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ORIGINAL ARTICLE

Prostate Cancer

Risk of cardiovascular thrombotic events after surgical castration versus gonadotropin-releasing hormone agonists in Chinese men with prostate cancer

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We investigated the cardiovascular thrombotic risk after surgical castration (SC) versus gonadotropin-releasing hormone agonists (GnRHa) in Chinese men with prostate cancer. All Chinese prostate cancer patients who were treated with SC or GnRHa from year 2000 to 2009 were reviewed and compared. The primary outcome was any new-onset of cardiovascular thrombotic events after SC or GnRHa, which was defined as any event of acute myocardial infarction or ischemic stroke. The risk of new-onset cardiovascular thrombotic event was compared between the SC group and the GnRHa group using Kaplan–Meier method. Multivariate Cox regression analysis was performed to adjust for other potential confounding factors. A total of 684 Chinese patients was included in our study, including 387 patients in the SC group and 297 patients in the GnRHa group. The mean age in the SC group (75.3 ± 7.5 years) was significantly higher than the GnRHa group (71.8 ± 8.3 years) ($P < 0.001$). There was increased risk of new cardiovascular thrombotic events in the SC group when compared to the GnRHa group upon Kaplan–Meier analysis ($P = 0.014$). Upon multivariate Cox regression analysis, age (hazard ratio [HR] 1.072, 95% confidence interval [CI] 1.04–1.11, $P < 0.001$), hyperlipidemia (HR 2.455, 95% CI 1.53–3.93, $P < 0.001$), and SC (HR 1.648, 95% CI 1.05–2.59, $P = 0.031$) were significant risk factors of cardiovascular thrombotic events. In conclusion, SC was associated with increased risk of cardiovascular thrombotic events when compared to GnRHa. This is an important aspect to consider while deciding on the method of androgen deprivation therapy, especially in elderly men with known history of hyperlipidemia.
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Keywords: androgen deprivation therapy; Chinese population; cardiovascular events; myocardial infarction; prostate cancer; stroke

INTRODUCTION

Since the first study by Huggins and Hodges[1] on the effect of castration on prostate cancer in 1941, many studies have looked into the role of androgen deprivation therapy (ADT) in treating prostate cancer. Classically, before the development of gonadotropin-releasing hormone antagonists, there were two well-accepted methods in reducing serum testosterone to a castration level, namely surgical castration (SC) by bilateral orchiectomy and regular gonadotropin-releasing hormone agonist (GnRHa) injections. It has been shown in a meta-analysis that the survival outcomes in patients with prostate cancer after receiving SC and GnRHa were similar.[2] However, there is a lack of evidence in the comparison between SC and GnRHa in terms of the possible long-term adverse events related to ADT. Some major adverse events, including myocardial infarction and stroke, may adversely affect survival especially in elderly men with prostate cancer. We conducted this study to investigate the risk of cardiovascular thrombotic events in Chinese men who received SC, compared to those who received GnRHa.

MATERIALS AND METHODS

All Chinese prostate cancer patients who were treated with ADT, either in the form of SC or GnRHa, from year 2000 to 2009 were reviewed. We evaluated the cardiovascular thrombotic risk after SC by comparing between the patients who received SC (SC group) with those who received GnRHa (GnRHa group). Patients who were given maximal androgen blockade were also included in our study. Patients who received GnRHa initially and then decided for SC were excluded from our study. The primary outcome was any new-onset of cardiovascular thrombotic events after SC or GnRHa. Cardiovascular thrombotic event was defined as any event of acute myocardial infarction or ischemic stroke.

Clinicopathological data including baseline prostate-specific antigen (PSA) level, Gleason score, clinical T-stage, presence of bone metastases, any treatment prior to ADT, PSA nadir level, and any disease progression in both the SC group and the GnRHa group were collected. Disease progression was defined as at least two serial rises in PSA (taken at least 1 week apart) from its nadir level. Initiation of any secondary hormone treatment for rising PSA was also considered as a progression event. Continuous data were either presented as mean or median values, and categorical data were presented as a percentage of the corresponding patient group.

