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**Original Research Article**

# Factors influencing bone metastasis in HER-2 negative breast cancer and the efficacy of capecitabine plus docetaxel

**Wei Zhang[1], Tianzuo Chen[1], Yan Gao, Yapeng Hu[1], Jingjing Zhao[2], Chunluan Yuan[3]***

*[1]Graduate Training Base of Lianyungang First People's Hospital of Jinzhou Medical University, [2]Lianyungang Clinical College of Nanjing Medical University/The First People's Hospital of Lianyungang, [3]Oncology Department, The First People's Hospital of Lianyungang, Lianyungang, Jiangsu 222000, China*

**For correspondence:* ***Email:*** *Yuanchunllyg@outlook.com*

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## Abstract

***Purpose:*** *The clinical data of HER-2 negative breast cancer patients were analyzed to investigate factors that influence bone metastasis.*

***Methods:*** *A total of 754 HER-2 negative breast cancer patients composed of the bone metastasis (237 patients) and non-bone metastasis (481 patients) group, were retrospectively and systematically evaluated for their clinicopathological characteristics, treatment modalities and their influencing factors. Both groups were administered a combined treatment of capecitabine and docetaxel and the statistical association between these factors and the development of bone metastases was investigated. Primary tumor location was identified through imaging while the hormone receptor status and tumour molecular classification were assessed by immunohistochemistry (IHC) on tumor samples and protein expression/genetic profiling, respectively.*

***Results:*** *A significant difference was seen between the groups in terms of T-stage, N-stage, hormone receptors, tumour molecular classification, axillary lymph node metastasis and quality of life scores (FACT-B) after combined therapy with capecitabine plus docetaxel ($p < 0.05$), while statistical significance was absent in terms of age and location of the primary site ($p > 0.05$). Furthermore, logistic regression analysis revealed that high T-stage, Luminal A molecular staging and the occurrence of axillary lymph node metastases were all risk factors for bone metastases in HER-2 negative breast cancer patients ($p < 0.001$).*

***Conclusion:*** *Combined therapy with capecitabine and docetaxel is effective in the treatment of bone metastases in patients with HER-2 negative breast cancer. A more comprehensive study involving a larger population of diverse patients will be conducted in the future to provide more reliable clinical data.*

***Keywords:*** *Breast cancer, Bone metastases, HER-2 negative, Capecitabine/docetaxel therapy*



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## INTRODUCTION

Breast cancer is the most common female malignancy with approximately 1.7 million new cases reported worldwide each year [1]. Bone, lung and liver metastases develop in more than 75 % of patients with intermediate to advanced breast cancer, with bone metastases being the most common [2-4]. Bone metastases,

secondary to breast cancer, are associated with an array of skeletal-related events (SREs) such as pathological fractures, hypercalcaemia and persistent bone pain [5]. The median time from diagnosis of bone metastases to the first SRE can be as short as 1.8 months, and the incidence of SREs increases significantly in the first 12 months after the diagnosis of bone metastases, resulting in an increased burden of life for breast cancer patients [6].

Cisplatin and paclitaxel are commonly recommended as adjuvant therapy for breast cancer patients in the early stages of the disease. However, their efficacy is unsatisfactory. Capecitabine and docetaxel are clinically effective in regulating nucleic acid synthesis to achieve anti-tumour effects [7]. Thus, accurate prediction of the risk of bone metastasis in breast cancer patients in the short term and more reasonable drug administration for risk control can provide relief to patients' pain and reduce their life and psychological burden. To this end, the current research was performed to investigate the factors that influence bone metastasis.

## METHODS

### Baseline patient profiles

The clinical data of 754 patients with HER-2 negative breast cancer, who were admitted to the First People's Hospital of Lianyungang, China, from January 2017 to September 2022, were retrospectively analyzed. The subjects comprised of 273 patients in the bone metastasis group and 481 patients in the non-bone metastasis group, with incidence rate of bone metastases of 36.21 %. All patients signed an informed consent form for treatment and participation in the study. In addition, the protocol was approved by the Ethics Committee of The First People's Hospital of Lianyungang (approval no. LW-20210328002-01) and all patients were treated in accordance with the NCCN guidelines for breast cancer treatment [8].

