ORIGINAL ARTICLE

Prostate Cancer

Intermittent, low-dose, antiandrogen monotherapy as an alternative therapeutic option for patients with positive surgical margins after radical prostatectomy

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The aim of the present study was to determine whether oncologic outcomes and adverse events associated with active on/off intermittent antiandrogen monotherapy (daily bicalutamide, 50 mg per day) are comparable with those of standard external beam radiation therapy (EBRT) or combined androgen blockade (CAB) therapy in prostate cancers with positive surgical margins after radical prostatectomy. Two hundred twenty-three patients with positive surgical margins post-radical prostatectomy who underwent active surveillance (AS, $n = 32$), EBRT without hormone therapy ($n = 55$), intermittent antiandrogen monotherapy without EBRT (IAAM, $n = 50$), or CAB without EBRT ($n = 86$), between 2007 and 2014, were reviewed retrospectively. Pathologic outcomes, biochemical recurrence rates, radiological disease progression, and adverse events were collected from medical records. Biochemical recurrence rates, biochemical recurrence-free survival rates, and radiological recurrence were not different between the groups ($P = 0.225$, 0.896, and 0.284, respectively). Adverse event rates and severities were lower for IAAM compared with EBRT or CAB (both $P < 0.05$), but were comparable to those for AS ($P = 0.591$ and 0.990, respectively). Grade ≥ 3 adverse events were not reported in the IAAM or AS groups. Erectile dysfunction and loss of libido rates were lower in the IAAM group compared with the EBRT and CAB groups ($P = 0.032$). Gastrointestinal complications were more frequently reported in the EBRT group ($P = 0.008$). Active on/off IAAM treatment might be an appropriate treatment option for patients with positive surgical margins after radical prostatectomy. Furthermore, regarding oncologic outcomes, IAAM was comparable to standard EBRT but had a milder adverse event profile.

INTRODUCTION

Prostate cancer (PCa) is one of the most common cancers in men. More than 90% of prostate cancers are organ confined and potentially curable after radical prostatectomy (RP).[1] However, 16.2%–42.2% of patients have positive surgical margins (PSM) after RP.[2] According to the 2016 National Comprehensive Cancer Network guideline, the standard treatment protocols for patients with PSM after RP and/or pelvic lymph node dissection are external beam radiation therapy (EBRT) or active surveillance (AS).[3] Because long-term complications such as genitourinary and gastrointestinal (GI) symptoms occur following EBRT,[4] this procedure might be considered excessive for patients who have already undergone RP. However, patients with confirmed PSM who choose AS risk missing the critical time point to control disease progression with minimal early treatment, and additional long-term treatment with EBRT ± androgen deprivation (AD) is sometimes necessary when the cancer burden increases.[3] Although physicians choose treatment methods based on a patient age or initial tumor characteristics, the choice of AS or EBRT remains a challenge.

We hypothesized that intermittent, low-dose, hormone therapy would be an effective alternative treatment and more proactive than AS, yet less excessive than EBRT. Hormone therapy can effectively block androgens and be stopped at any time if necessary; therefore, it could be a useful active on/off treatment method in patients with PSM. Although there is a difference in the purpose of curative versus potential palliative treatment between EBRT and intermittent hormonal therapy, intermittent hormonal therapy using combined androgen blockade (CAB: luteinizing hormone-releasing hormone [LHRH] agonist or antagonist plus antiandrogens) has been reported to improve the quality of life (QoL) in locally advanced or relapsing PCa without diminishing the efficacy of continuous AD.[5] Tunn et al.[6] studied intermittent hormonal therapy for PSA progression after RP. Their protocol included discontinuation if the PSA level fell below 0.5 ng ml⁻¹ after 6 months of hormone induction. They reported that testosterone levels were normalized during off-treatment periods and suggested that this could balance the benefits of long-term androgen withdrawal while reducing CAB-related side effects.[6] However, there are no reports regarding intermittent hormonal therapy with antiandrogen monotherapy in patients with PSM after RP. Therefore, we aimed to compare the efficacy and safety of intermittent antiandrogen monotherapy (IAAM) alone in patients with PSM after RP.

