Impact of early versus delayed androgen-deprivation therapy on survival outcomes of patients with localized prostate cancer who underwent radical prostatectomy and later developed metastasis: Can we define a PSA threshold?

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Abstract

**Background:** The benefits of early administration of androgen-deprivation therapy (ADT) in patients with prostate-specific antigen (PSA)-only recurrent prostate cancer (PCa) following radical prostatectomy (RP) are controversial. We investigated the impact of early versus delayed ADT on survival outcomes in patients with non-metastatic, localized or locally advanced PCa who received radiation therapy following RP and later developed distant metastasis.

**Methods:** A retrospective analysis was performed on 69 patients with non-metastatic, localized or locally advanced PCa who received radiation therapy following RP and later developed distant metastasis between January 2006 and December 2012. Patients were stratified according to the level of PSA at which ADT was administered (<2 ng/mL vs. ≥2 ng/mL). Study endpoints were progression to castration-resistant prostate cancer (CRPC)-free survival and cancer-specific survival (CSS) assessed by Kaplan-Meier analysis and Cox-regression models.

**Results:** Patients were stratified according to the level of PSA at which ADT was administered (<2 ng/mL vs. ≥2 ng/mL) based on the Youden sensitivity analysis. Delayed ADT at PSA ≥2 ng/mL was an independent prognosticator of cancer-specific mortality (p=0.047), and a marginally significant prognosticator of progression to CRPC (p=0.051). During the median follow-up of 81.0 (IQR 54.2-115.7) months, patients who received early ADT at PSA <2 ng/mL had significantly higher CSS rates than patients who received delayed ADT at PSA ≥2 ng/mL (p=0.002). Progression to CRPC-free survival was comparable between the two groups (p=0.331).

**Conclusions:** Early ADT at the PSA level of less than 2 ng/mL confers CSS benefits in patients with localized or locally advanced PCa previously treated with RP.

1. Background

Radical prostatectomy (RP) is used as a curative therapy for patients with prostate cancer (PCa). RP has been shown to confer excellent oncological control and long-term survival for localized PCa by reducing the risk of local tumor progression and metastasis [1]. RP can be used as a therapeutic option for various stages of PCa, from localized to high-risk disease [2]. Furthermore, recent evidence suggests a survival benefit when RP is included as part of multimodal therapy in patients with
oligometastatic PCa [3].

Androgen deprivation therapy (ADT) is the standard therapy for patients with metastatic PCa and can also be employed as part of multimodal therapy following RP. For patients exhibiting adverse pathological features, ADT can be used as an adjuvant therapy with radiation therapy (RT) to improve cancer-specific survival (CSS) and overall survival (OS) [4-8]. ADT can also be administered after prostate-specific antigen (PSA) recurrence with RT, depending on the presence of metastasis, as a salvage treatment [9]. However, the optimal value of PSA and the disease landscape in which ADT should be administered are still a matter of debate.

Early initiation of ADT may be superior to delayed ADT in terms of short-term oncological outcomes; however, the benefit of early ADT is unclear regarding CSS or OS outcomes [2]. Adverse effects of ADT, including hot flashes, sexual dysfunction, and osteoporosis, cannot be overlooked. Moreover, the advent of non-metastatic castration-resistant disease may be attributed to early administration of ADT [10]. On the other hand, 12% of patients receiving RP for localized or locally advanced PCa are destined to develop metastasis during the median follow-up of 2.2 years, and early ADT may be a feasible treatment option to delay the onset of metastatic progression [11,12].

