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Original Article

Acute and Late Genitourinary Toxicity after 72 Gy of Conventionally Fractionated Conformal Radiotherapy for Localised Prostate Cancer: Impact of Individual and Clinical Parameters

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Abstract

Aim: Our aim was to estimate the incidence of acute and late genitourinary toxicity in patients treated with three-dimensional conformal radiotherapy (3DCRT) for localised prostate cancer and to estimate the possible influence of individual and clinical characteristics.
Materials and methods: Between September 2009 and September 2013, 225 patients with localised prostate cancer were treated with 3DCRT. Ninety-four patients with an estimated risk of lymph node involvement ≤15%, according to the Roach formula, were evaluated in this study. All patients received a total dose of 72 Gy in 36 fractions. Acute and late genitourinary toxicity were graded according to the European Organization for Research and Treatment of Cancer radiation morbidity scoring scale. Characteristics such as age, smoking status, previous abdominal or pelvic surgery (PAPS), diabetes mellitus and the use of diuretics were analysed as possible predictive factors of toxicity. The median follow-up was 27 months.
Results: Grade ≥2 acute toxicity during 3DCRT developed in 25 of 94 patients (26.5%). Predictive factors of acute genitourinary toxicity grade ≥2 in the multivariate logistic regression analysis (MVA) were current smoking status ($P = 0.003$), PAPS ($P = 0.012$) and the use of diuretics ($P = 0.017$). The 2 and 3 year cumulative risk of late genitourinary toxicity grade ≥1 was 25.3% and 30.2%, respectively. In the MVA, acute genitourinary toxicity was significantly associated with late genitourinary toxicity ($P = 0.024$).
Conclusion: Current smoking status, PAPS and the use of diuretics have a significant effect on the occurrence of acute genitourinary toxicity grade ≥2. The occurrence of any grade of acute genitourinary toxicity has a significant influence on the development of any grade of late genitourinary toxicity.

Key words: Acute toxicity; conformal radiotherapy; genitourinary toxicity; late toxicity; prostate cancer

Introduction

External beam radiotherapy (EBRT) is frequently used as a definitive treatment in the management of localised prostate cancer. The importance of dose escalation for tumour control has been shown in numerous randomised trials [1,2]. By increasing the radiation dose, the risk of developing complications caused by injury to the bladder, prostatic urethra and rectum also increases.

Three-dimensional conformal radiotherapy (3DCRT) makes it possible to spare normal tissue [3]. Reductions in radiation toxicity as a result of using 3DCRT compared with previous techniques have already been reported [4], but randomised trials have shown no significant difference in the occurrence of acute or late genitourinary toxicity between conventional radiotherapy and 3DCRT [3,5,6]. Recognising that dose escalation was associated with a

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greater risk of toxicity if a greater volume of normal tissue was treated with high dose levels, intensity-modulated radiotherapy (IMRT) was implemented to further improve the conformality of the dose distribution, and thereby facilitate dose escalation for patients with localised prostate cancer. Image-guided radiotherapy (IGRT) represents a more accurate form of dose delivery for patients receiving radiotherapy for prostate cancer. Results of a phase III dose-escalation trials suggest that there were no significant differences with 3DCRT or IMRT for acute or late grade 2+ or grade 3+ genitourinary toxicity [7].

These facts lead to the assumption that in addition to the irradiation technique, other factors are probably involved in the occurrence of symptoms of genitourinary toxicity. In addition to the dose-volume effect reported in the literature, other factors that may affect the incidence of acute and late genitourinary toxicities, such as age, smoking, hormonal therapy, diabetes mellitus, use of certain drugs and genetic markers, have been mentioned in the literature [8–14].

The association between the acute and late effects of radiotherapy in prostate cancer has been observed by several investigators [15,16] and it was confirmed by the results obtained in the Medical Research Council RT01 trial [17].

Therefore, we conducted a longitudinal study among patients with localised prostate cancer in order to assess the incidence of acute and late genitourinary toxicity after 3DCRT at a single institution. Furthermore, we wanted to explore which of the clinical and patient-related factors are involved in the occurrence of acute and late genitourinary toxicity and determine possible correlations between them.

