

## RESEARCH ARTICLE

# Preventive Effects of Aspirin on Cardiovascular Complications in Prostate Cancer Cases after Endocrinotherapy

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### Abstract

**Objective:** To explore the preventive effect of aspirin on the cardiovascular complications in prostate cancer after endocrinotherapy. **Materials and Methods:** A total of 92 patients with prostate cancer were divided into observation group (n=44) and control group (n=48). The control group was treated with medical castration plus anti-androgenic drugs. Based on the above treatment, the observation group was added aspirin. The follow-up duration was 2 years. The changes of partial prothrombin time (PT), activated partial thromboplastin time (APTT), platelet aggregation rate (PAG), prostate-specific antigen (PSA) and serum testosterone (T) before and after treatment as well as incidence of cardiovascular disease were observed. **Results:** The 2-year survival rates of patients without cardiovascular disease in observation group and control group were 95.45% (42/44) and 72.92% (35/48), respectively, and significant difference was presented between two groups by comparison to the survival rates ( $\chi^2=8.5453$ ,  $p=0.0035$ ). There was no statistical significance between two groups as well as before and after treatment regarding PT ( $p>0.05$ ). After treatment, APTT went down and PAG was gradually on the rise in control group, while PAG down and APTT on the rise increasingly in observation group. Significant differences were presented between two groups as well as before and after treatment ( $p<0.01$ ). Both PSA and T levels were decreased significantly in two groups after treatment ( $p<0.01$ ), but there was no statistical significant between two groups ( $p>0.05$ ). **Conclusions:** Application of endocrinotherapy in prostate cancer can easily lead to occurrence of cardiovascular disease, but cardiovascular complications can be prevented by aspirin, without affecting the effect of endocrinotherapy.

**Keywords:** Prostate cancer - endocrinotherapy - cardiovascular disease - side effects - aspirin

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### Introduction

Prostate cancer is one of the most common malignant tumors in male urogenital system all over the world. According to statistics, the incidence and mortality of prostate cancer in male malignant tumors come in second, secondary to lung cancer (Danialy et al., 2014; Esfahani et al., 2015; Atoum et al., 2015). At the early stage of prostate cancer, no specific symptoms are presented and common manifestations are irritant or obstructive lower urinary tract symptoms. Nevertheless, at the advanced stage, its clinical manifestations mainly include anemia, general skeletal pain, pathological fracture and spinal compression (Van Poznak, 2015). Although prostate cancer can be cured by radical surgery or intra- and external irradiation at an early stage, most of patients with urinary tract or ostealgia symptoms are at an advanced stage when being diagnosed. They are usually accompanied by distant metastasis, and the 5-year survival rate is low. Therefore, endocrinotherapy is frequently selected to treat these kinds of patients as a positive therapeutic regimen in clinic (Thomsen et al., 2015).

The endocrinotherapy of prostate cancer refers to androgen deprivation therapy (ADT) or androgen ablation therapy, namely testicle-secreted testosterone (T) is inhibited via surgical and medical castration, or anti-androgenic drugs are applied to competitively inhibit the combination of androgen and its receptors in prostate cells, with purposes of inhibiting T transforming into dihydrotestosterone, decreasing in-vivo androgen level and blocking combination of androgen and its receptors so as to control the growth of prostate tumor cells. Except for radical surgery, endocrinotherapy is a major method in the treatment of prostate cancer at current. Its combination with surgery or radiotherapy can effectively control the number of cancer cells, ameliorate general condition, improve the quality of life and prolong the survival time (Linke et al., 2015). However, with endocrinotherapy being used extensively, relevant side effects are also paid more attention by clinicians gradually. Endocrinotherapy can induce a serious of metabolic changes, such as obesity, hypertension, atherosclerosis, type 2 diabetes mellitus and osteoporosis (Al-Khazaali et al., 2015), in which the perniciousness of cardiovascular disease is the most

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serious. This study compared and analyzed the changes of blood indexes in patients with prostate cancer before and after treatment as well as incidence of cardiovascular disease in order to investigate whether aspirin could prevent the occurrence of cardiovascular disease in prostate cancer after endocrinotherapy, hoping to provide a certain evidences for clinical administration.

