Patterns of Distant Metastases in Patients With Triple-Negative Breast Cancer — A Population-Based Study

Yang Gao
Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & Affiliated Cancer Hospital of Nanjing Medical University

Kang Gu
Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & Affiliated Cancer Hospital of Nanjing Medical University

Chuanzhen Bian
Department of Radiology, Children's Hospital of Nanjing Medical University

Ping Yan
Department of Neonatal Surgery, Children's Hospital of Nanjing Medical University

Yunian Zhao (✉ xueshuyouxiang@126.com)
Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & Affiliated Cancer Hospital of Nanjing Medical University

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Abstract

Background

Currently, the prognosis of triple-negative breast cancer (TNBC) patients remained poor mainly due to resistance, recurrence, metastasis and severe side effects. The study provided systematic insights into the patterns of TNBC distant metastases (DM), as well as investigating the related elements for the prognosis prediction of TNBC patients on the basis of on large sample.

Methods

We screened eligible patients with triple-negative breast cancer from the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2015. Besides, we analyzed differences in baseline characteristics among patients with diverse modes of metastasis. Meanwhile, we calculated proportional mortality ratio (PMR) and the expression of proportional trends in different patients. Subsequently, Kaplan-Meier (KM) analysis was employed to investigate the survival outcomes. Finally, the predictive and prognostic factors of DM were identified.

Results

In this study, we included 24,822 TNBC patients, including 1,026 DM patients and 23,796 non-DM patients. At the time of initial diagnosis, 4.1% of patients had DM, and 36.9% had multiple metastases. According to the study, the most common sites of metastasis in DM patients were bone (251 cases) and lung (244 cases), while the least common organ of metastasis was brain (37 cases). Age, tumor grade, T, N and marital status were deemed as risk elements of DM. T stage, insurance status, marital status, surgery treatment, chemotherapy, number of metastatic sites and metastatic sites also effect the diagnosis of DM significantly.

Conclusion

Our study showed that the most common site of metastasis in TNBC patients with DM was bone and the least common site was brain. Different modes of metastasis have different survival and prognostic characteristics. Thus, our research may have important implications for the clinical practice of TNBC patients in the future.

Introduction

Breast cancer (BC) remained the most severe public health problem that endangers women's lives and health in the world [1, 2], accounting for 10.4% of all cancers. Although there are still regional differences between different countries, breast cancer is still the leading cause of death among women aged 20-
BC is a heterogeneous disease. In view of genetic, epigenetic and transcriptome changes, its histological and biological characteristics are different. 95% of BC is adenocarcinoma, starting as a local disease [4]. Invasive/metastatic BC can be divided into nonspecific type (NST) cancer (60-75%) and special type (20%- 25%) [5]. In the aspect of biological characteristics, three kinds of molecular biomarkers (estrogen receptor (ER), progesterone receptor (PR) and HER2) are detected by molecular biological methods for the molecular type of BC [6–8], including estrogen receptor positive (ER+) type or progesterone receptor positive (PR+) type, human epidermal receptor 2 positive (HER2+) type and triple-negative BC (TNBC) [9, 10].

The incidence of TNBC in BC is about 10-15%, but it is one of the most aggressive subtypes [11]. TNBC distant metastasis (DM) refers to the metastasis of BC outside the ipsilateral breast, chest wall and regional lymph nodes, which is the main cause of death (COD) of BC. 6-10% of cases have metastasis at the time of diagnosis, and nearly 30% will relapse or metastasize [12]. About 25% of TNBC patients still have local recurrence and DM after active treatment. There are many metastases of BC such as brain, lung, liver, etc [13]. At present, there are few effective methods for the treatment of metastatic TNBC, resulting in poor prognosis of patients with metastatic TNBC. Therefore, it is urgent to further study the prediction and prognostic factors of DM in TNBC [14–17]. But, the shortcomings of previous studies are mostly single-center studies with small sample size and incomplete long-term follow-up information.

