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ORIGINAL ARTICLE

The risk of fragility fractures in men with prostate cancer treated with androgen deprivation therapy

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Abstract

Summary Androgen Deprivation Therapy (ADT) increases long-term fracture risk in prostate cancer. Our study showed a higher fracture risk within six months of ADT use, and current use was associated with a higher risk of fragility fractures. Attention is needed for the prevention of fragility fractures at the start of ADT.

Purpose Androgen Deprivation Therapy (ADT) is known to increase long-term fracture risk in men with prostate cancer (PCa), although the risk of fragility fractures remains unclear. This study aims to evaluate the risk of fragility and malignancy-related fractures in men with PCa treated with ADT.

Methods We conducted a retrospective cohort study of men with PCa. Follow-up time was divided into 30-day intervals and exposure (current, past, or no-ADT use). Current ADT use was stratified by duration of ADT use (≤182 days, 183–730 days, and > 730 days). Cause-specific Cox proportional hazard models were used to estimate the risk of fractures.

Results We included 471 patients (mean age 70.5 (±8.3) years). The mean follow-up time was 5.0 (±1.7) years in patients who never started ADT, 3.4 (±2.3) years and 4.1 (±2.0) years in patients who started ADT at baseline and during follow-up, respectively. In total, 60 patients had a fracture, 48 (80%) fragility, and 12 (20%) malignancy-related fractures. Current ADT use was associated with a higher risk of all fractures (HR 5.10, 95% CI 2.34–11.13) and fragility fractures (HR 3.61, 95% CI 1.57–8.30). The association with malignancy-related fractures could not be studied due to no events during no-ADT use. There was an increased risk of all fractures with longer duration of ADT use.

Conclusions Current ADT use was associated with a higher risk of fragility fractures than no-ADT use. A higher fracture risk was observed within the first six months of ADT use and persisted for longer durations.

Keywords Androgen Deprivation Therapy · Malignancy · Prostate cancer

Introduction

Worldwide, prostate cancer (PCa) is the most diagnosed malignancy among men [1]. In The Netherlands, about 12,000 patients are diagnosed with PCa annually [2], with approximately 90% of cases occurring in patients over the age of 60 and 30% in those aged over 75 [2]. The advancements in diagnosis and treatment have made a significant contribution to the increased 10-year survival rate up to 95% in men with localized PCa and 70% in men over 75 [3]. Androgen Deprivation Therapy (ADT) plays a considerable part in this improved survival [4]. ADT is administered to approximately one in two PCa patients at some point during their disease progression, either as (neo)adjuvant curative therapy in conjunction with radiotherapy for low or intermediate risk PCa, or as long-term management for advanced metastatic disease [5, 6]. While ADT has been proven to benefit survival rates, compelling evidence indicates that it also elevates the risk of long-term fractures [7–11], particularly in men who receive ADT as long term-treatment, but also in men who received ADT combined with radiotherapy [8]. It has been estimated that ADT is associated with a 0.6 to 4.6% reduction in bone mineral density (BMD), especially during the first year of therapy [12, 13], leading to a low BMD increasing the risk for the development of fragility fractures that are associated with an increased morbidity and mortality [14–16]. In addition to the approximately 20–25% of PCa patients that sustain malignancy-related fractures during the course of their disease [17]. Patients with PCa live with their disease for many years, and long-term consequences

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such as fragility fracture risk are an important consideration in ADT treatment. Consequently, current national and international guidelines recommend prevention of fragility fractures [18–21]. However, these current guidelines vary and lack detailed recommendations for managing fracture prevention in men starting or receiving ADT [22]. Nonetheless, the association between ADT and fracture risk has been consistently established, mainly in prescription-claims databases and national registries that have suggested that ADT is associated with a 1.5-fold increased risk of fragility fracture [10, 23, 24]. However, these studies do not include the effect of duration and exposure to ADT on fracture risk. A review on fracture risk [25] also describes an increased risk of fractures in men receiving ADT (OR 1.39; 95% CI, 1.26–1.52), positively correlated with the duration of ADT. However, heterogeneity in included population, treatment indications and disease stages potentially contribute to a variation in outcomes. Additionally, fracture risk in men on ADT can be confounded by pathologic fractures impairing the translation of the findings into the daily practice of fracture prevention.

