Hypofractionation with VMAT *versus* 3DCRT in Post-operative Patients with Prostate Cancer

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Abstract. *Aims: To retrospectively evaluate and compare the incidence of acute genitourinary (aGU), upper gastrointestinal (uGI) and rectal (lGI) injuries after radiotherapy with hypo-fractionation by volumetric modulation arc therapy (VMAT, the Hypo-RapidArc group) and conventional fractionation by three-dimensional conformal radiotherapy (3DCRT) in patients with localized prostate cancer treated, after radical prostatectomy, with prostatic bed irradiation. Patients and Methods: Between 2007 and 2012, 84 consecutive patients with clinically localized prostate cancer submitted to radical prostatectomy were also treated with irradiation to the prostate bed. Forty-five received 3DCRT and 39 Hypo-RapidArc. The median age was 67 and 69 years for 3DCRT and Hypo-RapidArc groups respectively. The median dose to the prostatic bed was 70 Gy in both groups: 2 Gy/fraction in the 3DCRT group and 2.5 Gy/fraction in the Hypo-RapidArc group. After radical prostatectomy, the median time-to-RT was 15 and 16 months respectively. Acute and late toxicities were scored according to the Radiation Therapy and Oncology Group/European Organization for Research and Treatment of Cancer system. Results: Grade 2aGU was recorded in 16% of cases in the 3DRCT group and in 10% in the Hypo-RapidArc group. No acute grade 2 upper gastrointestinal (uGI) toxicities were found in the 3DCRT versus 5% in the Hypo-RapidArc group. The incidence of grade 2 lower gastrointestinal (lGI) toxicities was 22% in the 3DCRT group versus 15% in the Hypo-RapidArc group. No grade 3 or greater toxicities were found in either group. In both groups, good planning target volume coverage was achieved: V95% was recorded as 96.3±3.6% (mean±standard deviation) and 95.7±8.9 for the 3DRCT and the Hypo-RapidArc groups, respectively. The mean rectal volume dose receiving at least 70 Gy was 9.1±10.8% and 0.1±0.6% respectively. The mean dose to the bladder was 49.5±12.3 Gy and 37.2±5.2 Gy respectively. Significant correlation between late rectal toxicity and the maximum dose to the rectum, V70Gy, was found in the 3DCRT group, while no significant correlations were found for acute toxicity. Conclusion: The results presented in this study demonstrate the feasibility of a moderate hypo-fractionation regimen with RapidArc in the postoperative setting. Longer-term data are needed to confirm late toxicity profiles.*

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In patients with prostate cancer (PC), radical prostatectomy (RP) is the most common therapeutic approach for eradicating organ-confined disease. After RP, radiotherapy (RT) can be prescribed in two different types of clinical scenarios (1, 2). With adjuvant intent, in the presence of high-risk factors after surgery, RT was shown to reduce the risk of failure in three prospective studies (3-5). With salvage intent, in cases of biochemical or clinical failure, RT offers a potentially curative treatment for selected patients (2, 6).

Although some authors concluded that higher doses to the prostate bed are recommended for achieving optimal disease-free survival (7, 8), the crucial issue of the optimal post-operative RT dose remains to be defined.

In the post-operative setting, residual microscopic disease, when present, is obviously composed of PC cells. It has always been assumed that PC cells have a higher sensitivity to fraction size then late- responding organs, including the rectum, due to a lower alpha/beta ratio (9). Despite this, excluding few exceptions, hypo-fractionation has been used almost exclusively in the radical setting (10, 11). The reason

for this choice may be mainly correlated to the fear of higher expected side-effects in the prostatic bed compared to conventional fractionation, due to the presence of healthy organs such as the bladder and rectum, already traumatized by surgery.

While timing of postoperative therapy may be crucial in the salvage setting to eradicate microscopic disease early, where RT is more effective (6, 12), the timing of RT delivery after RP can negatively impact on tolerability to the treatment. It was suggested that the time of recovery for bladder anastomosis and urethral tissue should play a significant role (13). Thus, toxicity after postoperative RT represents one of the most common reasons for the urologists' reluctance in sending their patients to radiation oncologists in adjuvant or early salvage settings, when RT could truly be effective in eradicating microscopic disease (14).

