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Present Situation of Bone Health Care for Prostate Cancer Patients on Androgen Deprivation Therapy

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Abstract

Background: Prostate cancer is a common malignant tumor in men in China. This study is done in south of china. We talk about present situation of bone health care for prostate cancer patients on androgen deprivation therapy because many study shown how clinicians do not make attention to this side effect (osteoporosis) of androgen deprivation therapy.

Objective: In our study, we want to be sure if physicians they wondering about the bone health care from the prostate cancer patient on ADT.

Methodology: Administration of Questionnaire. The data collected from individuals, clinicians during annual urological conference meetings, during the period from 2018 to 2020. We wrote down our questionnaires on the papers and gave it to clinicians.

Result: In our study from 508 Doctors we found that, each year they have seen many patients with prostate cancer 77%, then 55% use ADT to treat prostate cancer; 56% did not ask patients to complete bone density test, 54% did not ask patients to complete fracture risk assessment; and 63% of them did not put patients in bisphosphonates. Most of them 54% prescribed (put) patients in vitamin D supplementation, 57% in calcium.

Conclusion: Androgen Deprivation Therapy (ADT) is a mainstay of Prostate cancer treatment but also increases the risk of osteoporosis and fracture on prostate cancer patients. Most of clinicians are not screening the patient's bone mineral density test, and do not put patients on bisphosphonate, underestimate the risks of osteoporosis and fractures on prostate cancer patients on ADT. We must change guidelines of AUA, EAU, CUA have not claimed any requirement details on controlling bone complications of prostate cancer patients receiving ADT, more strict requirements to clinicians on urological disease guidelines about bone health control for prostate cancer patients receiving ADT.

Keywords: ADT; Bone health prostate cancer; Androgen deprivation therapy

Acronyms & Abbreviations

ADT: Androgen Deprivation Therapy; AUA: American Urology Association; BPH: Benign Prostatic Hyperplasia; CAB: Combined Androgen Blockade; CUA: China Urology Association; D: Day; DUX: Dual-energy X-ray Absorptiometry; DRE: Digital Rectal Examination; DTH: Dihydrotestosterone; EAU: European Association of Urology; FDA: Food and Drug Administration of the United States; FRAX: Fracture Risk Assessment Form; HGPIN: High-Grade Prostatic Intraepithelial Neoplasia; IGF-3: Insulin-Like Growth factor-3; IU: International Unit; LUTS: Lower Urinary Tract Symptoms; MRI: Magnetic Resonance Imaging; NCCN: The National Cancer Network; NOF: National Osteoporosis Foundation; OR: Odds Ratio; PC: Prostate Cancer; PCPT: The Prostate Cancer Prevention Trial; PSA: Prostate Specific Antigen; PSADT: Prostate Specific Antigen Doubling Time; TAB: Triple Androgen Blockade; TNM: Tumor Nodes Malignancy; UK: United Kingdom; 5AR: 5-A-Reductase

Introduction

Prostate cancer is a common malignant tumor in men in China. This study is done in south of china. Androgen Deprivation Therapy (ADT) is a mainstay of Prostate cancer treatment and has shown in randomized trials to improve overall survival for intermediate and high risk localized disease, as well as locally advanced and metastatic diseases [1,2].

We talk about present situation of bone health care for prostate cancer patients on androgen

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deprivation therapy because many study shown how Clinicians do not make attention to this side effect (osteoporosis) of Androgen deprivation therapy. The incidence of osteoporosis in the general population of the United States is about 12% [3]. After four years of ADT treatment, about 50% of patients will develop osteoporosis. After eight years of treatment, the incidence of osteoporosis is higher than 80% [4]. Some prospective studies have found that Bone Mineral Density (BMD) decreases by about 5% to 10% a year after ADT treatment [5]. During subsequent ADT treatment, bone mineral density will still be lost at a rate of 2% to 4.5% per year, which is significantly higher than the rate of physiological loss of about 0.5% to 1% per year in the general population [6].

A study in New Mexico in 2012 found that only about 13% of the subjects had baseline BMD tests, 21% had preventive treatment with bisphosphonates, and 16% and 10% had supplements of calcium or vitamin D [7]. In our study, we want to be sure if physicians in south of china are wondering about the bone health care from the prostate cancer patient on ADT.

Methodology of the Study

Administration of Questionnaire: The Data collected from individuals, clinicians during annual urological conference meetings. During the period from 2016 to 2018. We wrote down our questionnaires on the papers and gave it to clinicians.