## Materials and Methods

### General data

Approved by Hospital Ethics Committee, 92 patients with prostate cancer in Zhumadian Central Hospital were selected from Feb., 2011 to Apr., 2013. They were all confirmed by pathological biopsy from rectum prostate puncture, accompanied by metastasis or at a progressive stage. Inclusion criteria: 1) Less than 80 years old; 2) serum prostate-specific antigen (PSA) more than 10 ng/mL; 3) signing informed consent form by patients or their relatives. Exclusion criteria: 1) the patients complicated by cardiovascular and cerebrovascular diseases, such as angina pectoris, myocardial infarction, cardiac arrest, cerebral hemorrhage and infarction; 2) the patients complicated by blood disease or bleeding tendency and peptic ulcer; 3) the patients allergic to aspirin. Because application of endocrinotherapy combined with aspirin might increase the risk of digestive tract hemorrhage, the patients and their relatives should fully communicate with doctors in the selection of therapeutic regimens. According to the pathological condition and willing, 92 patients were divided into observation group (n=44) and control group (n=48). The patients in observation group were at the age of 55~78, with the median age of 67. There were 8, 16 and 20 cases respectively in phase T2b, T3 and T4, 6, 15 and 23 cases respectively with Gleason grading  $\leq 6$  points, =7 points and  $\geq 8$  points as well as 7, 9 and 28 cases respectively with 10~20, 20~40 and >40 ng/mL of PSA before treatment. The patients in control group were at the age of 54~76, with the median age of 65. There were 9, 14 and 25 cases respectively in phase T2b, T3 and T4, 8, 16 and 24 cases respectively with Gleason grading  $\leq 6$  points, =7 points and  $\geq 8$  points as well as 8, 11 and 29 cases respectively with 10~20, 20~40 and >40 ng/mL of PSA before treatment. There was no statistical significance between two groups by comparison to the baseline data before treatment, with better compatibility ( $p > 0.05$ ).

### Methods

**Treatment methods:** Based on the pathological condition, all patients were given calcium channel blockers as well as blockers of  $\alpha$  and  $\beta$  receptors to make blood pressure under 150/90 mmHg. No significant difference was shown between two groups by comparison to administration of antihypertensive drugs. The control group was treated with medical castration plus anti-androgenic drugs. Dosage regimen: Goserelin Acetate SR (AstraZeneca, China) was subcutaneously injected, 3.6 mg/28 d; Bicalutamide Tablets (AstraZeneca, China) was taken orally, 50 mg/d; Goserelin Acetate SR was injected first 1 week after administration of Bicalutamide Tablets.

Based on the treatment of control group, the observation group was added Aspirin Enteric-coated Tablets (Bayer, Germany), orally, 100 mg/d, and was given after injection of Goserelin Acetate SR.

**Detection methods:** Before and 6, 12, 18 and 24 months after treatment, partial prothrombin time (PT) and activated partial thromboplastin time (APTT) were detected by Germany TECO coagulometer, platelet aggregation rate (PAG) by American Helena platelet aggregometer, PSA and serum T by radioimmunoassay. Follow-up: Routine and telephone follow-up was performed every month. Blood routine, hepatorenal function, PSA and T levels were measured, and serious bleeding tendency, gastrointestinal bleeding and incidence of cardiovascular disease including coronary heart disease, myocardial infarction and sudden cardiac death were all observed.

### Observation indexes

The changes of PT, APTT, PAG, PSA and T levels were observed in two groups before and after treatment; Incidence of cardiovascular disease within 2 years and survival rates of patients without cardiovascular disease were compared in both groups.

### Evaluation criteria

Occurrence of cardiovascular disease was defined as presence of cardiovascular disease symptoms after treatment, such as angina pectoris, coronary heart disease, myocardial infarction and sudden cardiac death, or the examinations like myocardium zymogram, troponin I, electrocardiogram and echocardiogram indicated cardiovascular disease (coronary heart disease, myocardial infarction, etc.) was present.

### Statistical data analysis

Both SAS9.3 and SPSS 17.0 software were used for data analysis. The measurement data were expressed by the mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ). Paired t test was applied for comparison before and after treatment, independent-sample t test for comparison between two groups and analysis of variance for comparison among multiple samples. The enumeration data was compared with  $\chi^2$  test. Survival analysis was conducted using Kaplan-Meier method and Log-Rank test. All statistics were two-sided tests, with  $\alpha = 0.05$  as an inspection level.

## Results

### Comparison on the incidence of cardiovascular complications in two groups after treatment

During follow-up, only 2 patients in observation group suffered from angina pectoris, and the incidence was 4.55%; 13 patients in control group (7 cases of angina pectoris, 5 of myocardial infarction and 1 of sudden cardiac death) encountered cardiovascular disease, and the incidence came up to 27.08%. Significant difference was presented between two groups by comparison to the incidence ( $\chi^2 = 8.5453$ ,  $p = 0.0035$ ). Typical cases were shown in Figure 1.