Potential risk factors of cardiovascular thrombotic events including age and preexisting medical condition including diabetes

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mellitus, hypertension, hyperlipidemia, ischemic heart disease, history of ischemic stroke, and the duration of hormonal therapy were reviewed. To determine whether there were any significant differences in the baseline risk factors between the two groups, these factors were compared using independent sample *t*-test for continuous variables and Chi-square test for categorical variables. The risk of new-onset cardiovascular thrombotic event was compared between the SC group and the GnRHa group using Kaplan–Meier method, and the significance was determined by log-rank test. Furthermore, multivariate Cox regression analysis was performed to adjust for the potential risk factors mentioned. $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 684 Chinese patients was included in our study, including 387 patients in the SC group and 297 patients in the GnRHa group. The median baseline PSA level was 100 ng ml^{-1} in the SC group and 35.4 ng ml^{-1} in the GnRHa group. The majority of the patients (51.9%) in the SC group had a Gleason score of 8–10, compared to 35% in the GnRHa group; the majority of the patients (38.1%) in the GnRHa group had a Gleason score of <= 6. Most of the patients in both the SC group (52.7%) and the GnRHa group (45.5%) had clinical T2 disease. Almost half of the patients in the SC group (47.5%) had bone metastases at the time of treatment, compared to 17.5% in the GnRHa group. In the SC group, the majority of the patients (93.5%) did not have any treatment prior to SC. In the GnRHa group, 51.8% of the patients had radiotherapy and 16.2% of the patients had radical prostatectomy prior to GnRHa; while the remaining 32% of the patients received GnRHa as their primary treatment (**Table 1**). The median PSA nadir was 0.03 ng ml^{-1} in the SC group and 1.41 ng ml^{-1} in the GnRHa group. In the SC group, 69.5% of the patients developed disease progression compared to 45.5% in the GnRHa group.

Concerning the baseline risk factors between the two groups (**Table 2**), the mean age was 75.3 ± 7.5 years in the SC group and 71.8 ± 8.3 years in the GnRHa group ($P < 0.001$). However, there were higher rates of hypertension (37.0% in the SC group *vs* 47.8% in the GnRHa group, $P = 0.004$) and hyperlipidemia (11.6% in the SC group *vs* 24.2% in the GnRHa group, $P < 0.001$) in the GnRHa group. The duration of hormonal therapy in the SC group (49.3 ± 35.6 months) was longer than the GnRHa group (30.6 ± 26.5 months) ($P < 0.001$). There were no differences in the other baseline preexisting medical conditions between the two groups.

Concerning the cardiovascular thrombotic events (**Table 3**), in the SC group, 7.7% of the patients developed acute myocardial infarction and 8.8% of the patients developed ischemic stroke, adding up to a total of 16.5% of patients who developed cardiovascular thrombotic events. In the GnRHa group, 5.1% of the patients developed acute myocardial infarction, and 9.4% of the patients developed ischemic stroke, adding up to a total of 14.5% of patients who developed cardiovascular thrombotic events.

Upon Kaplan–Meier analysis (**Figure 1**), there was an increased risk of new cardiovascular thrombotic events in the SC group when compared to the GnRHa group ($P = 0.014$). Upon multivariate Cox regression analysis (**Table 4**), age (hazard ratio [HR] 1.072, 95% confidence interval [CI] 1.04–1.11, $P < 0.001$), hyperlipidemia (HR 2.455, 95% CI 1.53–3.93, $P < 0.001$) and SC (HR 1.648, 95% CI 1.05–2.59, $P = 0.031$) were significant risk factors of cardiovascular thrombotic events. Although the incidence of hypertension and the duration of hormonal therapy were different between the two groups, these two factors were not significant factors affecting the risk of cardiovascular thrombotic events upon multivariate Cox regression analysis.

