Published in final edited form as:

Prostate. 2015 May ; 75(7): 777–782. doi:10.1002/pros.22967.

Variant allele of HSD3B1 increases progression to castration-resistant prostate cancer

Gang Wu^{#1}, Shengsong Huang^{#1}, Kent L. Nastiuk², Jinliang Li¹, Jun Gu³, Ming Wu¹, Qimin Zhang¹, Hanqing Lin^{4,*}, and Denglong Wu^{1,*}

¹ Department of Urology, Tongji Hospital, Tongji University School of Medicine, Shanghai, PR China

² Department of Pathology and Laboratory Medicine, University of Rochester, Rochester, New York, USA

³ Department of Pathology, Tongji Hospital, Tongji University School of Medicine, Shanghai, PR China

⁴ State Key Laboratory of Molecular Biology, Shanghai Key Laboratory of Andrology, Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, PR China

These authors contributed equally to this work.

Abstract

BACKGROUND— 3β -hydroxysteroid dehydrogenase type 1 (3β HSD1), which is a rate-limiting enzyme that catalyzes the conversion of adrenal-derived steroid dehydroepiandrosterone to DHT, may be a promising target for treating castration-resistant prostate cancer (CRPC).

METHODS—From 2004 to 2011, a total of 103 consecutive patients presenting with advanced prostate cancer were included in this study. All patients were treated with surgical castration as androgen deprivation therapy (ADT). Germline DNA was extracted from archived tissue from each patient and sequenced. PSA half-time (representing rate to PSA nadir after ADT), the incidence of, and time to CRPC occurrence, and cause-specific mortality rates were determined during the 3-10 year follow-up. The perioperative data and postoperative outcomes are compared. The patients were retrospectively analyzed for survival time.

RESULTS—Of the 103 patient samples analyzed, 18 harbored a heterozygous variant (1245C) HSD3B1 gene, while 85 patients were homozygous wild-type (1245A) for HSD3B1. The two groups were homogenous for age, PSA, Gleason and metastases rate preoperatively. The incidence of CRPC observed in the variant group was significantly higher than that of wild-type group (100% vs 64.7%, respectively; $p = 0.003$). Despite this higher incidence of CRPC, there were no significant differences in time to develop CRPC, or in cause-specific mortality. Further, neither

* Correspondence to: Denglong Wu, Department of Urology, Tongji Hospital, Tongji University School of Medicine, XinChun Road 389, Shanghai, PR China. wudenglong2013@126.com (DL. Wu). Correspondence to: Hanqing Lin, State Key Laboratory of Molecular Biology, Shanghai Key Laboratory of Andrology, Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, PR China. hqlin@sibcb.ac.cn (HQ. Lin).

PSA half-time, nor time to biochemical recurrence (rising PSA is only one of the defining characteristics of CRPC) were different between the variant and wild-type groups.

CONCLUSION—Prostate cancer patients who harbored the heterozygous variant HSD3B1 (1245C) are more likely to develop to CRPC, but do not have shorter time to biochemical recurrence, shorter survival time or higher mortality risk.

Keywords

HSD3B; germline mutation; prostate cancer; castration-resistant prostate cancer; androgen deprivation therapy

INTRODUCTION

Prostate cancer is the most frequently diagnosed non-cutaneous cancer in men, and for men is the second leading cause of cancer-death in western countries and the sixth most common cause worldwide [1]. Prostate cancer can be diagnosed as local or clinically advanced, and the treatments vary from surveillance, radical local treatment, to androgen-deprivation therapy (ADT). Most advanced prostate cancer, not amenable to definitive therapy, initially responds favorably to various forms of ADT, such as medical (LHRH agonist) therapy or surgical castration. However, it invariably progresses to castration-resistant prostate cancer (CRPC) within two years [2-4]. There is evidence that residual intratumoral dihydrotestosterone (DHT) concentrations of ~1 nM persists following ADT. This can activate the androgen receptor (AR) to drive the expression of AR-induced genes, such as the TMPRSS2-ETS fusion oncogene, and can promote the development of CRPC [5-7].

