Bone metastases at initial diagnosed breast cancer —
A retrospective study based on SEER database

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Abstract

Background

To explore the features of incidence proportions and long-term survivals of breast cancer patients with bone metastasis when first diagnosed.

Methods

Data were extracted from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute. Stratifications were made according to molecular subtype, age, sex, race and other factors. We performed multivariable logistic and Cox regression analysis to detect predictors of occurrence of bone metastasis at first diagnosis and factors related to all-cause mortality.

Results

We identified 310789 patients with breast cancer within the study period. Approximately 3.6% patients were diagnosed as bone metastasis within the entire cohort and 50.5% of the metastasis cohort. The highest incidence was from the cohorts of HR+/HER2+ (5.0% of the entire cohort). N3, metastases to brain, lung and liver were associated with higher possibility of developing bone metastases. For survival, HR+/HER2+ experience the longest survival time (41 months) and triple-negative patients had the shortest survival period (10 months). lymph node status other than N0 and distal metastasis to brain, lung and liver as possible factors which were associated with higher all-cause mortality.

Conclusions

We recommend routine bone screen at first diagnosis within high risk patients.

Background

Breast cancer is one of the most common malignancy in female and nearly 12% of diagnosed breast cancer is metastatic (1-3). Bone metastases is a common site for metastases among breast cancer patients and counts for approximately 70% of disease specific death according to previous study (4-6). However, population-based study of robust estimates relating to the incidence of bone metastases at diagnosis of breast cancer is lacking, partly due to the International Classification of Diseases (ICD)
coding system did not label out metastases subtype of cancer patients. In previous autopsy studies, 74% of patients were found to have bone metastases, part of these patients was not clinically apparent prior to death(7). Because of lacking existed evidence, there is no recommendation for routine assessment or continued reassessment of bone metastases(8, 9). Thus, most patients with bone metastases are diagnosed by symptoms which usually necessitating interventions to prevent further adverse events(10). Studies of population-based for prognosis among patients with newly diagnosed bone metastases are currently lacking. Hence, the present study used the Surveillance, Epidemiology, and End Results(SEER) database to investigate the incidence proportion of bone metastases in breast cancer as main goal. The second aim of this study is to estimate survival data and find sociodemographic and clinical predictors relevant to poorer survival.

Methods
Data of cancer incidence, treatment and survival of nearly 30% of the US population from 20 cancer registries was included in the SEER database. We downloaded the data from 2010 to 2014 through SEER stat. We extracted data of patients of invasive breast cancer with confirmed bone metastases at initial diagnosed. Further screening was conducted to exclude bone metastases by autopsy or death certificate as well as patients without complete follow-up records. We studied the data by stratifying breast cancer by molecular subtype; hormone receptor-positive human epidermal growth factor receptor-2 negative (HR +/HER2-), HR+/HER2+, HR-/HER2+ and triple-negative breast cancer (TNBC). Calculation was made among exact number and incidence proportions after stratification by age, race and gender. Two kinds of incidence proportion were calculated, bone metastases divided by total breast cancer as the first and bone metastases divided by all metastases as the second. Multivariable logistic regression was performed to investigate the relevant influential factors of presence of bone metastases if there were available from SEER. By using Kaplan-Meier method, survival estimates were conducted. To identify covariates associated with mortality, multivariable Cox regression was performed. All data was obtained using SEER*Stat Software version 8.3.4 (https://seer.cancer.gov/seerstat/). Statistical analyses were performed by SPSS statistical software version 21. All P values were two-sided, and P≤0.05 was considered significant.
Results

