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Assessment of the role of vitamin D with or without bone-modulating therapy in non-metastatic breast cancer patients receiving adjuvant non-steroidal aromatase inhibitors

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***Abstract*---Background:** Breast cancer (BC) is classified into luminal A, luminal B, Human epidermal growth factor 2 receptors positive, and triple-negative subtypes, with adjuvant endocrine therapy recommended for hormone receptor-positive disease. This study aimed to evaluate whether vitamin D and bone-modifying therapy improve quality of life in patients with non-metastatic luminal breast cancer receiving non-steroidal Aromatase Inhibitors (NSAI) and whether these improvements are associated with better overall and disease-free survival. **Methods:** This prospective study was executed on 100 female participants identified with postmenopausal non metastatic (M0) luminal BC, were randomly placed into two equal groups: Group A: treated with adjuvant NSAI plus vitamin D supplementation with bone antiresorptive agents and group B: treated with adjuvant NSAI plus vitamin D supplementation without bone antiresorptive agents. **Results:** The mean physical well-being scores were 23.86, 25.17, and 25.8 in group A and 21.7, 22.6, and 22.91 in group B, as listed, with a significant p-value. The mean functional well-being (FWB) scores were 23.66, 25.25, and 25.98 in group A relative to 21.44, 22.93, and 23.23 in group B ($P<0.05$). **Conclusions:** Vitamin D normalization and bone-modifying agents help preserve bone health and prevent bone loss in postmenopausal women with luminal BC receiving adjuvant NSAIs.

***Keywords*---**Vitamin D, Bone Modulating Therapy, Non-Metastatic, Breast Cancer Patients, Adjuvant Non-Steroidal Aromatase Inhibitors.

Introduction

Breast cancer (BC) is the most frequently identified malignancy among females worldwide, with estrogen receptor-positive (ER+) tumors comprising about 70–80% of all BC cases. (Long, Qiu, Long, & Jin, 2025). For postmenopausal females identified with early-stage, hormone receptor-positive BC, non-steroidal aromatase inhibitors (NSAI) as anastrozole and letrozole have become the preferred adjuvant endocrine therapy. These agents act by inhibiting the aromatase enzyme responsible for peripheral conversion of androgens to estrogens, thereby achieving profound estrogen suppression. While effective in decreasing the probability of cancer recurrence and enhancing disease-free survival (DFS), the hypoestrogenic state induced by AIs is related with deleterious skeletal effects (Kuba et al., 2025).

Estrogen is a critical regulator of bone metabolism, particularly in females. It maintains skeletal integrity by suppressing osteoclastic bone resorption and promoting osteoblastic bone formation. Clinical studies have shown that females having AIs can experience a 2–4% annual reduction in bone mineral density (BMD) at the lumbar spine and hip, significantly exceeding the rate observed in natural menopause (Kuba et al., 2025). Vitamin D, a fat-soluble hormone, serves a critical role in calcium absorption, bone remodeling, and mineralization. Beyond its classical role in skeletal health, vitamin D has been implicated in multiple non-skeletal functions, including modulation of cell proliferation, differentiation,

apoptosis, and immune regulation—mechanisms that may be relevant to carcinogenesis and cancer progression (Liu, Tsai, Hsu, Wu, & Yang, 2025).

Hypovitaminosis D is highly prevalent among BC individuals, with some studies estimating deficiency rates as high as 80%, particularly in those undergoing endocrine therapy. Vitamin D deficiency not only exacerbates bone loss but may also potentiate musculoskeletal adverse effects and contribute to chronic pain syndromes, thereby impacting quality of life (QoL) and treatment compliance (Zemlin et al., 2024a).

Bone-modulating agents as bisphosphonates (zoledronic acid) and Receptor Activator of Nuclear Factor Kappa-B (RANK) ligand inhibitors (denosumab) are widely used to counteract AI-induced bone loss. These agents act by inhibiting osteoclast-mediated bone resorption and have documented efficacy in preserving BMD and reducing fracture probability in this population. Notably, several large randomized clinical trials, including ABCSG-12, ZO-FAST, and AZURE, have suggested that adjuvant bisphosphonate therapy may also decrease the probability of bone metastases and BC recurrence, particularly in postmenopausal or estrogen-depleted females (Onuma et al., 2024).