Therefore, we used SEER database to establish prognostic models for TNBC patients with different metastasis modes to further explore the risk factors affecting distant metastasis of tumor.

**Methods And Materials**

**Database**

We employed the "SEER*Stat 8.3.8" software (Version 8.3.6; NCI) to download the data from the SEER registry. The SEER database detailed information about cancer patients in the USA. In our study, we signed the data agreement and used the 10977-Nov2019 database. In addition, the Institutional Review Board allowed us to proper use of this public database.

**Patient identification**

The TNBC patients with positive pathology were retrospectively extracted from SEER 18 registry. All patients were diagnosed between 2010 and 2015 because data DM data were recorded from 2010. Inclusion criteria: (1) patients diagnosed with TNBC (C50.0-C50.6, C50.8-C50.9; AYA site recode/WHO 2008= 8.4 Carcinoma of the breast), (2) BC was the first primary malignancy of each patient, (3) patients with complete data of long-term follow-up. Exclusion criteria: (1) patients with bilateral tumors or unknown tumor laterality, (2) patients with unknown data on marital status, insurance status, household income, the administration of surgery, T stage, N stage, race, and tumor grade, (3) unknown metastatic status, (4) data were from autopsy or death certificate only.
Data extraction

For each patient, essential clinical characteristics and long-term survival outcomes were extracted using the “Case Listing Session”. Variables including race, age, year of diagnosis, tumor grade, laterality, AJCC 7th T stage, N stage, the administration of surgery/chemotherapy and radiotherapy, DM status, survival months, COD, insurance status, metastatic status, vital status and, household income were identified. Based on DM status, all patients were categorized into DM group and without DM group. Moreover, those in DM group were further subdivided based on the metastatic status.

For further analyses, age at diagnosis was divided into < 45, 45 - 69 and ≥ 70 years old, the race was classified into White, Black and Other. Furthermore, the pathological grade was divided into four levels: high, moderately, poorly and undifferentiated. Median household income was calculated to define high- and low-level household income.

Identification of prognostic characteristics

KM curves were used to explore the overall survive of DM or the metastatic site in TNBC patients. We analyzed COD in different groups of patients who died during long-term follow-up. Uni- and multivariable cox analyses were constructed to explore the risk factors of DM in TNBC patients. Finally, COX analyses were developed to find prognostic factors of OS and CSS.

Statistical analysis

In our study, data were mainly presented by n (%). Chi-square test was used for comparison between categorical variables. The fundamental analyses were completed on the basis of SPSS 23.0 software (SPSS Inc) and R software (Version 3.4.1). All analytical processes were two-sided, and P < 0.05 was deemed to have statistical significance.

Results

Characteristics of baseline and prognosis

Figure 1 presented the selection flow chart of this study. Table 1 indicated that our study ultimately identified 24,822 patients with TNBC, including 1,026 DM patients and 23,796 patients without DM. In general, most of the patients were aged 45-69 years old (61.44%), white (71.60%), early lesion (T1: 42.00%, N0: 63.79%), and tumor-directed surgery (92.56%). Compared with none-DM patients, those DM patients had older age (P = 0.003), higher probability of black (P < 0.001), later stage of diseases (P < 0.001), lower median household income (P = 0.002), lower married rate (P < 0.001) and lower insurance rate (P < 0.001). In addition, the rate of surgery and radiotherapy was significantly higher (P < 0.001) in patients without DM. But, there was no statistical difference in diagnosis year, laterality and chemotherapy.
### Table 1
Baseline characteristics of included patients (with DM vs. without DM).