In the modern era of RT, intensity-modulated RT (IMRT) with image guidance allows for drastic reduction of high dose involvement of organs at risk (OAR) surrounding the target volume, with better patient and target positioning (15). Thus, higher RT doses or other types of unconventional fractionation or different concomitant types of volumes, such as the pelvic area, have already been prescribed in a postoperative setting to improve cure rates, showing good toxicity profiles and presenting promising new RT approaches (16, 17). However, whereas new techniques seem to reduce acute toxicity in some series of patients (18, 19), the clinical impact of these new techniques remains to be clarified.

Based on the original investigation of Otto (20), the RapidArc technique (RA), the Volumetric Modulated Arc Therapy (VMAT) available on Varian linacs, has been recently introduced in clinical practice after an intensive validation at the planning level where it was compared to IMRT or other approaches, in a series of studies on various indications (18, 21-23).

In the current study, the feasibility and acute toxicity profile of patients treated with moderate hypo-fractionation with VMAT by means of RA were retrospectively analyzed. A dosimetric and tolerability comparison with patients treated in the same institution with thre-dimensional conformal RT (3DCRT) and conventional fractionation was also performed and the results are discussed.

Patients and Methods

Between 2007 and 2012, 84 consecutive patients, with clinically-localized prostate cancer, previously submitted to RP, received RT to the prostate bed at the Humanitas Cancer Center (Milan). Clinical and dosimetric data of these patients were prospectively collected and retrospectively evaluated for the present analysis. Surgery consisted of RP with or without pelvic lymph node dissection. Pre-treatment RT evaluation consisted of documented history, postoperative prostate-specific antigene (PSA) and physical examination, including performance status and digital rectal examination.

Specific recommendations were suggested regarding daily preparation for RT: comfortably full bladder (250-300 cm^3 water given 30 min before treatment) and empty rectum. Patients were submitted to planning computed tomography (CT) in the treatment position (supine, arm on the chest). Axial images were obtained at 5 mm intervals through the pelvis (from L1 to 10 cm under the level of ischiatic lower bone margin). Permanent reference marks were placed on the skin at the time of the planning CT scan. The outlining of the target and critical structures (OAR: bladder, femoral heads, rectum, intestinal cavity) was performed by the radiation oncologists. The clinical target volume (CTV) was the prostate bed only, including the vesico-urethral anastomosis, the bladder neck, and the retro-vesical space, as defined in recently published guidelines (24). Planning target volume (PTV) was defined as the CTV plus a 8 mm margin in all directions except cranial–caudal, where a 10 mm margin was used; in some cases, based on clinical judgement of the patients anatomy, the posterior margin toward the rectum was reduced. Out of the 84 patients 45 underwent 3DCRT. This group of patients received 35 to fractions of 2 Gy, reaching a total dose to the prostatic bed of 70-76 Gy (median 70 Gy). The remaining 39 patients were treated with RapidArc. Patients in this group were treated with a moderate hypo-fractionated schedule of 28 fractions of 2.5 or 2.55 Gy, five sessions per week, for a total dose of 70-71.4 Gy.

RapidArc plans consisted of one or two full arcs using 6-MV photon beams. The 3DCRT plan beam arrangement was with six fixed fields shaped by a multileaf collimator (MLC), or six arcs (30 degrees each) with lateral entrances, using 18-MV photon beams.

All dose distributions were calculated with the Anisotropic Analytical Algorithm on an Eclipse treatment planning system (Varian Medical Systems, Palo Alto, USA), setting a dose grid size of 2.5 mm. Patient positioning was checked with daily ConeBeam CT (CBCT).

Patient characteristics are summarized in Table I, stratifying the two groups of 3DCRT and RapidArc with moderate hypo-fractionation (Hypo-RapidArc).

Acute and late genitourinary (GU) injuries, upper gastrointestinal (uGI), and lower gastrointestinal (lGI) injuries for bowel and rectum respectively, were assessed for toxicities after RT using a previously adopted slightly modified version (18) of the Radiation Therapy and Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) medical scoring system. Visits during the treatment were scheduled every week and every 10 days for the Hypo-RapidArc and for the 3DCRT group respectively. After the treatment completion, follow-up was scheduled at four and 12 weeks and then every three months.

