

Scientific Article

Comparison Between Dose-Escalated Intensity Modulated Radiation Therapy and 3-Dimensional Conformal Radiation Therapy for Salvage Radiation Therapy After Prostatectomy



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Received April 20, 2021; accepted July 7, 2021

Abstract

Purpose: To compare long-term outcomes and late toxicity between patients treated with 3-dimensional conformal radiation therapy (3D-CRT) and with dose-escalated intensity modulated radiation therapy (IMRT) as salvage radiation therapy (SRT) after prostatectomy.

Methods and Materials: A total of 110 patients who had been treated at our institution between 2010 and 2018 with SRT for biochemical recurrence after radical prostatectomy were included. The patients were treated either by 3D-CRT with 64 Gy (59 patients) or by IMRT with 70 Gy (51 patients). The irradiation target was the prostate bed only (106 patients) or the prostate bed and pelvic region (4 patients). Twelve patients (11%) received concurrent androgen deprivation therapy. The differences in clinical outcomes and late gastrointestinal (GI) and genitourinary (GU) toxicity between the 3D-CRT and IMRT groups were retrospectively assessed. Toxicities were recorded using the Common Terminology Criteria for Adverse Events, version 5.0. Prostate-specific antigen (PSA) progression after SRT was defined as an increase in the serum PSA level of 0.2 ng/mL from the PSA nadir after SRT and confirmed by a second PSA measurement that was higher than the first.

Results: The median follow-up time was 7.8 years for 3D-CRT (range: 0.3-9.2 years) and 3.1 years for IMRT (range, 0.4-7.2 years). There was no significant difference in the 4-year biochemical no-evidence-of-disease (bNED) rate between the 3D-CRT and IMRT groups (43.5% vs 52.1%; $P = .20$). Toxicity analysis showed no significant difference in late GI or GU toxicities of grade 2 or greater between the 3D-CRT and IMRT groups. The respective 4-year cumulative rates of toxicity in the 3D-CRT and IMRT groups were as follows: grade ≥ 2 GI toxicity, 8.8% and 4.4% ($P = .42$); grade ≥ 2 GU toxicity, 19.1% and 20.3% ($P = .93$); and grade ≥ 2 hematuria, 5.3% and 8.0% ($P = .67$). In the 3D-CRT group, the 8-year cumulative rates of GI toxicity, GU toxicity, and hematuria of grade 2 or greater were 8.8%, 28.4%, and 12.6%, respectively.

Conclusions: Dose-escalated IMRT showed no improvements in bNED or late toxicity compared with 3D-CRT. In addition, the results suggest that GU toxicity can occur after a long period (even after 6 years), whereas GI toxicity is seldom newly observed after 4 years.

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Sources of support: This work had no specific funding.
Disclosures: none.

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<https://doi.org/10.1016/j.adro.2021.100753>

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Introduction

Salvage radiation therapy (SRT) after prostatectomy has been shown to improve outcomes in locally recurrent prostate cancer. Recently, 3-dimensional conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT) have replaced conventional 2-dimensional methods. However, the published literature does not adequately reflect the implementation of these newer methods. Regarding the reported randomized controlled trials (RCTs) of adjuvant radiation therapy (ART), the Southwest Oncology Group (SWOG) 8794 trial^{1,2} and the European Organisation for Research and Treatment of Cancer (EORTC) 22911 trial^{3,4} administered radiation therapy using conventional techniques. In contrast, the German Working Group on Radiation Oncology (ARO) 96-02 study^{5,6} administered radiation therapy using 3D-CRT. The lack of high-quality studies using newer radiation therapy methods makes it difficult to definitively determine optimal methods. Specifically, IMRT is a well-established technique for primary prostate cancer treatment, but its use in the postoperative setting has been limited. This is partly because any form of postoperative radiation therapy possibly causes moderate to severe late toxicity by the cumulative effect. However, IMRT has a potential to improve the treatment intensity by allowing a higher dose to be delivered to the target volume but limiting the irradiation of normal tissues.

Regarding the total irradiation dose in the postprostatectomy setting, the American Society for Radiation Oncology (ASTRO) consensus statements published by Cox et al⁷ in 1999 recommended a total dose of 64 Gy or slightly higher. The Memorial Sloan-Kettering Cancer Center (MSKCC)⁸ treated patients after prostatectomy with 66 Gy using 3D-CRT in the early 1990s. Since then, the MSKCC has gradually increased the dose up to 72 Gy, which has changed to being delivered using IMRT.⁸ At our institution, the total SRT dose was initially 64 Gy using 3D-CRT and was then increased to 70 Gy using IMRT. Now, we have chosen either 64 Gy or 66 Gy using IMRT (with or without androgen deprivation therapy [ADT], respectively). In this study, we assessed and compared the long-term outcomes and late toxicity between a 3D-CRT dose of 64 Gy in 32 fractions and an IMRT dose of 70 Gy in 35 fractions.

Materials and Methods

Patients

We retrospectively evaluated 110 patients with a median age of 66 years (range, 49-79 years) who had been treated with SRT for prostate-specific antigen

(PSA) recurrences after prostatectomy between July 2010 and May 2018. PSA recurrence was defined as a serum PSA level of ≥ 0.2 ng/mL confirmed by a second PSA measurement that was higher than the first. The restaging modality of both groups before SRT typically included computed tomography (CT) and bone scans. In the present study, none of the patients underwent prostate-specific membrane antigen (PSMA)-positron emission tomography (PET) or ¹⁸F-fluciclovine-PET. We treated such patients with a total dose of 64 Gy using 3D-CRT between July 2010 and May 2013, and then we switched to using a total dose of 70 Gy using IMRT between October 2014 and May 2018. Of all patients, 59 were treated with 3D-CRT and 51 with IMRT, including only 1 patient who was treated with IMRT in 2012. At the discretion of the attending urologist, ADT was administered to all patients with stage pN1 cancer and to certain patients with aggressive tumors. Among the 110 patients, 12 received concurrent ADT (3D-CRT, 2; IMRT, 10; $P = .011$). This study was conducted with the approval of the Institutional Review Board of the Cancer Institute Hospital of Japanese Foundation for Cancer Research (approval number: 2020-1099).

