Hypofractionated Intensity-modulated Radiotherapy with Simultaneous Integrated Boost after Radical Prostatectomy: Preliminary Results of a Phase II Trial

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Abstract. *Aim: To report the acute toxicity of a hypofractionated regimen of intensity-modulated radiotherapy with simultaneous integrated boost (SIB-IMRT) to the pelvic nodes and the prostatic bed after radical prostatectomy. Patients and Methods: Patients with prostate adenocarcinoma at high risk of relapse after radical prostatectomy or with biochemical relapse were deemed eligible for study. SIB-IMRT was prescribed to the whole pelvis (45-Gy delivered in 1.8-Gy fractions) and the prostatic bed [62.5 Gy, 2.5-Gy fractions, Equivalent Dose in 2-Gy fraction (EQD2)=68.75 Gy, α/β=3]. Acute toxicity was recorded and graded according to Radiation Therapy Oncology Group (RTOG) criteria. Results: Forty-nine patients were enrolled. No cases of grade ≥3 acute toxicity were recorded. Grade 2 acute genitourinary and gastrointestinal toxicity was observed in 9.6% and 29.7% of patients, respectively. Conclusion: After radical prostatectomy, hypofractionated high-dose SIB-IMRT enables for reduction of the overall treatment time, with an acute toxicity profile which compares favourably with that of conventionally fractionated high-dose three-dimensional conformal radiotherapy (3D-CRT).*

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Early adjuvant radiotherapy (RT) to the prostatic bed results in improvement in biochemical progression-free survival (BPFS) (1-3) with a potential impact on metastasis-free and overall survival (3) in patients with prostate cancer and high risk features such as extracapsular extension (ECE), positive surgical margins, and seminal vesicle involvement (SVI). Despite early adjuvant RT at a standard dose [equivalent dose in 2-Gy fractions (EQD2)=60-64 Gy], 25.7-34.9% of patients showed biochemical progression during follow-up (1-3). The predominant treatment failure site in patients post-prostatectomy is local (4). Early adjuvant RT with a higher dose (EQD2 ≥68 Gy, α/β=3) may reduce the risk of biochemical failure (5, 6). Retrospective data also suggest that whole-pelvis RT in the post-radical prostatectomy setting can provide improved biochemical recurrence-free survival for patients at high risk of lymph node involvement (7).

However, both dose-escalation and nodal irradiation increase the risk of morbidity. Post-operative intensity-modulated radiotherapy (IMRT) provides a significant reduction of rectum and bladder irradiation as compared to three-dimensional conformal radiotherapy (3D-CRT) (8), and hence reduced acute toxicity of nodal irradiation (9).

Based on an estimated α/β ratio in prostate cancer close to 1.5 Gy, hypofractionated RT provides a theoretical biological advantage over conventional fractionation (10). Hypofractionation is very convenient for the patient due to the few visits to the RT center during treatment. The simultaneous integrated boost (SIB)-IMRT technique allows for simultaneous delivery of different dose intensities to different target volumes, with a better coverage of target volume and sparing of adjacent organ tissues in relation to conformal sequential radiation or a combination of CRT and IMRT (11).

In a previous dose-escalation trial, it was shown that hypofractionated postoperative SIB-IMRT to the pelvic

nodes (45 Gy delivered in 1.8-Gy fractions) and the prostatic bed (62.5 Gy delivered in 2.5-Gy fractions, EQD2=68.75 Gy, α/β=3) is feasible in terms of acute toxicity, with a low incidence of severe gastrointestinal and genitourinary acute side-effects (12).

Based on the results of this dose-escalation study, a phase II study was planned for a long-term analysis of late toxicity and local control. Here we report the acute toxicity in comparison with a series of standard fractionated high-dose 3D-CRT.

Patients and Methods

This was a prospective phase II clinical trial of hypofractionated post-operative SIB-IMRT and it was approved by the Catholic University Institutional Review Board. The primary objective of this study was to estimate the late radiation morbidity in organs at-risk (OaRs, bladder and bowel). A secondary objective was to describe biochemical and clinical evidence of tumor control. Sample size was based on estimating the incidence of any late toxicity of grade 2 or more with reasonable precision. Assuming an incidence of at least 15% at two years (1-3), 43 patients would yield a 95% confidence interval of 0-15%.