This study aims to evaluate the risk of fragility and malignancy-related fractures in men with PCa treated with ADT compared to those not treated with ADT and the effect of duration and exposure to ADT on fracture risk in men with PCa treated with ADT. By exploring this aspect, we aim to provide further insights into the fracture risk associated with ADT and its implications for patient care and management.

Patients and methods

We conducted a retrospective cohort study in men diagnosed with PCa between 1 November 2014 and 31 December 2019. Data was extracted from the electronic health records of all patients diagnosed with PCa in VieCuri Medical Centre. The diagnosis of PCa was based on pathology reports and/or radiological confirmation. Data on fractures was collected until 31 May 2022. We excluded patients with a diagnosis > inclusion date ($n = 34$), with administrational error in coding of diagnosis ($n = 21$) and with missing/incomplete files ($n = 15$). Additionally, regarding treatment, we excluded patients on anti-androgen mono therapy ($n = 5$) and patients who were diagnosed or referred for treatment elsewhere ($n = 34$). After exclusion, data of 471 patients were included in this study. All included patients were followed from PCa diagnosis date until death, end of study, or a fracture, whichever came first. Patient, tumor, treatment, and fracture characteristics and date of death were retrieved from medical records. Date of PCa diagnosis was defined as date of pathological or radiological diagnosis. The stage of PCa at diagnosis was based on the TNM staging system and stratified as localized (T1-2/M0), locally advanced (T3-4/Nx-1/M0), advanced (M +) or unknown. This study was approved by the medical research ethics committee Academic Hospital Maastricht/University Maastricht (METC 2019–1266).

Definition of exposure

Use of ADT was determined using prescription data from the electronic health records. ADT use was defined as ≥ 1 dose GnRH-agonist monotherapy (gosereline, leuproreline) or in combination therapy with anti-androgens (bicalutamide, enzalutamide) at baseline (date of diagnosis) or during follow up. Exposure to ADT was defined in a time-dependent manner. Follow-up time was divided into 30-day intervals, and exposure (current, past, or no-ADT use) was determined at each interval based on prescription data. When there was an ongoing prescription at the start of an interval, an interval was classified as current ADT use. When ADT treatment was discontinued before the start of an interval, the interval was classified as past ADT use. When there were no ADT prescriptions before the start of an interval, it was classified as no-ADT use. Current ADT use was further stratified by duration of ADT use, which was determined at each interval, and which was defined as time since first ADT prescription (≤ 182 days, 183–730 days, and > 730 days). These intervals are derived from the Dutch PCa treatment guidelines [26], where ADT treatment is prescribed for 6-month neoadjuvant to radiation therapy, 2-year adjuvant to radiation therapy, or continuous ADT treatment in advanced disease stages.

Fractures

All fractures were verified by evaluation of X-ray reports and were recorded by type and date. In order to differentiate between fractures caused by malignancy and fragility fractures, as defined by Palmer et al. [26], all fractures were thoroughly examined. When a fracture was mentioned in the radiology reports, we conducted a detailed comparison of the fracture location with any known or newly discovered pathological lesions from CT or MR images, when available. This enabled us to ascertain whether the fracture occurred at the site due to a neoplasm, including metastasis. Moreover, we verified whether the fracture was treated as a "malignancy-related" fracture through orthopedic surgery or radiotherapy. "All fractures" is used when describing patients with a fracture regardless of their origin. Previous fractures were defined as fractures that had occurred before the date of PCa diagnosis.

Statistical analysis

Age and follow-up in years were presented as means and standard deviations (SD) and PSA as median and inter quartile range (IQR). A time-dependent exposure definition was

used in which follow-uptime was split into intervals, which were classified as either ADT current, past, or never exposed. This allowed patients to contribute person-time to different exposure groups. Current use was further stratified by duration of ADT treatment (≤ 182, 183–730, and > 730 days). As a sensitivity analysis, we used another stratification of the duration of ADT treatment (≤ 182, 183–365, 366–730, and > 730 days). As a second sensitivity analysis, we additionally adjusted for the current use of anti-osteoporosis medication.

Cause-specific Cox proportional hazard models were used to estimate the risk of all fractures, the risk of fragility fractures and malignancy-related fractures separately, and the risk of mortality with current use of ADT vs. no-ADT use. All analyses were adjusted for age and stage of disease. All analyses were performed using SAS (SAS version 9.4 (SAS Institute, Cary, NC, USA)).