Recently, the principal mechanisms of androgen-dependent prostate cancer progression to CRPC has been divided into two models [8]. The first, ‘adaptation’, where prostate cancer cells may encounter genetic or epigenetic events to adapt to the low-androgen environment following ADT, and includes alterations such as AR gene mutations and overexpression of AR gene. The second is a ‘selection’ model where subclones with variation in androgen-dependent prostate cancer cells appear prior to the clinical emergence of CRPC. The remaining androgen-dependent subclones undergo apoptosis in the castrate environment, while the castration-resistant subclones survive under the selective pressure of low-level androgen following androgen deprivation to emerge as CRPC.

The mechanisms underlying the development of castration resistance are still not well described and treatment options for CRPC are limited. Testes are the main source of testosterone, responsible for 90-95% of total androgen production in men [9]. Following surgical castration, serum testosterone is reduce 90%. The intraprostatic concentration of DHT, however, only shows a 60-75% reduction [10]. Negative feedback from testicular androgens normally prevents adrenal production of androgens. Following castration, however, low levels of circulating androgens stimulates the adrenal to increase androgen production. Recently, Chang et al. [11] proposed an interesting hypothesis to explain progression of prostate cancer to CRPC. They found that a SNP in a gene (HSD3B1) in CRPC, resulting in a gain-of-function in 3 β -hydroxysteroid dehydrogenase type 1 (3 β HSD1). The 1245C allele results in a coding change (N367T), that does not alter the

enzymatic activity. Instead, this change leads to reduced ubiquitination and degradation of the enzyme, resulting in increased enzyme abundance and thereby dehydroepiandrosterone (DHEA) conversion to DHT. This confers a growth advantage for human prostate cancer cells with this polymorphism in HSD3B1, and therefore promotes the development of CRPC in a xenograft model.

In order to determine whether this variant of the HSD3B1 gene increases the rate of progression of prostate cancer to CRPC in human patients, we sequenced 103 prostate cancer patients germline DNA samples, derived from testicular tissues of patients who were surgically castrated as ADT in Tongji hospital. Records from patients with wild-type or variant HSD3B1 gene were retrospectively analyzed for cause-specific mortality, overall and progression-free survival time of the two groups.

MATERIALS AND METHODS

Patients

We retrospectively studied 103 patients presenting with advanced prostate cancer, who underwent surgical castration as ADT in the Department of Urology, Tongji Hospital from January 2004 to January 2011. Anti-androgen medicine, typically flutamide, was prescribed following orchiectomy. Standard monitoring of the patient population for biochemical recurrence was as follows: PSA was monitored monthly after ADT for one year, then every three months for an additional two years. If the PSA level was lower than 0.02ng/ml, the oral anti-androgen was discontinued. If the PSA level increased, they were monitored weekly. PSA half-time (representing rate to PSA nadir following ADT), mortality rate, and frequency of CRPC development were obtained at the close of the study. The diagnosis of CRPC is following the guidelines of European Association of Urology [12]. Briefly, CRPC is defined as either 1) progressively rising PSA (1 wk apart, resulting in two 50% increases over the nadir, with PSA >2.0 ng/ml), or 2) an increase in tumor mass on bone scan, CT, or MRI despite a castrate level (<50 ng/dl) of testosterone. The former defines biochemical recurrence, while the latter is CRPC in its absence. This was a retrospective IRB-approved study. The perioperative data and postoperative outcomes were compared. The patients were retrospectively analyzed for survival time in January, 2014. The clinical information collected for each patient included the age at diagnosis of prostate cancer, Gleason score of biopsy samples, incidence of metastatic disease, interval of time between initial diagnosis and castration-resistant state, and cause and time of death.

DNA Isolation and HSD3B1 Sequence Analysis

Genomic DNA was extracted from paraffin samples of testicle from prostate cancer patients using Tissue Kit (QIAGEN, China). PCR products of the promoter region, all exons, exon-intron junctions and the 3'-UTR were sequenced to identify polymorphisms in HSD3B1. Primer sequences were as described in Chang et al. [11]. Due to the high frequency of one single-nucleotide polymorphism (SNP) in HSD3B1 in the Han population, we modified one primer pair. The modified upstream primer F1 was 5'-TTCACGTGTC CCGTGTTCA-3' and R1 was 5'-AAGCAGAAAACG GTGGAGTG-3'. DNA sequencing was carried out by

MeiJi biological Company, China. All PCR and sequencing studies were independently repeated.

