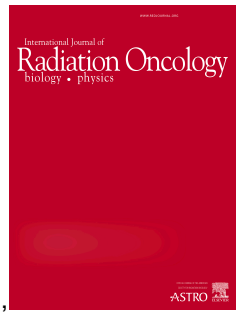

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Title Page

Toxicity and Biochemical Outcomes of Dose-Intensified Post-Operative Radiation Therapy for Prostate Cancer: Results of a Randomized Phase III Trial

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Running title: Post-operative RT for Prostate Cancer

Abstract

Purpose: To compare toxicity and biochemical control in post-prostatectomy patients treated with conventional (66 Gy) or dose-intensified (72 Gy) radiotherapy.

Methods: Patients who had stage pT3-4, positive surgical margins, or rising PSA ≥ 0.2 ng/mL following radical prostatectomy were randomly assigned to receive either 66 Gy in 33 fractions or 72 Gy in 36 fractions. A primary endpoint was to assess the difference in biochemical progression-free survival (bPFS) between these two cohorts, and secondary endpoints were to assess differences in genitourinary (GU), gastrointestinal (GI), and hematologic (HT) toxicities between these two cohorts. bPFS was estimated by the Kaplan–Meier method and toxicities were compared using the χ^2 test.

Results: Between September 2011 and November 2016, 144 patients were enrolled: 71 patients to the 66 Gy cohort and 73 patients to the 72 Gy cohort. The median follow-up time was 48.5 months (range: 14-79 months). There was no difference in 4-year bPFS between the 66 Gy and 72 Gy cohorts (75.9% vs. 82.6%; P = 0.299). However, in patients with a higher Gleason score (GS; 8-10), the 72 Gy cohort had statistically significant improvement in bPFS compared with the 66 Gy cohort (79.7% vs. 55.7%; P = 0.049). Toxicity analysis showed no difference in ≥2 acute or late GI or GU toxicities between these two cohorts. A total of 48 patients were scored as urinary incontinence before RT, of which 39 (81.3%) reported incontinence recovery or stable at 1-year follow-up, while only 9 (18.8%) patients reported worsening. There was no difference between the two cohorts in urinary incontinence either at baseline or at 1-year follow-up.

Conclusion: Dose escalation (72 Gy) demonstrated no improvement in 4-year bPFS compared

with the 66 Gy regimen. However, the dose escalation was not associated with greater acute or late GU or GI toxicities, and did not increase urinary incontinence.

Introduction

Post-operative radiotherapy (RT) is recommended for the treatment of prostate cancer patients with pathologic high-risk factors (positive surgical margin, capsule, or seminal vesicle invasion) or biochemical failure (1-3). A dose of 66-72 Gy is commonly used for post-operative RT. However, there are no specific recommendations on dose prescriptions, and significant variations and biases in dose prescription exist among institutions in current practice (4, 5).

Recent advances in RT, such as image-guided radiation treatment (IGRT), have significantly reduced irradiation-related toxicities, which make dose intensification become possible in many kinds of cancer, including prostate cancer (6, 7). Many retrospective studies (8) have reported a correlation between dose escalation and an increase in biochemical progression-free survival (bPFS) in post-operative RT of prostate cancer. A randomized controlled trial (RCT) on post-operative RT reported no difference in the incidence of acute toxicities between dose-intensified regimen (70 Gy) and the conventional dose regimen (64 Gy) using three-dimensional conformal radiation therapy (3D-CRT) or intensity-modulated radiation therapy (IMRT) (the Swiss SAKK 09/10 study) (9, 10). However, to the best of our understanding, there is no report from a prospective study comparing survival outcomes or toxicities between standard doses (66 Gy in 33 fractions) and intensified doses (72 Gy in 36 fractions) using IGRT technology.

In 2011, we initiated a randomized phase III trial to compare the effect of standard dose (66 Gy in 33 fractions) and higher dose (72 Gy in 36 fractions) RT on bPFS and toxicities (genitourinary, gastrointestinal, and hematologic) in post-operative patients with high-risk features (pT3-T4,

positive margins, or rising PSA ≥ 0.2 ng/mL). Here, we report the results of this phase III trial at a median follow-up of 48.5 months.

Methods and Materials

Patients

The medical ethics committee of XXX Hospital approved this randomized controlled phase III study (2016[XXX]). This study has also been registered at chictr.org.cn (ChiCTRXXX). All patients underwent radical prostatectomy at the discretion of the treating surgeon in our center. Patients were eligible if they had stage pT3-4, positive surgical margins, or rising PSA above 0.2 ng/ml following radical prostatectomy (RP). Any form of androgen deprivation therapy (ADT) was excluded. Before RT, the hematological indexes were normal and performance status had to be KPS 80 or higher. Enrolled patients were randomly assigned to receive 66 Gy in 33 fractions (2 Gy/f, 5 times weekly; 66 Gy cohort) or 72 Gy in 36 fractions (2 Gy/f, 5 times weekly; 72 Gy cohort). Image-guided intensity modulated radiation therapy/volumetric modulated arc therapy (IG-IMRT/VMAT) was used. Patients signed an informed consent form and were then randomized (1:1) to the above two cohorts. Randomization was performed by a random number table.