### Classification

The patients were grouped by different factors including age (whether they were older than 50 years), primary tumour location, T-stage, N-stage, Estrogen Receptor (ER), Progesterone Receptor (PR), tumour molecular classification (Luminal A, Luminal B or triple-negative), axillary lymph node metastasis and quality of life score after combined therapy with capecitabine plus docetaxel.

### Inclusion criteria

Patients aged 18 or above, with a diagnosis of early-stage breast cancer (stages I, II, or III), and hormone receptor-negative status (ER and PR), particularly for patients with triple-negative breast cancer (TNBC), were included as study subjects. Additionally, included patients had not received prior chemotherapy or radiotherapy for their current breast cancer, had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (indicating good overall health), had an expected lifespan of at least three months, and also possessed adequate organ functions, including bone marrow, liver and kidney. Patients were capable of adhering to study requirements and were also willing to participate in follow-up treatment.

### Exclusion criteria

This includes the presence of other active malignancies, severe cardiac disease or heart failure, known allergy to capecitabine or docetaxel, pregnancy or breastfeeding, uncontrolled infections or severe complications, severe hematological abnormalities (such as thrombocytopenia or anemia), and severe liver or kidney dysfunction.

Furthermore, patients who were receiving other clinical trial medications or treatments, as well as those who could not comply with the study protocol or could not undergo regular follow-up, were also excluded from the study.

### Patients handling and drug administration

Clinical data including age, location of the primary breast site, T-stage, lymph node metastasis, ER, PR and other clinical data characteristics were recorded. All patients included in the study were given capecitabine plus docetaxel and the statistical association between these factors and the development of bone metastases was investigated according to the presence of a significant improvement in the quality-of-life scores.

In the combination therapy of capecitabine and docetaxel, capecitabine was prescribed at a dose of 1250 mg/m² and administered orally, twice daily (morning and evening). The treatment continued for 14 consecutive days, after which patients were given a 7-day rest period culminating in a 21-day treatment cycle. On the other hand, docetaxel was administered at a dosage of 75 mg/m² and given intravenously over the course of 1 hour. Unlike capecitabine, docetaxel was administered less frequently, with

treatments occurring once every 3 weeks. Patients adhered very strictly to the dosing schedule provided by their healthcare provider to maximize the therapeutic benefits and minimize potential adverse effects. The clinical indicators and risk factors that predispose patients with this group of breast cancers to bone metastases were analyzed.

### Evaluation of parameters/indices

#### *Specific indicators*

In breast cancer clinical trials, specific indicators are used to categorize and analyze patient data effectively. Age was verified against medical records, with a cut-off of 50 years often used due to its prognostic significance.

### Primary tumor location

Primary tumor location was identified through imaging and biopsy, influencing treatment approaches. The T-stage, reflecting tumor size and local invasion, was assessed through clinical exams and pathology reports, following the TNM system. Also, the N-stage, indicative of regional lymph node involvement, was determined by biopsy and pathological analysis.

### Hormone receptor status

Hormone receptor status (ER and PR) was established through immunohistochemistry (IHC) on tumor samples, guiding endocrine therapy decisions.

### Tumor molecular classification

Tumor molecular classification into Luminal A, Luminal B, or Triple-Negative was based on IHC for protein expression and genetic profiling, affecting targeted therapy options. Axillary lymph node metastasis, a strong prognostic factor, was confirmed through sentinel node biopsy or dissection.

### Quality of life

Lastly, the impact of therapy on patients' quality of life was evaluated post-treatment using standardized questionnaires, such as the EORTC QLQ-C30 or FACT-B, to ascertain physical, emotional and social well-being. These indicators were meticulously selected for their relevance in understanding disease progression, treatment efficacy and patient outcomes, ensuring that clinical trial results are comprehensive and applicable to a wider population.

### Statistical analysis

Data analyses were performed using SPSS 26.0 statistical software. The differences in clinical data between patients with and without bone metastases were assessed using the chi-square test and the Mann-Whitney U test. Variables with statistically significant differences were included in a binary logistic regression analysis of factors influencing bone metastases in breast cancer. Values of $p < 0.05$ were considered statistically significant.