Materials and Methods

In the period from September 2009 to September 2013, all consecutive prostate cancer patients who were treated with 3DCRT at the Institute for Oncology and Radiology of Serbia were considered for enrolment in the study. Of 225 prostate cancer patients seen in this period, 94 met the following inclusion criteria: localised disease stage (T1–2), prostate-specific antigen (PSA) level $\leq$ 20, Gleason score $\leq$ 7, Karnofsky index $\geq$ 80 and an estimated risk of lymph node involvement $\leq$ 15% according to the Roach formula. Exclusion criteria were: disease stage $\geq$ T3, estimated risk of lymph node involvement $>$ 15%, according to Roach formula [18], the presence of enlarged lymph nodes (N1 stage), the presence of distant metastases (M1 stage), PSA level $>$ 20, Gleason score $\geq$ 8, Karnofsky index $<$ 80 and previous pelvic irradiation.

Application of androgen deprivation was not an exclusion criterion of our study. Neoadjuvant androgen blockade with Luteinizing hormone-Releasing hormone (LHRH) analogue was applied during 3–6 months, only for patients with Gleason score 7 (4+3), according to the approval of the Health Fund.

This study was conducted with the Ethics Committee of the Faculty of Medicine University of Belgrade approval and with patients' written informed consent.

We obtained data (characteristics of the study cohort, the toxicity scores and the dosimetric parameters) by carrying out a retrospective analysis of medical histories.

The characteristics of the study cohort are shown in Table 1. Patient age ranged from 56 to 81 years, with a mean age of 71 years. All patients with diabetes mellitus (13/94) had non-insulin-dependent diabetes mellitus. Previous abdominal or pelvic surgery (PAPS) included: gastric surgery three (3.19 %) patients; cholecystectomy 11 (11.70 %) patients; repair of inguinal hernia 13 (13.83 %) patients; appendectomy six (6.38 %) patients and other abdominal surgery six (6.38 %) patients. Only two patients had previous transurethral resection of the prostate (TURP). We did not record use of medications. Use of diuretics was a surrogate for hypertension with or without cardiovascular disease.

The median follow-up was 27 months (range 6–54 months).

EBRT was carried out as 3DCRT according to hospital protocol. Patients underwent computed tomography and were treated in the supine position, using an immobilisation device for the knees and feet, with an emptied rectum and comfortably full bladder. We did not use a specific bladder filling protocol. We asked the patients not to urinate 1–2 h before computed tomography and every day before treatment.

Two dose-volume groups were defined according to the estimated risk of seminal vesicle involvement, according to the Roach formula [18]. The first group was the prostate only group, if the risk was $\leq$ 15%, and the second group was the prostate and seminal vesicle group, if the risk was $\geq$ 15%. The clinical target volume (CTV) and the planning target volume (PTV) were used as standardised nomenclature according to International Commission on Radiation Units and Measurements recommendations (ICRU) 50 and ICRU 62 [19,20]. The CTV included the whole prostate. CTV1 included the whole prostate with entire seminal vesicle. CTV2 encompassed the same volume as the CTV. Margins for the PTV and PTV1 were 10 mm grown around the CTV and CTV1 except the posterior margin, which was reduced to 8 mm. Margins for PTV2 were reduced to 5 mm except the posterior margin, which was further reduced to 0 mm. Normal tissue volumes contoured included the bladder, rectum, bilateral femora and skin. The normal tissues were considered solid organs. The prescribed dose to the ICRU reference volume to cover the PTV, in the prostate only group, was 72 Gy. In the second group the prescribed dose to cover PTV1 was 66 Gy and to cover PTV2 was 6 Gy. Patients were treated using 15 MV X-rays with a 2 Gy daily fraction/5 days a week. For bladder and rectum, dose constraints were $\geq$65 Gy and $\geq$60 Gy, respectively, given to at least one-third of the organ. These values were taken from Emami *et al.* [21] as the dose that would probably result in a normal tissue complication probability of more than 5% after 5 years of follow-up.

During radiotherapy, all patients were monitored on a weekly basis for early toxicity and were given supportive care as needed, as part of the routine clinical follow-up. The radiation oncologist carried out the recording and grading

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