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Hypofractionated Postoperative IMRT in Prostate Carcinoma: A Phase I/II Study

GABRIELLA MACCHIA[1], GIAMBATTISTA SIEPE[2], ILARIA CAPOCACCIA[2], NAM P. NGUYEN[3], RICCARDO SCHIAVINA[4], SILVIA CAMMELLI[2], SARA GUERRI[2], ALESSANDRA ARCELLI[2], MILLY BUWENGE[2], MARIA NTRETA[2], SAVINO CILLA[5], VINCENZO VALENTINI[6], FRANCESCO DEODATO[1*] and ALESSIO G. MORGANTI[2*]

[1]Radiotherapy Unit, and [5]Medical Physic Unit, Giovanni Paolo II, Sacred Heart Catholic University, Campobasso, Italy; Departments of [2]Experimental, Diagnostic and Specialty Medicine – DIMES, and [4]Urology, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; [3]Department of Radiation Oncology, Howard University College of Medicine, Washington, DC, U.S.A.; [6]Radiation Oncology Department Gemelli-ART, Sacred Heart Catholic University, Rome, Italy

Abstract. *Aim: To report the outcome of hypofractionated radiotherapy after radical prostatectomy (RP) for prostate cancer (PCa) using simultaneous integrated boost-intensity modulated radiation therapy (SIB-IMRT). Patients and Methods: A total of 124 patients with PCa at high risk of relapse after RP or diagnosis of biochemical relapse were included. Patients received 62.5 Gy to the prostate bed and 45 Gy to pelvic nodes in 25 fractions. Androgen-suppressive therapy was prescribed based on National Comprehensive Cancer Network risk categories. Results: Median follow-up was 30 months. Only two patients (1.6%) developed grade 3 or more acute toxicity: one grade 3 skin toxicity (0.8%) and one grade 4 genitourinary toxicity (0.8%). Grade 2 acute gastrointestinal and genitourinary toxicity was recorded in 24.2% and 17.7% of patients, respectively. Five-year grade 2 or more gastrointestinal and genitourinary toxicity was 1.1% and 7.3%, respectively. Five-year biochemical relapse-free survival was 86.5%. Conclusion: After RP, hypofractionated IMRT-SIB demonstrated a favorable toxicity profile and encouraging results in terms of relapse-free survival.*

*These Authors contributed equally to this study.

Correspondence to: Giambattista Siepe, MD, Radiation Oncology Center, Department of Experimental, Diagnostic and Specialty Medicine – DIMES, University of Bologna, S. Orsola-Malpighi Hospital, via Massarenti 9, 40138 Bologna, Italy. Tel: +39 0512143564, e-mail: giambattista.siepe@gmail.com

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Three randomized trials demonstrated that adjuvant radiotherapy (RT) to the prostatic bed (PB) improves biochemical relapse-free survival (bRFS) (1-3), and may improve metastasis-free survival and overall survival (OS) patients with prostate cancer (PCa) at high-risk of relapse following radical prostatectomy (RP). The poor prognostic features in those trials included extra-capsular extension, seminal vesicles involvement and positive surgical margins. However, those studies which were based on a PB dose of 60 to 64 Gy were still associated with a 15.7 to 34.9% risk of biochemical relapse (1-3). Moreover, an analysis of patterns of failure demonstrated a significant risk of local failure despite adjuvant RT (4).

Higher radiation doses may reduce local failure and improve bRFS (5). In addition, whole-pelvis RT after RP has been reported to improve bRFS particularly in patients with a high risk of lymph node involvement (6). However, the combination of a higher radiation dose to the PB and pelvic nodal irradiation may increase treatment toxicity and reduce patient quality of life (QoL). Thus, use of radiotherapy techniques able to reduce healthy tissue irradiation and to allow radiation dose escalation to the PB with simultaneous irradiation of pelvic lymph nodes may potentially improve bRFS and QoL.