## RESULTS

### Clinical data analysis of patients with and without bone metastases

A significant difference was found between the patients in the bone metastasis group and those in the non-bone metastasis group in terms of T-stage, N-stage, ER, PR, tumour molecular classification, axillary lymph node metastasis and quality of life scores (FACT-B) after combined therapy with capecitabine plus docetaxel ($Z = -2.706$, $Z = -2.864$, $X2 = 75.954$, $X2 = 55.618$, $X2 = 114.854$, $X2 = 305.211$, $X2 = 66.945$, $p < 0.05$), while statistical significance was absent in terms of age and location of the primary site ($X2 = 2.888$ and $X2 = 1.903$, $p > 0.05$; Table 1).

### Logistic regression analysis

Statistically significant case numerical characteristics were included in a binary logistic regression analysis (Table 2 for details of variable assignments). The results showed that ER-positive, PR-positive, and high N-stage, though all statistically significant in terms of differences, were not statistically supported as risk factors for bone metastases in HER-2 negative breast cancer. Also, logistic regression analysis revealed that high T-stage, Luminal A molecular staging and the occurrence of axillary lymph node metastases were all risk factors for bone metastases in HER-2 negative breast cancer patients (OR = 4.352, 95 % CI = 2.147 to 8.823, $p < 0.001$; OR = 0.281, 95 % CI = 0.179 to 0.441, $p < 0.001$; OR = 12.766, 95 % CI = 6.712 to 24.283, $p < 0.001$; Tables 2 and 3).

## DISCUSSION

Studies have shown that bone metastases are the most common type of metastasis from breast cancer and that the risk of bone metastases increases as breast cancer develops over time. Patients with bone metastases present a relatively good prognosis compared to other metastases [9]. Nevertheless, the quality of life of

patients decreases as SREs rise, resulting in a significant increase in the burden of life and psychological burden of patients. With the availability of predictive index parameters for bone metastases in HER-2 negative breast cancer, early interventions against the risk of bone metastases are available to avoid the impact of premature bone metastases on the patient's quality of life and to improve the prognosis of the patient's quality of life by employing the most appropriate drugs for different patients with bone metastases.

**Table 1:** Clinicopathological characteristics of breast cancer patients with and without bone metastases

| Clinical feature | Bone metastasis group | Non-bone metastasis group | Test value | P-value |
|---|---|---|---|---|
| Age | | | | |
| ≤50 | 130(47.6) | 260(54.1) | **(**$X^2$)=2.888 | 0.64 |
| >50 | 143(52.4) | 221(45.9) | | |
| Location of primary focus | | | | |
| Left breast | 169(61.9) | 208(43.2) | $X^2$=1.903 | 0.704 |
| Right breast | 104(38.1) | 273(56.8) | | |
| T staging | | | | |
| T1 | 26(9.6) | 223(46.4) | | 0.003 |
| T2 | 182(66.5) | 201(41.8) | Z=-2.706 | |
| T3 | 39(14.3) | 44(9.1) | | |
| T4 | 26(9.6) | 13(2.7) | | |
| N staging | | | | |
| N0 | 14(5.1) | 260(54.1) | | <0.001 |
| N1 | 116(42.5) | 156(32.4) | Z=-2.864 | |
| N2 | 65(23.8) | 52(10.8) | | |
| N3 | 78(28.6) | 13(2.7) | | |
| ER | | | | |
| Positive | 222(81.3) | 234(48.6) | $X^2$ = | 0.017 |
| Negative | 51(18.7) | 247(51.4) | 75.954 | |
| PR | | | | |
| Positive | 195(71.4) | 208(43.2) | $X^2$ = | 0.040 |
| Negative | 78(28.6) | 273(56.8) | 55.618 | |
| Molecular classification of tumours | | | | |
| Luminal A | 182(65.9) | 130(27.1) | $X^2$=114.85 | 0.013 |
| Luminal B | 39(14.2) | 118(24.5) | 3 | |
| Triple negative | 52(19.8) | 233(48.4) | | |
| Lymph node metastasis | | | | |
| Axillary lymph node metastasis | 247(90.5) | 143(29.7) | $X^2$ =305.211 | <0.001 |
| No axillary lymph node metastasis | 26(9.5) | 338(70.3) | | |
| Functional Assessment of Cancer Therapy - Breast (FACT-B) score (FACT-B) after combined therapy of capecitabine plus docetaxel | | | | |
| Significant increase | 199(72.6) | 227(47.2) | $X^2$ = | 0.021 |
| No significant increase or decrease | 75(27.4) | 254(52.8) | 66.945 | |

