World Journal of Urology
https://doi.org/10.1007/s00345-018-02621-6

ORIGINAL ARTICLE

Clinically occult prostate cancer cases may distort the effect of testosterone replacement therapy on risk of PCa

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Received: 26 April 2018 / Accepted: 29 December 2018

Abstract

Background Although prostate cancer (PCa) screening is conducted before testosterone replacement therapy (TRT), clinically occult PCa cases may exist.

Methods To evaluate whether the possible inclusion of occult PCa cases distorts the effect of TRT on risk of PCa, we followed 776 hypogonadal males (TRT = 400, non-TRT = 376) from a urology center in Germany from 2004 to 2016, with a mean follow-up period of 7 years. We assumed occult cases might take 1–2 years (latency period) to become clinically detectable after receiving TRT. We selected several latency periods (12/18/24 months) and compared the risk of PCa in the TRT and non-TRT group over the latency period, from the end of latency period till the end of follow-up, and over the whole follow-up time.

Results Overall, 26 PCa cases occurred in the non-TRT group vs 9 cases in the TRT group. Within 18 months of follow-up, 9 cases occurred in the TRT group vs 0 cases in the non-TRT group; from the end of 18 months till the end of follow-up, 26 cases occurred in the non-TRT group vs 0 cases in the TRT group. The adjusted table showed seemingly adverse effects of TRT on PCa development within 18 months ($p = 0.0301$) and beneficial effects from the end of 18 months till the end of follow-up ($p = 0.0069$). Similar patterns were observed for 12 or 24 months as the latency period.

Conclusions TRT may make occult PCa cases detectable within early phase of treatment and present a beneficial effect in the long run. Future longitudinal studies are needed to confirm findings from our exploratory analyses.

Keywords Longitudinal study · Prostate cancer · Testosterone replacement therapy · Undetected cases · Prostate-specific antigen

Introduction

Prostate carcinoma may develop from an androgen-dependent epithelium; increase in the serum testosterone (T) level may stimulate cancer cell growth via androgen receptor activation or through androgen-metabolizing enzymes, especially at the early stage of PCa [1]. Being concerned about PCa progression following T replacement therapy (TRT), clinicians prescribe TRT with caution and give TRT to those without preexisting PCa or abnormal prostate-specific antigen (PSA) levels, such as hypogonadal males with a normal PSA level and unsuspicious findings at digital rectal examination or transrectal ultrasound, to enhance T levels and achieve the benefits of TRT on hypogonadal symptoms [2–5]. Despite the cautious selection of patients and predicable beneficial effects, the clinical use of TRT is still controversial, for concerns of potential inclusion of the clinically occult PCa cases.

PSA is a commonly used screening technique to detect PCa [6]. High PSA may suggest presence of PCa; however, undetectable or very low PSA does not mean that a patient is free of PCa. A study found 5.6%, 17.5%, 26.4%, and 36.4% biopsy positive results were reported for hypogonadal

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Published online: 18 January 2019

males with a PSA level of 1.0 or less, 1.1–2.0, 2.1–3.0, and 3.1–4.0 ng/mL, respectively [7]. Another study showed PCa was identified in 14% of a group of males with low T levels and PSA less than 4.0 ng/mL [8]. Providing TRT for these occult cases might lead to progression of PCa and make the occult cases clinically detectable, and inclusion of occult cases in the study population might bias the estimates of TRT effects on risk of PCa. Studies have reported the mean duration of the preclinical period (Fig. 1) from onset of PCa to clinical diagnosis for PCa was estimated to be 11–12 years for white men, and 1 year shorter for blacks [9]. However, the "latency period" (Fig. 1) that occult cases might take to become clinically detectable if TRT is administrated is unknown. Besides, no previous studies have evaluated the effect of TRT on PCa risk with taking into consideration the potential existence of occult PCa cases. The challenge is the difficulty of identifying these cases in practice.

In this study, we used de-identifiable data of 776 hypogonadal men from a registry study in Bremerhaven, Germany from 2004 through 2016 to assess the impact of potential occult PCa cases on estimates of TRT effects on PCa risk. We specified 12, 18, and 24 months as the possible latency periods and compared the risk of PCa in the two treatment groups (TRT/Non-TRT) over the latency period, from the end of latency period till the end of follow-up, and over the whole follow-up time.

