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ORIGINAL ARTICLE

Prostate Disease

Impact of androgen-deprivation therapy on the outcome of dose-escalation prostate cancer radiotherapy without elective pelvic irradiation

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The benefit of androgen-deprivation therapy (ADT) in combination with dose-escalated radiotherapy (DERT) for localized prostate cancer has not been determined in randomized studies. In this study, the benefit of ADT was assessed in patients uniformly treated with dose-escalated intensity-modulated radiation therapy (IMRT) to the prostate and seminal vesicles but not pelvis. In all, 419 patients with localized prostate adenocarcinoma underwent definitive IMRT (cumulative dose 78 Gy), with 32.6%, 33.1%, 32.1%, and 2.1% having T1 through T4 disease, respectively, and 51.2% having high-risk disease. ADT was given to 76.1% of patients. With a median follow-up of 60 months, 5-year biochemical failure-free, disease-free, and overall survival rates were 87%, 86%, and 87%, respectively. T stage was an independent predictor of all three rates. Five-year pelvic nodal recurrence rate was 2.9%. ADT improved biochemical failure-free and disease-free survival but not overall survival. ADT showed benefit in high-risk disease but not intermediate-risk disease. Late gastrointestinal and genitourinary toxicities ≥ grade 2 occurred in 11.0% and 6.7%, respectively. In conclusion, DERT with 78 Gy yields good disease control and low rate of pelvic nodal recurrence. ADT improves disease-free survival in patients with high-risk but not intermediate-risk disease.

INTRODUCTION

Prostate cancer is the second most common cancer in males worldwide.[1] Radiotherapy (RT) to prostate cancer achieves durable local disease control and is frequently used in patients unsuitable for radical prostatectomy. Dose-escalation trials conducted at different institutions showed that prostate RT with the dose of 78 Gy greatly improved biochemical failure-free and distant metastasis-free survival.[2–4] Recent advances in radiation delivery including intensity-modulated RT (IMRT) and image guidance have facilitated adaptation of dose-escalation in prostate RT while minimizing toxicity.[5,6]

For locally advanced and adverse-risk prostate cancer, randomized studies had shown survival benefit when androgen-deprivation therapy (ADT) was used in combination with RT.[7–10] These trials were carried out before dose-escalated RT (DERT) and the doses used in those studies were below 70 Gy. To date, there is scanty prospective randomized evidence for the role of ADT in DERT of prostate cancer. Furthermore, retrospective analyses of ADT in prostate cancer patients who undergo DERT are often confounded by the use of less than a 78-Gy RT dose, elective pelvic irradiation, and a range of RT delivery techniques.[11–13]

In this study, we aimed to determine the survival and disease control benefit of ADT in intermediate- and high-risk prostate cancer patients treated with 78-Gy DERT. At our institution, prostate cancer patients were treated definitively by delivering 78-Gy IMRT to the prostate and involved seminal vesicle(s) without elective pelvic nodal irradiation. Using this cohort of patients, all receiving similar radiotherapy exposure (field configuration and dosimetry), we investigated the impact of ADT on survival and patterns of failure in prostate cancer patients after DERT.

MATERIALS AND METHODS

We performed retrospective chart review of patients with localized prostate cancer who underwent definitive radiotherapy at National Taiwan University Hospital, Taipei, Taiwan, China. The study has been approved by the Institutional Ethics Committees in which it was performed and patients gave informed consent to the study. All patients had initial T stage determined by digital rectal examination. The cohort consisted entirely of Asian patients. All patients underwent step-and-shoot IMRT, tomotherapy, or volumetric-modulated arc therapy (VMAT). Patients were immobilized with vacuum cushions, with full bladder, and placed in prone positions unless contraindicated by comorbidities. An endorectal balloon with 60 cc of air was placed for each treatment fraction. The clinical target volume (CTV) consisted of the prostate and involved seminal vesicle(s). The planning target

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volume (PTV) expansions were 6 mm posteriorly (rectum), 6 mm inferiorly, and 10 mm anteriorly, bilaterally, and superiorly from the CTV. A total of 78 Gy was delivered in 39 fractions to 95% of the PTV. Routine on-board cone-beam computed tomography was used two to three times a week to verify target positions.

