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Original article

Relationships between bladder dose–volume/surface histograms and acute urinary toxicity after radiotherapy for prostate cancer

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ABSTRACT

Background and purpose: DUE01 is an observational study aimed at developing predictive models of genito-urinary toxicity of patients treated for prostate cancer with conventional (1.8–2 Gy/fr, CONV) or moderate hypo-fractionation (2.35–2.7 Gy/fr, HYPO). The current analysis focused on the relationship between bladder DVH/DSH and the risk of International Prostate Symptoms Score (IPSS) $\geqslant$ 15/20 at the end of radiotherapy.

Materials and methods: Planning and relevant clinical parameters were prospectively collected, including DVH/DSH, LQ-corrected (DVHc/DSHc) and weekly (DVHw/DSHw) histograms. Best parameters were selected by the differences between patients with/without IPSS $\geqslant$ 15/20 at the end of radiotherapy. Logistic uni- and backward multi-variable (MVA) analyses were performed.

Results: Data of 247 patients were available (CONV: 116, HYPO: 131). Absolute DVHw/DSHw and DVHc/DSHc predicted the risk of IPSS $\geqslant$ 15 at the end of radiotherapy (n = 77/247); an MVA model including baseline IPSS, anti-hypertensive, T stage, the absolute surface receiving $\geqslant$8.5 Gy/week and $\geqslant$12.5 Gy/week was developed (AUC = 0.78, 95% CI: 0.72–0.83). Similar AUC values were found if replacing DSHw with DVHw/DVHc/DSHc parameters. The impact of dose–volume/surface parameters remained when excluding patients with baseline IPSS $\geqslant$ 15 and in HYPO. IPSS $\geqslant$ 20 at the end of radiotherapy (n = 27/247) was mainly correlated to baseline IPSS and T stage.

Conclusions: Although the baseline IPSS was the main predictor, constraining v8.5w < 56 cc and v12.5w < 5 cc may significantly reduce acute GU toxicity.

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Knowledge regarding the predictors of genito-urinary (GU) toxicity after high-dose radiotherapy (RT) for prostate cancer is largely lacking [1–4]. Due to early tumour detection [5], patients treated with RT are increasingly younger, owing to longer life expectancy and more attention to Quality-of-life (QoL) issues. The incidence of moderate/severe GU toxicities, playing a major role on QoL, has increased in recent years, as a consequence of more aggressive treatments [1,2,6]; in contrast to the rectum, for which dose–volume models are available [1,7,8], no reliable models exist for bladder dose–volume effects [1–4].

A major cause of this lack is the difficulty in the prospective, possibly self-reported, assessment of GU symptoms in large studies: apart from some evidence that the dose in the urethra/bladder neck is predictive of severe toxicity [1,3,9,10], the correlation with bladder dose–volume histograms (DVHs) remains unclear [1,3,11–13].

Variable bladder filling is also a confounding factor; however, the bladder base is quite stable [14]. Relying on this evidence and on an investigation dealing with bladder dosimetry parameters, Carillo et al. [15] suggested that absolute dose–surface histo-

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gram (DSH) should better represent the dose effectively received by the wall.

A prospective multi-centre cohort study (DUE01) was activated in 2010 with the aim of developing predictive models for GU toxicity and erectile dysfunction [16,17]. Self-reported questionnaires (including the International Prostate Symptoms Score, IPSS) were prospectively filled in at different times by the enrolled patients.

Here we report the results of ad-interim analyses dealing with the risk of experiencing a high ($\geqslant$15 and $\geqslant$20) IPSS value at RT end (referred to as IPSS15end and IPSS20end), used as comprehensive scores.

Materials and methods

The DUE01 study

DUE01 started in April 2010 after the approval of the Ethics committee of the coordinating centre and of all the participating centres. Clinical data prospectively collected were: age, body-mass-index (BMI), diabetes, previous pelvic/abdominal surgery, previous transurethral resection of the prostate (TURP), use of drugs (e.g. anti-hypertensive, anti-coagulant, and anti-aggregant), smoking (yes/no), coffee (cups/day), clinical stage, pre-RT PSA, type and duration of hormonal therapy, IMRT (yes/no). Dosimetry parameters were also collected including: prescribed total/daily doses, seminal vesicle irradiation (yes/no), whole pelvis irradiation (WPRT, yes/no), CTV/PTV/bladder volumes, maximum dose to 1% of bladder (D1%). Full planning data were exported on a dedicated software (VODCA, MSS Inc. [15]); bladder DVHs/DSHs were calculated both in percent/absolute values (cc/cm^2). Moreover, as different fractionation schemes were allowed, weekly histograms (i.e. planned DVH/DSH calculated on 5 working days) were also considered (DVHw/DSHw); a similar approach was already used for acute toxicity, based on the evidence that the weekly dose highly impacts on acute effects more than the total dose [18,19]. In addition, DVH/DSH corrected for fractionation (DVHc/DSHc) using the linear-quadratic (LQ) model were calculated (α/β = 10 Gy and total treatment time/dose recovery factor equal to 0.7 Gy/day [20]).

