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Bone Management in Patients with Prostate Cancer: FRAX Combined with Bone Mineral Density Can Prevent Unnecessary Treatment

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Bone Management in Patients with Prostate Cancer: FRAX Combined with Bone Mineral Density Can Prevent Unnecessary Treatment

Running Title: FRAX with BMD can prevent unnecessary treatment

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Abstract: INTRODUCTION AND OBJECTIVES: Osteoporosis is a common consequence of androgen deprivation therapy (ADT) for prostate cancer. Up to 20% of men on ADT have suffered from fracture within 5 years. The WHO Fracture Risk Assessment Tool (FRAX) has been utilized to predict the 10-year probability of major osteoporotic and hip fracture. However, no large studies assessing the utility of FRAX with versus without dual-energy X-ray absorptiometry (DEXA) in prostate cancer patients have been performed. We validated the usefulness of FRAX combined with DEXA in men with prostate cancer. **METHODS:** FRAX was done in a total of 1,220 prostate cancer patients including those who underwent brachytherapy (n=547), radical prostatectomy (n=200), external beam radiation therapy (n=264), hormonal therapy only (n=187), and definitive treatment along with hormonal therapy (n=645) in Yokohama City University Hospital. Of these, 109 patients received DEXA. **RESULTS:** In men without receiving DEXA, the median (mean ± SD) risks for major osteoporotic and hip fracture were 8.5% (9.3 ± 4.8) and 3.2% (4.2 ± 3.9), respectively. One hundred sixteen (9.5%) and 634 (52.0%) of these patients had the major osteoporotic risk of more than 15% and hip fracture risk of more than 3%, respectively. In contrast, in men with DEXA, the median (mean ± SD) risks for major osteoporotic and hip fracture were 5.3% (5.4 ± 2.1) and 0.85% (1.3 ± 1.2), respectively. Two (0.2%) and 4 (8.0%) of these patients had the major osteoporotic risk of more than 15% and hip fracture risk of more than 3%, respectively [Table1]. In the same cohort who received DEXA, the risks for major osteoporotic ($p < 0.001$) and hip ($p < 0.001$) fracture were significantly lower in men with DEXA than in those without DEXA. **CONCLUSIONS:** Our results suggest that FRAX combined with DEXA might prevent unnecessary osteoporosis medication in prostate cancer patients.

Keywords: FRAX; DEXA; prostate cancer; fracture; osteoporosis

Introduction

The skeleton is the third most common site of metastatic cancer, and one-third to half of all cancers metastasize to bone [1]. Osteroporosis or low bone mineral density (BMD) is a highly prevalent health problem among the patients with prostate cancer. Men with prostate cancer are often at risk for other age-related adverse events, such as hip fractures. The risk of hip fractures can be increased in men with prostate cancer because bone integrity may be compromised by androgen deprivation therapy (ADT), occult bone metastases, or both [2–6]. Low BMD is a predictor of fracture risk.

Fracture Risk Assessment Tool (FRAX) is a fracture risk assessment tool developed by the World Health Organization (WHO) to predict the fracture risk of patients based upon clinical risk factors alone or in combination with BMD at the femoral neck [7]. Fracture risk varies depending on the

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geographic location and ethnicity, and the FRAX algorithm has been calibrated to account for this [7]. Algorithms are available for diverse ethnic groups, including Caucasians and "Asians", based largely on data from Japan and China [8]. It is a computer based algorithm which provides the 10-year probability of hip and major osteoporotic fractures (clinical spine, forearm, hip, or shoulder fracture) based upon the age, sex, body mass index, and clinical risk factors and BMD may enhance the fracture risk factors using FRAX [8,9]. We previously reported that ADT increases FRAX score in prostate cancer patients. FRAX score using with DEXA showed the higher accuracy than those without DEXA. On the other hand, DEXA costs about 50USD in Japanese insurance system. So, not all patients are eligible to be performed DEXA.

The influence from DEXA to FRAX score has been assessed in two studies for the patients in prostate cancer [10,11]. The one is decreasing FRAX score using DEXA, on the other hand another one showed the opposite results. The influences of DEXA to FRAX is controversial. The aim of the present study was to evaluate the effect of BMD on fracture risk prediction using FRAX in combination with or without DEXA in the largest cohort ever published in prostate cancer [8].

Materials & Methods

A total of 109 patients underwent BMD measurement at both lumber and proximal femur. BMDs (g/cm2) of the proximal femur and lumber spine, forearm, and total body were measured using the dual energy X-ray absorptiometry by using a XX (manufacturer). Date of birth, weight (kg), height (cm), and a yes or no response various clinical risk factors (CRFs: history of fracture, history of hip fracture in a parent, tobacco smoking, current use of glucocorticoids, rheumatoid arthritis, secondary osteoporosis, and daily consumption of the three or more units of alcohol) were entered into the FRAX questionnaire, and the fracture probability was calculated for each subject. Childhood fractures reported by subjects were not considered as fragility fractures. Data from each subject were entered into the FRAX algorithm and 10-year fracture probabilities were calculated using CRFs alone and in combination with femur neck T-scores. FRAX tool available at the web site "http://www.shef.ac.uk/FRAX/index.htm" was used to compute the probability of a major osteoporotic event and a hip fracture. The study protocol was approved by the Institutional Review Board at the Yokohama City University Hospital (Yokohama, JAPAN).

