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# Intermittent Versus Continuous Androgen Deprivation Therapy for Biochemical Progression After Primary Therapy in Hormone-Sensitive Nonmetastatic Prostate Cancer: Comparative Analysis in Terms of CRPC-M0 Progression

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## Abstract

**The risk of CRPC-M1 did not significantly vary according to the type of ADT used at progression. The risk of a CRPC-M0 progression increased 3.48 times using continuous ADT when compared to IAD.**

**Introduction:** To analyze whether the use of an intermittent (IAD) versus continuous (CAD) androgen deprivation therapy for the treatment of biochemical progression after primary treatments in prostate cancer can influence the development of nonmetastatic castration resistant prostate cancer (CRPC-M0).**Patients:** 170 male patients with an histologically confirmed diagnosis of PC, presenting a biochemical progression after primary treatments (82 after radical prostatectomy and 88 after external radiation therapy), nonmetastatic at imaging were considered for continuous (85 cases) or intermittent (85 cases) administration of androgen deprivation therapy. **Methods:** we retrospectively collect all data regarding histological diagnosis, primary treatment, imaging for M0-M1 staging, PSA at progression, time to biochemical progression from primary therapy, ADT used, IAD cycles, so to compare in 2 groups (IAD vs. CAD) time for progression from the beginning of ADT treatment and type of progression in terms of CRPC-M0 versus CRPC-M1 cases. **Results:** no significant ($P = .4955$) difference in the whole CRPC progression was found between IAD (25.8%) and CAD (30.5%) treatment at a mean of 32.7 $\pm$ 7.02 months and 35.6 $\pm$ 13.1 months respectively ($P = .0738$). Mean PSA at CRPC development was significantly higher in the IAD group (5.16 $\pm$ 0.68 ng/mL) than in the CAD group (3.1 $\pm$ 0.7 ng/mL) ($P < .001$). In all cases, imaging to detect M status at CRPC development was PET TC scan. At univariate analysis CAD administration significantly increases the RR for CRPC-M0 progression (RR 3.48; 95%CI 1.66-7.29; $P = .01$) when compared to the IAD administration, and this effect at multivariate analysis remained significant and independent to the other variables (RR 2.34, 95%CI 1.52-5.33; $P = .03$). **Conclusions:** in our population with biochem-

*Abbreviations:* PC, prostate cancer; ADT, androgen deprivation therapy; CRPC, castration resistant prostate cancer; IAD, intermittent androgen deprivation.

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ical progression after primary treatment for PC, the intermittent administration of ADT significantly reduces the risk to develop CRPC-M0 disease when compared to a continuous administration of ADT, whereas no difference between the 2 strategies in terms of CRPC-M1 progression exists.

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**Keywords:** Hormone therapy, Castration resistant, Prostatic neoplasm, Biochemical progression, Intermittent castration

## Introduction

For a long time, the evolution of prostate cancer (PC) was simply divided into 2 phases, hormone sensitive and hormone refractory. More recently, each of the 2 phases is further stratified into sections that have a clinical justification and are associated with a different management and therapeutic choice. Hormone sensitive PC, especially in the metastatic stage, is divided into progressive and de novo, low and high volume or risk[1] whereas castration-resistant PC (CRPC) is divided into nonmetastatic and metastatic.[2]

In particular, CRPC-M0 is really a new entity related to a particular natural history of the tumor. The development of resistance to castration therapy is in most cases associated with clinical progression and metastasis (CRPC-M1). In a limited percentage of cases, the development of a CRPC may precede the appearance of metastases for a variable number of months.[3] A non-negligible part of CRPC-M0 actually become oligometastatic when the imaging used switches from the traditional to the new generation (PET-CT scan).[4] The natural history of a CRPC-M0 generally begins with primary treatment (radical prostatectomy or radiation therapy), followed by biochemical progression.[5] Prolonged androgen deprivation therapy (ADT) of a biochemical progression can cause castration resistance before the tumor has the ability to spread distantly. Interest in CRPC-M0 has increased due to 3 clinical trials[6-8] resulting in the recommendation for next-generation antiandrogen therapy in high-risk cases.

Intermittent androgen deprivation therapy (IAD) may have one of the major indications in patients with biochemical progression after primary treatment.[9] The ambitious goal of intermittent therapy to delay tumor progression into a CRPC form has not been demonstrated but randomized trials have demonstrated noninferiority of IAD compared to continuous ADT in terms of survival, with possible benefits in terms of chronic side effects secondary to castration.[10,11]

*The aim* of this analysis is to evaluate whether, in patients with PC submitted to primary treatment followed by only biochemical progression and selected for ADT, an intermittent administration is able to reduce the development of a CRPC-M0 disease compared to the continuous administration.

## Materials and Methods

### *Population*

This is a comparative retrospective longitudinal clinical analysis in a real world setting on patients with prostatic adenocarcinoma and biochemical progression after primary treatment with radical prostatectomy (RP) or external radiation therapy (RT) submitted to continuous (CAD) versus intermittent (IAD) androgen deprivation therapy. It has been approved by our Institutional Internal Review Board. The study objectives called for a design that would detect statistically significant difference between groups of 25% at $P < .05$ with a power of 90% (Type II or beta error of 0.1). Using standard power analysis methods, a sample size of at least 80 subjects in each group of therapy (IAD vs. CAD) was estimated.