Compared to three-dimensional conformal radiotherapy, pelvic node irradiation with intensity-modulated radiotherapy (IMRT) has been reported to reduce the radiation dose to the bladder and rectum, thus minimizing treatment toxicity (7,8). Hypofractionated RT for PCa may also improve tumor control because of the low α/β value (1.5 Gy) (9). In addition, the technique of IMRT with simultaneous integrated boost (IMRT-SIB) allows for shorter treatment time and a superior

conformity index, which minimizes radiation dose to the organs at risk (OaRs) potentially reducing complication rates (10).

In a previous study, hypofractionated postoperative IMRT-SIB to the PB (62.5 Gy delivered in 2.5 Gy/fraction, equivalent dose (EQD_2): 68.75 Gy, α/β: 3) and the pelvic nodes (45 Gy delivered in 1.8 Gy/fraction) was reported to be feasible in terms of acute toxicity in patients who underwent postoperative RT for PCa (11). The current study reports long-term results in terms of bRFS and complication rates.

Patients and Methods

Study objectives. This was a prospective phase II clinical trial of hypofractionated postoperative IMRT-SIB which was approved by the Catholic University Institutional Review Board (Approval number: 576(A1416)/CE/2007). Any acute adverse events of the OaRs (bladder and bowel) were recorded and the incidence of any type of severe side-effect or long-term complication defined as grade 3 to 5 acute and grade 2 to 5 late toxicity was the primary end-point of the study. 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 2 years (1-3), 43 patients would yield a 95% confidence interval of 0-15%. The study's secondary end-point was to evaluate the incidence of biochemical and clinical relapse.

The trial was approved by the local Ethics Committee and registered in an international public registry (ClinicalTrials.gov Identifier: NCT03233672).

Eligibility. In this trial, we selected 124 patients (adjuvant therapy: 106 patients, salvage therapy: 18 patients) with high-risk PCa who underwent RP with or without lymphadenectomy. We defined high-risk patients as those who had at least one of the following risk factors: positive surgical margins, extra-capsular extension, seminal vesicles involvement, probability of nodal metastasis >7% (12) calculated by the Roach formula (13) after pelvic lymph node dissection with ≤13 nodes removed (14) and presence of any positive pelvic nodes. Patients with biochemical relapse, defined as an initial post-surgery serum prostate-specific antigen (PSA) level of 0.2 ng/ml or more with a second confirmatory PSA of the same value were also included (15). All patients had to be older than 18 years, have an Eastern Cooperative Oncology Group (ECOG) performance status from 0 to 1, 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, or chronic inflammatory bowel disease were excluded from the study. Complete history, medical examination, complete blood cell count, biochemistry, and serum PSA were performed before treatment. In addition, all patients underwent a pre-treatment computed tomography (CT) scan or magnetic resonance imaging (MRI) of the abdomen and pelvis and a bone scan for clinical staging. Written informed consent was obtained from each patient prior to simulation.

RT technique. The details of the IMRT-SIB technique were described in our previous report (11). In brief, the patient was simulated in a supine position with specific instructions to empty the bladder and rectum before simulation and each treatment. Oral contrast was given to outline the small bowel. A CT scan of the pelvis with 5 mm thickness per slice was performed. The PB and pelvic nodes were treated to 62.5 Gy in 2.5 Gy/fraction and 45 Gy in 1.8 Gy/fraction, respectively, with the following constraint: 95% of planning target volumes (PTV) received at least 95% of the prescribed dose (16); less than 25% of the rectum and less than 50% of the bladder received 70 Gy; less than 2% of the small intestine received 50 Gy, and less than 10% of the femoral heads received 50 Gy. The 'step and shoot' IMRT technique was used on a linear accelerator (Elekta Precise) equipped with multi leaf collimator with 40 leaf pairs 1 cm wide. Daily portal imaging and online corrections were carried out with adjustments in cases of isocenter deviations >3 mm (17).

