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Bowel dose-volume toxicity

Patient-reported intestinal toxicity from whole pelvis intensity-modulated radiotherapy: First quantification of bowel dose–volume effects

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ABSTRACT

Background and purpose: Intestinal toxicity is commonly experienced during whole-pelvis intensity-modulated radiotherapy (WPRT) for prostate cancer. The aim of the current study was to assess bowel dose–volume relationships for acute patient-reported intestinal symptoms of patients treated with WPRT for prostate cancer.

Materials and methods: Complete data of 206 patients were available; the median dose to pelvic nodes was 51.8 Gy (range 50.4–54.4, 1.7–2 Gy/fr). Intestinal symptoms were assessed as changes in the Inflammatory Bowel Disease Questionnaire scores relative to the Bowel Domain (IBDQ-B) between baseline and radiotherapy mid-point/end. The 25th percentiles of the most severe worsening from baseline (ΔIBDQ-B) were set as end-points. The impact of bowel loops and sigmoid colon dose–volume/surface parameters as well as selected clinical parameters were investigated using multivariate logistic regression.

Results: Analyses were focused on the four questions showing a median ΔIBDQ-B > 0. No dose volume/-surface parameters were predictive, other than ΔIBDQ5 ≥ 3 (loose stools): when grouping patients according to bowel DVHs (high risk: V20 > 470 cc, V30 > 245 cc, V42 > 110 cc; low risk: all the remaining patients), a two-variable model including high-risk DVH-shape (OR: 9.3) and age (protective, OR: 0.94) was assessed. The model showed good calibration (slope: 1.003, $R^2 = 0.92$) and was found to be robust after bootstrap-based internal validation.

Conclusions: Constraining the bowel loops may reduce the risk of loose stools. The risk is higher for younger patients.

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Despite the benefit of intensity-modulated radiation therapy (IMRT) in reducing toxicity from whole pelvis radiotherapy (WPRT) in the treatment of prostate cancer [1–5], intestinal complications remain a clinically significant issue with a largely underestimated impact on patient quality of life (QoL) [6]. While the existence of a dose–volume effect for the bowel is clearly recognized, a thorough assessment of quantitative relationships is still largely lacking [1–5,7–10]. Moreover, the few studies analyzing patients treated with WPRT for prostate cancer are mainly retrospective and focused on severe clinician-reported toxicities. However, there is growing evidence that patient-reported (PRO) scoring of bowel symptoms would be preferred in order to capture the true impact on QoL [1,6–8,10].

A prospective study aimed at assessing dosimetric and clinical predictors of acute and late PRO intestinal toxicity from radiotherapy including WPRT (IHU WPRT TOX) was therefore activated [11]. The purpose of the current analysis is to search for any possible correlation between clinical/dosimetry factors and acute gastro-

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intestinal (GI) symptoms after WPRT in a multi-institutional cohort of 206 patients. We focused on the ten symptoms pertaining to the Bowel domain as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ-B, [12]), already used to assess bowel symptoms after pelvic radiotherapy [13,14].

Materials and methods

The IHU WPRT-TOX study

The multi-Institutional IHU WPRT-TOX study (ClinicalTrials.gov NCT02803086), was initiated in January 2014, after approval from the Institutional Review Boards, with the goal of developing predictive models of Intestinal, Hematologic and Urinary Toxicity from radiotherapy for localized prostate cancer including WPRT [11,15]. A pilot study had previously (September 2012) been activated at the Coordinating Institute (San Raffaele, Milan).

According to protocol requirements, the validated Italian version of the IBDQ [16] was filled in at baseline, at RT mid-point and end, 3 and 6 months after radiotherapy and thereafter every 6 months up to 5 years. The IBDQ includes 32 questions scored on a seven-point scale (with lower scores corresponding to the more severe symptoms). In the current investigation, the ten items specifically pertaining to the intestinal symptoms [13,14] (IBDQ-B, see Supplementary Material) were analyzed. Overall, the IBDQ-B provides a score ranging from 10 (severe morbidity) to 70 (no symptoms).

Patient population, volumes, planning and delivery

This analysis included 206 patients with complete dosimetric data and IBDQ-B baseline scores: 80, 79 and 47 patients were treated with adjuvant (ADV), salvage (SALV) and radical (RAD) intent, respectively, in six participating Institutions. Of note, although controversial and not yet definitively assessed, WPRT for high-risk post-operative patients was delivered in many Institutions mainly on the basis of positive retrospective results and of increasing evidence that most biochemical relapses after post-prostatectomy radiotherapy were not associated with local relapses. Details of volume/margin definition, planning procedures, treatment and IGRT techniques are described in the Supplementary Material.

