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Transitioning from conformal radiotherapy to intensity-modulated radiotherapy after radical prostatectomy: Clinical benefit, oncologic outcomes and incidence of gastrointestinal and urinary toxicities

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ABSTRACT

Aim: The purpose of this study was to review genitourinary (GU) and gastrointestinal (GI) toxicity associated with high-dose radiotherapy (RT) delivered with 3-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) or volumetric arc therapy (VMAT) following radical prostatectomy (RP).
Background: RP is a therapeutic option for the management of prostate cancer (PrCa). When assessing postoperative RT techniques for PrCa, the published literature focuses on patients treated with 2-dimensional conventional methods without reflecting the implementation of 3D-CRT, IMRT, or VMAT.
Materials and methods: A total of 83 patients were included in this analysis; 30 patients received 3D-CRT, and 53 patients received IMRT/VMAT. Acute and late symptoms of the GU and lower GI tract were retrospectively graded according to the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer radiation toxicity grading systems. The relapse failure-free rate and overall survival were also evaluated.
Results: The rate of acute GU toxicity was 9.4% vs. 13.3% for the IMRT/VMAT and 3D-CRT groups ($p = 0.583$). The 5-year actuarial rates of late GI toxicity for IMRT/VMAT and 3D-CRT treatments were 1.9% and 6.7%, respectively. The rate of late GU toxicity for the IMRT/VMAT and 3D-CRT treatment groups was 7.5% and 16.6%, respectively ($p = 0.199$). We found no association between acute or late toxicity and the RT technique in univariate and multivariate analyses.
Conclusion: Postprostatectomy IMRT/VMAT and 3D-CRT achieved similar morbidity and cancer control outcomes. The clinical benefit of highly conformal techniques in this setting is unclear although formal analysis is needed.

1. Introduction

Radical prostatectomy (RP) is a therapeutic approach for the management of prostate cancer (PrCa) that provides excellent cancer control. Nonetheless, 15%–40% of patients experience biochemical recurrence (BCR) within 5 years after surgery.[1,2] Recurrence risk is greater among men with adverse pathologic features, such as positive surgical margins, seminal vesicle invasion, extraprostatic extension, and higher Gleason scores.[3–9] A difficult question is whether the administration of radiotherapy (RT) is preferred as adjuvant therapy (ART) when pathology risk factors for recurrence are present or as salvage therapy (SRT) after 2 confirmatory prostate-specific antigen (PSA) levels of >0.2 ng/mL. The use of ART involves the irradiation of patients who may never

Abbreviations: 3D-CRT, 3-dimensionalconformal radiotherapy; ADT, androgen deprivation therapy; ART, adjuvant radiotherapy; BCR, biochemical recurrence; CBCT, cone-beam computed tomography; CTV, clinical target volume; EORTC, European Organisation for Research and Treatment of Cancer; GI, gastrointestinal; GU, genitourinary; IMRT, intensity modulated radiotherapy; NCCN, National Comprehensive Cancer Network; OS, overall survival; PrCa, prostate cancer; PSA, prostate-specific antigen; RFF, relapse failure-free; RP, radical prostatectomy; RT, radiotherapy; RTOG, radiation therapy oncology group; SRT, salvage radiotherapy; VMAT, volumetric arc therapy.

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develop recurrence, exposing them to potential genitourinary (GU) and gastrointestinal (GI) effects of RT. However, SRT, when used in patients with BCR, could theoretically induce progression to metastatic disease.[10]

When assessing the RT techniques for PrCa in the postoperative setting, the published literature is largely focused on patients treated with 2-dimensional conventional methods without discussions on the implementation of 3-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), or volumetric arc therapy (VMAT). Thus, the lack of high-quality studies using newer RT techniques makes the search for optimal methods difficult.[11–14] The published literature about late side effects after treatment with image-guided IMRT, when compared to 3D-CRT, showed a reduction in Grade 2 GI toxicity (5-year IMRT, 1.9%; 5-year 3D-CRT, 10.2%; p = 0.02) without a reduction in risk of Grade 2 GU toxicity (5-year IMRT, 16.8%; 5-year 3D-CRT, 15.8%; p = 0.86). Patients who developed late Grade 2 GI or GU toxicity experienced resolution of their symptoms during the follow-up visits.[15] Hackman et al. published a randomized trial about adjuvant 3D-CRT versus no additional treatment in patients with prostatectomy and positive margins or extracapsular extension. GI and GU toxicity in most patients receiving adjuvant radiotherapy was scored as grade 1 or 2. However, they found higher grade 3 erectile dysfunction and grade 3 urinary incontinence, 9% and 6%, respectively, in patients treated with adjuvant radiotherapy.[16]

