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Research Article

Prostate-specific antigen kinetics in hypofractionated radiation therapy alone for intermediate- and high-risk localized prostate cancer

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ABSTRACT

Background: This study aimed to evaluate the treatment outcomes and define the prostate-specific antigen (PSA) kinetics as potential prognostic factors in patients with intermediate- or high-risk localized prostate cancer (PCa) who underwent moderately hypofractionated radiation therapy.

Methods: The study retrospectively reviewed the medical records of 149 patients with intermediate- or high-risk localized PCa who underwent definitive radiation therapy (70 Gy in 28 fractions) without androgen deprivation therapy. Clinical outcomes were analyzed based on risk stratification (favorable-intermediate, unfavorable-intermediate, and high-risk). The biochemical failure rate (BFR) and clinical failure rate (CFR) were stratified based on the PSA nadir and the time to the PSA nadir to identify the prognostic effect of PSA kinetics. Acute and late genitourinary and gastrointestinal adverse events were analyzed.

Results: Significant differences were observed in the BFR and CFR according to risk stratification. No recurrence was observed in the favorable intermediate-risk group. The 7-year BFR and CFR for the unfavorable intermediate-risk and high-risk groups were 19.2% and 9.8%, and 31.1% and 25.3%, respectively. Patients with a PSA nadir >0.33 ng/mL or a time to the PSA nadir <36 months had a significantly greater BFR and CFR. The crude rate of grade 3 late adverse events was 3.4% (genitourinary: 0.7%; gastrointestinal: 2.7%). No grade 4–5 adverse event was reported.

Conclusion: A significant difference in clinical outcomes was observed according to risk stratification. The PSA nadir and time to the PSA nadir were strongly associated with the BFR and CFR. Therefore, PSA kinetics during follow-up are important for predicting prognosis.

1. Introduction

According to GLOBOCAN estimates, 1.4 million new cases of prostate cancer (PCa) were diagnosed in 2020, making it the second most frequently diagnosed cancer in men worldwide.[1] Most PCa cases are diagnosed as being confined to the prostate.[2] Radiation therapy (RT) has been widely used as a treatment modality for PCa, serving the purposes of definitive, adjuvant, and salvage therapy[3,4] RT, as a definitive treatment, has demonstrated comparable treatment efficacy to radical prostatectomy.[5–7] The current treatment approach for localized PCa differs according to the risk stratification, initially proposed by D'Amico et al.[8] Clinical guidelines recommend definitive local treatment, such as RT or surgery, for patients with localized PCa and sufficient expected survival; the benefit of androgen deprivation therapy (ADT) differs according to risk stratification.[9,10] This recommendation is based on several randomized trials. Although not identical to the criteria proposed by D'Amico et al., trials that included patients at high risk of metastatic disease showed a survival benefit with ADT.[11,12] In contrast,

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results from trials with mainly low- and intermediate-risk cohorts showed that only a subgroup of the intermediate-risk group benefits from ADT.[13,14]

Since 2008, our group has used hypofractionated RT for the definitive treatment of localized PCa. The routine dose-fractionation scheme was 70 Gy in 28 fractions; this dose-escalated[15,16] and hypofractionated[17,18] regimen was established by several randomized trials. Administration of ADT was initially uncommon in our institution but increased because published evidence showed the advantages of using ADT for high-risk patients. This study used the current risk stratification to evaluate the treatment outcomes of patients with intermediate- or high-risk localized PCa who underwent moderately hypofractionated RT alone and to determine whether prostate-specific antigen (PSA) kinetics are a potential prognostic factor.

2. Materials and methods

2.1. Study population

This study was approved by the Institutional Review Board of Samsung Medical Center (approval no. 2023-04-110). The requirement for informed consent was waived because of the retrospective nature of the study. The study retrospectively reviewed medical records of patients with localized PCa who were stratified as intermediate- or high-risk based on the D'Amico risk stratification[8] and underwent definitive RT without ADT between January 2008 and November 2018. An intermediate risk included one of the following: cT2b–cT2c, Gleason score 7, or PSA 10–20 ng/mL; a high risk included cT3a–cT4, Gleason score 8–10, or PSA >20 ng/mL. The eligibility criteria included RT with a moderately hypofractionated regimen of 70 Gy delivered in 28 fractions, using intensity-modulated RT or proton therapy. Patients with a follow-up period of <1 year were excluded. A total of 149 patients were included in this study.