Before prostatectomy, staging studies typically included PSA tests, prostate biopsy, magnetic resonance imaging (MRI), and bone scans. In total, 102 patients (3D-CRT, 58; IMRT, 44) underwent retropubic radical prostatectomy, and 8 patients (3D-CRT, 1; IMRT, 7) underwent robotic-assisted laparoscopic radical prostatectomy. Prostatectomy included removal of the prostate gland and seminal vesicles, as well as pelvic lymphadenectomy. Pelvic lymphadenectomy was conducted with limited dissection for 92 patients (3D-CRT, 54; IMRT, 38) and with extended dissection for 12 patients (3D-CRT, 1; IMRT, 11). The extent of dissection was unknown for 6 patients.

Radiation therapy

The irradiation target was the prostate bed only for 106 patients, and the pelvic region was also irradiated in the remaining 4 patients who had had pelvic lymph node metastases as pathologic findings after surgery.

The clinical target volume (CTV) of the prostate bed was delineated on the basis of the EORTC guidelines⁹ for patients who underwent 3D-CRT and on the Radiation Therapy Oncology Group (RTOG) guidelines¹⁰ for patients who underwent IMRT. However, the CTV was often too large when delineated completely according to the guidelines. Thus, we tried to delineate as small a volume as possible, referencing the preoperative clinical information and the postoperative pathologic findings. The planning target volume (PTV) of 3D-CRT or IMRT

was defined as the CTV plus a 10-mm or 4-mm margin in all directions, respectively.

The 3D-CRT plans generally consisted of 7-field coplanar beams, with the prescribed dose administered to the isocenter using 10-MV photons, whereas IMRT was planned using volumetric modulated arc therapy, with the prescribed dose covering 95% of the volume of the PTV (D95) with 10-MV photons (Appendix E1). To accompany the 3D-CRT treatments, weekly image guidance was performed by orthogonal kilovoltage radiographs. In contrast, for the IMRT treatments, daily image-guided radiation therapy was performed by both orthogonal kilovoltage radiographs and cone beam computed tomography to verify the soft-tissue alignment.

Dose-volume histogram parameters

The dosimetric parameters of the PTV, rectum, and bladder were examined by referring to the dose-volume histograms. The D50 of the PTV and the V30-70 Gy, D2cc, mean dose, and maximum dose of the rectum and bladder wall were compared between 3D-CRT and IMRT.

International Prostate Symptom Score and quality-of-life score

The International Prostate Symptom Score (IPSS) and quality of life (QOL) assessment index were assessed before SRT and 1 month and every year after SRT.

Statistical analysis

Progression of PSA after SRT was defined as an increase in the serum PSA level of 0.2 ng/mL from the PSA nadir after SRT and confirmed by a second PSA measurement that was higher than the first. Time to event was measured from the first day of irradiation. The Kaplan-Meier method was used to estimate 4- and 8-year biochemical no evidence of disease (bNED), overall survival (OS), locoregional control (LRC, including pelvic nodes and prostate bed), and metastasis-free survival (MFS) rates. Cumulative rates between 3D-CRT and IMRT were compared using the log-rank test. Representative published prognostic factors for biochemical progression were selected as variables in univariate analysis, including pre-SRT PSA (<0.5 vs \geq 0.5 ng/mL), Gleason score (GS, \leq 7 vs \geq 8), dose/technique (64-Gy/3D-CRT vs 70-Gy/IMRT), surgical margin (negative vs positive), PSA doubling time (PSADT, <10 vs \geq 10 months), extracapsular extension (no vs yes), pathologic nodal disease (pN; N0 vs N1), and use of ADT (no vs yes). Four of the 8

variables that were significant or with relatively smaller *P* values in univariate analysis were then evaluated in multivariate analysis. The univariate analysis was done by the log-rank test and the multivariate analysis by the Cox regression hazards model.

We also assessed the rates of late adverse events of grade 2 or greater in the gastrointestinal (GI, rectal bleeding only) and genitourinary (GU, as the maximum GU toxicity and hematuria) tracts using the Kaplan-Meier method. The maximum GU toxicity was defined as the maximum urinary toxicity grade, including frequency, incontinence, stricture, and hematuria, that was observed during follow-up. Crude and cumulative rates were compared between 3D-CRT and IMRT using the Fisher exact probability test and the log-rank test, respectively. Late toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Because it was difficult to distinguish between grades 2 and 3 in some terms of the CTCAE, we supplemented the original definitions of grade 3 by referring to the Fox Chase Cancer Center scale.¹¹ Hematuria requiring transurethral coagulation or hyperbaric oxygen therapy and rectal bleeding requiring 3 administrations or more of argon plasma coagulation or hyperbaric oxygen therapy were classified as grade 3 late toxicity, whereas the remaining cases were classified as grade 2. Toxicity was retrospectively assessed through a review of the radiation oncologist's follow-up notes. All tests were considered to be statistically significant at *P* < .05. The analyses were conducted using SPSS, version 24 (IBM Corp, Armonk, New York).

Results

Clinical outcomes

The patient characteristics are shown in Table 1. The median time from prostatectomy to SRT was 27 months for 3D-CRT (range, 3 months to 8 years) and 25 months for IMRT (range, 3 months to 11.3 years). The median follow-up period after SRT was 7.8 years for 3D-CRT (range, 0.3-9.2 years) and 3.1 years for IMRT (range, 0.4 to 7.2 years; *P* < .001). The proportion of patients with a persistent increase in PSA level after prostatectomy was not significantly different between the 3D-CRT group (4 patients) and IMRT group (4 patients) (*P* = .83).