Results

After doing questionnaire request to 508 physicians, we find these:

The total number of Clinicians was 508 (Figures 1-3 & Table 1).

A= (1) B= (2) C= (3)

Discussion

ADT is the mainstay treatment for prostate cancer but can also negatively affect bone, metabolic, cardiovascular, sexual and cognitive health, fatigue and vasomotor flushing [8].

In males, besides the increase of bone cortex more than in females, the rate of bone loss is also slower with the increase of age. However, after 40 years of age, the total skeletal muscle of both sexes gradually decreased, and was replaced by adipose tissue. The annual loss rate of bone mineral density was 0.5% to 1.0% [9-11]. Studies have shown that the decrease of plasma free testosterone levels with biochemical activity is associated with the decrease of total bone mass in men aged 50 to 100 years [11]. Other risk factors for osteoporosis include alcohol abuse, diabetes, vitamin deficiency, long-term use of glucocorticoids, and exercise.

A Brazilian study found that the incidence of osteoporosis was 13.4% among urban people over 40 years old [10].

Some prospective studies have found that Bone Mineral Density (BMD) decreases by about 5% to 10% a year after ADT treatment [5]. During subsequent ADT treatment, bone mineral density will still be lost at a rate of 2% to 4.5% per year, which is significantly higher than the rate of physiological loss of about 0.5% to 1% per year in the general population [6]. The incidence of osteoporosis in the general population of the United States is about 12%. After four years of ADT treatment, about 50% of patients will develop osteoporosis. After eight years of treatment, the incidence of osteoporosis is higher than 80% [4]. In two studies based on SEER data, one study pointed out that ADT treatment increased the risk of fracture by 21% [12], and another study for more than 50,000 ADT patients found that the risk of fracture after 5 years of ADT treatment was 19.4%, and the risk of fracture increased significantly with the prolongation of treatment time [13].

Fracture patients need more intensive treatment, more care and

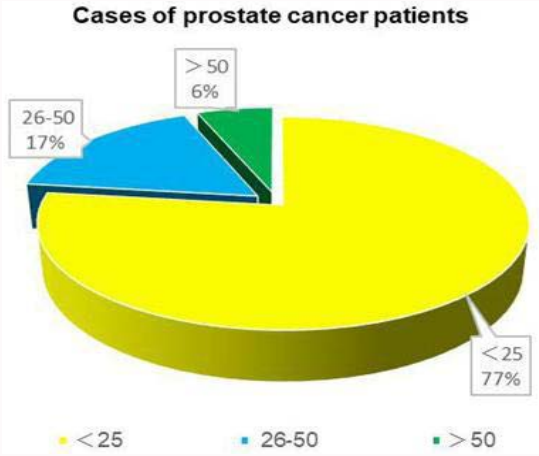

Figure 1: Prostate cancer patients seen by doctors each year.

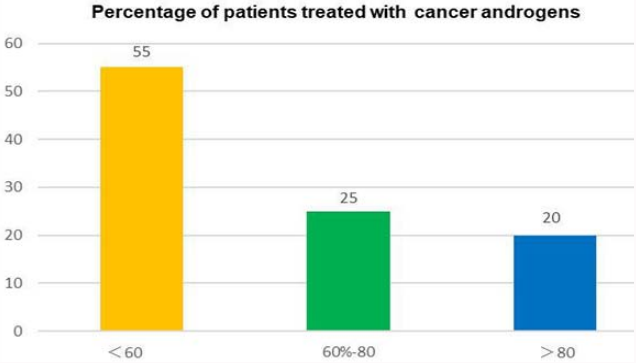

Figure 2: Percentage of patients treated with ADT.

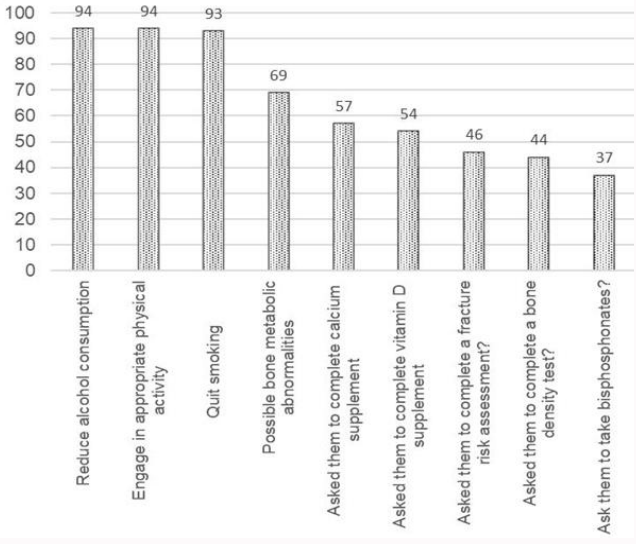

Figure 3: Resume from question 1-9.