PATIENTS AND METHODS

Patients

This study was approved by CHA Bundang Medical Center review board (IRB No. CHAMC 2017-03-018-002). We analyzed 223 patients

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with PSM after RP that was performed between 2007 and 2014. The data were analyzed retrospectively and divided into four therapeutic groups: (1) AS, which was performed by measuring prostate-specific antigen (PSA) at 6-month intervals and digital rectal examination at 1-year intervals; (2) EBRT using a four-field approach within 3 months of surgery, with radiation administered at 2.5 Gy per day with a median cumulative dose of 65.5 Gy; (3) IAAM; and (4) CAB. Inclusion criteria were PSM for histologically confirmed prostate adenocarcinoma after open RP with pelvic lymph node dissection, age ≥18 and <80 years, and a Gleason score ≥6. Exclusion criteria were previous chemotherapy or hormonal therapy (other than 1 month of neoadjuvant hormone therapy), postoperative hormone therapy combined with EBRT, and the presence of any other malignancy or metastatic disease. The indication for AS was a positive apex margin alone. Patients' characteristics and oncologic data were collected from medical records. Adverse events (AEs) were regarded as having occurred if mentioned at least once in these records, or if treatments or medications were prescribed for the relevant symptoms. The PSA levels were measured monthly in the EBRT, IAAM, and CAB groups.

Hormone therapy protocol

Patients who underwent IAAM and CAB adopted induction hormone therapy immediately after RP with monthly injections of LHRH analog (leuprolide acetate 3.75 mg or goserelin 3.6 mg, sc) and daily bicalutamide (50 mg per day, po) for 8.5 ± 6.3 months. Among patients who maintained PSA levels of <0.01 ng ml^{-1} during the induction period, 50 received active on/off IAAM (daily bicalutamide 50 mg per day, po). IAAM was stopped if PSA levels remained stable at <0.01 ng ml^{-1} for 6 months but was resumed on suspicion of recurrence during monthly follow-ups (i.e., if PSA levels rose above 0.1 ng ml^{-1} or doubled). The remaining 86 patients underwent intermittent or continuous CAB with LHRH analog (leuprolide acetate 3.75 mg or goserelin 3.6 mg, sc) and daily bicalutamide (50 mg per day, po) following the induction period (**Figure 1**).

Biochemical recurrence (BCR) was defined as two consecutive PSA measurements of 0.2 ng ml^{-1} in all groups.[7] Computed tomography (CT) or positron emission tomography-CT was performed during annual follow-up sessions or immediately if BCR was noted. Data on AEs were collected retrospectively and assessed using the Common Terminology Criteria for Adverse Events Version 4.0 of National Cancer Institute.

Statistical analyses

Patient characteristics and pathologic outcomes were compared using the Student's *t*-test, Chi-squared test, and Wilcoxon two-sample test. PSA changes were investigated using a linear mixed model. The BCR-free survival rate was evaluated using the Kaplan-Meier method. Statistical significance was defined as a $P < 0.05$. Statistical analyses were performed using the IBM SPSS statistics 23 software (SPSS, Inc., Chicago, IL, USA).

RESULTS

In the different patient groups ($n_{AS} = 32$, $n_{EBRT} = 55$, $n_{IAAM} = 50$, and $n_{CAB} = 86$), the mean age, initial PSA, clinical and pathological T stage, biopsy, and pathological outcomes after RP were fully comparable. The data are summarized in **Table 1**.

After adjuvant treatment, there were no differences in BCR and radiological recurrence rates between the groups (**Table 2**). Moreover, there were no differences in BCR-free survival rates between the groups during the follow-up period (mean 27.0 months; maximum 72 months; **Figure 2**). There was a sharp decrease in mean PSA levels by the end of the induction phase in the IAAM and CAB groups, which was maintained below 0.05 ng ml^{-1} until the last follow-up session (**Figure 3**).

The AE incidence and severity were lower in the IAAM group compared with the EBRT and CAB groups ($P < 0.05$ for each) but were comparable with those in the AS group ($P = 0.591$ and 0.990, respectively). Grade ≥3 AEs were not reported in either the IAAM or AS groups. The rate of erectile dysfunction and loss of libido was significantly lower in the IAAM group compared with the EBRT and CAB groups ($P = 0.032$). The rates of hot flashes were not significantly different between the IAAM and CAB groups, and any symptoms were treated using low-dose tamoxifen and cyproterone acetate as required. GI complications, including Grade 3 AEs, were more frequently reported in the EBRT group compared with the other groups. Furthermore, in the IAAM group, AEs were improved during the off periods (**Table 2**).
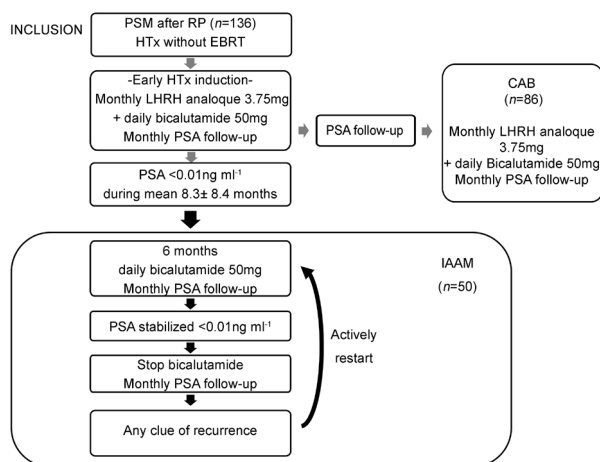