Results

We included 471 patients with PCa. In total, 227 patients received ADT treatment at diagnosis or during follow-up, while 244 patients were not treated with ADT (Fig. 1). The mean age of ADT users at baseline was 73.6 (± 9.8) years and 73.8 (± 8.4) years for those starting ADT during follow-up and in no-ADT users 67.5 (± 6.6) years. The mean follow-up time was 3.4 (± 2.3) years for patients receiving ADT at baseline, 4.1 (± 2.0) years in patients who started ADT during follow-up, and 5.0 (± 1.7) years in patients who never started ADT. ADT users had a more advanced stage of the disease at diagnosis and a higher Gleason/ISUP score. The proportion of patients who deceased during follow-up was 52.6% in patients who started with ADT at baseline, 27.5% in patients in whom ADT was initiated at some point during follow-up, and 6.6% in patients with no ADT-use (Table 1).

In total, 60 fractures were observed in 60 patients (all fractures), of these 48 (80%) had a fragility fracture and 12 (20%) a malignancy-related fracture. Overall, during (current and past) ADT use 30 patients with a fragility fracture and 12 with a malignancy-related fracture were observed, and 18 and 0 in the no-ADT users, respectively. Most patients sustained a clinical vertebral fracture (17 fragility and 7 malignancy-related fractures) or rib fractures (8 fragility fractures and 3 malignancy-related fractures) (Fig. 2).

As shown in Table 2, ADT use was associated with a higher risk of all fractures (HR 2.94, 95% CI 1.46–5.93) compared to no-ADT use. When stratified by recency of ADT use, current use was associated with a higher fracture risk (HR 5.10, 95% CI 2.34–11.13), while past ADT use was not (HR 1.63, 95% CI 0.67–3.99). All categories of ADT duration were significantly associated with a higher risk of all fractures ((HR 5.61, 95% CI 1.94–16.20) in ≤ 182 days (HR 4.76, 95% CI 1.92–11.81) in 183–730 days and (HR 5.18, 95% CI 2.06–13.03) in > 730 days of exposure), compared to no-ADT use. ADT use was associated with a higher mortality risk (HR 2.51, 95% CI 1.25–5.02) compared to no-ADT use. When stratified by recency, only past use was associated with a higher risk of mortality (HR 3.75, 95% CI 1.87–7.51), but there was no significant association between current ADT use and any of the duration categories and mortality risk.

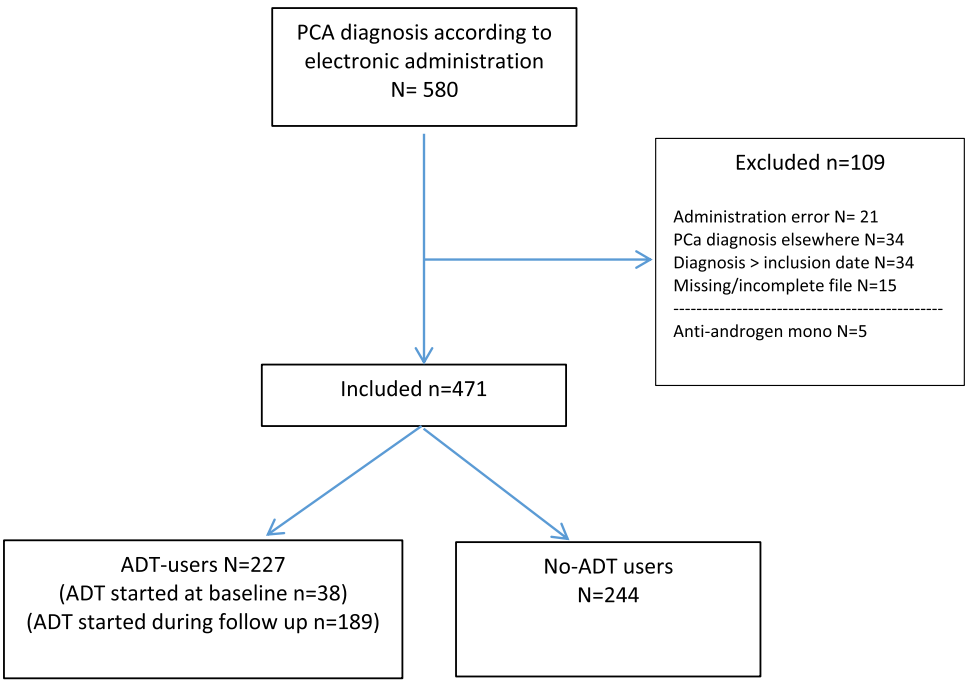

Fig. 1 Selection procedure of patients with prostate cancer with and without treatment with Androgen Deprivation Therapy