Eligibility. Patients with prostate adenocarcinoma after radical prostatectomy with positive surgical margins of resection or ECE or SVI and a predicted probability of nodal metastasis >7% (13) calculated by the Roach formula (14) with fewer than 13 nodes removed after pelvic lymph node dissection (15) or positive pelvic nodes were enrolled into this trial. Also patients with biochemical relapse [Prostate Specific Antigen (PSA) of ≥0.2 ng/ml, with a second confirmatory level of >0.2 ng/ml (16)] were deemed eligible. Patients had to be older than 18 years, with an Eastern Cooperative Oncology Group (ECOG) performance status <2, and adequate bone marrow function (hemoglobin concentration >8 g/dl, white blood cell count >3,000/mm^3, platelet count >75,000/mm^3). Patients with prior pelvic RT, distant metastases, macroscopic residual tumor, enlarged pelvic or para-aortic nodes at re-evaluation imaging after surgery, secondary malignancies, genetic syndromes of hyper-radiosensitivity, and chronic inflammatory bowel disease were excluded from the protocol. Pre-treatment evaluation included complete medical history, physical examination, complete blood cell count, biochemistry, serum PSA levels, computed tomographic (CT) scan or magnetic resonance imaging of the abdomen and pelvis, and bone scan.

RT technique. Details of the SIB-IMRT technique were provided in a previous dose escalation study (12). Briefly, treatment was simulated and performed in the supine position. Patients were instructed to acquire stable conditions of bladder and rectal filling. RT was planned based on the CT simulation performed after oral administration of contrast with 5-mm slices. SIB-IMRT was prescribed to the prostatic bed (17) (62.5 Gy delivered in 2.5-Gy fractions, EQD2=68.75 Gy, α/β=3) and the pelvic nodes (18) (45 Gy delivered in 1.8-Gy fractions). The dose was calculated so that the dose to 98% of planning target volumes (D98) was at least 95% of the prescribed dose (19). Less than 25% of the rectum and <50% of the bladder could receive 70 Gy, <2% of the small bowel could receive 50 Gy, and <10% of femoral heads could receive 50 Gy. The constraints for the OARs were adapted for hypofractionation using an α/β ratio of 3. Patients were treated with a linear accelerator (Elekta Precise) equipped with multileaf collimators with 40 leaf pairs each of 1-cm width. Treatment was delivered by step-and-shoot IMRT. Set-up accuracy was checked by daily portal images and on-line corrections were adopted in case of deviations of isocenter position greater than 3 mm, as previously described (20).

Toxicity evaluation. Acute toxicity was assessed weekly during treatment, at three weeks from the end of RT, and then at three 3 months using the Radiation Therapy Oncology Group (RTOG) acute scoring system (21).

Series of standard fractionated high-dose postoperative radiotherapy. Patients with prostate adenocarcinoma after radical prostatectomy who underwent adjuvant or salvage RT with standard 1.8-2 Gy fractionation to the prostatic bed and regional pelvic nodes at doses higher than conventional 60-64 Gy were selected. Data were derived from an electronic database of prospectively collected information. With regard to the RT technique, treatment set-up and volumes were the same as for the patients who underwent hypofractionated RT (except for the lack of specific guidelines for the definition of the prostatic bed). The treatment machines and set-up correction protocol did not differ. Differently from the hypofractionation group, patients who underwent conventionally fractionated RT were treated with a 3D-CRT technique for both pelvic (prophylactic nodal irradiation) and prostatic fossa irradiation as previously described (8).

Briefly, whole-pelvic RT (45 Gy, 1.8 Gy/fr) was delivered by means of a box technique using four beams at 15 MV (0°, 90°, 180°, and 270°) collimated with standard multileaf collimators with 40 leaf pairs each of 1-cm width, and was followed by a boost to the prostatic bed up to a total dose of 70 Gy (2 Gy fraction).

Statistical considerations. Comparison between the two patient groups (standard *versus* hypofractionated RT) was performed by using Student's *t*-test (quantitative data) and the chi-squared test (qualitative data). Statistical analysis was performed with SYSTAT, version 11.0 (SPSS, Chicago).

Results

Patients' characteristics. Between November 2008 and February 2012, 49 patients with prostate cancer met the inclusion criteria and were enrolled into the phase II trial of hypofractionated postoperative RT.

Fifty-two consecutive patients with prostate adenocarcinoma who underwent adjuvant or salvage RT with standard 2 Gy fractionation to the prostatic bed and regional pelvic nodes between February 2003 and October 2008, were selected from the electronic database.

