Diagnostic Accuracy of Lumbar Spine Bone Mineral Density (BMD) Measurements via Quantitative Computed Tomography (QCT) in the Assessment of Osteoporosis in Filipino Women Diagnosed with Breast Cancer using Dual-Energy X-ray Absorptiometry (DXA) as Gold Standard

Raquel Marie R. Cabatu, MD[1,3] Angela Krista V. Pedroso, MD[2,3], Irene S. Bandong, MD[1,2,3]

[1]*Department of Nuclear Medicine, St. Luke's Medical Center, Quezon City, Philippines, 1112*

[2]*Institute of Radiology, St. Luke's Medical Center, Quezon City, Philippines, 1112*

[3]*E-mail address: mariecabatu@gmail.com, angelakristapedroso@gmail.com, isbandong@stlukes.com.ph*

ABSTRACT

Background:

Breast cancer, chemotherapy and endocrine treatment are risk factors for osteoporosis. Dual-energy x-ray absorptiometry (DXA) remains the gold standard in the diagnosis of osteoporosis. A quantitative computed tomography (QCT) with a bone mineral density analysis software on the whole abdomen CT may be used for screening osteoporosis without additional radiation exposure or cost.

Objective:

To determine the accuracy of QCT in detecting osteoporosis among breast cancer patients using DXA as gold standard.

Methods:

This is a cross-sectional analytic study of 76 Filipino women with breast cancer who underwent both DXA and whole abdomen CT scans. The DXA measurements were obtained using Lunar iDXA manufactured by GE Healthcare while the QCT measurements were made using the BMD analysis software available in the Philips Extended Brilliance Workspace post-processing system.

Results:

Out of the 76 Filipino women with breast cancer, 92% were menopausal women with mean age of 58.9 (SD 8.7) years, 69.7% had IDCA and 94.7% had mastectomy. Majority had normal BMD (44.7%), 34.2% had osteopenia and 21.1% had osteoporosis based on DXA. QCT has 90% (95% CI: 55.5-99.8) sensitivity, 63.6% (95% CI: 30.1-89.1) specificity, 69.2% (95% CI: 50.1-83.5) PPV, 87.5 (95% CI:50.8-97.9) NPV, 2.5 (95% CI:1.1-5.6) LR(+) and 0.16 (95% CI:0.02-1.06) LR (-).

Conclusion:

The prevalence of osteoporosis and osteopenia among Filipino women with breast cancer was 21.1% and 34.2%. The sensitivity and specificity of QCT in detecting osteoporosis was 90% and 63.6%.

Keywords*: osteoporosis, osteopenia, QCT, DXA, breast cancer*

INTRODUCTION

Cancer, regardless of type, is a major risk factor for osteoporosis. Breast cancer, in particular, has been shown to have direct deleterious effect on bone metabolism even in the absence of bone metastases. Adjuvant chemotherapy and endocrine treatment for breast cancer also affect bone health by decreasing circulating estrogen levels or by inducing premature menopause or ovarian failure. Advancing age, metastatic disease to bone, reduced physical activity, and inadequate intake of calcium and vitamin D are other risk factors that further increase the risk of osteoporosis and fracture in cancer patients [1,2].

Successes in breast cancer treatment has led to an increase in its survival rate, which in turn increases the potential number of patients at risk for osteoporosis. During adjuvant therapy for breast cancer, the resulting rapid decrease in bone mineral density may necessitate aggressive pharmacotherapy to reduce morbidity from fracture and other healthcare-associated costs. Therefore, strategies to limit bone loss and screen for osteoporosis should be part of routine survivorship care. However, in the study done by Spangler et al. (2013), it was shown that a large proportion of patients with breast cancer receiving adjuvant chemotherapy do not receive BMD evaluation as recommended by existing American Society of Clinical Oncology guidelines [3].