Given the overlapping yet distinct roles of vitamin D and bone-modulating therapy in skeletal health and potentially in oncologic outcomes, understanding their combined and independent effects is of clinical importance. While vitamin D supplementation is routinely recommended during AI therapy, it is unclear whether it is sufficient as a standalone strategy to prevent bone loss in all patients, or whether early initiation of bone-modifying agents offers superior protection in certain subgroups. Moreover, the interplay among vitamin D status and the efficacy of bisphosphonates or denosumab in preventing skeletal events warrants further investigation (Onuma et al., 2024).

The aim of this work was to examine of the role of vitamin D and bone modulating therapy as regard improvement of the parameters of QoL in luminal non metastatic (M0) BC individuals treated with NSAI and assess if this primary end point consequently improves OS and DFS in luminal M0 BC individuals treated with NSAI.

Materials and Methods:

This prospective study was executed on 100 female participants diagnosed with postmenopausal M0 luminal BC suffering from low level of serum vitamin D and low bone density conducted in Clinical Oncology and Nuclear Medicine Department, Tanta University Hospitals from the period from March 2022 till June 2025. A documented form was gathered from the participants. The study was done after authorization from the Ethics Committee of the Faculty of Medicine, Tanta University Hospitals (approval code: 35323/3/22).

Inclusion criteria were postmenopausal females BC individuals that proved histologically to be luminal BC, negative metastatic work up, planned to receive NSAI ± luteinizing hormone receptor hormone agonist (LHRH), low serum vitamin

D level (<30ng/ml), low T- score in dual-energy X-ray absorptiometry (DEXA) scan (ranged from -1 to -2.4) and adequate hematological, renal and hepatic profiles.

Exclusion criteria were male patient, double malignancies, individuals with any bone disorder (including fracture) or affecting bone health e.g. hyperthyroidism, severe malabsorption syndrome and when the World Health Organization (WHO)/ Eastern Cooperative Oncology Group (ECOG) performance status was >2 (Kaur & Rayi, 2024).

All participants were placed randomly into two groups; each group contained 50 participants:
Group A (n=50): participants were treated with adjuvant NSAI plus vitamin D supplementation with bone antiresorptive agents and Group B (n=50): participants were treated with adjuvant NSAI plus vitamin D supplementation without bone antiresorptive agents.

All participants underwent accurate diagnosis and proper staging via [complete history, general and local clinical assessment, assessment of performance status according to WHO/ECOG (Eastern Cooperative Oncology Group) score (Kaur & Rayi, 2024) and nutritional screening by numeric rating scale (NRS) 2002 (Ana Cláudia Araújo Santana, Daiane Costa dos Santos, & Egea, 2024), investigations including pathology surgical excision (breast conservative surgery or modified radical mastectomy) and biomarkers on tissue, imaging studies encompassing (bilateral mamo-ultrasonography (US) or bilateral breast US, Chest X-ray or computed tomography (CT) chest, pelviabdominal US or Triphasic CT abdomen and pelvis with contrast, basal bone density image (BDI), DEXA scan, routine bone scan and If metastatic lesions were suspected, 18F-fluorodeoxyglucose positron emission tomography/ CT (18F-FDG PET/CT) and appropriate laboratory investigations were executed to aid in the detection and evaluation of metastatic disease.

Assessment and data collection:
All participants were examined as following before start treatment accurate staging, basal laboratory and imaging investigations (as level of vitamin D and bone DEXA scan), QoL assessment via Functional Assessment of Cancer Therapy-Breast (FACT-B) physical and functional wellbeing scales (PWS&FWS) (Version 4) (Al Maqbali et al., 2020; Su et al., 2025).

Follow up:
The level of vitamin D was examined regular every four months throughout therapeutic dose supplements used then was assessed every six months with FACT-B, serum total calcium, ionized calcium, phosphorus, 1,25 OH and months DEXA scan as routine follow up, up to three years. Clinical and laboratory records reviewed to assess the changes during treatment.

Treatment planning:
All participants had NSAI with or without LHRH agonist and vitamin D in therapeutic dose (200000 IU) every 4 weeks or (50000 IU) weekly till reaching more than 30 ng/ml; patients directed to receive daily requirement (800-1000 IU). Participants were advised to achieve adequate daily vitamin D requirements

through sunlight exposure, with the forearms, hands, or lower legs uncovered and without sunscreen. Recommended exposure durations were about 10–15 min for fair-skinned individuals and 25–40 min for those with darker skin. Also, they increase diets which contain small amounts of vitamin D e.g. liver, eggs or oily fish or they had daily 800-1000IU oral supplements. All these levels guided by the European Society for Clinical Nutrition and Metabolism **(**ESPEN) guidelines (Berger et al., 2022).