2.2. Treatment

Patients with localized PCa confined to the prostate were referred to the radiation oncology department if they had sufficient expected survival and preferred RT as the definitive treatment option. Prior to treatment, regional and metastatic diseases were ruled out using pelvic magnetic resonance imaging (MRI), computed tomography (CT), and bone scans.

To prepare for RT, the patients first underwent simulation CT and MRI scans. A rectal balloon was used during the simulation scans and treatment sessions to ensure reproducibility. The extent of RT (prostate ± seminal vesicle-only vs. whole-pelvic RT) was determined at the discretion of the treating radiation oncologists based on risk stratification and risk factors, including the clinical T stage, Gleason score, and initial PSA level. For all patients, the high-risk clinical target volume (HR-CTV) was defined to include the prostate; the seminal vesicle was added to the HR-CTV if evidence of invasion was present. Patients who underwent elective regional pelvic lymph node irradiation were also administered low-risk (LR-CTV), including the obturator, external iliac, internal iliac, and presacral lymph node areas. The CTVs were delineated according to published guidelines.[19,20] The planning target volume (PTV) was constructed by expanding the CTV by 3–10 mm. The HR-PTV received a dose fractionation of 70 Gy in 28 fractions; the LR-PTV received 50.4 Gy in 28 fractions, using a simultaneous integrated boost technique. The plans were optimized to cover 95% of the PTV with 100% of the prescribed dose.

After completing RT, the patients were evaluated for acute adverse events one month later during a visit to the outpatient clinic. Subsequent follow-up appointments were scheduled every 3–6 months to examine the PSA level.

2.3. Clinical outcomes

The clinical outcomes analyzed in this study were the biochemical failure rate (BFR), clinical failure rate (CFR), overall survival (OS), and prostate cancer-specific survival (PCSS). Biochemical failure was defined as an increase in the PSA level of ≥2.0 ng/mL compared to the PSA nadir level after RT or the administration of salvage ADT. Clinical failure was defined as evidence of disease progression on physical or radiological examination. An OS event was defined as the death of a patient from any cause, and a PCSS event was defined as a PCa-related death determined by a board-certified radiation oncologist. Clinical outcomes were measured at the start of any treatment and were calculated using the Kaplan–Meier method.

The intermediate-risk group was subclassified as favorable or unfavorable based on the stratification proposed by Zumsteg et al.[21] and endorsed by the National Comprehensive Cancer Network (NCCN).[9] A favorable intermediate risk was defined as having only one intermediate-risk factor, a Gleason score of 6 (3 + 3) or 7 (3 + 4), and <50% positive biopsy cores. All other patients were classified as having an unfavorable intermediate risk. Clinical outcomes were compared among the favorable intermediate-risk, unfavorable intermediate-risk, and high-risk groups using the log-rank test.

2.4. PSA kinetics and multivariate analysis

Because PSA kinetics significantly affect treatment outcomes,[22] the BFR and CFR were compared according to the PSA nadir level and time to the PSA nadir using the log-rank test. The PSA nadir was defined as the lowest PSA level during the follow-up period before recurrence. The time to the PSA nadir was defined as the time from the start of any treatment to the date of PSA testing at which the lowest PSA value was obtained. If the lowest value was reported multiple times, the earliest date of PSA testing was used. Cutoff points were set based on the median values of the PSA nadir and the time to the PSA nadir.

To evaluate potential variables that could influence clinical outcomes, univariate and multivariate analyses were performed for the BFR and CFR using the Cox proportional-hazards model. OS and PCSS were not included in these analyses because of their clinical relevance and number of events.

2.5. Adverse events and statistics

The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was used to grade the genitourinary and gastrointestinal adverse events. Adverse events that occurred during or within three months of the completion of RT were classified as acute events; those that occurred afterward were classified as late events. Adverse events with a grade of ≥3 were considered severely toxic. The crude rates of the acute and late adverse events with the highest grades were reported based on the extent of RT.