Inclusion criteria were histologically proved adenocarcinoma of the prostate, nonmetastatic disease at clinical staging, previous primary treatment with RP or RT, only biochemical progression after primary therapy, submission to intermittent or continuous androgen deprivation therapy at biochemical progression.

Exclusion criteria were other active oncological diseases or therapies, metastatic disease, clinical or radiological progression after primary treatment, follow-up less than 24 months.

From January 2015 to January 2020 eighty-five patients submitted to IAD treatment and 85 patients submitted to CAD were detected and included in Group 1 (IAD therapy) and Group 2 (CAD therapy) respectively. The characteristics of patients in the 2 Groups are described in Table 1 .

### *Methods*

All data were retrospectively collected. Histological diagnosis of prostatic adenocarcinoma was obtained at biopsy for all cases and also after surgery for cases submitted to RP as primary treatment. Following EAU guidelines, clinical staging was obtained using multiparametric magnetic resonance (mMR) for loco-regional and CT and bone scan or PET CT scan for systemic staging. Each patient was classified based on the D'Amico/EAU risk classes. As primary treatment patients were submitted to a laparoscopic or robotic radical prostatectomy with extended lymph-node dissection or external beam radiation therapy (IMRT) associated to a course of neoadjuvant and adjuvant androgen deprivation therapy (12 or 24 months) based on EAU guidelines recommendations.

Biochemical progression after RP was defined as a confirmed (3 consecutive determinations) elevated levels of total PSA over 0.2 ng/mL, whereas, after radiation therapy, as a PSA increase of 2.0 ng/mL over the nadir. Exclusion of clinical and radiological progression after primary treatment was obtained using total body choline or PSMA PET-CT scan. Time to biochemical progression and PSA levels at biochemical progression were recorded. Patients included in Group 1 were all submitted to a IAD protocol using LHRH agonists with an initial induction period of 6 months. All cases responded with a PSA nadir lower than 0.2 ng/mL in cases submitted to RP and lower than 0.4 ng/mL in cases submitted to RT and then ADT was withheld until PSA increased over 2.0 ng/mL ("off treatment phase"). The subsequent "on treatment phase" lasted for the time

**Table 1** Characteristics of the Population Submitted to IAD Versus Continuous ADT (CAD)

| ADT Scheme | IAD | Continuous ADT | P-Value |
|---|---|---|---|
| *Number cases* | 85 | 85 | / |
| *Age (y)* | 68.0 ± 2.17; 68 (64-72) | 66.3 ± 2.13; 67 (62-73) | **<.0001** |
| *BMI* | 25.8 ± 1.38; 25.6 (23.0-29.7) | 25.5 ± 1.43; 25.7 (23.2-30.3) | .1658 |
| *total PSA at PC diagnosis (ng/mL)* | 12.0 ± 3.0; 12.7 (4-18.6) | 13.9 ± 3.05; 13.2 (8.9-22.4) | **.0001** |
| *Number of lesions at mMR* | Total 77 (90%) | Total 74 (87%) | |
| 1 | 26 (33.7%) | 15 (20.2%) | .0607 |
| 2 | 51 (66.3%) | 54 (72.9%) | |
| 3 | 0 (0%) | 5 (6.9%) | |
| *Size (mm) of the primary lesion at mMR* | 13.7 ± 3.66; 14 (8-24) | 15.4 ± 3.9; 15 (9-27) | **.0039** |
| *Clinical T staging* | | | |
| T2 | 11 (12.9%) | 23 (27.0%) | **.0198** |
| T3a | 58 (68.2%) | 55 (64.7%) | |
| T3b | 16 (18.9%) | 7 (8.3%) | |
| *Clinical N staging* | | | |
| N0 | 79 (92.9%) | 82 (96.5%) | .3041 |
| N1 | 6 (7.1%) | 3 (3.5%) | |
| *Biopsy outcomes* | | | |
| % positive samples PC | 35.7 ± 11.5; 39 (20-75) | 43.2 ± 12.2; 40 (20-80) | **.0001** |
| Max % PC tissue per core | 48.6 ± 15.7; 52 (15-87) | 55.8 ± 13.2; 55 (30-100) | **.0015** |
| *ISUP grading at biopsy:* | | | |
| 1 | 0 | 0 | .6314 |
| 2 | 0 | 0 | |
| 3 | 53 (62.3%) | 56 (65.9%) | |
| 4 | 32 (37.7%) | 29 (34.1%) | |
| 5 | 0 | 0 | |
| *Risk classes (D'Amico)* | | | |
| Low | 0 | 0 | .1480 |
| Intermediate | 16 (18.8%) | 24 (28.2%) | |
| High | 69 (81.2%) | 61 (71.8%) | |
| *Primary treatment* | | | |
| - Radical prostatectomy with eLND | 40 (47.0%) | 42 (49.4%) | .7588 |
| - External radiotherapy + ADT | 45 (53.0%) | 43 (50.6%) | |
| *Pathological stage (T) at surgery* | | | |
| pT2 | 6 (15.0%) | 8 (19.0%) | .7024 |
| pT3a | 28 (70.0%) | 30 (71.4%) | |
| pT3b | 6 (15.0%) | 4 (9.6%) | |
| *Number lymph nodes removed at surgery* | 23.4 ± 3.8; 23 (20-33) | 21.9 ± 3.2; 23 (18-31) | .0563 |
| *Pathologic N stage at surgery* | | | |
| pN0 | 40 (100%) | 42 (100%) | .7588 |
| pN1 | 0 | 0 | |
| *ISUP grading at surgery* | | | |
| 1 | 0 | 0 | .0688 |
| 2 | 0 | 0 | |
| 3 | 27 (67.5%) | 20 (47.6%) | |
| 4 | 13 (32.5%) | 22 (52.4%) | |
| 5 | 0 | 0 | |
| *Surgical margin at surgery (R)* | | | |
| - Negative | 23 (57.5%) | 31 (73.8%) | .1195 |