The authors believe the results of this study may be helpful to assist radiation oncologists in the decision-making process of treating PrCa patients in countries with limited access to linear accelerators and unavailability of highly conformal radiation techniques like IMRT/VMAT.

2. Aim

The purpose of this study was to review GU and GI toxicity associated with the high-dose RT delivered with 3D-CRT and IMRT/VMAT in the postprostatectomy setting. The relapse failure-free rate (RFF) and overall survival (OS) were evaluated as well.

3. Materials and methods

At our institute, we treated patients after prostatectomy with doses of 66 Gy using 3D-CRT from 2013 to 2015. Since then, we have gradually increased our dose to 70–72 Gy, which we routinely deliver using IMRT/VMAT.

3.1. Study population and treatment

We conducted an observational retrospective study of a prospectively maintained database, including all patients undergoing pelvic RT after prostatectomy between January 2014 and January 2019, inclusive. All treatments were validated by the institutional GU tumor board committee meeting before beginning the RT. Eligible patients for ART had one or more of the following pathological risk factors: capsule perforation, positive surgical margins, pN1, or invasion of seminal vesicles. SRT was offered when BCR after surgery was declared after 2 confirmatory PSA levels of >0.2 ng/mL. Ultimately, a total of 83 patients were included in this analysis. Nineteen patients were excluded because of metachronic malignancies. Patient-related characteristics including age, National Comprehensive Cancer Network (NCCN) risk classification, Gleason score, pre-treatment serum PSA values, and status of neoadjuvant and adjuvant androgen deprivation therapy (ADT) were recorded.[17] The presence of coexisting diabetes mellitus was also documented, which is a known risk factor for GI and GU toxicities.[18]

3.2. RT procedure

Contouring volumes were made according to the RTOG consensus for postoperative conformal radiation therapy for prostate cancer.[19] Clinical target volume (CTV) encompassed the prostate and the seminal vesicles surgical bed at risk of harboring microscopic disease or involved following pathological features. The planning target volume included the CTV with a 10-mm margin, except posteriorly, where a 5-mm margin was used. Both groups were subject to the same dose-volume constraints for normal tissues. For each treatment, the patient was in the supine position. Preceding each treatment session, the patient underwent a bladder and bowel preparation protocol. Bladder preparation protocol consisted in asking patients to drink fluids regularly throughout the day and maintain a daily water intake of at least 1.5 L. Patients where asked to arrive 30 min prior to their appointment, to restrict from urinating at least 1 h prior to treatment and drink 500 mL water when prompted by a radiation therapist. If the bladder was not full enough, the radiation therapist asked to drink more water. Alternatively, an overfilled bladder needed some emptying. Bowel preparation included dietary guidance provided by a nutriologist, increase in gentle physical activity and an oral laxative liquid administered one day prior to simulation scan. The intake of an 8.6-mg tablet of oral sennosides daily at night was encouraged. If the bowel was distended with gas or solid at the moment of radiation treatment, the radiation therapists asked patients to go to the toilet again to empty. Thirty patients (ART or SRT) underwent 3D-CRT with a 15-MV linear accelerator. 3D-CRT plans consisted of 6-field coplanar beams with 15-MV photons and a prescribed dose of 66 Gy in 33 fractions of 2 Gy on the surgical prostate dissection bed with daily control of the beam position by kV cone-beam computed tomography-based IGRT (CBCT). IMRT plans consisted of 5-field coplanar beams and 1 arc for VMAT plans with 6-MV photons and a dose of 70−72 Gy in 2-Gy fractions. Daily kV CBCT was obtained for both 3D-CRT and IMRT/VMAT groups with matching realized on soft tissue and surgical clips. We avoid using 10-MV or 15-MV photons for IMRT/VMAT RT planning.