Materials and methods

Study population

We used de-identifiable data from a registry study in Germany. 776 men were recruited from one urology center in Bremerhaven, Germany from 2004 to 2016, where they had sought medical consultation for various urological complaints including sexual dysfunction. Hypogonadism diagnosis was confirmed if they had total T level $\leq$ 12.1 nmol/L (~ 350 ng/dL). Individuals who had androgen-dependent carcinoma of the prostate were excluded. Informed consent was obtained from study subjects. The study protocol was approved by the institutional review board (IRB) office. Participants were followed up routinely for updates in serum T and PSA levels and several other physical, laboratory, and imaging test results.

Study groups: TRT/Non-TRT

Patients with PSA less than 4 ng/mL were given option of TRT. Receiving TRT or not was based on patient's own choice at the beginning of study. Patients who decided to take TRT were classified as TRT group, and the rest were classified as non-TRT group. As described previously [10, 11], patients on TRT received injections of 1000 mg of testosterone undecanoate with the second injection 6 weeks after the first injection, followed by 12-week intervals throughout the observation time. Since every injection was administered and documented in the urology office, the adherence to testosterone was 100%.

Scheduled follow-up and outcome assessment

Patients in the TRT group were seen and followed up four times a year which are the times when they returned for their next injection. Each time throughout the observation time, PSA and T levels were measured. Digital rectal examination and transrectal ultrasound were performed each time during the first year of treatment and thereafter at least two times a year. In the non-TRT group, PCa screening was performed routinely once or twice each year as part of a general health assessment. PCa diagnosis was confirmed through biopsy. If PSA increased to 4 ng/mL and above or increased by more than 0.75 ng/mL within 12 months, or if there were suspicious findings on digital rectal examination or transrectal ultrasound, a biopsy was performed to determine if PCa was present. The diagnosis procedures followed the European Association of Urology guidelines on PCa [6].

Covariates

Information on age, family history of PCa, comorbidity conditions [e.g., benign prostatic hyperplasia (BPH), prostatitis, diabetes, cardiovascular disease (CVD)], alcohol use, and smoking status was collected at baseline. Body mass index

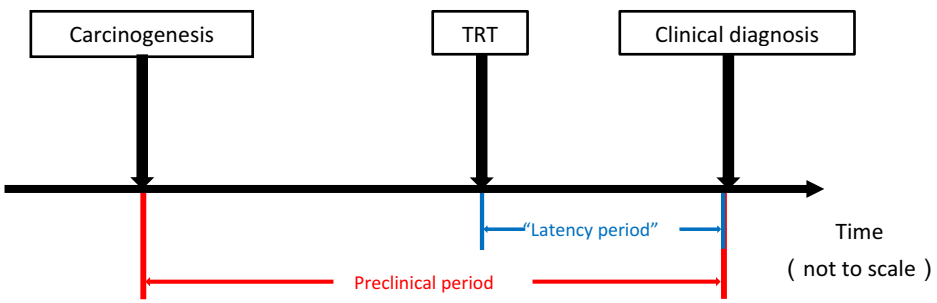

Fig. 1 Illustration of "preclinical period" and "latency period" in this study

(BMI) was calculated based on height and weight measured at baseline. All covariates were selected a priori based on previous research and current knowledge about the relationship of those factors with TRT and risk of PCa [12–14].

Statistical analysis

Demographic characteristics, life style, and baseline health condition were presented by exposure group (TRT/non-TRT). To see the overall effect of TRT on the risk of PCa overtime, as well as to check adequacy of applying cox proportional hazards regression model in the next steps, we first made Kaplan–Meier survival plots by group (TRT/non-TRT), treating the diagnosis of PCa as an event. We planned to use cox model if the assumption of proportional hazard holds, or 2 by 2 table with Chi square test of independence if assumption is violated. Considering the number of potential confounders and relatively rare events, to improve the power of our analyses, we applied propensity score matching (PSM) in the analysis to balance demographic characteristics and baseline health condition between TRT and non-TRT groups. The matching process was described at https://github.com/zhangxgz/Occult-PCa-cases/blob/master/PSM.docx.