Treatment and Follow-Up Procedures

Before RT, all patients underwent an abdominopelvic computed tomography (CT; Big Bore 16-row helical CT with 3-mm thick image reconstruction layer; Philips, Amsterdam, Netherlands) scan for planning purposes in the treatment position with a comfortably full bladder and empty rectum. The prostate bed clinical target volume (CTV) was contoured according to the Radiation Therapy Oncology Group (RTOG) consensus guidelines (11). High-risk (including T3-T4, GS 8-10, or PSA > 20 ng/mL) patients were also treated with whole pelvic radiotherapy (WPRT). The WPRT target volume was contoured according to RTOG guidelines (12). The planning target volume

(PTV) was defined as the CTV plus 5-mm margins in all directions. The 95% isodose encompassed the PTV. The WPRT dose was 46 Gy with 2 Gy per fraction. The organs at risk included the bladder, rectum, and femoral heads contoured according to RTOG guidelines. Constraints for organs at risk were as follows: rectal, volume receiving 60 Gy ≤ 20% and volume receiving 70 Gy ≤ 10%; bladder, volume receiving 60 Gy ≤ 30% and volume receiving 70 Gy ≤ 20%; and femoral heads, maximum dose ≤ 50 Gy.

Patient treatment plans were developed using 6-MV photons and the VMAT. For radiotherapy equipment and technology, a Trilogy linear accelerator (6-MV photons, 60-pair multilobed grating; Varian, Palo Alto, CA) or a Synergy linear accelerator (6-MV photons, 60-pair multilobed grating; Elekta, Stockholm, Sweden) was used. For the treatment planning system, Eclipse (Varian) or Monaco (Elekta) was used. Before treatment, daily image guidance with cone-beam CT was performed in all cases.

The primary endpoint was to assess differences in bPFS, defined as the time from completion of RT to biochemical progression or death, whichever came first. Biochemical progression was defined as a PSA increase of 0.2 ng/mL or higher from the post-RT nadir in a minimum of two consecutive measurements, or the initiation of salvage ADT (13). The second endpoints were to assess differences in acute and late genitourinary (GU) symptoms including urinary incontinence, gastrointestinal (GI) toxicities, and hematologic (HT) toxicities between these two cohorts. Acute and late toxicities (>90 days after RT completion) were graded using the RTOG toxicity criteria. The GU and GI toxicities were reported by physicians before, during, and after radiotherapy. For the evaluation of HT toxicity, a complete blood sample was to be obtained at least at the baseline, the irradiation midpoint, and the irradiation endpoint. Urinary incontinence was self-reported by

patients using the International Consultation on Incontinence Modular Questionnaire Short Form (ICIQ-SF) (14) at the beginning, end of RT and at the 1-year follow-up after completion of RT.

Statistical analysis

The sample size calculation was performed with PASS version 13.0 (NCSS, Kaysville, UT), based on the following assumptions: 1) the primary endpoints (bPFS rates at 5 years), were assumed to be 56% and 76% for the 66 Gy cohort and 72 Gy cohort, respectively (1-3, 5, 8); 2) the one-sided α-level was defined as 0.025 with a power (1-β) of 80%; and 3) the number of patients in the two cohorts should be equivalent. Accordingly, 71 patients per cohort were needed.

Patient and treatment characteristics were described and compared between cohorts using the Mann-Whitney U test for continuous variables and χ^2 tests for categorical variables. Incidence of acute toxicities was compared using the χ^2 test. Fisher's exact test was used when the probability frequency was less than 5. The cumulative incidence for late GU and GI events was analyzed and compared using the Kaplan–Meier method and log-rank test. The Kaplan–Meier method was also used to estimate bPFS, distant metastasis-free survival, and overall survival in the two cohorts, with a 95% confidence interval (CI). The log-rank test was used to test for survival differences between cohorts. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patient Characteristics

From September 2011 to November 2016, 144 patients meeting the inclusion criteria were enrolled, including 71 patients in the 66 Gy cohort and 73 patients in the 72 Gy cohort (Fig. 1). The median age was 65 (43-80). The median interval between surgery and RT was 8 months (1-143 months). Adjuvant RT (ART) was performed in 48 cases (33.3%) and salvage RT (SRT) in 96 cases (66.7%). The median time of post-operative biochemical recurrence was 14 months (range 5-76 months). WPRT was performed in 126 (87.5%) patients. Details were shown in Table 1.

Clinical outcomes

With a median follow-up of 48.5 months (14-79 months), the 4-year bPFS was not different (P = 0.299) between the 66 Gy (75.9%, 95% CI = 71.6-79.6%) and the 72 Gy cohort (82.6%, 95% CI = 78.8-85.7%; Fig. 2A). However, a subset analysis showed that in the patients with GS 8-10 (25 pts in 66 Gy cohort, 30 pts in 72 Gy cohort), the 4-year bPFS was 55.7% in the 66 Gy cohort (95% CI = 45.3-64.9%) and 79.7% in the 72 Gy cohort (95% CI = 74.2-84.1)%, respectively (P = 0.049; Fig. 2B).

A total of 126 patients (59 pts in 66 Gy cohort, 67 pts in 72Gy cohort) received prostate bed irradiation and WPRT, while the other 18 patients (12 pts in 66 Gy cohort, 6 pts in 72 Gy cohort) only received prostate bed irradiation. Overall, the 4-year bPFS was not different (P = 0.888) between the subgroup received WPRT (74.3%, 95% CI = 63.2-82.5%) and the subgroup received prostate bed RT alone (79.9%, 95% CI = 77.3-82.3%; Fig. E1A). Among patients received WPRT, the 4-year bPFS was not different (P = 0.648) between the 66 Gy (79.2%, 95% CI = 75.5-82.5%)

and the 72 Gy cohort (80.8%, 95% CI = 76.5-84.3%; Fig. E1B).