For group-B participants had antiresorptive agents every 6 months for 3 years. All participants followed regularly every 6 months by vitamin D level, ionized calcium and phosphorus levels, DEXA scan and evaluation of QoL via FACT-B (physical well-being (PWB) and functional well-being (FWB) scales). The DFS and OS with median of both were measured from the start of the randomization to time of event with comparison among the two groups.

Statistical analysis:

Analyses were executed via the R Statistical language (Team, 2020). Normal distribution was shown as the median, interquartile range, and range. The continuous variables following the normal distribution were shown as the mean, standard deviation, and range. Comparison among the groups were done via the Wilcoxon rank sum (Mann-Whitney) test and the two-sample T-test/Welch T-test for two-group comparisons. Comparisons among repeated measurements within each arm were executed via one-way, followed by a paired T-test with Holm-Bonferroni adjustment if ANOVA was significant. Categorical variables were shown as counts and percentages. The associations among the treatment arms and categorical variables were tested using Pearson's Chi-square test for independence of observations or the Chi-square test for trend in proportions (if the categorical variable was ordinal). Testing for paired categorical variables was executed via the Skillings-Mack Test, followed by the Stuart-Maxwell Marginal Homogeneity test if significant. Survival analysis was executed via Kaplan–Meier curves. Differences between groups were examined via the log-rank test. In cases where the median survival time was not reached, the mean survival time was documented with its corresponding confidence interval. A p-value 0.05 was selected (SG, 2003).

Results

The distribution of the investigated participants. **Figure 1**
the participants' profile were no significant difference among the investigated groups. **Table 1**
No significant difference was documented among the two groups in terms of laboratory investigations (vitamin D and calcium levels) and DEXA scan T-scores before starting the study. After 12 months, the average vitamin D levels were 30.8 in group A and 30.3 in group B, with no significant difference. The forearm T-score, spine T-score and femur T-score showing a significant improvement in T-scores in group A relative to group B after 12, 24, 36 months $p<0.05$. After 24 months, the mean vitamin D levels were 40.9 in group A and 39.1 in group B, with no significant p-value. After 36 months, the mean vitamin D levels were 43.6 in group A and 41.2 in group B, with no significant p-value. **Table 2**

The mean PWB scores were 23.86, 25.17, and 25.8 in group A and 21.7, 22.6, and 22.91 in group B, as listed, with a significant p-value**.** The mean FWB scores were 23.66, 25.25, and 25.98 in group A relative to 21.44, 22.93, and 23.23 in group B, as listed, with a significant p-value**. Table 3**

Concerning DFS events, group A who had a combination of vitamin D and bone-modifying agents were event-free relative to in group B who had only vitamin D, with no significant difference in the p-value. After 36 months of follow-up, the incidence of bone disease events was elevated in group B (5 events) than in group A (1 event). As the number of disease events did not reach 50% of participants, the median DFS could not be calculated. The mean time from randomization to event was 34.8 months in group A and 33.4 months in group B. No deaths occurred throughout the interval of the follow up in both groups, so the OS remained 100% in two groups till the end at 36 months after trial start. **Table 4**

Discussion:

BC is the leading cause of cancer-related mortality among females worldwide and ranks as the fourth most frequent cause of death globally (Bray et al., 2024). In Egypt, BC ranks as the second leading cause of cancer-related mortality, following hepatocellular carcinoma, and is related with a considerable estimated mortality rate (Azim et al., 2023).

All participants had NSAI with or without LHRH agonist and vitamin D in therapeutic dose (200000 IU) every four weeks or (50000 IU) weekly till reaching more than 30 ng/ml; participants directed to have daily requirement (800-1000 IU). For group-B participants received antiresorptive agents every six months for three years. Participants were examined at initiation and subsequently every 6 months with analysis at 12, 24, and 36 months. Evaluations encompassed laboratory tests evaluating serum vitamin D and calcium levels, bone mineral density measurement via DEXA scan, QoL examination via the FACT-B questionnaire (specifically the PWB and FWB scales), as well as clinical outcomes encompassing DFS, bone-specific DFS and OS.