Contemporary guidelines do not indicate the optimal timing for administering ADT following RP and state that treatment should be individualized depending on PSA kinetic parameters such as PSA doubling time (PSADT), PSA velocity (PSAV), patient anxiety, underlying comorbidities, and life expectancy [2]. Indeed, this disease spectrum poses uncertainty for both patients and physicians and warrants investigation. The primary endpoint of our study was the impact of early versus delayed ADT on survival outcomes in patients with localized or locally advanced PCa who received RP and later developed metastasis. The secondary study endpoint was the definition of a specific level of PSA-related parameters that can be utilized to select candidates for early initiation of ADT

2. Methods

2.1. Patient Selection

This multicenter study evaluated data from 923 consecutive patients with non-metastatic, localized or locally advanced PCa who received adjuvant or salvage radiation therapy for PSA-only recurrence
following RP between January 2006 and December 2012. Among these patients, were evaluated for 69 (7.5%) patients who later developed distant metastasis were selected for analysis (Fig. 1). The study’s protocol was approved by the institutional ethics committee (2017-0186-001).

2.2. Data Collection
The patients’ clinicopathological characteristics were retrieved from the institutional electronic medical records database. The variables included age, body mass index, Eastern Cooperative Oncology Group Performance Status Scale, National Comprehensive Cancer Network (NCCN) risk category, time to PSA recurrence, pathological Gleason score and stage, preoperative PSA level, PSA nadir at RP, PSA level at ADT initiation, PSAV and PSADT before ADT, PSA nadir after ADT, and time to PSA nadir.

Prostate cancer staging was determined according to the 7th version of the American Joint Committee on Cancer TNM system. Castration-resistant prostate cancer (CRPC) was defined as the progression of disease or an increase in serum PSA using the Prostate Cancer Working Group 2 criteria [13]. The progression of disease was diagnosed based on a continuous increase in serum PSA levels, new symptom development, or a metastatic lesion detected during ADT using bone scanning, computed tomography, magnetic resonance imaging, or positron emission tomography.

For all patients, the status of survival and cause of death were investigated using institutional electronic medical records, the National Cancer Registry Database, or the Social Security Death Index. Death was attributed to PCa if evidence of progressive metastatic CRPC was present, PCa was listed on the death certificate as the cause of death, or if the patient died of complications of PCa treatment.

2.3. Treatments
Robot-assisted laparoscopic RP was recommended for patients who were determined to be reasonable surgical candidates and desired surgical treatment. Surgery was performed with the extent of pelvic lymph node dissection being based upon the risk category of the patient. RT was delivered to the prostatic fossa with defined margins according to the guidelines of the European Organization for Research and Treatment of Cancer [14]. At both institutions, RT consisted
of 3D conformal radiation therapy from 2000 to 2007 and intensity-modulated external beam RT from 2007 to 2016. The median RT dose delivered was 6300 cGy (IQR 6300 - 6300 cGy).

ADT included luteinizing hormone-releasing hormone (LHRH) agonists only or combined androgen blockade. LHRH agonist was administered by injection every three or six months according to the physician's discretion.

All patients received the standard-of-care according to contemporary guidelines until death or the last follow-up.

2.4. Study Endpoints

The primary endpoint was progression to CRPC-free survival and CSS. The secondary endpoint was specific levels of PSA-related parameters that can be utilized to select candidates for the initiation of ADT.

2.5. Statistical analysis

The chi-square test and ANOVA were used to compare two or more variables, and the Mann-Whitney U test was used for the analysis of continuous variables. Survival analysis was evaluated and compared using the Kaplan-Meier method and compared with the log-rank test. The prognostic significances of PSAdT and PSADT before ADT, PSA at ADT, and PSA nadir after ADT were dichotomized at 2 ng/mL/year, 12 months, 2 ng/mL, and 1 ng/mL, respectively. These optimal cut-off values were based on predefined values and according to sensitivity analysis using Youden’s Index. Multivariate analyses were performed with Cox-proportional hazards regression models to adjust for potential confounders. All statistical analyses were performed using IBM SPSS software (version 21.0; IBM Corporation, Armonk, NY, USA). Differences with a p-value of <0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

Patient demographics and clinicopathological features of groups stratified by the PSA level at ADT of 2 ng/mL are presented in Table 1. There were no significant differences between the two groups regarding patient age, body mass index, performance status, preoperative PSA level, NCCN risk
category, pathological Gleason score and stage, type of RT, and PSA velocity and PSA doubling time before ADT.