Dosimetric data were evaluated and analyzed from the dose-volume histogram information for each treatment. Statistical significance of dosimetric data differences between groups was estimated by nont parametric test for independent samples. Possible correlations between dosimetric data and toxicities were sought, using the ANOVA univariate test.

Results

The median follow-up was 24.1 and 22.8 months in the 3DCRT and Hypo-RapidArc groups, respectively. Eighteen and five patients, respectively, were lost to follow-up; missing data were excluded from late toxicity analysis.

Acute toxicity data, available for all patients, are reported in Table II. Grade 2 GU toxicity was recorded as 16% and

Table I. *Patients' characteristics*.

		3DCRT	Hypo-RapidArc
N. of patients		45	39
Age, (year)	Median (Range)	67 (49-78)	69 (50-81)
PSA, postoperatively	Median (Range)	0.49 (0.01-12.33)	0.32 (0.01-3.25)
Gleason score	Median (Range)	7 (5-10)	7 (4-10)
Time from surgery to RT, (months)	Median	15	16
Follow-up, (months)	Median (Range)	24.1 (3-49)	22.8 (9-28)
TNM Stage	T1	0/45	2/39
	T2	22/45	16/39
	T3	20/45	20/39
	T4	1/45	1/39
	N0	38/45	35/39
	N1	1/45	1/39
	NX	4/45	0/39
	Recurrence	5/45	9/39

PSA=Prostate specific antigen, RT=radiotherapy, TNM: tumor, node, metastasis stage, 3DCRT=three dimensional conformal radiotherapy; Hypo-RapidArc: hypofractionated RapidArc.

10% of the cases in the 3DRCT and Hypo-RapidArc groups, respectively. No grade 2 uGI toxicities were found in the 3DCRT group, while they were 5% in the Hypo-RapidArc group. Grade 2 GI toxicities were recorded occurring in 22% and 15% of the cases in the 3DCRT and Hypo-RapidArc groups, respectively. No grade 3 or greater toxicities were found in either group.

Late toxicities is reported in Table III. Data showed a better rectal late toxicity profile in the Hypo-RapidArc group, where no toxicity greater than grade 1 was recorded, while in the 3DCRT group 9% of the patients presented grade 2-3 late toxicity. Conversely, for GU toxicity 11% of the patients in the Hypo-RapidArc group had a late toxicity greater than grade 1, while this rate was only 2% in the 3DCRT group.

Concerning dosimetric results, Figure 1 presents the average cumulative dose-volume histograms for the two groups and for CTV, PTV, bladder, rectum, femoral heads and healthy tissue. Table IV summarizes the main data for PTV, bladder and rectum.

For similar target coverage in the two groups, better bladder and rectum sparing was found in the Hypo-RapidArc group, as expected. In particular the rectal volume receiving a high dose of 70 Gy was marginal in the Hypo-RapidArc group, while it was almost 10% in the 3DCRT group.

Treatment for 10 patients in the Hypo-RapidArc group was planned constraining the rectal region overlapping the PTV to receive no more than 65.5 Gy (18). This fact did not reduce the target coverage in terms of $V_{95\%}$, but significant differences (p=0.02) were found for $D_{95\%}$ (94.7±2.3% and 96.2±1.8%) and for $D_{98\%}$ (92.8±3.1% and 94.8±1.9%) when constraining the overlapping area or not respectively. On the

Table II. *Acute toxicities experienced after therapy with three dimensional conformal radiation therapy (3DCRT) and hypofractionated Rapidarc (hypo-RapidArc)*.

	Grade	3DCRT	Hypo-RapidArc
Genitourinary	0	24/45 (53%)	13/39 (33%)
	1	14/45 (31%)	22/39 (56%)
	2	7/45 (16%)	4/39 (10%)
	3-4	0/45 (0%)	0/39 (0%)
Upper gastrointestinal	0	28/45 (62%)	28/39 (72%)
	1	17/45 (38%)	8/39 (20%)
	2	0/45 (0%)	2/39 (5%)
	3-4	0/45 (0%)	0/39 (0%)
Lower gastrointestinal	0	32/45 (71%)	20/39 (51%)
	1	3/45 (7%)	13/39 (33%)
	2	10/45 (22%)	6/39 (15%)
	3-4	0/45 (0%)	0/39 (0%

Table III. *Late toxicities experienced after therapy with three dimensional conformal radiation therapy (3DCRT) and hypofractionated Rapidarc (hypo-RapidArc)*.