In our study, baseline comparisons revealed no significant differences among the two groups concerning participants characteristics, vitamin D levels, bone mineral density T-scores at the forearm, spine, and femur or QoL as determined by the FACT-B questionnaire. After 12 months of follow-up, the mean vitamin D levels were 30.8 ng/mL and 30.3 ng/mL in groups A and B, as listed, with no significant difference. At 24 months, the mean levels increased to 40.9 ng/mL in group A and 39.1 ng/mL in group B, again without significant difference. By the end of the 36-month follow-up, the mean vitamin D levels reached 43.6 ng/mL in group A and 41.2 ng/mL in group B, with no significant intergroup difference observed.

These findings can be related to those of **(Zemlin et al., 2024b)** In their study, serum 25(OH)D concentrations were determined at initiation and every three months throughout the first year after diagnosis. Participants had vitamin D supplementation tailored to their levels, with a median weekly dose of 20,000 IU)

the median baseline 25(OH)D level was 24 ng/mL, increasing to a median of 48 ng/mL by study end.

At 12 months, the assessment of DEXA T-scores demonstrated significant improvements in group A relative to group B. Specifically, the proportion of participants with forearm T-scores ≥ -1 was significantly elevated in group A (37 participants, 74%) versus group B (20 participants, 40%). Similarly, the number of participants with spine T-scores ≥ -1 was greater in group A (21 participants, 42%) relative to group B (4 participants, 8%), reflecting a significant improvement favoring group A. For the femur, although the absolute number of participants with T-scores ≥ -1 was elevated in group B, the median change in T-score favored group A, with a median increase of 0.0 [IQR 0.0 to 0.5] relative to a median decrease of -0.1 [IQR -0.5 to 0.0] in group B, a difference that was significant.

At 24 months, these trends persisted and were even more pronounced. Forearm T-scores ≥ -1 were observed in 40 participants (83.3%) in group A versus 15 participants (33.3%) in group B. Spine T-scores ≥ -1 were noted in 31 participants (64.6%) in group A relative to only 3 participants (6.7%) in group B. For femur T-scores, 29 participants (60.4%) in group A versus 8 participants (17.8%) in group B had scores ≥ -1. The median change in femur T-scores remained significantly elevated in group A (0.0 [0.0 to 0.1]) versus group B (-0.1 [-0.2 to 0.0]). Importantly, all T-scores across forearm, spine, and femur in both groups remained above the osteoporosis threshold of -2.5 at this time point.

At the study conclusion after 36 months, group A continued to exhibit superior bone density outcomes. Forearm T-scores ≥ -1 were present in 43 patients (93.5%) in group A relative to 10 participants (23.3%) in group B. Spine T-scores ≥ -1 were found in 37 participants (80.4%) in group A versus only 1 participant (2.3%) in group B. Femur T-scores ≥ -1 were observed in 37 participants (80.4%) in group A relative to 8 participants (18.6%) in group B. The median changes in femur T-scores were 0.0 [0.0 to 0.4] in group A and 0.0 [-0.1 to 0.0] in group B, a significant difference. All participants in group A maintained T-scores above -2.5 across all sites, whereas in group B, 4 participants (9.3%) had forearm T-scores ≤ -2.5, 4 participants (9.3%) had spine T-scores ≤ -2.5, and 1 participant (2.3%) had femur T-scores ≤ -2.5, indicating the development of osteoporosis in a subset of group B.

Our results are aligned with those documented by (Ou, Lei, Wu, Guo, & Huang, 2024) In their study, participants were placed into two groups: one having oral calcitriol alone (control group, n=78) and the other having a combination of zoledronic acid and calcitriol (study group, n=72)) after 12 months, both groups demonstrated significant increases in BMD at the hip, femoral neck, and lumbar spine; however, the group treated with zoledronic acid exhibited significantly elevated BMD levels (P< 0.001).

In comparison to the findings ddocumented by (Gnant et al., 2022),demonstrated somewhat lower increases in BMD, (the ABCSG-18 trial was a prospective, double-blind, placebo-controlled phase 3 study involving 3,425 postmenopausal participants with early hormone receptor–positive BC subjected to aromatase inhibitor therapy.

