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Volumetric image-guided conformal radiotherapy for localized prostate cancer: Analysis of dosimetric and clinical factors affecting acute and late toxicity

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ABSTRACT

Aim: To identify factors influencing toxicity in patients affected by localized prostate cancer treated with conformal image-guided radiotherapy.

Background: Image guidance in combination with conformal techniques is the standard of care in localized prostate cancer, but factors affecting toxicity are still under investigation.

Materials and methods: 294 patients were analyzed. Median age at diagnosis was 71 year. 76 Gy (38 × 2 Gy) were delivered to the target volume. We used the χ^2 test to analyse associations between toxicity and dosimetric and clinical parameters. Multivariate analysis was performed using binary logistic regression. Kaplan–Meier method was used for survival analysis.

Results: Median follow-up was 62.9 months. Acute grade ≥2 gastro-intestinal toxicity (GI) was 12.1%. Acute genito-urinary (GU) toxicity of grade ≥2 was 33.9%. Actuarial 4 and 5 years late grade ≥2 GI was 3% and 4%, respectively. Four and 5-year late grade ≥2 GU toxicity was 6% and 10%. At multivariate analysis for acute toxicity rectal V_{70} was correlated with GI toxicity ($p = 0.01$, HR 2.73 CI 1.19–6.26), and smoking habit with GU toxicity ($p < 0.01$, HR 2.50 CI 1.51–4.14). For late toxicity, rectal V_{70} was correlated with gastro-intestinal toxicity ($p = 0.04$, HR 4.76 CI 1.07–21.13), and pre-radiotherapy urinary symptoms with genito-urinary toxicity ($p = 0.01$, HR 2.84 CI 1.29–6.22).

Discussion: Conformal image-guided radiotherapy shows low rates of toxicity. Smoking should be avoided during radiotherapy. Besides the evaluation of high doses received by the organs at risk, individual factors, such as co-morbidities and lifestyle choices, have an impact on normal-tissue complication risk.

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1. Background

Three-dimensional conformal radiotherapy (3DCRT) is a therapeutic option in the treatment of localized prostate disease, and favorable results have been reported in dose escalation-studies,[1–3] despite the delivery of high doses to the tumor is associated with an increased risk of acute and late toxicity.[4,5] In order to decrease the irradiation of organs at risk (OARs) allowing dose escalation to the target volume, new technologies such as intensity-modulated radiation therapy (IMRT) and image guidance have been introduced in the clinical practice.

Regarding the treatment planning and delivery, micro-multi-leaf collimators (micro-MLCs) which are characterized by small leaf width (3–5 mm) improve target dose distribution and normal tissues sparing both in 3DCRT and in IMRT,[6–8] and volumetric image guidance allows to check the daily treatment reproducibility. More specifically, by using an on-board cone-beam computed tomography (CBCT) system it is possible to match online the pelvic anatomy of the computed tomography (CT) with that of the cone-beam CT, comparing prostate position and rectal and bladder filling.[9,10] Together with the clinical implementation of new technologies, which will improve the dosimetric features of treatment plans and the radiotherapy delivery, the process of understanding those clinical factors that affect treatment tolerance and toxicity will be crucial for the selection of patients for a more personalized therapy.

2. Aim

In this retrospective study, we report acute and late toxicity in 294 patients affected by localized prostate cancer who underwent 3D conformal image-guided radiotherapy using a micro-MLC (4 mm leaf width at the isocenter) and a linac-integrate kV-cone-beam CT. Furthermore, we sought to identify dosimetric and clinical factors influencing toxicity.

3. Materials and methods

Between December 2006 and April 2016, 294 patients diagnosed with localized prostate cancer were treated with conformal (3DCRT) image guided radiotherapy (IGRT) in our Department. All patients provided informed consent. The clinical details of patients' cohort are shown in Table 1. Median age at diagnosis was 71 years (interquartile [IQR], 67–74). Median PSA level was 7.7 ng/ml (IQR, 5.3–11.2). All patients had pathologically confirmed prostate cancer and were stratified according to the National Comprehensive Cancer Network Criteria (NCCN): 121 patients were classified in the low-risk group, 69 in the favorable intermediate, 31 in the unfavorable intermediate-risk group and 73 in the high-risk group or locally advanced disease (67 and 6 patients, respectively). Androgen deprivation therapy (ADT) was prescribed in 132 patients at the time of radiotherapy (LH–RH analogues in 75 patients, antiandrogen in 18 patients and total androgen blockade in 39). We collected data about pre-treatment urinary symptoms, co-morbidities (diabetes, colitis, previous abdominal/pelvic surgery), the use of antihypertensive medication and anticoagulants and smoking habitude during radiotherapy.

All patients underwent planning CT with empty rectum and comfortably full bladder, and planning MRI was obtained in 128 patients within 20 min after CT scanning. Treatment protocol was described elsewhere.[11,12] Briefly, patients underwent planning CT in the supine position using ankle stocks for immobilization. Conformal treatment plans were obtained on the Pinnacle treatment planning system (Philips Medical System, Andover, MA), and were delivered using an Elekta Synergy S linear accelerator equipped with a micro-MLC (Beam Modulator™) and with an on-board kV-cone-beam CT used for volumetric image guidance.

In Table 2, for the whole cohort we reported the median values of the clinical target volume (CTV), the planning target volume (PTV) and those of the bladder and rectum. The CTV included the prostate in the low-risk group, and the prostate plus 2/3 of the seminal vesicles in the intermediate and high-risk groups. PTV was obtained by anisotropic expansion of CTV (5 mm in the posterior direction, 6 mm in all the others). The rectum and the bladder were contoured as solid organs.[12] A total dose of 76 Gy (38×2 Gy) was delivered to the prostate in low-risk patients, whereas intermediate and high-risk patients received 66 Gy (33×2 Gy) to the prostate and 2/3 of the seminal vesicles plus a sequential boost of 10 Gy (5×2 Gy) to the prostate only.

Toxicity was registered according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Acute toxicity (within 90 days from the start of radiotherapy) and late toxicity (>90 days from the start of radiotherapy) were analyzed, and grade $\geq$2 toxicity was correlated with clinical and dosimetric parameters. Dose–volume-histograms (DVHs) were used to provide a quantitative analysis. The maximum dose, the mean dose, and a set of appropriate $V\times$ (percent of OAR volume receiving the $\times$ dose) were evaluated for the rectum and bladder. For statistical analysis, dosimetric parameters were dichotomized by the median value. Concerning clinical variables, the assumption of antihypertensive medication and/or anticoagulants, the smoking habit during radiotherapy, a positive history for diabetes, colitis and previous abdominal surgery were analyzed.

Statistical Package for the Social Sciences version 22.0 (SPSS, Inc., Chicago, IL) was used for statistical analysis. The χ^2 test was used to analyse associations between grade $\geq$2 toxicities and dosimetric and clinical parameters. Multivariate analysis to predict the risk of grade $\geq$2 toxicity development was performed using binary logistic regression. Statistical significance was assumed at $p < 0.05$. The survival analysis was performed with the Kaplan–Meier method.

4. Results

The median follow-up for the whole population was 62.9 months (IQR, 43.2–86.9 months), calculated from the end date of radiotherapy. At 4 and 5-year overall survival (OS) was 94% and 89%, respectively, and cancer specific survival (CSS), 99% and 96%. Biochemical relapse-free survival (b-RFS) at 4 and 5 years was 89% and 87% (Fig. 1). Regarding dose–volume histograms parameters, the median volumes of the CTV, rectum