Statistical analysis

There were 42 Klinefelter's syndrome patients in the TRT group vs 0 in the non-TRT group. As Klinefelter's syndrome may have an effect on the PCa development, we conducted a sensitivity analysis after excluding all patients diagnosed with Klinefelter's syndrome at study entry.

Selection of latency periods

We assumed that (1) if an occult case with normal screening test results was enrolled in the study and started to take TRT, he might become clinically detectable (PSA > 4 ng/mL) within 2 years (latency period); (2) an occult case who decided not to take TRT might go through natural progression until became clinically detectable, typically 11–12 years after PCa onset as we mentioned previously. We also considered the scenario that all subjects, occult case or not, had the chance of developing PCa at any time point during the full follow-up; however, the occult cases might be more likely to transfer into a clinically detectable case within a short time period when given TRT. Based on this, we selected three possible lengths of latency period (12/18/24 months) and compared the risk of PCa in the two treatment groups (TRT/Non-TRT) over the latency period, from the end of latency period till the end of follow-up, and over the whole follow-up time.

Statistical analyses were performed with R version 3.3.3. Tests results were considered statistically significant at $\alpha = 0.05$.

Results

A total of 776 hypogonadal men aged 33–74 year were enrolled in this study, among which 400 men were on TRT and 376 were not. The average follow-up time was 7.03 years for non-TRT group and 6.90 years for TRT group. By the end of study, 26 PCa cases were reported in the non-TRT group, as compared to 9 in the TRT group (Table 1).

As presented in Table 1, the age distribution, BMI, alcohol consumption, baseline PSA levels, and comorbidity conditions were statistically significantly different between TRT group and non-TRT group. Compared to participants in the non-TRT group, those in the TRT group were likely to be younger (mean age at entry: 57.70 vs 63.94 year), with higher BMI (33.12 vs 30.12 kg/m^2) and lower PSA levels (1.76 vs 2.43 ng/mL). In addition, patients who decided to receive TRT were less likely to have had BPH and CVD, but more likely to have had prostatitis and prediabetes (HbA1c 5.7–6.4%).

After PSM, there were 398 TRT group subjects and 230 non-TRT subjects left. Table 2 showed that overall, there were 9 PCa cases in the TRT group as compared to 5 in the non-TRT group during the full follow-up period. Restricted to 18 months of follow-up, all 9 cases were reported in the TRT group; from the end of 18 months till end of follow-up time, all 5 cases were from the non-TRT group. Fisher's exact test showed that overall, there was no significant effect of TRT on risk of PCa ($p = 0.9999$); however, there was significant adverse effect of TRT on risk of PCa within 18 months of follow-up ($p = 0.0301$) and significant beneficial effect of TRT on risk of PCa from the end of 18 months till end of follow-up time ($p = 0.0069$). If we chose to use 12 or 24 months as the latency period, we also found an adverse effect of TRT within the latency period and beneficial effect afterwards, but the effect might not be significant. The sensitivity analyses were presented in Table 3. After excluding all Klinefelter's syndrome patients, we found the overall adjusted effect of TRT remained insignificant; within the pre-defined latency period, TRT showed an adverse effect within the latency period (significant within 18 months) and a significant protective effect afterwards.

Figure 2 shows the overall effect of TRT on risk of PCa during full follow-up period. The crossing curves indicate violation of proportional hazard function and potential changing impact of TRT on PCa incidence. Starting from 10 to 36 months, the survival probability (probability of not

