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Long-term Outcomes of Radiotherapy Regimen of 72 Gy in 30 Fractions for Prostate Cancer

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Abstract. *Background/Aim: The long-term efficacy and safety of moderately hypofractionated intensity-modulated radiation therapy (MH-IMRT) in prostate cancer remains uncertain. This study aimed to evaluate MH-IMRT regimen of 72 Gy in 30 fractions in patients with prostate cancer. Patients and Methods: The outcomes of 412 consecutive prostate cancer patients, who received MH-IMRT between May 2007 and December 2012, were retrospectively reviewed. The median patient age was 70.9 (range=50-84) years. Late gastrointestinal (GI) and genitourinary (GU) toxicity rates were evaluated according to the CTCAE ver. 3.0. The overall survival, biochemical relapse-free survival rate (bRFS), late GI toxicity, and GU toxicity rates were analyzed with the Kaplan–Meier method. Results: The median follow-up was 71.5 (range, 1.4-124.8) months. The 5-year bRFS rate was 93.2%. The 5-year grade ≥2 late GI and GU toxicity rates were 3.3% and 4.5%, respectively. Conclusion: MH-IMRT regimen of 72 Gy in 30 fractions was effective and safe for prostate cancer patients.*

Prostate cancer is one of the most common cancer types among males, with global incidence and mortality rates in 2012 estimated at 1,100,000 and 307,000 cases, respectively (1). Although lower than in Western countries, the incidence of prostate cancer in Japan continues to increase annually and is expected to be the second most common cancer, after lung cancer, among males until 2020 (2, 3).

External-beam radiotherapy (RT), as well as radical prostatectomy, for localized prostate cancer therapy have been associated with lower incidences of disease progression and metastases compared with active monitoring (4). The dosages of conventional fractionation, moderate hypofractionation, and extreme hypofractionation are approximately defined as 1.8-2.0, 2.2-4, and >4 Gy, respectively (5). RT with fewer and larger fractions is assumed to be suitable for prostate cancer because the alpha-beta ratio of prostate cancer is relatively lower (approximately 1-3 Gy) than for other cancers (approximately 10 Gy) and the surrounding tissue (*i.e.*, the rectum and bladder) (approximately 3-5 Gy) in a linear-quadratic model (6, 7). In brief, hypofractionated RT (H-RT) might theoretically improve control of prostate cancer and reduce toxicities, as compared with conventional RT (C-RT). A common problem with C-RT at 1.8-2 Gy per fraction is the long treatment duration of approximately 2 months (8, 9). On the other hand, H-RT is more convenient for patients and decreases the costs of treatment (10). Recent studies in Western countries demonstrated that moderately hypofractionated RT (MH-RT) for localized prostate cancer was not less effective or safe than C-RT (5, 11). Based on these promising results, MH-RT presents a viable treatment option for prostate cancer in non-Western populations, including those in East Asia. However, the efficacy and safety of MH-RT for patients in East Asia remain unknown.

Moderately hypofractionated intensity-modulated radiation therapy (MH-IMRT) was introduced for patients with prostate cancer in our institution in 2007. At that time, it was rare to treat prostate cancer patients with MH-IMRT in East Asia. The aim of the present study was to retrospectively assess the treatment outcomes of a MH-IMRT regimen of 72 Gy in 30 fractions for the treatment of prostate cancer in an East Asian population.

Materials and Methods

Patient population and pretreatment evaluation. The institutional review board of Miyakojima IGRT Clinic approved the study protocol and all the participants submitted informed consent prior to

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treatment. Between May 2007 and December 2012, 412 patients with prostate cancer were treated with an MH-IMRT regimen of 72 Gy in 30 fractions. Pretreatment evaluation included complete medical history, physical examination, complete blood cell count, biochemical screening profile, prostate-specific antigen (PSA) testing, magnetic resonance imaging, and biopsy. Risk groups were classified according to the clinical practice guidelines of the National Comprehensive Cancer Network (NCCN) (12). Exclusion criteria included lymph node involvement, metastatic disease, any other active malignancy, prior pelvic radiotherapy, and prostatectomy.