Regional failure was defined as pelvic lymph node recurrence. Distant failures were defined as metastases to lymph nodes located outside of the pelvis, bone, and other organs. Biochemical failure was defined according to the Phoenix definition (prostate-specific antigen [PSA] elevation exceeding nadir plus 2 ng ml^{-1}). Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) of the abdomen and pelvis and Technetium-99m bone scan were performed within 1 month of the biochemical recurrence. Gastrointestinal (GI) and genitourinary (GU) toxicities were determined using the Common Toxicity Criteria for Adverse Events version 4.0. Follow-up visits were every 3 months in the first 3 years and then every 6 months. Patients had PSA checked and toxicity evaluated at every visit.

The administration of ADT was left to the discretion of the prescribing physicians, mainly for intermediate- and high-risk patients and patients with large-sized prostate (for reducing prostate size before RT). ADT was administered neoadjuvantly more than 2 months before RT and continued concurrently with RT. Alternatively, maintenance ADT was administered concurrently with RT and maintained after RT for 2 years. Some patients received additional maintenance ADT as suggested by the National Comprehensive Cancer Network (NCCN) guideline. Patients typically received gonadotropin-releasing hormone (GnRH) agonist as monotherapy. An oral anti-androgen was usually initiated at the start of GnRH agonist therapy to prevent a rebound surge of androgen. A subset of patients received total androgen blockage with a combination of GnRH agonist and anti-androgen agent for their high-risk disease.

Follow-up duration, survival time, and event time were calculated from the start of RT. Kaplan–Meier analysis was performed for overall survival (OS), biochemical failure-free survival (BCFFS), and disease-free survival (DFS). Binary logistic regression was used for multivariate analysis. Chi-square analysis was used for toxicity profile analysis. All statistical analyses were performed using the software SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

RESULTS

A total of 433 prostate cancer patients received definitive radiotherapy to the prostate at the National Taiwan University Hospital, Taipei, Taiwan, China, from 2004 to 2010. After excluding 14 patients with M1 or N1 disease, we retrospectively analyzed survivals, patterns of failure, and toxicity profiles in 419 prostate cancer patients (**Figure 1**). Median follow-up was 60 months (range: 17 to 112 months). Median age at the time of diagnosis was 74 years. Based on PSA level, Gleason grade, and T stage, the risk of disease was high or very high in more than half of the patients (60.8%). All but 11 patients received 78 Gy. One patient who refused further treatment received only 76 Gy and 10 patients received only 74 Gy. RT techniques were step-and-shoot IMRT in 74.2%, VMAT in 16.9%, and tomotherapy in 8.8% of patients (**Table 1**). Only eight patients were treated in the supine position due to inability to lie prone. An endorectal balloon was placed at each RT session in 69.5% of patients.

Median ADT duration was 10 months (**Table 1**). ADT duration ranged from 2 to 72 months. ADT was used in 73.0% of the intermediate-risk patients and 96.9% of the high-risk patients. Short-course ADT (≤6 months) was used in 27.4% of patients.
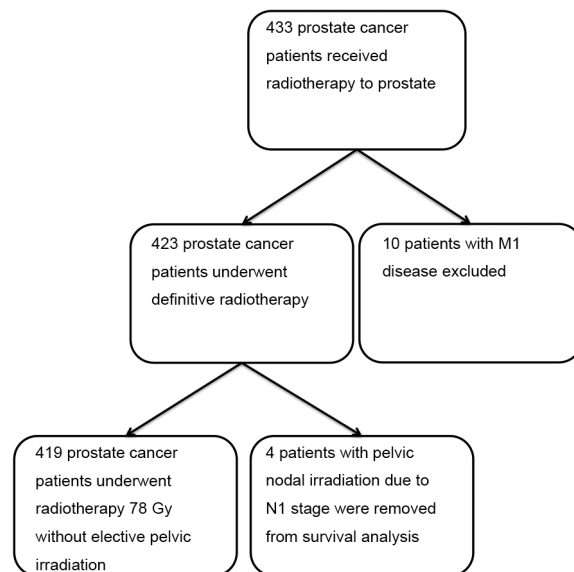

Figure 1: Selection scheme of prostate cancer patients who underwent radiotherapy to prostate/involved seminal vesicles at the National Taiwan University Hospital from 2004 to 2010.