3.2. Survival Prognosticators

On multivariable Cox regression analyses, delayed ADT (PSA ≥2 ng/mL) was an independent prognostic factor for cancer-specific mortality ($p = 0.047$; Table 2), and a marginally significant prognostic factor for progression to CRPC ($p = 0.051$; Table 3).

Patient age, body mass index, grade and stage, preoperative PSA, PSA nadir at RP, PSAV and PSADT prior to ADT, and time to PSA nadir following ADT were not independently associated with progression to CRPC and cancer-specific mortality.

3.3. Survival outcome

Survival outcomes were compared according to the level of PSA at ADT, stratified at 2 ng/mL (Table 4). During the median follow-up of 81.0 (IQR 54.2-115.7) months, patients who received ADT at PSA <2 ng/mL had significantly higher CSS rates than men who received ADT at PSA ≥2 ng/mL ($p = 0.002$; Fig. 2). Progression to CRPC-free survival was comparable between the two groups ($p = 0.331$; Fig. 3).

4. Discussion

ADT is a treatment option for all stages of PCa, from localized disease with a high risk of recurrence to castration-resistant disease [15]. Following RP, ADT can be used as an adjuvant therapy combined with RT to maximize survival outcomes in patients exhibiting adverse pathological features, including pT3 disease, positive surgical margin, Gleason score 8–10, and seminal vesicle invasion. The results of previous studies have suggested that the use of ADT in this clinical scenario may improve CSS and OS [4-9]. ADT can also be administered with RT at biochemical recurrence, depending on the presence of metastasis, as a salvage treatment option, which may result in clinical benefit [9]. However, the optimal level of PSA at which ADT should be administered is still controversial. In this study, we observed that delaying ADT following PSA elevation beyond 2 ng/mL was associated with increased risk of progression to CRPC and cancer-specific mortality.

In our study, a PSA cut-off value of 2 ng/mL based on Youden sensitivity analysis was revealed to be a prognostic factor for CSS in patients with PSA-only recurrent PCa following RP. Previous studies report
varying indications for initiating ADT following RP. Amling et al. suggested that a PSA value of greater than 0.4 ng/mL should be used to define PSA recurrence, since this cut-off point is associated with a significantly increased risk of biochemical and/or clinical progression over the following three years [16]. Freedland et al. reported that the risk of the need for secondary treatment following PSA recurrence depends on the cut-off value of PSA. On the basis of the finding that patients with a postoperative PSA greater than 0.2 ng/mL had a 100% 3-year risk of PSA progression, this cut-off point was suggested to be an appropriate indicator to initiate treatment [17]. Siddiqui et al. suggested that adjuvant ADT within 90 days following after RP improves CSS and systemic progression-free survival in node-negative patients. However, there were no significant differences in systemic progression-free survival or CSS between patients started on ADT at PSA values of 0.4, 1.0, and 2.0 ng/mL [18]. A randomized trial investigated the efficacy of immediate ADT versus delayed ADT of at least two years after randomization among patients with PSA recurrence following curative therapy and who were considered ineligible for curative treatment [19]. In the overall group, immediate ADT was associated with improved OS and time to clinical progression. However, there was no significant improvement of OS in the subgroup analysis, which included patients with PSA recurrence following curative therapy. The common limitation of these studies was that not all patients had received RT as multimodal therapy, as suggested by contemporary guidelines. In our study, all patients were treated with RT in an adjuvant or salvage setting according to the guidelines, which implies the generalizability of our data.