**Table 1. Comparison on PT in two Groups Before and after Treatment**

Groups	Before treatment (s)	After treatment (s)				F	p
		6 months	12 months	18 months	24 months		
Observation group	11.85±1.73	11.91±1.49	12.02±1.68	12.01±1.80	11.94±1.71	0.0779	0.9890
Control group	11.52±1.47	11.42±1.66	11.39±1.59	11.34±1.43	11.38±1.55	0.0928	0.9847
t	0.99	1.48	1.85	1.98	1.65	—	—
p	0.3256	0.1411	0.0679	0.0502	0.1029	—	—

**Table 2. Comparison on APTT in two Groups Before and after Treatment**

Groups	Before treatment (s)	After treatment (s)				F	p
		6 months	12 months	18 months	24 months		
Observation group	35.73±3.41	40.11±3.27*	41.24±3.26*	41.37±3.88*	41.45±3.40*	21.9398	3.3307E-15
Control group	35.96±3.39	31.22±3.13*	31.09±3.54*	30.99±3.01*	31.14±3.35*	20.8998	9.3259E-15
t	0.32	13.32	14.29	14.40	14.64	—	—
p	0.7466	<0.0001	<0.0001	<0.0001	<0.0001	—	—

Note: Compared with treatment before, \* $p<0.01$

**Table 3. Comparison on PAG in two Groups Before and after Treatment**

Groups	Before treatment (s)	After treatment (s)				F	p
		6 months	12 months	18 months	24 months		
Observation group	60.39±13.07	42.40±12.34*	40.24±11.69*	40.43±11.54*	40.37±11.87*	23.1083	6.6613E-16
Control group	60.51±11.15	68.92±11.33*	70.19±11.27*	70.39±12.03*	70.55±12.26*	6.5710	4.9843E-5
t	0.05	10.75	12.51	12.17	11.98	—	—
p	0.9622	<0.0001	<0.0001	<0.0001	<0.0001	—	—

Note: Compared with treatment before, \* $p<0.01$

**Table 4. Comparison on PSA in two Groups Before and after Treatment**

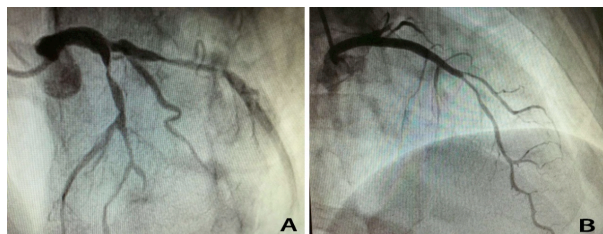
Groups	Before treatment (s)	After treatment (s)				F	p
		6 months	12 months	18 months	24 months		
Observation group	37.04±7.96	0.12±0.07*	0.19±0.05*	0.16±0.03*	0.11±0.04*	953.454	<0.0001
Control group	35.92±8.03	0.11±0.05*	0.17±0.08*	0.14±0.08*	0.12±0.06*	873.569	<0.0001
t	0.67	0.79	1.42	1.56	0.93	—	—
p	0.5039	0.4296	0.1583	0.1222	0.3540	—	—

Note: Compared with treatment before, \* $p<0.01$

**Table 5. Comparison on T Levels in Two Groups Before and after Treatment**

Groups	Before treatment (s)	After treatment (s)				F	p
		6 months	12 months	18 months	24 months		
Observation group	16.09±3.37	0.95±0.21*	0.72±0.15*	0.81±0.19*	0.80±0.13*	894.098	<0.0001
Control group	15.38±3.19	0.92±0.16*	0.78±0.14*	0.84±0.23*	0.83±0.17*	984.643	<0.0001
t	1.04	0.77	1.98	0.68	0.94	—	—
p	0.3020	0.4406	0.0502	0.4992	0.3475	—	—

Note: Compared with treatment before, \* $p<0.01$

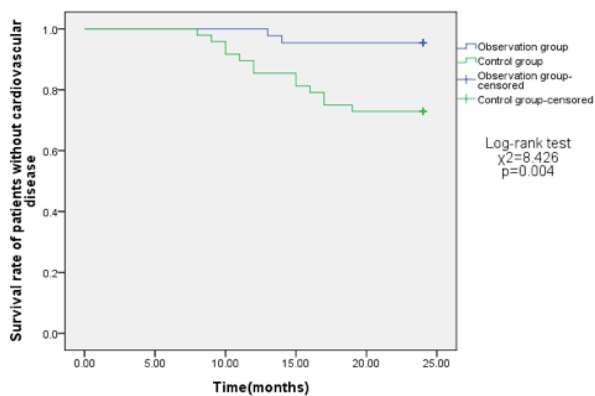


**Figure 1. Angiocardiology of the Patients Respectively Complicated by Myocardial Infarction and Angina Pectoris.** Note: A. Myocardial infarction: 95% proximal stenosis in the anterior descending branch of coronary artery and 85% stenosis in the middle segment of circumflex branch; B. Angina pectoris: 80% middle-segment stenosis in the anterior descending branch of coronary artery and total occlusion of circumflex branch

#### Comparison on PT, APTT, PAG, PSA and T levels in two groups before and after treatment

There was no statistical significant between two groups as well as before and after treatment regarding PT ( $p>0.05$ ) (Table 1).

