Radiotherapy and Oncology 118 (2016) 79–84

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Bone marrow toxicity

Dose–volume effects for pelvic bone marrow in predicting hematological toxicity in prostate cancer radiotherapy with pelvic node irradiation

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ARTICLE INFO

Article history:
Received 9 July 2015
Received in revised form 20 November 2015
Accepted 23 November 2015
Available online 15 December 2015

Keywords:
Hematologic toxicity
Bone marrow
Intensity-modulated radiotherapy
Prostate cancer

ABSTRACT

Purpose: To prospectively identify clinical/dosimetric predictors of acute/late hematologic toxicity (HT) in chemo-naïve patients treated with whole-pelvis radiotherapy (WPRT) for prostate cancer.
Material and methods: Data of 121 patients treated with adjuvant/salvage WPRT were analyzed (static-field IMRT $n = 19$; VMAT/Rapidarc $n = 57$; Tomotherapy $n = 45$). Pelvic bone marrow (BM) was delineated as ilium (IL), lumbosacral, lower and whole pelvis (WP), and the relative DVHs were calculated. HT was graded both according to CTCAE v4.03 and as variation in percentage relative to baseline. Logistic regression was used to analyze association between HT and clinical/DVHs factors.
Results: Significant differences ($p < 0.005$) in the DVH of BM volumes between different techniques were found: Tomotherapy was associated with larger volumes receiving low doses (3–20 Gy) and smaller receiving 40–50 Gy. Lower baseline absolute values of WBC, neutrophils and lymphocytes (ALC) predicted acute/late HT ($p \leqslant 0.001$). Higher BM V40 was associated with higher risk of acute Grade3 (OR = 1.018) or late Grade2 lymphopenia (OR = 1.005). Two models predicting lymphopenia were developed, both including baseline ALC, and BM WP-V40 (AUC = 0.73) and IL-V40+smoking (AUC = 0.904) for acute/late respectively.
Conclusions: Specific regions of pelvic BM predicting acute/late lymphopenia, a risk factor for viral infections, were identified. The 2-variable models including specific constraints to BM may help reduce HT.
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Hematologic toxicity (HT) may be an important side-effect of whole-pelvis radiotherapy (WPRT), but the association between radiation dose and HT remains unclear since the vast majority of the studies dealing with this issue have been carried out on patients treated with concurrent chemoradiation [1–3]. All these studies, possibly biased by an indiscernible effect of chemotherapy, considered acute HT only, and no data are so far available with respect to the impact of WPRT alone on bone marrow (BM) stem cell suppression, and to the incidence and severity of both acute and, more importantly, chronic HT.

Although still controversial, the interest in a possible role of WPRT in the radiation treatment of prostate cancer (PCa) is growing in both the radical and the post-operative setting, owing to its potential to sterilize microscopic lymph-nodal metastases [4,5].

The purpose of our study was therefore to prospectively identify clinical and dosimetric predictors of both acute and late HT after post-operative WPRT in a single-institution cohort of chemo-naïve patients irradiated for localized PCa; to our knowledge, HT was never investigated in this context.

The absence of any confounding effect due to chemotherapy is very intriguing, giving the possibility to explore the "true" dose–volume effect of irradiated BM. In addition, the possible different contribution of static and rotational IMRT techniques to the onset and persistence of HT was thoroughly examined.

Materials and methods

The IHU WPRT-TOX study

The IHU WPRT-TOX (Intestinal Hematologic Urinary Toxicity from post-prostatectomy Whole-Pelvis RadioTherapy) study was activated in September 2012 after the approval of the Institutional Review Board, with the goal of developing predictive models of

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http://dx.doi.org/10.1016/j.radonc.2015.11.020
0167-8140/

toxicity after WPRT for PCa. Before the study activation, a pilot study, prospectively monitoring HT was started in October 2011.

Patient population, radiation planning and treatment

This analysis pertains to the first 121 patients (70 of the pilot study and 51 of the observational protocol) who received WPRT with either adjuvant ($n = 72$) or salvage ($n = 49$) intent. Nineteen underwent step-and-shoot IMRT (SS-IMRT), 57 volumetric arc IMRT (Rapidarc, RA), 45 Helical Tomotherapy (TOMO).

The pre-treatment clinical data and dosimetric parameters analyzed are listed in Table 1.

Details of contouring, rationale for dose prescription and planning procedures [6] may be found in the Supplementary material.

Patients were assigned to the different IMRT techniques solely according to the machine availability, favouring rotational techniques since 2011, which led to the small number of patients treated with SS-IMRT.

Bone marrow volume definition

Contours of pelvic bones, used as a surrogate for pelvic BM, were delineated according to Mell et al. [1], defining four volumes (Fig. S1, Supplementary material): (1) ilium (IL), including the iliac crests extending to the superior border of the femoral heads, (2) lumbosacral spine (LS), extending from the most superior vertebral body where the lymph-node planning treatment volume (usually L4-5) contours begin, and inferiorly to include the entire sacrum, (3) lower pelvis (LP), consisting of the pubes, ischia, acetabula, and proximal femora, extending from the superior border of the femoral heads to the inferior border of the ischial tuberosities, and (4) whole pelvis (WP), consisting of the Boolean sum of the three subvolumes.

