in vivo *36*: 1375-1382 (2022)
doi:10.21873/invivo.12841

Lower Bladder Toxicity of Salvage *Versus* Adjuvant Modern Radiotherapy for Prostate Cancer Patients

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Abstract. *Background/Aim: In prostate cancer, postoperative radiotherapy timing is debated to avoid overtreatments and toxicities. This study compared acute and late rectal and bladder toxicities in the adjuvant and salvage setting. Patients and Methods: In total, 129 patients were analyzed in two groups: adjuvant radiotherapy (aRT) and salvage radiotherapy (sRT). Results: In aRT and sRT, grade 1 (G1) acute bladder toxicities were detected in 40 and 30 patients, and grade 2 (G2) in 1 and 6; G1 late bladder toxicities were described in 30 and 20, and G2 in 6 and 2, respectively. In aRT and sRT, acute G1 rectal toxicities were reported in 18 and 27 patients, and G2 in 5 and 4, respectively. Late rectal G1 toxicities were observed in 10 patients, G2 in 6 and G3 in 1 in the aRT. In sRT, 8 patients and 1 developed G1 and G2 toxicities, respectively. Regarding bladder toxicity, a higher incidence occurred in aRT; late toxicity was lower in sRT. Conclusion: Adjuvant and salvage RT in prostate cancer treatment resulted in acceptable toxicities.*

The role of adjuvant radiotherapy (aRT) after radical prostatectomy has been previously demonstrated in three randomized trials (1-6) prescribing aRT in cases of seminal vesicles invasion (SVI), positive surgical margins (PSM) or extracapsular extension (ECE). aRT has demonstrated to obtain reductions in biochemical recurrence, local recurrence, and clinical progression (7, 8).

Postoperative salvage radiotherapy (sRT) should be proposed in cases of biochemical [prostate specific antigen (PSA) levels of 0.2 ng/ml or higher] or local recurrence. A low pretreatment serum PSA level was the most important factor of sRT response (9-11).

However, the role and timing of postoperative treatment still remains a current, debated and interesting argument, with the possibility of treatment recommendation only in recurrences, in order to avoid overtreatment. Furthermore, RT delay could reduce treatment-related toxicity, improving quality of life (12, 13). In fact, urinary incontinence and urethral stricture formation, that could occur after radical prostatectomy, could be intensified with radiotherapy (14).

Furthermore, highly conformal radiotherapy techniques, such as intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), and image guided radiotherapy (IGRT), in contrast to standard 3D-CRT, in both adjuvant and salvage settings, could reduce gastrointestinal and genitourinary adverse events (15-17).

Three randomized trials compared adjuvant and salvage treatment and suggested early salvage RT as the preferable option for avoiding overtreatment and possible side-effects, whereas aRT does not improve PSA-free survival (18-20). Also, the prospectively planned systematic review and meta-analysis of the ARTISTIC collaboration confirmed these results. This meta-analysis included 2,153 patients of the RADICALS, GETUG-AFU 17, and RAVES trials, in order to assess aRT effects *versus* those of sRT (21). The proportion of patients free of biochemical progression at 5 years was high, approximately 88% in both groups (87% in RAVES, 88% in RADICALS, and 94% in GETUG-AFU 17) (21). These results suggest that aRT does not improve event-free survival in prostate cancer patients with localized or locally advanced disease, and sRT could be considered as standard of care (21, 22).

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Key Words: Adjuvant radiotherapy, bladder and rectal toxicities, modern radiotherapy techniques, prostate cancer, salvage radiotherapy.

Considering these recent results, we decided to retrospectively analyze acute and late rectal and bladder toxicity in patients receiving adjuvant and salvage RT.

Patients and Methods

One hundred twenty-nine prostate cancer patients, treated in the postoperative setting at the Radiation Oncology Department of Chieti, were retrospectively analyzed. All patients had histologically confirmed primary adenocarcinoma of the prostate, without extra pelvic disease and staged according to the tumor node metastasis (TNM) staging system. Informed consent was obtained from all individual participants prior to treatment.

Patients were stratified into two groups: patients treated with aRT and those treated with sRT. We proposed aRT in cases of pT3, SVI, PSM or ECE. aRT was prescribed within 6 months after radical prostatectomy, whereas sRT was recommended for biochemical failure of a postoperative PSA≥0.2 ng/ml.

The planning computed tomography (CT) scan was performed with 3-mm slices, with the patient in the supine position, using a leg immobilization system, with a controlled bladder filling and an empty rectum using an enema.

The clinical target volume (CTV) was limited to the prostatic bed including the original site of the seminal vesicles, according to the European Organisation for Research and Treatment of Cancer (EORTC) guidelines (23, 24). The planning treatment volume (PTV) included the CTV plus a 6 mm margin in all directions, except for 8 mm in cranio-caudal direction.

The prescribed total dose in conventional fractionation of 2 Gy/fraction, administered in five fractions weekly, was 66-72 Gy in aRT and sRT. If treated, pelvic lymph nodes were irradiated with doses of 40-50 Gy, 2 Gy/fraction, five fractions weekly. The dose was prescribed at the average of the PTV according to the International Commission of Radiation Units and Measurements recommendations. All patients in both settings were treated with IMRT or VMAT. Patient characteristics are summarized in Table I.

