Risk of ischemic stroke after androgen deprivation therapy for prostate cancer in the Chinese population living in Hong Kong

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Abstract

Objective: Previous reports on the risk of stroke after androgen deprivation therapy for prostate cancer were largely based on Caucasians. We investigated the risk of ischemic stroke after androgen deprivation therapy for prostate cancer in the Chinese population.

Methods: All Chinese prostate cancer patients who were treated primarily with radical prostatectomy or radiotherapy, with (androgen deprivation therapy group) or without (non-androgen deprivation therapy group) further androgen deprivation therapy, at our hospital from year 2000–09 were reviewed. Potential risk factors of ischemic stroke including age, baseline prostate-specific antigen, Gleason score, clinical T stage, hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, history of stroke, use of androgen deprivation therapy and duration of androgen deprivation therapy were reviewed. The risk of ischemic stroke after androgen deprivation therapy was analyzed with Kaplan–Meier and multivariate Cox regression analyses.

Results: A total of 452 patients were included, consisting of 200 patients in the non-androgen deprivation therapy group and 252 patients in the androgen deprivation therapy group. The androgen deprivation therapy group appeared to have increased risk of ischemic stroke when compared with the non-androgen deprivation therapy group ($P=0.063$) upon Kaplan–Meier analysis. Upon multivariate Cox regression analyses, older age (hazard ratio 1.13, 95% confidence interval 1.04–1.22, $P=0.003$), hyperlipidemia (hazard ratio 4.61, 95% confidence interval 2.01–10.54, $P<0.001$) and the use of androgen deprivation therapy (hazard ratio 3.32, 95% confidence interval 1.14–9.67, $P=0.028$) were associated with increased risk of ischemic stroke.

Conclusions: There was increased risk of ischemic stroke after androgen deprivation therapy for prostate cancer in the Chinese population. The risk of ischemic stroke should be considered while deciding on androgen deprivation therapy, especially in older patients with known history of hyperlipidemia.

Key words: prostate cancer, androgen deprivation therapy, stroke, Chinese population
Introduction

Androgen deprivation therapy (ADT) is the mainstay of treatment in advanced or metastatic disease. Early ADT could reduce prostate cancer-related morbidities including pathological fracture, spinal cord compression, ureteral obstruction and extra-skeletal metastases (1). On the other hand, the use of ADT may result in many side effects including general malaise, fatigue, loss in libido and vasomotor flushing (2,3). The use of ADT may also lead to major adverse events including diabetes, skeletal fracture, acute myocardial infarction and stroke. In the Caucasian population, several studies have shown that ADT would increase the risk of stroke (4–8). However, there is a lack of data concerning the association between ADT and stroke in the Asian population. Due to the genetic and physiological differences, the cardiovascular profile may differ between different ethnicities. In this study, we investigated the risk of ischemic stroke after ADT for prostate cancer in the Chinese population.

Patients and methods

All consecutive Chinese prostate cancer patients who were primarily treated with radical surgery or radiotherapy, with or without further ADT, from year 2000–09 were included in our study. Baseline characteristics including age, baseline prostate-specific antigen (PSA) level, Gleason score, clinical T stage and preexisting medical conditions including hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease and history of stroke were reviewed and compared between the two groups. Primary form of treatment and details of subsequent ADT including form and duration of ADT, treatment setting and approach were reviewed.

The electronic medical records of all casualty attendances and hospital admissions of the patients included were reviewed individually. The primary outcome of our study is any new event of ischemic stroke. Ischemic stroke is defined as any focal neurological deficit with corresponding radiological evidence of infarct on computed tomography (CT) brain scan. We compared the risk of ischemic stroke between the non-ADT group and the ADT group using Kaplan–Meier analysis and log rank test. Further multivariate Cox regression analyses including the potential risk factors of ischemic stroke were performed.

Concerning the comparison of baseline characteristics between the two groups, independent samples t-test was used for parametric continuous variables, Mann–Whitney U test was used for non-parametric continuous variables and x² test was used for categorical variables. All statistical analyses were performed using SPSS version 20.0. P value of <0.05 was considered to be statistically significant.