3.3. Follow-up and posttreatment periods

After RT, the patients were followed in the GU tumor clinic every 3 months to check serum PSA levels and physical findings. No additional treatment was performed unless the patients developed BCR or clinical failure.

3.4. Toxicity and oncologic outcomes

Acute GU and lower GI symptoms were retrospectively graded according to the Radiation Therapy Oncology Group (RTOG) and the European Organisation for Research and Treatment of Cancer (EORTC) radiation toxicity grading in the first 90 days of RT.[18] Late bladder and large intestine toxicities were defined according to the RTOG/EORTC classification system as those occurring >90 days after initiation of RT. The frequency of acute Grade 1, 2, and higher GI and GU toxicities and the frequency of late GI and GU toxicity at 5 years after the initiation of radiation therapy were the main objectives of this analysis. The RFF rate was also evaluated.

Table 1
Characteristics of patients in the 3D-CRT group versus the IMRT/VMAT group.

Variable[a]	3D-CRT n = 30 (36.1%)	IMRT/VMATn = 53 (63.9%)	*p*-Value
Median age at surgery, years (Range)	66.5 (52–77)	67 (45–75)	0.909
Diabetes (%)			
Yes	9 (30.0)	21 (39.6)	0.381
No	21 (70.0)	32 (60.4)	
PSA before surgery (%)			
Median (Range)	8.3 (1.9–49)	10.6 (1.4–63.3)	
<10	17 (56.7)	25 (47.2)	0.147
10.1–20	10 (33.0)	13 (24.5)	
>20.1	3 (10.0)	15 (28.3)	
NCCN category risk group (%)			
Low	1 (3.33)	5 (9.4)	
Intermediate	15 (50.00)	25 (47.2)	0.587
High	14 (46.67)	23 (43.4)	
Tumoral stage (%)			
T1	5 (16.6)	5 (9.4)	
T2	14 (46.6)	24 (45.3)	0.655
T3	11 (36.7)	23 (43.4)	
T4	0	1 (1.9)	
Biopsy Gleason score (%)			
Group 1 (6)	3 (10.0)	8 (15.1)	
Group 2 (3 + 4 = 7)	7 (23.3)	20 (37.7)	
Group 3 (4 + 3 = 7)	7 (23.3)	12 (22.6)	0.090
Group 4 (8)	5 (16.7)	10 (18.9)	
Group 5 (≥9)	8 (26.7)	3 (5.7)	
Lymph Node status (%)			
Positive	0 (0.0)	3 (5.6)	0.184
Negative	30 (100.0)	50 (94.3)	
Resection status (%)			
R0	8 (26.7)	17 (32.1)	0.606
R1	22 (73.3)	36 (67.9)	
Pre-RT PSA, median (Range)	0.3 (0.1–9.9)	0.4 (0.1–3.8)	0.342
Age at Radiotherapy, years, median (Range)	68 (53–79)	69 (45–79)	0.992
Time elapsed between surgery and RT Months (Median)	9.6 (0.2–127.6)	10.1 (1.5–146.3)	0.334
Neoadjuvant hormone therapy (%)			
Yes	2 (6.7)	7 (13.2)	0.469
No	28 (93.3)	46 (86.8)	
Timing of Radiotherapy (%)			
Adjuvant	13 (43.3)	25 (47.2)	0.736
Salvage	17 (56.6)	28 (52.8)	
Treatment region (%)			
Prostate Bed	30 (100.0)	50 (94.3)	0.184
Prostate bed + whole pelvic RT	0 (0.0)	3 (5.7)	
Radiotherapy fractionation (%)			
<70 Gy	30 (100)	7 (13.2)	
>70 Gy	0 (0)	46(86.8)	**<0.001**
Post-RT relapse (%)			
Yes	5 (16.7)	2 (3.8)	**0.042**
No	25 (33.3)	51 (96.2)	
Type of relapse after RT (%)			
Biochemical	4 (13.3)	1(1.9)	0.427
Pelvic Nodal	1 (3.3)	1(1.9)	
Follow up, months (Median)	50.8 (0.22–64)	16.7 (0.03–55.3)	**<0.001**
Oncologic Outcomes (%)			
5-yr RFF	81.1	94.5	0.344
5-yr Overall survival	96.5	92.6	0.689

Abbreviations: 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; VMAT, volumetric arc therapy; PSA, prostate-specific antigen; NCCN, National Comprehensive Cancer Network; RT, radiotherapy; RFF, relapse Failure-Free.