Incidence  We identified 310789 patients with breast cancer diagnosed from 2010 to 2014. Stratified by molecular subtype, there were 61.7%, 9.5%, 4.1%, 10.4%, 8.9% patients molecularly tested as HR+/HER2-, HR+/HER2+, HR-/HER2+, TNBC and unknown respectively. Among metastases to any site patients, there were 50%, 14%, 7.6%, 11% and 17.4% tested as HR+/HER2-, HR+/HER2+, HR-/HER2+, TNBC and unknown respectively. Within all included patients, 11300 had bone metastases which took up 3.6% of the entire cohort and 50.5% of metastases patients. The highest incidence proportion was from the HR+/HER2+ (5.0%) and HR-/HER2+ (4.5%) cohort. (Shown in Table 1). Based on our multivariable logistic regression analysis, HR+/HER2+ compared with HR+/HER2- (OR, 1.19; 95% CI, 1.06 -1.35; P = 0.003), N3 compared with N0 (OR, 2.76; 95% CI, 1.66-4.60; P < 0.01), metastases to brain compared with None (OR, 4.03; 95% CI, 2.67 -6.09; p<0.01), to lung compared with None (OR, 27.31; 95% CI, 20.06-37.17; p<0.01) and liver compared with None (OR, 10.45; 95% CI, 4.63-23.59; p<0.01) were associated with higher possibility of developing bone metastases. Triple-Negative was associated with lower risk of bone metastases at diagnosis compared with HR+/HER2- (OR, 0.72; 95% CI, 0.64-0.82; P <0.01). Other factors such as age, gender and marital status were not significantly related to developing bone metastases. (Shown in Table 2)

Survival  According to eligible data, patients stratified by molecular subtype with follow-up during the study time were summarized in Table 1. As shown in Figure 1, among patients with bone metastases at diagnose, HR+/HER2+ experienced the longest survival time (41 months) and triple-negative patients had the shortest survival period (10 months). Figures comparing bone metastases (median survival 30 months) with lung (21 months), brain (11 months) and liver (19 months) was shown as Figure 2, Figure 3 and Figure 4. Comparing with other distal organ metastases, bone metastases had longer survival time. By performing Cox Regression Analysis, we identified age between 61 to 80 (vs. age 18-40; hazard ratio[HR], 1.79; 95% CI, 1.68-1.91, p<0.01) and older than 80 (vs. age 18-40; HR, 5.32; 95% CI, 4.99-5.67, p<0.01), black race (vs. white; HR, 1.35; 95% CI, 1.30 -1.39, p<0.01), molecular subtype as HR-/HER2+ (vs. HR+/HER2-; HR, 1.55; 95% CI, 1.48 -1.
63; p<0.01) and Triple-negative (vs. HR+/HER2−; HR, 2.60; 95% CI, 2.52 -2.68; p<0.01), lymph node status N3 (vs. N0; HR, 3.21; 95% CI, 3.09 -3.35; p<0.01), N2 (vs. N0; HR, 2.42; 95% CI, 2.31 -2.54; p<0.01), N (vs. N0; HR, 1.75; 95% CI, 1.69 -1.80; p<0.01), distal metastases to brain (vs. None; HR, 2.22; 95% CI, 2.07 -2.40; p<0.01), lung (vs. None; HR, 1.97; 95% CI, 1.88 -2.07; p<0.01) and liver (vs. None; HR, 2.78; 95% CI, 2.64-2.92; p<0.01) as possible factors which were associated with greater all-cause mortality. Detailed data was shown in Table 3. Briefly, increased mortality and poorer survival were associated with more extent distal metastases and specific molecular subtype. Moreover, we also identified married (vs. unmarried, HR, 0.67; 95% CI, 0.65 -0.69, p<0.01) and insured (vs. uninsured, HR, 0.67; 95% CI, 0.62 -0.72, p<0.01) status as protective factor of all-cause mortality.

