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ORIGINAL RESEARCH

Hypofractionated postoperative helical tomotherapy in prostate cancer: a mono-institutional report of toxicity and clinical outcomes

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Purpose: This is a mono-institutional study of acute and late toxicities and early biochemical control of a retrospective series of 75 prostate cancer patients treated with moderate postoperative hypofractionation delivered by helical tomotherapy (HT).

Patients and methods: From April 2013 to June 2017, 75 patients received adjuvant (n=37) or salvage (n=38) treatment, delivering to prostate bed a total dose of 63.8 Gy (equivalent dose in 2-Gy fractions=67.4 Gy) using 2.2 Gy fractions. Whole-pelvis irradiation was performed in 63% of cases (median dose, 49.3 Gy; range, 48–55.1 Gy). Concurrent hormonal therapy was administered in 46% of cases. Common Terminology Criteria for Adverse Events (version 4.0) was adopted for acute and late genitourinary (GU) and gastrointestinal (GI) toxicity evaluations. Biochemical progression was defined as PSA level increase of ≥0.2 or more above the postoperative radiotherapy (RT) nadir.

Results: Acute GU toxicities were as follows: G1 in 46% and G2 in 4%, detecting no G≥3 events. For GI toxicity, we recorded G1 in 36% and G2 in 18%. With a median follow-up of 30 months (range, 12–58 months), we found late toxicity G2 GI in 6.6% and G≥2 GU in 5.3%, including two patients who underwent surgical incontinence correction. Acute GI≥2 toxicity and diabetes were found to be predictive of late GI≥2 toxicity (P=0.04 and P=0.0019). Actuarial 2- and 3-year biochemical recurrence-free survivals were 88% and 73%, respectively, for the entire population.

Conclusion: In our experience, moderate hypofractionated postoperative RT with HT was feasible and safe, with reports of low incidence of toxicity and promising biochemical control rates.

Keywords: prostate neoplasm, radiotherapy, hypofractionation, adjuvant, salvage

Introduction

Prostate cancer (PC) is the most common cancer in European Union in men older than 70 years, with a higher incidence in Northern and Western Europe (>200 cases per 100,000).[1] In localized PC, radiation therapy has an important role in definitive or postoperative setting with or without androgen deprivation therapy (ADT). Three important randomized trials with long follow-up (SWOG 8794, EORTC 22911, and ARO 96–02) reported significant improvements in biochemical recurrence-free survival (bRFS) with the use of adjuvant radiotherapy compared to radical prostatectomy alone among patients with adverse pathological features.[2–4]

On the other hand, two of these randomized trials, reporting that more than 40% of patients addressed to observation after surgery will not have any recurrence after 10 years of follow-up, underline the potential risk of overtreating a subgroup of patients

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exposed to short- and long-term side effects without the evidence of a clear benefit in terms of disease control.[5,6]

In these patients, initial observation after radical prostatectomy may be the correct choice, keeping salvage radiotherapy (RT) as a useful option in case of biochemical relapse.[7]

Briganti et al[8] recently developed a predictive nomogram to recognize patients for early salvage instead of adjuvant treatment.

In patients with adverse pathological features, therefore, few prospective multicenter randomized trials are currently ongoing and evaluating the timing of postoperative treatment (early vs deferred) and the duration of hormone therapy (none vs short-term vs long-term), aiming to clarify the contrasting evidence currently available from retrospective studies with insufficient follow-up or heterogeneous population.[9,10]

Several retrospective studies investigated the potential of dose escalation in the postoperative setting, confirming the positive correlation between higher doses and bRFS rates;[11–15] however, the optimal dose still remains controversial. Based on the radiobiological properties of PC, as a tumor more sensitive to higher doses per fraction, the growth of modern RT techniques lead to the current spread of moderate and extreme hypofractionated treatments for the nonsurgical patient.[16]

However, in contrast to the definitive setting, few data are available on hypofractionated postoperative RT.