Adjuvant hormonal therapy. Adjuvant hormonal therapy (AHT) was administered concurrently with postoperative RT. Patients were stratified according to risk category based on T stage and Gleason score (GS). Duration of AHT was 6 months and 24 months for those with pT >2 or GS=7, and pN1 or preoperative PSA >20 ng/ml or GS >7, respectively. Patients were informed about the different characteristics and side-effects of available hormonal therapies. They were then allowed to choose between the following AHT: luteinizing hormone-releasing hormone analog (leuprorelin at 3.75 mg every month or 11.25 mg every 3 months, intramuscularly) or anti-androgen agent (bicalutamide at 150 mg per os, daily).

Toxicity evaluation. Weekly evaluation of acute toxicity was performed during the treatment and then 3 weeks and 3 months after treatment according to the Radiation Therapy Oncology Group (RTOG) scale (18). Subsequently, patients underwent routine clinical examination and PSA monitoring every 6 months until the fifth year and annually thereafter. Late toxicity was evaluated with the RTOG-European Organization for Research and Treatment of Cancer-(EORTC) scale.

Statistical analysis. Statistical analysis was performed using Student's *t*-test (continuous variables) and the chi-squared test (categorical variables). Survival curves were calculated with the Kaplan–Meier method and compared with the log-rank test. Statistical analysis of data was performed using Systat, version 11.0 (Systat Software, San Jose, CA, USA).

Results

Patients characteristics. According to the study design, the trial was closed when 43 patients had a minimum follow-up of 2 years. At that time, 124 patients with PCa fulfilling the inclusion criteria were enrolled. Median follow-up was 30 months (range=13-92 months). Table I summarizes the patient characteristics. Most patients had pT3 stage (83.9%), positive surgical margins (84.7%), and high GS score (GS 7-10: 78.2%). Eighteen patients (14.5%) had relapses following RP and seven (5.6%) had pathological stage pN1 disease.

Toxicity. Acute adverse events are recorded in Table II. Only two cases (1.6%) of serious toxicities were recorded. There

Table I. *Patient characteristics*.

	Value
Age	
Median (range)	66 (45-77)
PSA pre-surgery	
Median (range)	7.6 (0.1-80.8)
PSA post-surgery	
Median (range)	0.1 (0-12.0)
Gleason score, n (%)	
6	27 (21.8%)
7	49 (39.5%)
8-10	48 (38.7%)
pT, n (%)	
2a	2 (1.6%)
2b	6 (4.8%)
2c	12 (9.7%)
3a	59 (47.6%)
3b	44 (35.5%)
4	1 (0.8%)
pN, n (%)	
0	94 (75.8%)
1	7 (5.6%)
X	23 (18.6%)
R, n (%)	
0	19 (15.3%)
1	105 (84.7%)
Hormonal adjuvant therapy, n (%)	
Type	
Not prescribed	25 (20.2%)
LH-RH analog	51 (41.1%)
Bicalutamide	48 (38.7%)
Duration	
6 Months	51 (41.1%)
24 Months	48 (38.7%)

PSA: Prostate-specific antigen; pT: patholological tumor stage; pN: pathological nodal stage; LH-RH: luteinizing hormone-releasing hormone; R: surgical margins.

Table II. *Acute toxicity*.

Type	Grade (%)				
	0	1	2	3	4
Gastrointestinal	41 (33.1%)	53 (42.7%)	30 (24.2%)	0 (0%)	0 (0%)
Genitourinary	40 (32.3%)	61 (49.2%)	22 (17.7%)	0 (0%)	1 (0,8%)
Skin	91 (73.4%)	30 (24.2%)	2 (1.6%)	1 (0.8)	0 (0%)

was one grade 3 skin toxicity (0.8%) and one grade 4 (0.8%) genitourinary (GU) toxicity. Actuarial 5-year grade 2 or more late GI and GU toxicity-free survival were 98.9% and 92.7%, respectively.