Our results are also consistent with those reported by (de Sire et al., 2022) who found a clear relation among vitamin D status and bone density, with mean lumbar spine T-scores of -2.3, -2.1, -1.7, and -1.5 corresponding to vitamin D levels of ≤9.9 ng/mL, 10–19.99 ng/mL, 20–29 ng/mL, and ≥30 ng/mL, respectively. Similarly, femoral neck T-scores improved progressively from -2.4 to -1.6 across these vitamin D categories.

In our study, QoL was examined via the PWB and FWB subscales of the FACT-B questionnaire. Both scales demonstrated improvement over time in both treatment groups; however, the degree of improvement was consistently greater in participants who had bone-modifying agents (Group A) relative to those who did not (Group B). At 12, 24, and 36 months, the mean PWB scores in Group A were 23.86, 25.17 and 25.8, as listed, relative to 21.7, 22.6 and 22.91 in Group B, with significant differences documented at each time point. Similarly, FWB scores increased in both groups but were significantly elevated in Group A at each follow-up: 23.66, 25.25 and 25.98 in Group A versus 21.44, 22.93 and 23.23 in Group B, as listed.

These findings are in full consistent with that of (Ou et al., 2024) After 12 months, both their study and control groups documented significant decline in QUALEFFO-41 scores, indicating improved QoL, with significantly greater improvements observed in the group receiving zoledronic acid in combination with calcitriol ($P < 0.05$).

Our findings are further supported by (Cross et al., 2022) demonstrated that females with sufficient 25(OH)D levels (>30 ng/mL) at diagnosis had significantly better HRQoL both at diagnosis and one year later relative to those with deficient levels (<20 ng/mL). Moreover, vitamin D deficiency one-year post-diagnosis was related with persistently poorer HRQoL outcomes, even among BC survivors who were taking vitamin D supplements.

These findings align with our results, where serial follow-up showed a relation among improved vitamin D levels and enhanced QoL, as reflected by improvements in the FACT-B (PWB and FWB) scales. This underscores the important role of maintaining adequate vitamin D levels not only for bone health but also for overall well-being in BC participants receiving AIS.

In our study, DFS analysis showed that 92% of participants in Group A (who had a combination of vitamin D and bone-modifying agents) remained event-free after 36 months of follow-up, relative to 86% in Group B (who had vitamin D alone), though this difference was not significant. Regarding bone-related events specifically, Group B experienced a higher number of bone disease events (5 cases) relative to only 1 case in Group A, also without significance. As the total number of disease events did not exceed 50% of the study population, the median DFS could not be calculated. However, the mean time from randomization to event was slightly longer in Group A (34.8 months) relative to Group B (33.4 months), suggesting a possible clinical benefit.

These results differ from those reported by (Gnant et al., 2022), bone marrow failure syndromes (BMFS) were 88.9% in the denosumab arm versus 86.4% in the

placebo arm. While the absolute differences in that study were smaller than those observed in our, the longer follow-up period, the use of denosumab specifically, and a much larger sample size likely contributed to the statistical power and ability to detect significant survival differences

Our data are in agreement with those documented by (Vliek et al., 2022) reported 3-year DFS rates of 94% in the ibandronate group and 91% in the control group. At five years, DFS was 89% in the ibandronate arm versus 86% in the control arm, with no significant difference (P=0.811).

In our study, there were no deaths recorded during the entire 36-month follow-up period in either group, resulting in an OS rate of 100% for both. This emphasizes the potential protective role of maintaining normal vitamin D levels, particularly in relation to OS. These data are in line with those documented by (İşbilen, Kus, Yeşil, Aktas, & Buyukbebeci, 2021) who also recorded a significant link among 25-hydroxy vitamin D levels and OS. Among the four patient subgroups in their study, only group 2—those with persistently insufficient vitamin D levels—exhibited significantly worse OS relative to group 1, who maintained adequate levels throughout (P=0.025). In contrast, our findings did not align with those of (Coleman et al., 2020) where 253 BMFS-related deaths were reported—137 (6%) in the denosumab group and 116 (5%) in the placebo group.
The limitations of the study were that single centre study, relatively dimensioned sample size.

Conclusions:

The integration of vitamin D normalization and bone-modifying agents in postmenopausal females with luminal participants receiving adjuvant NSAIs represents a powerful approach to preserving bone integrity and preventing debilitating bone loss (T-score ≥ -1), remains a cornerstone in the prevention and management of skeletal complications of AIs and improving long-term outcomes for patients, improving QoL and enhancing DFS outcomes.