Table 1: (From question 3 to 9) Percentage of prostate encourage patients to quit smoking reduce alcohol consumption doing physical activity, to possible bone metabolic abnormalities, supplement on vitamin D, calcium, bisphosphonates, bone density test, asked them to complete a fracture risk assessment.

Doctor's Ask	n	%	*p*
Quit smoking			
Yes	471	93	0.0001
No	37	7	
Engage in appropriate physical activity			
Yes	476	94	0.0001
No	32	6	
Possible bone metabolic abnormalities			
Yes	349	69	0.001
No	159	31	
Asked them to complete vitamin D supplement			
Yes	274	54	0.07
No	234	46	
Asked them to complete calcium supplement			
Yes	292	57	0.001
No	216	43	
Asked them to complete a bone density test			
Yes	226	44	0.007
No	282	56	
Asked them to complete a fracture risk assessment			
Yes	236	46	0.02
No	272	54	
Ask them to take bisphosphonates			
Yes	186	37	0.001
No	322	63	

rehabilitation assistance. Many patients may no longer be able to move independently. At the same time, the occurrence of fracture in such patients also causes greater social, psychological and economic burden on patients and their families [14]. A British study shows that the cost of treatment for hip fractures is about 12,000 pounds, while the cost of screening, assessing and preventive treatment for osteoporosis and fracture risk is only about 335 pounds a year [15]. In addition, in the United States, the annual cost of treating osteoporosis-related fracture events is about $4.1 billion, and only by raising health concerns, Bone Mineral Density (BMD) monitoring and preventive treatment, can the cost of social health be greatly reduced and the quality of life of patients significantly improved [16].

Bone health examination, prevention and treatment of bone-related events

Osteoporosis and fracture are high-risk adverse consequences of ADT treatment. Many studies suggest that besides baseline bone mineral density measurements and annual periodic bone mineral density reviews before the start of ADT treatment, regular fracture risk assessment should be conducted with WHO Fracture Risk Assessment Form (FRAX) [17-20]. All ADT patients should be supplemented with calcium (1,000 mg/day to 1,200 mg/day) and vitamin D (800 IU/day to 1000 IU/day) through food or medicine. Bisphosphonates can effectively improve the bone mineral density of patients. For patients with osteoporosis or previous history of fracture detected by bone mineral density test, and patients with high risk of fracture assessed by FRAX, they should be used to prevent osteoporosis and fracture [18,20-22].

FRAX fracture risk assessment form defines fracture risk as [18]: Fracture risk within 10 years: Low risk: <10%; medium risk: 10% to 20%; high risk: >20%; or hip fracture risk >3%. Patients receiving ADT should routinely use calcium and vitamin D. Despite the lack of prospective randomized controlled clinical trials on whether supplementation of calcium and vitamin D can improve BMD, a review of 12 clinical controlled studies in 2012 used calcium (500 mg/d to 1000 mg/d) and vitamin D (200 IU/d to 500 IU/d) as control groups to test the protective effects of other drugs on BMD. The review concluded that the above-mentioned calcium and vitamin D can improve BMD. The dosage of Vitamin D is too low to supplement bone loss [23]. The American Osteoporosis Foundation recommends that at least 1,200 mg of calcium and 800 IU to 1000 IU vitamin D should be taken daily from food or drug supplements for all men over 50 years of age. This recommendation should also be a good recommendation for prostate cancer patients undergoing ADT treatment [24].

Bisphosphonates can increase bone mineral density. A 2001 study found that about 3.3% of patients treated with leuprorelin alone had bone loss in the lumbar spine, 2.1% of patients had bone loss in the greater trochanter of the femur and 1.8% of patients had pelvic bone loss. Those treated with leuprorelin plus pamidronate (60 mg, once every 12 weeks) had bone loss. There was no decrease in bone mineral density [25]. A recent study also found that there was no significant osteopenia in ADT patients treated with riser sodium phosphate after 2 years compared with those treated with ADT alone [26]. Another 2003 study also found that zoledronic phosphate and alendronate could protect prostate cancer patients treated with ADT from bone mineral density loss. The experiment gave zoledronic phosphate 4 mg every three months for a year, increasing BMD by 5.6%.