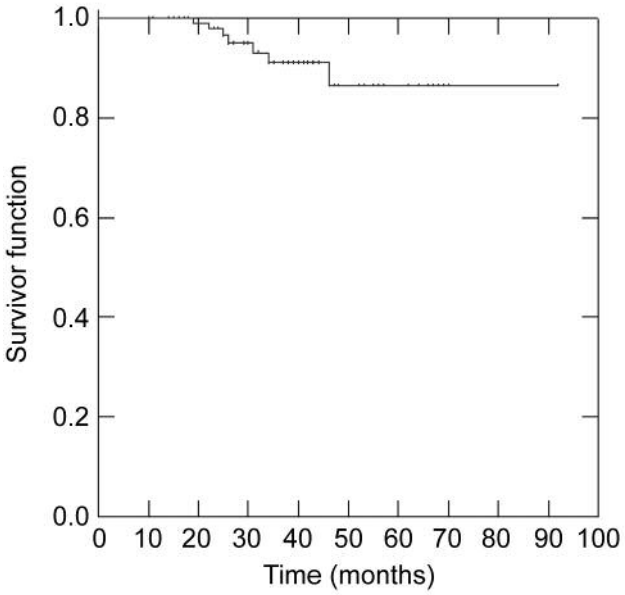

Figure 1. *Actuarial biochemical relapse-free survival*.

Biochemical and clinical control and survival. Actuarial 3-year and 5-year bRFS were 91.1% and 86.5%, respectively (Figure 1). Actuarial 5-year bRFS was 87.9% and 79.5% for adjuvant therapy and biochemical relapse respectively. Actuarial 3-year and 5-year local control and metastasis-free survival were 99.9% and 94.9%, and 98.1% and 98.1%, respectively. No patient died. On univariate analysis, no statistically significant differences were recorded in terms of bRFS. The only parameter that significantly correlated with local control was surgical margin status (Tables III and IV).

Discussion

In theory, the PCa α/β ratio is significantly lower compared to surrounding OaRs such as the bladder and bowel (10, 19, 20). Thus, we postulated that hypofractionated RT with IMRT-SIB may potentially improve the therapeutic ratio by lowering the complication rates and improving outcome in patients with high risk of recurrence following RP for prostate cancer. The primary end-point of this study was to evaluate the patient tolerance to treatment. The secondary end-point was to evaluate bRFS.

As reported in Table II, the toxicity profile was found to be favorable, with only one grade 4 acute GU toxicity and acceptable long-term toxicity. Indeed, our study corroborated the normal organ-sparing property of IMRT reported in other studies and summarized in Table V (8, 11, 21-33).

The rate of serious acute toxicity was very low in almost all studies of postoperative RT of PCa based on hypofractionated

Table III. *Impact of tumor and treatment parameters on 3- and 5-year biochemical disease-free survival rates.*

Factor	No. of patients	%	3-Year (%)	5-Year (%)	*p*-Value
pT					
2a	2	1.6	100	100	0.923
2b	6	4.8	100	100	
2c	12	9.7	80.0	80.0	
3a	59	47.6	88.6	88.6	
3b	44	35.5	95.5	84.8	
4	1	0.8	100	100	
pN 0	94	75.8	94.6	89.6	0.143
1	7	5.6	75.0	75.0	
x	23	18.6	80.4	80.4	
Margin status					
R0	19	15.3	81.2	81.2	0.071
R1	105	84.7	92.7	88	
PSA					
Pre-surgery					
0-10 ng/ml	79	63.7	93.8	93.8	0.225
10-20 ng/ml	32	25.8	82.2	82.2	
>20 ng/ml	13	10.5	100	66.7	
Post-surgery					
<0.2 ng/ml	92	74.2	92	86.3	0.203
0.2-0.5 ng/ml	20	16.1	79.1	79.1	
>0.5 ng/ml	12	9.7	100	100	
Gleasonscore					
2-6	27	21.8	92.9	92.9	0.518
7	49	39.5	87.7	73.1	
8-10	48	38.7	94.7	94.7	
Adjuvant HT					
Received					
No	25	20.2	77.2	77.2	0.105
Yes	99	79.8	95	90	
Type					
LHRH analog	51	41.1	95.8	85.2	0.268
Bicalutamide	48	38.7	94.7	94.7	
Duration					
6 Months	51	41.1	93.2	84.7	0.216
24 Months	48	38,7	97	97	
RT role					
Adjuvant	106	85.5	93.1	87.9	0.179
Salvage	18	14.5	79.5	79.5	

pT: Pathological stage; pN: pathological nodal stage; PSA: prostate-specific antigen; HT: hormonal therapy; RT: radiotherapy.