Patient characteristics. Patient characteristics are listed in Table I. The median follow-up duration was 71.5 (range, 1.4-124.8) months and the median patient age was 70.9 (range, 50-84) years. According to the NCCN criteria, 41 (10.0%) patients were classified as low-risk, 150 (36.4%) as intermediate-risk, 185 (44.9%) as high-risk, and 36 (8.7%) as very high-risk. Neoadjuvant and adjuvant androgen deprivation therapy (ADT) were delivered to 296 (71.8%) and 190 (46.2%) patients, respectively. Neoadjuvant ADT was delivered to 34.1% of patients with low-risk disease, 51.7% with intermediate-risk, 92.0% with high-risk, and 97.2% with very high-risk disease, and adjuvant ADT was delivered to 14.6%, 21.9%, 66.3%, and 83.3%, respectively. The median duration of neoadjuvant and adjuvant ADT were 5.9 (range, 0.1-96.2) and 18.8 (range, 0.1-103.3) months, respectively.

Treatment. All the patients were evaluated by non-contrast computed tomography (CT) in the supine position using a BrightSpeed™ CT scanner (GE Healthcare, Chicago, IL, USA). Anatomic contouring of the prostate, seminal vesicles, rectum, and bladder was performed. For low-risk patients, the clinical target volume (CTV) was defined as the prostate and for all other patients, the CTV was created by adding a margin of 2 mm in all directions from the prostate and seminal vesicles. The planning target volume (PTV) was generated by adding a margin of 5 mm in all directions other than in the posterior direction, where the margin was 3 mm. For low-risk patients, the radiation dose was 72 Gy in 30 fractions to the PTV of the prostate. For all other patients, the radiation dose was 72 Gy in 30 fractions to the PTV of the prostate and 66 Gy in 30 fractions to the PTV of the seminal vesicles with the simultaneously integrated boost technique. To optimize the dose distribution within the PTV, $V_{107\%}$≤3% (a volume of at least 3% within PTV should not receive >107% of the prescribed dose) was used along with $D_{95\%}$≥97% (a volume of ≥97% within the PTV can receive a dose that is 95% of the prescribed dose). The rectal dose-volume constraints were D_{max}≤105%, $V_{90\%}$≤8 cc, $V_{80\%}$≤10 cc, $V_{70\%}$≤13 cc, and $V_{50\%}$≤19 cc. The bladder dose-volume constraints were D_{max}≤105%, $V_{90\%}$≤20%, $V_{80\%}$≤30%, and $V_{70\%}$≤40%. Plans were generated with BrainSCAN (ver. 5.31) RT Treatment Planning Software (Brainlab AG, Munich, Germany) with the pencil beam algorithm before November 2010 and thereafter with iPlan RT Dose (ver. 4.1.2) software (Brainlab AG) with the Monte Carlo algorithm. All the patients underwent 8- or 9-field IMRT using a 6-MV linear accelerator (Novalis, Brainlab AG). Daily image guidance was performed. Treatments were performed on consecutive days.

Evaluation of clinical outcomes. In principle, the biochemical response was evaluated according to the PSA level and the incidences of rectal and urinary bleeding every 3 months after treatment. Biochemical failure was assessed using the Phoenix Nadir +2 definitions (an increase of ≥2 ng/ml above the nadir PSA level) (13). Late gastrointestinal (GI) and genitourinary (GU) toxicities were scored using the Common Terminology Criteria for Adverse Events ver. 3.0 criteria (14). The last visit or date of contact was used to censor surviving patients at the time of analysis.

Table I. *Patient characteristics*.

Characteristic	Median (range)
Age (years)	70.9 (50-84)
NCCN risk	n (% of total patients)
Low	41 (10.0%)
Intermediate	150 (36.4%)
High	185 (44.9%)
Very high	36 (8.7%)
	Median (range)
Initial PSA (ng/ml)	10.23 (0.89-500)
Gleason score	n (% of total patients)
≤6	95 (23.1%)
7	169 (41.0%)
8	64 (15.5%)
9	75 (18.2%)
10	9 (2.2%)
T stage	n (% of total patients)
T1c	108 (26.0%)
T2a	90 (21.6%)
T2b	41 (10.1%)
T2c	64 (16.1%)
T3a	72 (17.3%)
T3b	35 (8.4%)
T4	1 (0.2%)
Neoadjuvant ADT	296 (71.8%)
Adjuvant ADT	190 (46.2%)
	Median (range)
Median duration of neoadjuvant ADT (months)	5.9 (0.1-96.2)
Median duration of adjuvant ADT (months)	18.5 (0.1-103.3)

PSA, Prostate-specific antigen; ADT, androgen deprivation therapy; NCCN, National Comprehensive Cancer Network.