[a] Mann–Whitney two-sample statistic used for continuous variables, Chi^2 used for categorical variables. Log-rank used for comparing survival outcomes.

3.5. Statistical analysis

The balance of baseline characteristics between the two groups was tested by the Mann–Whitney U test and Chi-square test. Multivariate regression analysis was used to evaluate the independent prognostic factors that were predefined for both acute and late toxicity. The covariates age, neoadjuvant ADT, coexisting diabetes mellitus, and treatment technique (IMRT vs. 3D-CRT) were assessed for all toxicity analyses. Acute Grade 2 toxicity was further considered in the analysis of late GI and GU toxicity. All multivariate analyses were adjusted for baseline characteristics. All tests were two-sided and considered to be statistically significant at $p < 0.05$. The Kaplan–Meier method was used to estimate the cumulative rate of late complications. For late toxicities, the toxicity-free interval was defined as the interval from the date of the last RT treatment to the date of toxicity.

4. Results

4.1. Patient and tumor characteristics

A total of 83 patients with a median age of 68 years (range, 45–79 years) were included in this study (30 receiving 3D-CRT; 53 receiving IMRT/VMAT). The median follow-up period was 4.3 years (range, 7 months–15 years) for the entire cohort, 4.2 years (0.22–64) for the 3D-CRT group, and 1.4 years (0.03–55.3) for the

Table 2
Acute Grade 2 GI toxicity.

Factor	Univariate analysis	Multivariate analysis	
	p-Value	OR	*p*-Value
Age, continuous	0.375	0.98	0.630
Diabetes, yes vs no	0.663	0.70	0.691
Treatment technique, 3D-CRT vs IMRT/VMAT	0.663	0.67	0.649

Abbreviations: OR, odds ratio; 3D-CRT, 3-dimensional conformal radiotherapy; GI, gastrointestinal; IMRT, intensity-modulated radiotherapy; VMAT: volumetric modulated arc therapy.

Table 3
Late GI toxicity.

Factor	Univariate analysis	Multivariate analysis	
	p-Value	OR	*p*-Value
Acute RTOG Grade 2 GI toxicity	0.691	9.20	0.176
Age, continuous	0.304	0.89	0.167
Diabetes, yes vs. no	0.262	7.21	0.148
Treatment technique, 3D-CRT vs IMRT/VMAT	0.262	6.27	0.792

Abbreviations: OR, odds ratio; 3D-CRT, 3-dimensional conformal radiotherapy; GI, gastrointestinal; IMRT, intensity-modulated radiotherapy; RTOG, radiation therapy oncology group; VMAT: volumetric modulated arc therapy.

Table 4
Acute GU Toxicity.

Factor	Univariate analysis	Multivariate analysis	
	p-Value	OR	*p*-Value
Age, continuous	0.578	1.02	0.618
Diabetes, yes vs no	0.044	4.23	0.060
Treatment technique, 3D-CRT vs IMRT/VMAT	0.583	1.78	0.440

Abbreviations: OR, odds ratio; 3D-CRT, 3-dimensional conformal radiotherapy; GU, genitourinary; IMRT, intensity-modulated radiotherapy; RTOG, radiation therapy oncology group; VMAT: volumetric modulated arc therapy.

Table 5
Late GU toxicity.

Factor	Univariate analysis	Multivariate analysis	
	p-Value	OR	*p*-Value
Acute RTOG Grade 2 GU Toxicity	0.421	1.89	0.072
Age, continuous	0.536	0.97	0.656
Diabetes, yes vs. no	0.098	0.27	0.235
Treatment technique, 3D-CRT vs. IMRT/VMAT	0.199	2.34	0.247

Abbreviations: OR, odds ratio; 3D-CRT, 3-dimensional conformal radiotherapy; GU, genitourinary; IMRT, intensity-modulated radiotherapy; RTOG, radiation therapy oncology group; VMAT: volumetric modulated arc therapy.