Table IV. *Impact of tumor and treatment parameters on 3- and 5-year local relapse-free survival.*

Factor	No. of patients	%	3-Year (%)	5-Year (%)	*p*-Value
pT					
2a	2	1.6	100	100	0.997
2b	6	4.8	100	100	
2c	12	9.7	100	100	
3a	59	47.6	97.9	97.9	
3b	44	35.5	100	90	
4	1	0.8	100	100	
pN 0	94	75.8	98.7	94	0.799
1	7	5.6	100	100	
x	23	18.6	100	100	
Margin status					
R0	19	15.3	92.9	92.9	0.043
R1	105	84.7	100	95.7	
PSA					
Pre-surgery					
0-10 ng/ml	79	63.7	100	100	0.144
10-20 ng/ml	32	25.8	96.4	96.4	
>20 ng/ml	13	10.5	100	66.7	
Post-surgery					
<0.2 ng/ml	92	74.2	100	94.7	0.193
0.2-0.5 ng/ml	20	16.1	92.3	92.3	
>0.5 ng/ml	12	9.7	100	100	
Gleasonscore					
2-6	27	21.8	100	100	0.647
7	49	39.5	100	85.7	
8-10	48	38.7	97.5	97.5	
Adjuvant HT					
Received					
No	25	20.2	100	100	0.512
Yes	99	79.8	98.7	94	
Type					
LHRH analog	51	41.1	100	90	0.806
Bicalutamide	48	38.7	97.3	97.3	
Duration					
6 Months	51	41.1	97.6	89.4	0.216
24 Months	48	38,7	100	100	
RT role					
Adjuvant	106	85.5	98.8	94.1	0.305
Salvage	18	14.5	100	100	

pT: Pathological stage; pN: pathological nodal stage; PSA: prostate-specific antigen; HT: hormonal therapy; RT: radiotherapy.

RT. Among three studies that reported significant toxicity, the rate of grade 3 to 4 acute GU toxicity was only 2-3% (21-23). However, there was some discrepancy in the literature about long-term toxicity. Even though most studies reported a favorable long-term safety profile, Syndikus *et al*. reported 9% and 46% rates of grade 2-4 GI and GU toxicity, respectively (24). We postulate that the use of a Cobalt machine instead of a linear accelerator and a conventional RT technique which was unable to spare the OaRs may account for excessive toxicity. Grade 2-4 long-term GI and GU toxicity ranged from 0-9% and 0-16.5% respectively in other studies. They were 1.1% and 7.3% at 5 years in our study. Thus, our long-term complication rates were comparable to those reported in the literature. The range of complication rates may reflect different dose fractionation or various technique of RT in a heterogeneous patient population.

Looking at the bRFS reported in the literature, that ranged from 72.9-85.5% at 2-3 years, our 5-year bRFS rate of 86.5% compared favorably to other studies with similar RT