|                      | Total | Without DM | With DM | P Value |
|----------------------|-------|------------|---------|---------|
| **N**                | 24,822| 23,796     | 1,026   |         |
| **Age**              |       |            |         | 0.003   |
| < 45                 | 4,563 | 4,407      | 156     |         |
| 45-69                | 15,250| 1,4620     | 630     |         |
| ≥ 70                 | 5,009 | 4,769      | 240     |         |
| **Race**             |       |            |         | <0.001  |
| White                | 17,773| 17,078     | 695     |         |
| Black                | 5,148 | 4,877      | 271     |         |
| Other                | 1,901 | 1,841      | 60      |         |
| **Year of Diagnosis**|       |            |         | 0.714   |
| 2010                 | 3,972 | 3,813      | 159     |         |
| 2011                 | 4,109 | 3,942      | 167     |         |
| 2012                 | 4,080 | 3,927      | 153     |         |
| 2013                 | 4,083 | 3,904      | 179     |         |
| 2014                 | 4,200 | 4,020      | 180     |         |
| 2015                 | 4,378 | 4,190      | 188     |         |
| **Laterality**       |       |            |         | 0.968   |
| Left                 | 12,783| 12,254     | 529     |         |
| Right                | 12,039| 11,542     | 497     |         |
| **Grade**            |       |            |         | <0.001  |
| Grade I              | 490   | 479        | 11      |         |
| Grade II             | 4,150 | 3,983      | 167     |         |
| Grade III            | 19,992| 19,162     | 830     |         |

Data were n (%), unless otherwise specified.

DM=distant metastasis; ¹Grade I = Well differentiated; Grade II = Moderately differentiated; Grade III = Poorly differentiated; Grade IV = Undifferentiated. ²Median household income: defined by earnings above the median of the median household income in this sample.
|                          | Total | Without DM | With DM | P Value |
|--------------------------|-------|------------|---------|---------|
| Grade IV                 | 190   | 172        | 18      |         |
| T stage                  |       |            |         | <0.001  |
| T1                       | 10,424| 10,340     | 84      |         |
| T2                       | 10,528| 10,229     | 299     |         |
| T3                       | 2,240 | 2,026      | 214     |         |
| T4                       | 1,630 | 1,201      | 429     |         |
| N stage                  |       |            |         | <0.001  |
| N0                       | 15,834| 15,618     | 216     |         |
| N1                       | 6,192 | 5,713      | 479     |         |
| N2                       | 1,567 | 1,442      | 125     |         |
| N3                       | 1,229 | 1,023      | 206     |         |
| Surgery                  |       |            |         | <0.001  |
| No                       | 1,847 | 1,271      | 576     |         |
| Yes                      | 22,975| 22,525     | 450     |         |
| Chemotherapy             |       |            |         | 0.736   |
| No/Unknown               | 5,795 | 5,551      | 244     |         |
| Yes                      | 19,027| 18,245     | 782     |         |
| Radiotherapy             |       |            |         | <0.001  |
| No/Unknown               | 13,170| 11,587     | 688     |         |
| Yes                      | 11,652| 12,209     | 338     |         |
| Median household income² |       |            |         | 0.002   |
| Low                      | 13,170| 12,576     | 594     |         |
| High                     | 11,652| 11,220     | 432     |         |
| Marital status           |       |            |         | <0.001  |

Data were n (%), unless otherwise specified.

DM=distant metastasis; \(^1\) Grade I = Well differentiated; Grade II = Moderately differentiated; Grade III = Poorly differentiated; Grade IV = Undifferentiated. \(^2\)Median household income: defined by earnings above the median of the median household income in this sample.
The most common sites of metastasis in DM patients were bone (24.46%) and lung (23.78%), while the least common organ of metastasis was brain (3.61%). Besides, we found that nearly 36.94% patients had two or more metastases (Table 2). Compared with patients with multiple organ metastases, patients with single organ metastases were more likely to undergo surgery and less likely to receive radiotherapy. (52.86% vs. 28.50%, P < 0.001; 30.6% vs. 36.9%, P = 0.037). But, no statistically significant differences were found in comparison with other variables. Eventually, the patients were chopped up into four groups (simple brain, simple bone, simple liver, and simple lung), and the comparison between groups was shown in Table S1. Compared with other sites, patients with lung metastasis later stage of diseases while patients with brain metastasis underwent radiotherapy more frequently (P = 0.021, P < 0.001).
Table 2
Baseline characteristics of patients with DM, stratified by the number of metastatic sites