The 4-year bNED rates for 3D-CRT and for IMRT were 43.5% and 52.1%, respectively (Fig 1A). There was no significant difference between the 2 groups (*P* = .20). The 4-year OS, LRC, and MFS rates for 3D-CRT were 100%, 96.5%, and 96.4%, respectively, and those for IMRT were 100%, 95.2%, and 92.2%, respectively. There were no significant differences in any of these rates

Table 1 Characteristics of patients receiving 3D-CRT or IMRT*

Parameter	3D-CRT (n = 59)	IMRT (n = 51)	P value
Age, median (range), y	68 (49-77)	66 (49-79)	.29
Interval between surgery and SRT, median (range), mo	27 (3-96)	25 (3-136)	.24
Follow-up, median (range), y	7.8 (0.3-9.2)	3.1 (0.4-7.2)	<.001
Pre-SRT PSA, maximum (range), ng/mL	0.36 (0.11-5.00)	0.38 (0.05-1.95)	.82
Pre-SRT PSA level			
<0.5 ng/mL	50 (85%)	41 (80%)	.55
≥0.5 ng/mL	9 (15%)	10 (20%)	
PSADT			
<10 mo	43 (73%)	35 (71%)	.24
≥10 mo	9 (15%)	14 (29%)	
Unknown	7 (12%)	0 (0%)	
Extracapsular extension [†]	59	51	
Negative	34 (58%)	27 (53%)	.62
Positive	25 (42%)	24 (47%)	
Surgical margin			
Negative	32 (54%)	19 (37%)	.09
Positive	27 (46%)	32 (63%)	
Concurrent ADT	2 (3%)	10 (20%)	.011
Diabetes mellitus [‡]	7 (12%)	6 (12%)	>.99
Anticoagulant use [‡]	8 (14%)	3 (6%)	.22
Pelvis radiation	0 (0%)	4 (8%)	.03
Tumor stage [†]			
≤2	33 (56%)	25 (51%)	.62
3a	17 (29%)	16 (33%)	
3b	8 (14%)	10 (20%)	
4	1 (2%)	0 (0%)	
Gleason score [†]			
≤6	4 (7%)	6 (12%)	.13
3+4	15 (25%)	10 (20%)	
4+3	10 (17%)	17 (33%)	
8-10	30 (51%)	18 (35%)	
Initial PSA level, ng/mL			
≤10	28 (48%)	32 (63%)	.24
10-20	22 (37%)	12 (24%)	
>20	9 (15%)	7 (14%)	
D'Amico classification			
Low	2 (3%)	2 (4%)	.37
Intermediate	18 (31%)	22 (43%)	
High	39 (66%)	27 (53%)	

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; ADT = androgen deprivation therapy; IMRT = intensity modulated radiation therapy; PSADT = prostate-specific antigen doubling time; SRT = salvage radiation therapy.

* Data are presented as number (percentage) of patients unless otherwise indicated.

† Based on pathological findings.

‡ Measured at the time of SRT. Significant values are in bold.

between 3D-CRT and IMRT ($P = .84$, $.995$, and $.34$, respectively) (Appendix E2).

Among the 61 patients who developed biochemical progression after SRT, 4 had regional lymph node recurrences and 8 had distant metastases (bone, 7; para-aortic lymph node, 1) identified using a CT or bone scan. All the patients with biochemical progression were subsequently treated with salvage ADT. One patient received salvage radiation therapy, as well, for pelvic nodal recurrence. Table 2 presents the

results of univariate and multivariate analysis of prognostic factors associated with biochemical progression. Univariate analysis revealed that a pre-SRT PSA level ≥ 0.5 ng/mL ($P = .014$) and a GS ≥ 8 ($P = .03$) were significantly different, whereas a dose/technique of 64-Gy/3D-CRT ($P = .20$) and negative surgical margin ($P = .20$) showed a weak, but not statistically significant, association with biochemical progression (Fig 1A-D). Multivariate analysis revealed that a pre-SRT PSA level ≥ 0.5 ng/mL ($P = .014$) and a GS ≥ 8