(*continued on next page*)

**Table 1** (*continued*)

| ADT Scheme | IAD | Continuous ADT | P-Value |
|---|---|---|---|
| - Positive | 17 (42.5%) | 11 (26.2%) | |
| *PNI at surgery* | | | |
| Positive | 25 (62.5%) | 38 (90.5%) | **.0026** |
| Negative | 15 (37.5%) | 4 (9.5%) | |
| *Postoperative total PSA (ng/mL) at 1 mo (in cases submitted to RP)* | 0.08 ± 0.09; 0.05 (0.01-0.4) | 0.02 ± 0.01; 0.03 (0.01-0.7) | **<.0001** |
| *Adjuvant therapies after surgery* | | | |
| - RT | 26 (65.0%) | 19 (45.2%) | .2236 |
| - ADT | 0 | 0 | |
| *Adjuvant ADT therapy at RT* | | | |
| Total cases | 45 (100%) | 43 (100%) | .9983 |
| 12 mo | 3 (6.0%) | 3 (6.9%) | |
| 24 mo | 42 (94.0%) | 40 (93.1%) | |
| *PSA (ng/mL) at biochemical progression after primary treatment* | | | |
| All (either after RP or RT) | 2.07 ± 2.36; 2.2 (0.4-4.2) | 1.10 ± 1.20; 0.5 (0.3-3.7) | **.0009** |
| After RP | 0.5 ± 0.11; 0.5 (0.4-0.8) | 0.4 ± 0.11; 0.5 (0.3-0.8) | **<.0001** |
| After RT | 3.4 ± 2.57; 3 (2.1-4.2) | 2.8 ± 0.38; 3.3 (2.5-3.7) | **<.0001** |
| *Time to biochemical progression (mo) from primary therapy* | | | |
| All (either after RP or RT) | 28.3 ± 10.2; 30 (3-42) | 30.0 ± 8.2; 30 (6-48) | .2328 |
| After RP | 19.1 ± 8.6; 24 (3-30) | 22.5 ± 6.3; 24 (6-30) | **.0037** |
| After RT | 34.2 ± 6.0; 36 (12-42) | 34.9 ± 4.5; 36 (18-48) | .3907 |
| *Imaging at biochemical progression* | | | |
| TC + bone scan | 0 | 0 | .2184 |
| PET TC choline | 76 (89.4%) | 78 (91.7%) | |
| PET TC PSMA | 9 (10.6%) | 7 (8.3%) | |
| *Time at beginning of ADT (IAD vs. continuous) from primary therapy (mo)* | 27.5 ± 10.1; 30 (4-42) | 29.0 ± 8.1; 30 (6-48) | .2870 |
| *Total PSA (ng/mL) at baseline (IAD or continuous ADT)* | 2.5 ± 0.8; 2.7 (1.0-4.2) | 1.8 ± 0.9; 2.7 (1.0-4.2) | **<.0001** |
| *Total PSA (ng/mL) after the first 6 mo (induction period) of ADT* | 0.22 ± 0.17; 0.2 (0.01-1) | 0.41 ± 0.33; 0.4 (0.1-1.8) | **<.0001** |
| *Number of cycles of IAD* | | | |
| 2 | 1 (1.0%) | / | / |
| 3 | 10 (11.8%) | | |
| 4 | 58 (68.3%) | | |
| 5 | 16 (18.9%) | | |
| *CRPC development (number of cases)* | 22 (25.8%) | 26 (30.5%) | .4955 |
| *Time to CRPC development (mo)* | 32.7 ± 7.02; 32 (19-45) | 35.6 ± 13.1; 36 (18-60) | .0738 |
| *PSA (ng/mL) at CRPC development* | 5.16 ± 0.68; 5.2 (2.7-6.2) | 3.1 ± 0.7; 2.7 (2.4-4.5) | **<.0001** |
| *Imaging to detect CRPC* | | | |
| TC+ bone scan | 0 | 0 | .4425 |
| PET TC choline | 19 (86.3%) | 19 (73.1%) | |
| PET TC PSMA | 3 (13.7%) | 7 (26.9%) | |
| *M status at CRPC development* | | | |
| M0 | 1 (4.5%) | 8 (30.7%) | **.0203** |
| M1 | 21 (95.5%) | 18 (69.3%) | |