Categorical variables were compared using the chi-squared test, and continuous variables were compared using the Student's t-test. For all statistical tests, $p < 0.05$ was defined as statistically significant. All statistical analyses were conducted using the R software (version 4.2.1; The R Foundation for Statistical Computing; Vienna, Austria).

3. Results

3.1. Patient characteristics and treatment

Patient characteristics and treatment specifics are summarized in Table 1. The median follow-up period was 4.49 years (range: 1.08–13.63 years). The median age of all patients was 73 years (range: 52–89 years). Most patients (98.6%) performed well (Eastern Cooperative Oncology Group performance status 0–1) in the radiation oncology department. A total of 103 (69.1%) patients were rated as having an intermediate risk, and 46 (30.9%) patients were rated as high-risk. Among the intermediate-risk group, 35 (23.5%) patients were classified as favorable, and 68 (45.6%) were unfavorable. Most intermediate-risk patients (95.1%) underwent prostate-only RT; 41.3% of the high-risk patients received whole-pelvic RT. In addition, proton therapy was administered to 7 patients (4.7%), all classified as having an unfavorable intermediate risk.

3.2. Clinical outcomes by risk stratification

In the favorable intermediate-risk group, no events occurred for any of the four clinical outcomes, resulting in a BFR and CFR of 0% and an OS and PCSS of 100% at every time point. For the other two groups, the 3-, 5-, and 7-year BFRs were 0%, 4.8%, and 19.2%, respectively, for the unfavorable intermediate-risk group and 9.2%, 19.6%, and 31.1%, respectively, for the high-risk group. For CFR, the 3-, 5-, and 7-year rates were 0%, 4.8%, and 9.8%, respectively, for the unfavorable intermediate-risk group and 9.1%, 25.3%, and 25.3%, respectively, for the high-risk group. Significant differences in the BFR ($p = 0.006$) and CFR ($p = 0.002$) were observed among the three groups. The 3-, 5-, and 7-year OS rates in the unfavorable intermediate-risk and high-risk groups were 98.5%, 90.9%, and 86.5% and 93.4%, 84.5%, and 71.5%, respectively. For PCSS, no events were reported in the unfavorable intermediate-risk group. In the high-risk group, the 3-, 5-, and 7-year survival rates were 97.7%, 95.3%, and 95.3%, respectively. No significant differences in OS or PCSS were observed among the three groups (OS: $p = 0.145$; PCSS: $p = 0.093$). The Kaplan–Meier curves for these four clinical outcomes are shown in Fig. 1.

3.3. PSA kinetics and multivariate analysis

The median PSA nadir value was 0.33 ng/mL (range: 0.01–3.15 ng/mL), and the median time to the PSA nadir was 37.4 months (range: 6.9–109.4 months). The results of the univariate and multivariate analyses of the BFR and CFR are summarized in Table 2. Multivariate analysis showed that the BFR was significantly associated with the clinical T stage (cT3 vs. cT1–2, hazard ratio (HR) 0.045, 95% confidence interval (CI) 0.004–0.582, $p = 0.017$), risk stratification (high vs. intermediate, HR 14.05, 95% CI 1.245–158.5, $p = 0.033$), PSA nadir (per 1 ng/mL, HR 31.72, 95% CI 5.214–193.0, $p < 0.001$), and time to the PSA nadir (per month, HR 0.899, 95% CI 0.840–0.963, $p = 0.002$). The CFR was significantly associated with the PSA nadir (HR 6.093, 95% CI, 2.049–18.12; $p = 0.001$) and time to the PSA nadir (HR 0.918, 95% CI, 0.865–0.975; $p = 0.005$). A lower PSA nadir and a longer time to the PSA nadir were the only variables significantly associated with a lower BFR and CFR.

The BFR and CFR stratified using the PSA nadir and time to the PSA nadir are shown in Fig. 2. Patients with a PSA nadir ≥0.33 ng/mL had significantly greater values for the BFR ($p < 0.001$) and CFR ($p = 0.002$) than patients with a lower PSA nadir. Patients with a time to the PSA nadir of ≤36 months had a significantly greater BFR and CFR than those who had a longer time to the PSA nadir (both $p < 0.001$).