REVIEW OF LITERATURE

Osteoporosis is a metabolic bone disorder defined as decreased bone strength and increased risk for fracture. Globally, osteoporosis is estimated to affect approximately 200 million women and cause more than 8.9 million fractures annually [4,5]. In general, osteoporotic fractures result in decreased mobility, functional autonomy, and quality of life. Hip fractures are associated with increased mortality during the 12 months following the fracture, resulting in prolonged hospitalization and increased risks of complications from prolonged immobility, such as deep vein thrombosis, pulmonary embolism, and pressure ulcers. Vertebral fractures, on the other hand, are associated with chronic back pain, gross deformity, and decreased pulmonary function [6]. Given the high cost associated with osteoporosis and fractures and the resulting increased risk of death from complications, screening and treatment of high-risk patients are paramount.

The diagnosis of osteoporosis is based on quantitative assessment of BMD, which is considered the best predictor of osteoporotic fractures. BMD is defined as the amount of bone mass per unit volume, which is measured in vivo by densitometric techniques [7]. BMD values can also be expressed as a T-score or Z-score, which represents the number of standard deviations (SD) with respect to a reference average value. According to the WHO criteria, BMD that is at least 2.5 standard deviations below the average value for young healthy women (i.e. T-score <2.5 SD) is considered osteoporotic [5]. BMD measurements may also be used to estimate future fracture risk and monitor response to therapy.

The gold standard for diagnosis of osteoporosis is dual-energy x-ray absorptiometry (DXA). DXA is the most commonly used and most validated method for assessing bone mineral density. And because the World Health Organization (WHO) defined threshold levels for the diagnosis of osteoporosis with DXA (Table 1), it has become the current standard of reference for the clinical diagnosis of osteoporosis [7].

DXA is a projectional x-ray based technology that measures the attenuation values of bone in two dimensions (i.e. from an anteroposterior image) to quantify bone mineral content, which is expressed in grams per square centimeter. It has been shown to accurately measure BMD at specific sites (e.g. lumbar spine and hip), using effective radiation doses equivalent to a chest x-ray, with good reproducibility [7,8]. However, the technique is limited by its inability to distinguish between cortical and trabecular bone. BMD estimates using DXA may also be affected by the presence of osteomalacia, degenerative changes such as osteophytosis and osteochondrosis, vascular calcifications, severe scoliosis and other vertebral deformities, and differences in body habitus [7,8]. Furthermore, the utility of DXA in the local setting is constrained by limited accessibility to DXA machines [9].

TABLE 1. WHO Criteria for Osteoporosis using DXA

DIAGNOSTIC CRITERIA	T-SCORE
Normal	T-score at or above –1.0 SD
Low Bone Mass (Osteopenia)	T-score between –1.0 and –2.5 SD
Osteoporosis	T-score at or below –2.5 SD
Severe Osteoporosis	T-score at or below –2.5 SD and fragility fracture/s

Another x-ray-based method of BMD assessment is quantitative computed tomography (QCT). QCT enables quantitative determination of volumetric BMD using a calibration phantom imaged with the patient which allows for conversion of Hounsfield units to bone mineral units. Advancements in CT post-processing software has allowed for phantom-less BMD assessment, using the patient as reference. In phantom-less QCT BMD analysis, the adjacent paraspinal muscle and subcutaneous fat are used. With this method, beam hardening and scatter artifacts caused by an external phantom, as well as operator errors from mishandling of the phantom, are thus avoided [10].

BMD analysis using QCT has several advantages over DXA. In QCT, cortical and trabecular bone can be evaluated separately. The ability of QCT to measure purely trabecular bone is particularly important since trabecular bone is metabolically more active and is found to be affected earlier and to a greater extent than cortical bone in osteoporosis. In this respect, QCT is more sensitive than DXA in detecting early bone loss and can thus be used for earlier detection of osteoporosis. Also, QCT BMD measurements of trabecular bone are not affected by degenerative changes and extraosseous calcifications as well as variations in body habitus, thereby circumventing some of the inherent limitations of DXA and providing more accurate BMD analyses [10].
It is important to note that the WHO-defined diagnostic categories for osteoporosis are based on T-scores of hip

BMD. However, there are no consensus standards for assigning diagnostic categories based on spine BMD measurements. Studies have shown that hip BMD and spine BMD T-scores are very different, and using spine BMD T-scores may lead to overestimation of hip fracture risk. According to the American College of Radiology practice guideline for quantitative CT bone densitometry [8], the existing WHO diagnostic categories for bone mineral density should only be applied for DXA and QCT hip T-scores. For QCT spine BMD measurements, the category definitions shown in Table 2 are used to approximate the corresponding WHO diagnostic categories for hip BMD measurements.