**Table 2:** Logistic regression analysis variable assignment

| Factor | Variable | Assignment |
|---|---|---|
| ER | $X_1$ | Negative = 0<br>Positive = 1 |
| PR | $X_2$ | Negative = 0<br>Positive = 1 |
| T staging | $X_3$ | T1, T2 = 0<br>T3, T4 = 1 |
| N staging | $X_4$ | N0 = 0<br>N1~3 = 1 |
| Molecular tumour classification | $X_5$ | Luminal A = 0<br>Non luminal A= 1 |
| Lymph node metastasis | $X_6$ | No axillary lymph node metastasis =0<br>Axillary lymph node metastasis =1 |

**Table 3:** Logistic regression analysis of factors influencing bone metastases in HER-2 negative breast cancer

| Variable | Regression coefficient | Standard Error | P-value | OR value | 95% Confidence interval | |
|---|---|---|---|---|---|---|
| | | | | | Lower limit | Upper limit |
| T staging | 1.471 | 0.369 | 0.000 | 4.352 | 2.147 | 8.823 |
| N staging | 0.449 | 0.436 | 0.302 | 1.567 | 0.667 | 3.681 |
| ER | -0.088 | 0.283 | 0.756 | 0.916 | 0.526 | 1.596 |
| PR | 0.353 | 0.229 | 0.135 | 1.423 | 0.896 | 2.261 |
| Molecular classification | -1.269 | 0.328 | 0.000 | 0.281 | 0.179 | 0.441 |
| Lymphatic metastases | 2.547 | 0.365 | 0.000 | 12.766 | 6.712 | 24.283 |

The recommended chemotherapy drugs for breast cancer include anthracycline, paclitaxel and cyclophosphamide. However, a recurrence of the disease leads to poor prognosis and renders second-line treatment impractical. Docetaxel is a paclitaxel drug that promotes the polymerization of microtubulin and inhibits its depolymerization, thereby disrupting the mitotic formation of tumour cells to exert anti-tumour effects. Capecitabine, a new oral fluorouracil carbamate, activates the conversion of cellular thymidine phosphorylase into 5-fluorouracil, exerting anti-tumour effects with less destructive side effects on normal tissue cells [8,10]. In this study, patients with bone metastases receiving capecitabine plus docetaxel showed a significant improvement in quality-of-life scores than those without bone metastases. The results suggested that capecitabine plus docetaxel provide clinical and prognosis benefits for HER-2 negative breast cancer patients with bone metastases. Thus, its clinical use is recommended in the context of drug safety.

Novel bone interventions targeting small molecule inhibitors and nanoparticles are highly promising in the near future [11]. Previous results have shown that a primary lesion with a maximum diameter > 2 cm, an aspect ratio ≤ 1, uneven internal echogenicity, poorly defined borders and Adler flow grade II-III are independent risk factors for axillary lymph node metastasis from breast cancer [12-14]. In this study, the analysis of clinical data identified high T-stage, Luminal A and axillary lymph node metastasis as influencing factors for bone metastasis in HER-2 negative breast cancer patients. This provides a more effective and reliable preventive treatment option for patients without bone metastasis.

### Limitations

The study has some limitations. Firstly, the limited sample size of this study may result in some biases in the conclusion of the study. In addition, the study lacks data on the treatment information, including surgical protocols and medication regimens.

## CONCLUSION

Combined therapy of capecitabine and docetaxel is effective in the treatment of bone metastases in patients with HER-2 negative breast cancer. The occurrence of bone metastases in HER-2 negative breast cancer is statistically correlated with T-stage, N-stage, ER, PR, molecular tumour staging, axillary lymph node metastasis and patient quality of life scores after combined therapy with capecitabine plus docetaxel. High T-stage, Luminal A and axillary lymph node metastasis were all risk factors.

## DECLARATIONS

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None provided.

### *Ethical approval*

None provided.

### *Availability of data and materials*

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### *Conflict of Interest*

No conflict of interest associated with this work.

### *Contribution of Authors*

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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