3.4. Adverse events

The rates of the genitourinary and gastrointestinal adverse events with the highest grades are summarized in Table 3. Genitourinary events were more frequent among the acute adverse events (17.4%) than gastrointestinal events (0.7%). However, most acute adverse events were grade 1. No grade ≥3 acute adverse

Table 1
Patient characteristics and treatment

Characteristics	Favorable intermediate (N = 35)	Unfavorable intermediate (N = 68)	High (N = 46)	*P*
Age at diagnosis (median, year)	70 (range, 57–83)	73 (range, 52–82)	75 (range, 53–89)	0.190
ECOG performance status				0.412
0	32 (91.4%)	52 (76.5%)	38 (82.6%)	
1	3 (8.6%)	15 (22.1%)	7 (15.2%)	
2	0 (0.0%)	1 (1.5%)	1 (2.2%)	
Initial PSA level (median, ng/mL)	6.00 (range, 2.91–15.23)	6.30 (range, 1.91–18.51)	8.62 (range, 2.08–65.11)	0.006
Clinical T stage				<0.001
T1c	3 (8.6%)	1 (1.5%)	0 (0.0%)	
T2a	14 (40.0%)	8 (11.8%)	2 (4.3%)	
T2b	6 (17.1%)	21 (30.9%)	1 (2.2%)	
T2c	12 (34.3%)	38 (55.9%)	2 (4.3%)	
T3a	0 (0.0%)	0 (0.0%)	36 (78.3%)	
T3b	0 (0.0%)	0 (0.0%)	5 (10.9%)	
Gleason score				<0.001
6	23 (65.7%)	14 (20.6%)	6 (13.0%)	
7	12 (34.3%)	54 (79.4%)	34 (73.9%)	
8	0 (0.0%)	0 (0.0%)	3 (6.5%)	
9	0 (0.0%)	0 (0.0%)	2 (4.3%)	
10	0 (0.0%)	0 (0.0%)	1 (2.2%)	
Radiation therapy extent				<0.001
Prostate ± seminal vesicle	34 (97.1%)	64 (94.1%)	27 (58.7%)	
Whole pelvis	1 (2.9%)	4 (5.9%)	19 (41.3%)	
Radiation therapy modality				0.013
Intensity-modulated radiation therapy	35 (100.0%)	61 (89.7%)	46 (100.0%)	
Proton therapy	0 (0.0%)	7 (10.3%)	0 (0.0%)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