Statistical Methods

Data were recorded prospectively into a database, including preoperative clinical and patient demographics, and postoperative parameters. PSA half-time, pathologic Gleason score, occurrence of CRPC development, time to CRPC and cause-specific mortality were also recorded. Fisher's test was used to determine the statistical difference of proportions between the groups. The Kaplan–Meier plots and statistical box plots were carried out using SPSS16.0 software. Metastases rate before ADT and frequency of CRPC development were expressed as percentages. Other data were expressed as mean $\pm$ standard deviation (SD), and $p < 0.05$ was considered statistically significant.

RESULTS

1. Patient Perioperative Data

Data from 103 patients were included in this study, including 85 patients with wild-type genotype, and 18 patients who were heterozygous for the 1245C variant HSD3B1 (Fig. 1). The two groups were homogenous as to age, PSA level before ADT, Gleason score of biopsy samples and metastases at presentation (Table 1).

2. Patient postoperative outcomes

Patients were followed for 3 to 10 years postoperatively, and their outcomes, including PSA half-time, time to CRPC and overall mortality are presented in Table 2, as well as for the occurrence of CRPC. There were no significant differences in PSA half-time, or time to CRPC occurrence between the two groups. The mean follow-up time of the 1245C group is 3.39 ± 2.46 years, the other is 3.82 ± 2.03 years. There is no difference between the follow-up time in the two groups ($p=0.43$).

2.1 Relationship between variant HSD3B1 and the frequency of CRPC

occurrence—All patients with the germline 1245C allele of HSD3B1 developed CRPC, as defined above. Of the 85 patients in the wild-type group, 55 (64.7%) developed CRPC. There was a significant difference in the incidence of CRPC between the two groups ($p = 0.003$, Fig. 2). Despite this difference, there was no significant difference in the time to biochemical recurrence, as defined by rising PSA post castration, between these two groups ($p = 0.935$, Figure 4).

2.2 Relationship between variant HSD3B1 and the mortality rate—There were 29 patients who died due to prostate cancer in the wild-type group, 2 died of other causes at the time of the analysis; the cause-specific mortality was 34.1%. The mean survival time of wild-type group was 6.0 years. 5 patients died of prostate cancer in the variant group, a rate of 27.8%. There was no difference between the two groups in cause-specific mortality (Fig. 3).

2.3 Survival time of the two groups—The median progression-free survival time of the variant group was 22 months (95% CI 17.8-26.1) versus 23 months (95% CI 15.3 –30.7) for the wild-type group.

DISCUSSION

PSA levels in advanced prostate cancer patients continue to rise, even following ADT. Eventually these patients progress to CRPC [12]. In addition to androgen's important role in the development and growth of primary prostate cancer, residual androgen derived from adrenal has been hypothesized to be involved in CRPC emergence. The enzyme 3β HSD is a major component of the androgen biosynthetic pathway. It catalyzes the conversion of DHEA to androstendione in steroidogenic tissues such as the adrenal, and may be important in the production of androgens fueling CRPC development in a castrate environment. The HSD3B gene family contains two genes and five pseudogenes, all of which are located in chromosome 1p13 [13, 14]. The HSD3B1 gene encodes the enzyme 3β HSD1, which is mainly expressed in the placenta and peripheral tissues, including prostate, breast, and skin. The HSD3B2 gene encodes the enzyme 3β HSD2 is predominantly expressed in classical steroidogenic organs, such as adrenals, testis, and ovary [15-17]. However, transcripts for both enzymes have been found in CRPC [5, 18]. Several polymorphisms in HSD3B2 have been identified as causative for congenital adrenal hyperplasia, a rare autosomal recessive inheritance, which can alter development of primary or secondary sex characteristics in patients [19].