Figure 1: The study design flowchart for intermittent antiandrogen monotherapy and combined androgen blockade. PSM: positive surgical margin; RP: radical prostatectomy; HTx: hormone therapy; LHRH: luteinizing hormone-releasing hormone; EBRT: external beam radiation therapy; IAAM: intermittent antiandrogen monotherapy; CAB: combined androgen blockade therapy; PSA: prostate-specific antigen.
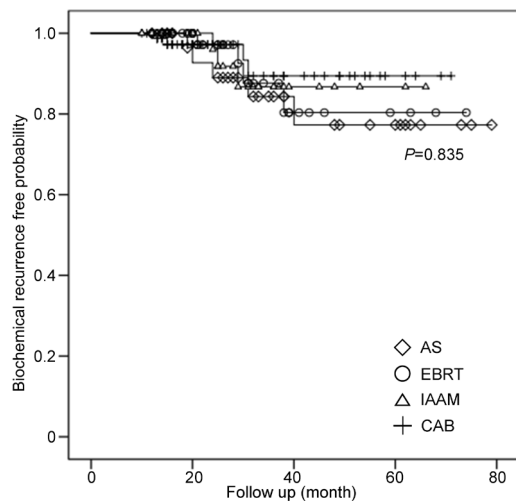

Figure 2: Biochemical recurrence-free survival rate. AS: active surveillance; EBRT: external beam radiation therapy; IAAM: intermittent antiandrogen monotherapy; CAB: combined androgen blockade therapy.

Table 1: Patient and disease characteristics

Positive surgical margin after RP	AS	EBRT	IAAM	CAB	P			
					All group	EBRT/IAAM/CAB	IAAM/CAB	EBRT/CAB
Positive surgical margin after RP, n (%)	32 (14.3)	55 (24.7)	50 (22.4)	86 (38.6)				
Age (year, mean±s.d.)	73.3±6.9	71.3±5.7	71.8±8.3	72.0±7.7	0.579	0.514	0.839	0.774
Initial PSA (ng dl⁻¹, mean±s.d.)	4.1±1.8	3.9±2.7	3.9±2.8	4.0±2.3	0.379	0.697	0.843	0.679
Biopsy Gleason score, n (%)								
≤6	13 (40.6)	19 (34.5)	16 (32.0)	24 (27.9)	0.466	0.957	0.862	0.960
7–8	17 (53.1)	23 (41.8)	24 (48.0)	45 (52.3)				
≥9	2 (6.3)	13 (23.6)	10 (20.0)	17 (19.8)				
Clinical T stage, n (%)								
≤T2	18 (56.3)	10 (18.2)	11 (22.0)	10 (11.6)	<0.001*	0.437	0.457	0.757
T3	14 (43.8)	45 (81.8)	39 (78.0)	76 (88.4)				
Pathologic Gleason score, n (%)								
≤6	8 (25.0)	5 (9.1)	6 (12.0)	8 (9.3)	0.143	0.997	0.999	0.999
7–8	22 (68.8)	36 (65.5)	32 (64.0)	59 (68.6)				
≥9	2 (6.3)	14 (25.5)	12 (24.0)	19 (22.1)				
Pathological T stage, n (%)								
≤T2	14 (43.8)	6 (10.9)	7 (14.0)	8 (9.3)	<0.001*	0.870	0.871	0.992
T3	18 (56.3)	49 (89.1)	43 (86.0)	78 (90.7)				
Pathological outcomes after RP, n (%)								
Extracapsular extension	18 (56.3)	43 (78.2)	39 (78.0)	72 (83.7)	0.018*	0.811	0.876	0.877
Seminal vesicle invasion	3 (9.4)	15 (27.3)	12 (24.0)	22 (25.6)	0.239	0.986	0.998	0.997
Lymph node invasion	0 (0.0)	8 (14.5)	6 (12.0)	13 (15.1)	0.142	0.967	0.968	0.999