A total of 10 patients developed distant metastasis, including 6 patients in the 66 Gy cohort and 4 patients in the 72 Gy cohort. The 4-year distant metastasis-free survival was not different between the two cohorts, at 95.2% (95% CI = 94.4-95.8%) for the 66 Gy cohort and 95.5% (95% CI = 94.4-96.4%) for the 72 Gy cohort, respectively (P = 0.191). A total of 6 patients died; 3 in the 66 Gy cohort and 3 in the 72 Gy cohort. The 4-year overall survival was therefore not different between the two cohorts, at 95.3% (95% CI = 94.4-96.0%) and 95.5% (95% CI = 95.1-95.8%) for the 66 Gy and 72 Gy cohorts, respectively (P = 0.658).

Toxicity

GU toxicity

Acute GU toxicity events mainly included urinary pain, urinary frequency, urinary urgency, nocturia, and dysuria. For the 66 Gy and 72 Gy cohorts, the incidence of acute grade 1 GU toxicity was 74.6% and 82.2%, respectively, while the incidence of acute grade 2 GU toxicity was 5.6% and 4.1% respectively. Grade 3 GU toxicity was observed in only 1 patient (1.4%) belonging to the 72 Gy cohort. This patient experienced dysuria in the sixth week of RT, which required an indwelling catheter. There was no statistical difference in the incidence of acute GU toxicity between the two cohorts (P = 0.472).

The most common late GU toxicity was discontinuous macroscopic hematuria, which was usually observed after 1.5 years after the completion of RT, and the majority of these cases resolved without treatment. The incidence of late grade 1 GU toxicity was 15.5% and 12.3% for the 66 Gy and 72 Gy cohorts, respectively, and the incidence of late grade 2 GU toxicity was 8.5%

and 11.0% for the two cohorts, respectively. Late grade 3 GU toxicity was observed in 1 patient in the 72 Gy cohort, who received urethral dilatation due to stricture. There was no statistical difference between the two cohorts in the incidence of late GU toxicity (P = 0.677). The cumulative incidence of late grade 2 GU toxicity at 4 years was 10.4% (95% CI = 8.9-12.1%) in the 66 Gy cohort and 15.5% (95% CI = 11.8-17.8%) in the 72 Gy cohort, respectively (P = 0.521; Fig. 1)

A specific analysis was performed to examine the impact of post-operative RT on urinary continence recovery. In the two cohorts combined, 87 patients received RT within 12 months after RP, of which 27 (31.0%) had urinary incontinence at the beginning of RT (baseline). Fifty-seven patients received RT more than 12 months after RP, and twenty-one (36.8%) of them had urinary incontinence at baseline. Patients with a longer interval (>12 months) between RP and RT showed no superiority in recovery of urinary continence. For the two cohorts, there was no significant difference in the incidence of incontinence at baseline, with 38.0% (27/71) of the 66 Gy cohort and 28.8% (21/73) of the 72 Gy cohort, respectively (P = 0.239). Of the 48 patients scored as urinary incontinence before RT, 85.2% (23/27) of patients in the 66 Gy cohort reported urinary continence recovery or stable at 1 year after RT, compared to 76.2% (16/21) in the 72 Gy cohort (P = 0.296) (table 3).

GI toxicity

Acute GI toxicity mainly manifested as adverse reactions in the lower digestive tract, including diarrhea, proctitis, tenesmus, fecal incontinence, and rectal pain. The incidence of acute grade 1 GI toxicity was 47.9% and 52.1% for the 66 Gy and 72 Gy cohorts, respectively, and the incidence of acute grade 2 GI toxicity was 7.0% and 6.8%, respectively, for these two cohorts. Neither

cohort had acute grade ≥3 reaction. There was no significant difference in the incidence of acute GI toxicity between the 2 cohorts (P = 0.879).

Late GI toxicity was mainly diarrhea. Anal and rectal hemorrhage were rare. The incidence of late grade 1 GI toxicity was 8.5% and 8.2% for the 66 Gy and 72 Gy cohorts, respectively, and the incidence of late grade 2 GI toxicity was 1.4% and 2.7%, respectively, for these two cohorts. There was no late grade ≥3 toxicity event in either cohorts. No significant difference in incidence of late GI toxicity between the two cohorts was obtained (P = 0.852).

Acute hematologic toxicity

Acute HT was evaluated according to the RTOG criteria. There was no significant difference in the incidence of acute HT between the two cohorts. However, the incidence of acute leukopenia was significantly higher in patients who received WPRT compared to those receiving radiation to the prostate bed alone (P = 0.049). After receiving WPRT, the incidence of acute grade 1 and 2 leukopenia was 41.3% and 5.6%, respectively, although no grade 3 leukopenia was reported (Table 2).

Discussion

Post-operative RT with a dose of 66-72 Gy in standard dose fractionation (1.8-2 Gy per fraction) is recommended to treat prostate cancer patients with adverse pathological risk factors or PSA relapse after RP, according to the National Comprehensive Cancer Network's (NCCN) guidelines for prostate cancer. Results of some retrospective studies showed a post-operative dose escalation might contribute to a longer survival (4, 5, 8, 15). For example, results of a meta-analysis of many respective studies were initially reported in 2012 (8) and subsequently updated in the 2016 American Society for Radiation Oncology (ASTRO) meeting (16). A total of 10,034 patients from 71 studies between 1996 and 2015 were reported in this meta-analysis. The median follow-up time and median dose were 52 months and 65.8 Gy, respectively. The bPFS was reported to increase by 2% for every 1 Gy increase in RT dose. However, the risk of GI and GU toxicities also increased after dose intensification. In contrast, the results of this phase III randomized trial did not demonstrate survival benefits in patients receiving 72 Gy compared with the 66 Gy cohort. However, a subset analysis on patients with high GS scores (8-10) showed the higher dose (72 Gy in 36 fractions) provided a statistically significant benefit in bPFS. This has not been previously reported. Moreover, the results of this study did not show an increase in GU or GI toxicities between the 66 Gy and 72 Gy cohort.