TABLE 2. QCT Trabecular Spine BMD Range Values and Equivalent WHO Diagnostic Categories

QCT Trabecular Spine BMD Range	Equivalent WHO Diagnostic Category
BMD >120 mg/cm^3	Normal
BMD ≥80 mg/cm^3 but ≤120 mg/cm^3	Osteopenia
BMD <80 mg/cm^3	Osteoporosis

One important advantage of QCT BMD assessment is that it can be easily integrated into the CT work flow and will not necessitate additional radiation exposure [10]. In patients with breast cancer who do not receive routine osteoporosis screening but undergo abdominal CT scans for disease surveillance, retrospective BMD analysis of previous CT scans using the phantom-less post-processing method can be done to screen for bone loss and establish a baseline BMD for future monitoring if antiresorptive therapy is started.

The objective of this study is to compare BMD measurements of L1-L3 derived from quantitative CT and from DXA in patients with biopsy-proven breast cancer. The study aims to test the hypothesis that the BMD measurements using CT is strongly correlated with BMD measurements from DXA. If so, routine abdominal CT done as part of initial metastatic workup or surveillance may be utilized for opportunistic screening of osteoporosis in these high-risk patients, without incurring additional radiation exposure or cost.

Significance of the Study

Patients with breast cancer are at increased risk for osteoporosis because of extensive use of chemotherapeutic agents that induce early menopause, thereby increasing bone turnover and bone loss. Increasing survival rates from breast cancer afforded by early and effective treatment also increases the incidence of and morbidity from complications such as pathologic fractures. Osteoporosis is a silent progressive disease and measuring BMD early in breast cancer patients who are at increased risk can potentially avoid or reduce morbidity from pathologic fractures. Not all breast cancer patients routinely undergo osteoporosis screening. However, many patients undergo whole abdomen CT scans as part of disease surveillance. Opportunistic screening for osteoporosis using CT studies may be done without additional radiation exposure or cost. In addition, few studies have compared BMD measurements using CT and DXA in patients with breast cancer who are at increased risk for osteoporosis.

The aim of this study is to determine the accuracy of QCT, in terms of sensitivity and specificity, in detecting osteoporosis among breast cancer patients using DXA as gold standard.

MATERIALS AND METHODS

Study Design

This is an institutional review board-approved cross-sectional analytic study of 76 Filipino women with breast cancer who underwent DXA and whole abdomen CT scans no more than 1 year apart in our institution from 2012 to 2018.

Recruitment was done during the study period by the primary investigators in the nuclear medicine department upon encountering patients that meet the inclusion criteria. An entry interview was conducted by a member of the study team for prospective participants. The benefits and advantages of participation were emphasized to them, and the procedure explained. Upon voluntary agreement to join the study, informed consent was obtained.

Target population and study setting

All adult female patients aged 25-90 diagnosed with breast cancer who have whole abdomen CT scans and

DXA bone densitometry studies done 6 to 12 months apart from January 1, 2012 to December 31, 2018 at St. Luke's Medical Center – Quezon City. The inclusion criteria were adult female patients aged 40-90; patients with biopsy-proven breast carcinoma, menopausal patients, either medical, surgical, or age-related; patients who have received or are receiving cancer treatment and patients who have whole abdomen CT scan and DXA bone densitometry done 6 to 12 months apart. The exclusion criteria were patients with compression deformities in the lumbar vertebrae, patients with prior surgery involving the lumbar spine, patients with DXA scans that have excluded either L1, L2, or L3 vertebrae or have used other lumbar vertebrae other than L1, L2, and L3 in its analysis of BMD

Description of Study Procedure

QCT BMD measurements

Whole abdomen CT studies were retrieved from the picture archiving PACS. QCT measurements were made by the radiology resident using the BMD analysis software available in the Philips Extended Brilliance Workspace post-processing system. A constant region of interest (ROI) was placed in the center of each of three vertebral bodies (e.g. L1 to L3), using adjacent paraspinal muscle and subcutaneous fat for calibration. For each patient, measurements were performed by a single investigator (radiology resident) twice on each vertebra. Measurements from L1 to L3 and the average BMD from L1 to L3 were taken, and the average of the two measurements made were calculated. Based on the given cut-off values of QCT, the average values obtained were classified as normal, osteopenia, or osteoporosis.