Statistical analysis. Data analysis was performed using JMP Pro 13 statistical software (SAS Institute Inc., Cary, NC, USA). All the intervals were calculated from the first day of RT. Biochemical relapse-free survival (bRFS), disease-specific survival, overall survival, and late GI and GU toxicity rates were calculated using the Kaplan–Meier method, and groups were using the log–rank test. A probability (p) value of <0.05 was considered statistically significant. Statistical tests were based on a two-sided significance level.

Results

Of the 412 patients, 35 experienced biochemical relapse (1 with low-risk disease, 12 with intermediate-risk, 14 with high-risk, and 8 with very high risk). The 5- and 8-year bRFS rates were 93.2% [95% confidence interval (CI)=90.0-95.3%] and 86.1% (95% CI=77.6-91.7%), respectively (Figure 1A). For patients with low-risk, intermediate-risk, high-risk, and

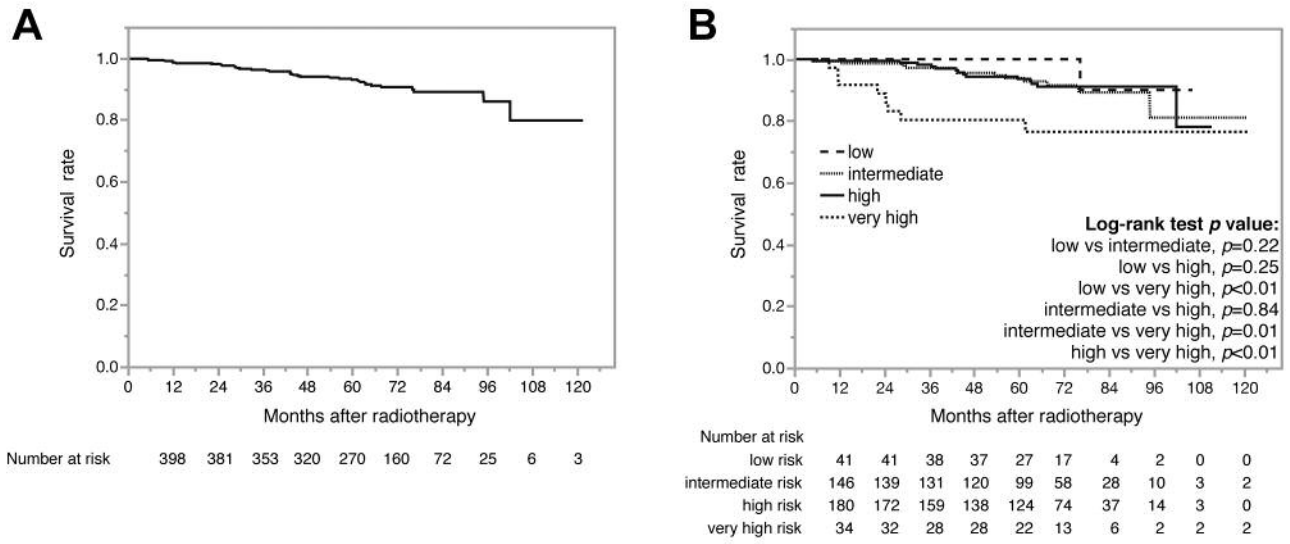

Figure 1. *Biochemical relapse-free survival (bRFS). (A) Overall bRFS and (B) bRFS rates stratified by NCCN risk groups. The 5-year actuarial prostate-specific antigen (PSA) relapse-free survival rates were 93.2%, 100%, 93.9%, 93.6%, and 80.3% for all, low-, intermediate-, high-risk, and very high-risk patients, respectively.*