Radiotherapy was delivered with conventional fractionation (1.7–2 Gy/fr, $n = 83$) or moderate hypo-fractionation (2.15–2.65 Gy/fr, median 2.35 Gy/fr, $n = 123$).

The median 2 Gy-equivalent dose (EQD2, assuming $\alpha/\beta = 3$) to the prostatic bed was 71.4 Gy (range: 66.6–78, $n = 159$) with 51.8 Gy (50.4–54) being delivered to the pelvic nodes. In the case of radical intent, the median EQD2 to the prostate was 77 Gy (70–80, $n = 47$) and the dose to the pelvic lymph nodes was 52.5 Gy (50.4–54.4) (Supplementary Material). Of note, despite the use of hypofractionation at the primary tumor level, the pelvic were always treated at a daily dose $\leq$2 Gy with a total number of fractions between 27 and 30.

Small bowel and sigmoid-colon delineation

Small bowel (SB) and sigmoid-colon (SC) were manually delineated by a single observer at each Institute. Instructions for the delineation of SB loops and SC were provided to the physicians of each participating Institute prior to the initiation of the study (Supplementary Material); a centralized review of the contouring was performed at the referral Institute before exporting DVHs. Any missing contours were delineated by a single observer of the referral center (C.S.): in the current population this occurred in less than 10% of patients.

Delineation was previously found to be robust with respect to intra- and inter-observer variability [17]: an example of contouring is shown in the Supplementary Material (Fig. S1).

Full planning data were exported to software (VODCA, MSS Inc. http://www.vodca.ch [18]) dedicated to radiotherapy data managing and elaboration; DVHs and the corresponding dose–surface histograms (DSHs) were calculated in percent/absolute value (%/cm^3), and the volumes receiving $\geq$5, 10, 15, 20, 25, 30, 35, 40 and (in steps of 2 Gy) up to 68 Gy were extracted (V5–V68) for SC and SB.

Endpoint definition for acute GI toxicity and clinical data

This analysis was focused on the worsening of bowel symptoms: the maximum variation of the IBDQ-B score between baseline and radiotherapy mid-point or end (ΔIBDQ-B) was considered. Subsequently, an analysis of the maximum variation for each single question was performed. For questions showing a median worsening $\geq$1, the 25th percentile values of the score variations were considered as end-points. Similarly, the 25th percentile of the score variation was considered as end-point for ΔIBDQ-B.

The following variables were prospectively recovered and considered in the analyses: hormonal treatment neoadjuvant to radiotherapy (yes/no), presence of hemorrhoids (yes/no), age (years), body-mass-index (kg/m^2), smoking (yes/no), diabetes (yes/no), use of anti-hypertensives (yes/no), adjuvant hormonal therapy (prescribed at radiation oncologist/urologist preference, yes/no), radiotherapy intent (radical/post-operative).

Statistical analyses

Patients with moderate/severe symptoms before the beginning of radiotherapy (i.e., baseline value <5) were excluded from the analyses.

In the case of a single missing value (out of ten questions), the IBDQ-B was evaluated by replacing the missing value by the mean score for the patient in question [12,16]. In the case of more than one missing item, the questionnaire was not considered and the patient was excluded. For the specific item analyses, only patients without missing data were included. Simple imputation methods (substitution of the missing value of a continuous predictor with the mean, or the most frequent category for a categorical predictor) were used to replace the missing values for clinical parameters; for dosimetric variables, patients with missing data were excluded.

Average absolute and relative DVHs/DSHs of the patients with/without toxicity for SB and SC were compared through two-sided t-tests for all endpoints, as previously described [11]: the parameters corresponding to p-values < 0.05 were selected to be tested in a logistic regression analysis. Univariable logistic regression was performed to assess correlations between the considered end-points and all clinical/dosimetric parameters. All variables with a p-value < 0.20 at univariable analysis were entered into a backward stepwise multivariate logistic regression, retaining variables with p-value < 0.05. Goodness-of-fit was assessed by the Hosmer and Lemeshow (H&L) test and the Brier score (a measure of the residuals normalized to the number of patients); the performance of the models was evaluated through the calibration plot (slope and regression coefficient R^2). Internal validation was performed by 1000 bootstrap resamplings: the corresponding calibration plots were considered in order to evaluate the robustness of the original models. Analyses were performed with R software [19].