In the blank control group, the average loss of bone mineral density was 2.2% [27]. Two other studies showed that alendronate had similar protective effects on bone mineral density as zoledrophosphate [18,28]. A recent study (2013) found that patients with prostate cancer received 100 mg of calcium daily [29], 400 IU of vitamin D, and 70 mg of alendronate weekly before ADT treatment had a 1.7% increase in spinal bone mineral density compared with those before treatment, while those in the blank control group had a 1.9% decrease in bone mineral density ($p<0.001$). A review of 15 related experimental articles published in 2012 found that bisphosphonates significantly reduced the risk of fracture (RR: 0.80; P=0.005) and the incidence of osteoporosis (RR: 0.39; $P<0.00001$) in a total of 2,634 patients [30].

Selective estrogen receptor modulators raloxifene and toremifene were also used in ADT patients. In a 12-month period of 48 ADT patients, 60 mg of Reynoxifene per day increased the average BMD by 1.1% (+-0.4%) while in the control group, the average BMD decreased by 2.6% (+-0.7%) ($p<0.001$) in ADT patients who were not treated with Reynoxifene [31]. In a phase III clinical trial of ADT treatment for more than 1200 prostate cancer patients, those randomly assigned to the 80 mg termifen group daily had a 50% reduction in the incidence of new spinal fractures after 2 years of treatment compared with the control group (4.9% *vs.* termifen group, 2.5%; $P<0.001$). However, the incidence of thrombosis in the treatment group (2.6%) was higher than that in the control group (1.1%). However, the role of termifen in preventing bone-related events in ADT has not been recognized by

the Food and Drug Administration of the United States (FDA) [32].

Among other possible causes of bone mineral density loss, a study involving prostate cancer patients treated with non-metastatic ADT found that the prevalence of other risk factors for osteoporosis included 49.3% smoking, 3.3% corticosteroid use, 2% hyperthyroidism, 13.3% alcoholism, and 1.2% patients. Previous history of fracture [33].

The National Cancer Network (NCCN) officially recommended ADT patients in 2009 for baseline and subsequent annual bone mineral density measurements; and in 2012, FRAX was recommended for fracture risk assessment [34]. In 2013, the National Osteoporosis Foundation (NOF) updated its guidelines on managing the risk of osteoporosis [27,35]. The new guidelines recommended that all patients over 50 years of age should use a bone mineral Density Analyzer (DXA) to baseline Bone Mineral Density (BMD) before treatment if they need drugs that may lead to bone mineral density reduction [36]. Many literatures believe that proper physical exercise, sunbathing, smoking cessation, reducing alcohol consumption, and supplementation of calcium and vitamin D can reduce but not completely prevent the occurrence of osteoporosis [37-41].

Current status of bone health management in patients undergoing ADT treatment

There is still a deep gap between NCCN and NOF guidelines on the management of bone complications in ADT patients and clinical practice. A large multicenter retrospective study published in 2015 found that 30,846 prostate cancer patients treated with ADT met the research criteria [42]. Among them, those with both baseline bone mineral density measurements and prophylactic treatment with bisphosphate preparations met the research criteria [42]. There were only 278 patients, accounting for 0.9% of all patients; 2,702 patients who received baseline bone mineral density monitoring but did not use bisphosphate preparation, accounting for 8.76% of all patients; 931 patients who received bisphosphate preparation treatment but did not undergo bone mineral density examination, accounting for 3.02% of the total patients; and the vast majority of patients (87.3%, n=26,935) did not undergo bone mineral density. No bisphosphate preparation was used for the determination. A 2014 study of prostate cancer patients treated with ADT in Texas showed that only 197 (8.6%) of the 2,290 eligible patients underwent baseline bone mineral density testing [1]. A study in New Mexico in 2012 found that only about 13% of the subjects had baseline BMD tests, 21% had preventive treatment with bisphosphonates, and 16% and 10% had supplements of calcium or vitamin D [7]. Another single-center study found that about 58.8% of patients underwent baseline DXA bone mineral density tests before treatment, of which about 20.3% underwent baseline DXA bone mineral density tests.

Subsequent BMD follow-up monitoring was carried out in 12.7% of the patients treated with bisphosphonate, 35.6% of the patients and 36.9% of the patients were supplemented with calcium and vitamin D [39]. Another study found that only 9% of patients underwent the test [43]. A Canadian study found that since the British Cancer agency published in 2004 that prostate cancer patients should undergo BMD tests prior to ADT treatment, the percentage of ADT prostate cancer patients who underwent BMD tests in the province has risen from 7.5% to 25% [44], while an Ontario study has found a similar increase since 1995, reaching 1% in 2008 8% [45]. ADT treatment can lead to a significant increase in the incidence of osteoporosis and fracture in patients. BMD examination can help doctors understand the patient's bone mineral density and assess the risk of fracture, which is conducive to the formulation of more individualized treatment programs [24].