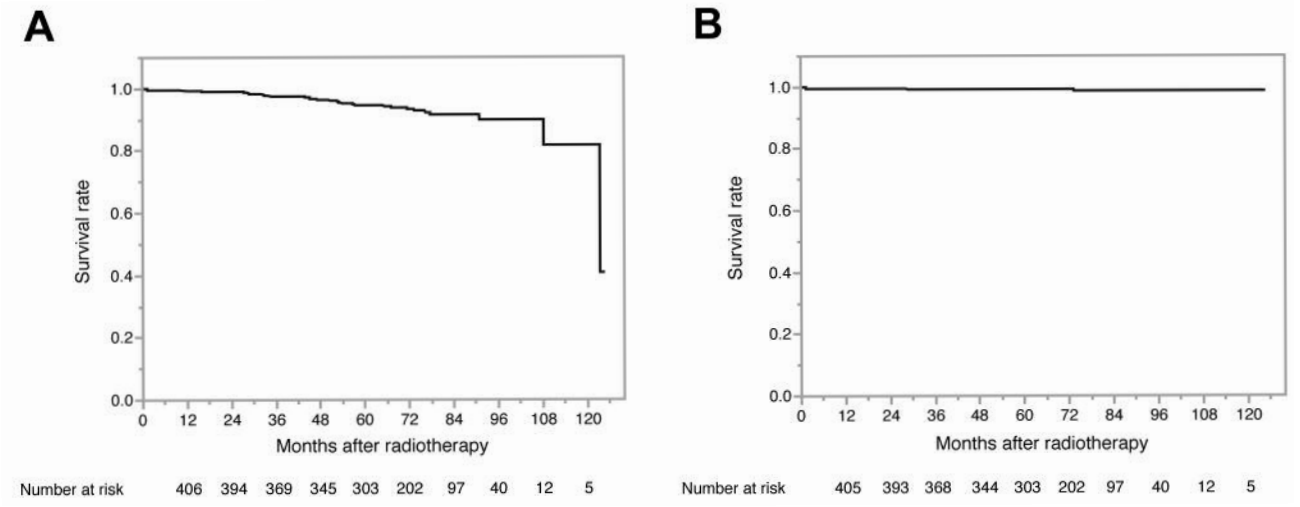

Figure 2. *Overall survival and disease-specific survival. (A) Overall survival and (B) disease-specific survival. The 5-year actuarial overall survival and disease-specific survival rates were 95.1% and 99.7%, respectively.*

very high-risk disease, the 5-year bRFS rates were 100%, 93.9% (95% CI=88.1-96.9%), 93.6% (95% CI=88.5-96.5%), and 80.3% (95% CI=64.0-90.3%), and the 8-year bRFS rates were 90% (95% CI=53.3-98.6%), 81.1% (95% CI=59.6-92.5%), 91.1% (95% CI=85.2-94.8%), and 76.5% (95% CI=59.3-87.8%), respectively. The log-rank test revealed that very high-risk group was statistically significant risk factor for bRFS comparing with other risk groups (*vs*. low-risk, $p<0.01$; *vs*. intermediate-risk, $p=0.01$; *vs*. high-risk, $p<0.01$). There was no statistical difference between low-, intermediate-, and high-risk groups (Figure 1B). The 5- and 8-year overall survival rates were 95.1% (95% CI=92.3-96.9%) and 90.4% (95% CI=84.8-94.0%), respectively, and the 5- and 8-year disease-specific survival rates were 99.7% (95% CI=98.1-100.0%) and 99.2% (95% CI=96.6-99.8%), respectively (Figure 2A and B). Over the course of the study