In Table I, the main patients' characteristics are summarized and compared according to treatment group (hypofractionation and control group). Patients in the hypofractionation group were slightly older. Fifteen patients underwent salvage RT because of PSA failure, most of them (n=10) were in the hypofractionation group. Among patients who underwent adjuvant RT, more patients had positive pelvic nodes in the control group. Patients in the control group also had a greater mean number of pelvic lymph-nodes surgically removed. The

Table I. *Main clinical parameters of the two subgroups (hypofractionated and conventionally fractionated post-operative RT).*

Parameter	All patients	Hypofractionated RT (phase II trial), n=49	Conventionally fractionated RT (control group) n=52	*p*-Value* (*t*-test or c^2)
Age, years				
Mean (standard deviation)	64 (6.3)	65 (5.2)	62 (7.1)	0.058
Median (range)	65 (46-78)	66 (50-74)	64 (46-78)	
Diabetes , n (%)	9 (8.9)	4 (8.0)	5 (9.6)	n.s.
Hypertension, n (%)	45 (44.5)	21 (42.8)	24 (46.1)	n.s.
Salvage RT, n (%)	15 (14.8)	10 (20.4)	5 (9.6)	0.16
• PSA at recurrence, ng/ml, mean value	1.12	1.25	0.88	n.s.
• Gleason score >7, n (%)	3 (20.0)	2 (20.0)	1 (20.0)	n.s.
• Positive resection margins , n (%)	3 (20.0)	1 (10.0)	2 (40.0)	n.s.
Adjuvant RT, n (%)	86 (85.1)	39 (79.6)	47 (90.4)	0.16
• ECE, n (%)	74 (73.2)	35 (89.7)	39 (82.9)	n.s.
• SVI, n (%)	24 (23.7)	12 (30.7)	12 (25.5)	n.s.
• Positive resection margins, n (%)	65 (64.3)	27 (69.2)	38 (80.8)	n.s.
• Positive lymph-nodes, n (%)	7 (6.9)	0 (0.0)	7 (14.8)	0.01
• Pre-surgery PSA, ng/ml, mean value	12.6	10.2	14.6	0.08
• Post-surgery PSA, ng/ml, mean value	0.29	0.27	0.23	n.s.
• Gleason score >7, n (%)	21 (20.7)	14 (35.8)	7 (14.8)	0.08
• Time to RT, months, mean value	4.3	4.5	4.2	n.s.
• N° of resected nodes, mean value	7.4	4.6	9.3	<0.01
Adjuvant hormone (≥ 3 months), n (%)	75 (74.2)	36 (73.4)	39 (75.0)	n.s.

*Only *p*-values <0.20 are reported.

mean pre-operative PSA tended to be higher in the control group, while more patients in the hypofractionation group had a Gleason score higher than 7. Seventy-five patients (74.2%) received adjuvant androgen deprivation therapy as combined androgen deprivation [bicalutamide at 50 mg and luteinizing-hormone-releasing hormone (LH–RH) analogous] or bicalutamide at 150 mg in monotherapy without any significant difference between the groups.

Acute toxicity. Acute toxicity is shown in Table II. Grade ≥ 1 acute genitourinary toxicity occurred in 72 patients (71.2%) without significant difference between groups (p=0.51). Twenty patients (19.8%), complained of grade 2 acute genitourinary toxicity. Grade 2 acute genitourinary toxicity was less frequent among patients who underwent hypofractionated RT (9.6% *versus* 28.8%, p=0.02). No cases of grade 3 acute genitourinary toxicity was recorded, however 2 patients (1.9%, one patient in the hypofractionation and 1 in the control group) developed acute bladder obstruction during treatment requiring the temporary placement of an urethral catheter. Thirty patients (29.7%) developed grade 2 acute gastrointestinal toxicity, mainly rectal pain requiring analgesics or intermittent rectal bleeding, with only three patients (2.9%, one patient in the hypofractionation and two in the control group) experiencing diarrhea requiring medical treatment. No cases of grade 3 acute gastrointestinal toxicity were recorded. No significant difference was found according to fractionation for either the incidence or the severity of gastrointestinal toxicity.