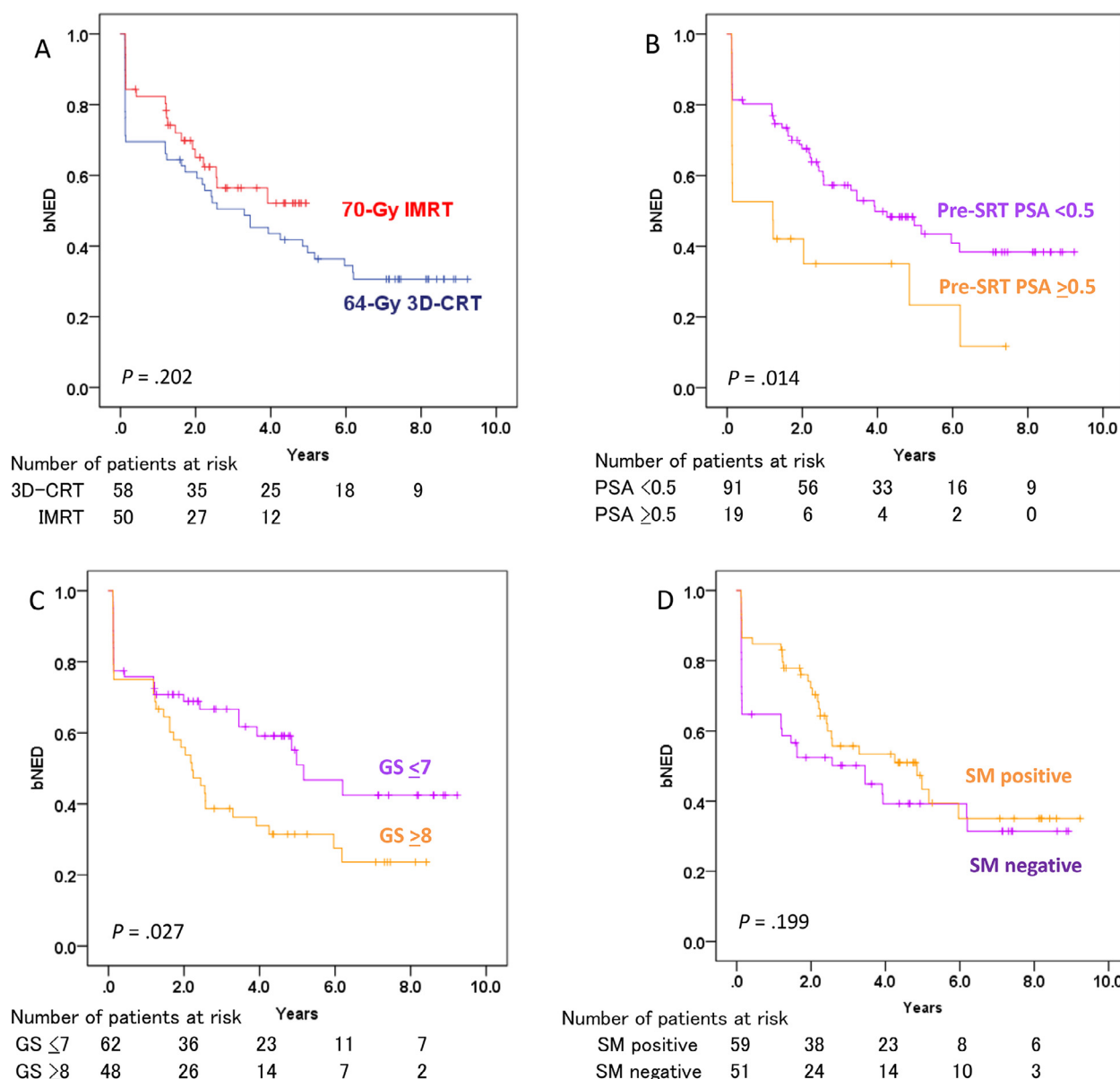


Fig. 1 Rate of biochemical no evidence of disease after salvage radiation therapy (SRT). (A) 64-Gy 3-dimensional conformal radiation therapy versus 70-Gy intensity modulated radiation therapy. (B) Prostate-specific antigen level before SRT, <0.5 versus ≥0.5 ng/mL. (C) Gleason score, ≤7 versus ≥8. (D) Surgical margin, negative versus positive.

($P = .02$) were independent predictors of biochemical progression.

Late gastrointestinal toxicity

Patients treated with IMRT showed a lower crude rate of late rectal bleeding of grade 2 or greater at 4 years than did those who underwent 3D-CRT, but the difference was not statistically significant (3D-CRT, 8.5%; IMRT, 3.9%; $P = .28$). The 8-year rate of grade ≥2 late rectal bleeding after 3D-CRT was 8.5%, which was the same as the rate at 4 years (the median

follow-up period of the IMRT group did not reach 8 years). Only 1 patient showed grade 3 late rectal bleeding (3D-CRT, 1.7%; IMRT, 0%). The cumulative rates of 4-year and 8-year late rectal bleeding of grade ≥2 were both 8.8% in the 3D-CRT group, whereas the 4-year cumulative rate in the IMRT group was 4.4% ($P = .42$) (Fig 2A and Table 3).

Late genitourinary toxicity

The 4- and 8-year crude rates of grade ≥2 late GU toxicity (as the maximum GU grade) in the 3D-CRT group

Table 2 Univariate and multivariate analysis for predictors of biochemical progression after SRT

Factors	Analysis, <i>P</i> value		Hazard ratio (95% CI)
	Univariate	Multivariate	
Pre-SRT PSA level (<0.5 vs ≥0.5 ng/mL)	.01	.014	2.16 (1.17-3.99)
Gleason score (≤7 vs ≥8)	.03	.016	1.89 (1.13-3.18)
Dose and technique (64-Gy 3D-CRT vs 70-Gy IMRT)	.20	.51	0.83 (0.47-1.45)
Surgical margin (negative vs positive)	.20	.23	0.73 (0.44-1.22)
PSADT (<10 mo vs ≥10 mo)	.67	-	-
Extracapsular extension (no vs yes)	.47	-	-
pN (N0 vs N1)	.59	-	-
Use of ADT (no vs yes)	.95	-	-

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; ADT = androgen deprivation therapy; IMRT = intensity modulated radiation therapy; pN = pathological nodal disease; PSADT = prostate-specific antigen doubling time; SRT = salvage radiation therapy.

Significant values are in bold.