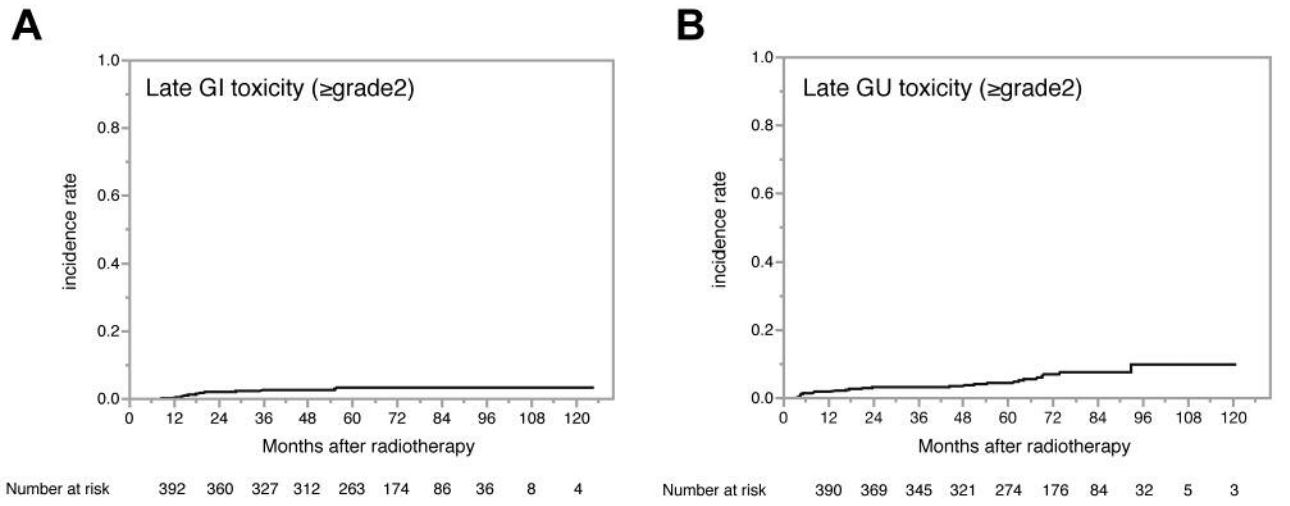

Figure 3. *Late gastrointestinal (GI) and genitourinary (GU) toxicities. Grade ≥2 late GI toxicity (A) and grade ≥2 late GU toxicity (B). The 5-year actuarial GI and GU toxicity rates were 3.3% and 4.5%, respectively.*

period, 29 (7.0%) patients died, including 2 (4.9%) who died from progression of prostate cancer. These 2 patients experienced biochemical relapse at 11.8 and 45.9 months, and died at 28.1 and 73.4 months after RT, respectively.

In total, 33 (8.0%), 8 (1.9%), and 4 (1.0%) patients developed grades 1, 2, and 3 GI toxicities, respectively. The patients with grade 3 GI toxicity experienced rectal bleeding, which required endoscopic ablation at 13.9, 15.7, 17.8, and 55.6 months after RT, respectively. No patient experienced grade ≥4 GI toxicity. The 5- and 8-year ≥grade 2 late GI toxicity rates were 3.3% (95% CI=1.9-5.8%) and 3.3% (95% CI=1.9-5.8%), respectively (Figure 3A). In total, 12 (2.9%), 19 (4.6%), and 6 (1.4%) patients developed grade 1, 2, and 3 GU toxicity, respectively. All the patients with grade 3 GU toxicity experienced bleeding from the bladder, that required endoscopic ablation at 3.7, 16.6, 54.4, 61.5, 73.8, and 92.8 months after RT, respectively. No patient experienced grade ≥4 GU toxicity. The 5- and 8-year grade ≥2 late GU toxicity rates were 4.5% (95% CI=2.8-7.1%) and 9.9% (95% CI=5.7-16.6%), respectively (Figure 3B).

Discussion

Over the last 2 years, several large phase 3 studies were conducted in Western countries to determine whether MH-RT is inferior to C-RT (Table II). According to these results, MH-RT is now an emerging strategy for the treatment of prostate cancer.

The FROFIT trial randomized 1,206 intermediate-risk prostate cancer patients to 78 Gy in 39 fractions over 7.8 weeks (C-RT) or 60 Gy in 20 fractions over 4 weeks (MH-RT). After a median follow-up of 6 years, the 5-year bRFS rates for the C-RT and MH-RT groups were both 85%, late grade ≥2 GI toxicity rates were 11% and 7%, and grade ≥2 GU toxicity rates were 19% and 20%, respectively. This study concluded MH-RT was not inferior to C-RT (15). The CHHiP trial randomized 3,216 predominantly intermediate-risk prostate cancer patients to 74 Gy in 37 fractions over 7.4 weeks (C-RT), 60 Gy in 20 fractions over 4 weeks (MH-RT1), or 57 Gy in 19 fractions over 3.8 weeks (MH-RT2). After a median follow-up of 5.2 years, the 5-year bRFS rates were 88.3%, 90.6%, and 85.9%, the late grade ≥2 GI toxicity rates were 13.7%, 11.9%, and 11.3%, and the grade ≥2 GU rates were 9.1%, 11.7%, and 9.6% in the C-RT, MH-RT1, and MH-RT2 groups, respectively. This study concluded MH-RT1 that only was not inferior to C-RT (16). The RTOG0415 trial randomized 1,115 low-risk prostate cancer patients to 73.8 Gy in 41 fractions over 8.2 weeks (C-RT) or 70 Gy in 28 fractions over 5.6 weeks (MH-RT). After a median follow-up of 5.8 years, the 5-year bRFS rates were 85.3% and 86.3%, the late grade ≥2 GI toxicity rates were 14% and 22%, and the grade ≥2 GU toxicity rates were 19% and 23% in the C-RT and MH-RT groups, respectively. This study concluded that despite the increased adverse events in H-RT-treated patients, MH-RT was not inferior to C-RT (17). The Dutch HYPRO trial randomized 820 predominantly high-risk prostate cancer patients to 78 Gy in 39 fractions over 7.8 weeks (C-RT) or 64.6 Gy in 19 fractions over 6.3 weeks (3 days a week, MH-RT). After a median follow-up of 5 years, the 5-year bRFS rates were 77.1% and 80.5%, the 3-year late grade ≥2 GI toxicity rates were 17.7% and 21.9%, and the grade