WPRT has been controversial in post-operative radiation of prostate cancer. There is no level 1 evidence to demonstrate superiority in survival benefits in patients receiving WPRT compared with prostate bed irradiation, even though WPRT was reported to improve bPFS in some retrospective studies (17, 18). In addition, there is a significant concern of treatment-related toxicities in patients receiving WPRT, especially after pelvic nodal dissection, compared with

prostate bed irradiation. Despite the above concerns, post-operative WPRT is commonly utilized to treat prostate cancer patients with high risk factors, even though the definition of these risk factors varies among institutions. Results of one survey showed that over 70% of radiation oncologists consider utilizing WPRT in their post-prostatectomy settings (19). In this study we used WPRT to treat 87% patients, showing no difference in late GI or GU toxicities compared with prostate bed RT alone. However, we did observe significant HT toxicity (leukopenia) during the RT course. The impact of leukopenia on the clinical outcomes remains unclear, even though leukopenia is associated with poor survival outcomes in other disease sites. RTOG has completed a phase III study comparing RT to RT with a short course of ADT in patients with high-risk factors after prostatectomy (RTOG 0534), where one of the secondary endpoints was to compare WPRT with prostate bed RT alone. The preliminary results of RTOG 0534 have been presented at the 2018 ASTRO meeting which showed the addition of WPRT resulted in further improvement in free-from-progression (FFP) rate with only a slight increase in toxicity. The 5-year FFP rate of patients receiving prostate bed RT, prostate bed RT with short-term ADT, and prostate bed RT with WPRT and short-term ADT were 71%, 81%, and 87%, respectively, all of which were statistically significant. Meanwhile, considering the prevalence of advanced imaging techniques such as prostate specific membrane antigen (PSMA) scans and Axumin positron emission tomography (PET)-CT, we believe patients originally defined as post-operative biochemical failure were found to have a high incidence of pelvic lymph node metastasis by these advanced images (20, 21), and therefore, use of WPRT might need additional justification.

Two RCTs (GETUG-AFU 16 and RTOG 9601) (22, 23) and some retrospective studies have shown that ADT combined with SRT improved outcomes in select groups of patients (higher PSA

level before SRT, pT3b/4, grade group ≥ 4). Therefore, men after surgery with high-risk features and biochemical failure are now considered for ADT. Unfortunately, use of ADT was not conclusive at the time when this protocol was developed, and use of ADT was not allowed in this trial. The small survival difference associated with dose escalation observed in high-risk (GS 8-10) patients in this trial might not therefore be significant if use of ADT were allowed in these patients. We are waiting for long term results from RTOG 0534 to answer this type of question.

Another RCT assessing dose-intensified post-operative RT is the Swiss SAKK 09/10 study, which began to enroll patients in 2011. A total of 350 patients were randomly assigned to either 64 Gy or 70 Gy SRT treatments. The results of acute toxicities and urinary continence recovery have been reported (9, 10). The incidence of acute grade 2 and 3 GU toxicity in the 64 Gy group was 13.0% and 0.6%, respectively, while those in the 70 Gy group were 16.6% and 1.7%. The acute grade 2 and 3 GI toxicity in the 64 Gy group was 16.0% and 0.6%, respectively, while those in the 70 Gy group were 15.4% and 2.3%. There was no significant difference in the incidence of acute toxicities between the two groups. In terms of urinary control, 32% of patients had urinary incontinence at baseline, while 44% and 41% of patients in the 64 Gy and 70 Gy groups recovered within 3 months after radiotherapy, respectively. Toxicity rates in our study are in agreement with those in the Swiss SAKK 09/10 study. We observed only one acute grade 3 GU toxicity event and no acute grade 3 GI toxicity event in this study. One possible reason is that all patients in our study received IG-IMRT/VMAT, while over 40% of patients received 3D-CRT in the Swiss SAKK 09/10 study. The results of the phase III RTOG 0126 trial have demonstrated that IMRT is significantly associated with reduction of acute GI and GU grade ≥2 toxicities when high-dose RT was used compared to 3D-CRT (24).

To evaluate the impact of post-operative RT on urinary incontinence, the International Consultation on Incontinence Questionnaire Short Form (ICIQ-UI SF) (12) was applied in this study. Compared with other traditional methods, such as daily urine pad count and 24 h urine pad weight count, the ICIQ-UI SF is validated to be effective and convenient in evaluating urinary incontinence (12). Changes in the ICIQ score indicate that urinary incontinence becomes better or worse, and no change indicates stable. Based on the questionnaire results, we have found that 48 patients (33.3%) were scored as having urinary incontinence at baseline. Post-operative RT did not increase the degree of urinary incontinence in this group of patients. One year after finishing RT, 81.3% (39/48) of patients reported urinary incontinence recovery (18.8%) or stable (62.5%). Only 18.8% of patients thought their incontinence became more severe, with symptoms including stress or activity. In patients without urinary incontinence, post-operative RT did not result in additional incidences of incontinence in this study.