	Grade	3DCRT	Hypo-RapidArc
Genitourinary	0	21/27 (47%)	24/34 (61%)
	1	5/27 (11%)	6/34 (15%)
	2	1/27(2%)	3/34 (8%)
	3	0/27 (0%)	1/34 (3%)
Rectal	0	22/27 (49%)	33/34 (85%)
	1	1/27 (2%)	1/34 (3%)
	2	3/27 (7%)	0/34 (0%)
	3	1/27 (2%)	0/34 (0%)

contrary, parameters related to high doses to the rectum did not correlate with better sparing in patients where the overlapping region was constrained: $D_{2\%}$ was 67.4±0.7% and 66.6±1.4% for constrained overlapping area and not, respectively.

Correlations between clinical toxicity data and dosimetry to specific OARs were sought. No significant correlations were found between acute toxicity for rectum or bladder and the grade of toxicity, while a significant correlation was found between late rectal toxicity and the maximum dose to the rectum ($D_{1\%}$ and $D_{2\%}$, $p<0.02$) and the rectal volume receiving more than 70 Gy (V_{70Gy}, $p<0.05$). This result was found in the 3DCRT group.

Table IV. *Summary of the dose statistics stratified by the two groups.*

Organ	Parameter	3DCRT	Hypo-RapidArc	*p*-Value
PTV	Mean (Gy)	71.1±2.5	70.4±0.9	n.s.
	D1% (%)	101.9±1.7	103.4±0.7	0.04
	V95% (%)	96.3±3.6	95.7±8.9	n.s.
	V105% (%)	0.0±0.0	0.0±0.0	n.s.
Bladder	Mean (Gy)	49.5±12.3	39.2±13.4	<0.001
	D1% (Gy)	72.1±2.5	71.9±0.9	n.s.
	V45Gy (%)	63.8±20.4	44.0±21.1	<0.001
	V60Gy (%)	51.6±19.9	29.9±15.7	<0.001
	V70Gy (%)	22.2±21.4	13.2±10.6	0.02
Rectum	Mean [Gy]	42.1±9.4	37.2±5.2	0.005
	D1% (Gy)	71.6±2.6	67.2±1.1	<0.001
	V45Gy (%)	51.0±15.2	38.8±9.3	<0.001
	V60Gy (%)	34.2±11.4	18.9±6.8	<0.001
	V70Gy (%)	9.1±10.8	0.1±0.6	<0.001

n.s.: Statistically not significant; Dx=dose received by at leaxt x% of the volume; Vx=volume receiving at least x Gy of dose.

Discussion

A few retrospective studies have investigated the use of IMRT and hypo-fractionation RT for patients with prostate cancer in the postoperative setting. Postoperative IMRT reduced rectal and bladder volume involvement in high radiation dose regions (25). Compared to conventional techniques, when static or rotational IMRT techniques were applied, a reduction of acute GI injury after radical prostatectomy was shown (15). The median follow-up is a limit of this study in terms of the absolute evaluation of the long-term toxicity, although this was not a primary endpoint of the study which rather aimed at the assessment of the acute effects of the treatment.

Kruser *et al.* treated 108 patients with 65 Gy in 26 fractions of 2.5 Gy with IMRT or tomotherapy and with endo-rectal balloon and a posterior margin from CTV to PTV of 5 mm (26). Acute grade 2 or greater GU toxicities were recorded in 7% of patients and a case of acute grade 3 GU toxicity of obstruction was noted. Acute grade 2 GI toxicities occurred in 14% of patients and no cases of acute grade 3 intestinal toxicity were reported.