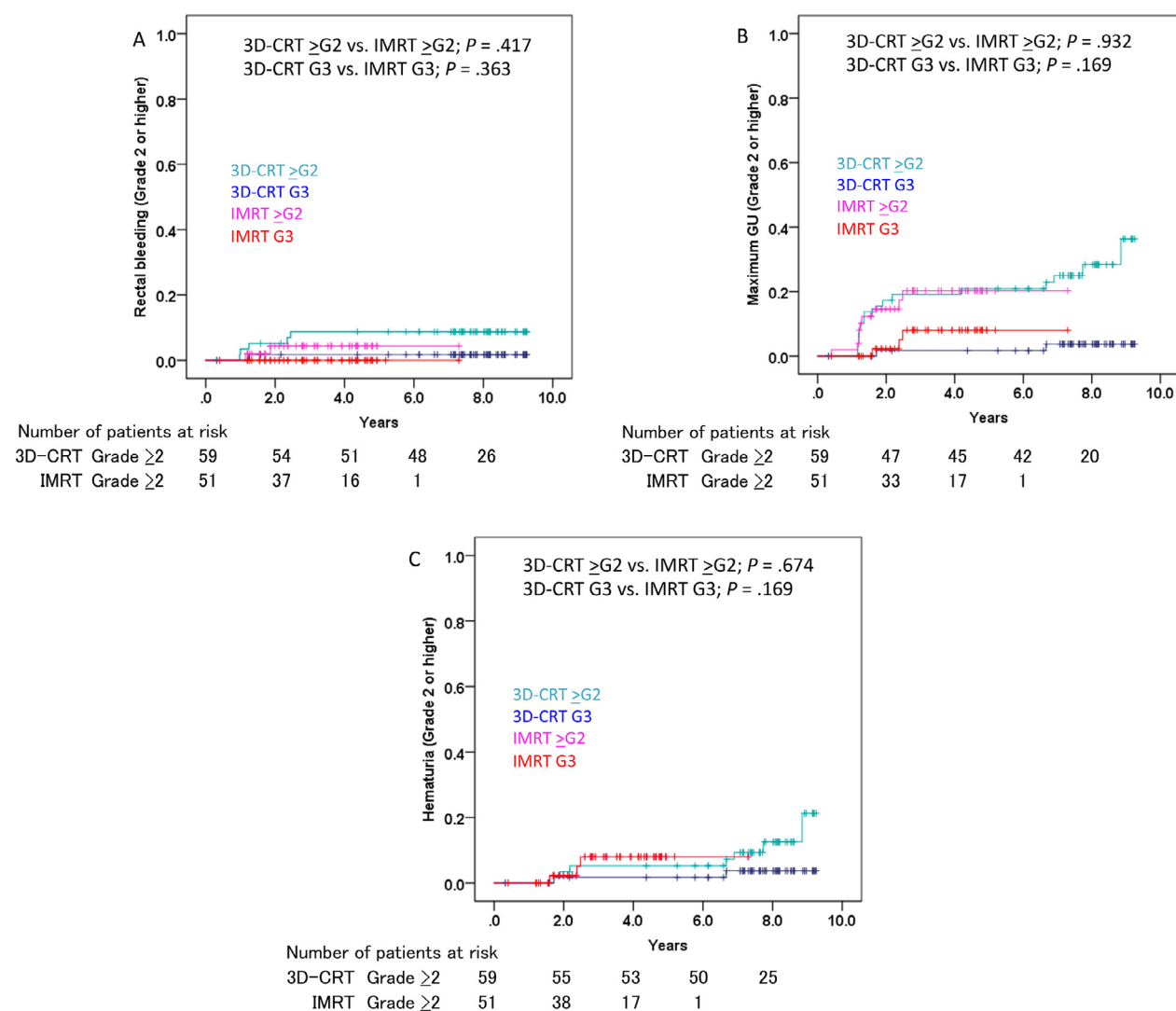


Fig. 2 Cumulative rates of late gastrointestinal and genitourinary (GU) toxicity after 64-Gy 3-dimensional conformal radiation therapy versus 70-Gy intensity modulated radiation therapy. (A) Rectal bleeding. (B) Maximum GU toxicity. (C) Hematuria.

Table 3 Crude and cumulative rates of late GI and GU toxicity of grade 2 or greater for 64-Gy 3D-CRT versus 70-Gy IMRT

Toxicity	64-Gy 3D-CRT (n = 59)		70-Gy IMRT (n = 51)		P value
	4 y	8 y	4 y	8 y	
Crude rate, %					
Rectal bleeding	8.5	8.5	3.9	-	.28*
Hematuria	5.1	11.9	5.9	-	.59*
Maximum GU [†]	18.6	27.1	17.6	-	.55*
Cumulative rate, %					
Rectal bleeding	8.8	8.8	4.4	-	.42
Hematuria	5.3	12.6	8.0	-	.67
Maximum GU [†]	19.1	28.4	20.3	-	.93

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; GI = gastrointestinal; GU = genitourinary; IMRT = intensity modulated radiation therapy.

* Compared at 4 years.

† Maximum GU was defined as the maximum grade of urinary toxicity, including frequency, incontinence, stricture, and hematuria, observed during follow-up.

were 18.6% and 27.1%, respectively. The 4-year rate of the IMRT group was 17.6%, which was not statistically different from that of the 3D-CRT group ($P = .55$). The cumulative rates of 4-year and 8-year late GU toxicity of grade ≥ 2 were 19.1% and 28.4%, respectively, among the 3D-CRT group, whereas the 4-year cumulative rate of late GU toxicity among the IMRT group was 20.3% ($P = .93$). Twelve patients who developed grade ≥ 2 late GU toxicity after SRT had already had baseline urinary dysfunction of grade ≥ 2 before SRT (3D-CRT, 6; IMRT, 6). The most frequently observed form of grade 2 urinary toxicity was incontinence (13 patients [11.8%]). The instances of grade 3 urinary toxicity, which were observed in 5 patients (3D-CRT, 2; IMRT, 3), were all hematuria. The 4- and 8-year crude rates of grade ≥ 2 hematuria in the 3D-CRT group were 5.1% and 11.9%, respectively, whereas the 4-year rate of grade ≥ 2 hematuria in the IMRT group was 5.9% ($P = .59$). The cumulative rates of 4-year and 8-year late hematuria of grade ≥ 2 were 5.3% and 12.6%, respectively, among the 3D-CRT group. The corresponding 4-year cumulative rate of the IMRT group was 8.0% ($P = .67$) (Fig 2B, 2C, and Table 3). The average onset time of grade ≥ 2 hematuria from the start of SRT was 50.4 months (range, 19-106 months) for the entire cohort. The corresponding averages for the 3D-CRT and IMRT groups were 61.1 months (range, 20-106 months) and 25.3 months (range: 19-29 months), respectively.