Mean ± SD, median, (range).
Number of cases (%).
Abbreviations: ADT= androgen deprivation therapy; BMI= body mass index; CRPC= castration resistant prostate cancer; IAD= intermittent androgen deprivation; mMR= multiparametric magnetic resonance; PNI= perineural invasion; RP= radical prostatectomy; RT= external radiation therapy.

needed to reach the nadir PSA level again with a stable or decreasing value. One cycle was defined as the completion of a "on" and "off" phase. During IAD, serum PSA levels were measured every 8 to 12 weeks during the "on" treatment period and every 4 to 8 weeks during the "off" phases. In Group 2, all patients were submitted to a continuous administration of ADT using LHRH agonists and followed using serum PSA determination at 3-month interval. In both Groups testosterone levels were monitored at the same intervals of PSA determination and clinical progression was verified using PET-CT scan at 12-month intervals or upon detection of therapy failure.

Treatment failure (castration-resistance) was defined when PSA increased despite ADT administration over 2.0 ng/mL and 25% above nadir, with testosterone below 20 ng/dL. CRPC development during ADT therapy in the 2 Groups was distinguished in M0 or M1 on the basis of total body PET-CT scan. In each Group, the number of cases, time to development from the beginning of ADT, PSA levels at development of M0 or M1 CRPC was described.

### *Statistical Analysis*

Statistical analyses were carried out using the STATA 17.0 package. Descriptive statistics were used to characterized different parameters (mean, median, range). Differences between values were assessed using Student *t* test. Between-Therapy Group differences (IAD vs. CAD) were tested using repeated measures analysis of variance (MANOVA). The degree of association among the different variables was determined using the Pearson's r correlation test. COX univariate and multivariate analyses were performed to identify the relative risk (RR and 95% CI) for each variable in predicting the development of M0 and M1 CRPC. Kaplan Meier survival curve in terms of time to CRPC development were also used. Number of populations in the 2 groups was defined using a standard power analysis method for a design that would detect statistically significant differences between groups of 25% at $P < .05$ with a power of 90% (Type II or beta error of 0.1).

## Results

### *Comparative Analysis Between IAD and CAD Group*

170 patients fulfilling inclusion and exclusion criteria were collected and included in Group 1 (IAD treatment 85 cases) and Group 2 (CAD treatment 85 cases). Characteristics of the population in the 2 Groups are described in Table 1. In particular, in both groups the majority of cases were clinically staged at N0 (Group 1 = 92.9% and Group 2 = 96.5%; $P = .3041$) and a higher percentage of T3b was found in Group 1 (18.9%) than in Group 2 (8.3%) ($P = .0198$). ISUP grading distribution was similar ($P = .6314$) in the 2 Groups and in both Groups, patients were similarly distributed on the basis of the primary treatment (RP in 47.0% and 49.4% of cases; RT in 53.0% and 50.6% of cases; $P = .7588$). All cases submitted to RT as primary treatment performed adjuvant ADT almost all for 24 months (94.0% and 93.1% in the 2 Groups). Mean total PSA at biochemical progression after primary treatment was significantly ($P = .0009$) higher in IAD group (PSA = 2.07 ± 2.36 ng/mL) than in CAD group (PSA = 1.10 ± 1.20 ng/mL), with higher values in cases submitted to RT (Group 1: 3.4 ± 2.57 and Group 2: 2.8 ± 0.38) and lower in those submitted to RP (Group 1: 0.5 ± 0.11 and Group 2: 0.4 ± 0.11). Mean time to biochemical progression was similar ($P = .2328$) between the 2 groups (Group 1: 28.3 ± 10.2 months and Group 2: 30.0 ± 8.2 months). In all cases a PET CT scan (mainly using choline) was used to exclude radiological and clinical progression at beginning of ADT. Mean total PSA at baseline before ADT treatment was significantly ($P < .001$) higher in IAD (2.5 ± 0.8 ng/mL) than in CAD (1.8 ± 0.9 ng/mL) group. Mean follow-up during IAD and CAD was similar (IAD:39.5 ± 5.8 months; CAD 41.6 ± 9.8 months). In the IAD group all 85 cases responded to the first induction period of 6 months of ADT and the majority of cases (87.2%) concluded at least 4 cycles.

