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Research paper

# Assessing fracture risk in early stage breast cancer patients treated with aromatase-inhibitors: An enhanced screening approach incorporating trabecular bone score

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## ABSTRACT

*Introduction:* Aromatase-inhibitors (AIs) are commonly used for treatment of patients with hormone-receptor positive breast carcinoma, and are known to induce bone density loss and increase the risk of fractures. The current standard-of-care screening tool for fracture risk is bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA). The fracture risk assessment tool (FRAX®) may be used in conjunction with BMD to identify additional osteopenic patients at risk of fracture who may benefit from a bone-modifying agent (BMA). The trabecular bone score (TBS), a novel method of measuring bone microarchitecture by DXA, has been shown to be an independent indicator of increased fracture risk. We report how the addition of TBS and FRAX®, respectively, to BMD contribute to identification of elevated fracture risk (EFR) in postmenopausal breast cancer patients treated with AIs.

*Methods:* 100 patients with early stage hormone-positive breast cancer treated with AIs, no prior BMAs, and with serial DXAs were identified. BMD and TBS were measured from DXA images before and following initiation of AIs, and FRAX® scores were calculated from review of clinical records. EFR was defined as either: BMD $\leq -2.5$ or BMD between $-2.5$ and $-1$ plus either increased risk by FRAX® or degraded microstructure by TBS.

*Results:* At baseline, BMD alone identified 4% of patients with EFR. The addition of FRAX® increased detection to 13%, whereas the combination of BMD, FRAX® and TBS identified 20% of patients with EFR. Following AIs, changes in TBS were independent of changes in BMD. On follow-up DXA, BMD alone detected an additional 1 patient at EFR (1%), whereas BMD + FRAX® identified 3 additional patients (3%), and BMD + FRAX® + TBS identified 7 additional patients (7%).

*Conclusions:* The combination of FRAX®, TBS, and BMD maximized the identification of patients with EFR. TBS is a novel assessment that enhances the detection of patients who may benefit from BMAs.

## ARTICLE INFO

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*Abbreviations:* AIs, Aromatase-Inhibitors; DXA, Dual-energy X-ray absobimetry; FRAX®, Fracture risk assessment tool; TBS, Trabecular bone score; BMD, Bone mineral density; WHO, World Health Organization; EFR, Elevated Fracture Risk

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## 1. Introduction

Aromatase-Inhibitors (AIs) are commonly used in the treatment of post-menopausal women with a history of hormone receptor-positive breast carcinoma, and have been shown to decrease bone mineral density (BMD) and increase the risk of bone fragility fractures [1].

The National Comprehensive Cancer Network Task Force (NCCN) currently recommends screening of fracture risk in all patients initiating AIs by obtaining clinical history, dual-energy X-ray absorptiometry (DXA) scans and with the use of the fracture risk assessment tool (FRAX®) calculator. If T-score is less than or equal to −2.0 at any site or if the FRAX® 10-year absolute risk of fracture is greater than 20% for any major fracture or greater than 3% for hip fracture, bone modifying-agents (BMAs) such as bisphosphonates or denosumab, are recommended. For women with increased risk of fractures initiating AI therapy, BMAs such as bisphosphonates or denosumab can be recommended, both which have been shown to decrease the risk of bone fracture in the setting of AI therapy [2,3]. The current gold standard screening tool for the diagnosis of osteoporosis in the absence of fragility fractures is DXA.

Many patients without osteoporotic BMD suffer fragility fractures. It is important to highlight that the majority of fractures actually occur in patients with a T-score above the osteoporotic range [4], making the osteoporosis threshold (BMD T score $\leq$ 2.5) inadequate to identify all patients at risk. Furthermore, BMD does not evaluate the degree of bone microarchitectural deterioration, which may represents an independent factor contributing to increased bone fragility [5].

The trabecular bone score (TBS) is an innovative gray-level texture measurement that utilizes lumbar spine DXA images to discriminate changes in bone microarchitecture [6]. Specifically, TBS measures tridimensional bone areas with different trabecular and microstructural characteristics. TBS has been shown to be an independent indicator of increased fracture risk [7]. Furthermore, the combination of TBS microstructure evaluation with BMD measured by DXA has been shown to be superior to either measurement alone in the assessment of fracture risk [8].