In conclusion, the results of this phase III study demonstrated no difference in 4-year bPFS between 66 Gy and 72 Gy regimens using modern IGRT technology. However, the dose escalation has not resulted in increase in late GI or GU toxicities. Furthermore, our subset analysis of the GS 8-10 patients, showed a marginal improvement in bPFS with dose escalation ($P = 0.049$). This observation could result from dose escalation, the nature of a phase III randomization trial, advantage of IGRT, uniform target volumes for RT, and the fact that this was a single-center trial. Certainly, this observation could also be confounded by use of WPRT in majority of enrolled patients (not stratified) and lack of ADT allowed in this study. Further follow-up is still needed to determine the impact of dose escalation on long term survival outcomes in the post-operative

setting.

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Figure legends

Figure 1. Cumulative incidence of late grade 2 and 3 genitourinary (GU) toxicity

Figure 2. Biochemical progression-free survival (bPFS) for (A) whole patients and (B) patients with Gleason score 8-10

Supplementary figures

Figure E1. Biochemical progression-free survival (bPFS) for (A) whole patients, (B) whole pelvic radiotherapy (WPRT) subgroup, and (C) non-WPRT subgroup.

Table 1. Clinical and pathologic characteristics

Characteristic	66 Gy group	72 Gy group	All patients	P
Study sample, n (%)	71 (49.3)	73 (51.7)	144 (100)	
Age at RT (year),				0.446
Median (range)	65.0 (56.0- 80.0)	66.5 (43.0- 76.0)	65.0 (43.0- 80.0)	
aRT/sRT, n (%)				0.346
aRT	21 (29.6)	27 (37.0)	48 (33.3)	
sRT	50 (70.4)	46 (63.0)	96 (66.7)	
T stage, n (%)				0.400
pT2	26 (36.6)	18 (24.7)	44 (30.6)	
pT3a	25 (35.2)	27 (37.0)	52 (36.1)	
pT3b	19 (26.8)	26 (35.6)	45 (31.3)	
pT4	1 (1.4)	2 (2.7)	3 (2.1)	
Gleason score, n (%)				0.506
6	5 (7.0)	2 (2.7)	7 (4.9)	
7	41 (57.7)	41 (56.2)	82 (56.9)	
8	10 (14.1)	10 (13.7)	20 (13.9)	
9	14 (19.7)	20 (27.4)	34 (23.6)	
10	1 (1.4)	0 (0.0)	1 (0.7)	
ISUP, n (%)				0.069
1	5 (7.0)	2 (2.7)	7 (4.9)	
2	24 (33.8)	13 (17.8)	37 (25.7)	
3	16 (22.5)	28 (38.4)	44 (30.6)	
4	11 (15.5)	10 (13.7)	21 (14.6)	
5	15 (21.1)	20 (27.4)	35 (24.3)	
Resection margins, n (%)				0.064
R0	37 (52.1)	26 (35.6)	63 (43.8)	
R1	34 (47.9)	47 (64.4)	81 (56.2)	
PSA max before RP, n (%)				0.283
≤10	18 (25.4)	13 (17.8)	31 (21.5)	
10-20	26 (36.6)	23 (31.5)	49 (34.0)	
≥20	27 (38.0)	37 (50.7)	64 (44.4)	
Time from surgery to RT (month),				0.290
Median (Range)	10.0 (1.0-143.0)	8.0 (1.0, 96.0)	8.0 (1.0, 143.0)	
RP hospital, n (%)				0.723
PUFH	59 (83.1)	59 (80.8)	118 (81.9)	
Out of PUFH	12 (16.9)	14 (19.2)	26 (18.1)	

Characteristic	66 Gy group	72 Gy group	All patients	P
Lymphadenectomy, n (%)				0.644
None	29 (40.8)	26 (35.6)	55 (38.2)	
Obturator lymph node biopsy	37 (52.1)	39 (53.4)	76 (52.8)	
Pelvic lymph node dissection	5 (7.0)	8 (11.0)	13 (9.0)	
Median PSA at random assignment (ng/mL)	0.2	0.2	0.2	0.268
WPRT, n (%)	59 (83.1)	67 (91.8)	126 (87.5)	0.115
Follow up time (month),				0.627
Median (Range)	50.0 (14.0, 79.0)	45.0 (15.0, 79.0)	48.5 (14.0, 79.0)	

Abbreviations: aRT = adjuvant radiation therapy; ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen; PUFH = Peking University First Hospital; RP = radical prostatectomy; RT = radiation therapy; sRT = salvage radiation therapy; WPRT = whole pelvic radiotherapy.

Note: P values were calculated by Mann-Whitney U test or Chi-square test where appropriate.