Dose-volume histogram parameters

The maximum dose, D2cc, and V70Gy to the rectum and bladder wall in the IMRT group were significantly higher than those in the 3D-CRT group, whereas the mid-dose volumes (rectum, V50Gy; bladder, V40Gy; and bladder, V50Gy) were significantly lower. The mean

dose to the rectum was significantly lower in the IMRT group despite the higher prescription dose ($P < .001$), whereas the mean dose to the bladder was not significantly different ($P = .93$) (Appendix E3 and Appendix E4).

IPSS and QOL scores

The IPSS and QOL scores of 96 patients were recorded before and after SRT (3D-CRT, 52; IMRT, 44). The mean IPSS and QOL scores before SRT were 6.96 (range, 2-15) and 2.54 (range, 0-5) for the 3D-CRT group and 6.33 (range, 0-25) and 2.60 (range, 0-5) for the IMRT group, respectively. The maximum mean IPSS after SRT was observed at 1 month after SRT in both groups (3D-CRT, 7.73; IMRT, 8.05; $P = .77$). There was no significant difference either in IPSS or QOL scores between the 3D-CRT and IMRT groups at any time point (Fig 3A-B).

Discussion

Clinical outcomes

We compared 3D-CRT with a 64-Gy dose and IMRT with a 70-Gy dose in terms of bNED, OS, LRC, and MFS after SRT, and we ultimately found no statistically significant differences in any of these levels. The results for this study's entire cohort, including rates of 41.9% for bNED, 100% for OS, 96.5% for LRC, and 94.9% for MFS at 5 years, were comparable with those of previous studies, which found rates of 38% to 67% for bNED, 97% to 100% for OS, 86% to 96% for LRC, and 81% to 98% for MFS at 5 years (Appendix E5).^{5,8,12-16} The relatively better PSA control of the IMRT group (Fig 1A;

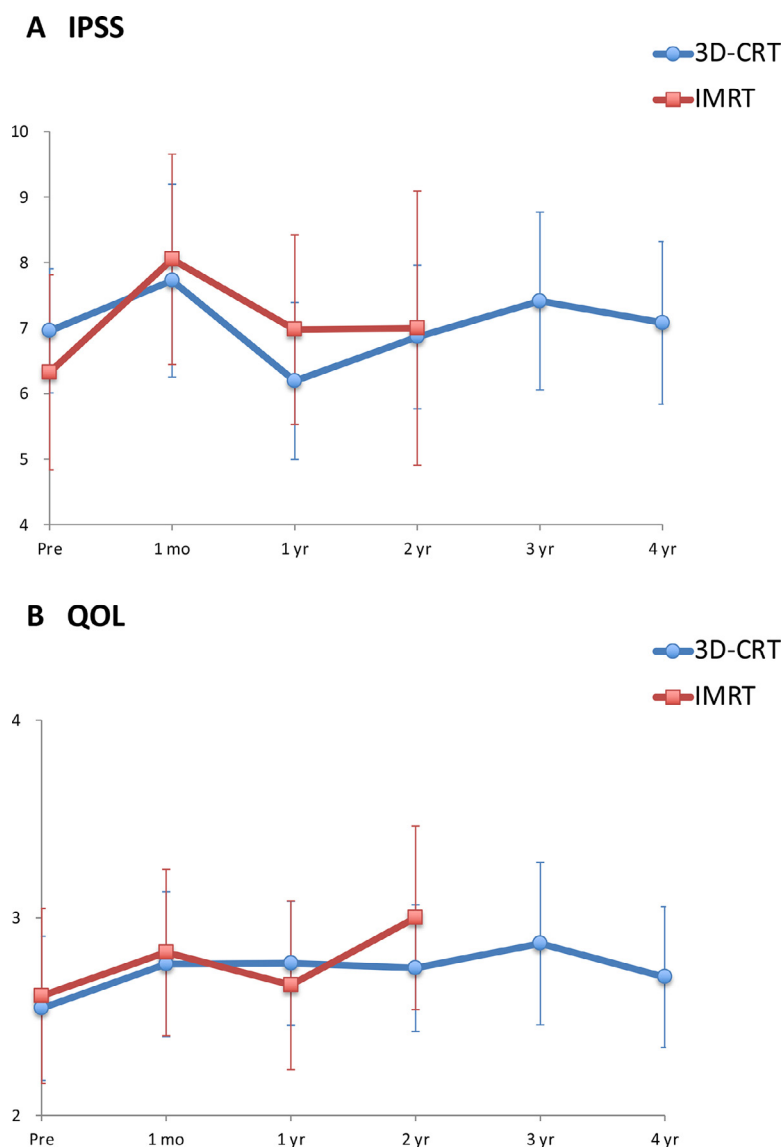


Fig. 3 International Prostate Symptom Score (IPSS) and quality-of-life (QOL) scores for 64-Gy 3-dimensional conformal radiation therapy versus 70-Gy intensity modulated radiation therapy. (A) IPSS. (B) QOL score. Error bars show 95% confidence intervals.

$P = .20$) should be considered partly as an effect of the more frequent use of ADT in the IMRT group (use of ADT: 3D-CRT, 3.3%; IMRT, 19.6%; $P = .011$), which was administered according to recent evidence.^{17,18} However, bNED rates in most recent SRT trials are approximately 70% to 80% at 5 years,¹⁷⁻²² which are higher than reported here. This suggests that the patient population of the present study was more heterogeneous or at higher risk, did not undergo SRT as early, and did not receive as much ADT compared with the cited trials.