Acute and late toxicities were assessed according to the Radiation Therapy Oncology Group (RTOG) scale and the RTOG/EORTC late radiation scoring system (25). All patients were followed up after the end of radiotherapy every 3 months for the first year, every 6 months for the second and third years, and annually thereafter. Treatment-related toxicity, blood count and biochemical analyses examination, including PSA levels, were assessed in every follow-up visit.

Table I. *Patients and treatment characteristics in adjuvant and salvage radiotherapy.*

	Adjuvant n=65 n (%)	Salvage n=64 n (%)
Median age (range)	68 (47-78)	69 (51-81)
Surgery		
Prostatectomy	26 (40.0%)	40 (62.5%)
Prostatectomy+lymphadenectomy	39 (60.0%)	24 (37.5%)
Gleason Score		
≤6	1 (1.5%)	17 (26.6%)
=7	34 (52.3%)	30 (46.8%)
>7	30 (46.2%)	17 (26.6%)
Resection status		
R0	14 (21.5%)	37 (57.8%)
R1	51 (78.5%)	27 (42.2%)
pT		
2a	4 (6.2%)	7 (10.9%)
2b	0 (0.0%)	8 (12.6%)
2c	2 (3.1%)	30 (46.8%)
3a	32 (49.2%)	17 (26.6%)
3b	27 (41.5%)	2 (3.1%)
pN		
0	29 (44.6%)	37 (57.8%)
1	10 (15.4%)	2 (3.1%)
x	26 (40.0%)	25 (39.1%)
Neural Infiltration		
Negative	11 (16.9%)	24 (37.5%)
Positive	54 (83.1%)	40 (62.5%)
Vascular infiltration		
Negative	48 (73.8%)	51 (79.7%)
Positive	17 (26.2%)	13 (20.3%)
Lymphatic infiltration		
Negative	52 (80.0%)	52 (81.3%)
Positive	13 (20.0%)	12 (18.7%)
Time surgery-radiotherapy	5.6 months	50.4 months
Median (IQR)	(4.9-6.7)	(27.3-93.5)
Median Max PSA pre radiotherapy (Range)	0.0 (0-0)	0.5 (0.3-1.2)
Hormonal therapy	38 (58.5%)	41 (64.1%)
Arterial hypertension	18 (27.7%)	28 (43.8%)
Cardiovascular events	8 (12.3%)	11 (17.2%)

Statistical analysis. Descriptive statistics relied on median and interquartile ranges (IQR) for continuous variables and on absolute and relative frequencies for categorical variables. Differences in median were tested with the Mann-Whitney test, whereas differences in proportions were tested with the Chi-squared test. Univariable logistic regression models were fitted to test predictors of early and late toxicity. All tests were two sided. The level of significance was set at $p<0.05$. Analyses were performed using the R software environment for statistical computing and graphics (version 4.0.2).

Results

Patient population. A total of 129 prostate cancer patients were analyzed: 65 treated in the aRT and 64 in the sRT setting. The median age was 69 years (IQR=47-81 years). Proportion of patients and tumors characteristics in both settings are reported in Table I. A total of 100 patients (77.5%) were treated with VMAT and 29 patients (22.5%) with IMRT. The median total dose was 66 Gy in both settings, with a mean total dose of 66.70 Gy in aRT and 66.90 Gy in sRT. Pelvic lymph nodes were irradiated in 31 patients (24%), 22 in the aRT setting with a median dose of 46 Gy (range=40-50 Gy) and 9 in the sRT, all irradiated with 46 Gy.

In the sRT group, mean post-operative PSA was 0.3 ng/ml (SD: 0.59) with a range between 0.01 and 4.06 ng/ml; 36 patients (56.3%) had a PSA <0.2, 22 (34.6%) a PSA in a range of 0.2-1, and 6 patients (9.3%) a PSA >1. All aRT

Table II. *Acute and late bladder and rectal toxicity according to RTOG/EORTC scale in adjuvant and salvage radiotherapy.*

TOXICITY	aRT	sRT	aRT	sRT	aRT	sRT	aRT	sRT
	G0		G1		G2		G3	
Acute bladder toxicity	24 (37.0%)	28 (43.7%)	40 (61.5%)	30 (46.9%)	1 (1.5%)	6 (9.4%)	0 (0%)	0 (0%)
Late bladder toxicity	29 (44.6%)	42 (65.7%)	30 (46.2%)	20 (31.2%)	6 (9.2%)	2 (3.1%)	0 (0%)	0 (0%)
	G0		G1		G2		G3	
Acute rectal toxicity	42 (64.6%)	33 (51.6%)	18 (27.7%)	27 (42.2%)	5 (7.7%)	4 (6.2%)	0 (0%)	0 (0%)
Late rectal toxicity	48 (73.9%)	55 (85.9%)	10 (15.4%)	8 (12.5%)	6 (9.2%)	1 (1.6%)	1 (1.5%)	0 (0%)

RTOG: Radiation Therapy Oncology Group; EORTC: European Organization for Research and Treatment of Cancer; aRT: adjuvant radiotherapy; sRT: salvage radiotherapy.

patients had a pre-radiotherapy PSA <0; in the sRT setting the median maximum PSA level was 0.5 ng/ml (range=0.3-1.2 ng/ml). The time interval between surgery and the start of radiation treatment was 5.6 months (range=4.9-6.7 months) and 50.4 months (range=27.3-93.5 months), respectively, in the aRT and sRT groups.

Acute and late toxicities. Patients were assessed for acute rectal and bladder toxicities, according to the RTOG scale, within the first 3 months after the end of radiation treatment.