Table 2. Acute and late toxicities

Toxicity and RTOG Highest Grade	All patients, n (%)			WPRT subgroup, n (%)			Non-WPRT subgroup, n (%)			All patients, n (%)		
	66 Gy group	72 Gy group	P	66 Gy group	72 Gy group	P	66 Gy group	72 Gy group	P	Non-WPRT group	WPRT group	P
Study sample	71	73		59	67		12	6		18	126	
Acute GU			0.472			0.400			0.712			0.153
0	14 (19.7)	9 (12.3)		11 (18.6)	7 (10.4)		3 (25.0)	2 (33.3)		5 (27.8)	18 (14.3)	
1	53 (74.6)	60 (82.2)		44 (74.6)	56 (83.6)		9 (75.0)	4 (66.7)		13 (72.2)	100 (79.4)	
≥2	4 (5.6)	4 (5.5)		4 (6.8)	4 (6.0)		0 (0.0)	0 (0.0)		0 (0.0)	8 (6.3)	
Acute GI			0.879			0.982			0.057			0.599
0	32 (45.1)	30 (41.1)		26 (44.1)	30 (44.8)		6 (50.0)	0 (0.0)		6 (33.3)	56 (44.4)	
1	34 (47.9)	38 (52.1)		29 (49.2)	32 (47.8)		5 (41.7)	6 (100.0)		11 (61.1)	61 (48.4)	
≥2	5 (7.0)	5 (6.8)		4 (6.8)	5 (7.5)		1 (8.3)	0 (0.0)		1 (5.6)	9 (7.1)	
Late GU			0.677			0.564			0.765			0.373
0	54 (76.1)	55 (75.3)		45 (76.3)	50 (74.6)		9 (75.0)	5 (83.3)		14 (77.8)	95 (75.4)	
1	11 (15.5)	9 (12.3)		10 (16.9)	9 (13.4)		1 (8.3)	0 (0.0)		1 (5.6)	19 (15.1)	
≥2	6 (8.5)	9 (12.3)		4 (6.8)	8 (11.9)		2 (16.7)	1 (16.7)		3 (16.7)	12 (9.5)	
Late GI			0.852			0.872						0.302
0	64 (90.1)	65 (89.0)		52 (88.1)	59 (88.1)		12 (100.0)	6 (100.0)	-	18 (100.0)	111 (88.1)	
1	6 (8.5)	6 (8.2)		6 (10.2)	6 (9.0)		0 (0.0)	0 (0.0)		0 (0.0)	12 (9.5)	
≥2	1 (1.4)	2 (2.7)		1 (1.7)	2 (3.0)		0 (0.0)	0 (0.0)		0 (0.0)	3 (2.4)	
Acute leukopenia			0.469			0.310			0.193			0.049
0	40 (56.3)	42 (57.5)		29 (49.2)	38 (56.7)		11 (91.7)	4 (66.7)		15 (83.3)	67 (53.2)	
1	29 (40.8)	26 (35.6)		28 (47.5)	24 (35.8)		1 (8.3)	2 (33.3)		3 (16.7)	52 (41.3)	
≥2	2 (2.8)	5 (6.8)		2 (3.4)	5 (7.5)		0 (0.0)	0 (0.0)		0 (0.0)	7 (5.6)	
Acute hypo-hemoglobin			0.255			0.183			0.467			0.112
0	49 (69.0)	58 (79.5)		38 (64.4)	52 (77.6)		11 (91.7)	6 (100.0)		17 (94.4)	90 (71.4)	
1	21 (29.6)	15 (20.5)		20 (33.9)	15 (22.4)		1 (8.3)	0 (0.0)		1 (5.6)	35 (27.8)	

	All patients, n (%)			WPRT subgroup, n (%)			Non-WPRT subgroup, n (%)			All patients, n (%)		
Toxicity and RTOG Highest Grade	66 Gy group	72 Gy group	P	66 Gy group	72 Gy group	P	66 Gy group	72 Gy group	P	Non-WPRT group	WPRT group	P
≥2	1 (1.4)	0 (0.0)		1 (1.7)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	1 (0.8)	
Acute thrombocytopenia			0.540			0.882			0.146			0.799
0	67 (94.4)	67 (91.8)		55 (93.2)	62 (92.5)		12 (100.0)	5 (83.3)		17 (94.4)	117 (92.9)	
1	4 (5.6)	6 (8.2)		4 (6.8)	5 (7.5)		0 (0.0)	1 (16.7)		1 (5.6)	9 (7.1)	

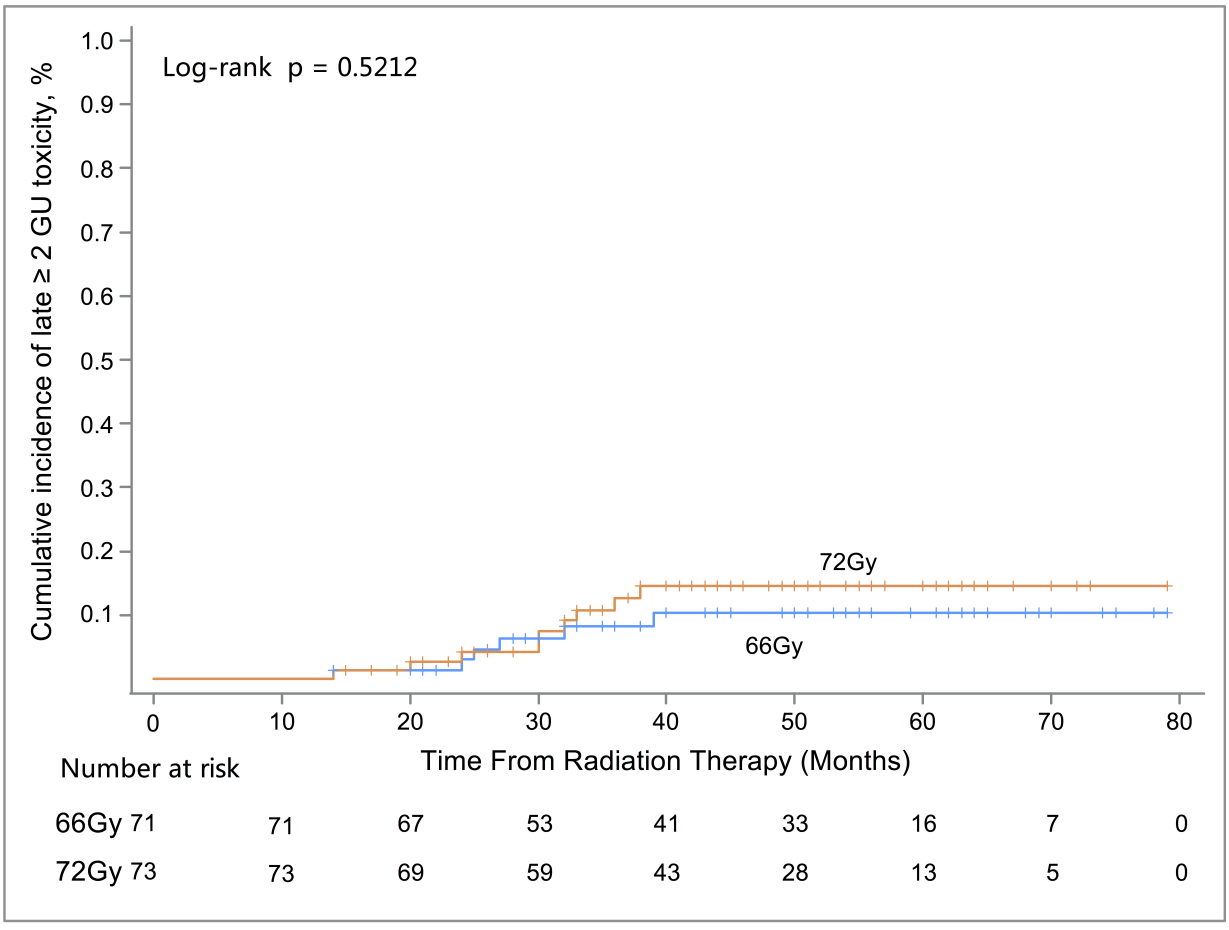
Abbreviations: GI = gastrointestinal; GU = genitourinary; RTOG = Radiation Therapy Oncology Group; WPRT = whole pelvic radiotherapy.