DXA BMD measurements

DXA bone densitometry studies were obtained from PACS. The DXA measurements were obtained using Lunar iDXA manufactured by GE Healthcare. The previously made BMD measurements using the standard DXA protocol were retrieved (by the nuclear medicine resident). Resulting T-scores were subsequently classified as normal, osteopenia, or osteoporosis.

Sampling method:

Purposive sampling was done.

Study maneuver

Adult female patients aged 40 to 90 years with biopsy-proven breast carcinoma who have either received or are receiving cancer treatment and have had whole abdomen CT scans and DXA bone densitometry scans done 6 to 12 months apart were included. Patients with compression deformities in the lumbar vertebrae, those with prior lumbar spine surgery, and patients whose DXA scans have excluded either L1, L2, or L3 vertebrae or have used other lumbar vertebrae other than L1, L2, and L3 in its analysis of BMD were excluded.

Nuclear Medicine databased on bone mineral density was reviewed from January 1, 2012 to December 31, 2018 for recruitment of participants. Medical records of all eligible participants were reviewed and the following were collected age and BMI, histologic type of cancer, stage of disease, and treatment received.

The readers (radiologist and nuclear medicine physician) were provided with the list of included participants for the study. QCT and DXA measurements were made independently. The readers were blinded of the QCT and DXA readings of each participant.

Sample Size Estimation

Sample size was calculated based on the sensitivity of QCT in the diagnosis of osteoporosis and the prevalence of osteoporosis among breast cancer patients. Assuming that the sensitivity of QCT is 100% (Bansal et al., 2011), with a maximum allowable error of 5% and a reliability of 95%, initial sample size calculated was 16. Dividing this value by the prevalence of osteoporosis among breast cancer patients assumed to be 26% (Bansal et al., 2011), final sample size required is 62.

Statistical Analysis

Data were encoded and tallied in SPSS version 10 for windows. Descriptive statistics were generated for all variables. For nominal data frequencies and percentages were computed. For numerical data, mean ± SD were generated. Analysis of the different variables was done using McNemar test. Point and 95% CIs were calculated for the sensitivity, specificity, PPV, NPV, and LRs.

RESULTS

A total of 76 subjects were included in the study, and their demographic characteristics are listed in Table 3. Of the 76 subjects, 6 were premenopausal and 70 were menopausal. Mean age was 58 years and majority were overweight, with mean BMI of 26.3. The most common histologic type of breast cancer was invasive ductal

TABLE 3. Demographic Characteristics of Filipino Women with Breast Cancer

	Premenopausal (n=6)	Menopausal (n=70)	Total (n=76)
Age (in years)			
Mean ± SD	44.50 ± 5.68	58.89 ± 8.67	57.75 ± 9.30
BMI			
Mean ± SD	24.78 ± 5.31	26.48 ± 3.98	26.34 ± 4.08
Histologic Type			
DCIS	0	4 (5.7%)	4 (5.3%)
IDCA	5 (83.3%)	48 (68.6%)	53 (69.7%)
ILCA	0	6 (8.6%)	6 (7.9%)
Mucinous CA	0	1 (1.4%)	1 (1.3%)
No Data	1 (16.7%)	11 (15.7%)	12 (15.8%)
Disease Stage			
0	0	3 (4.3%)	3 (3.9%)
I	1 (16.7%)	9 (12.9%)	10 (13.2%)
IA	0	2 (2.9%)	2 (2.6%)
II	1 (16.7%)	9 (12.9%)	10 (13.2%)
IIA	1 (16.7%)	6 (8.6%)	7 (9.2%)
IIB	2 (33.3%)	12 (17.1%)	14 (18.4%)
IIC	0	1 (1.4%)	1 (1.3%)
III	0	10 (14.3%)	10 (13.2%)
IIIA	1 (16.7%)	2 (2.9%)	3 (3.9%)
IIIB	0	4 (5.7%)	4 (5.3%)
IIIC	0	6 (8.6%)	6 (7.9%)
IV	0	2 (2.9%)	2 (2.6%)
No Data	0	4 (5.7%)	4 (5.3%)
Treatment Received			
Lumpectomy	0	3 (4.3%)	3 (3.9%)
Mastectomy	6 (100%)	66 (94.3%)	72 (94.7%)
Core needle biopsy	0	1 (1.4%)	1 (1.3%)
Radiotherapy	5 (83%)	25 (35.7%)	31 (40.8%)