Table II. *Summary of published studies reporting treatment outcomes of hypofractionated RT for prostate cancer.*

Study	RT technique	Follow-up (median)	Risk group	Arm	5-year bRFS	Late GI ≥G2	Late GU ≥G2
PROFIT (15)	IMRT or 3D-CRT	6 years	Intermediate	78 Gy/39 Fx	85%	11%	19%
				60 Gy/20 Fx	85%	7%	20%
CHHiP (16)	IMRT	5.2 years	Mainly intermediate	74 Gy/37 Fx	88.3%	13.7%	9.1%
				60 Gy/20 Fx	90.6%	11.9%	11.7%
				57 Gy/19 Fx	85.9%	11.3%	6.6%
RTOG0415 (17)	IMRT or 3D-CRT	5.8 years	Low	73.8Gy/41 Fx	85.3%	14%	23%
				70 Gy/28 Fx	86.3%	22%	30%
Dutch HYPRO (18-19)	IMRT or 3D-CRT	5 years	Mainly high	78 Gy/39 Fx	77.1%	17.7%	39.0%
				64.6 Gy/19 Fx*	80.5%	21.9%	41.3%
MDACC (20)	IMRT	6 years	Mainly intermediate	75.6 Gy/42 Fx	Not reported	5.1%	16.5%
				72 Gy/30 Fx		10.0%	15.8%
Present study	IMRT	6 years	Mainly intermediate and high	72 Gy/30Fx	93.2%	3.3%	4.5%

RT, Radiation therapy; bRFS, biochemical relapse-free survival; GI, gastrointestinal toxicity; GU, genitourinary toxicity; IMRT, intensity-modulated radiation therapy; 3D-CRT, three dimensional-conformal radiation therapy; Fx, fractions. *3 days a week.

≥2 GU toxicity rates were 39.0% and 41.3% in the C-RT and MH-RT groups, respectively. These studies concluded MH-RT was not superior to C-RT, neither in terms of 5-year bRFS nor in terms of late GU and GI toxicities (18, 19). The MDACC trial randomized 203 predominantly intermediate-risk prostate cancer patients to 75.6 Gy in 42 fractions over 8.4 weeks (C-RT) or 72 Gy in 30 fractions over 6 weeks (MH-RT). After a median follow-up of 6 years, the late grade ≥2 GI toxicity rates were 16.5% and 15.8%, and the grade ≥2 GU toxicity rates were 5.1% and 10.0% in the C-RT and MH-RT groups, respectively. This study is ongoing (20). Taken together, the 5-year bRFSs rates ranged from 80.6% to 90.5% in the MH-RT arms. In our study, the overall 5-year bRFS rate was 93.2%. Given that our patients predominantly had intermediate- and high-risk disease, the results of this retrospective analysis were satisfactory. In addition, the rate of late GI and GU toxicities in our patients were relatively lower than in previous studies. In our study, the 5-year late grade ≥2 GI and GU toxicity rates were 3.3% and 4.5%, while previous studies reported rates of 7%-22% and 5.2%-39%, respectively. A possible reason for the high rate of late toxicities in previous studies seemed to be the radiation technique. In brief, several randomized studies, including the PROFIT, RTOG0415, and HYPRO trials, permitted IMRT and three dimensional-conformal radiation therapy (3D-CRT), while the CHHiP and MDACC trials permitted only IMRT. Thus, MH-IMRT for prostate cancer might be better than 3D-CRT. Finally, at least a 10-year follow-up should be considered after HF-IMRT, since late GU toxicity was more frequently encountered by long-term follow-up, as compared with late GI toxicity.

Conclusion

An MH-IMRT regimen of 72 Gy in 30 fractions effectively controlled the disease with acceptable toxicities in the studied cohort of East Asian prostate cancer patients.

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