*$P<0.05$. RP: radical prostatectomy; AS: active surveillance; EBRT: external beam radiation therapy; IAAM: intermittent antiandrogen monotherapy; CAB: combined androgen blockade therapy; PSA: prostate-specific antigen; s.d.: standard deviation
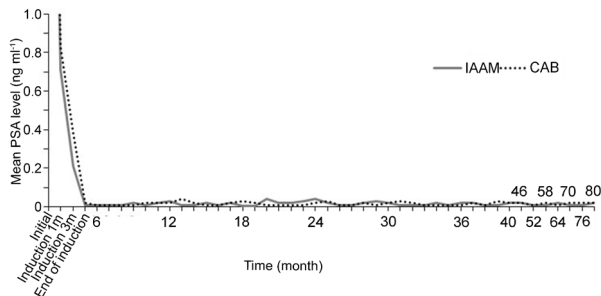

Figure 3: Mean prostate-specific antigen levels. IAAM: intermittent antiandrogen monotherapy; CAB: combined androgen blockade therapy; PSA: prostate-specific antigen.

DISCUSSION

AD suppresses the growth of PCa cells by inhibiting the synthesis (LHRH agonists or antagonist) and peripheral action (steroidal or nonsteroidal antiandrogens) of testosterone.[8,9] However, because continuous AD causes some deterioration in QoL, the benefits and disadvantages of intermittent usage of AD have been intensely debated.[8–12] Off-treatment intervals of AD are associated with QoL improvements owing to the recovery of serum testosterone levels.[6] A recent randomized trial showed that both intermittent and continuous AD had similar efficacies, tolerabilities, and QoL outcomes in patients with recurrent or locally advanced PCa.[5] Moreover, one study in patients with metastatic PCa showed that intermittent AD produced a small overall survival benefit and was equivalent to continuous AD regarding cancer control.[13] Therefore, in low tumor burden-PCa such as that in the present cohort, cancer control via intermittent AD might be comparable with continuous AD.

Recently, Antonelli *et al.*[14] reported a 31.9% (91/285) PSM rate following open RP and a 24.4% (71/291) PSM rate following robot-assisted laparoscopic prostatectomy. They determined that pathologic T stage >2, Gleason score >6, and the surgical technique employed were factors associated with a PSM.[14] For treatment, a few studies have evaluated hormone therapy in patients with localized PCa treated with RP; the majority of which focused on BCR after RP.[6,15] Tunn *et al.*[6] reported that, at follow-up day 1000, androgen-independent progression rates in BCR patients after RP following intermittent AD (leuprorelin acetate 11.25 mg every 3 months [depot] plus cyproterone acetate 200 mg per day for the first 4 weeks) or continuous AD were not significantly different, despite normalization of testosterone levels during off-treatment periods in the intermittent group. Sciarra *et al.*[15] treated patients whose PSA levels rose above 0.4 ng ml⁻¹ with intermittent AD (triptorelin 3.75 mg per month); after 6 months of treatment, patients whose PSA nadirs were ≤0.1 ng ml⁻¹ and had an off-phase interval of ≥48 weeks showed good response to intermittent AD and delayed development of castration-resistant PCa (CRPC). Ku *et al.*[16] reported that intermittent AD was associated with an increased median time to CRPC development compared with continuous AD. These studies suggest that intermittent AD could be an effective treatment for certain cases of PSM after RP.

The protocols for intermittent AD, including the off-treatment interval and restart indication, vary by institution.[6,8,17,18] Most studies have used combined androgen blockade with a gonadotropin-releasing hormone agonist plus antiandrogen therapy in locally advanced, metastatic cancer. For patients with BCR after RP, Tunn *et al.*[6] stopped gonadotropin-releasing hormone agonist and antiandrogen administration if PSA levels fell below 0.5 ng ml⁻¹ and restarted therapy when levels rose above 3 ng ml⁻¹; they reported similar oncologic outcomes between the intermittent and continuous AD groups.[6] Furthermore, Duchesne *et al.*[19] emphasized the importance of early androgen deprivation for BCR, showing that immediate