A group of 172 consecutive patients with prostate cancer received RT post-operatively to the prostatic bed and pelvic lymph-nodal area with adjuvant or salvage intent with various techniques: 3DCRT, helical tomotherapy or linac IMRT (15). The tomotherapy group was treated with 28 fractions in moderate hypo-fractionation. Patients treated with IMRT had a reduced risk of acute toxicity. With respect to uGI and lGI, the acute toxicity profile of patients treated by tomotherapy was even better when compared to that of the patients treated with 3DCRT. The authors concluded that the risk of acute toxicity following postoperative RT delivered with IMRT was reduced compared to that of 3DCRT. The most significant reduction concerned the uGI, mainly owing to better bowel sparing with IMRT.

Excellent results for tolerability were reported by Cozzarini *et al.*, treating 50 consecutive patients with 58 Gy in 20 fractions (five/week) to the tumor bed with tomotherapy after prostatectomy (27). Results were also compared with a retrospective series of patients treated with conventionally fractionated RT. Acute grade 2-3 RTOG GU and acute grade 2 intestinal toxicities were similar in the tomotherapy and 3DCRT groups: 12% *vs.* 15.6% and 4% *vs.* 7%, respectively, while acute grade 2 proctitis was 0% *vs.* 9% in the tomotherapy and 3DCRT groups, respectively.

Acute toxicity was also evaluated by the same authors in 35 patients candidate to radical or post-operative RT treated to the pelvis with tomotherapy and receiving a concomitant boost to the prostate or the prostatic bed within a moderately hypo-fractionated regimen in 28-33 fractions: 6% experienced grade 2 cystitis, requiring medical treatment (19). With respect to the lGI tract, 3% of grade 2 proctitis was recorded.

In the present study, similar results were found, comparing 3DCRT *vs.* Hypo-RapidArc, in terms of acute toxicity greater than grade 2. The rectal late toxicity profile was better in the Hypo-RapidArc group; the converse was found for late GU toxicity. A significant correlation was found in the 3DCRT group between late rectal toxicity and a high dose delivered to the rectum (V_{70Gy} and $D_{2\%}$). Such high doses, as shown in Table IV, were not delivered in the Hypo-RapidArc group. This confirmed the importance of a high dose level as valuable dosimetric parameter in clinical toxicity. It was indeed in the attempt of reducing rectal toxicity in the Hypo-RapidArc group that reduction of rectal high dose was applied in some patients in the -rectum overlapping target region, delivering no more than 65.5 Gy there.

Reggiori *et al.* compared rectal anatomical variations using CBCT before and after treatment sessions in prostate cancer treatment with RapidArc (28). Those variations, depending on session time, might, as consequence, lead to dosimetric uncertainties during delivery. IGRT with CBCTs were regularly