Long-course ADT (>6 months) was used in 46.1% of patients. Patients with age ≥70 yeras less frequently received ADT >6 months (age <70: 58.2% *vs* age ≥70: 46.4%). Patients with high-risk disease more frequently received ADT >6 months (intermediate-risk: 37.7% *vs* high-risk: 56.1%). Neoadjuvant ADT was given in 57.3% of patients. Concurrent and maintenance ADTs were used in 73.5% and 55.1% of patients, respectively.

Five-year BCFFS, DFS, and OS were 87%, 86%, and 87%, respectively. Biopsy proven local failure, regional pelvic lymph node failure, and distant failure (24 in bone, 4 in distant lymph node, and 1 in liver) occurred in 2, 12, and 29 patients, respectively. Fifty-four patients had biochemical failure according to the Phoenix definition. On univariate analysis, clinical T stage, Gleason grade, and risk group but not PSA were associated with all BCFFS ($P < 0.001$, $P < 0.001$, and $P = 0.423$), DFS ($P < 0.001$, $P < 0.001$, and $P = 0.146$), and OS outcomes ($P = 0.007$, $P = 0.046$, and $P = 0.546$). The use of ADT was associated with improved BCFFS ($P = 0.028$) and DFS ($P = 0.009$) but not OS ($P = 0.53$). Neither ADT duration (short-course ≤ 6 month *vs* long-course >6 months) nor treatment technique had impact on BCFFS, DFS, or OS. On multivariate analysis, T stage (odds ratio = 0.27, $P < 0.001$ and odds ratio = 0.24, $P < 0.001$), Gleason grade (odds ratio = 0.29, $P < 0.001$ and odds ratio = 0.33, $P < 0.001$), and the use of ADT (odds ratio = 2.40, $P = 0.014$ and odds ratio = 2.90, $P = 0.002$) were independent factors associated with BCFFS and DFS, respectively. T stage was the only independent prognosticator (odds ratio = 0.36 for T3–T4 *vs* T1–T2, $P = 0.003$) associated with OS (**Table 2**). As compared to patients with T1–T2 disease, patients with T3–T4 disease had worse 5-year BCFFS (77% *vs* 93%, $P < 0.001$), DFS (74% *vs* 92%, $P < 0.001$), and OS (81% *vs* 92%, $P = 0.007$) (**Figure 2**).

The use of ADT was notably an independent factor for BCFFS and DFS. Patients who received concurrent ADT with RT had improved 5-year BCFFS (88% *vs* 83%, $P = 0.028$) and DFS (88% *vs* 80% $P = 0.009$) but not OS (85% *vs* 89%, $P = 0.53$) (**Table 2**). Both short-course and long-course ADT improved BCFFS (88% and 82% *vs* 67%, $P < 0.001$)

Table 1: Patient characteristics, tumor trait, RT dose and technique, and status of ADT (*n*=419)

Variable	n (%)
Age (years)	
<70	139 (33.2)
≥70	280 (66.8)
cT stage	
1a	5 (1.2)
1b	6 (1.4)
1c	127 (30.3)
2a	53 (12.6)
2b	43 (10.3)
2c	42 (10.0)
3a	74 (17.7)
3b	60 (14.3)
4	9 (2.1)
Gleason	
<7	128 (30.5)
7	189 (45.1)
8–10	102 (24.3)
PSA (ng ml⁻¹)	
<10	121 (28.9)
10–20	124 (29.6)
≥20	174 (41.5)
Risk	
Low	42 (9.8)
Intermediate	122 (29.1)
High	187 (44.6)
Very high	68 (16.2)
RT dose (Gy)	
<78	11 (2.6)
78	408 (97.4)
Technique	
Step and shoot IMRT	311 (74.2)
VMAT	71 (16.9)
Tomotherapy	37 (8.8)
Patient setup	
Supine	8 (1.9)
Prone	411 (98.1)
Endorectal balloon	
No	128 (30.5)
Yes	291 (69.5)
ADT	
No ADT	111 (26.5)
ADT	308 (73.5)
Type	
Neoadjuvant	240 (57.3)
Concurrent	308 (73.5)
Maintenance	231 (55.1)
Duration	
Median (months)	10
Range (months)	2–72
≤6	115 (27.4)
>6	193 (46.1)
Total	419 (100.0)