Discussion

Several analyses and reviews of tumor control in prostate cancer (10, 22) have suggested an α/β value in the range of 1 to 3 Gy for prostate cancer, which is relatively lower than the value typically ascribed to the adjacent OARs, such as the bladder and rectum (23). This represents a unique opportunity to improve the therapeutic ratio by using a hypofractionated approach. To our knowledge, this was the first phase II trial of high-dose postoperative hypofractionated SIB-IMRT to the prostatic bed and the regional pelvic nodes in patients with prostate cancer. Acute tolerance to this hypofractionated treatment was quite good, with only one patient (1.9%) who developeddeveloping acute bladder obstruction requiring the temporary placement of an urethral catheter, and about 30% and 10% of patients experiencing acute grade 2 or more gastrointestinal and genitourinary toxicity, respectively. These results compare favorably with those achieved in a series of patients treated with similar total dose of conventionally fractionated postoperative 3D-CRT. Despite accelerated treatment, cases of acute grade 2 genitourinary toxicity were even less frequently reported among patients treated with hypofractionated RT (9.6% *versus* 28.8% of

Table II. *Acute toxicity (RTOG criteria) in the two groups (hypofractionated and conventionally fractionated post-operative RT).*

	All patients, n=101	Hypofractionated RT (phase II trial), n=49	Conventionally fractionated RT (control group) n=52	*p*-Value* (c^2)
Gastrointestinal, n (%)				
Grade 0	28 (27.7)	11 (22.4)	17 (32.6)	n.s.
Grade 1	43 (42.5)	22 (44.8)	21 (40.3)	n.s.
Grade 2	30 (29.7)	16 (32.6)	14 (26.9)	n.s.
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	n.s.
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	n.s.
Genitourinary, n (%)				
Grade 0	29 (28.7)	16 (30.7)	13 (25.0)	n.s.
Grade 1	50 (49.5)	27 (51.9)	23 (44.2)	n.s.
Grade 2	20 (19.8)	5 (9.6)	15 (28.8)	0.02
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	n.s.
Grade 4	2 (1.8)	1 (1.9)	1 (1.9)	n.s.

conventionally fractionated RT, p 0.02), and the incidence of acute gastrointestinal toxicity was not significantly increased. Different RT techniques between the two groups (IMRT *versus* 3D-CRT) probably explain such results. Indeed, in a previous dosimetric analysis, it was shown that postoperative SIB-IMRT in prostate cancer significantly reduces irradiation to the rectum and bladder compared with both 3D-CRT and hybrid 3D-CRT and IMRT (8).

In this phase II trial of hypofractionated SIB-IMRT, the incidence of acute grade 2 or more genitourinary toxicity and diarrhea was very similar to the one reported by Alongi and co-workers (9) (7.4% and 1.8%, respectively) in a retrospective series of 54 patients with prostate cancer who received postoperative hypofractionated SIB-IMRT (mean dose per fraction=2.35 Gy) by helical tomotherapy (HTT). However Alongi and colleagues did not observe any cases of acute lower gastrointestinal toxicity of grade 2 or more with HTT. Such a difference could be due to disparities between the two series in rectal dose distribution (discrepancies in treatment technique or target volume definition), in hypofractionation schedule (less hypofractionation in the Alongi *et al*. series), or in the study design (prospective *versus* retrospective in the Alongi *et al*. series). It should be emphasized that similarly to Alongi and colleagues, the median dose delivered to the prostatic bed was significantly higher than 60-66 Gy, as reported for most multi-institutional series (1, 2) both in the conventional and hypofractionation group. Moreover, all patients underwent pelvic nodal irradiation. Despite higher RT dose, acceleration, and larger treatment volumes, acute toxicities reported herein were similar. For example, the incidence of acute grade 2 or more gastrointestinal toxicity was 32.6% in our high-dose series and 23.6% in the RT arm of the EORTC 22911 trial (1); 11.5% of patients experienced acute grade 2 or more genitourinary side-effects in our series, while more than 20% of patients did in the RT arm of the EORTC 22911 trial (21.6% of patients, reported increased frequency of passage of urine, and 11.4% of dysuria). It should be considered that these studies started in the late 1980s and used large radiation portals without modern technologies. Currently image-guided RT and IMRT yield better positioning control of patients and target, and a drastic reduction of high-dose involvement of OARs surrounding the target volume (24).

In conclusion, despite acceleration, acute tolerance of hypofractionated high-dose SIB-IMRT compares favorably with that of conventionally fractionated high-dose 3-CRT, enabling a reduction in the overall treatment time.

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