With a median follow-up of 22 months (IQR=11.5-35.8), late rectal and bladder toxicities were assessed with the RTOG/EORTC scale. Table II reports acute and late toxicities.

Acute grade 1 (G1) rectal toxicities were reported in 18 (27.7%) aRT patients and 27 (42.2%) sRT patients, and 5 (7.7%) and 4 (6.2%) patients developed grade 2 (G2) rectal adverse events with aRT and sRT, respectively.

Regarding late rectal toxicity, G1 was reported in 10 patients (15.4%), G2 in 6 (9.2%), and G3 in one patient (1.5%) in the aRT group. In the sRT arm, 8 patients (12.5%) and one (1.6%) patient developed G1 and G2 toxicity, respectively. G1 acute bladder toxicities were detected in 40 (61.5%) and 30 (46.9%) patients, whereas G2 toxicities were reported in 1 (1.5%) and 6 (9.4%) patients in the aRT and sRT groups, respectively. G1 late bladder toxicities were described in 30 (46.2%) and 20 (31.2%) patients and G2 toxicities were reported in 6 (9.2%) and 2 (3.1%) patients in the aRT and sRT groups, respectively.

A higher incidence of late bladder toxicity was observed in the aRT compared to that in the sRT (55.4% *versus* 34.4%, p=0.041); a similar trend, although not reaching a statistically significant difference was observed for acute bladder toxicity (63.1% *versus* 56.2%, p=0.071). In the univariate logistic regression model, sRT was associated with a lower rate of bladder late toxicity with an OR=0.42 (0.20-0.85, p=0.017). Regarding acute and late rectal toxicities, we did not observe a statistically significant difference in aRT *versus* sRT arms. Considering the prophylactic pelvis irradiation, we did not report any statistically significant higher rate of acute and late rectal and bladder toxicities in both aRT and sRT.

Discussion

We report a retrospective analysis of rectal and bladder toxicities in aRT *versus* sRT. The number of adverse events in our retrospective analyses was low, with G3 late rectal toxicity occurring only in 1 patient (1.5%) in the aRT group. As in previous studies, in our prostate cancer patients, aRT showed more acute and late rectal and bladder toxicities compared to the sRT.

The benefit of aRT in respect to the wait-and-see police has been demonstrated in three randomized trials [with the first results from two of them (1, 5) with a median follow-up of about 5 years and confirmed with a 10-years follow-up (2, 4, 6)] for patients with pT3 (R0 or R1) or pT2 (R1). There was a reduction in the risk of both local relapse and biochemical progression by approximately 20% at 5 years, reserving laterally salvage radiotherapy (1, 2, 4-6). In particular, Wiegel *et al*. demonstrated that patients benefited from immediate RT regardless of the undetectable values of PSA after radical prostatectomy (6).

Regarding toxicity, the EORTC 22911 trial on 1,005 patients obtained a cumulative incidence of late G3 toxicity at 5 years of only 4.2% (1), and late adverse events of any type and of any grade more frequent in the postoperative irradiation group than those in the wait-and-see group (10-year cumulative incidence of 70.8% *vs*. 59.7%; p=0.001) (2). The rate of toxicity on 193 patients in the aRT arm, using 3D-CRT, in the German trial (ARO 96–02/AUO AP 09/95) was low, with only one event of G3 urinary toxicity, without G4 events, and a cumulative rate of adverse bladder and rectum events in 21.9% in the aRT arm (5). The longer follow-up of about 9 years (111 months) continued to report only one event of G3

Table III. *Studies evaluating outcomes and toxicities in prostate cancer patients undergoing adjuvant and salvage radiotherapy.*

Author years	Study type	aRT	sRT	Doses	5-yr bPFS (aRT *vs.* sRT)	5-yr OS (aRT *vs.* sRT)	5-yr DFS (aRT *vs.* sRT)	Toxicity scale	Bladder toxicities ≥G2 (pts) (aRT *vs.* sRT)		Rectal toxicities ≥G2 (pts) (aRT *vs.* sRT)	
									Acute	Late	Acute	Late
RADICALS-RT Parker 2020 (18)	P	676	696	52.5 Gy (2.625 Gy/die) 66 Gy (2 Gy/die)	85% *vs.* 88% (p=0.56)	–	–	RTOG/EORTC	3%[α] (20) *vs.* <1%[α] (2)	4%[α] (24) *vs.* <1%[α] (2)	1%[α] (10) *vs.* <1%[α] (3)	1%[α] (6) *vs.* <1%[α] (2)
GETUG-AFU 17 Sargos 2020 (19)	P	212	212	66 Gy (2 Gy/die)	92% *vs.* 90% (p=0.42)	96% *vs.* 99% (5 yr)	–	RTOG/EORTC (v3)	17% (37) *vs.* 4% (9)	27% (58) *vs.* 7% (14)	11% (23) *vs.* 4% (9)	8% (17) *vs.* 5% (11)
RAVES Kneebone 2020 (20)	P	166	167	64 Gy (2 Gy/die)	86% *vs.* 89% (p=0.86)	99% *vs.* 98% (5 yr)	96% *vs.* 96% (5 yr)	CTCAE (v3)	70% (116)	*vs.* 54% (90)	14% (24)	*vs.* 10% (16)
Nath 2010 (31)	R	13	37	62-68 Gy (2 Gy/die)	–	–	–	RTOG/EORTC (v3)	14%[¥] (7)	18%[¥] (9)	8%[¥] (4)	2%[¥] (1)
Detti 2012 (28)	R	42	33	60-74 Gy (2 Gy/die)	42% *vs.* 33%	69.8 %¥	55.6%[¥]	RTOG/EORTC	1.3%* (1)	–	1.3%* (1)	–
Present study	R	65	64	66-72 Gy (2 Gy/die)	–	–	–	RTOG/EORTC	1.5% (1) *vs.* 9.4% (6)	9.2% (6) *vs.* 3.1 (2%)	7.7% (5) *vs.* 6.2% (4)	10.7% (7) *vs.* 1.6% (1)