|                     | 1 site | >1 site | P value |
|---------------------|--------|---------|---------|
| N                   | 647    | 379     |         |
| Age                 |        |         | 0.151   |
| < 45                | 97     | 59      |         |
| 45-69               | 386    | 244     |         |
| ≥ 70                | 164    | 76      |         |
| Race                |        |         | 0.466   |
| White               | 432    | 263     |         |
| Black               | 179    | 92      |         |
| Other               | 36     | 24      |         |
| Year of Diagnosis   |        |         | 0.128   |
| 2010                | 110    | 49      |         |
| 2011                | 101    | 66      |         |
| 2012                | 105    | 48      |         |
| 2013                | 103    | 76      |         |
| 2014                | 107    | 73      |         |
| 2015                | 121    | 67      |         |
| Laterality          |        |         | 0.223   |
| Left                | 343    | 186     |         |
| Right               | 304    | 193     |         |
| Grade<sup>1</sup>   |        |         | 0.998   |
| Grade I             | 7      | 4       |         |
| Grade II            | 105    | 62      |         |
| Grade III           | 524    | 306     |         |

Data were n (%), unless otherwise specified. DM=distant metastasis; <sup>1</sup> Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; <sup>2</sup>Median household income: defined by earnings above the median of the median household income in this sample.
|                  | 1 site | >1 site | P value |
|------------------|--------|---------|---------|
| Grade IV         | 11     | 7       | 0.007   |
| T stage          |        |         |         |
| T1               | 58     | 26      |         |
| T2               | 205    | 94      |         |
| T3               | 139    | 75      |         |
| T4               | 245    | 184     |         |
| N stage          |        |         | 0.389   |
| N0               | 146    | 70      |         |
| N1               | 295    | 184     |         |
| N2               | 81     | 44      |         |
| N3               | 125    | 81      |         |
| Surgery          |        |         | <0.001  |
| No               | 305    | 271     |         |
| Yes              | 342    | 108     |         |
| Chemotherapy     |        |         | 0.530   |
| No/Unknown       | 158    | 86      |         |
| Yes              | 489    | 293     |         |
| Radiotherapy     |        |         | 0.037   |
| No/Unknown       | 449    | 239     |         |
| Yes              | 198    | 140     |         |
| Median household income | |     | | 0.852 |
| Low              | 376    | 218     |         |
| High             | 271    | 161     |         |
| Marital status   |        |         | 0.636   |
| Never Married    | 148    | 96      |         |

Data were n (%), unless otherwise specified. DM=distant metastasis; ¹ Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ² Median household income: defined by earnings above the median of the median household income in this sample.
|                        | 1 site | >1 site | P value |
|------------------------|--------|---------|---------|
| Married                | 290    | 161     |         |
| Previous married       | 209    | 122     |         |
| Insurance status       |        |         | 0.088   |
| Uninsured             | 27     | 25      |         |
| Insured                | 620    | 354     |         |

Data were n (%), unless otherwise specified. DM = distant metastasis; ¹ Grade I = Well differentiated; Grade II = Moderately differentiated; Grade III = Poorly differentiated; Grade IV = Undifferentiated; ² Median household income: defined by earnings above the median of the median household income in this sample.

**Proportional Death Rate**

The results of subgroup analyses are shown in Figure 3. Compared with the non-DM group, the mortality rate from BC in DM group was significantly increased (77.57–94.75%), while the mortality rate from other causes (21.15–4.68%) and the mortality rate from unknown causes (1.28–0.57%) were significantly decreased (Figure 2A). In other words, once BC patients had DM, they have a greater chance of dying from their disease. This trend became more pronounced with the increase of metastatic sites (Figure 2B). It is worth noting that DM in brain causes all the deaths (Figure 2C).