Herein, we report our preliminary results of postprostatectomy hypofractionation schedule using helical tomotherapy (HT; Accuray, Inc., Sunnyvale, CA, USA), which associates intensity modulated radiotherapy (IMRT) delivered with a helical system with an image guidance system based on daily megavoltage computed tomography (CT) scan.

Materials and methods

This is a retrospective mono-institutional analysis of 75 patients with histologically proven adenocarcinoma of the prostate undergoing moderate postoperative hypofractionated RT delivered by HT.

Adjuvant treatment, given within 6 months after surgery with PSA ≤0.2 ng/mL, was performed in the presence of adverse pathological features (extracapsular extension, invasion of seminal vesicles, positive margins, and lymph nodal involvement). Salvage therapy was delivered 6 months after surgery with PSA ≥0.2 ng/mL.

ADT was administered, according to the discretion of the referring urologist, in patients with seminal vesicle invasion, nodal involvement, Gleason Score >7, or PSA >20 ng/mL.

This study was approved by the Steering Ethical Committee Palermo 2. Written informed consent was obtained from all patients to review their medical records, as required by the institutional review board. All patients' data are confidential and anonymously recorded.

The primary aim was to report the acute and late toxicities, and the secondary endpoint was to evaluate early biochemical control.

Radiation planning and treatment

All patients underwent a 2.5 mm thickness slice CT simulation. Planning CT and treatment were performed with a full bladder (500 mL of water was given 30 minutes before the procedure) and empty rectum in a supine position with flexed legs positioned in knee and ankle devices. As organs at risk (OARs), we delineated bladder, rectum, small bowel, intestinal cavity, and femoral heads. Prostate bed and pelvic lymph nodes clinical target volumes (CTV1–CTV2) were delineated using Radiation Therapy Oncology Group consensus guidelines.[17,18] The planning target volume (PTV) 1 (PTV1) was obtained adding to CTV1 a margin of 5 mm in all directions. The CTV2 was expanded by 5–7 mm to generate PTV2. Following American Urological Association/American Society for Radiation Oncology guidelines,[19] recommending a minimum doses of 64 and 65 Gy_2 for adjuvant and salvage RTs, respectively, and assuming an α/β=1.5 Gy for PC, we adopted 2.2 Gy fractions to deliver a total dose of 63.8 Gy (equivalent dose in 2-Gy fractions [EQD_2]=67.4 Gy) to prostate bed and a median dose of 49.3 Gy (EQD_2=45.1 Gy; range, 48–55.1 Gy) in conventional fractionation (1.7–1.9 Gy/fx) to the pelvic lymph nodes using simultaneous integrated boost (SIB) technique. Pelvic lymph nodes irradiation was planned in patients with the following pathological features: pN+ and/or lymph nodal dissection <10 nodes and/or Gleason Score >8.

The dosimetric goal was to cover 95% of PTVs with at least 95% of the prescribed dose; OARs planning constraints were as follows: V56Gy ≤35% and V60Gy ≤25% for rectum, and V55Gy ≤50% and V60Gy ≤30%–35% for bladder. For the intestinal cavity, the dose was reduced as low as possible.

Inverse IMRT planning was performed using the Tomotherapy (Accuray, Inc.) planning software. Our image guided radiotherapy protocol consists of a daily megavoltage computed tomography (MVCT) considering the intrafraction variability of OARs to check setup accuracy and to assess appropriate bladder filling and rectal emptying.

Toxicity evaluation

The acute and late genitourinary (GU) and gastrointestinal (GI) radiation-related toxicities were scored according to the Common Terminology Criteria for Adverse Events (CTCAE,

version 4.0). Biochemical progression was defined as PSA level increase of ≥0.2 or more above the postoperative RT nadir.

Clinical evaluation of acute toxicity was performed weekly during the treatment and then at 40 and 90 days after the end of RT. Afterward, we evaluated the late events every 3–6 months for the first 2 years and then at biannual and annual intervals.