Dose–volume histograms (DVHs) were calculated both in percent/absolute values (%/cm^2) and the volumes receiving $\geqslant$3, 5, 10, 20, 30, 40 and 50 Gy were extracted (V3-50) for each BM volume, as well as the body DVHs in order to further investigate possible associations between HT and the irradiation of the peripheral blood.

Table 1
Summary of patients characteristics.

	Observed values ($n = 121$ patients)
Age (years, median, range)	66 (48–78)
BMI (kg/m^2, median, range)	26 (18–37)
Diabetes (yes)	8 (7%)
Hormotherapy (yes)	41 (34%)
Hypertension (yes)	55 (45%)
Smoking (yes)	24/112
Missing	9/121
Prescription dose to PTV (Gy, range)	70–75.6; 65.5–71.4
Dose/fraction (Gy, range)	1.8–2; 2.35–2.55
Prescription dose to pelvis (Gy, median, range)	50.4–52.5; 51.8
Dose/fraction (Gy, range)	1.75–2; 1.85
CONV	$n = 39$ (32%)
HYPO	$n = 82$ (68%)
TOMO	$n = 45$ (37%)
RA	$n = 57$ (47%)
SS-IMRT	$n = 19$ (16%)
Volume PTV LN (cc, median, range)	1071.6 (687–1567)
Days between surgery and RT (median, range)	154 (44–6256)
WBC at baseline (μL^{-1}, median, range)	6600 (3200–12100)
ANC at baseline (μL^{-1}, median, range)	3900 (1901–9900)
ALC at baseline (μL^{-1}, median, range)	1900 (580–5600)

Abbreviations: BMI = body mass index; CONV = conventional fractionation; HYPO = hypofractionation; TOMO = Helical tomotherapy irradiation technique; RA = arc volumetric Rapid Arc irradiation technique; SS-IMRT = step and shoot intensity modulated radiation therapy technique; PTV LN = planning target volume lymph-nodes; WBC = absolute white blood cell count; ANC = absolute neutrophil count, ALC = absolute lymphocyte count.

Endpoints for acute and late HT

Absolute counts of red blood cells (RBC), platelets (PLT), Hemoglobin (Hb), white blood cells (WBC), neutrophils (ANC) and lymphocytes (ALC) were prospectively collected at baseline, at RT mid-point and end, at 3–12 months. HT was graded both according to CTCAE v4.03 [7] and as variation in percentage with respect to baseline. Patients with abnormal baseline levels were excluded.

Given the scanty variations of RBC, Hb and PLT, the endpoints of interest for this study were defined as:

1) 25th percentile of the variation of ALC with respect to baseline at nadir;
2) acute Grade 3+ (G3) lymphopenia, defined as cut-off ALC at nadir (ALCend) <500/μL for toxicity;
3) late Grade 2 (G2) lymphopenia, defined as ALC at 1 year after RT conclusion (ALC12m)<800/μL and $\geqslant$500/μL for toxicity;
4) 25th percentile of the variation of ANC with respect to baseline at nadir (ANC%half);
5) 25th percentile of the variation of WBC with respect to baseline at nadir (WBC%half).

Statistical analyses

A previously applied method based on DVH differences between patients with/without HT was used to select the most discriminative DVH parameters [8]: for all endpoints, absolute and relative average DVHs for patients with/without toxicity for each BM structures were compared through two-sided *t*-tests: fraction of BM receiving XXGy corresponding to the lowest *p*-values were selected to be tested in a logistic regression analysis, a powerful tool to select the most discriminative dosimetric variables to be included in the univariate analysis. The clinical variables prospectively collected and tested were: age, body-mass-index (kg/m^2), smoking (yes/no), hypertension (yes/no), concomitant and/or adjuvant hormotherapy prescribed at radiation oncologist/urologist preference (yes/no), diabetes (yes/no), time elapsed from prostatectomy to irradiation. Univariate logistic regression was performed to assess correlation between the considered end-points and all clinical variables, dosimetric parameters and baseline cell counts. All variables with a *p*-value <0.20 at univariate analysis were entered into a backward stepwise multiple logistic regression, retaining variables with *p*-value $\leqslant$0.05.

The Receiver Operating Characteristic (ROC) curves were then used to assess the most predictive cut-off values. The discriminative power of the models was assessed by the area under ROC curve (AUC). Regression coefficients were then used to develop a nomogram predictive of HT risk probability. Finally, the performance of the models was evaluated through the calibration plot; models were internally validated by bootstrap to obtain overfitting-corrected estimates of predicted *vs.* observed values using nonparametric smoothers.

Analyses were performed with R software [9].

Results

Table 1 summarizes the patient characteristics included in this analysis.

Table 2 shows the BM and body dosimetric parameters by treatment technique and corresponding *p*-values (relative doses in Table S1 and Fig. S2, Supplementary material). In particular,