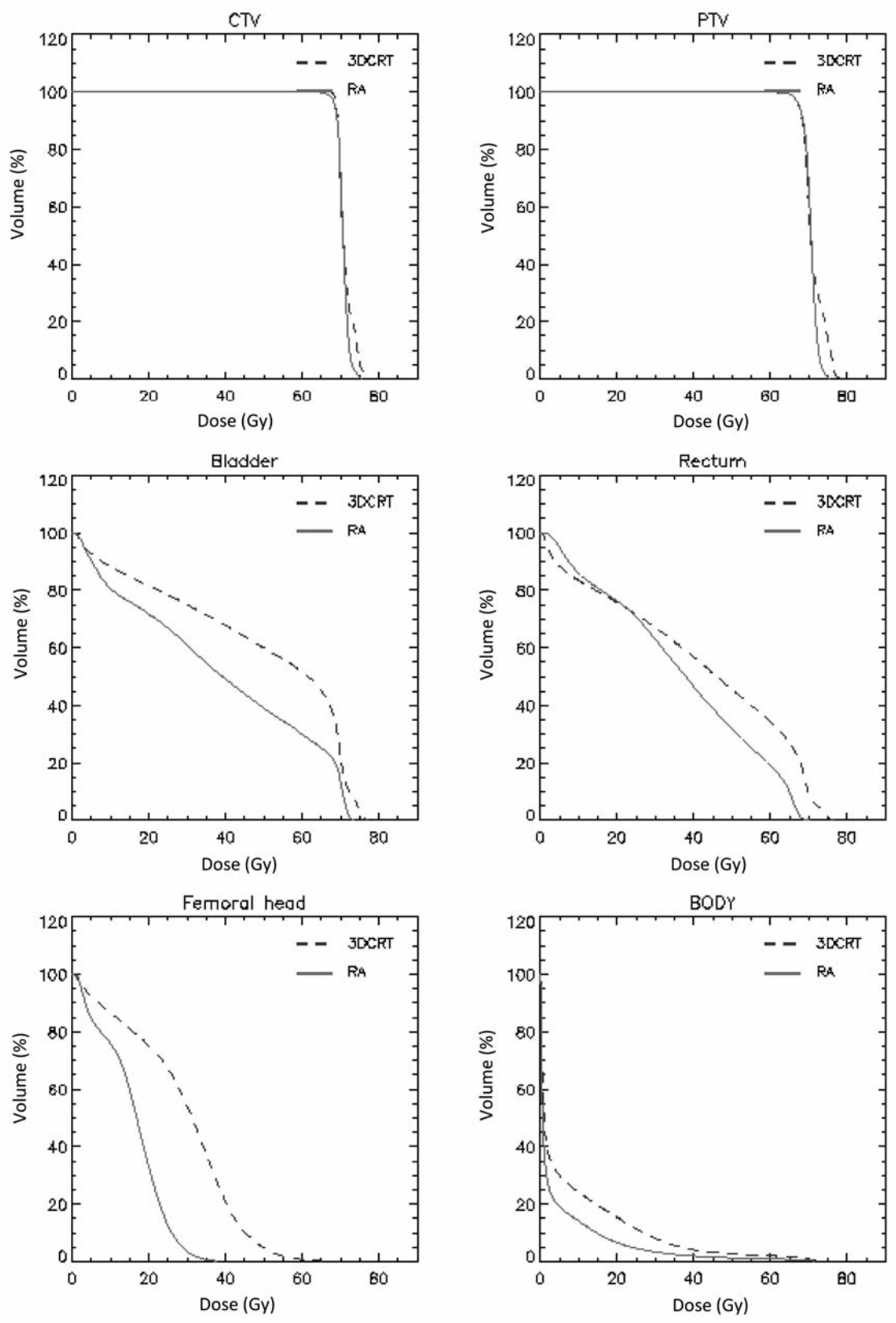

Figure 1. *Comparison of average dose-volume histograms for the two population groups for clinical target volumes (CTV), planning target volumes (PTV), rectum, bladder, femoral heads and healthy tissue (BODY in the figure).*

performed, as organ movement is an important issue in this region. In the present study, for both groups, only set-up corrections were applied on CBCT matching, and no specific protocols for organ motion correction online (tumor tracking), nor specific check of rectum filling (or displacement for gas or fecal residual) were set. These uncertainties could influence final toxicity to some extent, especially when higher doses per fraction are prescribed. For that reason, after toxicity data collection, we regularly suggested to all prostate cancer patients, to empty the rectum and fill the bladder before and during each treatment session. We also halted the session and invited the patient to repeat the rectum and bladder preparation procedure, in cases of unsatisfactory conditions during CBCT examination.

A limitation of the present study, other than the limited number of patients per group, was related to the changes of methods of toxicity data collection, due to changes in the schedule of visits during treatment. At our Institution, clinical examination became more frequent after RapidArc implementation (from every 10 days to once a week). Thus, more attention to toxicity stratification was probably paid in the more recent Hypo-RapidArc group and a possible underestimation of toxicity cannot be excluded in the less recently treated patients of the 3DCRT group. In the present study, grade 2 GI toxicity was recorded in fewer than 20% of cases, in line with literature data for conventional fractionation (29). In fact, moderate and severe acute lGI side-effects, although typically transient in nature, may occur cumulatively in approximately 25% of patients treated. We also did not record any type of acute grade 3 toxicity and we know that acute toxicity greater than grade 2 can also be severe enough to actually determine an interruption of the continuity of the treatment, with a potentially detrimental effect. Accordingly with this consideration, in the absence of grade 3 or more acute toxicity, we did not record any interruptions due to acute side-effects during treatment in the present postoperative series.

Conclusion

The results of our study show that moderate hypo-fractionation by RapidArc is feasible in a postoperative setting. Longer-term data are awaited to confirm or render the late toxicity profile data and clinical efficacy in the Hypo-RapidArc group of patients more robust.

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