IMRT/VMAT group. The difference in follow up between groups can be explained by the date IMRT/VMAT techniques were implemented as this occurred in 2016. Patient treatment characteristics are listed in Table 1. In patients treated with SRT, the median time from prostatectomy to SRT was 26 months (range, 8 months–12 years), and in patients with ART, the median time from prostatectomy to ART was 3 months (range, 1 month–21 months). All patients treated with doses >70 Gy received IMRT/VMAT while patients treated with <70 Gy received 3D-CRT.

4.2. Treatment-related toxicity

4.2.1. GI toxicity

The overall rate of acute GI toxicity for the cohort was 8.4%, and it was not associated with treatment technique on univariate analysis (IMRT/VMAT: 9.5% vs. 3D-CRT: 6.6%; p = 0.663) (Fig. 1). Grade 2 GI adverse events were observed in 2 patients in the 3D-CRT group, and Grade 2 or higher GI adverse events were noted in 3 patients in the IMRT/VMAT group (Grade 2, n = 2; Grade 3, n = 1). For acute Grade 2 and acute Grade 3 GI toxicities, there was no association with a treatment technique on univariate analysis (IMRT/VMAT 3.8%; 3D-CRT 6.6%; p = 0.554 and IMRT/VMAT 1.9%; 3D-CRT 0%; p = 0.449, respectively) and multivariate analysis (OR 0.67; p = 0.649; Table 2).

Patients treated with IMRT/VMAT had a lower rate of late GI toxicity at 5 years than patients treated with 3D-CRT (1.9% and 6.7%, respectively). Late GI toxicity was not associated with a treatment technique on univariate and multivariate analysis (Table 3). There was no late Grade 3 GI toxicity (Fig. 2a).

4.2.2. GU toxicity

The overall rate of acute GU toxicity was 21.7%. The rate of acute GU toxicity was not associated with a treatment technique on univariate analysis (9.4% vs. 13.3%; p = 0.583 for IMRT/VMAT and 3D-CRT, respectively) and multivariate analysis (OR 1.77; p = 0.440). Five patients had Grade 2 adverse events, and 1 patient had Grade 3 toxicity, 4 patients were in the 3D-CRT group, and 2 patients were in the IMRT group. The rate of acute Grade 2 acute GU toxicity was not associated with a treatment technique on univariate analysis (IMRT/VMAT 3.8%; 3D-CRT 10%; p = 0.252), the rate of acute Grade 3 GU toxicity was not associated with a treatment technique on univariate analysis, either (IMRT/VMAT 0%; 3D-CRT 3.3%; p = 0.181; Table 4). For multivariate analysis, acute Grade 2 toxicity was not associated with a treatment technique (OR 3.9, p = 0.174; Fig. 1).

The overall rate of late GU toxicity was 10.84%. The rate of late GU toxicity was not associated with a treatment technique on univariate analysis (7.5% vs. 16.6%, p = 0.199 for IMRT/VMAT and 3D-CRT, respectively) and multivariate analysis (OR, 2.34, p = 0.247). Seven patients developed Grade 2 adverse events, of whom 5 patients were in the 3D-CRT group, and 2 were in the IMRT/VMAT group (Table 5). There were no Grade 3 GU adverse events. Two patients in the IMRT/VMAT group developed anastomosis stricture that was treated with periodic dilations (Fig. 2b).

4.2.3. Survival outcomes

The overall 5-year actuarial RFF was 81.1% (95% CI, 59.8–91.8) in patients treated with 3D-CRT and 94.5% (95% CI, 79.1–98.7) in patients irradiated with IMRT/VMAT (p = 0.344; Fig. 3a). Overall survival following RT with 3D-CRT and IMRT/VMAT was 96.5% (95% CI, 78.6–99.5) and 92.6% (95% CI, 69.8–98.4), respectively (p = 0.689; Fig. 3b).