Therefore, the study recommends that combining vitamin D with bone-modifying agents in patients receiving AIs can synergistically improve bone health and treatment outcomes, regular monitoring of vitamin D levels and assessment of bone health is essential, patients ought to be educated about the importance of adherence to therapy, further research is necessary to examine the applicability of the combined use of bone-modifying agents and vitamin D supplementation in premenopausal populations and in individuals with diverse molecular subtypes of participants, encompassing human epidermal growth factor 2 receptors (HER2)-positive and triple-negative diseases and special attention toward future effective oral form of bone modifying agent.

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Nil

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HER2-positive	Human epidermal growth factor 2 receptors
TNBC	Triple-negative breast cancers
NSAI	Non-steroidal Aromatase Inhibitors
DFS	Disease-free survival
OS	Overall survival
PWB	Physical well-being
FWB	Functional well-being
ER+	Estrogen receptor-positive
AIs	Aromatase inhibitors
LHRH	Luteinizing hormone receptor hormone agonist
ECOG	Eastern cooperative oncology group
US	Ultrasonography
CT	Computed tomography
BDI	Basal bone density image
FACT-B	Functional Assessment of Cancer Therapy-Breast
ESPEN	European Society for Clinical Nutrition and Metabolism

Table 1: Participants' profile

		Group A (N = 50)	Group B (N = 50)	P-value
Age (years)		52.6 ± 10.7	52.2 ± 10.8	0.853
NRS 2002, n (%)	**1**	33 (66.0%)	30 (60.0%)	0.534
	2	17 (34.0%)	20 (40.0%)	
ECOG, n (%)	**0**	24 (48.0%)	27 (54.0%)	0.548
	1	26 (52.0%)	23 (46.0%)	
ER, n (%)	**Negative**	0 (0.0%)	0 (0.0%)	>0.999
	Positive	50 (100.0%)	50 (100.0%)	
PR, n (%)	**Negative**	8 (16.0%)	15 (30.0%)	0.096
	Positive	42 (84.0%)	35 (70.0%)	
HER2 overexpression, n (%)	**No**	37 (74.0%)	40 (80.0%)	0.476
	Yes	13 (26.0%)	10 (20.0%)	
Ki67, n (%)	**Negative (<15%)**	21 (42.0%)	22 (44.0%)	0.840
	Positive (≥15%)	29 (58.0%)	28 (56.0%)	
Luminal subtypes, n (%)	**A**	11 (22.0%)	17 (34.0%)	0.181
	B	39 (78.0%)	33 (66.0%)	
T stage, n (%)	**T1**	11 (22.0%)	11 (22.0%)	0.256
	T2	27 (54.0%)	34 (68.0%)	
	T3	7 (14.0%)	2 (4.0%)	
	T4	5 (10.0%)	3 (6.0%)	
N stage, n (%)	**N0**	21 (42.0%)	17 (34.0%)	0.756
	N1	12 (24.0%)	16 (32.0%)	
	N2	13 (26.0%)	14 (28.0%)	
	N3	4 (8.0%)	3 (6.0%)	
AJCC stage, n (%)	**IA**	7 (14.0%)	6 (12.0%)	0.774
	IIA	11 (22.0%)	12 (24.0%)	
	IIB	11 (22.0%)	12 (24.0%)	
	IIIA	12 (24.0%)	14 (28.0%)	
	IIIB	5 (10.0%)	3 (6.0%)	
	IIIC	4 (8.0%)	3 (6.0%)	
Grade, n (%)	**1**	0 (0.0%)	2 (4.0%)	0.310
	2	46 (92.0%)	45 (90.0%)	
	3	4 (8.0%)	3 (6.0%)	
Chemotherapy, n (%)	**No**	12 (24.0%)	9 (18.0%)	0.461
	Yes	38 (76.0%)	41 (82.0%)	
Surgery, n (%)	**BCS**	25 (50.0%)	24 (48.0%)	0.841
	MRM	25 (50.0%)	26 (52.0%)	
Radiotherapy, n (%)	**No**	0(0%)	0(0%)	--
	Yes	50(100%)	50(100%)	

Data are shown as mean ± SD or frequency (%). * Significant at $p<0.05$. NRS: Nutritional Risk Screening, ER: Estrogen receptor, HER2: Human epidermal growth factor 2 receptors.