Statistical analyses

Frequencies and percentages are reported for GU and GI toxicities; medians and ranges were calculated for continuous variables. Statistical analyses were performed with chi-squared tests assuming $P \leq 0.05$ as statistically significant. Survival curves were generated with Kaplan–Meier method. All statistical analyses were carried out using MedCalc statistical software package, version 18.5 (Mariakerke, Belgium).

Results

From April 2013 to June 2017, 75 patients with median age of 68 years (range, 54–84 years) were treated with hypofractionated radiation therapy after prostatectomy. Patients' characteristics are summarized in Table 1. Adjuvant treatment was performed in 37 (49%) patients and salvage therapy in 38 (51%) patients. ADT was administered in 34 (46%) patients.

A total dose of 63.8 Gy (EQD_2=67.4 Gy) to prostate bed was delivered. Pelvic lymph nodes irradiation with a median dose of 49.3 Gy (range, 48–55.1 Gy) in conventional fractionation was administered in 47 (63%) patients.

All 75 patients completed the planned treatment without any interruption, with good tolerance.

Acute GU toxicities were as follows: G1 in 35 (46%) and G2 in three (4%) patients, no G≥3 events were detected; the main symptom reported was urinary tract pain, which occurred in 18 (24%) patients. For GI toxicity, we recorded G1 in 36% of patients (n=27) and G2 in 18% of patients (n=14). Most frequent GI adverse event was diarrhea in 19 (25%) cases. Table 2 presents specific acute symptoms reported according to CTCAE, version 4.0.

After a median follow-up of 30 months (range, 12–58 years), we detected G2 GI late toxicity in five (6.6%) cases; no G3 toxicity was observed, and G≥2 GU late toxicity was observed in four (5.3%) patients, consisting of two G2 late events and two G3 patients who underwent surgical incontinence correction after 24 and 36 months, respectively (Figure 1).

Also, dosimetric parameters, bladder and rectum V45 and V60, were not related to acute and late toxicity patterns, respectively. Only acute GI G2 toxicity and diabetes were found to be predictive of late GI G2 toxicity (P=0.04 and P=0.0019, respectively).

In a subgroup analysis, a higher incidence of acute GI G2 toxicity in patients who underwent whole-pelvis irradiation was observed, detecting 12 cases (25%) vs two events

Table 1 Patients' characteristics

Characteristics	Median (range) or n (%)
Age (years)	68 (54–84)
Follow-up (months)	30 (12–58)
Diabetes	
Yes	17 (23)
No	58 (77)
PSA pre-RT (ng/mL)	0.19 (0–7.03)
Gleason Score	
≤7	58 (77)
≥8	17 (23)
pT	
pT2a	1 (2)
pT2b	6 (8)
pT2c	17 (23)
pT3a	22 (29)
pT3b	27 (36)
pT4	1 (2)
pN+	
No	63 (84)
Yes	12 (16)
Surgical margins	
Negative	44 (59)
Positive	31 (41)
RT	
Adjuvant	37 (49)
Salvage	38 (51)
Pelvic nodal RT	
No	28 (37)
Yes	47 (63)
RT+ADT	
No	41 (54)
Yes	34 (46)

Abbreviations: ADT, androgen deprivation therapy; RT, radiotherapy.

Table 2 Acute GI and GU adverse events according to the CTCAE version 4.0 scale

GI symptoms	Grade 1	Grade 2	Grade 3
Tenesmus	11	8	–
Diarrhea	15	4	–
Rectal bleeding	–	1	
Hemorrhoids	1	1	–
GU symptoms	**Grade 1**	**Grade 2**	**Grade 3**
Urinary tract pain	16	2	–
Urinary frequency	8	–	–
Incontinence worsening	1	–	–
Urgency	7	1	–

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal; GU, gastrourinary.