Questionnaires were given to the patients before RT, at its end, at 3 and 6 months after RT and subsequently every 6 months up to 5 years. Further information is included in the Supplementary material (S1).

End-points for acute GU toxicity

The aim of the current work was to analyse the first (at least) 161 patients (i.e. minimum required number for ad-interim analysis, Supplementary material S1), focusing on the correlation between IPSS15end/IPSS20end and clinical/dosimetric parameters. IPSS15end is a useful quantitative score for moderate/severe GU toxicities [21]; IPSS20end classifies more severe toxicities [22]. Regarding IPSS15end, the analyses were repeated excluding patients with baseline IPSS $\geqslant$ 15, as baseline IPSS is a predictor of end therapy IPSS [10,12,13,16].

Dose–volume/surface parameters: assessing best predictors

Average DVH/DSH/DVHw/DSHw/DVHc/DSHc of patients with/without IPSS15end = 1 and with/without IPSS20end = 1 were compared through two-sided t-tests to assess the most discriminative values, according to the lowest *p*-values. Once the best parameters had been selected, receiver operating characteristic (ROC) curves were used to assess the most predictive volume/surface cut-off values through the corrected Youden index (it corresponds to the maximum vertical distance between the ROC curve and the diagonal line). Analyses were repeated separately in the groups (CONV: 1.8–2 Gy/fr; HYPO: 2.35–2.7 Gy/fr).

Statistical analysis and multi-variable models

First, univariate logistic analysis was carried out for the whole group and for patients with baseline IPSS < 15: all clinical/technical variables and the best predicting DVH/DSH/DVHw/DSHw/DVDc/DSHc parameters were considered. Variables with a *p*-value <0.20 were included in a backward logistic multi-variable model, retaining in the model variables with a *p*-value $\leqslant$0.20. Univariate analysis was then used to select variables to be included in the stepwise procedure: Bonferroni corrections were not made, given the small number of multi-variable models and their high statistical significance (*p*-values <0.0001, see results).

The Odds Ratio (OR) was reported to express the strength of association between each variable and IPSS15end/IPSS20end. The discriminative power of the models was measured by the area under the ROC curve (AUC). Goodness-of-fit was assessed by the Hosmer and Lemeshow (H&L) test. SPSS v.17 (SPSS Inc. Chicago, IL), Medcalc v.12 (Medcalc software bvba, Mariakerke, Belgium) were used for analyses; internal validation was carried out through bootstrapping (1000 resamplings, R 2.15.2 software, http://www.R-project.org). Internal validation assessed our "optimism" in evaluating the performance of a model (discrimination capability through AUC) on the same exact population on which the model was developed (called apparent performance): optimism was defined as the difference between true performance and apparent performance.

Results

Patient characteristics

At the time of analysis (June 2013) 247 patients had complete data (CONV: 116, HYPO: 131, Table 1). HYPO/CONV patients were treated to a median dose of 70.5 Gy (2.35–2.7 Gy/fr) and 78 Gy (1.8–2.0 Gy/fr) respectively; 83/247 (33.6%) received WPRT (52/31 in HYPO/CONV).

Seventy-seven patients (31.2%) had an IPSS $\geqslant$ 15 at the end of radiotherapy (46/31 in HYPO/CONV) and 27 (10.9%) had an IPSS $\geqslant$ 20, (15/12 in HYPO/CONV).

Finding best DVH/DSH/DVHw/DSHw/DVHc/DSHc predictors

The parameters discriminating best between patients with/without IPSS15end = 1 were the absolute surface/volume receiving >8.5 Gy/week (s8.5w/v8.5w) and >12.5 Gy/week (s12.5w/v12.5w); lower *p*-values were found for DSHw (Fig. 1). Results were confirmed in HYPO while they were not confirmed in CONV (see Supplementary material S2).

When considering DVHc/DSHc, the absolute bladder volume/surface receiving >2 Gy-equivalent 60 Gy (v60c/s60c) and 80 Gy (v80c/s80c) were the most predictive (S2) while DVH/DSH were not predictive. The above defined most discriminative values of DSHw/DVHw/DSHc/DVHc were selected for the next analyses. The %DSHw/DVHw/DVHc/DSHc also discriminated between patients with/without IPSS15end = 1 but at a lower level (S2).

Correlation between IPSS15end and clinical/dosimetric parameters

A summary of the univariate analysis is reported in the Supplementary material S3.

The best cut-off values for absolute DVHw/DSHw were: v8.5w < 56 cc, v12.5w < 5 cc; s8.5w < 79 cm^2 and

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