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Original research article

Volumetric image-guided highly conformal radiotherapy of the prostate bed: Toxicity analysis

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ARTICLE INFO

Article history:
Received 6 April 2016
Received in revised form
24 July 2016
Accepted 21 October 2016
Available online 24 November 2016

Keywords:
Prostate bed
Image-guided radiotherapy
Conformal radiotherapy
Toxicity

ABSTRACT

Aim: To evaluate toxicity of high conformal image-guided radiotherapy of the prostate bed.
Background: Radiotherapy of the prostate bed has a pivotal role in the post-operative and salvage settings, but few clinical data are available on the use of daily image guidance in combination with highly conformal techniques, and data on long-term results are lacking.
Materials and methods: We analyzed 118 patients irradiated on the prostate bed using conformal plans processed with a micro-multileaf collimator, and daily checking treatment set-up with a cone-beam CT system. Correlation between toxicity and clinical-dosimetric parameters was assessed by the Cox regression model and log-rank test. Survival analyses were performed with the Kaplan–Meier method.
Results: Median follow-up was 54.08 months. Late grade ≥2 gastro-intestinal (GI) and genito-urinary (GU) toxicity were 3.4% and 4.2%, respectively. Actuarial 4-year late grade ≥2 GI and GU toxicities were 4% and 6%, respectively. Four-year relapse-free survival was 87%. At log-rank test, acute grade ≥2 GI toxicity is associated with the use of antihypertensives ($p = 0.03$), and there is a trend toward significance between the use of anticoagulants and late grade ≥2 GI toxicity ($p = 0.07$). At Cox analysis, acute grade ≥2 GU toxicity is correlated with the percentage of bladder volume receiving more than 65 Gy ($p = 0.02$, HR 1.87 CI 1.25–2.8), and the maximal dose to the rectum is correlated to the development of late grade ≥2 GI toxicity ($p = 0.03$, HR 2.75 CI 1.10–6.9).
Conclusions: Conformal volumetric image-guided radiotherapy of the prostate bed leads to low toxicity rates.

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http://dx.doi.org/10.1016/j.rpor.2016.10.006

1. Background

Radiotherapy of the prostate bed improves biochemical control in patients with adverse pathological features after radical prostatectomy,[1,2] increases overall survival and reduces the risk of metastasis.[3] Several studies investigated acute and long-term toxicity after post-prostatectomy radiotherapy,[4–6] but few clinical data are available on the use of daily image guidance and of highly conformal techniques, such as intensity modulated radiotherapy (IMRT).[7–10]

2. Aim

In the current study we evaluated acute and late toxicity, and analyzed the impact of patient characteristics and rectal and bladder dose-volume parameters on the development of toxicity after highly conformal image-guided radiotherapy.

3. Materials and methods

From August 2007 to May 2015, 118 patients underwent adjuvant or salvage 3-dimensional conformal image-guided radiotherapy (IGRT) using an on-board cone beam computed tomography (CBCT) system, after radical prostatectomy (RP). Table 1 summarizes the clinical features of this patient population. With a median time of 6.45 months (range, 1.93–11.86) from RP, adjuvant radiotherapy was administered in 80 (67.8%) patients because of positive margins, seminal vesicle invasion, or extraprostatic extension (pT3). Thirty-eight patients (32.2%) received salvage radiotherapy for a rising PSA after RP, with

Table 1 – Patient characteristics (a), and co-morbidities status (b) (118 patients).

	Mean	Median	Range		No. of patients
(a) Patient characteristics					
Age (years)	66.5	67	51–79		
PSA (ng/ml) before RP	13.57	9	1.9–120		
Pathological stage				T2a	6
				T2b	7
				T2c	24
				T3a	43
				T3b	37
				T4	1
Surgical margins				Positive	52
				Negative	66
Gleason score				6	21
				7 (3 + 4)	31
				7 (4 + 3)	30
				8	25
				9	11
PSA (ng/ml) before EBRT	0.86	0.16	0–19.7		
Treatment setting				Post-operative	80
				Salvage	38
Pre-EBRT urinary symptoms[a]				Yes	33
				No	85
Androgen deprivation therapy				Yes	46
				No	72
(b) Co-morbidities status					
Diabetes				Yes	9
				No	109
Colitis				Yes	2
				No	116
Smoking abitude				Yes	48
				No	70
Abdominal surgery				Yes	47
				No	71
Antihypertensive medication				Yes	46
				No	72
Anticoagulants				Yes	22
				No	96

Abbreviations: RP = radical prostatectomy; EBRT = external beam radiation therapy.
[a] Stress incontinence.