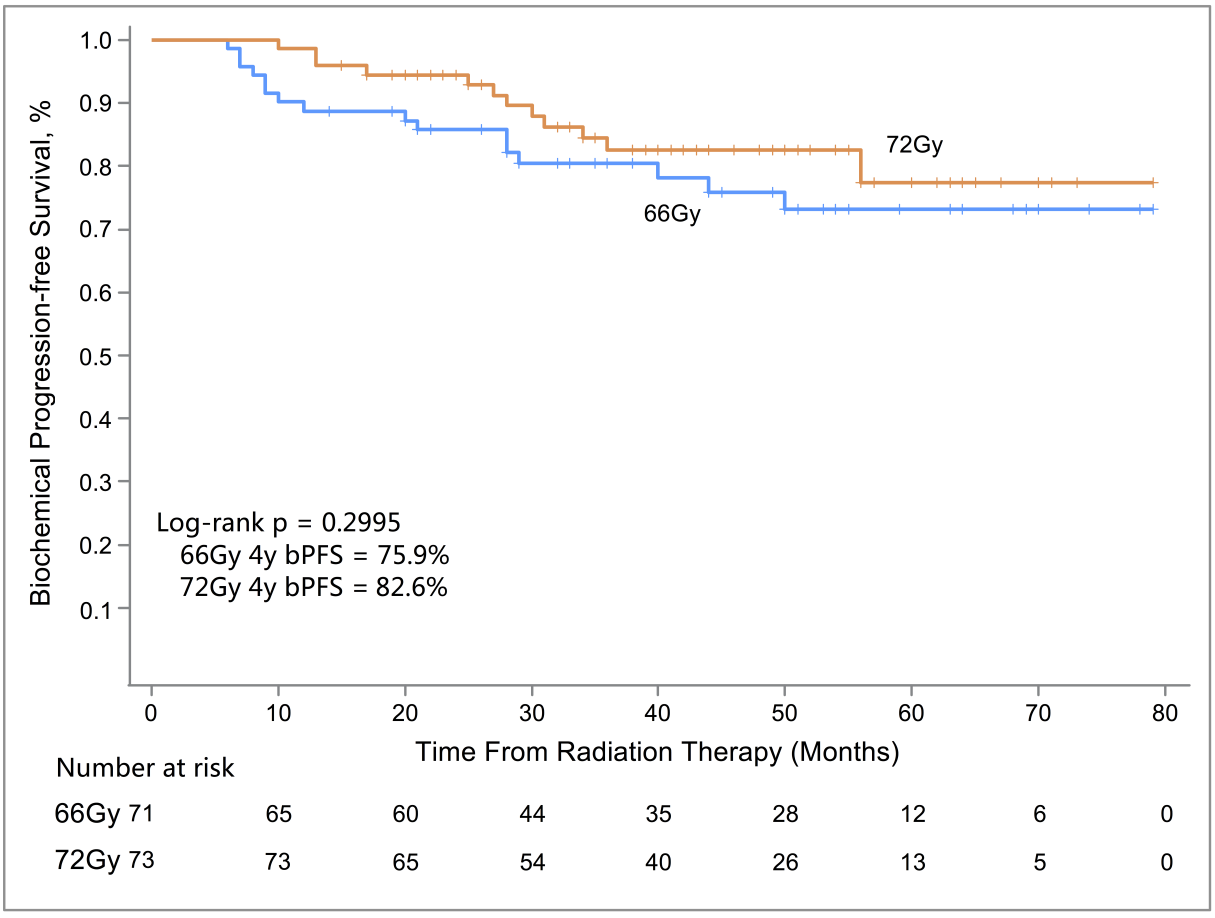
Table 3. Urinary incontinence at baseline and one year after RT