In an effort to optimize the identification of postmenopausal women treated with adjuvant AIs at risk of bone fragility fractures, we evaluated a screening model that integrates the novel TBS tool with FRAX® and DXA. We then studied if our tools represent independent variables in this clinical context, and enumerated the relative contribution of adding TBS to the standard screening approaches most commonly observed in the clinic (BMD ± FRAX®).

## 2. Materials and methods

### 2.1. Patient selection

Patients were identified via institutional databases at Memorial Sloan Kettering Cancer Center under an Institutional Review Board waiver of consent. Using DataLine services we identified 309 unique patients who were diagnosed with breast cancer at MSKCC between the years of 2005 and 2012, who were post-menopausal (defined as ≥60 years old or ≥50 years old with amenorrhea for > 12 months), were treated with an AI, and who had at least 2 DXAs performed at MSKCC. Through a chart review, we then eliminated patients who were treated with BMAs prior to baseline or follow-up DXA. We also excluded all patients with a BMI over 37, as TBS has not been validated in this population. We then selected the patients who had a baseline DXA within 3 months of starting the AI, and a follow up DXA more than 6 months but less than 36 months after the first one. This search yielded to 100 unique patients who were included in our analysis.

### 2.2. BMD, TBS, and FRAX assessment

As per standard-of-care at MSKCC, BMD from femoral neck, total hip and lumbar spine was measured by DXA (GE-lunar). TBS measurements were performed in the Bone Disease Center at the Lausanne University Hospital (CHUV), Lausanne, Switzerland (TBS iNsight® Software version 1.8, Med-Imaps, Pessac, France) using anonymized spine DXA files to ensure blinding of the Swiss investigators to all clinical parameters and outcomes. The approach was similar to the one used in other studies [7]. BMD and TBS were evaluated at baseline and at follow-up. FRAX® score was calculated utilizing the clinical information from patients' charts, and using the online algorithm [9].

BMD was interpreted using World Health Organization (WHO) guidelines, which define risk according to T-score, which is the standard deviation difference between a patient's BMD and that of a young-adult reference population. A T-score of ≤ −2.5 indicates clinical osteoporosis. Osteopenia is defined as a borderline T-score (between −1.0 and −2.5), whereas normal BMD is defined as T-score > −1.0.

TBS, being a continuous variable as BMD, was interpreted using the tertile approach extracted from the fracture data of a large Canadian cohort. Degraded microarchitecture represents the highest risk, and is defined as a TBS value of ≤1.2. Partially degraded microarchitecture represents borderline risk, and is defined as values between 1.2 and 1.35, whereas normal microarchitecture is defined as TBS ≥1.35 [6,7].

FRAX® assessment was conducted via retrospective medical records review and calculated through the online algorithm (https://www.shef.ac.uk/FRAX).

### 2.3. Definition of at-risk populations

Using BMD, TBS, and FRAX®, we evaluated three screening paradigms for identifying patients with high fracture risk who would be suitable for pharmacologic therapy with a BMA. The first screening paradigm is BMD alone using osteoporosis (T ≤ −2.5) as a threshold for positivity. The National Osteoporosis Foundation recommends BMA therapy for this population based upon models that predict a favorable cost-benefit ratio [10].

The second screening paradigm is BMD plus FRAX®, which is the standard screening practice endorsed by the National Comprehensive Cancer Network (NCCN) and National Osteoporosis Foundation [10]. For BMD plus FRAX®, the threshold for positivity is either osteoporosis by BMD, or osteopenia by BMD plus a FRAX 10-year probability of a hip fracture ≥3% or a 10-year probability of a major osteoporosis-related fracture ≥20%. These thresholds were determined based upon modeling predicting favorable cost-benefit ratio, specific to the United States population [10].

Finally, we tested a novel screening paradigm of BMD plus FRAX® plus TBS. For this method, we defined positivity to elevated fracture risk (EFR) as either: 1) osteoporosis by BMD (T-score ≤ −2.5); 2) osteopenia + high FRAX® score (as above); or 3) osteopenia + low TBS score (degraded microarchitecture, i.e. TBS ≤1.2).

### 2.4. Statistical analysis

Statistical analysis was performed using IBM Statistical Package for