Table 2 – Toxicity per grade for all patients and per treatment group separately.

Toxicity	Grade	Post-operative (N = 80)	Salvage (N = 38)	p-value
Gastro-intestinal	Acute < 2	79 (98.7%)	36 (94.7%)	0.4
	Acute ≥ 2	1 (1.2%)	2 (5.2%)	
	Late < 2	78 (97.5%)	36 (94.7%)	0.39
	Late ≥ 2	2 (2.5%)	2 (5.2%)	
Genito-urinary	Acute < 2	75 (93.7%)	35 (92.1%)	0.51
	Acute ≥ 2	5 (6.2%)	3 (7.8%)	
	Late < 2	77 (96.2%)	36 (94.7%)	0.52
	Late ≥ 2	3 (3.7%)	2 (5.2%)	

a median time from RP of 51.11 months (range, 5.43–197.86). As there was no significant difference in the incidence of any grade ≥2 toxicity between patients treated in post-operative or salvage setting (Table 2), we performed a pooled analysis.

All patients underwent CT (2.5 slice thickness) under radiotherapy planning conditions in the supine position; bowel and bladder preparation were prescribed[11] in order to have an empty rectum and a full bladder during the CT scan and the treatment course. For each patient the clinical target volume (CTV), consisting of the prostate bed, was defined as suggested by Poortmans et al.[12] Rectum and bladder were defined as solid organs; the rectum was considered from recto-sigmoid junction to the lowest level of the ischial tuberosities, and the bladder was contoured in its entirety. Planning target volumes (PTVs) were generated by an asymmetric expansion of CTVs (6 mm at the posterior margin, and 8 mm in all other directions). Conformal treatment plans were obtained on Pinnacle3 version 8.0 m (Philips Medical System, Andover, MA). For the whole patient population, a total median dose of 66 Gy (range, 66–76 Gy) at 2 Gy per fraction was prescribed to the PTV (Table 3). Radiotherapy treatment was delivered using Elekta Synergy® S linear accelerator equipped with the Beam ModulatorTM, which is a high definition multileaf collimator (4 mm leaf width at the isocenter),[13] and with a kV-CBCT system for daily image-guidance. CBCTs images were used for on-line comparison with planning CT.[11] Rectal and bladder volumes were checked, and on-line corrections were performed before the treatment session (set-up errors greater than 3 mm were corrected).

Table 4 – Radiation Therapy Oncology Group (RTOG) toxicity in 118 patients.

	Grade 0–1	Grade ≥2	Grade 3
Acute			
GI toxicity	97.5% (115/118)	2.5% (3/118)	0% (0/118)
GU toxicity	93.3% (110/118)	6.7% (8/118)	2.5% (3/118)
Late			
GI toxicity	96.6% (114/118)	3.4% (4/118)	0% (0/118)
GU toxicity	95.8% (113/118)	4.2% (5/118)	3.3% (4/118)

Acute (within 90 days from the start of radiotherapy), and late toxicities were scored by the radiation oncologist, according to the RTOG/EORTC toxicity scale.[14] Toxicity was reported as the highest toxicity in each patient.

Dose–volume-histograms (DVHs) were used to provide a quantitative analysis. Maximum and mean dose, and a set of appropriate Vx (percent of OAR volume receiving the x dose) were evaluated for the rectum and bladder. Statistical analysis was carried out using a commercial statistical software package (SPSS 9.0; SPSS Inc., Chicago, IL). Correlation between dose volume parameters considered as continuous variables and grade ≥2 toxicity was assessed by the Cox regression model. Correlation between grade ≥2 late toxicity and clinical parameters was performed using the log-rank test for categorical variables. The survival analysis and the cumulative incidence of late toxicity were performed with the Kaplan–Meier method. The Cox-model was used for multivariate analysis.

Table 3 – Dose–volume-histogram parameters (118 conformal plans).

	Mean organ volume (cc) (range)	Mean volume (%) (range)	Maximum dose (Gy) (range)	Mean dose (Gy) (range)	Minimum dose (Gy) (range)
Rectum	39.2 (15.3–82.8)		68.6 (50–76.7)	42.5 (29–60)	7.9 (5.3–32.4)
V65		20 (1–35)			
V60		26.8 (6–55)			
V50		39.5 (17–65)			
Bladder	115.6 (25.8–375)		70.1 (51–71.7)	40.1 (11.2–58.8)	6.3 (1.2–28.5)
V65		22 (1–52)			
V60		31 (3–63)			
V50		40 (9–68)			
PTV	115.9 (27.5–238.8)			67.8 (66–76)	

Table 5 – Correlation between toxicity and clinical variables (logrank test).