Some studies have suggested a dose response in SRT, including nomograms by Stephenson et al²³ and Tendulkar et al,²⁴ a meta-analysis by King,²⁵ and an MSKCC study by Goenka et al.²⁶ In contrast, other studies such as the SAKK 09/10 trial^{27,28} and the current study did not

observe an advantage when the dose was escalated to greater than 64 Gy. A possible interpretation of this finding is that 64 Gy delivered to the prostate bed may be sufficient for treating microscopic disease, although imaging before SRT (ie, MRI and PSMA-PET scans) may detect macroscopic disease in the prostate bed, which likely benefits from such a dose escalation. Moreover, more sensitive scans such as these detect disease outside of the standard prostate bed CTV that was used for most patients in this study. Thus, management of biochemical recurrences after prostatectomy is evolving, and 64 Gy to the prostate bed alone is likely sufficient for only a small proportion of the patients we treat. Furthermore, we are most confident in a successful outcome for patients with only microscopic disease limited to the surgical bed (eg,

those with a GS of 6-7 and a pre-SRT PSA level <0.5 ng/mL).

Stephenson et al²⁹ reported a 4-year progression-free probability of 45% for their retrospective cohort of 500 men treated at 5 American academic radiation oncology centers. They also reported that the significant predictors of PSA progression after SRT were a GS ≥ 8 ($P < .001$), pre-SRT PSA level ≥ 2.0 ng/mL ($P < .001$), negative surgical margins ($P < .001$), PSADT ≤ 10 months ($P = .001$), and seminal vesicle invasion ($P = .02$). Other studies have also shown that PSADT is a prognostic factor after SRT.^{30,31} In this study, a pre-SRT PSA level ≥ 0.5 ng/mL and a GS ≥ 8 were significantly associated with PSA progression, as confirmed by multivariate analysis, whereas other factors were not. Administration of SRT concurrent with an early increase in the PSA level might improve the probability of long-term PSA control.

A small RCT³² reported a statistically significant difference in bNED for 72 Gy versus 66 Gy among patients with a GS ≥ 8 ($P = .049$). However, in the present study, there was no significant difference between 3D-CRT and IMRT in bNED, LRC, MFS, and OS among patients with a GS ≥ 8 ($P = .99, .46, .70, \text{ and } .85$, respectively).

Late toxicity

The purpose of this study was to determine whether 70 Gy of dose-escalated IMRT was associated with more or less late toxicity than 64 Gy of 3D-CRT. The results did not show any significant changes in late GU or GI toxicity in the IMRT group compared with the 3D-CRT group. Similarly, Goldin et al³³ compared IMRT with conventional RT in the SRT setting and found no significant differences in the rates of long-term GI morbidity (Rate ratio (RR), 0.95; 95% CI, 0.66-1.37), urinary nonincontinent morbidity (RR, 0.93; 95% CI, 0.66-1.33), urinary incontinence (RR, 0.98; 95% CI, 0.71-1.35), or erectile dysfunction (RR, 0.85; 95% CI, 0.61-1.19). In contrast, the superiority of IMRT in terms of late GI toxicity has been shown in some studies. Goenka et al⁸ reported that IMRT was independently associated with a reduction of GI toxicity of grade ≥ 2 compared with 3D-CRT at 5 years (IMRT, 1.9%; 3D-CRT, 10.2%; $P = .02$), whereas IMRT was not associated with a reduction of GU toxicity of grade ≥ 2 at 5 years (IMRT, 16.8%; 3D-CRT, 15.8%; $P = .86$). Jani et al³⁴ also reported that the late GU toxicity rate was not significantly different between 3D-CRT and IMRT ($P = .17$), but the late GI toxicity rate was lower in IMRT ($P = .001$). The reason for these results could be that the radiation dose irradiated to the urethra and/or the bladder neck and trigone region, which are included in the PTV, was not reduced by IMRT, whereas the dose to the rectum can be significantly reduced by using IMRT.

A large randomized trial (SAKK 09/10)^{27,28} comparing long-term outcomes of conventional versus dose-

escalated SRT has recently been reported, soon to be published, and its findings are consistent with the findings in this retrospective study. We adopted the same dose-fractionation as that used in the SAKK 09/10 trial, but we used only IMRT for the dose-escalated group. The results were partly the same; that is, 64 Gy and 70 Gy yielded the same bNED rates. However, in the SAKK 09/10 trial, the 70-Gy group showed a higher rate of late GI toxicity, whereas in the current study, no significant difference was found between the 2 groups. Therefore, we interpret this study's results to mean that although the IMRT group had a higher prescription dose of 70 Gy, the better dose distribution of IMRT in sparing the rectum compensated for the higher dose and eventually resulted in a similar GI toxicity rate with the 64-Gy 3D-CRT group.

Rectal bleeding occurred within 2 years after SRT in almost all cases in this study, and the GU toxicity rate at 8 years was greater than that at 4 years. Feng et al³⁵ examined late GI and GU toxicity in patients treated with adjuvant or salvage RT after surgery based on a pooled database of 11 institutions using the RTOG late toxicity scoring system. They reported that 4%, 7%, and 12% of the patients experienced grade ≥ 2 late GU toxicity at 1, 2, and 5 years, respectively. Other studies have also reported that the GU toxicity rate increased with time, suggesting that GU complications can manifest for a long period.^{36,37} The current study showed that the average onset time of grade ≥ 2 hematuria was nearly 5 years. The longest time to onset after 3D-CRT treatment was 106 months. Considering findings regarding the time-onset behaviors of GI and GU toxicity, we speculated that there was a relatively small possibility that we would find statistically significant differences between the IMRT and 3D-CRT groups. However, of note, the follow-up period of the IMRT group was significantly shorter compared with that of the 3D-CRT group, raising the possibility that late differences may emerge if the IMRT arm reaches a similar median follow-up of 8 years. Furthermore, because of our small sample size, the statistical power of the present study was insufficient to detect a significant difference in an infrequent event such as severe GI toxicity.