The mechanisms by which advanced prostate cancers progress to CRPC are poorly defined. However, the effect of adrenal androgens on the growth of prostate cancer cells is well recognized, and inhibiting the production of androgens is a critical focus in the development of therapeutics for CRPC, including the recently approved androgen synthesis inhibitor drug abiraterone acetate [20]. Recently, however, a SNP of 3β HSD1 has been discovered to be a potential cause of the elevated DHT concentrations in patients with CRPC [6, 11]. This SNP changes A to C at nucleotide position 1245 in HSD3B1 and thereby asparagine (N) to threonine (T) at amino acid position 367 of 3β HSD1. In prostate cancer cell lines and xenografts, this change increases the enzyme's resistance to protein ubiquitination and degradation, leading to a substantial increase in protein half-life from 2.1 to 27 hours [11]. The higher steady-state enzyme level increases the conversion of DHEA to androstenedione, sustaining DHT concentrations and promoting the development of CRPC [11]. Chang et al. [11] also show that some human CRPC tumors with the homozygous wild-type allele may gain a somatic mutation encoding 3β HSD1 (367T), and some tumors with the heterozygous allele may have an accompanying loss of heterozygosity in tumor tissue of the wild-type allele, yielding higher tumor 3β HSD1 levels.

To identify any potential clinical role in prostate cancer of polymorphisms in the HSD3B1 gene, we screened DNA samples from prostate cancer patients who underwent ADT via surgical castration. Historically, it has been thought that castration leads to the sharp decline in serum testosterone levels, and androgen produced by the adrenal glands will be the sole source to promote the growth of prostate cancer cells. However, androgens derived from the adrenal are unlikely to be sufficient to drive the development of CRPC. The recent

description of intratumoral androgen synthesis [5,18], as well as the recent report by Chang et al. [11] showing that castration selects for tumors that are either heterozygous or homozygous HSD3B1 variant (1245C), has altered our understanding of CRPC development. This suggests that the rate of CRPC occurrence and mortality in our variant group should be higher than that of the normal group, while survival time should be shorter. Based on the results of the present study, the first to report on HSD3B1 germline variant effect on patient outcomes, we find the incidence of CRPC is significantly higher in patients with the 1245C allele. However, we find no difference in PSA half-time following castration, in cause-specific mortality, or in survival time between the two groups. We speculate the castration leads to a sharp drop in testosterone levels, resulting in tumor regression due to androgen withdrawal induced apoptosis, and a concomitant drop in PSA levels. Since the selection of resistant tumor cells, and therefore the development of CRPC is a relatively slow process, and prostate cancer is generally slow growing, it may take months to years to develop clinically significant CRPC. This may explain why we find the PSA half-time after ADT between the mutant and wild-type bearing 3 β HSD1 patients is not different between the groups. Park and colleagues [21] showed that the patients with a short PSA half-time and a short PSA doubling time after the PSA nadir have a poor prognosis, which is consistent with the outcomes seen in our study.

There are four characteristics of our study population that may contribute to the absence of significant differences in mortality and survival: (i) The mean lifetime of Chinese people is 71. A majority of our patient population who underwent orchiectomy was older than 70 years, so their prospective life time is short. (ii) A majority of our patients had advanced disease, with more than 70% of the patients having distant metastasis prior to ADT via orchiectomy. (iii) Since these were advanced prostate cancer patients who did not undergo prostatectomy, we can only report biopsy-derived Gleason score, and we do not have an accurate clinical stage and grade. (iv) The patient population interrogated by Chang et al. [11], is Caucasian, while ours is Han Chinese, and the incidence of prostate cancer varies amongst these populations, and so may the effect of mutation on mortality.

In conclusion, the purpose of our study was to verify the effect of germline mutation of the gene encoding 3 β HSD1 on the clinical course of CRPC in patients. We find that our patients with a heterozygous variant (1245C) HSD3B1 gene develop CRPC at increased frequency, but do not have shorter survival time or higher mortality risk. There are several limitations in present study. First, sample size is one of the most important issues for evaluating a rare mutation-associated effect on cancer. While the statistically significant association between the variant HSD3B1 and CRPC risk was based on 18 carriers in 103 cases, a larger sample size is warranted to confirm the association. Second, Chang et al. [11] showed that three of 25 (12%) human CRPC tumors with homozygous wild-type inheritance acquired a somatic mutation encoding 3 β HSD1 (367T) under the pressure of low-level androgen, and 3 of 11 (27%) tumors with heterozygous inheritance lost the wild-type allele, and therefore only express the mutant 3 β HSD1 (367T). We were not able to observe a similar selection due to a lack of tumor DNA post-ADT. In conclusion, HSD3B1 variant (1245C) has a significant effect on the frequency of CRPC, but its effect on overall survival and time to progression, as well as its value as a target for drug development, await study in a larger population.