### *CRPC M0 or M1 Progression in the IAD Versus CAD Group*

A CRPC progression was detected in 25.8% (22 cases) and 30.5% (26 cases) of cases in IAD and CAD groups respectively ($P = .4955$). At CRPC progression in all cases serum testosterone levels were below 10 ng/dL. Mean time to CRPC development was similar ($P = .0738$) between the 2 groups (Group 1: 32.7 ± 7.02; Group 2: 35.6 ± 13.1).Mean PSA levels at CRPC development was significantly ($P < .0001$) higher in IAD group (5.16 ± 0.68 ng/mL) than in CAD group (3.1 ± 0.7 ng/mL).M status in the 48 cases with CRPC progression defined in all cases using PET CT scan, was significantly ($P = .0203$) different between the 2 Groups, mainly M1 (IAD: 95.5% and CAD: 69.3%) but a higher percentage of M0 CRPC was found in CAD (30.7% = 8 cases) than in IAD (4.5% = 1 case) group. Considering the whole population of 85 cases for each group, a CRPC-M0 was found in 1.2% and 9.4% of cases in the IAD and CAD treatment respectively, whereas the percentage of CRPC M1 was similar (IAD 24.7% and continuous ADT 21.7%).

Using a Kaplan Meier analysis, the 5-year survival rate free of CRPC-M0 progression was high (94.7%) in the whole population but significantly ($P = .03$) higher in the IAD (98.8%) versus the CAD (90.6%) group (HR: 3.48; 95% CI 1.66-7.29) (Figure 1A). On the contrary the 5-year survival rate free of CRPC-M1 progression was similar ($P = .96$) between IAD (75.3%) and CAD (78.8%) group (HR 2.35; 95% CI 0.35-5.63) (Figure 1B).

### *Correlation Analysis Among CRPC Progression and Variables*

Correlations among each form of CRPC (M0 and M1) progression and the clinical and pathological variables of our population are described in Table 2. CRPC M0/M1 progression significantly correlated with T staging (r = 0.2802; $P = .0002$) and ISUP grading (r = 0.2627; $P = .0005$) but not with PSA at biochemical progression, time to biochemical progression from primary therapy or PSA level at baseline to ADT ($P > .05$). CRPC M0/M1 progression correlated with PSA level after the first 6 months of ADT (r = 0.2655; $P = .0004$).

### *Univariate and Multivariate Analysis in Terms of M0 or M1 CRPC Progression*

A logistic regression analysis was carried out to identify the predictive value of different clinical and pathological variables in terms of CRPC-M0 (Table 3) or M1 (Table 4) progression. At the univariate

**Figure 1** (A) Kaplan Meier curve in terms of 5-year survival rate free of CRPC-M0 progression comparing IAD and Continuous ADT groups. (B) Kaplan Meier curve in terms of 5-year survival rate free of CRPC-M1 progression comparing IAD and Continuous ADT groups. IAD= intermittent androgen deprivation; CAD = continuous androgen deprivation.