Table 1 Baseline characteristics at prostate cancer diagnosis

	ADT users $N=227$				No-ADT users $N=244$	
	ADT use start at baseline* $N=38$		ADT use during follow up# $N=189$			
Age (mean, SD)	73.6	9.8	73.8	8.4	67.5	6.6
Previous fractures (N, %)$						
- No fracture	5	13.2	32	16.9	31	12.7
- 1 fracture	31	81.6	148	78.3	205	84.0
≥ 1 fracture	2	5.3	9	4.8	8	3.3
Gleason/ISUP score						
- ≤ 6/1	0	0	9	4.8	158	64.8
- 3 + 4 = 7/2	1	2.6	22	11.6	43	17.6
- 4 + 3 = 7/3	1	2.6	20	10.6	18	7.4
- 8/4	6	15.8	46	24.3	13	5.3
- 9–10/5	24	63.2	79	41.8	11	4.5
- Unknown	6	15.8	13	6.9	1	0.4
PSA (median, IQR)	306.5	134.0–904.0	26.0	11.5–67.5	7.9	5.7–11.0
Risk stage						
- T1-2, M0	1	2.6	65	34.4	218	89.3
- T3-Nx1, M0	14	36.8	82	43.4	21	8.6
- M1	23	60.5	39	20.6		
- Unknown	0		3	1.6	5	2.0
Follow-up in years (mean, SD)	3.4	2.3	4.1	2.0	5.0	1.7
Mortality (N, SD)	20	52.6	52	27.5	16	6.6
Current use of anti-osteoporosis treatment	7	18.4	3	1.6	2	0.8

ADT Androgen Deprivation Therapy, *ISUP* International Society of Urological Pathology, *PSA* prostate-specific antigen, *T,N,M* tumor, nodes, metastases

*Based on at least 1 current ADT use at time of PCa diagnosis

#Based on at least 1 current ADT use period during follow-up

$Before PCa diagnosis

^When there was an ongoing prescription at the start of an interval, an interval was classified as current ADT use. When ADT treatment was discontinued before the start of an interval, the interval was classified as past ADT use. When there were no ADT prescriptions before the start of an interval, it was classified as no-ADT use.

As shown in Table 3, current ADT use was associated with an increased risk of fragility fracture in (HR 3.61, 95% CI 1.57–8.30), compared to no-ADT use, and past ADT use was not. All categories of ADT duration were significantly associated with a higher risk of fragility fractures (HR 4.17, 95% CI 1.29–13.49 in ≤ 182 days; HR 3.04, 95% CI 1.10–8.40 in 183–730 days; and HR 3.93, 95% CI 1.42–10.87 in > 730 days of exposure), compared to no-ADT use. Only past ADT use was associated with a higher mortality risk (HR 3.76, 95% CI 1.88–7.51) compared to no-ADT use. When stratified by duration, ADT use was not associated with a higher risk of mortality in any of the ADT duration categories.

The association between malignancy-related fractures and ADT stratified by recency and duration could not be studied because there were no patients that sustained a malignancy-related fracture in the no-ADT use group.

The sensitivity analysis in which we studied four different groups of duration of ADT showed similar results as the original stratification into three groups (Supplemental Table 1). Additional adjustment for current use of anti-osteoporotic medication did not significantly alter the results.