After treatment, APTT went down in control group, whereas it was on a progressive rise in observation group. Significant difference was presented between two groups as well as before and after treatment ( $p<0.01$ ) (Table 2). After treatment, PAG was increased in control group gradually, while decreased significantly in observation group. Significant difference was manifested between two groups as well as before and after treatment ( $p<0.01$ ) (Table 3).



**Figure 2. The Survival Curve of Patients Without Cardiovascular Disease in Two Groups**

Both PSA and T levels were decreased dramatically in two groups after treatment ( $p < 0.01$ ), but there was no statistical significant between two groups ( $p > 0.05$ ) (Table 4, 5).

#### *Comparison on the survival rates of patients without cardiovascular disease in two groups*

The 2-year survival rates of the patients without cardiovascular disease were 95.45% (42/44) in observation group and 72.92% (35/48) in control group. There was statistical significance between two groups compared with the survival rates ( $\chi^2 = 8.5453$ ,  $p = 0.0035$ ) (Figure 2).

## Discussion

In recent years, the ratio of endocrinotherapy in the treatment of prostate cancer has increased to some extent, and that of patients treated with medical castration has elevated to 47% from 12%. The symptoms of more than 80% of patients can be relieved after treatment (Krahn et al., 2011), but endocrinotherapy can increase the incidence of cardiovascular disease. It is reported that decrease of androgen level is a risk factor that induces cardiovascular events (Rosano et al., 2015) and the risk of ischemic stroke increases in the patients treated with androgen blockade (Saad, 2012; Teoh et al., 2015). Additionally, low level of T is also an independent risk factor resulting in atherosclerosis, except for age, obesity, dyslipidemia and insulin resistance (Vaidya et al., 2015).

After endocrinotherapy, coagulation disorder is a crucial risk factor that causes cardiovascular complications. The study displayed that the change of androgen level was associated with abnormal coagulation. Decrease of T/free T could activate thrombin, inhibit dissolution of fibrous proteins and make the body in hypercoagulable state to cause plaque bleeding and thrombosis, leading to atherosclerosis and increased incidence of ischemic cardiovascular disease (Glueck et al., 2014). After endocrinotherapy, the level of serum T in patients with prostate cancer went down, while those of fibrin peptide A (FPA) and plasminogen activator inhibitor-1 (PAI-1) up, consequently resulting in increased incidence of thromboembolic disease (Prabhat et al., 2010).

Among the guidelines for cardiovascular diseases in various countries, aspirin is the only drug that is

recommended to be used in the primary prevention of cardiovascular disease, which can reduce the incidence and mortality of myocardial infarction. The study displayed that aspirin could reduce the total rate of myocardial infarction, and the patients who took low-dose aspirin for a long time could obtain benefits dramatically (Park et al., 2015). And a lot of study demonstrated that application of aspirin in the primary prevention could markedly decrease the major cardiovascular events (Schrör, 2015; Williams et al., 2015; Battistoni et al., 2015).

The research results in this study revealed that the incidence of cardiovascular disease was 27.08% (sudden cardiac death occurred in one case) in control group, while 4.55% in observation group, suggesting that aspirin could decrease the risk of cardiovascular events and make the patients with prostate cancer who received endocrinotherapy obtain benefits. After treatment, both PSA and T levels were decreased dramatically in two groups, but there was no statistical significant between two groups, indicating that addition of aspirin could not affect the efficacy of endocrinotherapy. Besides, APTT in observation group was significantly higher than in control group, while PAG lower than in control group, showing that aspirin could decrease the incidence of cardiovascular disease through alleviation of blood hypercoagulability and prevention of thrombosis.

To sum up, application of endocrinotherapy in prostate cancer can easily lead to occurrence of cardiovascular disease. However, after endocrinotherapy, low-dose aspirin can ameliorate blood hypercoagulability, inhibit platelet aggregation and resist thrombosis, consequently exert a preventive effect on the occurrence of cardiovascular disease, without affecting the efficacy of endocrinotherapy. In this study, no one encounters aspirin-induced serious adverse reactions, including bleeding tendency, but it still needs enlarging sample size and performing long-term follow-up to verify whether this therapeutic regimen is popularized in clinic or not.

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