Table 2: Treatment outcomes and adverse effects

Positive surgical margin after RP	AS (n=32)	EBRT (n=55)	IAAM (n=50)	CAB (n=86)	P			
					All group	EBRT/IAAM/CAB	IAAM/CAB	EBRT/CAB
Biochemical recurrence, n (%)	5 (15.6)	4 (7.3)	3 (6.0)	4 (4.7)	0.225	0.933	0.990	0.934
CRPC progression, n (%)	1 (3.1)	1 (1.8)	0 (0.0)	0 (0.0)	0.315	0.289	-	0.390
Radiological disease progression, n (%)	2 (6.3)	3 (5.5)	0 (0.0)	2 (2.3)	0.284	0.375	0.758	0.811
Disease-specific death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)				
Follow-up (month, mean±s.d., with range in parentheses)	39.0±19.6 (14–79)	28.7±17.7 (12–74)	23.9±13.7 (12–68)	23.3±18.9 (12–71)	0.038*	0.597	0.983	0.879
Adverse effects, n (%)	12 (37.5)	40 (72.7)	26 (52.0)	68 (79.1)	<0.001*	0.010*	0.013*	0.861
New onset loss of libido or erectile dysfunction	11 (34.4)	28 (50.9)	19 (38.0)	55 (64.0)	0.005*	0.032*	0.035*	0.502
Hot flashes	0 (0.0)	0 (0.0)	7 (14.0)	16 (18.6)	<0.001*	0.004*	0.711	<0.001*
Gynecomastia or mammalgia	0 (0.0)	0 (0.0)	6 (12.0)	18 (20.9)	<0.001*	0.001*	0.375	0.004*
GU complication: incontinence, urgency	9 (28.1)	23 (41.8)	15 (30.0)	29 (33.7)	0.507	0.630	0.978	0.815
GI complication	2 (6.3)	18 (32.7)	5 (10.0)	11 (12.8)	0.001*	0.008*	0.971	0.043*
Adverse effects by severity, n (%)								
Grade 1: mild	5 (15.6)	16 (29.1)	14 (28.0)	15 (17.4)	<0.001*	0.010*	0.044*	0.701
Grade 2: moderate	7 (21.9)	21 (38.2)	12 (24.0)	51 (59.3)				
Grade 3: severe	0 (0.0)	3 (5.5)	0 (0.0)	2 (2.3)				
Grade 4/5: life-threatening/disabling/death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)				

*P<0.05. RP: radical prostatectomy; AS: active surveillance; EBRT: external beam radiation therapy; IAAM: intermittent antiandrogen monotherapy; CAB: combined androgen blockade therapy; CRPC: castration-resistant prostate cancer; GU: genitourinary; GI: gastrointestinal; s.d.: standard deviation

AD significantly improved overall survival compared with delayed intervention in PSA-relapsed PCa after previous curative therapy. Based on these reports, we developed an IAAM protocol that we hypothesized would be sufficient to control patients with PSM status without BCR, and that would be an alternative, effective option compared with EBRT or AS. The main purposes of our protocol were (1) administering antiandrogen monotherapy with minimum side effects compared to existing hormone therapy protocols or EBRT, and (2) immediate administration of a strict on/off regimen upon early detection of BCR as evidenced by PSA >0.1 ng ml^{-1} or doubling. Recently, Calais da Silva *et al*.[12] reported an antiandrogen monotherapy (cyproterone acetate 300 mg per day) protocol, but it was administered for locally advanced or metastatic PCa. To date, intermittent antiandrogen monotherapy has not been evaluated in patients with PSM after RP without BCR.

Previously, Morgan *et al*.[20] analyzed three randomized controlled trials of adjuvant radiotherapy following RP for pathologic T3 or PSM PCa. They reported that PCa-specific death rates were 3.0% (15/503) in the AS group and 1.6% (8/502) in the adjuvant radiotherapy group. Together, the three trials revealed a 53% decrease in BCR with adjuvant radiotherapy compared with AS.[20] Individually, the SWOG 8794 trial showed that radiotherapy was associated with a reduced 10-year risk of BCR (72% *vs* 42%) for patients with a postsurgical PSA of <0.2 ng ml^{-1} while the 5-year cumulative incidences of BCR were 21.4% in the radiotherapy group and 44.2% in AS group.[21] In the EORTC 22911 trial, BCR-free survival rates in the irradiated versus AS groups were 74.0% versus 52.6%, respectively.[22] In the present study, BCR, radiologic progression, and CRPC progression were not significantly different among the four groups and BCR rates at the end of the follow-up period (mean 27.1 months) were 15.6%, 7.3%, 6.0%, and 4.7%, respectively. The inconsistencies between the previous and present studies might be due to a selection bias (i.e., lower pathologic T stage and extracapsular extension rates in the AS group and a relatively short-term follow-up). In addition, in the present study, the BCR rate in the AS group (15.6% at 39.0 months) was much lower than that in previous studies (5-year BCR, 44.2%).[22] Furthermore, the findings of similar oncologic outcomes between the IAAM, EBRT, and CAB groups in the present study suggested that IAAM is efficacious in patients with PSM after RP. There was one case (3.1%) of CRPC progression in the AS group compared with 0 case of CRPC in the IAAM or CAB groups. However, the difference was not significant, most likely because of the small sample size. Nevertheless, the present findings indicate that early hormone suppression might prevent CRPC progression in PCa patients with PSM.