Table 1: The clinicopathological data of the cohort

	SC group (n=387) (%)	*GnRHa group (n=297) (%)*
Median baseline PSA level (ng ml^{-1})	100	35.4
Gleason score		
<=6	96 (24.8)	113 (38.1)
7	90 (23.3)	80 (26.9)
8–10	201 (51.9)	104 (35)
Clinical T-stage		
1	37 (9.6)	54 (18.2)
2	204 (52.7)	135 (45.5)
3	116 (30)	99 (33.3)
4	30 (7.7)	9 (3.0)
Presence of bone metastases	184 (47.5)	52 (17.5)
Any prior treatment		
Radical prostatectomy	10 (2.6)	48 (16.2)
Radiotherapy	15 (3.9)	154 (51.8)
No prior treatment	362 (93.5)	95 (32)
Median PSA nadir (ng ml^{-1})	0.03	1.41
Any disease progression	269 (69.5)	135 (45.5)

PSA: prostate-specific antigen; SC: surgical castration; GnRHa: gonadotropin-releasing hormone agonists

Table 2: Comparisons between the SC and GnRHa groups

	Whole cohort (n=684)	*SC group (n=387)*	*GnRHa group (n=297)*	*P*
Mean age (year)	73.7±8.0	75.3±7.5	71.8±8.3	<0.001
Diabetes mellitus, *n* (%)	109 (15.9)	60 (15.5)	49 (16.5)	0.725
Fasting glucose (mmol l^{-1})	5.72±0.92	5.72±0.87	5.73±0.96	0.974
HbA1c (%)	6.03±0.85	6.01±0.87	6.04±0.84	0.802
Hypertension, *n* (%)	285 (41.7)	143 (37.0)	142 (47.8)	0.004
Hyperlipidemia, *n* (%)	117 (17.1)	45 (11.6)	72 (24.2)	<0.001
History of ischemic heart disease, *n* (%)	58 (8.5)	32 (8.3)	26 (8.8)	0.821
History of stroke, *n* (%)	54 (7.9)	34 (8.8)	20 (6.7)	0.324
Duration of hormonal therapy (month)	41.3±33.3	49.3±35.6	30.6±26.5	<0.001

SC: surgical castration; GnRHa: gonadotropin-releasing hormone agonists; HbA1c: glycated hemoglobin

Table 3: Cardiovascular thrombotic events in the cohort

	Whole cohort (n=684)	*SC group (n=387)*	*GnRHa group (n=297)*
Cardiovascular thrombotic events, *n* (%)	107 (15.6)	64 (16.5)	43 (14.5)
Acute myocardial infarction, *n* (%)	45 (6.6)	30 (7.7)	15 (5.1)
Ischemic stroke, *n* (%)	62 (9.0)	34 (8.8)	28 (9.4)

SC: surgical castration; GnRHa: gonadotropin-releasing hormone agonists

DISCUSSION

Since the first study by Huggins and Hodges[1] on the effect of castration on prostate cancer, the use of ADT has been widely used especially in patients with advanced or metastatic prostate cancer. SC in the form of bilateral orchiectomy and medical castration in the form of GnRHa were the two most established methods of androgen deprivation. The meta-analysis by Seidenfeld *et al.*[2] compared the different modalities of ADT and concluded that the efficacy of GnRHa was equivalent to SC. However, apart from the clinical efficacy, major long-term adverse

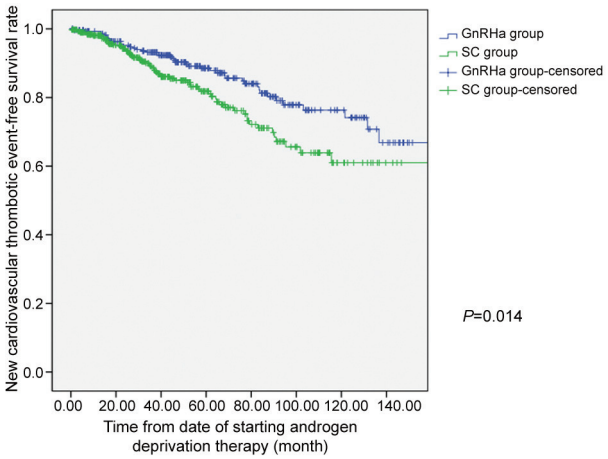

Figure 1: Kaplan–Meier analysis on the new cardiovascular thrombotic event-free survival rates in the SC and GnRHa groups. SC: surgical castration; GnRHa: gonadotropin-releasing hormone agonists.