aRT: Adjuvant radiotherapy; sRT: salvage radiotherapy; bPFS: biochemical progression-free survival; OS: overall survival; DFS: disease-free survival; pts: patients; [α]G3-4 toxicities; *only G3 toxicity; [¥]all patients; P: prospective; R: retrospective; yr: years.

urinary toxicity (6). Also, Thompson *et al*. reported adverse events more frequently in the 214 patients of the aRT arm compared to the 211 patients of the sRT arm, with a percentage of 23.8% and 11.9%, respectively, including rectal complications (3.3% *vs*. 0%), urethral strictures (17.8% *vs*. 9.5%), and urinary incontinence (6.5% *vs*. 2.8%) (26).

Nowadays, sRT is administered to patients with a biochemical recurrence, whereas aRT is preferred for patients with adverse pathological factors such as SVI, PSM, or ESE (27).

The decision to administer salvage or adjuvant RT could be guided not only by the potential benefits of treatment but also by the potential treatment toxicity delay (28).

aRT could provoke late urinary and gastrointestinal toxicity in 10-20% of patients. The SWOG trial reported proctitis and rectal bleeding in 3.2% of patients receiving aRT, urethral stricture in 17%, urinary incontinence in 6.5%, and a higher overall rate of adverse events (3). Similarly, salvage treatment caused diarrhea in 31% of patients and proctitis in 41% (29).

It is well known that both acute GI and GU toxicities, in terms of prevalence and severity, generally peak at 6 weeks into sRT, decreasing over time/after treatment (30). Furthermore, serious acute toxicity (grade >3) is uncommon in prostatic radiotherapy.

To date, there are three randomized trials comparing adjuvant *versus* salvage radiotherapy (Table III) (18-20). All trials mostly used doses of 64-66 Gy (2 Gy/die), with the GETUG-AFU 17 adding 46 Gy to the pelvic lymph nodes, when necessary. Even in our center, the prescribed dose was 66-72 Gy (2 Gy/die), with doses of 40-50 Gy in case of pelvic lymph nodes treatment. Therefore, we can compare our results with the results of these three trials, in terms of toxicity, since we used the same doses and toxicity scale [RTOG/EORTC in two of the three trials (18, 19)].

Currently, the phase III RADICALS trial randomized patients with PSA biochemical progression to early radiotherapy or to delayed treatment (18). PSA progression was defined as either two consecutive rising PSA amounts with a PSA of greater than 0.1 ng/mL, or three consecutive rising PSA amounts (18). RTOG adverse events were more commonly reported in the aRT group (676 patients) in comparison with the sRT group (696 patients), with grade 3-4 haematuria occurring in 20 (3%) patients in the aRT group compared to two (<1%) patients in the sRT group, in the first 2 years after randomisation. Beyond 2 years, grade 3-4 haematuria occurred in 4% (24 patients) and <1% (2 patients) in the aRT and sRT group, respectively. Similarly, grade 3-4 urethral stricture was more frequent in the adjuvant (6%) *vs*. salvage setting (4%) within 2 years post-randomisation. Diarrhoea, proctitis, and cystitis had low severity, with 1% of patients reporting G3 or G4 events in both groups (18).

This trial seems to suggest a policy of wait-and-see, reserving salvage RT in cases of a PSA biochemical progression, considering the higher percentage of adverse events in the aRT group (18).

The GETUG-AFU 17 phase III trial arrived at the same conclusion in 424 patients, reporting RTOG/EORTC acute genitourinary adverse events of grade ≥2 in 17% and 4% in the aRT and sRT group ($p<0.0001$), respectively, and gastrointestinal events in 11% and 4% in the aRT and sRT group ($p=0.010$), respectively. Late grade ≥2 genitourinary adverse events were reported in 27% and 7% in the aRT and sRT group ($p<0.0001$) respectively, including urinary incontinence, urinary frequency, and haematuria. Without a statistical significance ($p=0.24$), late grade ≥2 gastrointestinal toxicities occurred in 8% and 5% in the aRT and sRT, respectively (19). Similarly, we did not reach a statistical significance in both acute and late rectal toxicities, reaching a G2 acute rectal adverse event in 7.7% and 6.2% in the aRT and sRT, respectively ($p=0.22$). Regarding late rectal toxicities, we reported a 9.2% of G2 and 1.5% of G3 in the aRT group, and 1.6% of G2 in the sRT arm ($p=0.15$).

Similar results of higher toxicity in the aRT group were obtained in the RAVES trial with a total of 333 patients, 166 randomly assigned in the aRT group, and 167 in the sRT group. With a median follow-up of 6.1 years, CTCAE G2 or worse genitourinary toxicity rate was lower in the sRT group (90 patients, 54%) than that in the aRT group (116 patients, 70%). The G2 or worse gastrointestinal toxicity rate was similar between the two groups: 10% (16 patients) and 14% (24 patients) in the sRT and aRT, respectively (20).