Table 1 Characteristics of participants by group

Characteristics	Non-TRT ($n=376$)		TRT ($n=400$)[a]		p value
	Mean ± SE[b]	Range	Mean ± SE[b]	Range	
	N (%)		N (%)		
Baseline					
Entry age (years)	63.94 ± 4.68	45–74	57.70 ± 7.40	33–71	< 0.001
Follow-up (years)	7.03 ± 1.83	2–11	6.90 ± 2.86	0.75–10.25	0.476
BMI (kg/m^2)	30.12 ± 4.22	22.15–46.98	33.12 ± 5.42	21.91–46.51	< 0.001
T (nmol/L)	9.70 ± 1.15	5.89–12.13	9.82 ± 1.24	5.89–12.13	0.1465
PSA (ng/mL)	2.43 ± 1.27	0.20–7.90	1.76 ± 0.93	0.08–3.90	< 0.001
Family history of PCa (yes)	45 (11.97)	–	39 (9.75)	–	0.3556
Smoking (yes)	138 (36.70)	–	154 (38.50)	–	0.6565
Alcohol (yes)	186 (49.47)	–	135 (33.75)	–	< 0.001
BPH (yes)	191 (50.80)	–	157 (39.45)	–	0.001863
CVD (yes)	103 (27.39)	–	73 (18.25)	–	0.002656
Prostatitis (yes)	48 (12.77)	–	168 (42.00)	–	< 0.001
Diabetes					
Type 1	0 (0.00)	–	21 (5.25)	–	< 0.001
Type2	153 (40.69)	–	133 (33.25)	–	
Prediabetes[c]	5 (1.33)	–	45 (11.25)	–	
No	218 (57.98)	–	201 (50.25)	–	
Endpoint					
PCa (yes)	26 (6.91)	–	9 (2.25)	–	0.001741

[a]Two participants had missing data on baseline BPH

[b]Mean ± SE for numerical variables and N (%) for categorical variables

[c]HbA1c 5.7%–< 6.5%

Table 2 Crude and adjusted 2 × 2 tables assessing the relationship between TRT and PCa, over the latency period (12/18/24 months), from the end of latency period till the end of follow-up, and over the whole follow-up time

Follow-up period	Full		Within 12 months		From end of 12 months till end of follow-up		Within 18 months		From end of 18 months till end of follow-up		Within 24 months		From end of 24 months till end of follow-up	
	PCa	Total	PCa	Total	PCa	Total	PCa	Total	PCa	Total	PCa	Total	PCa	Total
Crude														
TRT	9	398	5	398	4	393	9	398	0	389	9	398	0	398
Non-TRT	26	376	0	376	26	376	0	376	26	376	2	376	24	374
p value	0.0027		0.0622		< 0.001		0.0038		< 0.001		0.06473		< 0.001	
After propensity score matching, weighted														
TRT	9	398	5	398	4	393	9	398	0	389	9	398	0	389
Non-TRT	5	230	0	230	5	230	0	230	5	230	0	230	5	230
p value	0.9999		0.1641		0.3016		0.0301		0.0069		0.0301		0.0069	

Two participants with interrupted treatment were excluded from the analysis

developing PCa) for TRT group was consistently lower as compared to the non-TRT group; after 36 months, the survival probability for TRT was consistently higher compared to that for non-TRT group.

Discussion

In this longitudinal study, we found a significant adverse effect of TRT on the risk of PCa if only following the cohort within the predefined latency period (18/24 months)

Table 3 Crude and adjusted 2×2 tables assessing the relationship between TRT and PCa, over the latency period (12/18/24 months), from the end of latency period till the end of follow-up, and over the whole follow-up time, after excluding patients with Klinefelter's syndrome diagnosis at baseline

Follow-up period	Full		Within 12 months		From end of 12 months till end of follow-up		Within 18 months		From end of 18 months till end of follow-up		Within 24 months		From end of 24 months till end of follow-up	
	PCa	Total	PCa	Total	PCa	Total	PCa	Total	PCa	Total	PCa	Total	PCa	Total
Crude														
TRT	9	356	5	356	4	351	9	356	0	347	9	356	0	347
Non-TRT	26	376	0	376	26	376	0	376	26	376	2	376	24	374
p value	0.005458		0.02682		< 0.001		0.001444		< 0.001		0.03291		< 0.001	
After propensity score matching, weighted														
TRT	9	356	5	356	4	351	9	356	0	347	9	356	0	347
Non-TRT	10	217	0	217	10	217	0	217	10	217	2	217	8	215
p value	0.2288		0.1624		0.01239		0.01562		< 0.001		0.2209		< 0.001	