**Discussion**

In this study, we describe that the incidence of identified bone metastases among patients with newly diagnosed breast cancer and characterize the subsequent survival of such patients. We found that patients with HR+/HER2+ has the highest incidence proportion of bone metastases while triple-negative sub-types the lowest. Moreover, the effect of black race, insurance status and marital status on bone metastases rate is not obvious. Patients in the bone metastases cohort were likely diagnosed as a result of kinetic system symptoms given that guidelines for breast cancer patients do not recommend screening imaging of the bone. So, the true incidence of breast cancer with bone metastases is likely underestimated by the results in the study. We also found that HR+/HER2+ experience the longest survival time (41 months) and triple-negative patients had the shortest survival period (10 months) among patients with bone metastases at diagnose. The development of bone metastases is multifactorial. Metastases through blood is very common in distant metastases in breast cancer. It increases the risk of cancer metastases that breast cancer transfers through the abundant blood flow of vertebral-venous plexus to bone (11). Otherwise, bone is suggested to be a large repository of growth-stimulating factors including fibroblast growth factors, platelet-derived growth factors, and bone morphogenetic proteins. These factors could promote tumor growth and provide a basic ground for tumor metastases (12, 13). It is reported that skeletal metastases often
occur in HR+/HER2- patients with breast cancer when it recurrences. As is shown in our research, the HR+/HER2+ patients has the highest incidence proportion of bone metastases. Previous reports showed that dissemination of breast cancer cells took place long before the detection of breast cancer metastases. Under many circumstances, these cells die during dissemination. Unfortunately, parts of these cancer cell might survive and exist in a dormant state in bone marrow (14, 15). And the dormant cells with HR+ could be reactivated by steroid hormone. As a result, they subsequently develop metastases in bone as they can hijack normal biological processes concerning bone remodeling(16). We found the outcome of bone metastases patients was better than those with other organ like the brain, liver, or lung metastases and HR+/HER2+ patients experienced the longest survival time (41 months). HR+ patients with breast cancer are sensitive to targeted therapy, endocrine therapy can remit the tumor and improve the survival of patients. HER2+ patients are sensitive to anti-HER2 therapy (17, 18). Thus, that is probably why patients with HR+, HER2+ status have better outcome. Breast cancer patients are closely associated with bone metastases (19). Previous research found that 62.5% of patients with initial metastases breast cancer were diagnosed with bone metastases (20). However, Current National Comprehensive Cancer Network(NCCN), American Society of Clinical Oncology, and European School of Oncology-Metastatic Breast Cancer guidelines for breast cancer do not include the use of routine bone screening in breast cancer patients, based on a lack of demonstrated survival advantage in existed nonrandomized retrospective studies(21). In spite of the progress of treatments, a great number of female under high risks of bone metastases was still undetected. A study by Jensen and its colleagues (22), reported that bone metastasis occurred in 4% of 35912 female patients, with an average follow-up of 3.9 years. A further study in Japan reported that 690 patients out of 5023(13.7%) developed bone metastases within 10 years after breast cancer surgery(23). Our study revealed that HR+/HER2+ (5%), N3 stage (22%) and other organs metastases (60%) took up the largest proportion when stratified by molecular subtype, lymph node stage and organ metastases. Therefore, we suggest that routine bone staging should be recommended in HR+/HER2+, N3 or other organs metastases breast cancer patients. Bone metastases can lead to bone resorption. This can lead to several skeletal-related events like bone...
pain, pathological fracture, spinal cord compression.(24). The current American Society of Clinical Oncology (ASCO) evidence-based clinical practice guidelines recommended the use of bisphosphonates in breast cancer if any sign of metastatic bone destruction was shown for preventing further destruction and skeletal-related events(25). Our analysis have identified HR+/HER2+,N3 and other organs metastases as poor prognostic factors. We firmly believe that early bone scanning and standardized treatment with bisphosphonates for these patients can reduce the incidence of skeletal-related events hence prolong their survival. There are some limitations in our study. Due to the nature of retrospective study, selection bias and missing data are inevitable. Another limitation was that we were only accessible to the data of presence of bone metastases at initial diagnosis which means patients who developed bone metastases in later process were excluded in our study. Despite these limitations, our study provides insight into the epidemiology of bone metastases in patients with newly diagnosed breast cancer.