Even with a shorter follow-up, in our retrospective analyses, as in the previous studies, a higher incidence of late bladder toxicity was observed in the aRT compared to that in the sRT (55.4% *versus* 34.4%, $p=0.041$); a similar trend, although not reaching a statistically significant difference, was observed for acute bladder toxicity (63.1% *versus* 56.2%, $p=0.071$).

The prospectively planned systematic review and meta-analyses of the ARTISTIC collaboration was performed before the results of the RADICALS, GETUG-AFU 17, and RAVES trials were known. The aim of these meta-analyses was to assess aRT (performed 6 months after surgery) *vs*. sRT effects (21), with the primary outcome of event-free survival. The RAVES trial was the only one designed to assess whether sRT was non-inferior to aRT in terms of biochemical progression. The risk of bias was defined as low for the three trials. All three trials recruited localized or locally advanced prostate cancer patients (pT3-4 or pT3-4a and R1 or pT2-3). All patients were treated with doses of 64-66 Gy (2 Gy/die) with the possibility of 52.5 Gy (2.625 Gy/die) in the RADICALS.

The proportion of patients free of biochemical progression at 5 years was high: 87% in RAVES, 88% in RADICALS, and 94% in GETUG-AFU 17 trial (21). The meta-analysis reported an event-free survival of 88% at 5 years, that corresponded to a 1% absolute difference between early sRT and aRT at 5 years. Furthermore, there was no evidence to suggest that event-free survival following aRT depended on pre-surgical PSA, Gleason score, SVI and surgical margins. It was not possible to evaluate the effects of hormone therapy on event-free survival, nor the effect of RT timing in node-positive patients. The subgroups analyses of the ARTISTIC study had low power considering the low event rate overall and did not show a benefit from aRT in the different subgroups.

On the other hand, all three trials reported higher adverse events in the aRT setting, with increased urinary morbidity (RADICALS-RT), G2 or greater genito-urinary toxicity (RAVES) and G2 or greater late genito-urinary toxicity and erectile dysfunction (GETUG-AFU 17).

Our study, using VMAT and IMRT techniques, reported low adverse events, with 1.5% patients suffering G3 late rectal toxicity only in the aRT group. Similar rate of low toxicity was observed in a retrospective analysis of 50 patients treated with adjuvant or salvage RT with IMRT techniques, and median dose of 68 Gy (range=62-68 Gy). No G3 or higher acute GI or GU toxicities were observed; late G2 GI and GU events occurred in 1 (2%) and 8 patients (16%), respectively. Only a single (2%) G3 or higher late toxicity was observed (31).

A low rate of toxicity was also observed by Detti *et al*. in 307 patients: only one patient, receiving conventional high-dose radiotherapy (mean total dose of 66.7 Gy, range=60-74 Gy), suffered G3 acute urinary and rectal toxicity, with no cases of acute grade 4 urinary and bowel toxicity (28).

Instead, a higher percentage of acute GI and GU G2 toxicities (24.2% and 17.7%) occurred in a population of 124 patients, treated with hypofractionated RT (62.5 Gy to the prostate bed and 45 Gy to the pelvic nodes) after radical prostatectomy using simultaneous integrated boost IMRT. Grade 4 GU toxicity was reported only in a patient (0.8%) (32).

Surely, dose constraints investigation could be an interesting evaluation, in order to reduce GI and GU adverse events, as examined in 86 patients reporting a 5-year cumulative rate of 18% and 7% for hematuria and rectal hemorrhage (33). Furthermore, a retrospective analysis comparing five different RT methods, high-dose-rate brachytherapy (HDR-BT), low-dose-rate (LDR-BT), external-beam RT, including conventionally fractionated RT, moderate-hypofractionated RT, and ultra-hypofractionated RT (UHRT), concluded that toxicities were slightly lower with HDR-BT. The cumulative incidence of late GU grade≥2 toxicities was the highest with UHRT and significantly higher with UHRT than with HDR-BT ($p=0.005$). Higher symptom score peaks were noted 4 weeks after therapy with LDR-BT than those after external beam radiation therapy (34).

Bladder toxicity was well described in a retrospective study evaluating also possible correlations between toxicity

and age or cardiovascular disease. With a longer follow-up period (99 months), which allowed investigation of long-term urinary effects in 742 patients, G2 or greater acute toxicity was observed in 19% of patients, with 19% and 17% in the adjuvant and salvage cohorts, respectively. The incidence of acute G3 toxicity was 8% overall, with a risk almost identical in the aRT and sRT setting (8% and 6%, respectively) (35). Older age and greater radiation doses resulted in worse toxicity profiles (35). A phase III trial is necessary to address the question of optimal dose for sRT.

Our study has some limitations. First, it is a retrospective study with a small number of patients. Second, the study does not provide a dose–volume histogram for organs at risk, such as the bladder and rectum. Thus, the possible potential correlation between the dosimetric parameters of the normal organs and radiation toxicity was not examined. Third, the median follow-up of our study was 22 months; it can thus be considered too short to permit an accurate estimation of the late toxicity incidence.

Despite these limitations, we provide preliminary results regarding acute and late rectal and bladder toxicities in the adjuvant *versus* salvage treatment setting. Furthermore, with a longer follow-up, we would have confirmed the promising results of offering early sRT as an alternative of aRT, in order to avoid or postpone possible adverse events. We could also have evaluated event-free survival, confirming the good outcomes of a salvage treatment.