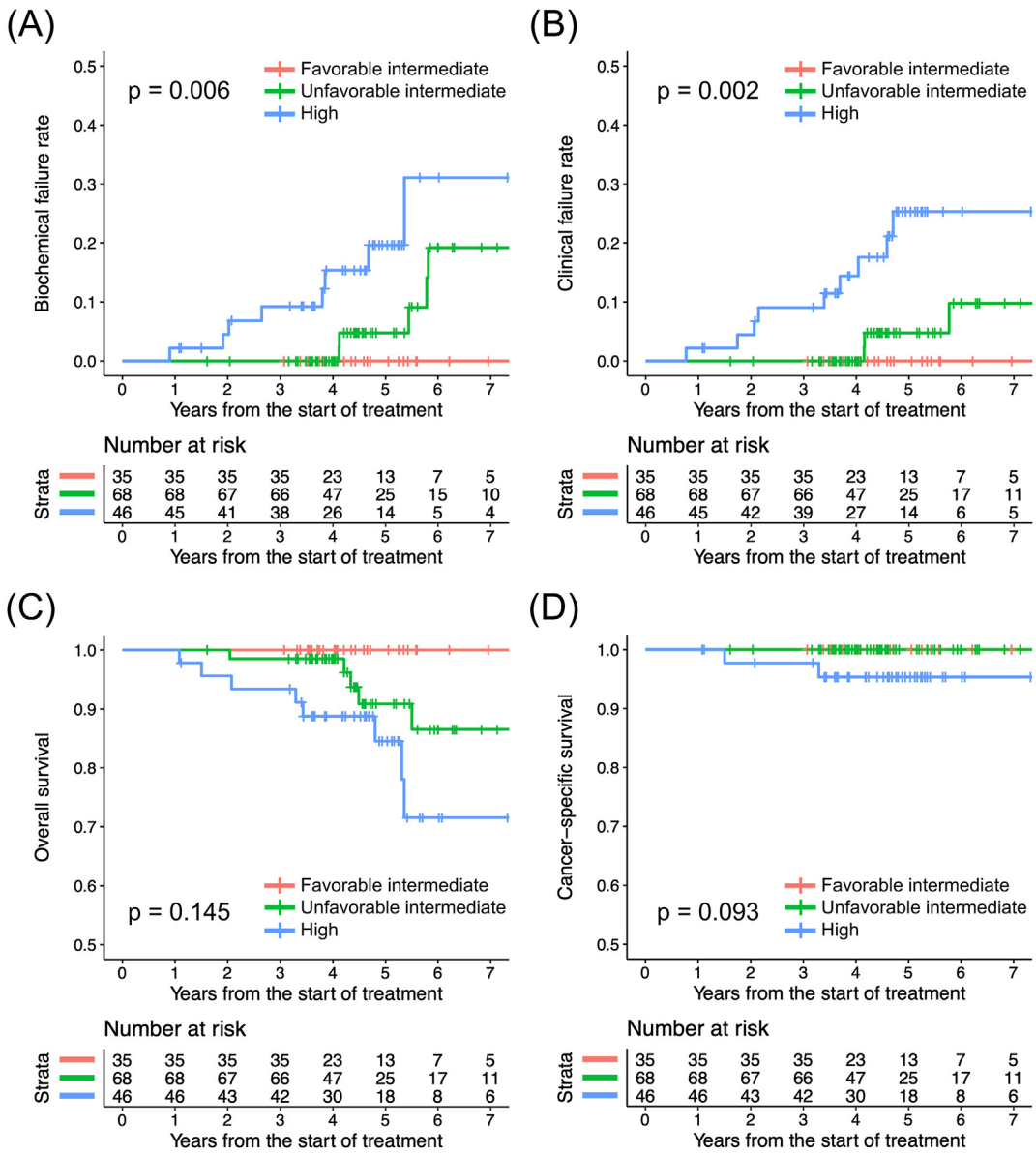

Figure 1. Kaplan–Meier curves of (A) the biochemical failure rate, (B) the clinical failure rate, (C) overall survival, and (D) prostate cancer–specific survival of patients with high-risk localized prostate cancer, according to the risk stratification.

Table 2
Univariate and multivariate analyses, including prostate-specific antigen kinetics for biochemical and clinical failure

Variable (comparison vs. reference)	Biochemical failure (number of events = 13)						Clinical failure (number of events = 12)					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age at diagnosis (continuous, per year)	1.004	0.915–1.102	0.932	1.100	0.984–1.231	0.095	1.033	0.932–1.144	0.539	1.090	0.977–1.215	0.121
PSA level at diagnosis (continuous, per 1 ng/mL)	1.080	1.043–1.119	<0.001	1.030	0.955–1.110	0.446	1.069	1.032–1.107	<0.001	1.013	0.958–1.070	0.656
Clinical T stage (cT3 vs. cT1–2)	2.907	0.969–8.723	0.057	0.045	0.004–0.582	0.017	4.219	1.336–13.33	0.014	0.196	0.024–1.597	0.128
Gleason score (8–10 vs. 6–7)	12.49	3.292–47.37	<0.001	1.588	0.121–20.79	0.724	12.63	3.318–48.10	<0.001	1.305	0.138–12.30	0.816
Risk stratification (high vs. intermediate)	4.840	1.559–15.03	0.006	14.05	1.245–158.5	0.033	7.502	2.021–27.85	0.003	7.689	0.986–59.97	0.052
RT extent (whole pelvis vs. prostate ± seminal vesicle)	4.309	1.265–14.68	0.020	4.535	0.495–41.53	0.181	4.165	1.223–14.19	0.023	3.056	0.520–17.95	0.216
PSA nadir (continuous, per 1 ng/mL)	9.834	4.210–22.97	<0.001	31.72	5.214–193.0	<0.001	6.185	3.067–12.47	<0.001	6.093	2.049–18.12	0.001
Time to PSA nadir (continuous, per month)	0.912	0.870–0.955	<0.001	0.899	0.840–0.963	0.002	0.898	0.851–0.946	<0.001	0.918	0.865–0.975	0.005

Abbreviation: CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen.