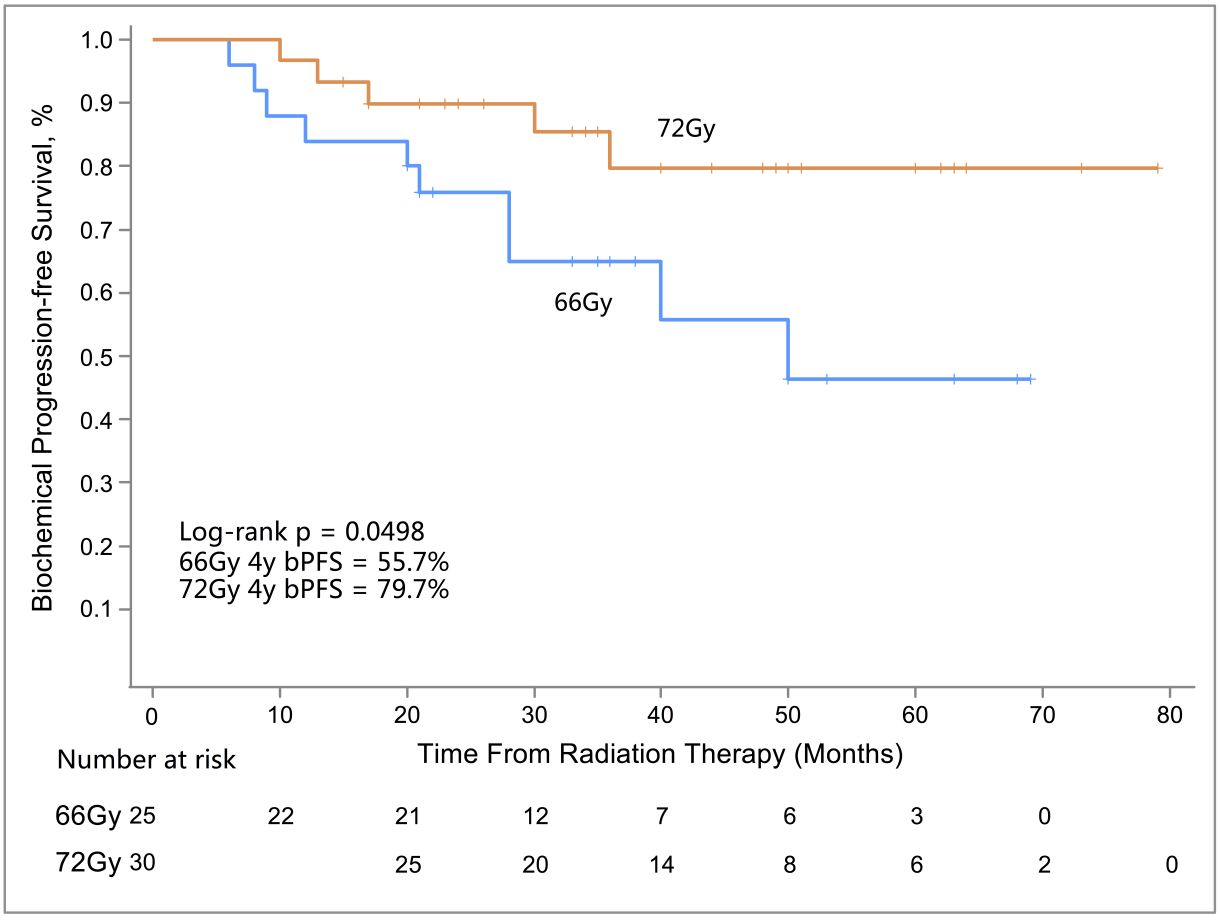
	66 Gy group	72 Gy group	All patients	P
Study sample, n	71	73	144	
Baseline* UI, n (%)				0.239
No	44 (62.0)	52 (71.2)	96 (66.7)	
Yes	27 (38.0)	21 (28.8)	48 (33.3)	
UI after RT, n (%)				0.412
No	37 (52.1)	43 (58.9)	80 (55.6)	
Yes	34 (47.9)	30 (41.1)	64 (44.4)	
Change of UI from baseline to 1 year after RT				
Study sample, n	27	21	48	
UI recovery, n (%)	7 (25.9)	2 (9.5)	9 (18.8)	0.296
UI stability, n (%)	16 (59.3)	14 (66.7)	30 (62.5)	
UI worsening, n (%)	4 (14.8)	5 (23.8)	9 (18.8)	

Abbreviations: RT = radiation therapy; UI = Urinary incontinence.

* Baseline means at the beginning of RT.


Cumulative incidence of late ≥ 2 GU toxicity, %
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
Log-rank p = 0.5212
72Gy
66Gy
0
10
20
30
40
50
60
70
80
Time From Radiation Therapy (Months)
Number at risk
66Gy 71 71 67 53 41 33 16 7 0
72Gy 73 73 69 59 43 28 13 5 0


Biochemical Progression-free Survival, %
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
72Gy
66Gy
Log-rank p = 0.2995
66Gy 4y bPFS = 75.9%
72Gy 4y bPFS = 82.6%
0
10
20
30
40
50
60
70
80
Time From Radiation Therapy (Months)
Number at risk
66Gy 71 65 60 44 35 28 12 6 0
72Gy 73 73 65 54 40 26 13 5 0


Biochemical Progression-free Survival, %
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
72Gy
66Gy
Log-rank p = 0.0498
66Gy 4y bPFS = 55.7%
72Gy 4y bPFS = 79.7%
0
10
20
30
40
50
60
70
80
Time From Radiation Therapy (Months)
Number at risk
66Gy 25 22 21 12 7 6 3 0
72Gy 30 25 20 14 8 6 2 0