(7%) in the prostate bed alone subgroup. Actuarial 2- and 3-year bRFSs were 88% and 73%, respectively, for the entire population (Figure 2).

We failed to find any significant correlation among pelvic RT (P=0.25), adjuvant or salvage intent (P=0.28), hormone therapy (P=0.32), and bRFS rates.

At the time of the analysis, all patients are alive except one who died because of cerebrovascular disease.

Discussion

Our clinical experience with postprostatectomy moderate hypofractionation using HT confirmed that, with this delivery technique, toxicities are quite low and similar to those observed in other hypofractionation studies in this setting.[20]

The use of hypofractionation in PC comes from the well-known evidence of the very low α/β ratio of the tumor that leads to improved tumor control using higher doses per fraction.[21,22]

As these evidences are supported by several randomized Phase III trials for the definitive patient,[23–25] few studies in literature evaluated hypo-RT in the postoperative setting, reporting favorable toxicity profiles with very low rates of G>2 toxicity (Table 3).[26–35]

Fersino et al[30] reported only one case of acute G3 urinary toxicity in their series of 125 patients (64 adjuvant and 61 salvage) treated with hypofractionated volumetric modulated arc therapy (VMAT), and at the time of final assessment, they collected no G>2 late toxicity.

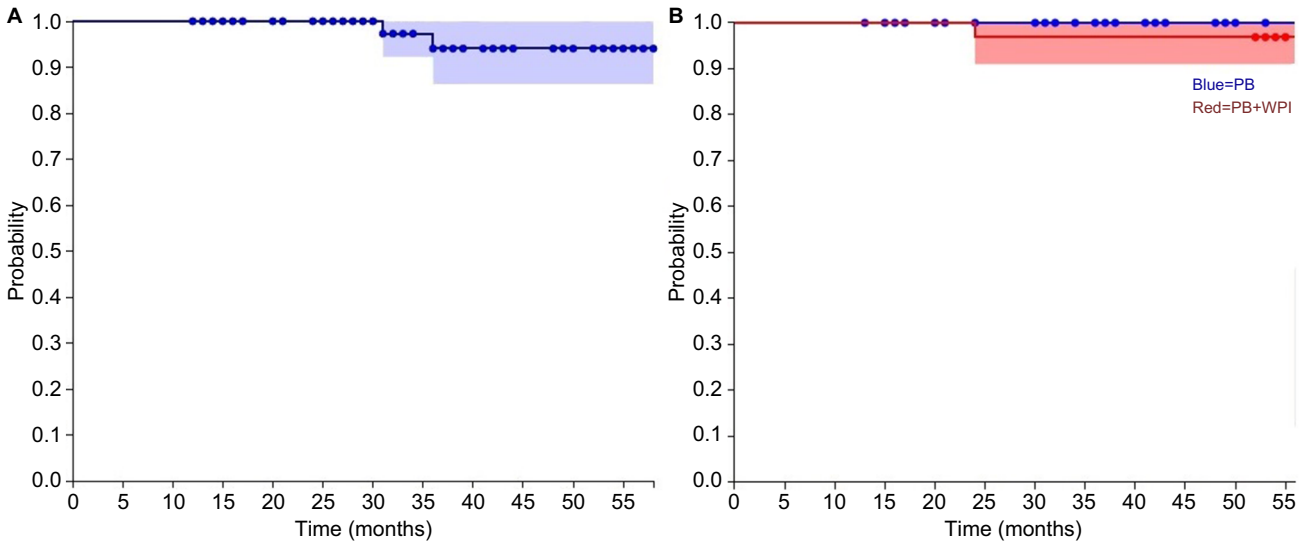

Figure 1 G3 toxicity free-survival curves for the entire population (**A**) and according to radiotherapy volumes (**B**) (prostate bed only vs prostate bed and whole-pelvis irradiation)

Abbreviations: PB, prostate bed; WPI, whole pelvis irradiation.