Discussion

This study demonstrates that the risk of sustaining a fragility fracture is almost 4 times higher in patients that started with ADT treatment following PCa diagnosis, and the risk is already higher within the first 6 months of ADT use. Furthermore, this study showed that the risk of sustaining any fracture (both fragility and malignancy-related) is fivefold

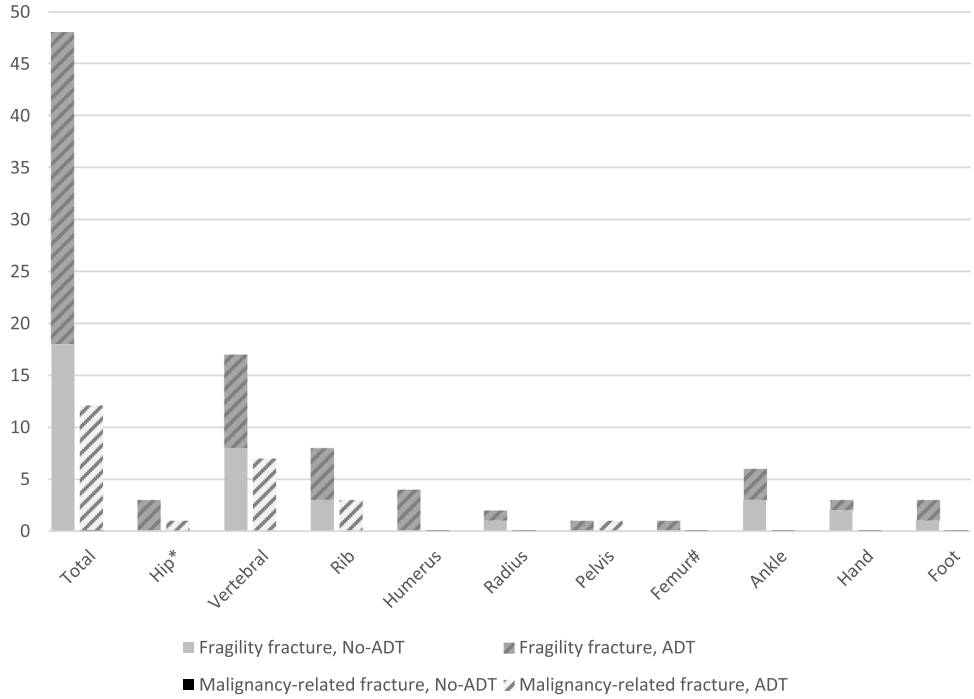

Fig. 2 Malignancy-related fractures and fragility fractures in ADT and no-ADT users. *Intertrochanteric, subtrochanteric, and femoral neck. #Femoral shaft fractures. Of 471 included met with PCa, a total of 60 (12.7%) fractures were observed, 48 (10.2%) fragility fractures, and 12 (2.6%) malignancy-related fractures

Table 2 Association of ADT use (by recency and duration) with the risk of all fractures and mortality

			Unadjusted	Adjusted for age	Adjusted for age + risk classification
	Fractures (N = 60)*	*Incidence rate/1000PY*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*
No-ADT use	18	14.3	Ref	Ref	Ref
ADT use	42	48.6	3.46 (1.99–6.02)	3.22 (1.79–5.80)	2.94 (1.46–5.93)
By recency					
Past use	8	23.0	1.49 (0.65–3.46)	1.40 (0.59–3.32)	1.63 (0.67–3.99)
Current use	34	65.9	5.09 (2.84–9.12)	4.76 (2.57–8.82)	5.10 (2.34–11.13)
By duration					
≤ 182 days	7	66.6	5.63 (2.15–14.75)	5.18 (1.92–13.99)	5.61 (1.94–16.20)
183–730 days	13	56.2	4.68 (2.17–10.07)	4.35 (1.96–9.65)	4.76 (1.92–11.81)
> 730 days	14	78.1	5.23 (2.56–10.67)	4.94 (2.37–10.30)	5.18 (2.06–13.03)
	Mortality (N = 88)	*Incidence rate*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*
No-ADT use	16	12.7	Ref	Ref	Ref
ADT use	72	83.3	6.51 (3.79–11.19)	5.00 (2.82–8.88)	2.51 (1.25–5.02)
By recency^					
Past use	35	100.4	8.19 (4.49–14.94)	6.35 (3.39–11.88)	3.75 (1.87–7.51)
Current use	37	71.7	5.42 (3.00–9.81)	4.08 (2.18–7.63)	1.25 (0.57–2.74)
By duration					
≤ 182 days	8	76.1	4.84 (1.98–11.88)	3.49 (1.39–8.76)	1.24 (0.45–3.42)
183–730 days	14	60.5	4.28 (2.05–8.94)	3.16 (1.47–6.79)	1.10 (0.45–2.66)
> 730 days	15	83.7	7.22 (3.51–14.86)	5.63 (2.67–11.86)	1.47 (0.59–3.67)