Results

A total of 452 patients were included in our study, consisting of 200 patients in the non-ADT group and 252 patients in the ADT group. The median follow-up was 72.9 months. The mean age was 68.2 ± 5.9 years in the non-ADT group and 69.5 ± 6.5 in the ADT group (P = 0.031). The median PSA was 9.75 ng/ml in the non-ADT group and 27.1 ng/ml in the ADT group (P < 0.001). Patients in the ADT group had higher risk disease in terms of both Gleason score (P < 0.001) and clinical T stage (P < 0.001). Preexisting medical conditions including hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease and history of stroke were similar between the two groups (Table 1).

Concerning the primary form of treatment (Table 2), 68.5% of the non-ADT group had radical prostatectomy while 73.4% of the ADT group had radiotherapy. In the ADT group, 81.8% of the patients had GnRH agonist as an adjuvant therapy, and 96.0% were given ADT in a continuous approach. The mean duration of ADT was 40.3 ± 34.1 months in the ADT group.

A total of 37 patients developed new event of ischemic stroke; 5.0% in the non-ADT group (10 out of 200 patients) and 11.0% in the ADT (27 out of 252 patients). The ADT group appeared to have an increased risk of developing new ischemic stroke (P = 0.063) upon Kaplan–Meier analysis (Fig. 1). Upon multivariate Cox regression analyses (Table 3), older age [hazard ratio (HR) 1.13, 95% confidence interval (CI) 1.04–1.22, P = 0.003], hypertension (HR 4.61, 95% CI 2.01–10.54, P < 0.001) and the use of ADT (HR 3.32, 95% CI 1.14–9.67, P = 0.028) were associated with increased risk of developing ischemic stroke. Although the PSA level and disease status (Gleason score and clinical T stage) were different between the two groups; they were not significant factors associated with the risk of developing

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of the cohort</th>
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<tbody>
<tr>
<td>Non-ADT group (N = 200)</td>
</tr>
<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Median PSA level (ng/ml)</td>
</tr>
<tr>
<td>Gleason score</td>
</tr>
<tr>
<td>≤6</td>
</tr>
<tr>
<td>7</td>
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<tr>
<td>8–10</td>
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<tr>
<td>Clinical T stage</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Preexisting ischemic heart disease</td>
</tr>
<tr>
<td>History of stroke</td>
</tr>
</tbody>
</table>

ADT, androgen deprivation therapy.
Table 2. Treatment information of the cohort

<table>
<thead>
<tr>
<th>Form of radical treatment</th>
<th>Non-ADT group (N=200)</th>
<th>ADT group (N=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical prostatectomy</td>
<td>68.5%</td>
<td>25%</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>22%</td>
<td>73.4%</td>
</tr>
<tr>
<td>Radical prostatectomy and adjuvant radiotherapy</td>
<td>9.5%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

Form of ADT
- GnRH agonist
- Bilateral orchiectomy
- GnRH agonist followed by bilateral orchiectomy

ADT treatment setting
- Adjuvant
- Salvage

ADT approach
- Continuous ADT
- Salvage ADT
- Intermittent ADT

Mean duration of ADT (months)
- 40.3 ± 34.1

Figure 1. Kaplan–Meier analysis on the new ischemic stroke-free survival rate after androgen deprivation therapy.

Table 3. Multivariate Cox regression analyses for risk of developing ischemic stroke

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.13 (1.04–1.22)</td>
</tr>
<tr>
<td>Baseline PSA</td>
<td>1.00 (0.99–1.01)</td>
</tr>
<tr>
<td>Gleason score</td>
<td>0.92 (0.62–1.37)</td>
</tr>
<tr>
<td>Clinical T stage</td>
<td>0.74 (0.43–1.28)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.65 (0.66–4.17)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.96 (0.37–2.46)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>4.61 (2.01–10.54)</td>
</tr>
<tr>
<td>Preexisting ischemic heart disease</td>
<td>0.73 (0.24–2.24)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>2.38 (0.67–8.38)</td>
</tr>
<tr>
<td>Use of ADT</td>
<td>3.32 (1.14–9.67)</td>
</tr>
<tr>
<td>Duration of ADT</td>
<td>1.00 (0.98–1.01)</td>
</tr>
</tbody>
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PSA, prostate-specific antigen.