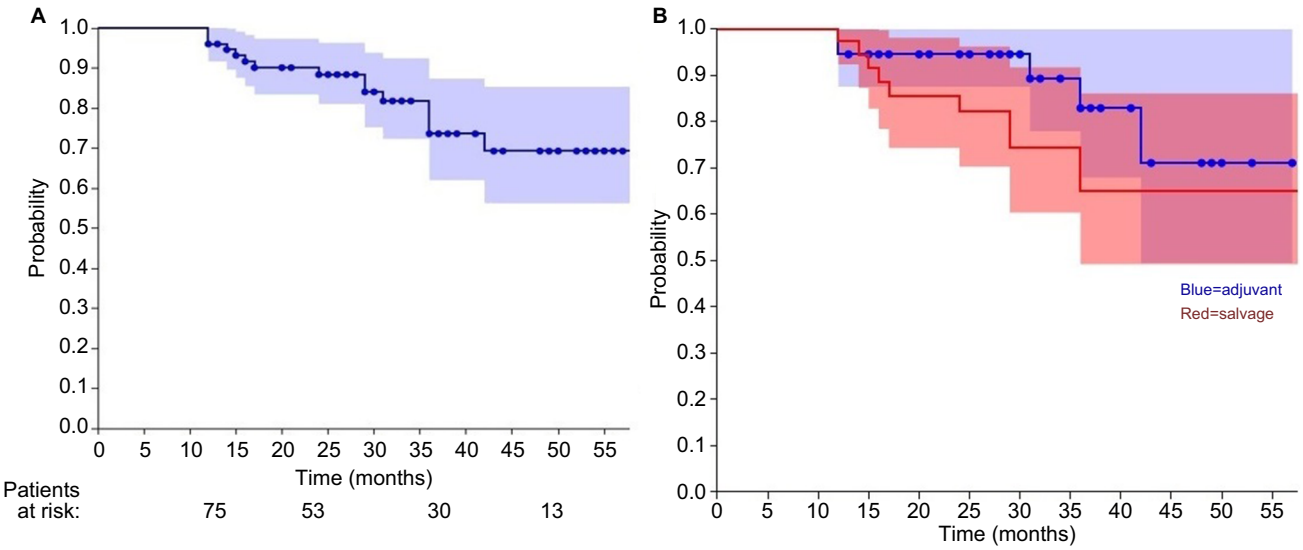

Figure 2 Biochemical relapse-free survival curves for the entire population (**A**) and stratified for adjuvant and salvage treatment (**B**).

Similar results were observed in the study by Massaccesi et al[27] in their prospective trial of postoperative IMRT to the whole pelvis (45 Gy/25fx) plus a SIB of 62.5 Gy/25fx delivered to the prostate fossa, observing no G>2 acute toxicity in their series of 49 patients.

More recently, the same RT schedule was evaluated by Macchia et al[29] who published data about 124 patients using SIB-IMRT technique with concurrent hormonal therapy; with a median follow-up of 30 months, the authors observed one case of acute G4 urinary adverse event, and 5-year GI and GU toxicity rates of 1.1% and 7.3%, respectively; therefore, they also collected very promising results in terms of biochemical control, with 2- and 3-year bRFS rates of 96.5% and 91.1%, respectively, remarking the role of IMRT in improving the radiobiological effectiveness of treatment and assuring an excellent OARs sparing.

Actually, data on the use of HT in the hypofractionation postoperative setting are limited. Katayama et al[33] in their series of 40 patients treated in the postprostatectomy setting with 54 Gy in 18 fractions delivered to prostate bed reported excellent data in terms of acute toxicity, with no G3 adverse event observed, despite a report on late side effects is currently lacking.

Kruser et al[34] reported only one G3 GU acute toxicity event, and no G3 late side effect in their series of 108 patients (59 with tomotherapy and 49 with linear accelerator-based IMRT) who underwent a hypofractionated schedule of 65 Gy/2.5 Gy/fx. Similarly, Barra et al[35] published their study on 64 patients treated with the same schedule, collecting only G1 acute GU and GI toxicities and reporting late G3 GU adverse events only in 3.3% of cases.