ADT Androgen Deprivation Therapy, *PY* person years, *n* number

*All fractures, including 12 malignancy-related fractures (exclusively in ADT-users)

Table 3 Association of ADT use (by recency and duration) with the risk of fragility fractures and mortality

			Unadjusted	Adjusted for age	Adjusted for age + risk classification
	Fragility fractures (N = 48)	*Incidence rate/1000PY*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*
No-ADT use	18	14.3	Ref	Ref	Ref
ADT use	30	34.1	2.45 (1.36–4.39)	2.03 (1.08–3.82)	2.27 (1.08–4.75)
ADT use by recency*					
Past use	8	22.5	1.48 (0.64–3.44)	1.25 (0.52–2.98)	1.43 (0.57–3.56)
Current use	22	42.1	3.22 (1.71–6.07)	2.68 (1.35–5.29)	3.61 (1.57–8.30)
By duration					
0–182 days	5	47.4	4.15 (1.40–12.26)	3.32 (1.08–10.17)	4.17 (1.29–13.49)
183–730 days	8	34.2	2.84 (1.18–6.86)	2.32 (0.93–5.82)	3.04 (1.10–8.40)
> 730 days	9	48.9	3.23 (1.43–7.30)	2.76 (1.18–6.421)	3.93 (1.42–10.87)
	Mortality (N = 95)	*Incidence rate*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*
No-ADT use	16	12.7	Ref	Ref	Ref
ADT use	79	89.8	7.01 (4.09–12.00)	5.59 (3.18–9.85)	2.75 (1.39–5.46)
ADT use by recency					
Past use	35	98.2	7.93 (4.35–14.45)	6.39 (3.43–11.90)	3.76 (1.88–7.51)
Current use	44	84.1	6.39 (3.59–11.40)	5.04 (2.75–9.25)	1.67 (0.78–3.56)
By duration					
0–182 days	9	86.3	5.45 (2.30–12.90)	4.08 (1.68–9.89)	1.58 (0.59–4.20)
183–730 days	16	68.5	4.78 (2.35–9.74)	3.70 (1.77–7.72)	1.39 (0.59–3.27)
> 730 days	19	103.3	8.97 (4.43–17.73)	7.30 (3.62–14.73)	2.10 (0.88–4.99)

ADT Androgen Deprivation Therapy, *PY* person years, *n* number

*When there was an ongoing prescription at the start of an interval, an interval was classified as current ADT use. When ADT treatment was discontinued before the start of an interval, the interval was classified as past ADT use. When there were no ADT prescriptions before the start of an interval, it was classified as no-ADT use

in patients that started with ADT treatment. Our findings regarding the overall fracture risk are in line with those reported in several epidemiological studies that showed an association between ADT and an increased fracture risk. A recently published meta-analysis of 16 studies with a total population of 519,168 men with PCa by Wu et al. [25] also showed that ADT use was associated with an increased fracture risk (OR 1.39; 95% CI 1.26–1.52). The primary outcome in this study was "any fracture" and included studies with fragility fractures as well as malignancy-related fractures but the authors did not perform stratified analyses for fragility fractures and malignancy-related fractures respectively. The authors concluded that although ADT is associated with an increased risk of any fracture and the risk is positively correlated with the duration of ADT, heterogeneity in study populations (e.g., age, disease stage, and treatment duration) contribute to outcomes with low to moderate certainty of evidence [25].