PSA: prostate-specific antigen; RT: radiation treatment; ADT: androgen-deprivation therapy; IMRT: intensity-modulated radiation therapy; VMAT: volumetric-modulated arc therapy
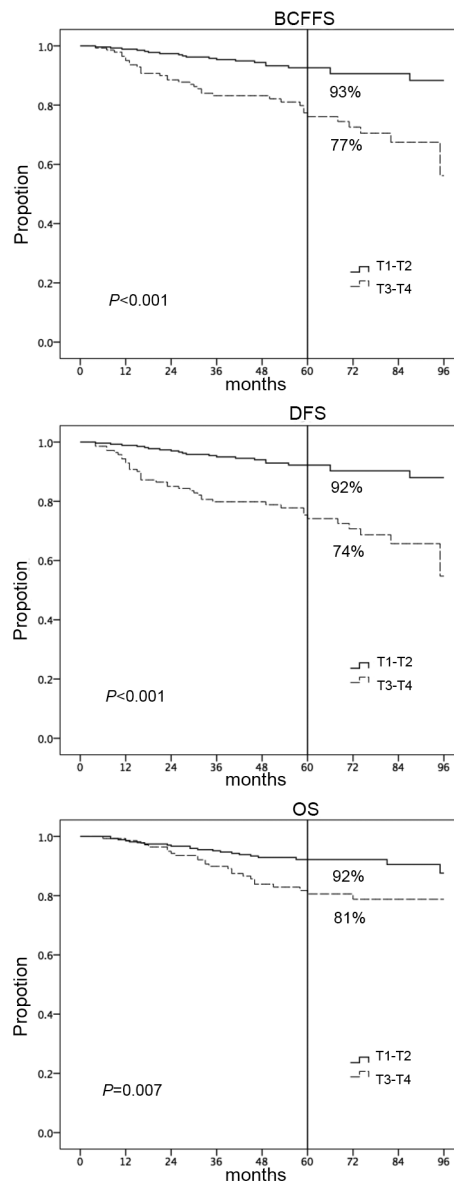

Figure 2: Kaplan–Meier analyses of biochemical failure-free survival (BCFFS), disease-free survival (DFS), and overall survival (OS) of 419 prostate cancer patients by T1–T2 versus T3–T4.

intermediate-risk: $P = 0.651$), or DFS in patients with intermediate-risk of the disease ($P = 0.24$) (**Figure 3**).

Prostate RT incurred ≥ grade 2 acute gastrointestinal (GI) and genitourinary (GU) toxicity in 9.5% and 5.7% of patients, respectively. No patient suffered from late grade 4 or 5 GI toxicity or late grade 5 GU toxicity. Three patients (0.7%) had late grade 4 hematuria that required surgical (cystoscopic) interventions. Cumulative 5-year incidences of late GI toxicity and GU toxicity grade 2/grade 3 were 6.9%/4.1% and 3.6%/2.4%, respectively (**Table 3**).

DISCUSSION

Dose-escalation to 78 Gy is becoming routine given its benefits, which have been shown by prior randomized studies. Since 2004 at our institution, the treatment in all prostate cancer patients has been conformal radiation to a dose level of 78 Gy covering only the prostate and involved seminal

and DFS (87% and 82% *vs* 62%, $P < 0.001$) in patients with high-risk of prostate cancer but had no effect on OS, BCFFS (high-risk: $P = 0.102$;

Table 2: 5-year overall survival, BCF-free survival, and disease-free survival with univariate and multivariate Cox regression analyses