Clinical variable	Acute GI grade ≥2 *p*-value	Late GI grade ≥2 *p*-value	Acute GU grade ≥2 *p*-value	Late GU grade ≥2 *p*-value
Prescription dose	0.40	0.11	0.35	0.49
Hormonal therapy	0.08	0.92	0.13	0.50
Nicotine consumption	0.89	0.15	0.53	0.32
Use of antihypertensives	0.03	0.11	0.51	0.29
Diabetes	0.61	0.53	0.73	0.45
Previous abdominal surgery	0.77	0.43	0.79	0.80
Presence of colitis	0.77	0.71	–	–
Use of anticoagulants/antiaggregants	0.40	0.07	0.83	0.37
Pre-RT symptoms	–	–	0.29	0.62

4. Results

With a median follow-up of 54.08 months (range, 4.9–103.1 months) from the end date of radiotherapy, 93 (78.8%) patients were free from biochemical recurrence, 18 (15.2%) had a biochemical recurrence (of whom 11 also with metastatic disease), 2 (1.7%) patients were dead from prostate cancer, 1 (0.8%) patient was dead from another cause. Four patients (3.4%) were lost at follow-up. Four-year relapse-free survival was 87%.

Table 4 reports the frequency of genito-urinary (GU) and gastro-intestinal (GI) toxicity. Taking into account GI toxicity, no patient experienced G3 acute or late toxicity; 3 (2.5%) patients had G2 acute toxicity (urgency and proctitis requiring medication), and 25 (21.2%) patients had G1 acute toxicity (urgency, mucus loss). Grade 2 late GI toxicity was registered in 4 (3.3%) patients (bleeding in 3 cases, and proctitis in 1), G1 late toxicity in 4 patients (proctitis in 3 cases, mucus loss in 1). Actuarial 3 and 4 years late grade ≥2 GI toxicity were 2% and 4%, respectively (Fig. 1a).

Acute genito-urinary toxicity was as follows: there were 3 (2.5%) cases of G3 toxicity (2 obstructions, and 1 gross hematuria), 5 (4.2%) cases of G2 toxicity (4 with dysuria and 1 with spasm, requiring medication), and 37 (31.3%) cases of G1 (dysuria, frequency, and urgency). Four patients (3.3%) experienced grade 3 late GU toxicity (3 urethral strictures, and 1 gross hematuria), 1 (0.8%) patient had G2 late toxicity (frequency and urgency requiring medication), and 19 (16.1%) patients G1 late toxicity (frequency, or microscopic hematuria). Actuarial 3 and 4 years late grade ≥2 GU toxicity were 5% and 6%, respectively (Fig. 1b). Univariate analysis (log-rank test for categorical variables) for the correlations between acute and late toxicity and clinical variables (Table 5) evidenced that acute grade ≥2 GI toxicity is strongly associated with the use of antihypertensive medication ($p = 0.03$), and with concomitant androgen deprivation therapy (protective; weak correlation, $p = 0.08$). Finally, there is a trend toward significance between the use of anticoagulants and late grade ≥2 GI toxicity ($p = 0.07$). Cox proportional hazard regression model for continuous variables (Table 6) showed that acute grade ≥2 GU toxicity is strongly correlated with the bladder-V_{65} DVH parameter ($p = 0.02$, HR 1.87 CI 1.25–2.8); finally, the maximal dose to the rectum correlated with developing late grade ≥2 GI toxicity ($p = 0.03$, HR 2.75 CI 1.10–6.9).