Table 2: Comparison among group A and group B of laboratory tests and DEXA scan before starting the study, after 12, 24, 36 months.

		Group A N = 50	Group B N = 50	P-value
Laboratory investigation and DEXA scan before starting the study				
Basal evaluation	**Vitamin D (ng/ml)**	17.6 ± 4.9	16.4 ± 5.0	0.226
	Ionized Ca (mmol/l)	1.2 ± 0.1	1.2 ± 0.1	0.479
Forearm T-score	**Forearm T-score**	-0.7 ± 1.0	-0.5 ± 1.1	0.315
	≤-2.5	0 (0.0%)	0 (0.0%)	>0.999
	>-2.5 to<-1	19 (38.0%)	19 (38.0%)	
	≥ -1	31 (62.0%)	31 (62.0%)	
Spine T-score	**Spine T-score**	-1.7 ± 0.9	-1.4 ± 0.9	0.062
	≤-2.5	0 (0.0%)	0 (0.0%)	>0.999
	>-2.5 to<-1	43 (86.0%)	43 (86.0%)	
	≥ -1	7 (14.0%)	7 (14.0%)	
Femur T-score,	**Femur T-score**	-1.2 ± 0.8	-0.9 ± 0.9	0.104
	≤-2.5	0 (0.0%)	0 (0.0%)	0.295
	>-2.5 to<-1	35 (70.0%)	30 (60.0%)	
	≥ -1	15 (30.0%)	20 (40.0%)	
Laboratory investigation and DEXA scan after 12 months				
Basal evaluation	**Vitamin D (ng/ml)**	30.8 ± 5.3	30.3 ± 4.8	0.651
	Ionized Ca (mmol/l)	1.2 ± 0.1	1.2 ± 0.1	0.554
Forearm T-score	**Forearm T-score**	-0.2 ± 1.0	-0.9 ± 0.8	**<0.001***
	≤-2.5	0 (0.0%)	0 (0.0%)	
	>-2.5 to<-1	13 (26.0%)	30 (60.0%)	
	≥ -1	37 (74.0%)	20 (40.0%)	
Change in forearm T-score		0.2 [0.0 to 0.8]	-0.1 [-0.6 to 0.0]	**<0.001***
Spine T-score	**Spine T-score**	-0.8 ± 1.2	-1.5 ± 0.7	**<0.001***
	≤-2.5	0 (0.0%)	0 (0.0%)	
	>-2.5 to<-1	29 (58.0%)	46 (92.0%)	
	≥ -1	21 (42.0%)	4 (8.0%)	
	Change in spine T-score	0.5 [0.1 to 1.3]	0.0 [-0.1 to 0.0]	
Femur T-score,	**Change in Femur T-score**	0.0 [0.0 to 0.5]	-0.1 [-0.5 to 0.0]	**<0.001***
	≤-2.5	0 (0.0%)	0 (0.0%)	
	>-2.5 to<-1	28 (56.0%)	35 (70.0%)	
	≥ -1	22 (44.0%)	15 (30.0%)	
Laboratory investigation and DEXA scan after 24 months				
Basal evaluation	**Vitamin D (ng/ml)**	40.9 ± 5.2	39.1 ± 5.3	0.098
	Ionized Ca (mmol/l)	1.2 ± 0.0	1.2 ± 0.0	0.350
Forearm T-score, n (%)	**Forearm T-score**	0.0 ± 0.9	-1.0 ± 0.8	**<0.001***
	≤-2.5	0 (0.0%)	0 (0.0%)	
	>-2.5 to<-1	8 (16.7%)	30 (66.7%)	
	≥ -1	40 (83.3%)	15 (33.3%)	
	Change in forearm T-score	0.0 [0.0 to 0.0]	0.0 [-0.3 to 0.0]	**0.005***