Table V. *Comparison of our results with those of other non-randomized studies.*

Authors (8, 11, 21-33)	No. of pts	Treatment technique	Setting (%)		Dose range, Gy (median)	Dose per fraction, Gy (median)	Acute toxicity ≥G3(scale) (%)		Late toxicity ≥G2(scale) (%)		bRFS (%)
			Adj	Salv			GI	GU	GI	GU	
Syndikus *et al*. 1996	115	NR	77.4	22.6	PB: 50-55 (52*)	PB: 2.0-3.1 (2.76*)	NR	NR	9R/E†	$46.1^{R/E\dagger}$	NR
Lee *et al*. 2004	37	3DCRT WPRT-HTT	0	100	PB: 50-52.5	PB: 2.5-2.6	0^{R}	0^{R}	$3^{R/E\dagger}$	$0^{R/E\dagger}$	24-Month: 83 36-Month: 74
Cozzarini *et al*. 2007	23	IMRT-SIB	78.3	21.7	PB: 64.4-72, 28-33 fr PNI: 50.4-54, 28-33 fr	NE	0^{R}	0^{R}	NR	NR	NR
Cozzarini *et al*. 2008	50	IMRT	100	0	PB: 58	PB: 2.9	0^{R}	2^{R}	$0^{R/E}$	$12^{R/E}$	NR
Wong *et al*. 2008	50	IMRT	100	0	PB: 65-70 PNI: 54-56	PB: 2.5 PNI: 2	0^{R}	0^{R}	2-Year: $4^{R/E\ddagger}$	2-Year: $4^{R/E}$	24-Month: 72.9
Alongi *et al*. 2009	43	IMRT	NR	NR	PB: 64.4-70 PNI: 50.4-54	PB: 2.2-2.6 (2.35) PNI: 1.8-2 (1.85)	0^{R}	0^{R}	NR	NR	NR
Kruser J *et al*. 2011	108	IMRT	0	100	PB: 65-70 PNI: 52-56 (14 pts)	PB: 2.5 PNI: 2	0^{R}	1^{R}	$4^{\dagger R/E}$	$15^{R/E\dagger}$	NR
Koukourakis M *et al*. 2012	48	IMRT 3DCRT	43.8	56.2	PB: 51 PNI: 37.8	PB: 3.4 PNI: 2.7	0^{C}	0^{C}	$0^{C/E\dagger}$	$0^{C/E\dagger}$	41-Month: 85.4
Alongi *et al*. 2013	39	VMAT	76.9	23.1	PB: 70-71.4 (70)	2.5-2.55	0^{R}	0^{R}	$0^{R/E\dagger}$	$11^{R/E\dagger}$	NR
Ippolito *et al*. 2013	25	IMRT-SIB	100	0	PB: 56.8, 59.7, 61.25, $62.5^{\$}$, PNI: 45	PB: 2.27, 2.39, 2.45, 2.5, PNI: 1.8	0^{R}	0^{R}	NR	NR	NR
Massaccesi *et al*. 2013	49	IMRT-SIB	79.6	20.4	PB: 62.5 PNI: 45	PB: 2.5 PNI: 1.8	0^{R}	2^{R}	NR	NR	NR
Cozzarini *et al*. 2014	247	IMRT-SIB	67.6	32.4	PB: 65.8-72.8 (71.4) PNI: 50-52	PB: 2.5-2.9 (2.5)	NR	NR	NR	5-Year: $16.5^{C4\S}$	NR
Katayama S *et al*. 2014	39	IMRT	28.2	71.8	PB: 54	PB: 3	0^{C4}	0^{C4}	NR	NR	NR
Gladwish A *et al*. 2015	30	IMRT	13.3	86.7	PB: 51	PB: 3	0^{C3}	3^{C3}	2-Year: 6C3	2-Year: 6C3	24-Month: 83
Lewis SL *et al*. 2016	56	IMRT	23.2	76.8	PB: 57.5-65 (65)	PB: 2.5	0^{C4}	0^{C4}	$0^{C4\dagger}$	$66^{C4\dagger}$	NR
Current series	124	IMRT-SIB	85.5	14.5	PB: 62.5 PNI: 45	PB: 2.5 PNI: 1.8	0^{R}	0.8^{R}	3-Year: 1.1 5-Year: $1.1^{R/E}$	3-Year: 7.3 5-Year: $7.3^{R/E}$	24-Month: 96.5 36-Month: 91.1 60-Month: 86.5