In conclusion, adjuvant and salvage RT were well-tolerated, with acceptable toxicity in both arms. However, aRT does not improve event-free survival compared to early sRT in prostate cancer patients with localized or locally advanced disease. Consequently, with the possibility of avoiding or postponing RT and its possible side effects, early sRT should be considered as a treatment option.

Conflicts of Interest

The Authors declare that they have no conflicts of interest regarding this study.

Authors' Contributions

AV, AA, CR, DG and LC designed and coordinated the study and the analysis. CR, DF, MB and VM collected the data. AV and AA reviewed and approved data selection. CR, DF and MB performed the main data analysis. CR, DF and MB drafted the article. MM and MDN performed statistical data analysis. AV, AA, DG and LC critically revised the study and the article. All Authors reviewed and approved the final article.

References

1 Bolla M, van Poppel H, Collette L, van Cangh P, Vekemans K, Da Pozzo L, de Reijke TM, Verbaeys A, Bosset JF, van Velthoven R, Maréchal JM, Scalliet P, Haustermans K, Piérart M and European Organization for Research and Treatment of Cancer: Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet *366(9485)*: 572-578, 2005. PMID: 16099293. DOI: 10.1016/S0140-6736(05)67101-2

2 Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, Verbaeys A, Bosset JF, van Velthoven R, Colombel M, van de Beek C, Verhagen P, van den Bergh A, Sternberg C, Gasser T, van Tienhoven G, Scalliet P, Haustermans K, Collette L and European Organisation for Research and Treatment of Cancer, Radiation Oncology and Genito-Urinary Groups: Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet *380(9858)*: 2018-2027, 2012. PMID: 23084481. DOI: 10.1016/S0140-6736(12)61253-7

3 Swanson G, Thompson I, Tangen C, Miller G, Lucia M, Troyer D, Paradelo J, Chin J, Messing E, Canby-higano E, Forman J and Crawford D: Phase III randomized study of adjuvant radiation therapy *versus* observation in patients with pathologic T3 prostate cancer (SWOG 8794). International Journal of Radiation Oncology*Biology*Physics *63*: S1, 2019. DOI: 10.1016/j.ijrobp.2005.07.007

4 Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, Messing E, Forman J, Chin J, Swanson G, Canby-Hagino E and Crawford ED: Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol *181(3)*: 956-962, 2009. PMID: 19167731. DOI: 10.1016/j.juro.2008.11.032

5 Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Störkel S, Willich N, Semjonow A, Souchon R, Stöckle M, Rübe C, Weissbach L, Althaus P, Rebmann U, Kälble T, Feldmann HJ, Wirth M, Hinke A, Hinkelbein W and Miller K: Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol *27(18)*: 2924-2930, 2009. PMID: 19433689. DOI: 10.1200/JCO.2008.18.9563

6 Wiegel T, Bartkowiak D, Bottke D, Bronner C, Steiner U, Siegmann A, Golz R, Störkel S, Willich N, Semjonow A, Stöckle M, Rübe C, Rebmann U, Kälble T, Feldmann HJ, Wirth M, Hofmann R, Engenhart-Cabillic R, Hinke A, Hinkelbein W and Miller K: Adjuvant radiotherapy *versus* wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. Eur Urol *66(2)*: 243-250, 2014. PMID: 24680359. DOI: 10.1016/j.eururo.2014.03.011

7 Thompson IM, Valicenti RK, Albertsen P, Davis BJ, Goldenberg SL, Hahn C, Klein E, Michalski J, Roach M, Sartor O, Wolf JS Jr and Faraday MM: Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. J Urol *190(2)*: 441-449, 2013. PMID: 23707439. DOI: 10.1016/j.juro.2013.05.032

8 Valicenti RK, Thompson I Jr, Albertsen P, Davis BJ, Goldenberg SL, Wolf JS, Sartor O, Klein E, Hahn C, Michalski J, Roach M 3rd, Faraday MM and American Society for Radiation Oncology/American Urological Association: Adjuvant and salvage radiation therapy after prostatectomy: American Society for Radiation Oncology/American Urological Association guidelines. Int J Radiat Oncol Biol Phys *86(5)*: 822-828, 2013. PMID: 23845839. DOI: 10.1016/j.ijrobp.2013.05.029

9 Briganti A, Wiegel T, Joniau S, Cozzarini C, Bianchi M, Sun M, Tombal B, Haustermans K, Budiharto T, Hinkelbein W, Di Muzio N, Karakiewicz PI, Montorsi F and Van Poppel H: Early salvage radiation therapy does not compromise cancer control in patients with pT3N0 prostate cancer after radical prostatectomy: results of a match-controlled multi-institutional analysis. Eur Urol *62(3)*: 472-487, 2012. PMID: 22633803. DOI: 10.1016/j.eururo.2012.04.056

10 Stephenson AJ, Shariat SF, Zelefsky MJ, Kattan MW, Butler EB, Teh BS, Klein EA, Kupelian PA, Roehrborn CG, Pistenmaa DA, Pacholke HD, Liauw SL, Katz MS, Leibel SA, Scardino PT and Slawin KM: Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. JAMA *291(11)*: 1325-1332, 2004. PMID: 15026399. DOI: 10.1001/jama.291.11.1325

11 Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, Anscher MS, Michalski JM, Sandler HM, Lin DW, Forman JD, Zelefsky MJ, Kestin LL, Roehrborn CG, Catton CN, DeWeese TL, Liauw SL, Valicenti RK, Kuban DA and Pollack A: Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol *25(15)*: 2035-2041, 2007. PMID: 17513807. DOI: 10.1200/JCO.2006.08.9607