Table 4: Cox regression analysis for risk of developing cardiovascular thrombotic events

	Hazard ratio	*95% CI*	*P*
Age	1.072	1.04–1.11	<0.001
Diabetes mellitus	1.393	0.86–2.26	0.178
Hypertension	1.295	0.86–1.96	0.303
Hyperlipidemia	2.455	1.53–3.93	<0.001
Preexisting ischemic heart disease	1.194	0.66–2.16	0.368
History of stroke	0.703	0.31–1.61	0.379
Surgical castration	1.648	1.05–2.59	0.031
Duration of hormonal therapy (<12 vs >12 months)	0.681	0.35–1.31	0.251

CI: confidence interval

events related to SC and GnRHa would be another important aspect to look into. Hence, we initiated this study to investigate the risk of cardiovascular thrombotic events between patients who received SC and those who received GnRHa.

In the literature, six large-scale studies investigated the risk of myocardial infarction[3–7] or stroke[3,4,8] after ADT. The study by Keating *et al.*[6] is one of the landmark studies investigating the cardiovascular risk after ADT. The reported unadjusted rates for developing coronary heart disease ($P < 0.001$), myocardial infarction ($P < 0.001$) and sudden cardiac death ($P < 0.001$) were higher for men treated with GnRHa than those who were not on hormonal treatment; the unadjusted rates for developing myocardial infarction ($P = 0.01$) and sudden cardiac death ($P < 0.001$) were also higher for men treated with SC than those who were not on hormonal treatment. After adjusting for patients' and tumor characteristics, the use of GnRHa remained as a risk factor for developing coronary heart disease ($P < 0.001$), myocardial infarction ($P = 0.03$) and sudden cardiac death ($P = 0.004$); whereas SC was no longer a significant risk factor for developing coronary heart disease ($P = 0.74$), myocardial infarction ($P = 0.44$) or sudden cardiac death ($P = 0.85$) compared to those who were not on hormonal treatment. However, although it included a large cohort of 73,196 prostate cancer patients, the results may be confounded by some important cardiovascular risk factors including hypertension and hyperlipidemia that were not reported in this study. Moreover, the cardiovascular risk after GnRHa and SC was compared to men who were not on hormonal treatment. Whether there is any significant difference in the cardiovascular risk between SC and GnRHa remained unknown.

Concerning the other five studies, in the subgroup analyses on patients receiving SC, two studies did not show increased risk of myocardial infarction[7] or stroke[4] when compared to patients not receiving ADT. However, both studies only included a limited number of potential risk factors in their analyses, which may interfere with the results. Three studies showed increased risk of myocardial infarction[3,5] or stroke[3,8] in patients receiving SC when compared to patients not receiving ADT. Two of the three studies[3,8] included a more comprehensive list of preexisting medical conditions upon multivariate analyses, and the results were deemed to be more reliable. Nevertheless, in the analyses of the aforementioned studies, the risks of myocardial infarction or stroke after ADT, either in the form of SC or GnRHa, were compared to those who did not receive any ADT; none of the studies directly compared the risk of myocardial infarction or stroke between patients receiving SC and GnRHa. Based on the current literature, it is difficult to conclude whether there is any difference in the risks of myocardial infarction or stroke between SC and GnRHa.

Whether there is any difference in the risks of myocardial infarction or stroke between SC and GnRHa in the Chinese population is even more unclear. While different ethnicities have significant genetic and physiological differences, the cardiovascular disease profile may also differ. Looking into the literature, no study has compared the cardiovascular risks between SC and GnRHa in the Chinese population before.

In our study, we compared the risk of cardiovascular thrombotic events, namely myocardial infarction and ischemic stroke, between patients receiving SC and GnRHa. When compared to the GnRHa group, there was an increased risk of new cardiovascular thrombotic events in the SC group upon Kaplan-Meier analysis ($P = 0.014$), and SC was also a risk factor of cardiovascular thrombotic events upon multivariate Cox regression analysis (HR 1.648, 95% CI 1.05–2.59, $P = 0.031$). To explain the results, we have to look into the hormonal changes that would occur after SC and GnRHa.