Conclusions
It gave physicians another thought when evaluating the utility of bone screening among patients with high risk of bone metastases. We recommend that routine bone staging be used in HR+/HER2+, N3 or other organs metastases breast cancer patients.

Abbreviations
HER2, human epidermal growth factor receptor 2
HR, hormone receptor
TNBC, triple-negative breast cancer. + ,positive; − ,negative
OR, Odds ratio
CI, confidence interval
HR, hazard ratio
NCCN, National Comprehensive Cancer Network

Declarations

Ethics approval and consent to participate
This article does not contain any studies with human participants performed by any of the authors.

Consent for publication
Not applicable

Availability of data and material
The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests
The study no grant Conflicts of interest All authors declared they have no potential conflicts of interest.

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Authors' contributions
The article was mainly written by Zheng Wang and Xiaoli Tang and they contributed equally to the study. Qi Zhang, Xiaoqing Wu, Meiyuan Yang and Zhixiang Jin helped with date analyzing and paper editing. The whole study was instructed by Daorong Wang.

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Tables

Table 1. Incidence of breast cancer with initial bone metastasis by the molecular subtype

| molecular Subtype | With Breast Cancer | With Metastatic Disease | With Bone Metastases | Among Entire Cohort |
|-------------------|--------------------|-------------------------|----------------------|---------------------|
| HR+/HER2−         | 208405             | 11159                   | 6516                 |                     |
| HR+/HER2+         | 29431              | 3164                    | 1478                 |                     |
| HR−/HER2+         | 12769              | 1707                    | 577                  |                     |
| TNBC              | 32462              | 2476                    | 896                  |                     |
| Unknown           | 27722              | 3867                    | 1833                 |                     |
| All subtypes      | 310789             | 22373                   | 11300                |                     |

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; TNBC, triple-negative breast cancer.

Table 2. Multivariable Logistic Regression for the Presence of Bone Metastases at Diagnosis of Breast Cancer
| Variable                  | Patients with bone metastases | Among Entire Cohort | N=310789  | N=11300  | OR(95%CI)  |
|---------------------------|-------------------------------|---------------------|----------|---------|------------|
| **Age at diagnosis**      |                               |                     | 18-40    | 683     | 1[Reference] |
|                           |                               |                     | 41-60    | 4195    | 0.98(0.92-1) |
|                           |                               |                     | 61-80    | 5003    | 1.00(0.94-1) |
|                           |                               |                     | >80      | 1419    | NA         |
| **Sex**                   |                               |                     | male     | 130     | 1[Reference] |
|                           |                               |                     | female   | 11170   | NA         |
| **Race**                  |                               |                     | White    | 8747    | 1[Reference] |
|                           |                               |                     | Black    | 1723    | 1.11(0.87-1) |
|                           |                               |                     | Other    | 782     | 1.06(0.83-1) |
|                           |                               |                     | Unknown  | 48      | NA         |
| **Marital status**        |                               |                     | Unmarried | 5895 | 1[Reference] |
|                           |                               |                     | Married   | 4761    | 1.01(0.92-1) |
|                           |                               |                     | Unknown  | 644     | NA         |
| **Median household income** |                             |                     | White    | 11300   | NA         |
| **High school education** |                               |                     | White    | 11300   | NA         |
| **Insurance status**      |                               |                     | Uninsured | 505  | 1[Reference] |
|                           |                               |                     | Insured  | 10527   | 1.09(0.96-1) |
|                           |                               |                     | Unknown  | 268     | NA         |
| **Subtype**               |                               |                     | HR+/HER2− | 6516 | 1[Reference] |
|                           |                               |                     | HR+/HER2+ | 1478 | 1.19(1.06-1) |
|                           |                               |                     | HR−/HER2+ | 577  | 0.95(0.79-1) |
|                           |                               |                     | Triple-negative | 869 | 0.72(0.64-1) |
|                           |                               |                     | Unknown  | 1833    | NA         |
| **Lymph node status**     |                               |                     | N0      | 2540    | 1[Reference] |
|                           |                               |                     | N1      | 3617    | 1.45(0.87-2) |
|                           |                               |                     | N2      | 907     | 1.49(0.89-2) |
|                           |                               |                     | N3      | 2881    | 2.76(1.66-4) |
|                           |                               |                     | NX Adjust | 1349 | 1.73(1.04-2) |
|                           |                               |                     | NA      | 6       | NA         |
| **Brain metastases**      |                               |                     | None    | 444     | 1[Reference] |
|                           |                               |                     | Yes     | 800     | 4.03(2.67-6) |
| **Metastases of lung**    |                               |                     | None    | 2271    | 1[Reference] |
|                           |                               |                     | Yes     | 2982    | 27.31(20.0-37.1) |
| **Metastases of liver**   |                               |                     | None    | 1692    | 1[Reference] |
|                           |                               |                     | Yes     | 2626    | 10.45(4.63) |