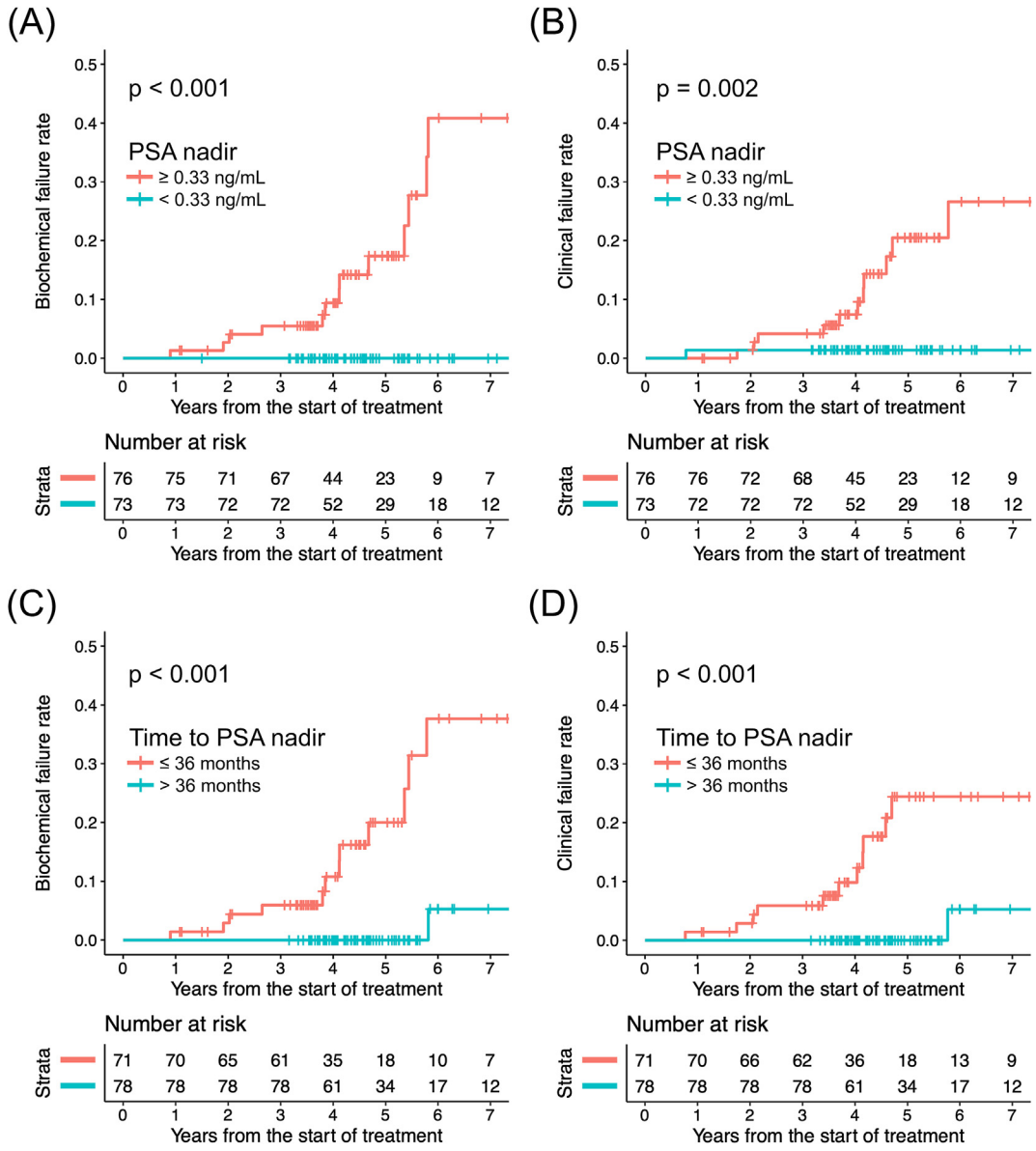

Figure 2. Kaplan–Meier curves of the (A) biochemical failure rate and (B) clinical failure rate by prostate-specific antigen (PSA) nadir and the (C) biochemical failure rate and (D) clinical failure rate by time to PSA nadir.