There are two postulations on why bilateral orchiectomy is associated with increased risk of cardiovascular thrombotic events when compared to GnRHa. Firstly, the risk of cardiovascular thrombotic events may be related to the degree of testosterone suppression. Although the clinical efficacy by GnRHa was generally regarded as equivalent to SC,[2,9,10] the degree of testosterone suppression may differ between them. It has been shown previously that SC could reduce serum testosterone to a lower level than GnRHa.[11] Using the chemiluminescent method in serum testosterone measurement, the serum testosterone level after SC (95% CI 12–17 ng dl^{-1})[12] appeared to be lower than that after GnRHa (95% CI 23.0–35.9 ng dl^{-1}).[13] This difference in testosterone concentration may not be as important in terms of prostate cancer control, but it may have an effect on the long-term adverse events related to ADT. A number of studies have shown that low testosterone level was associated with increased cardiovascular risk.[14,15] Androgen receptors are expressed in adipose tissues, and androgens could active hormone-sensitive lipase leading to lipolysis in adipose tissue.[16] Thus, androgen suppression may induce unfavorable changes in body composition including weight gain, loss of muscle mass and increased fat mass.[16] ADT may also affect insulin sensitivity, and predisposes to the development of diabetes mellitus and metabolic syndrome.[17,18] Hence, a lower testosterone level after SC may lead to increased risk of cardiovascular thrombotic events as shown in our study. Moreover, testosterone is a potent coronary vasodilator through inhibitory actions on the calcium channels,[19] and the use of testosterone replacement has been shown to improve the

ischemic threshold for hypogonadal men with angina.[20] A low serum testosterone level may also increase the risk of myocardial infarction through this mechanism.

Secondly, the cardiovascular risk may be related to the level of follicle-stimulating hormone (FSH). For patients receiving GnRHa, there would be an FSH surge during the first few weeks of treatment, which would then decrease rapidly and remain suppressed at a low level of − 54.8% from baseline.[21] On the contrary, SC would affect the FSH level through a negative feedback mechanism via the hypothalamic-pituitary-gonadal axis, which would result in an elevated FSH level up to + 300% from baseline.[10] While FSH receptors have been found on the luminal endothelial surface of proliferating tissue,[22] they may play a role in endothelial cell function and lipid metabolism that may increase the risk of cardiovascular events[23] in men receiving SC. In a study which pooled data from six phase three prospective randomized trials comparing between GnRHa and gonadotropin-releasing hormone antagonists, it was shown that the risk of cardiac events within 1 year of treatment was lower in men treated with gonadotropin-releasing hormone antagonists (HR 0.44, 95% CI 0.26–0.74, $P = 0.002$).[23] As the median FSH level in patients receiving gonadotropin-releasing hormone antagonists (−88.5% from baseline) was lower than those who received GnRHa (−54.8% from baseline),[21] this finding supported our hypothesis that higher FSH level may be one of the mechanisms for the increased risk of cardiovascular events. However, the above postulations were based on the results of previous studies and were not justified by the data presented from our study; further prospective studies are required to investigate on these important issues.

To our knowledge, this is the first study directly comparing the risk of cardiovascular events between patients who received SC versus those who received GnRHa. This is also the first study investigating this clinical question in the Chinese population. The main limitation is the retrospective nature of our study. Without a standardized protocol with prospective data collection, the accuracy of the results may be affected. Secondly, although the duration of hormonal therapy was not a factor affecting the risk of cardiovascular thrombotic events in our analysis, patients who received GnRHa may have lower risk of cardiovascular events if an intermittent hormonal therapy approach was adopted. Thirdly, the use of maximal androgen blockade was not investigated. In our study, the percentage of patients who developed disease progression in the two groups was different (69.5% in the SC group and 45.5% in the GnRHa group). As the patients who developed disease progression after SC or GnRHa would usually be considered for maximal androgen blockade, the use of maximal androgen blockage in the two groups may be different, and the results may be affected. Moreover, a lower degree of cancer control in the SC group may also increase the risk of cardiovascular thrombotic events, and the accuracy of our results may be affected. Nevertheless, as the occurrence of a cardiovascular event may adversely affect survival, we believe that the adverse events related to ADT are equally important to its clinical efficacy while deciding on the method of androgen deprivation. Further prospective trials comparing between SC and GnRHa are necessary to provide more convincing evidence on this important aspect.

AUTHOR CONTRIBUTIONS

JYCT and CFN carried out the study. JYCT, SYSC, PKFC and CFN participated in the study design. JYCT, SYSC and PKFC collected the data. JYCT, SYSC and PKFC helped statistical analyses. JYCT, DMCP, HYC, SSMH and CFN coordinated the study. JYCT and CFN drafted the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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