5. Discussion

For PrCa patients, new and promising radiation treatments have been developed recently. Although IMRT has been shown to reduce toxicity when compared with 3D-CRT, the benefits have not been clearly defined in the postoperative setting. This study represents a single-institutional experience directly comparing acute and long-term toxicities in patients treated with 3D-CRT and IMRT/VMAT following RP. In contrast to prior findings of IMRT being associated with reduced GI morbidity compared with CRT in the salvage treatment setting,[15,20] we found no significant difference in the present study in any outcome between the IMRT/VMAT and 3-dimensional techniques for postprostatectomy RT. Our findings are compatible

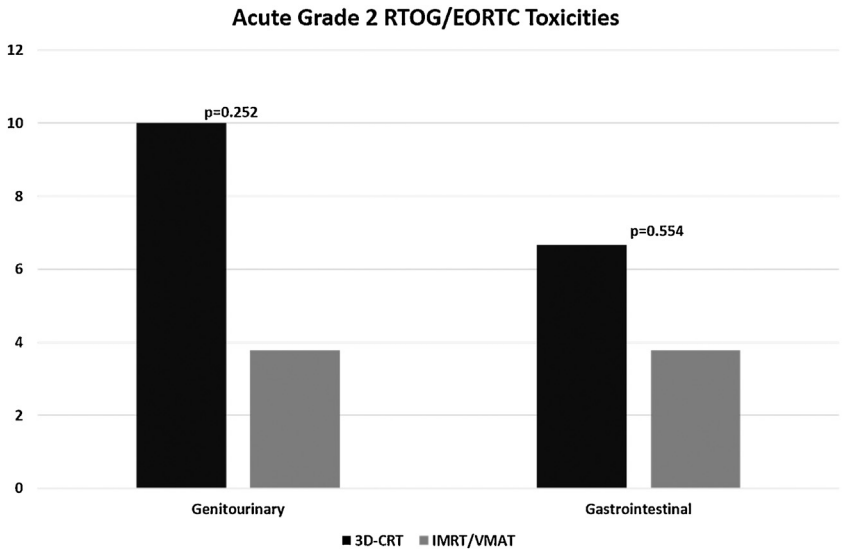

Fig. 1. Acute Grade 2 toxicity graded according to RTOG/EORTC. Abbreviations: IMRT, intensity-modulated radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy; RTOG, radiation therapy oncology group; EORTC, European Organisation for Research and Treatment of Cancer.

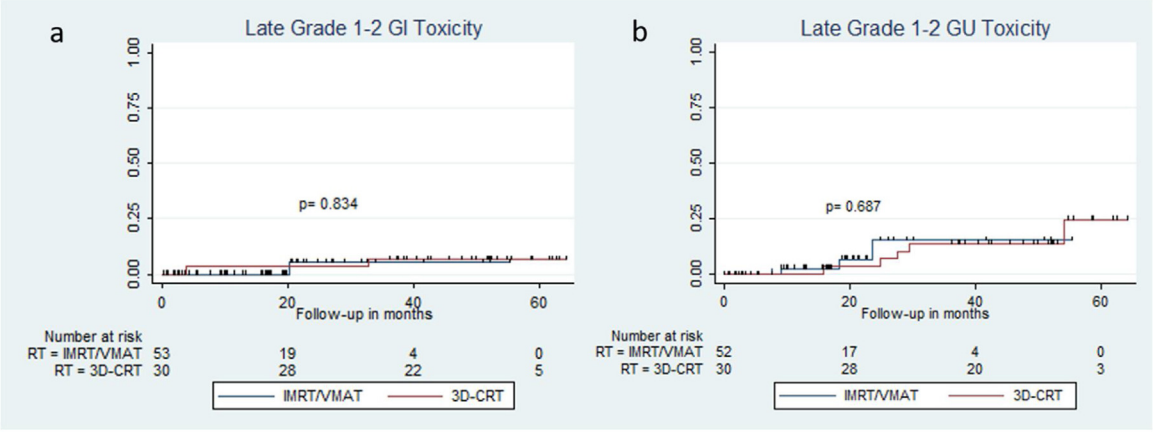

Fig. 2. The rates of late Grade 2 (a) GI and (b) GU toxicity after treatment are illustrated. Abbreviations: GI, gastrointestinal; GU, genitourinary; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; VMAT, volumetric modulated arc therapy.