12 Suardi N, Gallina A, Lista G, Gandaglia G, Abdollah F, Capitanio U, Dell'Oglio P, Nini A, Salonia A, Montorsi F and Briganti A: Impact of adjuvant radiation therapy on urinary continence recovery after radical prostatectomy. Eur Urol *65(3)*: 546-551, 2014. PMID: 23415377. DOI: 10.1016/j.eururo.2013.01.027

13 Sineshaw HM, Gray PJ, Efstathiou JA and Jemal A: Declining use of radiotherapy for adverse features after radical prostatectomy: results from the National Cancer Data Base. Eur Urol *68(5)*: 768-774, 2015. PMID: 25896124. DOI: 10.1016/j.eururo.2015.04.003

14 Choo R, Pearse M, Danjoux C, Gardner S, Morton G, Szumacher E, Loblaw DA and Cheung P: Analysis of gastrointestinal and genitourinary morbidity of postoperative radiotherapy for pathologic T3 disease or positive surgical margins after radical prostatectomy using national cancer institute expanded common toxicity criteria. Int J Radiat Oncol Biol Phys *72(4)*: 989-995, 2008. PMID: 18436391. DOI: 10.1016/j.ijrobp.2008.02.044

15 Murray JR, McNair HA and Dearnaley DP: Rationale and development of image-guided intensity-modulated radiotherapy post-prostatectomy: the present standard of care? Cancer Manag Res *7*: 331-344, 2015. PMID: 26635484. DOI: 10.2147/CMAR.S51955

16 Berlin A, Cho E, Kong V, Howell KJ, Lao B, Craig T, Bayley A, Chung P, Gospodarowicz M, Warde P, Catton C, Bristow RG and Ménard C: Phase 2 trial of guideline-based postoperative image guided intensity modulated radiation therapy for prostate cancer: Toxicity, biochemical, and patient-reported health-related quality-of-life outcomes. Pract Radiat Oncol *5(5)*: e473-e482, 2015. PMID: 25899220. DOI: 10.1016/j.prro.2015.02.015

17 De Bari B, Fiorentino A, Arcangeli S, Franco P, D'Angelillo RM and Alongi F: From radiobiology to technology: what is changing in radiotherapy for prostate cancer. Expert Rev Anticancer Ther *14(5)*: 553-564, 2014. PMID: 24579695. DOI: 10.1586/14737140.2014.883282

18 Parker CC, Clarke NW, Cook AD, Kynaston HG, Petersen PM, Catton C, Cross W, Logue J, Parulekar W, Payne H, Persad R, Pickering H, Saad F, Anderson J, Bahl A, Bottomley D, Brasso K, Chahal R, Cooke PW, Eddy B, Gibbs S, Goh C, Gujral S, Heath C, Henderson A, Jaganathan R, Jakobsen H, James ND, Kanaga Sundaram S, Lees K, Lester J, Lindberg H, Money-Kyrle J, Morris S, O'Sullivan J, Ostler P, Owen L, Patel P, Pope A, Popert R, Raman R, Røder MA, Sayers I, Simms M, Wilson J, Zarkar A, Parmar MKB and Sydes MR: Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. Lancet *396(10260)*: 1413-1421, 2020. PMID: 33002429. DOI: 10.1016/S0140-6736(20)31553-1

19 Sargos P, Chabaud S, Latorzeff I, Magné N, Benyoucef A, Supiot S, Pasquier D, Abdiche MS, Gilliot O, Graff-Cailleaud P, Silva M, Bergerot P, Baumann P, Belkacemi Y, Azria D, Brihoum M, Soulié M and Richaud P: Adjuvant radiotherapy *versus* early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial. Lancet Oncol *21(10)*: 1341-1352, 2020. PMID: 33002438. DOI: 10.1016/S1470-2045(20)30454-X

20 Kneebone A, Fraser-Browne C, Duchesne GM, Fisher R, Frydenberg M, Herschtal A, Williams SG, Brown C, Delprado W, Haworth A, Joseph DJ, Martin JM, Matthews JHL, Millar JL, Sidhom M, Spry N, Tang CI, Turner S, Wiltshire KL, Woo HH, Davis ID, Lim TS and Pearse M: Adjuvant radiotherapy *versus* early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. Lancet Oncol *21(10)*: 1331-1340, 2020. PMID: 33002437. DOI: 10.1016/S1470-2045(20)30456-3

21 Vale CL, Fisher D, Kneebone A, Parker C, Pearse M, Richaud P, Sargos P, Sydes MR, Brawley C, Brihoum M, Brown C, Chabaud S, Cook A, Forcat S, Fraser-Browne C, Latorzeff I, Parmar MKB, Tierney JF and ARTISTIC Meta-analysis Group: Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. Lancet *396(10260)*: 1422-1431, 2020. PMID: 33002431. DOI: 10.1016/S0140-6736(20)31952-8

22 Sachdev S, Carroll P, Sandler H, Nguyen PL, Wafford E, Auffenberg G, Schaeffer E, Roach M 3rd, Evans CP and Hussain M: Assessment of postprostatectomy radiotherapy as adjuvant or salvage therapy in patients with prostate cancer: a systematic review. JAMA Oncol *6(11)*: 1793-1800, 2020. PMID: 32852528. DOI: 10.1001/jamaoncol.2020.2832