carcinoma (69.7%). Most patients receiving treatment were diagnosed at stage II, and majority underwent mastectomies (94.7%).

Table 4 shows the prevalence of normal BMD, osteopenia, and osteoporosis among Filipina women with breast cancer using DXA and QCT. According to QCT classification, a total of 10 (13.2%) had normal BMD, 38 (50.0%) had osteopenia and 28 (36.8%) had osteoporosis. According to DXA classification, a total of 34 (44.7%) had normal BMD, 26 (34.2%) had osteopenia and 16 (21.1%) had osteoporosis.

Table 5 shows the distribution of osteoporosis, osteopenia, and normal BMD among menopausal women based on DXA and QCT

TABLE 4. Prevalence of Normal BMD, Osteopenia, and Oeteoporosis among Filipino Women with Breast Cancer

	Menopausal	Total
QCT Classification		
Normal		
Osteopenia	8 (11.4%)	10 (13.2%)
Osteoporosis	35 (50.0%)	38 (50.0%)
	27 (38.6%)	28 (36.8%)
DXA Classification		
Normal		
Osteopenia	32 (45.7%)	34 (44.7%)
Osteoporosis	24 (34.3%)	26 (34.2%)
	14 (20.0%)	16 (21.1%)

Table 6 shows the comparison of QCT and DXA in detecting osteopenia and osteoporosis among breast cancer patients using DXA as gold standard. There was no significant difference noted between QCT and DXA in the detection of osteoporosis among menopausal women ($p<0.0001$).

Table 7 shows the accuracy of QCT in detecting osteopenia and osteoporosis among breast cancer patients using DXA as gold standard. Among menopausal women, the sensitivity of QCT in detecting osteopenia was 100% (95% CI: 69.2% to 100%) while the specificity was 25.0% (95% CI:10.7% to 44.9%).

In detecting osteoporosis among menopausal women, the sensitivity of QCT was 90.0% (95% CI: 55.5% to 99.8%) while the specificity was 63.6% (95% CI: 30.8% to 89.1%).

TABLE 5. Distribution of Menopausal Women According to QCT and DXA Results using DXA and QCT

		DXA			Total
		Osteoporosis (n=16)	Osteopenia (n=26)	Normal (n=34)	
	QCT				
	Osteoporosis	9	14	4	27
Menopausal	Osteopenia	4	10	21	35
	Normal	1	0	7	8

TABLE 6. Comparison of QCT and DXA in Detecting Osteopenia and Osteoporosis

	Osteopenia	DXA		Total	*p-value**
		Osteopenia	Normal		
	QCT				
Menopausal	Osteopenia	10	21	31	<0.0001 (S)
	Normal	0	7	7	
	Osteoporosis	**DXA**		**Total**	***p-value****
		Osteoporosis	**Normal**		
	QCT				
Menopausal	Osteoporosis	9	4	13	0.38 (NS)
	Normal	1	7	8	

TABLE 7. Accuracy of QCT in Detecting Osteopenia and Osteoporosis Among Breast Cancer Patients Using DXA as Gold Standard

		Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR- (95% CI)
Osteopenia	**Menopausal**	100 (69.2 – 100)	25.0 (10.7 – 44.9)	32.3 (27.8 – 37.1)	100 (56.1 – 100)	1.3 (1.1 – 1.7)	0
Osteoporosis	**Menopausal**	90.0 (55.5 – 99.8)	63.6 (30.8 – 89.1)	69.2 (50.1 – 83.5)	87.5 (50.8 – 97.9)	2.5 (1.1 – 5.6)	0.16 (0.02 – 1.06)

DISCUSSION

Prior studies have shown that QCT is superior in BMD analysis [12] and is more sensitive in detecting osteoporosis [13] compared to DXA. However, these studies have focused more in the detection of osteoporosis rather than osteopenia. Our results proved that QCT and DXA are indeed at par in detecting osteoporosis in post-menopausal patients, and that QCT may be more sensitive than DXA in detecting osteopenia.

According to the study of premenopausal women with breast cancer by Ramin et al. (2018) [14], the incidence of osteopenia and osteoporosis are higher in breast cancer survivors, and that those who receive chemotherapy and aromatase inhibitors (AI) or tamoxifen are at higher risk of developing osteopenia and osteoporosis when compared to cancer-free women. They have observed greater than twofold increased risk of osteopenia and osteoporosis in women diagnosed with ER-positive tumors, which is likely due to hormone therapy rather than to differences in tumor biology. Reduction of BMD is a well-known side effect of AI and this is a concern for early breast cancer patients for whom endocrine therapy is indicated, because they survive for many years after treatment. Any decrease in BMD puts them at risk for fractures as these women age. In general, a 10 to 12% loss in BMD can be compared to a 1 point drop in T-score, and an increase of the fracture risk by 2.6 times [16]. Hence, QCT may be used in BMD assessment to increase detection rates of osteopenia and osteoporosis in this population.

Important differences in measurements of BMD between DXA and CT should be considered. DXA is a planar measurement of density expressed as grams of mineral per square centimeter scanned (g/cm2), while the values obtained from CT scans are volumetric (g/mm3). Dual x-ray absorptiometry includes the posterior elements of the spine, and may be inaccurate in the presence of severe spinal degeneration, scoliosis, or following lumbar surgery. Computed tomography techniques such as QCT has higher radiation exposure when compared to DXA and can be limited to specific regions of interest, such as the vertebral body trabeculae [17].

An advantage of using QCT in BMD assessment is its ability to do 3D quantification of BMD which increases the accuracy of measurements by circumventing the osseous factors that usually affect DXA BMD estimates such as degenerative changes. QCT can also be used in opportunistic screening, which is further facilitated by the relative ease of use of the BMD analysis software available without need for use of phantoms for calibration.

LIMITATIONS OF THE STUDY

This study did not take into consideration the date of breast cancer diagnosis or the onset of chemotherapy or hormone replacement therapy relative to the time the CT and DXA studies were performed.

Hormone replacement therapy and intake of aromatase inhibitors are among the treatments which can affect bone mineral densities. There is lack of data in what treatments the included participants received and the time relative to the BMD assessment was done. It is also not determined if the BMD assessment of the participants are baseline values or they have a history of treatment for osteoporosis. Patient characteristics such as history of fracture or familial osteoporosis could not be ruled out.

CONCLUSIONS

This study showed that 21.1% of Filipino women with breast cancer had osteoporosis and 34.2% had osteopenia. QCT had 90% sensitivity and 63.6% specificity in detecting osteoporosis among menopausal Filipino women with breast cancer. Furthermore, results showed that QCT is comparable with DXA in the detection of osteoporosis among premenopausal and menopausal women. However, there was a significant difference between QCT and DXA in the detection of osteopenia among menopausal women. In this light, QCT may be used in the opportunistic screening for osteoporosis in order to increase detection rates in both premenopausal and postmenopausal populations of Filipina women with breast cancer.

RECOMMENDATIONS

It is recommended to increase the sample size and note treatments such hormonal therapies which can affect BMD. It is also important to determine fracture history and presence of familial osteoporosis as these factors may further increase in the risk of osteoporosis. The most common cause of bone loss in women is menopause and aging, therefore, a cancer-free comparison of similar age and menopausal status is important when assessing bone loss.

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