In the present study, IAAM was associated with a lower incidence of and less severe AEs compared with EBRT or CAB; all AEs related to IAAM were Grade 1 or 2. However, because of RP, the rate of AEs such as genitourinary symptoms and erectile dysfunction is slightly higher than those reported previously.[19,22] In the present study, IAAM was superior to CAB (regarding erection, libido, and gynecomastia) and EBRT (regarding GI complications). Although hot flash and gynecomastia rates in the IAAM group were higher than those in the EBRT group, these events were Grades 1–2. Therefore, IAAM could be considered a safe alternative to EBRT in patients with PSM after RP. A previously reported phase 3 randomized trial showed AE rates of 75.4% and 72.5% following intermittent and continuous AD, respectively;[5] these rates were higher than those in the present study using IAAM (52.0%). These findings indicate that QoL might be improved using our IAAM protocol compared with other intermittent AD protocols, although further studies would be needed to validate this possibility.

Large-scale randomized studies in patients with metastatic PCa have reported significantly better erectile function at 3 months when using intermittent AD compared with continuous AD,[23] with sexual activity restored to pretreatment levels at 6 months into the off period and significantly greater sexual activity at 30 months (24.9% *vs* 6.4%, respectively).[12] In the present study, the rate of erectile dysfunction and loss of libido in the IAAM group were significantly lower compared with those in the EBRT and CAB groups and were comparable with those in the AS group. Based on these data, antiandrogen monotherapy might be an excellent treatment option for maintaining erectile function.

Acute GI complications such as bowel dysfunction have been reported in 22% of patients at 6 weeks post-EBRT, which mostly resolved within 2 years.[24] Rectal bleeding has been identified as the most frequent late AEs following EBRT with onset occurring within the first 2 years after treatment.[25] In the present study, all three Grade 3 AEs in the EBRT group were GI complications (intractable rectal bleeding, ulceration, and fistula). Therefore, GI complications tended to be higher grade and were more likely to require hospitalization compared with non-GI complications. Two of the patients who experienced Grade 3 GI AEs had diabetes, and one patient was elderly (72 years old). These findings are congruent with previously reported GI complication risk factors after EBRT.[26]

Our IAAM protocol had the advantage of a low incidence of AEs with comparable oncologic outcomes to standard EBRT or CAB. Additionally, it reduced medical costs owing to less total drug use. However, IAAM had a few disadvantages compared with AS. Overall, IAAM might be more suitable for patients with PSM after RP, who wish to undergo treatment but preserve sexual function, social activity, and physical capacity, under the condition of more frequent follow-ups.

The present study had limitations. The retrospective design could result in selection bias concerning the pathologic status of the AS group compared with the other three groups. Furthermore, the retrospective design could have an impact on the reporting of AEs. The follow-up duration was limited (mean 27.1 months) because of the transfer of stabilized patients to their regional hospitals. To overcome this limitation, future multi-institutional investigations in cooperation with regional hospitals will be necessary. Furthermore, our cohort was too small for subgroup analysis of bladder neck, apical, anterior, and posterior margin status. Therefore, a large-scale investigation aimed at obtaining prospective long-term follow-up data is planned to identify patients who would be eligible for IAAM as opposed to standard EBRT.

The present study is the first to demonstrate the efficacy and safety of IAAM alone in patients with PCa and PSM after RP. Our active on/off IAAM protocol could be considered as an alternative option for PSM after RP because it has less AEs compared with EBRT while maintaining similar oncologic outcomes.

AUTHOR CONTRIBUTIONS
KHC carried out the project development, data collection, management, statistical analysis, and manuscript writing and editing. SRL and YKH carried out data collection. DSP carried out project development and manuscript editing. All authors read and approved the final manuscript.

COMPETING INTERESTS
All authors declared no competing interests.

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