Dose-volume histogram parameters

We found that the mean dose to the rectum and the moderate-dose volumes (rectum, V50Gy; bladder, V40/50Gy) were significantly lowered by IMRT, although the maximum doses to the rectum and bladder (D2cc and V70Gy) in the IMRT group were significantly higher than those in the 3D-CRT group. Akthar et al³⁸ reported that the bladder V70Gy value was an impactful dosimetric variable, whereas no rectal dose metric correlated with QOL or late toxicity (V70, 65 Gy, and 40 Gy to the

bladder were approximately 18%, 45%, and 76%, respectively, and to the rectum, 6%, 21%, and 54%, respectively). Furthermore, the total dose (64.8 Gy) was shown to affect late GI toxicity. In addition, several authors have shown that the rectal volume receiving the moderate-high dose is important to the development of late rectal toxicity.³⁹⁻⁴² This study's results show that IMRT's better dose distribution compensated for its higher maximum dose than 3D-CRT's lower moderate-dose parameters, and eventually, we clinically observed similar toxicity rates between the 70-Gy IMRT and 64-Gy 3D-CRT groups.

Limitations of this study and future trends in SRT

This study has several limitations. First, it was retrospective in nature, so it was subject to all of the inherent biases of retrospective studies. There were multiple differences between the patients who underwent 3D-CRT and IMRT. The findings may therefore be explained by numerous factors other than simply dose/technique. Actually, patients receiving IMRT in the present study were more likely to have pN1 cancer and to have more pelvic radiation therapy, more extended lymph node dissections, more ADT, variable CTVs, smaller PTVs, and daily image guidance using cone beam computed tomography. The influences of these differences on outcomes were not fully evaluated. However, we did not observe a significant difference between groups regarding bNED or GU or GI toxicity, even when we excluded 4 patients with stage pN1 cancer who were all included in the IMRT group ($P = .23$, $.46$, and $.96$, respectively). In the future, if pelvic radiation therapy becomes more commonly included in prostate SRT, IMRT may yield larger differences in toxicity.^{22,43} Second, our sample size was relatively small and therefore insufficient to detect a difference in a rare event such as severe GI toxicity or to find a benefit of dose escalation for eradicating true local recurrence, if any. Therefore, our conclusions are tentative until confirmed by appropriate RCTs. Third, the follow-up period of the IMRT group was significantly shorter than that of the 3D-CRT group, lacking median 8-year data. It may be possible to detect a difference between 3D-CRT and IMRT at later follow-up times.

Recently, 2 large-scale RCTs (RTOG 9601 and GETUG-AFU 16) showed that adding ADT to SRT had a positive effect on OS and/or biochemical progression-free survival (bPFS) and MFS.^{16,17} This is reflected in the ASTRO/American Urological Association guidelines, a previous version of which were published in 2013. Those guidelines were revised in 2018, and a new statement that ADT should be offered to candidates for SRT was added.^{44,45} In contrast, early

SRT (eSRT), a new concept in the history of comparison between adjuvant and salvage RT after prostatectomy, is being established. Three RCTs (SWOG8794, EORTC22911, and ARO 96-02)¹⁻⁶ showed that ART significantly improved bPFS. However, improvements in MFS and OS were seen in the patients treated with ART in the SWOG study only.^{1,2} Recently, the results of 3 RCTs (RAVES, RADICALS, and GETUG-AFU 17) comparing ART with eSRT have been published, providing much needed evidence on the optimal timing of postprostatectomy RT.¹⁹⁻²¹ Across those 3 trials, 1075 and 1078 men were allocated to undergo ART and eSRT, respectively. All of those studies' results showed that there was no difference in 5-year bPFS between ART and eSRT, whereas ART increased the risk of urinary or genitourinary toxicity and erectile dysfunction compared with eSRT.⁴⁶ Guidelines and policy regarding the standard choice for management after prostatectomy may soon be updated reflecting these new findings.

All of these recent findings seem to suggest that the clinical practice of SRT is still changing drastically and that a one-size-fits-all treatment such as 70-Gy IMRT for all patients with PSA values of >0.2 ng/mL after prostatectomy might not be an optimal strategy. Even dose de-escalation using IMRT with the addition of an ADT aid for selected patients and earlier intervention before the PSA level reaches >0.2 ng/mL, aiming to reduce toxicity without compromising clinical outcomes, would be a possible future strategy. In accordance with the aforementioned worldwide trend and also on the basis of the findings of this study that clinical outcomes and late toxicity are similar between 64-Gy 3D-CRT and 70-Gy IMRT, we have moved to a new strategy of administering 64-Gy IMRT with ADT to patients with a high probability of metastasis and 66-Gy IMRT without ADT to other patients.

Conclusion

We compared 64-Gy 3D-CRT with 70-Gy IMRT in terms of outcomes and late toxicity in patients treated with SRT after prostatectomy who had a median follow-up of 5.5 years across all cohorts. We did not find any significant change in late GU or GI toxicity or any improvement in the bNED rate in the dose-escalated IMRT group. We interpret these findings to mean that IMRT could successfully compensate for its higher prescription dose by having a better dose distribution, achieving equivalent toxicity to 3D-CRT, but IMRT failed to show any benefits of dose escalation. Now, we have switched to a new strategy of administering 64 Gy to 66 Gy of dose-deescalated IMRT with or without ADT, aiming for earlier intervention based on individual patients' conditions after prostatectomy.

Acknowledgments

We thank Richard Lipkin, PhD, from Edanz, for editing a draft of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.adro.2021.100753.

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