This gap between clinical practice and NCCN and NOF guidelines is global [20], which indirectly leads to the increase of bone-related events such as fragile fracture, the decline of patients' quality of life and the increase of family and social costs. These can be monitored and prevented. At present, there is still a lack of clinical research on bone health management of prostate cancer patients treated with ADT.

Analysis of the possible causes of the present situation

The specific reasons for the disconnection between the guidelines and clinical practice are not yet clear. Possible influencing factors include:

1. Clinical doctors and nurses lack sufficient knowledge of the danger of osteoporosis and the high risk of fracture [1,46].

2. AUA, EAU, CUA and other guidelines for prostate cancer patients undergoing ADT treatment lack specific requirements for prevention and treatment of bone complications.

3. Patients' compliance with long-term bone mineral density testing, drug prevention and lifestyle changes was not high [47].

4. Other socio-economic and cultural factors also contribute to this gap [1,14]. Studies have found that [1]: Compared with people aged 66 to 74 and over 75, the use of DXA is slightly higher; among low-income people with non-cancer, people with lower income use DXA less to examine BMD, but in patients undergoing ADT treatment, there is no effect of economic income on DXA detection rate; patients living in big cities and remote villages, who are treated with ADT, have DXA. The rate of DXA examination is higher than that of patients living in small towns. It may be that patients living in remote areas go to big cities for medical treatment, so the DXA examination rate is similar to that of people living in big cities. In terms of racial factors, the DXA examination rate of African Americans is only half that of white people. Osteoporosis testing in the elderly has been recommended by a variety of guidelines, but very few people (70%) do it.

Doctors may have underestimated the risk of osteoporosis in men and the benefits of DXA monitoring for the elderly [48,49]. A questionnaire survey of doctors in large hospitals in India showed that only about 50% of the doctors surveyed had explained that ADT treatment might increase the risk of osteoporosis and fracture [46]. Some studies for the general population have shown that men have less knowledge of osteoporosis warnings, prevention and treatment, and lifestyle changes than women [50,51]. A study found that more than half of prostate cancer patients treated with ADT did not receive warnings about treatment-related side effects, including increased risk of osteoporosis and fracture [52], and most did not receive adequate vitamin D and calcium supplements [53].

Similar findings were found in another study that patient characteristics had an impact on BMD testing and bisphosphonate use: BMD testing increased with age [42], except for those over 85 years old; BMD testing varied among races, with fewer blacks taking BMD tests than whites (OR 0.6, 95% CI 0.54-0.72), while Asians taking B tests. The number of MD patients was higher than that of the white population (OR 1.6, 95% CI 1.36-1.88); patients with different stages of tumors had different rates of BMD examination. Patients with higher stages (T3) had higher BMD monitoring rates

(OR 1.7, 95% CI 1.49-1.96) than those with lower stages (T0-T1); patients in different regions of the United States had different rates of BMD examination, and those living in the West also had differences. Populations, with a higher BMD rate than those in other regions, live in the middle of the country.

The rate of BMD examination in the western, northeastern and southern areas is lower than that in the western areas. If the BMD rate in the central and western areas is taken as the base, the BMD examination rate in the western areas is 20% (OR 1.2, 95% CI 1.02-1.33).

The influence of patient characteristics on the use of bisphosphonate; older patients (80 to 84 years old) had a higher rate of bisphosphonate use than younger patients (65 to 69 years old) (OR 1.3, 95% CI 1.07-1.54); compared with early patients (T0-T1), patients with stage T2-T4 had a higher rate of bisphosphonate use (T2, OR 1.6, 95% CI 1.41-1.83; T3, OR 2.9, 95% CI 2.40-3.54; T4, OR 5, 95% C 2.9, 95%). I (4.04-7.59); the difference of bisphosphonate application in different regions, the ratio of bisphosphonate application in the western region was higher than that in the northeast and South regions (OR 0.7, 95% CI 0.61-0.82 in the northeast; OR 0.6, 95% CI 0.52-0.73 in the south).