**Survival Results**

As shown in Figure 3A, B, Non-dm patients had a better survival advantage (OS and CSS) than DM patients. Besides, patients with a single metastasis had a better survival advantage (OS and CSS) than patients with multiple metastases. In patients with multiple metastases, patients with two metastases had better OS and CSS than patients with more than two metastases (Figure 3E, F). What is more, the greater the number of metastases in DM patients, the worse the survival advantage (OS and CSS) (Figure 3G, H). Patients with brain metastasis or liver metastases had the worst OS and CSS of all metastatic sites (Figure 4A, B). Figure 4C-4F indicated the survival analyses of patients with two and three metastatic sites. However, in patients with two or three metastatic sites, there were no statistically significant differences in OS and CSS between different metastatic types. Table 3 showed that older TNBC patients, higher T, and higher N were at higher risk for DM, stage T, insurance status, number of managed surgery, chemotherapy, government metastatic style, and important factors affecting the operating system of DM patients (Table 4), and stage T, insurance status, surgical management, number of metastatic lesions, and marital status were significantly correlated with CSS (Table 5). Besides, the multivariate COX analysis indicated that T stage, insurance status, chemotherapy management, surgical method and metastatic site were obvious factors affecting OS in patients with a single metastatic site.
(Table 6). T stage, insurance status, surgical method, chemotherapy method, and site of metastasis were correlated with CSS (Table 7).
Table 3
Uni- and multivariate logistic regression analyses of risk factors for patients with DM

| Variable   | Univariate       | Multivariate     |
|------------|------------------|------------------|
|            | **OR** | **95% CI** | **P value** | **OR** | **95% CI** | **P value** |
| Age        |        |             |             |        |             |             |
| < 45       | Reference |        |             |        | Reference |             |
| 45-69      | 1.217  | 1.018-1.455 | 0.031       | 1.430  | 1.183-1.730 | <0.001       |
| ≥ 70       | 1.422  | 1.157-1.746 | 0.001       | 1.582  | 1.254-1.997 | <0.001       |
| Race       |        |             |             |        |             |             |
| White      | Reference |        |             |        | Reference |             |
| Black      | 1.365  | 1.182-1.577 | <0.001      | 1.057  | 0.899-1.242 | 0.502       |
| Other      | 0.801  | 0.613-1.047 | 0.104       | 0.761  | 0.572-1.011 | 0.060       |
| Grade¹     |        |             |             |        |             |             |
| Grade I    | Reference |        |             |        | Reference |             |
| Grade II   | 1.826  | 0.985-3.385 | 0.056       | 1.058  | 0.549-2.037 | 0.867       |
| Grade III  | 1.886  | 1.033-3.443 | 0.039       | 0.851  | 0.449-1.612 | 0.620       |
| Grade IV   | 4.557  | 2.110-9.843 | <0.001      | 1.426  | 0.619-3.289 | 0.405       |
| Laterality |        |             |             |        |             |             |
| Left       | Reference |        |             |        |             |             |
| Right      | 0.997  | 0.880-1.130 | 0.968       |        |             |             |
| T stage    |        |             |             |        |             |             |
| T1         | Reference |        |             |        |             |             |
| T2         | 3.598  | 2.820-4.591 | <0.001      | 2.829  | 2.205-3.631 | <0.001       |
| T3         | 13.002 | 10.057-16.809 | <0.001 | 7.916  | 6.043-10.370 | <0.001 |
| T4         | 43.970 | 34.541-55.973 | <0.001 | 21.616 | 16.643-28.077 | <0.001 |