	BCF-free survival					Disease-free survival					Overall survival				
	Rate (%)	P	OR	P	95% CI	Rate (%)	P	OR	P	95% CI	Rate (%)	P	OR	P	95% CI
Age															
≥70	82	0.271	1.54	0.176	0.83–2.87	80	0.02*	1.8	0.058	0.98–3.28	88	0.324	0.62	0.178	0.31–1.24
<70	89					89					89				
cT															
T3–T4	77	<0.001*	0.27	<0.001*		74	<0.001*	0.24	<0.001*	0.12–0.47	81	0.007*	0.36	0.003*	0.18–0.71
T1–T2	93					92					92				
Gleason															
8–10	71	<0.001*	0.29	<0.001*	0.15–0.55	71	<0.001*	0.33	<0.001*	0.17–0.61	82	0.046*	0.67	0.256	0.34–1.33
<8	92					91					90				
PSA															
≥20	85	0.423	1.03	0.936	0.53–1.99	83	0.146	0.88	0.694	0.46–1.67	85	0.546	0.91	0.78	0.47–1.76
<20	89					88					90				
Risk															
Low	98	<0.001*				96	<0.001*				95	0.04*			
Intermediate	96					95					95				
High	84					86					86				
Very-high	65					62					80				
ADT															
Yes	88	0.028*	2.40	0.014*	1.20–4.80	88	0.009*	2.90	0.002*	1.46–5.74	89	0.53	1.82	0.087	0.92–3.61
No	83					80					85				
ADT duration (month)															
≤6	92	0.904				91	0.686				86	0.247			
>6	87					87					91				
Technique															
ssIMRT	86	0.456				85	0.394				86	0.07			
VMAT	95					94					95				
Tomo	92					92					100				
Total	87					86					87				

ADT: androgen-deprivation therapy; OR: odds ratio; ssIMRT: step-and-shoot intensity-modulated radiation therapy; VMAT: volumetric-modulated arc therapy; Tomo: helical tomotherapy; BCF: biochemical failure; CI: confidence interval; *P<0.05

Table 3: Acute (during radiotherapy and within 6 months after radiotherapy) and late (>6 months after radiotherapy) gastrointestinal and genitourinary toxicities (n=419)

CTCAE v4.0 toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
GI toxicity					
Acute	222 (53.0)	157 (37.5)	40 (9.5)	0	0
Late	325 (77.6)	48 (11.5)	29 (6.9)	17 (4.1)	0
GU toxicity					
Acute	260 (62.1)	135 (32.2)	23 (5.5)	1 (0.2)	0
Late	355 (84.7)	35 (8.4)	15 (3.6)	10 (2.4)	3 (0.7)

CTCAE v4.0: Common Toxicity Criteria for Adverse Events Version 4.0; GU: genitourinary; GI: gastrointestinal

vesicles. Our study showed equivalent or better disease control and toxicity profiles when compared to previous DERT randomized controlled trials.[2–4] In addition, our result showed improved BCFFS and DFS when ADT is combined with DERT. The NCCN guideline recommends short-term ADT of 4–6 months and long-term ADT of 2–3 years with RT for intermediate- and high-risk prostate cancer patients, respectively. However, these recommendations are based on randomized trials conducted with RT dose <70 Gy. To date, there is scanty randomized evidence to support the combined use of ADT with DERT to treat prostate cancer.

Results from previous retrospective analyses favor the use of ADT in high-risk prostate cancer patients treated with DERT. Valicenti *et al.* retrospectively analyzed the data from dose-escalation trial RTOG 9406 and found a strong trend toward improved disease-free survival associated with long-term ADT (P = 0.0507) in patients with PSA >20 who received a cumulative RT dose above 73.8 Gy.[14] A review by Feng *et al.* of the results of DERT (75–79.2 Gy) in patients with high-risk prostate cancer[13] found that addition of ADT decreased the 5-year cumulative incidence of biochemical failure and distant metastases (35% *vs* 13%, P < 0.001). Similar studies were also performed in intermediate-risk prostate cancer patients treated with DERT. Castle *et al.* reported that 6-month ADT improved the 5-year DFS of intermediate-risk patients treated with DERT (75.6 or 78 Gy) (97% *vs* 88%, P = 0.04).[12] Bian *et al.* also found that the addition of short-term ADT to DERT (>75 Gy) improved failure-free survival in patients with an intermediate-risk of prostate cancer (hazard ratio 0.36, P = 0.004).[11] Both studies showed that disease control due to ADT was more pronounced in patients with unfavorable intermediate-risk prostate cancer (GS 4 + 3, T2c, or >50% core positive)[11,12] and that ADT played a role in DERT. Nevertheless, they were confounded by inclusion of patients receiving <78 Gy and patients receiving elective pelvic irradiation, and by differences in treatment techniques. The recent Spanish randomized trial showed the favorable biochemical control by adding long-term ADT, as compared to short-term ADT, to DERT for patients with intermediate- and high-risk disease.[15]