Discussion

Huggins et al. (9) first described the effect of castration on serum phosphatases in metastatic prostate cancer in 1941. Since then, ADT has gained an important role in the management of prostate cancer, and there is increasing use of ADT in men across different stages of prostate cancer (10). Adjuvant use of ADT has been shown to confer survival benefit in node-positive prostate cancer following radical prostatectomy and pelvic lymphadenectomy (11), and also in locally advanced prostate cancer following external irradiation (12,13). For advanced prostate cancer, early use of ADT has been shown to reduce cancer-related morbidities including spinal cord compression, ureteral obstruction and extra-skeletal metastases when compared with deferred ADT (1). Unfortunately, while ADT is the mainstay of treatment in metastatic prostate cancer, whether it can prolong survival in this group of patients remained controversial. On the other hand, major adverse events related to ADT including diabetes mellitus (4,5,14), skeletal fracture (15,16), acute myocardial infarction (17,18) and prostate cancer following external irradiation (12,13) are detrimental and may result in life-threatening consequences. While the majority of the literature was based on the Caucasian population, we conducted this study to investigate the risk of ischemic stroke after ADT in the Chinese population.

In our study, we included all consecutive prostate cancer patients who were treated primarily with radical surgery or radiotherapy from year 2000–09, and compared between those who were given ADT (ADT group) and those who were not given any ADT (non-ADT group). There was no selection bias in our study. The majority of the patients in the ADT group had GnRH agonist as the form of ADT, and most of them had ADT as an adjuvant therapy. Adjuvant ADT was generally given to patients with node-positive disease following radical prostatectomy and lymphadenectomy, or to patients with high-risk prostate cancer (PSA > 20 ng/ml, Gleason score ≥ 8) or clinical Stage T2c-3a following radiotherapy. We hypothesized that the use of ADT may result in increased risk of thromboembolic events, and in particular, ischemic stroke as investigated in our study. Hemorrhagic stroke was not considered as the primary outcome of our study, as it has a different pathophysiology from ischemic stroke, and in most cases were closely related to hypertension instead.

For our cohort, the incidence of ischemic stroke was calculated to be 7.87 cases per 1000 person-years in the non-ADT group. This is comparable to the previously published data on the rate of ischemic stroke in men aged 65–74 with a quoted incidence of 8.45 cases per 1000 person-years in our locality (19), whereas in the ADT group, the incidence of ischemic stroke was calculated to be 16.14 cases per 1000 person-years. It appears that the incidence of ischemic stroke in the ADT group is much higher than that in the non-ADT group and also in the general population. Upon Kaplan–Meier analysis, the ADT group appeared to have increased risk of ischemic stroke (P = 0.063). The baseline characteristics differed between the two groups in terms of their age and disease status (PSA, Gleason score and clinic T stage).

Nevertheless, the use of ADT (HR 3.32, 95% CI 1.14–9.67, P = 0.028) was associated with increased risk of developing ischemic stroke after adjusting for these possible confounding factors upon multivariate analyses. Age (HR 1.13, 95% CI 1.04–1.22, P = 0.003) and hyperlipidemia (HR 4.61, 95% CI 2.01–10.54, P < 0.001) were also risk factors for developing ischemic stroke upon multivariate Cox regression analyses, hence we should be cautious in starting ADT for elderly patients with known hyperlipidemia. Since there is
no regular monitoring of the lipid profile in our cohort, we do not have comprehensive information on the rate of new-onset hyperlipidemia after the initial treatment. Hence, we were not able to provide the rate of ischemic stroke in patients with hyperlipidemia induced by ADT, but not at baseline, in our cohort. Whether patients who develop hyperlipidemia only after the use of ADT are at higher risk of developing ischemic stroke is an interesting clinical question that remained to be answered.

A number of studies have investigated the association between ADT and stroke (4–8,20). The majority of them demonstrated increased risk of stroke (4–6) or transient ischemic attack (6) after ADT. On the contrary, one study (20) compared the incidence of stroke between men with prostate cancer who were given endocrine treatment, with age- and residency-matched men from the general population but showed no increased risk of stroke during endocrine treatment for prostate cancer. All of these studies were based on Caucasians and there is lack of data regarding the risk of stroke after ADT in the Asian population. Up to date, there is only one study investigating the risk of stroke after ADT in the Asian population (21). It is a prospective case–control study on 365 Chinese prostate cancer men and it did not demonstrate any increased risk of stroke after ADT (adjusted HR 1.09, 95% CI 0.80–1.50) during a 5-year follow-up (21). However, the number of patients who received hormone therapy was relatively small (64 patients in total), which may possibly hinder the power of the study.