events were reported. Gastrointestinal events (43.6%) occurred more frequently than genitourinary events (6.7%); however, two-thirds were grade 1. Among all patients, 5 (3.4%) experienced grade 3 late adverse events: 4 gastrointestinal (hematochezia) and 1 genitourinary (hematuria). No grade 4–5 late adverse event was reported. When compared according to the extent of RT, no statistically significant difference was observed in the rates of adverse events.

4. Discussion

This study reports the clinical outcomes and adverse events associated with definitive RT alone for intermediate- or high-risk localized PCa. A significant difference in clinical outcomes was observed according to the risk stratification. High BFR and CFR rates were found in the high-risk group; however, no recurrence events were observed in the favorable intermediate-risk group. This result suggests that ADT may not be necessary to treat favorable intermediate-risk patients with definitive RT.

This study also evaluated PSA kinetics as a potential prognostic factor for moderately hypofractionated RT. In multivariate analyses for BFR and CFR, a low PSA nadir and a longer time to the PSA nadir were independently associated with better outcomes. This finding reaffirms the prognostic value of PSA kinetics, even when considering other risk factors such as the Gleason score and risk stratification. In addition, the rate of late adverse events in grade $\geq$3 was low (3.4%) and consisted mainly of hematuria and hematochezia. No grade 4–5 adverse events were observed.

The effectiveness of adding ADT to definitive RT for high-risk PCa has been described in prospective randomized trials.[11,12] In addition, the clinical superiority of long-term ADT over short-term ADT when added to definitive RT for high-risk PCa has been established through randomized trials.[23,24] Although these trials predate the widespread use of the D'Amico risk stratification, the addition of long-term ADT to definitive RT for high-risk, localized PCa has been well-established among clinicians. Interestingly, even without ADT, high-risk patients in this retrospective study showed good clinical outcomes compared with those in historical

Table 3
The highest-grade genitourinary and gastrointestinal adverse events

Adverse events	All patients (N = 149)	Subgroup analysis by RT extent		
		Prostate ± seminal vesicle only (N = 125)	Whole pelvic RT (N = 24)	*P*
Acute genitourinary				0.058
0	123 (82.6%)	100 (80.0%)	23 (95.8%)	
1	23 (15.4%)	23 (18.4%)	0 (0.0%)	
2	3 (2.0%)	2 (1.6%)	1 (4.2%)	
Acute gastrointestinal				1.000
0	148 (99.3%)	124 (99.2%)	24 (100.0%)	
1	1 (0.7%)	1 (0.8%)	0 (0.0%)	
Late genitourinary				0.893
0	139 (93.3%)	116 (92.8%)	23 (95.8%)	
1	7 (4.7%)	6 (4.8%)	1 (4.2%)	
2	2 (1.3%)	2 (1.6%)	0 (0.0%)	
3	1 (0.7%)	1 (0.8%)	0 (0.0%)	
Late gastrointestinal				0.329
0	84 (56.4%)	71 (56.8%)	13 (54.2%)	
1	49 (32.9%)	43 (34.4%)	6 (25.0%)	
2	12 (8.1%)	8 (6.4%)	4 (16.7%)	
3	4 (2.7%)	3 (2.4%)	1 (4.2%)	

Abbreviation: RT, radiation therapy.

trials. For example, in the European Organization for Research and Treatment of Cancer (EORTC) 22863 trial, the 5-year clinical disease-free survival rate was 40% in the RT-only group and 74% in the combined-treatment group.[25] In the current study, the 5-year CFR was 25.3% in the high-risk group that did not receive ADT. Notably, selected high-risk patients were included in this study. Although classified as high-risk, 87.0% of the patients in the high-risk group had a Gleason score of 6–7, and the median initial PSA level was 8.62 ng/mL. Even with relatively favorable features, the high-risk patients in this study may have had better treatment outcomes if ADT had been combined with definitive RT.