3DCRT: 3D Conformal radiotherapy, BRFS: biochemical relapse-free survival, [C]: Common Terminology Criteria for Adverse Events, [E]: European Organization for Research and Treatment of Cancer, G: grade, GI: gastrointestinal, GU: genitourinary, IMRT: intensity-modulated radiotherapy, NE: not evaluable, NR: not reported, PB: prostate bed, PNI: prophylactic nodal irradiation, pts: patients, [R]: Radiation Therapy Oncology Group, SIB: simultaneous integrated boost, VMAT: volumetric-modulated arc therapy. *Mean, †crude, ‡R/E modified, $dose escalation, §G3/G4 toxicity.

technique. In addition, our bRFS was significantly improved compared to those reported in the previous three randomized studies using the conventional RT technique. Thus, despite a population of patients at high risk for recurrence, we achieved a significant improvement in bRFS while shortening the treatment time, which may be both cost-effective and potentially improve patient QoL. We postulate that the combination of hormonal therapy with a higher radiobiological dose and selective pelvic irradiation may account for this better outcome.

Indeed, previous studies have reported a beneficial effect of AHT on survival when androgen deprivation was added to RT in patients with PCa at high risk for recurrence (34-36). Hormonal therapy may act as a radiosensitizer (synergistic effect) or may act independently of RT in inducing cancer cell apoptosis (35). In addition, systemic therapy may improve survival by reducing distant failures in patients who may have had occult metastases at the time of surgery (37).

The positive impact of a higher dose to the PB has been investigated previously. Radiation dose escalation has been reported to improve bRFS in patients at high risk of recurrence following RP for PCa and, in particular, for those who had positive surgical margins (38). Selective pelvic lymph node irradiation in patients at high risk of pelvic failure has also been reported to improve bRFS compared to prostate irradiation alone (39). Thus, the use of an intensified treatment may have accounted for a reduction of distant metastases and locoregional failures, thereby improving survival.

The superior bRFS in our study was achieved with minimal serious acute and long-term toxicity. The sharp gradient dose distribution moving away from the target with IMRT allows significant sparing of normal OAR such as the bowel and bladder (40). In addition, the SIB technique allows superior sparing of normal organs compared to the sequential boost technique with similar homogeneity (41). Thus, our study demonstrated that a hypofractionated RT regimen using IMRT-SIB provides an effective radiobiological therapeutic ratio for improving survival and simultaneously reducing complications rates.

A paradoxical result of our study was the higher local control recorded in patients with R1 resection compared to patients with R0 resection. This finding might be explained by the worse prognostic features of patients undergoing R0 compared to R1 resection: a higher percentage of stage pT3b-4 tumors (41.2% *vs*. 35.2%), lower percentage of patients receiving AHT (68.4% *vs*. 81.9%), higher percentage of salvage treatments (36.8% *vs*. 10.5%), higher percentage of patients with Gleason score >7 (47.4% *vs*. 37.1%), and higher mean postoperative PSA value (0.67±1.33 *vs*. 0.32±1.28 ng/ml).

Even though our study resulted in an excellent bRFS in patients with biochemical recurrence following RP for PCa, we plan to further improve the outcome in future prospective studies through innovative imaging such as ^{18}F-choline positron-emission tomography scan and 3T multi-parametric MRI (42). These new diagnostic technologies may be more accurate at detecting sites of recurrence compared to conventional studies such as bone or CT scan. As a result, we may be able to target residual disease effectively with IMRT and radiation dose escalation, or consider systemic therapy with/without stereotactic RT distant metastases are present at the time of relapse.

In conclusion, hypofractionated postoperative RT with IMRT-SIB provides excellent long-term bRFS with minimal rate of late complications when combined with AHT in patients at high risk of recurrence following RP for PCa. A shortened treatment time may improve patient QoL and may also be cost-effective. Further prospective studies are needed to confirm this hypothesis.

Conflicts of Interest

No actual or potential conflicts of interest exist regarding this article.

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