Two participants with interrupted treatment were excluded from the analysis

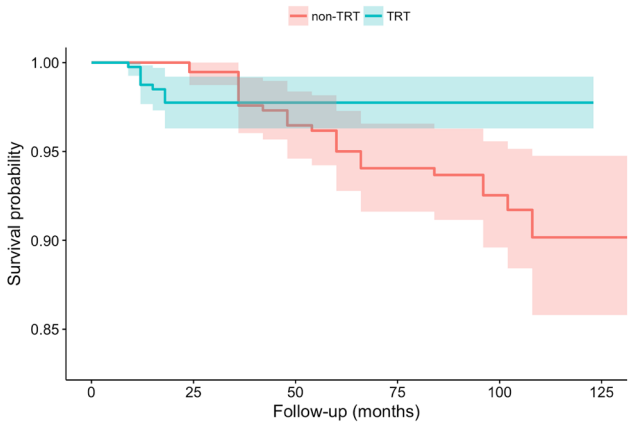

Fig. 2 Kaplan–Meier curves of probability of developing PCa by group, without adjustment. Two participants with interrupted treatment were included in the analysis and treated as censored at the time they stopped receiving treatment

while a significant protective effect in the same cohort from the end of latency period till end of follow-up time.

These seemingly contradictory findings of our study can be explained partially by the possible inclusion of occult cases in the study population, though all of the study participants had a negative enrollment screening result. These occult cases were coming from males with depressed T concentrations [T levels ≤ 12.1 nmol/L (~ 350 ng/dL)], and they would have a greater period before PCa diagnosis if no T treatment was given, because PSA production is androgen-dependent, and insufficient T would lead to low PSA production [15]. In the TRT group, exogenous T initiation elevates patients' T levels and actually increases the likelihood of PCa diagnosis that were being masked by low PSA. If occult PCa cases were non-differentially distributed between TRT and non-TRT groups, the occult cases in the TRT group became clinically detectable within a shorter time period after treatment, which explains the seemingly adverse effect of TRT on PCa risk we observed at the beginning of the study (within latency period). On the other hand, the protective effect of TRT observed in later follow-up period (from end of latency period till end of follow-up time) could be overestimated, because study participants left in the TRT were in general "healthier" than those in the non-TRT group. The occult cases in the TRT group had already been "activated" by T administration at the beginning of study and the rest in the TRT group were likely just "normal" subjects, whereas occult cases in the non-TRT group finally got their PSA increased and became clinically detectable in later follow-up years. In other words, we were comparing the PCa incidence between the rest in the TRT group ("normal" subjects) and the rest in the non-TRT group ("normal" subjects + occult cases). The TRT effect over the whole follow-up time is not significant in our study, and this is possibly because the TRT effect on occult cases ("adverse", making them clinical detectable) cancels out the TRT effect on "normal" individuals (beneficial). In any case, failing to consider occult cases may obscure the true effect of TRT on PCa.

Our findings also suggested that different lengths of study period in longitudinal studies may lead to different conclusions about TRT effects on risk of PCa, which may account for some inconsistent results from previous studies. If the study population was a mixture of subjects physically free of PCa and those with false negative screening test results, we might get a positive association between TRT and PCa incidence when the follow-up period is relatively short, because occult cases might be activated by increases in T and emerge quickly in the treatment group, whereas those in the non-TRT have not got sufficient time to become clinically

detectable cases. Eisenberg and colleagues [16] conducted a study to determine the role of T therapy in PCa risk and found no change in PCa risk for males aged > 40 years; however, Kaplan–Meier survival curves showed that within 7.5 years of follow-up, the probability of developing PCa was significantly higher in T therapy group, whereas beyond 7.5 years, the probability of developing PCa was much lower in the T therapy group, indicating changing of TRT effect on PCa during the follow-up period, which is consistent with our findings. In a 3-year study investigating T Therapy and PCa risk ($n = 70$, hypogonadal males, normal PSA at baseline), Amory et al. [17] found that 3 cases in the treatment group as compared to 1 case in the placebo group; a 3-month study ($n = 406$, hypogonadal males, normal PSA at baseline) [18, 19] investigating the T therapy effect on body composition and sexual function found 2 PCa cases in the treatment group vs 0 cases in the placebo group; both of the two studies observed a higher risk of PCa following T therapy among PSA normal (< 4 ng/mL) hypogonadal males during fairly short follow-up period. We might also find that studies with a short study period observed fewer PCa cases [20] in the T therapy group, or no statistical difference of PCa cases between treatment and placebo groups; it probably depends on the distribution of occult cases in the two comparison groups.