In our study, PSAV, PSADT, and Gleason score were not independently associated with survival endpoints. On the other hand, several studies have recommended that these parameters be utilized to decide on the timing of ADT at PSA-recurrence following RP [19-29]. Van den Bergh, et al. reported in a systematic review that early ADT cannot be recommended as the standard-of-care in the setting of PSA recurrence or local recurrence, and that ADT should be reserved for patients with the highest risk of disease progression, defined as short PSADT of less than 6–12 months or Gleason score of greater than 8 [21]. Algarra, et al. reported seminal vesical involvement and PSAV of greater than 0.84 ng/mL/year, in addition to PSADT, to be adverse features associated with disease progression in
patients who received ADT at PSA recurrence [22]. In a cohort of patients with mainly high-risk
disease, faster PSADT, higher Gleason score, and early intervention were associated with a lower risk
of CSS [25]. The significance of PSADT was consistent in patients receiving intermittent ADT, in which
a PSADT and PSA nadir of less than 1 ng/mL during the first cycle was associated with improvement in
CRPC-free survival [24]. On the other hand, studies have reported higher PSA and PSA nadir after
starting ADT, rather than PSADT or PSAV, to be significant indicators for CSS [28,29]. As seen in these
studies mentioned above, the parameters utilized for clinical endpoints were inconsistent, which
defers a definite conclusion. Moreover, various cut-off points were used for stratification of PSADT or
PSAV, if they were not evaluated as continuous variables. To the best of our knowledge, the present
study is the first to suggest an optimal cut-off point of PSA to initiate ADT in order to confer CSS
benefit in patients who underwent RT after PSA-only recurrence. Our results are meaningful because
the patients included in our study were a homogeneous group who were treated with RT and standard
care according to contemporary guidelines until death or last follow-up.

Based on accumulating evidence, there has been a paradigm shift in considering aggressive
treatments targeted at both the primary tumor and metastatic lesions of PCa to avoid or delay the
need for palliative treatments and to achieve maximal survival benefit [3]. PSA recurrence is the most
common pattern of disease relapse following RP, observed in up to 35% of patients with clinically
localized PCa [30, 31]. In an era of aggressive treatments such as RP for the treatment of
oligometastatic PCa, it is certain that more patients will experience post-operative PSA recurrence
and would be candidates for ADT. Whether ADT alone or in combination with systemic chemotherapy
is considered in this clinical scenario, we believe that our findings provide relevant evidence for
decision-making and patient stratification in future clinical trials.

The strengths of our study are the inclusion of detailed PSA kinetic data, comorbidities, performance
status, and clinicopathological data that were available for all patients. At the same time, we
acknowledge several limitations: first, our study is limited by its retrospective design. Sampling
intervals used to estimate PSA kinetics were not standardized. Second, the potential existence of bias
regarding subgroup differences may have confounded the results, although there were no statistically
significant differences between the two groups stratified by the level of PSA at ADT. Third, patient and physician preferences affected the implementation of specific treatments. Finally, differences in adverse effects and quality-of-life following ADT were not investigated. However, a notable finding of our study was that the early administration of ADT was not associated with an early advent of non-metastatic CRPC.

5. Conclusions

Early ADT at the PSA level of less than 2 ng/mL confers a CSS benefit in patients with localized or locally advanced PCa previously treated with RP. Future larger-scale analyses are warranted to validate our results.

Abbreviations

ADT: androgen-deprivation therapy

CRPC: castration-resistant prostate cancer

CSS: cancer-specific survival

NCCN: National Comprehensive Cancer Network

OS: overall survival

PCa: prostate cancer

PSA: prostate-specific antigen

PSADT: PSA doubling time

PSAV: PSA velocity

RP: radical prostatectomy

RT: radiation therapy

Declarations

Ethics approval and consent to participate

This study was approved by the Yonsei University Health System Institutional Review Board (2017-0186-001). Informed consent was waived from the Yonsei University Health System Institutional Review Board since patients’ information was collected during the routine clinical practice and patients were identified by anonymized investigator-generated code not linkable to their personal data. The same Institutional Review Board granted access to the institutional databases used in this
study.

**Consent for publication:** Not required

**Availability of data and materials:** The dataset analyzed during the current study is available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests.

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**Author’s contributions**

Study concept and initial design: HKA, KCK; Acquisition of data: HKA, KSL, DK; Data analysis: HKA, KSL; Manuscript writing: HKA, KCK; Critical revision for important intellectual content: BHC, KHR, SJH.