In this study, only the prostate and involved seminal vesicles were treated with DERT, only 78 Gy was administered, and only IMRT was performed, thereby eliminating differences in RT fields and techniques. Therefore, as compared to the treatment planning and delivery in
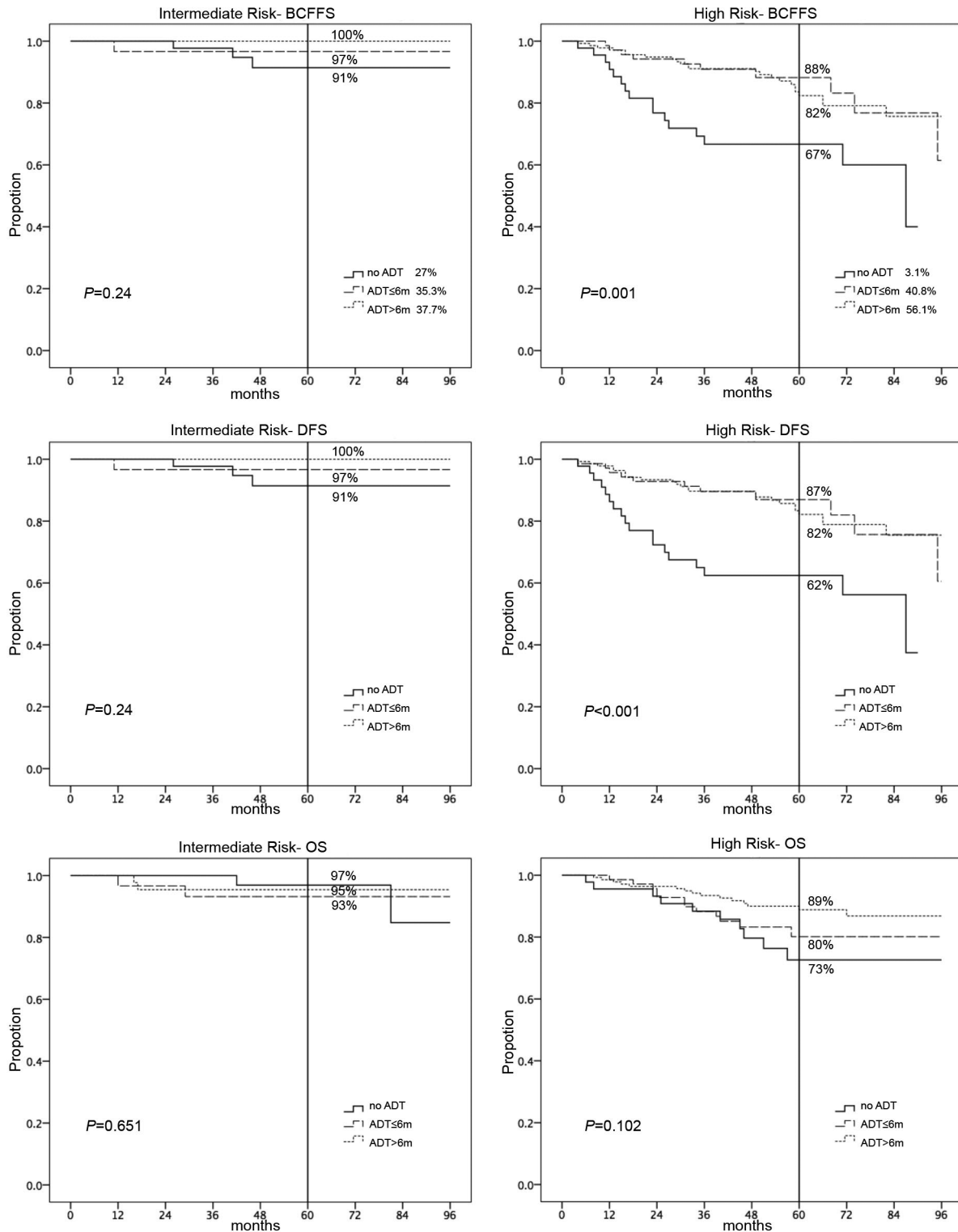
Figure 3: Kaplan–Meier analyses of biochemical failure-free survival (BCFFS), disease-free survival (DFS), and overall survival (OS) by androgen-deprivation therapy (ADT) in intermediate-risk and high-risk prostate cancer patients.