As in our study, a large Swedish registry study by Wallander et al. [10] reported an increased risk of fragility fractures of (HR 1.40, 95% CI 1.28–1.53) in men treated with ADT compared to PCa patients without ADT and patients without PCa. However, the men treated with ADT included in this study were older compared to our study (82 years ± 7.0 vs 70.5 ± 8.3), and this study reported a statistical interaction between age and risk of fracture. In comparison to these previous studies, our results distinguish between malignancy-related and fragility fractures by manually reviewing all radiology reports, additionally, our analyses were adjusted for age and stage of disease. According to our results, the patients with PCa on ADT treatment represent a group with a high risk of fractures, especially fragility fractures (HR 3.62, 95% CI 1.57–8.32). This was also found by Lee et al. [11] with a comparable design and approach to our study, involving 741 Chinese PCa patients. They found that ADT was significantly associated with risk of fragility fractures (HR 3.60, 95% CI 1.41–9.23) [11] which is very similar to the findings in our study. The findings in these previous studies and in our study emphasize that although there are geographical variations in peak bone mass and skeletal geometry, as well as lifestyle and environmental factors associated with fracture risk, ADT use is associated with an increased fracture risk of fragility fractures among patients with divers ethnologically characteristics.

Regarding ADT exposure, Shahinian et al. [7] showed a dose-dependent increase of the risk (RR 1.45, 95% CI 1.36

to 1.56) of any fracture during the first year of PCa with an administration of > 9 doses of ADT. Wu et al. [25] found an increased risk of "any fracture" with increased dosages in their analyses, with ORs of 1.08 in low, 1.20 in medium, and 1.54 in high dosage. However, no sensitivity analysis could be conducted for this stratification because the included studies were adjusted for more than 4 factors. Moreover, in our study we also found an increased risk of all fractures and especially of fragility fractures in men treated with ADT even when exposed less than 6 months. We believe that a possible explanation for this observation, which is not in line with the studies by Shahinian et al. [7] and Wu et al. [25], could possibly be explained by the different inclusion criteria and methods used in those studies as compared to the present study. Wu et al. [25] and Shahinian et al. [7] only included patients who survived the first 5 years after the prostate cancer diagnosis, and did not suffer from a fracture during the first 12 months. Furthermore, they performed a time-fixed analysis which was stratified by the total received ADT doses within the first year after diagnosis. This finding, however, emphasizes that preventive strategies have to be implemented at the time of ADT treatment initiation, even in patients who receive short-term (neo) adjuvant curative treatment in conjunction with radiotherapy.

This study has several strengths and limitations. We used real-world data including longitudinal information on ADT prescription as well as radiographically confirmed fractures. Further with respect to the fractures, we were able to distinguish malignancy-related fractures from fragility fractures. Additionally, by initiating follow-up from the point of diagnosis and treatment, which enabled the timely observation of fracture risk. The limitations of our study are the single-center observational design with a relatively small sample size and number of events (fractures). Due to the finding that there were no patients that sustained a malignancy-related fracture in the no-ADT users, the association between ADT stratified by recency and duration and malignancy-related fractures could not be studied. Furthermore, due to the nature of our data collection, which is based on real-world data, we were unable to present a comprehensive analysis on body mass index or comorbidities associated with fracture risk because we only had partial information at baseline or during follow up. Nonetheless, our study found a higher risk of fragility fractures that are significant risks to the PCa patient, as these fractures have been proven to have a major impact of their mortality risk and quality of life [8, 27]. In many patients with PCa, there is anxiety around treatment and fear of complications and disease progression [28]. In those who are at high risk of fractures, improving preventive strategies are important to optimally benefit from ADT. In general, the overall survival of men with PCa on ADT should be aimed for without compromising quality of life due to fractures, with a timely start of preventive strategies. However, fracture prevention in PCa patients on ADT is not well implemented; there are low rates of diagnostic testing, low rates of education and diet and lifestyle guidance, and low rates of pharmacological management to reduce fracture risk [29]. Actively and systematically screened and treated PCa patients on ADT had a 72% lower hip fracture rate compared to a non-screened control group [30]. A known highly effective approach for systematically screening fracture risk in patients is through Fracture Liaison Services (FLS). FLSs have demonstrated a reduction in both subsequent fractures and mortality according to Vranken et al. [31]. Moreover, the professionals engaged in FLSs have extensive expertise and experience in fracture prevention which could potentially be applied to prevent fragility fractures in patients with PCa on ADT thereby offering the opportunity to improve patient care.

Conclusion

In men with prostate cancer, current ADT use was associated with a higher risk of fragility fractures than no-ADT use. A higher fracture risk was observed within the first six months of ADT use and persisted for longer durations. Therefore, attention is needed for the prevention of fragility fractures at the start of ADT.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-024-07180-8.

Declarations

Conflicts of interest None.

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