All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content, and have given final approval of the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Tables

Table 1. Clinicopathological characteristics of patients with localized prostate cancer who underwent radical prostatectomy and later developed metastasis.
|                                | Overall | PSA at ADT | p     |
|--------------------------------|---------|------------|-------|
|                                |         | <2 ng/mL   | ≥2 ng/mL |       |
| N                              | 69      | 31 (45.0%) | 38 (55.0%) | NS    |
| Age (years)                    | 69.0 (67.0 – 72.5) | 68.5 (71.5 – 75.8) | 71.0 (69.0 – 70.5) | 0.861 |
| BMI (kg/m2)                    | 22.9 (21.9 – 26.8) | 21.9 (22.6 – 26.1) | 23.1 (21.7 – 27.3) | 0.765 |
| ECOG performance status        |         |            | 0.644 |
| ≤1                             | 60 (86.9%) | 27 (87.1%) | 33 (86.8%) |
| ≥2                             | 9 (13.1%)  | 4 (12.9%)  | 5 (13.2%)  |
| Preoperative PSA (ng/mL)       | 17.4 (7.4 – 50.0) | 20.0 (9.3 – 43.0) | 14.8 (8.6 – 75.5) | 0.256 |
| PSA velocity                   |         | 0.191      |       |
| ≥2 ng/mL/year                  | 38 (55.1%) | 16 (51.6%) | 22 (57.9%) |
| <2 ng/mL/year                  | 31 (44.9%) | 15 (48.4%) | 16 (42.1%) |
| PSA doubling time              |         | 0.246      |       |
| ≥12 months                     | 33 (47.8%) | 14 (45.2%) | 19 (50.0%) |
| <12 months                     | 36 (52.2%) | 17 (54.8%) | 19 (50.0%) |
| NCCN risk category             |         | 0.197      |       |
| Low                            | 7 (10.1%)   | 5 (16.2%)  | 2 (5.3%)  |
| Intermediate                   | 18 (26.1%)  | 9 (29.0%)  | 9 (23.7%)  |
| High                           | 44 (63.8%)  | 17 (54.8%) | 27 (71.0%) |
| Pathologic Gleason score       |         | 0.582      |       |
| ≤6                             | 13 (18.8%)  | 7 (22.6%)  | 6 (15.8%)  |
| 7                              | 15 (21.7%)  | 8 (25.8%)  | 7 (18.4%)  |
| ≥8                             | 41 (59.5%)  | 16 (51.6%) | 25 (65.8%) |
| Pathological T stage           |         | 0.541      |       |
| T2                             | 12 (17.4%)  | 7 (22.6%)  | 5 (13.1%)  |
| T3                             | 47 (68.1%)  | 20 (64.5%) | 27 (71.1%) |
| T4                             | 10 (14.5%)  | 4 (12.9%)  | 6 (15.8%)  |
| Type of radiation therapy      |         | 0.158      |       |
| Adjuvant                       | 11 (15.9%)  | 5 (16.1%)  | 6 (15.8%)  |
| Salvage                        | 58 (84.1%)  | 26 (83.9%) | 32 (84.2%) |

Data are median (interquartile range) and number (%).
ADT = androgen-deprivation therapy; BMI = body mass index; CCI = Charlson Comorbidity Index; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen