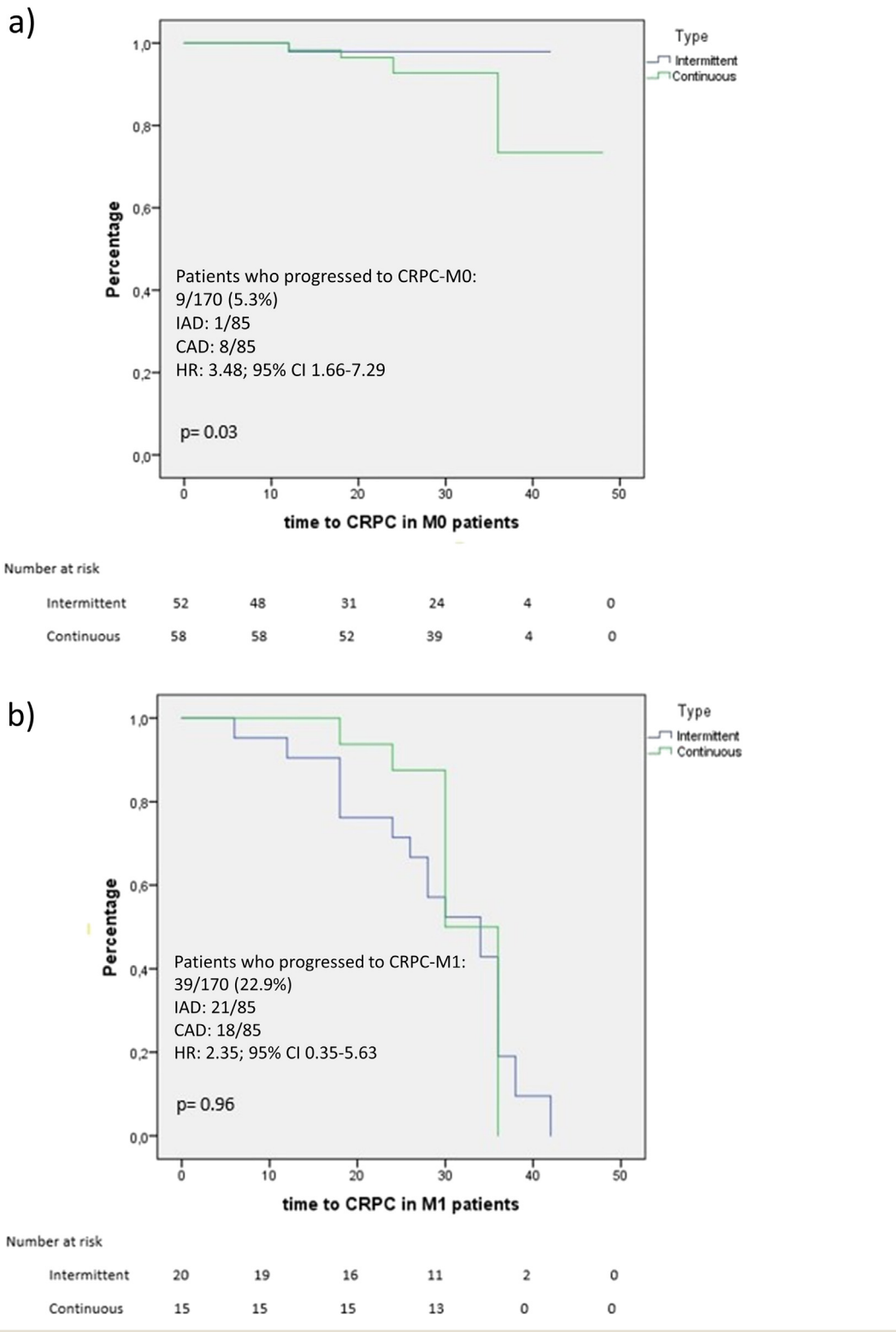

**Table 2** Correlation Coefficients (Pearson) Among CRPC M0/M1 Development and the Other Clinical and Pathological Variables

| Correlation | Coefficient | *P* Value |
|---|---|---|
| CRPC M0/M1-age | -0.03441 | .656 |
| CRPC M0/M1- BMI | 0.05944 | .4413 |
| CRPC M0/M1- risk class | 0.1048 | .1739 |
| CRPC M0/M1 - preoperative PSA | -0.02274 | .7685 |
| CRPC M0/M1- size primary lesion at MR | 0.1467 | .07235 |
| CRPC M0/M1 - PIRADS score | **0.2172** | **.007389** |
| CRPC M0/M1- cT | **0.2802** | **.0002152** |
| CRPC M0/M1 - percentage positive cores at biopsy | 0.1112 | .149 |
| CRPC M0/M1 - Max percentage PC per core | 0.1073 | .1638 |
| CRPC M0/M1 - ISUP GRADING at biopsy | **0.2627** | **.0005389** |
| CRPC M0/M1 - pT at surgery | **0.2802** | **.0002152** |
| CRPC M0/M1- ISUP grading at surgery | 0.1988 | .0733 |
| CRPC M0/M1 - surgical margins | 0.07011 | .5314 |
| CRPC M0/M1 - PNI at surgery | 0.04268 | .7034 |
| CRPC M0/M1 - postoperative PSA | 0.1572 | .161 |
| CRPC M0/M1 - PSA at biochemical progression (all RP and RT) | -0.002852 | .9748 |
| CRPC M0/M1 - time to biochemical progression (all RP and RT) | 0.01015 | .8964 |
| CRPC M0/M1 - time to ADT beginning | -0.06056 | .4327 |
| CRPC M0/M1 - PSA at baseline to ADT | 0.08609 | .2643 |
| CRPC M0/M1 - PSA after 6 mo ADT | **0.2655** | **.0004663** |

Evaluation on the whole population of 170 cases.
Abbreviations: ADT= androgen deprivation therapy; BMI= body mass index; CRPC= castration resistant prostate cancer; IAD= intermittent androgen deprivation; mMR= multiparametric magnetic resonance; PNI= perineural invasion; RP= radical prostatectomy; RT= external radiation therapy. In bold significant values

analysis the risk of CRPC-M1 progression significantly increased only according to the clinical T staging ($P = .04$) with an HR of 4.41 (95% CI 0.85-22.92) for T3b when compared to T2 cases. In particular the risk of CRPC-M1 did not significantly vary according to the type of ADT used at progression (IAD vs. CAD $P = .78$). On the contrary, the risk of a CRPC-M0 progression significantly increased according to the type of ADT at biochemical progression ($P = .01$) and the type of primary therapy ($P = .04$); in particular it increased 3.48 times (95% CI 1.66-7.29) using continuous ADT when compared to IAD and 3.45 times (95% CI 1.12-5.45) in cases submitted to radiotherapy when compared to radical prostatectomy . At the multivariate analysis, only the type of ADT at progression maintained an independent predictive value in terms of risk for CRPC-M0 ($P = .03$; HR 2.34; 95%CI 1.52-5.33).

## Discussion

This is the first analysis in the literature targeted on the role of different ADT modalities in terms of development of CRPC-M0 in a real-world population. The identification of a CRPC-M0 phase in the natural history of PC is of relatively recent acquisition and represents a deviation from the normal course which foresees the development of metastases and precedes castration resistance. CRPC-M0 is a progressive disease resulting from the treatment of biochemical progression after primary therapy (surgery or radiation therapy) with ADT. In different experiences, approximately 27% of all patients undergoing RP or RT develop a biochemical progression[12] and the treatment of patients with PSA-only recurrence is a difficult decision balanced between the attempt to delay the appearance of metastases and the risk of creating an overtreatment in patients whose disease may not influence their quality of life or survival in the next 5 years.