As a large population screening technique, PSA testing has been widely used to identify clinically significant PCa cases [21]. Since 1990s when PSA was first introduced, the sensitivity of PSA testing has improved up to 80% at cut-off of 4 ng/mL [22], yet still almost 20% cancer cases are missed because of a false negative screening test result, and this is more likely to occur among males with low T levels, because the androgen sensitivity of PCa may cause men with low T to have falsely normal PSA levels [8, 23]. Thus, PSA test without concurrent testing of T levels may limit the use of PSA test in cancer diagnosis, especially among males with depressed T levels [15]. In our study population, all participants in the treatment group had baseline PSA levels < 4 ng/mL; therefore, there was no indication of biopsy if other physical and imaging exams also showed negative test results. However, we could not be sure if there had been carcinogenesis going on; a more sensitive biomarker in conjunction with PSA testing method without compromising the specificity would be necessary to provide more precise treatment guidance for clinicians and reduce possible adverse outcomes due to misdiagnosis.

Our study was the first to examine the effect of TRT on risk of PCa with taking into account the occult PCa cases among PCa "free" hypogonadal males. However, limitations should be noted. First, the study subjects were limited to a European population and those with hypogonadism, which may weaken the external validity of this study. At this time, our observations can only be applied to European males with testosterone levels ≤ 12.1 nmol/L (~ 350 ng/dL). Future studies concerning study population with different characteristics and with no specific inclusion criterion are needed to further verify our study findings. Second, the latency period choice of this study was arbitrary. It was based on our speculation that cases occurring shortly after study begun in the treatment group were most likely occult cases that were "activated" by TRT administration. It is possible that the true latency period is longer than what we proposed. However, the longer the period we select as the latency period, the harder it would be to tell whether the cases are TRT- "activated" occult cases or just naturally occurring "normal" cases. We assumed 12–24 months are relatively short time periods and cases emerging during this period were less likely to be naturally occurring cases. Besides, the Kaplan–Meier curves suggested the effect changing point was within 36 months (crossing point), which indicated the choice of 1–2 years was reasonable. Third, some of the baseline characteristics between the two groups were different, making confounding a potential issue. However, we applied PSM to balance the distribution of each baseline characteristics between the two groups, and made sure the treatment group and the propensity score matched untreated group were overall comparable in the analyses. A previous study using the same source of data also applied PSM, which revealed no differences between the total group of patients in the registry and the propensity score matched group [24]. This statistical technique has been widely used in observational studies [25].

Conclusions

It is important to recognize that inclusion of potential occult PCa cases may distort the effects of TRT on risk of PCa. PSA test without concurrent testing of T levels may limit the use of PSA test in cancer diagnosis, especially among men with depressed T levels. PCa screening should not be neglected in hypogonadal men; T measurements at regular intervals should become part of the routine examination in middle-aged and elderly men. Without knowing the presence of clinically occult PCa cases, the patient should be adequately counseled for possible consequences following TRT. PCa screening at early stage (12–24 months) of treatment is crucial; improved screening techniques are needed to detect early-stage PCa during "latency period". Last but not least, future formal studies are required to confirm the hypothesis generated from this study.

Author contribution XZ: project development, manuscript writing. YZ: project development, data analysis. FS: manuscript editing. KH: data collection and management. AH: data collection and management. XX: project development, manuscript editing.

Compliance with ethical standards

Conflict of interest Dr. Farid Saad has a financial relationship with Bayer AG.

Animal and human participants The project involved human subjects. All human subjects provided written informed consent with guarantee of confidentiality. IRB approved the study protocol.

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