Table 2. Cox-regression models for the association of risk factors with progression to cancer-specific mortality.
|                  | Univariate          |          |          |         |          |          |         |          |         |
|------------------|---------------------|----------|----------|---------|----------|----------|---------|----------|---------|
|                  | HR                  | 95% CI   | p        | HR      | 95% CI   | p        | HR      | 95% CI   | p       |
| Age              | 1.036               | 0.922-1.165 | 0.552   | 1.036   | 0.922-1.165 | 0.552   |
| Body mass index  | 0.994               | 0.767-1.288 | 0.963   | 0.994   | 0.767-1.288 | 0.963   |
| **ECOG PS**      |                     |          |          |         |          |          |         |          |         |
| ≤1               | 1                   |          |          |         |          |          |         |          |         |
| ≥2               | 3.063               | 0.651-14.42 | 0.157   | 3.063   | 0.651-14.42 | 0.157   |
| **Gleason score**|                     |          |          |         |          |          |         |          |         |
| ≤7               | 1                   |          |          |         |          |          |         |          |         |
| ≥8               | 5.743               | 1.264-26.09 | 0.024   | 3.844   | 0.834-17.72 | 0.084   |
| **Pathological stage** |                 |          |          |         |          |          |         |          |         |
| ≤T2              | 1                   |          |          |         |          |          |         |          |         |
| ≥T3              | 2.939               | 0.896-9.631 | 0.075   |         |          |          |         |          |         |
| **Time to PSA recurrence** |              |          |          |         |          |          |         |          |         |
|                  | 0.864               | 0.691-1.081 | 0.201   |         |          |          |         |          |         |
| **Preoperative PSA** | 0.994               | 0.981-1.008 | 0.376   | 0.994   | 0.981-1.008 | 0.376   |
| **PSA nadir at RP** | 1.802               | 0.619-5.240 | 0.281   | 1.802   | 0.619-5.240 | 0.281   |
| **PSAV before ADT** |                     |          |          |         |          |          |         |          |         |
| <2 ng/mL/year    | 1                   |          |          |         |          |          |         |          |         |
| ≥2 ng/mL/year    | 0.940               | 0.268-3.298 | 0.923   |         |          |          |         |          |         |
| **PSADT before ADT** |                     |          |          |         |          |          |         |          |         |
| <12 months       | 1                   |          |          |         |          |          |         |          |         |
| ≥12 months       | 0.996               | 0.971-1.021 | 0.737   |         |          |          |         |          |         |
| **PSA at ADT**   |                     |          |          |         |          |          |         |          |         |
| <2 ng/mL         | 1                   |          |          |         |          |          |         |          |         |
| ≥2 ng/mL         | 6.495               | 1.432-29.47 | 0.015   | 5.211   | 1.076-25.23 | 0.047   |
| **PSA nadir after ADT** |                 |          |          |         |          |          |         |          |         |
| <1 ng/mL         | 1                   |          |          |         |          |          |         |          |         |
| ≥1 ng/mL         | 4.353               | 1.276-14.86 | 0.019   | 2.234   | 0.624-8.003 | 0.217   |
| **Time to PSA nadir** | 0.972               | 0.864-1.092 | 0.631   | 0.972   | 0.864-1.092 | 0.631   |

ADT = androgen-deprivation therapy; CI = confidence interval; ECOG PS = Eastern Cooperative
Oncology Group performance status; HR = hazards ratio; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time; PSAV = prostate-specific antigen velocity