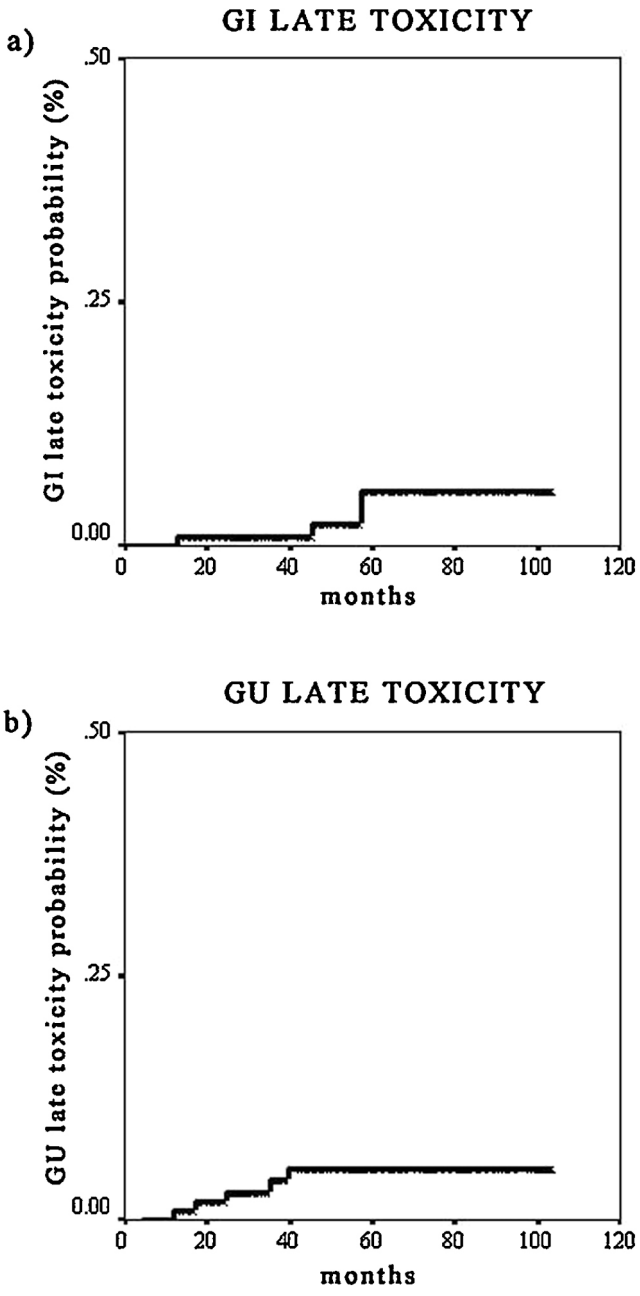

Fig. 1 – Kaplan–Meier curves. (a) Late gastro-intestinal toxicity. (b) Late genito-urinary toxicity.

Table 6 – Correlation between toxicity and clinical variables (Cox proportional hazards regression).

DVH parameter	Gastro-intestinal late toxicity			Genito-urinary acute toxicity		
	p-value	Exp (B)	95% CI Exp (B)	*p*-value	Exp (B)	95% CI Exp (B)
V50	0.55	0.63	0.14–2.79	0.69	1.25	0.98–1.58
V60	0.44	2.80	0.21–3.73	0.06	0.46	0.26–0.79
V65	0.57	0.68	0.19–2.53	0.02	1.87	1.25–2.80
D_{max}	0.03	2.75	1.10–6.94	0.89	1.01	0.85–1.20
D_{mean}	0.65	0.95	0.75–1.19	0.15	0.97	0.93–1.01

The multivariate analysis showed no statistically significant variable.

5. Conclusion

Radiotherapy of the prostate bed has a pivotal role in post-operative and salvage settings[1–3; 15 Krengli], but the clinical benefit of new technologies, such as IMRT and IGRT, in these patients is not clear yet[16] and few data are available in the literature.[7–9,17] Some phase II studies investigated acute toxicity in hypofractionated IMRT of the prostate bed using image-guidance,[18–20] but data on long-term results are lacking. In the pelvic region, 3-D prostate radiation therapy treatment plans processed with a micro-multileaf collimator provide high conformal treatments that are dosimetrically comparable with IMRT plans, but are less demanding in terms of equipment, personnel and time.[21] Finally, daily IGRT for the pelvis seems to be determinant, allowing precise targeting and organs at risk sparing.[20] On the other hand, concerns have been raised about the additional dose from daily image-guided procedures such as kV-CBCT,[22] and many works have been published up to now investigating the dose delivered with CBCT during radiotherapy.[23] In particular, Spezi et al.[24] calculated the concomitant dose received by patients undergoing Elekta XVI kV-CBCT for pelvic IGRT, using the Monte Carlo method. A single CBCT delivers a mean dose of 1–3 cGy to the target volume, 1–2 cGy to the rectum, and 2–6 cGy to the femoral heads. In our series, we did not take into account the dose coming from daily kV-CBCT. We believe that information for image guidance dose to organs is important as we are in the IGRT era, but the probabilistic risk associated with the additional image-guided procedures is difficult to assess, and the low additional dose of kV-CBCT technique represents a small risk to the patient, especially if compared with the benefits provided by image guidance.