Statistical Analysis

A paired-sample-t-test was used to compare differences in 10-year probabilities of fracture between FRAX models with or without DEXA

Results

A total of 109 men who were both performed FRAX and DEXA were recruited to participate in this study. Their demographic characteristics including various CRFs are presented in Table1. The median and mean T score in vertebral body and thigh bone were 0 (0.02 ± 1.91) and -0.4 (-0.36 ± 1.03). The median and mean in vertebral body and thigh bone YAM were 112 (112.5 ± 26.1) and 115 (123.9 ± 89.5) in Table2. From the FRAX model, the median and mean 10-year probability of a major osteoporotic fracture and hip fracture risk based on clinical risk factors alone was 7.9 (8.1 ± 3.3)% and 2.6 (2.9 ± 2.0)%. Using the FRAX model, in combination with femur neck T-scores, the mean 10-year probability of a hip fracture decreased as 5.1 (5.5 ± 2.2) % and 0.9 (1.4 ± 1.3) %. Comparing between with DEXA and without DEXA group, the major fracture risk more than 15% and hip fracture risk more than 3% with DEXA group was significantly lower than without DEXA group (with DEXA: 2 (1.8%) and 10 (9.1%), without DEXA: 4 (3.7%) and 10 (9.1%). [Figure 1 & Table 3].

Figure 1. FRAX score combination with or without DEXA.

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Table 1. Patients' Background (n=109).

	number (%) or median (range, mean ± SD)
Age (yr)	72 (55-84, 71.6 ± 5.8)
Body Weight (kg)	64 (38-87, 64,8 ± 6.1)
Body Height (cm)	165 (151-185, 165,8 ± 6.1)
Previous fracture	68 (62.4%)
Parent Fracturred Hip	5 (4.6%)
Current Smoking	13 (11.9%)
Glucocorticoid Intake	2 (1.8%)
Rheumatoid arthritis	1 (1.0%)
Secondary osteoporosis	6 (5.5%)
Alcohol 3 or more units per day	41 (37.6%)

Table 2. DEXA results in prostate cancer patients （n = 109）.

	median (range, mean ± SD)
Vertebral Body	
BMD	1.05 (0.603, 1.738, 1.05 ± 0.23)
T score	0 (-3.7, 5.8, 0.02 ± 1.91)
Z score	0.6 (-1.6, 4, 0.65 ± 1.18)
YAM	112 (11, 185, 112.5 ± 26.1)
Thighbone	
BMD	0.909 (0.408, 1.407, 0.90 ± 0.16)
T score	-0.4 (-3.4, 3.3, -0.36 ± 1.03)
Z score	0.9 (-1.8, 4.3, 0.91 ± 0.94)
YAM	115 (69, 1033, 123.9 ± 89.5)

BMD: bone mineral density, YAM: young adult mean

Table 3. 10-year fracture risk without vs with DEXA (n = 109).

Major osteoporotic risk		Major osteoporotic risk (more than 15%)	
FRAX w/o DEXA	FRAX w DEXA	FRAX w/o DEXA	FRAX w DEXA
7.9% (8.1 ± 3.3)	5.1% (5.5 ± 2.2)	3.7% (4/109)	1.8% (2/109)
Hip fracture risk		Hip fracture risk (more than 3%)	
FRAX w/o DEXA	FRAX w DEXA	FRAX w/o DEXA	FRAX w DEXA
2.6% (2.9 ± 2.0)	0.9% (1.4 ± 1.3)	43.1% (47/109)	9.1% (10/109)

Discussions

This study revealed that the 10-year probability of a major osteoporotic fracture based on a combination of clinical risk factors and femur neck T-scores was significantly higher than the fracture probability based on clinical risk factors alone in prostate cancer patients. This study showed that BMD in prostate cancer patients were relatively good whether they performed ADT or not. Our previous study indicated that long ADT time increased FRAX score. ADT is known to cause a decrease in BMD, and, therefore patients who receive ADT should be assumed to have secondary osteoporosis when calculating fracture risk using the FRAX tool [2,12]. Though FRAX score with BMD increases the accuracy to fracture risk, not all patients were eligible to be performed DEXA because of costs.

Osteoporosis and osteopenia are generally regarded as health issues. While recognition and treatment of osteoporosis in women has been low, risk of fracture in men is even less appreciated [13,14]. FRAX is a tool developed to assist the primary care physician in a systematic approach to risk assessment with and without the use of BMD [8]. Fracture risk is known to vary by country, even in individuals with similar clinical risk factors [15]. The National Osteoporosis Foundation (NOF) recommends that men over 70 years undergo BMD testing. The 10-year probability of a major

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osteoporotic fracture increases when femur neck T-scores are added to clinical risk factors in the FRAX algorithm, and this population have a high fracture probability even in the absence of clinical risk factors [16,17].

This study revealed that adding DEXA decreases FRAX score. A 10-year probability of major osteoporotic risk more than 15% or 20% and hip fracture more than 3% is considered a clinically relevant risk [7]. This is also supported the previous study [10]. On the other hand, some reports showed that using DEXA increase FRAX score, so the association between DEXA and FRAX score is controversial [11]. Out study included the 109 prostate cancer patients' DEXA results and this is the largest population ever published in prostate cancer patients. This study suggests that due to the decreasing of FRAX score using with DEXA, unnecessary osteoporosis treatment is avoided.

Several limitations exist in the present study. The first one is that we did not check the patients' real fracture with following-up time. We just evaluate the endpoint as FRAX score only. FRAX was developed by World Health Organization to predict the fracture risk and this score was made by racial differences and validated. In addition, this score is usually used as a clinical courses. Therefore, we thought assessing the fracture risk using FRAX score is valuable. The second one is that we obtained the data in a variety range of prostate cancer therapy. And we did not assess when the best time to check FRAX score is. So, further study is programmed to check the FRAX score continuously during the time of cancer treatment.

In conclusion, among Japanese prostate cancer patients, the 10-year probability of a major osteoporotic fracture decreases when femur neck T-scores are added to clinical risk factors in the FRAX algorithm.

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Conflicts of Interest: We declare no conflicts of interest.

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