The addition of ADT to definitive RT for intermediate-risk PCa remains debatable. Clinical trials predating the current risk stratification system showed that ADT lowered the recurrence rate; however, translation into a survival benefit was inconsistent.[13,26] Recent trials with updated risk stratification and dose-escalated RT have also shown discrepancies. The PCS III and RTOG 0815 trials reported less recurrence and greater PCSS, but no difference in OS, in patients treated with RT combined with ADT.[27,28] Because of the significant adverse events associated with ADT,[29] determining the optimal criteria for ADT administration in intermediate-risk patients is crucial. The sub-classification of intermediate-risk groups has been found to be effective in multiple studies.[14,30,31] The current study used the NCCN subclassification of the intermediate-risk group.[9] None of the patients with favorable intermediate-risk PCa who underwent definitive RT without ADT showed recurrence. This result may indicate that the favorable intermediate–risk group exhibited favorable clinical outcomes without ADT, consistent with the NCCN guidelines.

The PSA nadir and time to the PSA nadir are well-known prognostic factors after definitive RT. Multiple studies have validated the prognostic value of these factors for definitive RT without ADT.[22,32] The current study found prognostic significance for the PSA nadir and time to the PSA nadir, even after considering other known prognostic factors. This finding shows the importance of PSA kinetics for estimating prognosis during follow-up. However, it should also be noted that the time to the PSA nadir is subject to lead-time bias, and its prognostic power may weaken when adjusted.[33] The cutoff points for the PSA nadir level and time to the PSA nadir in this study were set at 0.33 ng/mL and 36 months, respectively, based on median values. Patients not meeting these criteria had a worse prognosis, suggesting the need for cautious follow-up.

Hypofractionated RT is a well-established, definitive treatment for localized PCa. The current NCCN guidelines recommend a moderately hypofractionated regimen as the preferred option.[9] Modern dose-fractionation regimens for definitive RT are based on dose-escalation trials that showed clinical benefit from dose-escalated regimens but with more adverse events.[15,16] Although moderately hypofractionated regimens, including those used in this study, have not shown high toxicity rates,[17,18] late adverse events are concerning, and strategies for minimizing adverse events should be explored; a good example is the perirectal hydrogel spacer.[34] Furthermore, hypofractionated regimens with >3 Gy per fraction have recently been implemented in clinical practice;[35] however, the dose to organs at risk (OARs) should be managed with caution when using such regimens. Our group recently implemented a further hypofractionated regimen (dose per fraction up to 3.2 Gy) with a perirectal hydrogel spacer and expects to report the outcomes of this strategy following sufficient follow-up.

This study had several limitations that must be addressed. Because of its retrospective nature, treatment allocation was at the discretion of the treating clinicians, and the results were subject to selection bias. Although we attempted to mitigate this bias through multivariate analysis, it could not be eliminated. The number of events was limited, hindering the statistical power of this study. In addition, events may have been underreported because of the retrospective nature of this study; for PCSS, incomplete and ambiguous mortality reports may have increased underreporting. Despite these limitations, this study demonstrates the efficacy of definitive RT alone for intermediate- or high-risk localized PCas in real-world clinical settings and provides valuable insights for clinicians.

In summary, this study identified a significant difference in risk-stratified clinical outcomes from moderately hypofractionated RT alone for patients with intermediate- or high-risk localized PCa. No recurrence events were reported in the favorable subgroup of the intermediate-risk patients, suggesting that the NCCN subclassification of the intermediate-risk group is relevant to clinical practice. The PSA nadir level and time to the PSA nadir were strongly associated with clinical outcomes, even after adjusting for other known prognostic factors, indicating prognostic significance for PSA kinetics during follow-up. Further studies are necessary to confirm the suggested cutoff points for the PSA nadir level (0.33 ng/mL) and the time to the PSA nadir (36 months) used in this study. The

hypofractionated regimen with 70 Gy in 28 fractions was tolerated well with minimal adverse events. The rate of grade 3 late genitourinary and gastrointestinal adverse events was low, with cases showing hematuria or hematochezia.

Conflict of interest

The authors declare that they have no competing interests.

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