We retrospectively analyzed patients irradiated on the prostate bed using highly conformal shaped fields with a micro-multileaf collimator (median total dose, 66 Gy; 2 Gy per fraction), and daily checking treatment set-up with volumetric image-guidance. Limitations of our study are the number of patients and the absence of patient self-assessed toxicity. The strengths are the homogeneity of the patient population and treatment modality, together with the long median follow-up. Our analysis showed a good toxicity profile. With a median follow-up of 54.08 months, we reported a late grade ≥2 GI and GU toxicities of 3.4% and 4.2%, respectively. Actuarial 4 years late grade ≥2 GI and GU toxicities were 4% and 6%, respectively.

A recent retrospective study by Nath et al.[7] analyzed 50 patients treated with adjuvant or salvage IMRT to a median dose of 68 Gy (range, 62–68 Gy). The prostate bed localization was obtained via planar kV imaging, performed on a daily basis using existing surgical clips as a surrogate for the prostate bed. With a median follow-up of 24 months (range, 13–38 months), acute grade 2 GI and GU toxicities were 8% and 14%, respectively. No acute grade 3 toxicity was reported. Late grade ≥2 GI and GU toxicities were 2% and 18%, respectively. The 2-year cumulative incidence of late grade ≥2 GI and GU toxicities were 2% and 16%, respectively.

Using 3D-conformal radiotherapy (median dose, 66 Gy), Bellavita et al.[4] reported a late grade ≥2 GU and GI toxicities of 13.2% and 6% in 182 patients, respectively (median follow-up of 55.6 months).

It is to say that comparison between studies is quite difficult because of differences in total prescribed dose, radiation technique, and toxicity scales (Table 7). Nevertheless, differences exist in contouring between studies, and between different consensus guidelines.[25] Maybe the introduction of MRI in the target definition phase will contribute to perform a better delineation of CTV and OARs.[26,27]

Analyzing our toxicity data in correlation with patients' clinical variables, the log-rank test evidenced a protective effect of hormonal therapy on the intestinal tissue (weak correlation), as reported in other studies[28,29] and demonstrated in animal models.[30] We found that antihypertensive medication increases the risk of acute GI toxicity, whereas it seems to have a protective effect in the series by Fellin et al.[31] Finally, the use of anticoagulants or antiaggregants is weakly associated to late GI toxicity, as reported by Choe et al.[29] and Takeda et al.[32]

Our Cox proportional hazards regression confirms the relation between dose–volume parameters (maximal dose to the rectum, and bladder V_{65}) and toxicity. Hence, new treatment strategies addressed to reduce the irradiation of normal tissues might allow dose escalation and hypofractionation,[20] which are becoming common in the post-prostatectomy setting. However, the recent population-based study by Goldin et al.[16] evidences a relative lack of comparative effectiveness with data demonstrating the superiority of IMRT in respect to 3DCRT in terms of outcomes (disease recurrence, and late toxicity).

The role of new technologies in the post-prostatectomy radiotherapy needs to be further investigated. Our results confirm the importance of high conformal radiotherapy, and image-guidance in this setting of patients. In particular, 3D-plans processed with a micro-multileaf collimator providing highly conformal treatments, and the use of daily CBCT to

Table 7 – RT technique, fractionation scheme, and toxicity rate from different studies.

Author	Patients (*n*)	RT technique	Total dose (Gy)	Fractions (*n*)	Toxicity scoring	G ≥ 2 acute toxicity		G ≥ 2 late toxicity	
						GI (%)	GU (%)	GI (%)	GU (%)
Bolla[1,33]	457	2D-simulation	60	30	WHO/RTOG	23.2	33.3	2.5	21.3
Wiegel[2]	148	3DCRT	60	30	RTOG	–	–	1.4	2.7
Thompson[3,34]	214	2D-simulation	60–64	30–32	(QoL questionnaires)	–	–	3.3	24.3
Katayama[19]	39	IMRT, daily image guidance	54	18	CTCAE v4.0	18	0	–	–

WHO = World Health Organization; RTOG = Radiation Therapy Oncology Group; QoL = quality of life; CTCAE = Common Terminology Criteria for Adverse Events.

check radiotherapy delivery lead to low acute and late toxicity rates.

Conflict of interest

None declared.

Financial disclosure

None declared.

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