25–28 fractions. Rectum was defined by the outer wall as being from anal verge to the initial sigmoid flexion. Patients were asked to empty the rectum before the planning computed tomography and before each treatment session. The suggested rectal dose-volume constraint was for the volume receiving 50 Gy to be <65%. In more details, treatment characteristics have been described elsewhere (8).

Study instrument for assessment of LRT

To detect and grade problems with defecations according to various grading systems (23–26), an in-house-made questionnaire, used already for several years, was used as the study instrument. Questionnaire is filled in for the first time before the start of treatment, then after 6 and 12 months, and yearly thereafter.

Problems with defecations were addressed regarding stool frequency, pain, rectal bleeding, fecal urgency, and incontinence. Problems related to incontinence and bleeding were scored according to modified RTOG scale (25); for the others, SOMA scale was applied (24).

How distressing were problems with defecations for patients was evaluated with 5-level scale (1 = without problems to 5 = big problems).

Observed outcome

LRT was assessed on the basis of deterioration of defecation problems (DDP) during the follow-up period. DDP was defined as the deterioration in the grade of defecation problems between the initial state (just before HDRBT + EBRT) and the state at the end of the second, the third, the fourth, and the fifth year of follow-up. The following scale was used: 1, no DDP; 2, minor deterioration (DDP for one grade); 3, major deterioration (DDP for two or more grades). Because minor and major deterioration were the categories of interest, these two categories were combined, and the observed outcome designated as relative DDP (RDDP; 0 = no, 1 = yes).

To achieve a sufficiently large number of observed patients, analysis of association between RDDP and potential risk factors was carried out only in those who completed 3 years of follow-up.

Risk factors for RDDP

Two groups of risk factors were observed. The first group consisted of HDRBT, EBRT, and supportive treatment factors: number of implanted needles ($N_{implanted\ needles}$), planning imaging (1 = CT, 2 = MRI), number of interventions ($N_{interventions}$) (0 = 1, 1 = ≥2), dose-volume factors related to HDRBT: PTV1 volume, minimal dose received by 100% of PTV1 ($Dmin_{PTV1}$), and 90% of PTV1 ($D90_{PTV1}$), by 100% of the PTV2 ($Dmin_{PTV2}$); the minimal dose received by the most exposed 1 cc of rectum ($D1cc_{rect}$), $D2cc_{rect}$, and the dose to 90% of the rectum ($D90_{rect}$); dose-volume factors related to EBRT: rectal volume (EV_{rec}), minimal dose received by the most exposed 2 cc of rectum ($ED2cc_{rect}$), maximal ($EDmax_{rect}$), and mean ($EDmean_{rect}$) rectal dose, rectal volumes irradiated with ≥30 Gy/≥40 Gy/≥50 Gy ($EV30/40/50_{rect}$). All dosimetric factors were retrospectively extracted from DVHs stored in

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