Table 3. Cox-regression models for the association of risk factors with progression to castration-resistance.
|                                      | Univariate |                   |                  | Multivariate |                   |                  |
|--------------------------------------|------------|------------------|------------------|--------------|------------------|------------------|
|                                      | HR         | 95% CI           | p                | HR           | 95% CI           | p                |
| Age                                  | 0.951      | 0.884 - 1.023    | 0.173            |              |                  |                  |
| Body mass index                      | 1.085      | 0.928 - 1.269    | 0.306            |              |                  |                  |
| ECOG PS                              |            |                  |                  |              |                  |                  |
| ≤1                                   | 1          | reference        |                  |              |                  |                  |
| ≥2                                   | 0.504      | 0.139 - 1.829    | 0.298            |              |                  |                  |
| Gleason score                        |            |                  |                  |              |                  |                  |
| ≤7                                   | 1          | reference        |                  |              |                  |                  |
| ≥8                                   | 2.202      | 0.894 - 5.424    | 0.086            |              |                  |                  |
| Pathological stage                   |            |                  |                  |              |                  |                  |
| ≤T2                                  | 1          | reference        |                  |              |                  |                  |
| ≥T3                                  | 0.779      | 0.168 - 3.607    | 0.749            |              |                  |                  |
| Time to PSA recurrence               | 0.938      | 0.870 - 1.011    | 0.092            |              |                  |                  |
| Preoperative PSA                     | 1.004      | 0.994 - 1.015    | 0.408            |              |                  |                  |
| PSA nadir at RP                      | 2.113      | 0.847 - 5.270    | 0.109            |              |                  |                  |
| PSAV before ADT                      |            |                  |                  |              |                  |                  |
| <2 ng/mL/year                        | 1          | reference        |                  |              |                  |                  |
| ≥2 ng/mL/year                        | 1.487      | 0.604 - 3.657    | 0.388            |              |                  |                  |
| PSADT before ADT                     |            |                  |                  |              |                  |                  |
| <12 months                           | 1          | reference        |                  |              |                  |                  |
| ≥12 months                           | 0.983      | 0.961 - 1.005    | 0.134            |              |                  |                  |
| PSA at ADT                           |            |                  |                  |              |                  |                  |
| <2 ng/mL                             | 1          | reference        |                  |              |                  |                  |
| ≥2 ng/mL                             | 3.184      | 1.104 - 9.179    | 0.032            | 3.934        | 0.994 - 15.57    | 0.051            |
| PSA nadir after ADT                  |            |                  |                  |              |                  |                  |
| <1 ng/mL                             | 1          | reference        |                  |              |                  |                  |
| ≥1 ng/mL                             | 3.792      | 1.286 - 11.19    | 0.016            | 1.301        | 0.669 - 4.382    | 0.511            |
| Time to PSA nadir                    | 0.955      | 0.872 - 1.046    | 0.324            |              |                  |                  |

ADT = androgen-deprivation therapy; CI = confidence interval; ECOG PS = Eastern Cooperative
Oncology Group performance status; HR = hazards ratio; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time; PSAV = prostate-specific antigen velocity

Table 4. Oncological outcomes of patients with localized prostate cancer who underwent radical prostatectomy and later developed metastasis.

| PSA at ADT       |          |       |       |
|------------------|----------|-------|-------|
|                  | <2 ng/mL | ≥2 ng/mL |       |
| Time to metastasis (months) | 33.5 (14.0-42.3) | 31.2 (12.3-41.1) | 0.971 |
| Metastatic site  |          |       |       |
| Bone             | 27 (87.1%) | 33 (86.8%) | 0.468 |
| Lymph nodes      | 3 (10.0%) | 5 (13.2%) | 0.621 |
| Viscera          | 2 (6.5%) | 3 (7.9%) | 0.133 |
| CRPC (%)         | 17 (53.1%) | 30 (51.7%) | 0.548 |
| Time to CRPC (months) | 55.5 (35.2-97.8) | 42.5 (32.3-73.8) | 0.051 |
| CRPC-free progression, 5y (%) | 70.8% | 64.7% | 0.311 |
| Death, N (%)     | 7 (21.9%) | 22 (37.9%) | 0.001 |
| Time to CSM (months) | 72.0 (45.0-108.9) | 65.0 (52.5-90.0) | 0.045 |
| CSS, 5y (%)      | 86.1% | 68.7% | 0.002 |
| Follow-up (months) | 83.5 (70.5-118.5) | 78 (52.4-94.0) | 0.074 |

Data are median (interquartile range) and number (%).

ADT = androgen-deprivation therapy; CRPC = castration-resistant prostate cancer; CSS = cancer-specific survival; PSA = prostate-specific antigen

Figures
Figure 1

Flowchart of patient selection.
Figure 2

Kaplan-Meier curves showing cancer-specific survival, stratified by the PSA level at ADT of 2 ng/mL.
Kaplan-Meier curves showing with progression to castration-resistance prostate cancer-free survival, stratified by the PSA level at ADT of 2 ng/mL.