**Abbreviations:** HER2, human epidermal growth factor receptor 2; HR, hormone receptor. + Denotes positive; – denotes negative; *, Only significant results presented (P < .05).

Table 3. Multivariable Cox Regression for All-Cause Mortality Among Patients With Bone Metastases
| Variable                        | Patients with bone metastases | All-Cause Mortality |
|--------------------------------|--------------------------------|---------------------|
|                                | N=310789                       | N=11300             |
| **Age at diagnosis**           |                                | HR (95% CI)         |
| 18-40                          | 14420                          | 683                 |
| 41-60                          | 121261                         | 4195                |
| 61-80                          | 139968                         | 5003                |
| >80                            | 35140                          | 1419                |
| **Sex**                        |                                |                     |
| male                           | 2463                           | 130                 |
| female                         | 308326                         | 11170               |
| **Race**                       |                                |                     |
| White                          | 246328                         | 8747                |
| Black                          | 34532                          | 1723                |
| Other                          | 27399                          | 782                 |
| Unknown                        | 2530                           | 48                  |
| **Marital status**             |                                |                     |
| Unmarried                      | 126952                         | 5895                |
| Married                        | 164497                         | 4761                |
| Unknown                        | 19340                          | 644                 |
| **Median household income**    |                                |                     |
| Uninsured                      | 5578                           | 505                 |
| Insured                        | 296862                         | 10527               |
| Unknown                        | 8349                           | 268                 |
| **Insurance status**           |                                |                     |
| HR+/HER2−                       | 208405                         | 6516                |
| HR+/HER2+                      | 29431                          | 1478                |
| HR−/HER2+                      | 12769                          | 577                 |
| Triple-negative                | 32462                          | 869                 |
| Unknown                        | 27722                          | 1833                |
| **Lymph node status**          |                                |                     |
| N0                             | 201597                         | 2540                |
| N1                             | 65219                          | 3617                |
| N2                             | 15031                          | 907                 |
| N3                             | 12828                          | 2881                |
| NX Adjust                      | 15668                          | 1349                |
| NA                             | 446                            | 6                   |
| **Brain metastases**           |                                |                     |
| None                           | 302684                         | 444                 |
| Yes                            | 1268                           | 800                 |
| **Metastases of lung**         |                                |                     |
| None                           | 299688                         | 2271                |
| Yes                            | 5379                           | 2982                |
| **Metastases of liver**        |                                |                     |
| None                           | 298602                         | 1692                |
| Yes                            | 4426                           | 2626                |

**Abbreviations:** HER2, human epidermal growth factor receptor 2; HR, hormone receptor. + Denotes positive; − denotes negative. * Only significant results presented (P < .01). NA, not available.

**Figures**
Figure 1

Survival analysis among patients with initial bone metastases stratified by subtype
Figure 2

Survival metastatic bone and lung
Figure 3

Survival metastatic bone and brain
Figure 4

Survival metastatic bone and liver