CONCLUSION

Our population prostate cancer patients who have a variant of the HSD3B1 gene are more likely to progress to CRPC, but do not have shorter time to biochemical recurrence, shorter survival time or higher mortality than wild-type patients.

ACKNOWLEDGMENTS

We thank Longxia Xu, Kailun Fang, Yanru Wang and other members in Chen lab (Shanghai Key Laboratory of Andrology, Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences) for technical help. This work was supported by funds from National Natural Science Foundation of China (81172426) and Shanghai Education Commission Research and Innovation projects (12ZZ034).

REFERENCES

1. Baade PD, Youlten DR, Krnjacki LJ. International epidemiology of prostate cancer: geographical distribution and secular trends. *Mol Nutr Food Res*. 2009; 53(2):171–184. [PubMed: 19101947]
2. Yuan X, Balk SP. Mechanisms mediating androgen receptor reactivation after castration. *Urol Oncol*. 2009; 27(1):36–41. [PubMed: 19111796]
3. Attard G, Cooper CS, de Bono JS. Steroid hormone receptors in prostate cancer: a hard habit to break? *Cancer Cell*. 2009; 16(6):458–462. [PubMed: 19962664]
4. Jiao L, Deng Z, Xu C, Yu Y, Li Y, Yang C, Chen J, Liu Z, Huang G, Li LC, Sun Y. MicroRNA-663 Induces Castration-Resistant Prostate Cancer Transformation and Predicts Clinical Recurrence. *J Cell Physiol*. 2014; 229(7):834–44. [PubMed: 24243035]
5. Montgomery RB, Mostaghel EA, Vessella R, Hess DL, Kalhorn TF, Higano CS, True LD, Nelson PS. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. *Cancer Res*. 2008; 68(11):4447–4454. [PubMed: 18519708]
6. Sharifi N. Mechanisms of androgen receptor activation in castration-resistant prostate cancer. *Endocrinology*. 2013; 154(11):4010–4017. [PubMed: 24002034]
7. Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R, Sun XW, Varambally S, Cao X, Tchinda J, Kuefer R, Lee C, Montie JE, Shah RB, Pienta KJ, Rubin MA, Chinnaiyan AM. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. *Science*. 2005; 310(5748):644–648. [PubMed: 16254181]
8. Zong Y, Goldstein AS. Adaptation or selection--mechanisms of castration-resistant prostate cancer. *Nat Rev Urol*. 2013; 10(2):90–98. [PubMed: 23247694]
9. Belanger A, Brochu M, Cliche J. Levels of plasma steroid glucuronides in intact and castrated men with prostatic cancer. *J Clin Endocrinol Metab*. 1986; 62(5):812–815. [PubMed: 2937801]
10. Mostaghel EA, Page ST, Lin DW, Fazli L, Coleman IM, True LD, Knudsen B, Hess DL, Nelson CC, Matsumoto AM, Bremner WJ, Gleave ME, Nelson PS. Intraprostatic androgens and androgen-regulated gene expression persist after testosterone suppression: therapeutic implications for castration-resistant prostate cancer. *Cancer Res*. 2007; 67(10):5033–5041. [PubMed: 17510436]
11. Chang KH, Li R, Kuri B, Lotan Y, Roehrborn CG, Liu J, Vessella R, Nelson PS, Kapur P, Guo X, Mirzaei H, Auchus RJ, Sharifi N. A gain-of-function mutation in DHT synthesis in castration-resistant prostate cancer. *Cell*. 2013; 154(5):1074–1084. [PubMed: 23993097]
12. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F, Mottet N. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol*. 2014; 65(2):467–479. [PubMed: 24321502]
13. Rheume E, Lachance Y, Zhao HF, Breton N, Dumont M, de Launoit Y, Trudel C, Luu-The V, Simard J, Labrie F. Structure and expression of a new complementary DNA encoding the almost exclusive 3 beta-hydroxysteroid dehydrogenase/delta 5-delta 4-isomerase in human adrenals and gonads. *Mol Endocrinol*. 1991; 5(8):1147–1157. [PubMed: 1944309]