Also in our population, the use of HT guaranteed an acceptable tolerability, in agreement with other hypofractionation experiences in this setting.

The interpretation of these findings in the light of other published data is challenging due to differences in treatment schedules and inhomogeneity of treated population.[36]

Similar to these and other IMRT studies, in our series, there was no association between GU toxicity and clinical or dosimetric parameters, although observing GU side effects being slightly more severe than GI ones.

Delineation of target volumes may have contributed to our side effects patterns, as we adopted Radiation Therapy Oncology Group guidelines. Compared to EORTC and FROGG guidelines, Radiation Therapy Oncology Group delineates a volume of prostate bed CTV encompassing a larger volume of bladder, maintaining a significantly lower exposure of rectum and mesorectal fascia.[37,38] As reported by Ko et al,[39] the vesico-urethral anastomosis represents the most frequent site of relapse, and it must be encompassed with posterior bladder wall in prostate bed CTV, leading to high exposure of normal bladder tissue, with an increased risk both in terms of frequency and severity of acute and late GU toxicities.

With regard to GI side effects, in our series, no G3 acute or late toxicity was observed as we reported only G2 adverse events in 18% and 6%, respectively, and we found diabetes and acute GI toxicity to be predictive of late GI toxicity.

Despite the real benefit in terms of clinical outcomes is still under debate even for the definitive setting,[40,41] we decided to treat pelvic lymph nodes for patients at risk of nodal involvement still reporting a higher incidence, yet not statistically significant, of GI toxicity, compared to patients not addressed to whole-pelvis irradiation (P=0.06). This may be explained by the most frequent adoption of a safe schedule of 49.3 Gy in conventional fractionation that we mainly applied in pN0 patients but positive for other histopathological risk factors. Longobardi et al[42] reported an excellent profile of toxicity both in definitive and in postoperative setting, in their series of 178 patients who underwent whole-pelvis bed irradiation+SIB to prostate/prostate with HT.

Our favorable toxicity rates can also be related to our prescription dose. Albeit the optimal dose for prostate bed still remains controversial,[7,31,36] compared to other studies on hypofractionated postprostatectomy RT, we adopted a more conservative EQD_2 prescription (67.4 Gy_2), which allowed to reach a curative dose, maintaining a low probability of toxicity compared to the 2.5 Gy/fx schedule, which is the most reported in literature (Table 3).

Indeed, Cozzarini et al[31] investigated late toxicity patterns in a mono-institutional cohort of 247 patients treated with moderate hypofractionated HT, reporting a higher incidence of G3 urinary toxicity in the >2 Gy/fx subgroup. This is one of the largest series about late sequelae in postoperative prostate hypofractionation, with a median follow-up of 69 months and G3–4 late urinary incidence of 16.5%. Keeping in mind the different schedules adopted in this series (65.8 Gy/2.35 Gy/fx; 71.4 Gy/2.5–2.6 Gy/fx; and 58 Gy/2.9 Gy/fx). The authors explained these findings to be due to the negative effect of surgery, which does not allow the potential of bladder urothelium recovery from radiation-induced damage, resulting in a higher risk of urinary late toxicity when doses per fraction >2.55 Gy are used.[43]

Also different from the study by Cozzarini et al, we used a tighter margin of 0.5 cm from CTV to PTV, which is considered the minimum recommended when daily online image guidance is adopted.[44]

As in conventional fractionation, the use of image guided radiotherapy represents an established tool to lower