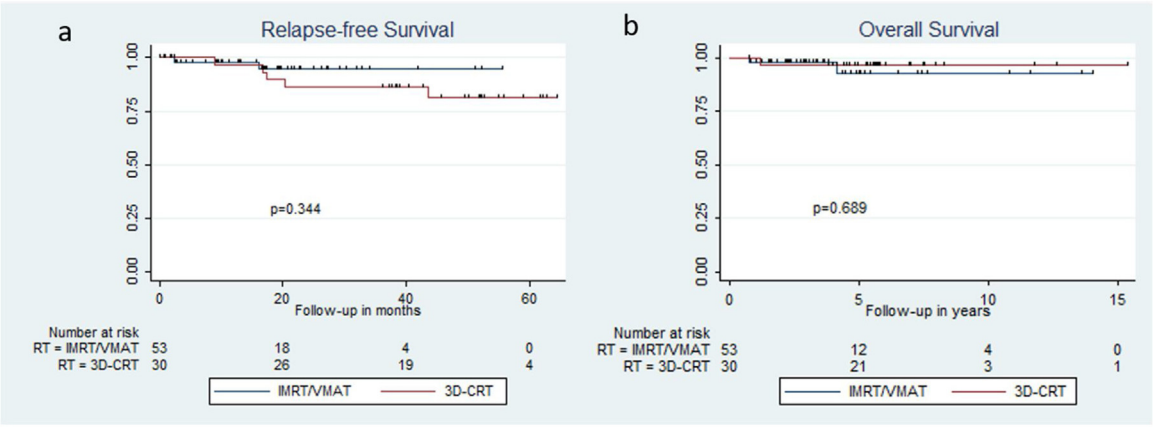

Fig. 3. Relapse-free survival after treatment (a) and (b) overall survival are illustrated. Abbreviations: 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; VMAT, volumetric modulated arc therapy.

with other authors who could not demonstrate differences in acute or long-term GI and GU morbidity.[21] One potential explanation for these findings is the lower postprostatectomy radiation dose used in patients in the 3D-CRT (66 Gy) group with lower toxicity than patients receiving radical RT. Another possible explanation is that the associated morbidities of prostatectomy like urinary incontinence and erectile dysfunction is usually perceived by patients as more troublesome than GI and GU toxicities associated with post-

operative RT.[22,23] A recent study by Boladeras et al. aimed to find an association between dose-volume histogram (DVH) parameters from radiotherapy treatment plans and quality of life in prostate cancer patients. Worse GI and GU symptoms in patients correlated with higher DVH dose distributions.[24]

The two treatment groups in our study had an equally good relapse-free survival rate, although the study population was too small to detect a meaningful difference in oncologic control outcomes. A larger population-based study or carefully matched pair analysis is needed to examine this issue in more detail.

Our study has several limitations. First, we were unable to independently assess the impact of dose from the treatment technique, as only IMRT/VMAT patients received doses >70 Gy. However, despite the higher doses, it is encouraging that patients treated with IMRT/VMAT demonstrated reduced late GI and GU toxicity even when this reduction rate was not significant. Second, adverse events were retrospectively evaluated, raising the possibility that some events were missed. An additional possible confounding variable in this assessment is that patients treated with 3D-CRT were treated in an earlier era than patients treated with IMRT/VMAT, reflecting the pattern of practice of many centers transitioning from 3D-CRT to highly conformal techniques in México. Nonetheless, most late GU events were clearly evident and observed within 5 years of treatment initiation in patients treated with 3D-CRT, and the observation period for these patients was sufficiently long.

6. Conclusions

We present a comparison of acute and late effects in patients treated with high-dose postoperative RT using 3D-CRT or IMRT/VMAT. Even though patients treated with IMRT/VMAT were more likely to be treated with a higher dose than patients treated with 3D-CRT, we did not see an increase in late GU and GI toxicity. Our results suggest that the benefit from IMRT/VMAT techniques in the postprostatectomy setting remains unclear. The clinical benefit in terms of reducing the incidence of acute and late GI and GU toxicity in the postoperative management of PrCa treatment has yet to be elucidated.

Conflict of interest

None declared.

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