23 Poortmans P, Bossi A, Vandeputte K, Bosset M, Miralbell R, Maingon P, Boehmer D, Budiharto T, Symon Z, van den Bergh AC, Scrase C, Van Poppel H, Bolla M and EORTC Radiation Oncology Group: Guidelines for target volume definition in post-operative radiotherapy for prostate cancer, on behalf of the EORTC Radiation Oncology Group. Radiother Oncol *84(2)*: 121-127, 2007. PMID: 17706307. DOI: 10.1016/j.radonc.2007.07.017

24 Michalski JM, Lawton C, El Naqa I, Ritter M, O'Meara E, Seider MJ, Lee WR, Rosenthal SA, Pisansky T, Catton C, Valicenti RK, Zietman AL, Bosch WR, Sandler H, Buyyounouski MK and Ménard C: Development of RTOG consensus guidelines for the definition of the clinical target volume for postoperative conformal radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys *76(2)*: 361-368, 2010. PMID: 19394158. DOI: 10.1016/j.ijrobp.2009.02.006

25 Cox JD, Stetz J and Pajak TF: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization

for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys *31(5)*: 1341-1346, 1995. PMID: 7713792. DOI: 10.1016/0360-3016(95)00060-C

26 Thompson IM Jr, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, Messing E, Forman J, Chin J, Swanson G, Canby-Hagino E and Crawford ED: Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA *296(19)*: 2329-2335, 2006. PMID: 17105795. DOI: 10.1001/jama.296.19.2329

27 King CR: Adjuvant *versus* salvage radiotherapy for high-risk prostate cancer patients. Semin Radiat Oncol *23(3)*: 215-221, 2013. PMID: 23763888. DOI: 10.1016/j.semradonc.2013.01.009

28 Detti B, Scoccianti S, Cassani S, Cipressi S, Villari D, Lapini A, Saieva C, Cai T, Pertici M, Giacomelli I, Livi L, Ceroti M, Nicita G, Carini M and Biti G: Adjuvant and salvage radiotherapy after prostatectomy: outcome analysis of 307 patients with prostate cancer. J Cancer Res Clin Oncol *139(1)*: 147-157, 2013. PMID: 22986810. DOI: 10.1007/s00432-012-1309-9

29 Jung C, Cookson MS, Chang SS, Smith JA Jr, Dietrich MS and Teng M: Toxicity following high-dose salvage radiotherapy after radical prostatectomy. BJU Int *99(3)*: 529-533, 2007. PMID: 17155969. DOI: 10.1111/j.1464-410X.2006.06661.x

30 Pearse M, Choo R, Danjoux C, Gardner S, Morton G, Szumacher E, Loblaw A and Cheung P: Prospective assessment of gastrointestinal and genitourinary toxicity of salvage radiotherapy for patients with prostate-specific antigen relapse or local recurrence after radical prostatectomy. Int J Radiat Oncol Biol Phys *72(3)*: 792-798, 2008. PMID: 18707818. DOI: 10.1016/j.ijrobp.2008.05.063

31 Nath SK, Sandhu AP, Rose BS, Simpson DR, Nobiensky PD, Wang JZ, Millard F, Kane CJ, Parsons JK and Mundt AJ: Toxicity analysis of postoperative image-guided intensity-modulated radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys *78(2)*: 435-441, 2010. PMID: 19939580. DOI: 10.1016/j.ijrobp.2009.08.023

32 Macchia G, Siepe G, Capocaccia I, Nguyen NP, Schiavina R, Cammelli S, Guerri S, Arcelli A, Buwenge M, Ntreta M, Cilla S, Valentini V, Deodato F and Morganti AG: Hypofractionated postoperative IMRT in prostate carcinoma: a phase I/II study. Anticancer Res *37(10)*: 5821-5828, 2017. PMID: 28982907. DOI: 10.21873/anticanres.12025

33 Shirai K, Suzuki M, Akahane K, Takahashi Y, Kawahara M, Yamada E, Wakatsuki M, Ogawa K, Takahashi S, Minato K, Hamamoto K, Saito K, Oshima M, Konishi T, Nakamura Y, Washino S and Miyagawa T: Dose-volume histogram-based predictors for hematuria and rectal hemorrhage in patients receiving radiotherapy after radical prostatectomy. In Vivo *34(3)*: 1289-1295, 2020. PMID: 32354921. DOI: 10.21873/invivo.11904

34 Ito M, Sasamura K, Takase Y, Kotsuma T, Oshima Y, Minami Y, Suzuki J, Tanaka E, Ohashi W, Oguchi M, Okuda T, Suzuki K and Yoshioka Y: Comparison of physician-recorded toxicities and patient-reported outcomes of five different radiotherapy methods for prostate cancer. Anticancer Res *41(5)*: 2523-2531, 2021. PMID: 33952480. DOI: 10.21873/anticanres.15030

35 Cozzarini C, Fiorino C, Da Pozzo LF, Alongi F, Berardi G, Bolognesi A, Briganti A, Broggi S, Deli A, Guazzoni G, Perna L, Pasetti M, Salvadori G, Montorsi F, Rigatti P and Di Muzio N: Clinical factors predicting late severe urinary toxicity after postoperative radiotherapy for prostate carcinoma: a single-institute analysis of 742 patients. Int J Radiat Oncol Biol Phys *82(1)*: 191-199, 2012. PMID: 21109361. DOI: 10.1016/j.ijrobp.2010.09.027

Received February 2, 2022
Revised February 16, 2022
Accepted February 17, 2022