ADT may predispose the development of ischemic stroke through changes in glucose and lipid metabolism. Previous studies have shown positive correlation between testosterone levels and insulin sensitivity (22–24). The low testosterone level after ADT may induce insulin resistance and predispose the development of diabetes mellitus. Androgen also plays an important role in lipid metabolism. Androgens could active hormone-sensitive lipase through androgen receptors and cause lipolysis of the adipose tissue (25). Hence, androgen suppression may induce changes in body composition including weight gain, loss of muscle and increased fat mass (26). The resulting metabolic syndrome may accelerate the development of atherosclerosis and therefore increase the risk of ischemic stroke.

The use of ADT has a relatively high HR of 3.32 (95% CI 1.14–9.67) in our study when compared with that quoted in the Caucasian population (HR ranging from 1.18 to 1.81) (4,5,7). This may be accounted by the differences in androgen receptor genetic polymorphisms between Asians and Caucasians; namely the CAG repeat length polymorphism and the deletion of UGT2B genes. It was previously shown that the androgen receptor CAG repeat length polymorphism could modify the effect of testosterone on insulin sensitivity (27). In men with shorter CAG lengths, an increase in testosterone level appeared to worsen insulin sensitivity, but the effect attenuated with rising CAG length and finally turned to the opposite effect at a CAG length of longer than 23, in which a lower testosterone level appeared to worsen insulin sensitivity (27). The Chinese population have longer CAG repeats than the Caucasian population (28) with an average CAG length of around 23 (29,30), which incidentally lies at the turning point of effect modification. In another study by Nadeau et al. (31) which included 320 Asian and 526 Caucasian, 70% of the Asian men had two UGT2B17 gene deletions and concomitant UGT2B28 gene deletion, compared with 17% in the Caucasian men. Men with two UGT2B17 gene deletions and concomitant UGT2B28 gene deletion appeared to have a 23% reduction in testosterone level although it was statistically insignificant ($P = 0.125$). The testosterone level may be lower in Asian men due to the higher rates of UGT2B gene deletions when compared with the Caucasian population. Due to the above-mentioned genetic differences, Chinese men may possibly have lower testosterone level and poorer insulin sensitivity upon androgen suppression, and may result in increased risk of diabetes, metabolic syndrome and eventually thromboembolic events, and in particular ischemic stroke in our context.

An interesting finding of our study is that the duration of ADT does not appear to be associated with the risk of ischemic stroke upon multivariate analyses. In the literature, there is only one study which provided information on the effect of ADT duration on the risk of stroke (6). Compared with patients who were not given any ADT, a >40% increased risk was observed in patients who were given 5–24 months of ADT. However, this association became insignificant in patients who were given ≥25 months of ADT. There are two postulations to explain this observation. Firstly, ADT reduces insulin sensitivity within a short period of time (32), which does not necessarily confer a greater cumulative risk with time. Physiologic studies have demonstrated that short-term GnRH agonists significantly increase fat mass, but long-term treatment does not cause further fat accumulation (33). Secondly, any possible association between ADT duration and the risk of stroke might be masked by the depletion of susceptible phenomenon (6). Patients who were susceptible to experiencing a stroke may develop stroke at an early stage of treatment, where as patients who were on ADT for longer period were more likely to be those who tolerated it. The above postulations may possibly explain the non-cumulative effect of ADT on the risk of ischemic stroke, which however prompt further studies on this interesting observation.

To our knowledge, this is the first study that demonstrated the association between ADT and stroke in the Chinese population. However, there are several limitations in our study. Firstly, the follow-up protocol was not standardized and the accuracy of the results may be affected. Severe potential risk factors of stroke including smoking history and body mass index could not be retrieved for analyses. Secondly, the serum testosterone level was not routinely checked or monitored in our cohort, the castrate levels in our cohort could not be ascertained and any association between the testosterone level and stroke risk could not be established. Thirdly, the use of maximal androgen blockade was not investigated, and this may potentially confound the results of our study.

Nevertheless, we believe the risk of ischemic stroke should be considered upon the initiation of ADT. While there is no strong evidence that ADT could prolong survival in metastatic prostate cancer, the adverse events related to ADT may be detrimental and outweigh its potential benefits. Further prospective studies will be needed to address these important concerns of ADT.

**Conflict of interest statement**

None declared.

**References**