CRPC-M0 is a transient disease stage characterized by castrate testosterone levels, resistance to ADT and absence of detectable metastases in imaging exams, together with a progressively rising PSA at an increase of 25% from nadir at a minimum rise of 2 ng/mL.[13] The real prevalence of CRPC-M0 is unknown but it is estimated for a relatively small proportion (2%-8%) of the total PC cases.[14] Approximately 60% of all patients with CRPC-M0 progress to metastatic disease within 5 years, with a higher risk for younger age, high Gleason score, reduced PSA doubling time (<6 months).[15] The interest in this disease stage increased through the development of 3 large phase III trials, Prosper, Spartan and ARAMIS[6-8] that evaluated metastasis-free survival in patients treated with enzalutamide, apalutamide or daralutamide.

In the present retrospective analysis, we showed that in our real-world population of 170 patients submitted to ADT for biochemical progression after RP or RT, the type of administration of hormone therapy was associated with the development of CRPC-M0 but not of CRPC-M1. On 28.2% of cases (48/170) who developed castration resistance at a median of 33 months from ADT beginning, 18.7% of those showed a CRPC-M0 stage. While no significant (0.4955) differences in terms of whole CRPC development and time to CRPC was found, the use of Intermittent ADT therapy (IAD) was associated with a reduced ($P = .0203$) percentage of CRPC-M0 disease (4.5%) when compared to continuous ADT (30.7%). IAD has been found to have 2 purposes: to delay the time to tumor progression due to castration resistance and to reduce side effects

**Table 3** COX Regression Analysis to Identify Predictors for CRPC-M0 Development

| *Variable* | | *Univariate* | | | *Multivariate* | | |
|---|---|---|---|---|---|---|---|
| | | **HR** | **95% CI** | ***P*-Value** | **HR** | **95% CI** | ***P*-Value** |
| **Risk class** | Intermediate | 1.0 | - | - | - | - | - |
| | High | 2.01 | 0.42-9.69 | .38 | | | |
| **Number of lesions at mMR** | 1 | 1.0 | - | - | - | - | - |
| | ≥2 | 3.93 | 0.49-31.53 | .19 | | | |
| **Preoperative PSA (ng/mL)** | </=10 | 1.0 | - | - | - | - | - |
| | >10 | 0.91 | 0.18-4.42 | .90 | | | |
| **Type of primary treatment** | RP | 1.0 | - | - | - | - | - |
| | RT | 3.45 | 1.12-5.45 | **.04** | 0.89 | 0.76-2.53 | .07 |
| **PSA at progression after primary treatment(ng/mL)** | < 1.0<br>>1.0 | 1.0<br>3.69 | 0.91-14.91 | .07 | - | - | - |
| **Time to biochemical progression (mo)** | <12<br>12-24<br>>24 | 1.0<br>0.94<br>1.64 | 0.16-5.33<br>0.31-8.63 | .94<br>.55 | - | - | - |
| **Total PSA after first 6 mo of ADT (ng/mL)** | 0.2<br>0.2-0.4<br>>0.4 | 1.0<br>1.31<br>1.74 | 0.67-2.54<br>0.80-3.78 | .42<br>.16 | - | - | - |
| **Clinical T stage** | pT2 | 1.0 | - | - | - | - | - |
| | pT3a | 1.26 | 0.73-2.15 | .40 | | | |
| | pT3b | 1.57 | 0.84-3.34 | .15 | | | |
| **ISUP grading (biopsy)** | 3 | 1.0 | - | - | - | - | - |
| | 4 | 0.93 | 0.52-1.63 | .79 | | | |
| **Type of ADT** | IAD | 1.0 | - | - | - | - | - |
| | Continuous | 3.48 | 1.66-7.29 | **.01** | 2.34 | 1.52-5.33 | **.03** |

Abbreviations: ADT= androgen deprivation therapy; CRPC= castration resistant prostate cancer; IAD= intermittent androgen deprivation; mMR= multiparametric magnetic resonance; RP= radical prostatectomy; RT= external radiation therapy.