other retrospective studies, our study was uniform, allowing for better risk-stratified assessment of hormone efficacy. In our study, the addition of ADT improved DFS, especially in high-risk patients. In patients

with intermediate-risk prostate cancer, dose-escalation of RT alone resulted in a 5-year DFS rate of over 90%. The use of short-course ADT or long-course ADT added no benefit to DFS (97% and 100% *vs*

91%, *P* = 0.24) (**Figure 2**). Notably, intermediate-risk patients treated with long-course ADT >6 months had no disease recurrence at 5 years. Our result contradicts previous retrospective analyses by Bian *et al.* and Castle *et al.*[11,12] Possibly the high dose (78 Gy) used in our study and image guidance with IMRT had improved outcome sufficiently to eliminate any observable ADT benefit. Currently, RTOG study 0815 is randomizing intermediate-risk patients to receive either DERT alone or DERT combined with short-term ADT. These results will guide us in avoiding the side effects of ADT (e.g., gynecomastia, hot flush, muscle wasting, osteoporosis, decreased libido, impotence, and risk of cardiovascular disease)[16] from unnecessary treatment.

To ensure precise delivery of high-dose radiation, many institutions utilize implanted fiducials or electromagnetic transponders to track organ motion. At our institution, we used an alternative approach, endorectal balloons, to immobilize the prostate and rectum while treating our patients in the prone position. Target locations were verified with scheduled cone-beam computed tomography. This combined use of endorectal balloons and image guidance has been proven effective in prostate immobilization and localization.[17] Michalski *et al.* reported a 3-year grade 2+ late GI toxicity rate of 15.1% in prostate cancer patients treated with IMRT (79.2 Gy).[18] Comparatively, the grade 2+ late GI toxicity rate in our cohort was 11.0% and endorectal balloon use further decreased the incidence to 8.6%. Our approach yielded acceptable rates of DERT-related GI toxicity in prostate cancer patients.

Our study had several shortcomings. First, patients who did not receive ADT possibly had clinical contraindications such as poor performance status or severe cardiovascular disease. Patients' comorbidities could have influenced estimates of the disease control benefit of ADT. However, the detailed information of these comorbidities was not available for each patient in this retrospective study. Second, our patient population was entirely Asian, which may make our finding less applicable to patients in Western countries, especially with more ADT use in Asia.[19] Despite these shortcomings, our retrospective analysis of a large cohort of patients who underwent uniform radiation treatment provides useful information regarding the addition of ADT to DERT. Our data may represent the quality of care in specific Asian countries and provide the useful information of ADT combined with DERT.

CONCLUSIONS

DERT delivered to the prostate and involved seminal vesicles provides durable disease control with few pelvic nodal recurrences and distant metastases. Moreover, sparing the pelvis in DERT of the prostate lowers the rate of severe late GI toxicity. DERT alone results in excellent disease control in intermediate-risk disease, yet adding ADT provides no additional benefit. Combining ADT with DERT improves disease-free survival in high-risk disease.

AUTHOR CONTRIBUTIONS

WHH, CYH, and JCH designed the study, analyzed the data, and drafted the manuscript. CCW, KHL, CHC, HJY, SPL, MKL, and YSP designed the study and analyzed the data. All authors reviewed and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing financial interests or other conflicts of interest in relation to this study.

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