14. McBride MW, McVie AJ, Burridge SM, Brintnell B, Craig N, Wallace AM, Wilson RH, Varley J, Sutcliffe RG. Cloning, expression, and physical mapping of the 3beta-hydroxysteroid dehydrogenase gene cluster (HSD3BP1-HSD3BP5) in human. *Genomics*. 1999; 61(3):277–284. [PubMed: 10552929]
15. El-Alfy M, Luu-The V, Huang XF, Berger L, Labrie F, Pelletier G. Localization of type 5 17beta-hydroxysteroid dehydrogenase, 3beta-hydroxysteroid dehydrogenase, and androgen receptor in the human prostate by in situ hybridization and immunocytochemistry. *Endocrinology*. 1999; 140(3): 1481–1491. [PubMed: 10067877]
16. Gingras S, Moriggl R, Groner B, Simard J. Induction of 3beta-hydroxysteroid dehydrogenase/delta5-delta4 isomerase type 1 gene transcription in human breast cancer cell lines and in normal mammary epithelial cells by interleukin-4 and interleukin-13. *Mol Endocrinol*. 1999; 13(1):66–81. [PubMed: 9892013]
17. Gingras S, Simard J. Induction of 3beta-hydroxysteroid dehydrogenase/isomerase type 1 expression by interleukin-4 in human normal prostate epithelial cells, immortalized keratinocytes, colon, and cervix cancer cell lines. *Endocrinology*. 1999; 140(10):4573–4584. [PubMed: 10499513]
18. Cai C, Chen S, Ng P, Bubley GJ, Nelson PS, Mostaghel EA, Marck B, Matsumoto AM, Simon NI, Wang H, Balk SP. Intratumoral de novo steroid synthesis activates androgen receptor in castration-resistant prostate cancer and is upregulated by treatment with CYP17A1 inhibitors. *Cancer Res*. 2011; 71(20):6503–6513. [PubMed: 21868758]
19. Welzel M, Wustemann N, Simic-Schleicher G, Dorr HG, Schulze E, Shaikh G, Clayton P, Grotzinger J, Holterhus PM, Riepe FG. Carboxyl-terminal mutations in 3beta-hydroxysteroid dehydrogenase type II cause severe salt-wasting congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2008; 93(4):1418–1425. [PubMed: 18252794]
20. Shore N, Mason M, de Reijke TM. New developments in castrate-resistant prostate cancer. *BJU Int*. 2012; 109(Suppl 6):22–32. [PubMed: 22672122]
21. Park YH, Hwang IS, Jeong CW, Kim HH, Lee SE, Kwak C. Prostate specific antigen half-time and prostate specific antigen doubling time as predictors of response to androgen deprivation therapy for metastatic prostate cancer. *J Urol*. 2009; 181(6):2520–2524. [PubMed: 19371894]

Fig. 1.
Patients in the mutated group have an (A)denine to (C)ytocine transversion at nucleotide 1245 in the HSD3B1 gene.

Fig. 2.

The incidence of CRPC development in the two groups. There was a significant difference in the incidence of CRPC between the two groups ($P = 0.003$).

Fig. 3. Kaplan–Meier plot of overall survival of the two groups. Due to the small group size and low mortality amongst patients with the HSD3B1(1245C) mutation, the median overall survival time is unknown, while it was 6 years (95% CI 4.8 -7.2) for the wild-type group. There was no significant difference between these two groups ($P = 0.289$).

Fig. 4.

Kaplan–Meier plot of progress-free survival of the two groups. The median progression-free survival time of the mutated group was 22 months (95% CI 17.8-26.1) while it was 23 months (95% CI 15.3 -30.7) for the wild-type group. There was no significant difference between these two groups ($P = 0.935$).

Table 1

Perioperative Data.

	mutated group	normal group	P-value
Mean age(year)	75.8±1.7	76.8±1.0	0.678
PSA level before ADT	237±132	152±37	0.391
Gleason before ADT	7.67±0.42	7.4±0.45	0.397
Metastases rate before ADT	5(27.8%)	39(45.9%)	0.158

Table 2

Postoperative characteristics of patients undergoing ADT

	mutated group	normal group	P-value
PSA half time (months)	1±0.63	1±0.75	0.642
Incidence of CRPC(n,%)	18 (100%)	55 (64.7%)	0.003
Time to CRPC(months)	18.5±11.9	15.6±9.1	0.441
Cause-specific mortality (n,%)	5(27.8%)	29(34.1%)	0.603