The 2009 National Comprehensive Cancer Network (NCCN) recommended screening with Dual-energy X-ray Absorptiometry (DXA) prior to initiation of ADT [5]. NCCN 2012 guidelines recommend using the Fracture Risk Assessment Algorithm (FRAX) to assess fracture risk [4,6]. However, few studies have evaluated FRAX scores in patients with prostate cancer receiving ADT.

Some study showed how the BMD screening in patients with prostate cancer undergoing ADT increased between 1995 and 2008, reaching 18% in 2008, in a separate study in Ontario. The same study showed also how bisphosphonates or denosumab therapy reduces this risk for fracture [1,54-60].

Multiples studies have been shown to improve bone health and reduce fractures in patients receiving ADT, 11 significant gaps remain in the quality of bone health care. Rates of BMD testing in men receiving ADT remain low, even among men with prior fragility fracture or preexisting osteoporosis [61]. In other studies, the prescription of calcium (16% to 19%), vitamin D (10% to 19%), and bisphosphonates (5% to 21%) among ADT users has been shown to be poor [13,62]. (Refer Improving Bone Health in Men with Prostate Cancer Receiving Androgen deprivation therapy: Results of a Randomized Phase 2 Trial). To compare with what we found in our study, 57% of Doctors asked the patients to complete calcium supplement, vitamin D 54%, and bisphosphonates 37%. Even in our study the result seems to be higher to this previous study, is still under hundred percent that we wish to [63-65].

Other study showed that Only 13% underwent bone density measurement by Dual Energy X-ray Absorptiometry (DXA) and, of those measured, more than half had osteoporosis [66]. Only 19% of the men received both calcium and vitamin D supplements. In the same study a total of 24 men sustained a fracture after starting ADT [67]. Other study showed after assessment of skeletal risk, only 13% had BMD measured, 5 were osteoporotic and twenty-four men experienced fracture after ADT initiation. Fracture sites included hip [36], vertebrae [54], rib [68], forearm [67,69,70]. In our study 44% of clinicians asked the patients to do bone density test, which still low to hundred percent we need.

We saw in other studies that, 50% of clinicians put they patients on ADT, -Subsequent BMD follow up monitoring shows 35% of them gave bisphosphate to the patients and 36% patients were supplement with Vitamin D [39], 9% of patients underwent the test [44]. A Canadian study found that the BMD test in province increased from 7.5% to 25%. Concerning our study, from 508 doctors we found that ,each year they have seen many patients with prostate cancer 77%, 55% of clinicians put patients on ADT, 37% of them gave bisphosphonates, 54% on vitamin D, and 57% on calicium. 46% asked the patients to complete a fracture risk assessment, 69% presented patients possible bone metabolic abnormalities (osteoporosis, increased fracture risk), 94% clinicians encourage patients in doing appropriate physical activity, 94% also encourage to patients to reduce alcohol consumption, and 93% to quit smoking.

Conclusions

Androgen Deprivation Therapy (ADT) is a mainstay of prostate cancer treatment and has shown, but also increase the risk of osteoporosis and fracture on prostate cancer patients. The most of clinicians in south of china are not screening the patient's bone mineral density test, and do not put patients on bisphosphonate, underestimate the risks of osteoporosis and fractures on prostate cancer patients on ADT.

Because of Guidelines of AUA, EAU, CUA have not claimed any requirement details on controlling bone complications of prostate cancer patients receiving ADT, we suggest for future study (PROPOSOL):

- The lack of patient adherence with long-term BMD screening, fracture prophylaxis, and lifestyle measures.

- Other social, economic and psychological factors.

- More strict requirements on urological disease guidelines about bone health control for prostate cancer patients receiving ADT.

- Implementation of the multifaceted educational intervention targeted to healthcare providers increased physician's awareness of osteoporosis and appropriate BMD testing, as well as use of the appropriate osteoporosis medication.

- Education on patients and their family members about complications and risks related with prostate cancer treatments, increasing their adherence for bone health events screening and prevention.

- Additional research is needed to further identify the determinants of low utilization and variation of BMD measurement and fracture prophylaxis in this population.

Recommendations

1. At the level of guidelines, the prevention and treatment of bone-related events in prostate cancer patients treated with ADT should be strengthened.

2. Education and guidance on the necessity and urgency of bone mineral density testing fracture risk assessment and preventive treatment for these patients.

3. To educate patients and their relatives about the complications and hazards that may be caused by the treatment of diseases, and to strengthen and consolidate patients' compliance.

4. Conduct further research to understand the specific causes of

the gap between clinical and NCCN guidelines in order to improve the prognosis of these patients.

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