Table 3 Other hypofractionated postoperative IMRT studies

Study	Median follow-up	Patients (n)	ADT%	Fractionation schedules (Gy)	Technique	Acute TOX: GI – GU ≥G2	Late TOX: GI – GU ≥G2	bRFS
Alongi et al[26]	23	84	NR	70–71.4 Gy/2.5–2.55 Gy/fx	VMAT	GI=20% GU=10%	GI=0% GU=11%	NR
Massaccesi et al[27]	NR	49	73.4	62.5 Gy/2.5 Gy/fx	IMRT-SIB	GI=29.7% GU=9.6%	NR	NR
Lewis et al[28]	48	56	18	57.5–65 Gy/2.5 Gy/fx	IMRT	GI=4% GU=4%	GI=3.6% GU=66%	4 years: 75%
Macchia et al[29]	30	124	45	62.5 Gy/2.5 Gy/fx (WPI: 45 Gy/1.8 Gy/fx)	VMAT	GI=0% GU=0.8%	GI=1.1% GU=7.3%	3 years: 91% 5 years: 86.5%
Fersino et al[30]	18	125	NR	65.5–71.4 Gy/2.2–2.4 Gy/fx (WPI: 50.4–54 Gy/1.8–2 Gy/fx)	VMAT	GI=8.8% GU=13.6%	GI=8% GU=12%	3 years: 94% (adj) 77% (sal)
Cozzarini et al[31]	98	247	54	58–72.8 Gy/2.35–2.9 Gy/fx (WPI: 50–52 Gy/1.8 Gy/fx)	HT	GI=4% GU=12%	GI=NR GU=18.5%	NR
Wong et al[32]	19	50	8	65–70 Gy/2.5 Gy/fx (WPI: 54–56 Gy/2 Gy/fx)	HT	GI=2% GU=8%	GI=4% GU=4%	2 years: 72.9%
Katayama et al[33]	NR	39	12.8	54 Gy/3 Gy/fx	HT	GI=11% GU=10.3%	NR	NR
Kruser et al[34]	32	108	17	65–70 Gy/2.5 Gy/fx (WPI: 52–56 Gy/2 Gy/fx)	VMAT/HT	GI=14% GU=7%	GI=4% GU=15%	4 years: 67%
Barra et al[35]	15.5	64	48.4	62.5 Gy/2.5 Gy/fx (WPI: 50 Gy/2 Gy/fx)	VMAT/HT	GI=0% GU=0%	GI=0% GU=6.6%	NR
Our experience	30	75	46	63.8 Gy/2.2 Gy/fx (WPI: 48–55 Gy/1.7–1.8 Gy/fx)	HT	GI=18% GU=4%	GI=6.6% GU=5.3%	3 years: 73%

Abbreviations: ADT, androgen deprivation therapy; ART, adjuvant radiotherapy; bRFS, biochemical recurrence-free survival; CTCAE, Common Terminology Criteria for Adverse Events; CTV, clinical target volume; GI, gastrointestinal; GU, genitourinary; HT, helical tomotherapy; MVCT, megavoltage computed tomography; OAR, organ at risk; PC, prostate cancer; PTV, planning target volume; SIB, simultaneous integrated boost; TOX, toxicity; VMAT, volumetric modulated arc therapy ; IMRT, intensity modulated radiotherapy; NR, not reported; WPI, whole pelvis irradiation.

toxicity rates in the postoperative setting as it allows a more precise coverage of the target, minimizing OARs exposure, with a remarkable improvement of the therapeutic ratio.[45,46]

Consistent with these findings, at the time of the final analysis, the impact of our schedule in terms of biochemical control reflects in a 3-year bRFS of 73% rate in agreement with literature data ranging from 72.9% to 85.5% at 2–3 years[20], confirming the efficacy of our treatment schedule.

The important limitations of our study are the relatively low number of patients and short follow-up. Moreover, we lack a well-designed quality of life study.

Conclusion

Our clinical experience with moderate postoperative hypofractionation using HT confirms low toxicity rates. In addition, we found encouraging preliminary data on biochemical control. Nevertheless, a longer follow-up is required for definitive assessment of clinical outcome.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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