Spine T-score	**Spine T-score**	0.0 ± 1.2	-1.8 ± 0.6	**<0.001***
	≤-2.5	0 (0.0%)	0 (0.0%)	
	>-2.5 to<-1	17 (35.4%)	42 (93.3%)	
	≥ -1	31 (64.6%)	3 (6.7%)	
	Change in spine T-score,	0.2 [0.0 to 1.9]	0.0 [-0.4 to 0.0]	
Femur T-score	**Femur T-score**	-0.5 ± 0.9	-1.4 ± 0.7	**<0.001***
	≤-2.5	0 (0.0%)	0 (0.0%)	
	>-2.5 to<-1	19 (39.6%)	37 (82.2%)	
	≥ -1	29 (60.4%)	8 (17.8%)	
	Change in femur T-score	0.0 [0.0 to 0.1]	-0.1 [-0.2 to 0.0]	
Laboratory investigation and DEXA scan after 36 months				
Basal evaluation	**Vitamin D (ng/ml)**	43.6 ± 5.0	41.2 ± 4.9	**0.024***
	Ionized Ca (mmol/l)	1.2 ± 0.0	1.2 ± 0.1	0.342
Forearm T-score	**Forearm T-score**	0.2 ± 0.8	-1.5 ± 0.9	**<0.001***
	≤-2.5	0 (0.0%)	4 (9.3%)	
	>-2.5 to<-1	3 (6.5%)	29 (67.4%)	
	≥ -1	43 (93.5%)	10 (23.3%)	
	Change in forearm T-score	0.0 [0.0 to 0.0]	0.0 [-0.7 to 0.0]	
Spine T-score	**Spine T-score**	0.4 ± 1.0	-1.9 ± 0.6	**<0.001***
	≤-2.5	0 (0.0%)	4 (9.3%)	
	>-2.5 to<-1	9 (19.6%)	38 (88.4%)	
	≥ -1	37 (80.4%)	1 (2.3%)	
	Change in spine T-score	0.0 [0.0 to 0.4]	0.0 [-0.2 to 0.0]	**<0.001***
Femur T-score	**Femur T-score**	-0.2 ± 0.8	-1.6 ± 0.7	**<0.001***
	≤-2.5	0 (0.0%)	1 (2.3%)	
	>-2.5 to<-1	9 (19.6%)	34 (79.1%)	
	≥ -1	37 (80.4%)	8 (18.6%)	
	Change in femur T-score	0.0 [0.0 to 0.4]	0.0 [-0.1 to 0.0]	

Data are shown as mean ± SD or frequency (%).* Significant at P<0.05. DEXA: Dual-Energy X-Ray Absorptiometry

Table 3: PWB scale changes and FWB scale changes in our study

	Time at measurement (Months)				P-value
	PWB scale				
	0	12	24	36	
Group A					
Mean ± SD	17.32 ± 3.51	23.86 ± 1.86	25.17 ± 1.33	25.80 ± 1.02	**<0.001***
Number of patients	50	50	48	46	
Group B					
Mean ± SD	18.44 ± 3.05	21.70 ± 2.97	22.62 ± 2.11	22.91 ± 1.87	**<0.001***
Number of patients	50	50	45	43	
FWB scale					
Group A					
Mean ± SD	17.46 ± 3.85	23.66 ± 2.08	25.25 ± 1.48	25.98 ± 1.04	**<0.001***
Number of patients	50	50	48	46	
Group B					
Mean ± SD	17.52 ± 2.96	21.44 ± 2.73	22.93 ± 2.26	23.23 ± 1.93	**<0.001***
Number of patients	50	50	45	43	

Data are shown as mean ± SD. * Significant at $p<0.05$.

Table 4: Disease events and specific site of events, the mean time of DFS and death events in both groups

		Group A (N = 50)	Group B (N = 50)	p-value
Progression, n (%)	**No**	46 (92.0%)	43 (86.0%)	0.338
	Yes	4 (8.0%)	7 (14.0%)	
Progression sites	**Liver, n (%)**	0 (0.0%)	2 (28.6%)	0.491
	Bone, n (%)	1 (25.0%)	5 (71.4%)	0.242
	Brain, n (%)	1 (25.0%)	0 (0.0%)	0.364
	Lung, n (%)	2 (50.0%)	1 (14.3%)	0.491
	Local, n (%)	0 (0.0%)	1 (14.3%)	>0.999
Time from study's start to progression		36.0 [36.0 - 36.0]	36.0 [36.0 - 36.0]	0.301
RMST (95% CI)		34.80 (33.59 to 36.01)	33.36 (31.46 to 35.26)	0.211
Death, n (%)		50 (100.0%)	50 (100.0%)	--

Data are presented as frequency (%) or median. * Significant at $p<0.05$.

Figure legends:
Figure 1: The flowchart of the enrolled participants