related to ADT.[10] In a subset of patients with biochemical relapse after primary treatment (RT), Crook et al[16,17] concluded that IAD was not inferior to continuous therapy with regards to the time to progression and overall survival, but no analysis in terms of CRPC-M0 was carried on. In our population, we showed that in this setting of patients, IAD therapy can reduce the risk to develop a CRPC-M0 disease (1/85 cases) when compared to a continuous administration of ADT. The risk of CRPC-M0 development increased 3.48 times (1.66-7.29: 95%CI) using a continuous ADT when compared to IAD administration ($P = .01$) and the effect of ADT administration remained a significant ($P = .03$) and independent risk factor for CRPC-M0 disease also at the multivariate analysis. In particular, IAD treatment was able to significantly reduce the risk of CRPC-M0 disease, independently to the type of primary treatment (surgery vs. RT) and the clinical risk classes of PC. Importantly, in our real-world population, the imaging used to detect M status at progression to a CRPC was the more sensitive new imaging with PET-CT scan and not the old imaging with bone scan and CT scan as in previous clinical trials. On the contrary the 5-year survival rate free of CRPC-M1 progression was similar ($P = .96$) between IAD (75.3%) and CAD (78.8%) (HR 2.35; 95% CI 0.35-5.63) and the risk of CRPC M1 progression significantly increased only according to the clinical T staging ($P = .04$) with an HR of 4.41 (95% CI 0.85-22.92) for T3b when compared to T2 cases and did not significantly varied according to the type of ADT used at progression (IAD vs. CAD $P = .78$). The demonstration that IAD is associated with a lower development of CRPC-M0 has no effect on patient survival or on the subsequent development of metastases but defines an ability to influence the natural history of progression.

*Limitations and strengths:* This is a retrospective analysis on patients longitudinally followed during ADT administration and it is not possible to evaluate the impact on overall survival. Our study represents a real-world situation, the population in the 2 treatment groups are well balanced in terms of clinical and pathologic characteristics of the PC and type of primary treatment. Only PSA levels at baseline to ADT administration and at CRPC development was significantly ($P < .001$) different between the 2 groups with higher levels in the IAD population. Moreover, the absence or presence or metastases at CRPC progression was defined in all cases with the more sensitive new imaging (PET-CT scan), an aspect that makes the data noncomparable with previous clinical trials using the old imaging, but it defines M status more accurately.

**Table 4** COX Regression Analysis to Identify Predictors for CRPC- M1 Development

| *Variable* | | *Univariate* | | | *Multivariate* | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | *P*-Value | HR | 95% CI | p-Value |
| **Risk class** | Intermediate | 1.0 | - | - | - | - | - |
| | High | 2.19 | 0.49-9.74 | .30 | | | |
| **Number of lesions at mMR** | 1 | 1.0 | - | - | - | - | - |
| | ≥ 2 | 1.06 | 0.24-4.65 | .94 | | | |
| **Preoperative PSA (ng/mL)** | </=10 | 1.0 | - | - | - | - | - |
| | >10 | 0.54 | 0.07-4.35 | .56 | | | |
| **Type of primary treatment** | RP | 1.0 | - | - | - | - | - |
| | RT | 3.93 | 0.50-30.48 | .19 | | | |
| **PSA at progression after primary treatment(ng/mL)** | < 1.0<br>> 1.0 | 1.0<br>1.21 | 0.44-3.26 | .70 | - | - | - |
| **Time to biochemical progression (mo)** | <12<br>12-24<br>>24 | 1.0<br>0.92<br>0.15 | 0.08-1.09<br>0.01-1.72 | .59<br>.13 | - | - | - |
| **Total PSA after first 6 mo of ADT (ng/mL)** | 0.2<br>0.2-0.4<br>>0.4 | 1.0<br>0.42 | 0.53-1.19 | .10 | - | - | - |
| **Clinical T stage** | T2 | 1.0 | - | - | - | - | - |
| | T3a | 1.60 | 0.33-7.77 | .55 | | | |
| | T3b | 4.41 | 0.85-22.92 | **.04** | | | |
| **ISUP grading (biopsy)** | 3 | 1.0 | - | - | - | - | - |
| | 4 | 2.03 | 0.65-6.27 | .22 | | | |
| **Type of ADT** | IAD | 1.0 | - | - | - | - | - |
| | Continuous | 2.35 | 0.35-5.63 | .78 | | | |

Abbreviations: ADT= androgen deprivation therapy; CRPC= castration resistant prostate cancer; IAD= intermittent androgen deprivation; mMR= multiparametric magnetic resonance; RP= radical prostatectomy; RT= external radiation therapy.

## Conclusions

In a real-world analysis, we showed that the intermittent administration of ADT is associated to a lower percentage of CRPC-M0 progression and it can reduce the risk of more than 3 times when compared to a continuous ADT administration without significantly changing the overall percentage of CRPC progression. However, this is a retrospective analysis and no clinical conclusions can be obtained; further prospective studies may be warranted.

### *Clinical Practice Points*

- We investigated on PC patients submitted to ADT for biochemical progression after primary therapy.
- The risk of CRPC-M1 did not significantly vary according to the type of ADT used at progression.
- The risk of a CRPC-M0 progression significantly increased according to the type of ADT at biochemical progression.
- The risk of a CRPC-M0 progression increased 3.48 times using continuous ADT when compared to IAD.
- IAD treatment was able to significantly reduce the risk of CRPC-M0 disease, independently to the type of primary treatment (surgery vs. radiotherapy) and the clinical risk classes of PC.
- The 5-year survival rate free of CRPC-M0 progression was significantly ($P = .03$) higher in the IAD (98.8%) versus the continuous ADT (90.6%) group.

## Disclosure

No conflict of interest are present for all authors.

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