DM: distant metastasis; OR: odds ratio; CI: confidence interval; ¹Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ²Median household income: defined by earnings above the median of the median household income in this sample;
| Variable                  | Univariate | Multivariate |
|--------------------------|------------|--------------|
| **N stage**              | <0.001     | <0.001       |
| N0                       | Reference  |              |
| N1                       | 6.062      | 5.148-7.139  | <0.001 | 3.197 | 2.682-3.811 | <0.001 |
| N2                       | 6.268      | 4.996-7.863  | <0.001 | 2.372 | 1.855-3.032 | <0.001 |
| N3                       | 14.560     | 11.908-17.803| <0.001 | 4.304 | 3.435-5.393 | <0.001 |
| Insurance status         | <0.001     |              |
| Insured                  | Reference  |              |
| Uninsured                | 0.443      | 0.331-0.593  | <0.001 | 0.817 | 0.592-1.128 | 0.219 |
| Marital status           | <0.001     |              |
| Never Married            | Reference  |              |
| Married                  | 0.583      | 0.497-0.683  | <0.001 | 0.851 | 0.712-1.017 | 0.076 |
| Previous married         | 0.973      | 0.821-1.153  | 0.753 | 1.110 | 0.914-1.349 | 0.294 |
| Household income²        | 0.002      |              |
| Low                      | Reference  |              |
| High                     | 0.815      | 0.718-0.925  | 0.002 | 0.889 | 0.775-1.020 | 0.094 |

DM: distant metastasis; OR: odds ratio; CI: confidence interval; ¹Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ²Median household income: defined by earnings above the median of the median household income in this sample;
Table 4
Univariate and Multivariate Cox regression analyses of prognostic factors for OS in patients with DM

| Variable | Univariate | | | Multivariate | | |
| --- | --- | --- | --- | --- | --- | --- |
| | HR | 95% CI | P value | HR | 95% CI | P value |
| Age | | | | 0.269 |
| < 45 | Reference | | | Reference | | |
| 45-69 | 1.059 | 0.875-1.281 | 0.556 | 1.086 | 0.892-1.323 | 0.411 |
| ≥ 70 | 1.386 | 1.113-1.724 | 0.003 | 1.213 | 0.954-1.542 | 0.115 |
| Race | | | | 0.770 |
| White | Reference | | | | | |
| Black | 1.029 | 0.884-1.199 | 0.711 | | | |
| Other | 0.919 | 0.685-1.234 | 0.575 | | | |
| Grade<sup>1</sup> | | | | 0.741 |
| Grade I | Reference | | | | | |
| Grade II | 1.050 | 0.553-1.994 | 0.880 | | | |
| Grade III | 0.952 | 0.510-1.778 | 0.877 | | | |
| Grade IV | 0.904 | 0.410-1.992 | 0.801 | | | |
| Laterality | | | | 0.494 |
| Left | Reference | | | | | |
| Right | 1.047 | 0.917-1.196 | 0.494 | | | |
| T stage | | | | <0.001 | 0.016 |
| T1 | Reference | | | Reference | | |
| T2 | 1.015 | 0.779-1.324 | 0.911 | 1.136 | 0.868-1.487 | 0.353 |
| T3 | 1.040 | 0.789-1.370 | 0.781 | 1.146 | 0.865-1.519 | 0.341 |

OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; <sup>1</sup>Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; <sup>2</sup>Median household income: defined by earnings above the median of the median household income in this sample.
| Variable          | Univariate          |          |          |          |          |
|-------------------|---------------------|----------|----------|----------|----------|
|                   | T4                  | 1.376    | 1.065-1.777 | 0.014    | 1.387    | 1.068-1.802 | 0.014 |
|                   | N stage             |          | 0.545    |          |          |          |        |
|                   | N0                  |          |          |          | Reference |          |        |
|                   | N1                  | 1.098    | 0.919-1.313 | 0.303    |          |          |        |
|                   | N2                  | 1.127    | 0.887-1.431 | 0.329    |          |          |        |
|                   | N3                  | 1.162    | 0.942-1.434 | 0.160    |          |          |        |
| Insurance status  |<0.001               |          |          |          | 0.003    |          |        |
|                   | Uninsured           | Reference |          | Reference |          |          |        |
|                   | Insured             | 0.575    | 0.431-0.768 | <0.001   | 0.644    | 0.479-0.865 | 0.003 |
| Marital status    |<0.001               |          | 0.039    |          |          |          |        |
|                   | Never Married       | Reference |          | Reference |          |          |        |
|                   | Married             | 0.764    | 0.646-0.903 | 0.002    | 0.808    | 0.680-0.961 | 0.016 |
|                   | Previous married    | 1.023    | 0.858-1.219 | 0.799    | 0.925    | 0.763-1.120 |        |
| Median household income\(^2\) |          |          | 0.625    |          |          |          |        |
|                   | Low                 | Reference |          |          |          |          |        |
|                   | High                | 0.967    | 0.846-1.106 | 0.625    |          |          |        |
| Surgery           |<0.001               |          |          |<0.001    |          |          |        |
|                   | No                  | Reference |          | Reference |          |          |        |
|                   | Yes                 | 0.510    | 0.445-0.585 | <0.001   | 0.586    | 0.507-0.678 | <0.001 |
| Chemotherapy      |<0.001               |          |          |<0.001    |          |          |        |
|                   | No/Unknown           | Reference |          | Reference |          |          |        |
|                   | Yes                 | 0.372    | 0.319-0.434 | <0.001   | 0.373    | 0.316-0.440 | <0.001 |

OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; \(^1\)Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; \(^2\)Median household income: defined by earnings above the median of the median household income in this sample.
| Variable                      | Univariate | Multivariate |
|-------------------------------|------------|--------------|
| Radiotherapy                  | 0.012      | 0.868        |
| No/Unknown                    | Reference  | Reference    |
| Yes                           | 0.833      | 0.012        |
|                               | 0.723-0.960| 0.987        |
|                               | 0.850-1.147| 0.868        |
| Number of metastatic sites    | <0.001     | <0.001       |
| 1 site                        | Reference  |              |
| 2 sites                       | 1.595      | 1.463        |
|                               | 1.371-1.856| 1.249-1.713  |
|                               | <0.001     | <0.001       |
| > 2 sites                     | 2.323      | 2.255        |
|                               | 1.857-2.906| 1.768-2.845  |
|                               | <0.001     | <0.001       |

OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; \(^1\) Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; \(^2\) Median household income: defined by earnings above the median of the median household income in this sample.
Table 5
Univariate and Multivariate Cox regression analyses of prognostic factors for CSS in patients with DM

| Variable   | Univariate | Multivariate |
|------------|------------|--------------|
|            | HR 95% CI  | P value      | HR 95% CI  | P value |
| Age        |            |              |            |         |
| < 45       | Reference  | Reference    |            |         |
| 45-69      | 1.038 0.855-1.261 | 0.703       | 1.062 0.869-1.298 | 0.557   |
| ≥ 70       | 1.321 1.056-1.654 | 0.015       | 1.166 0.911-1.492 | 0.222   |
| Race       |            |              |            |         |
| White      | Reference  |             |            | 0.831   |
| Black      | 1.025 0.876-1.199 | 0.760       |            |         |
| Other      | 0.929 0.688-1.255 | 0.633       |            |         |
| Grade<sup>1</sup> |            |              |            | 0.757   |
| Grade I    | Reference  |             |            |         |
| Grade II   | 0.993 0.522-1.888 | 0.983       |            |         |
| Grade III  | 0.900 0.482-1.681 | 0.741       |            |         |
| Grade IV   | 0.902 0.409-1.988 | 0.798       |            |         |
| Laterality |            |              |            | 0.365   |
| Left       | Reference  |             |            |         |
| Right      | 1.065 0.929-1.220 | 0.365       |            |         |
| T stage    |            |              | <0.001     | 0.014   |
| T1         | Reference  | Reference    |            |         |
| T2         | 1.018 0.773-1.341 | 0.898       | 1.143 0.864-1.511 | 0.349   |
| T3         | 1.096 0.824-1.456 | 0.529       | 1.207 0.904-1.612 | 0.203   |

OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; <sup>1</sup>Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; <sup>2</sup>Median household income: defined by earnings above the median of the median household income in this sample.
| Variable          | Univariate     | Multivariate   |
|-------------------|----------------|---------------|
| T4                | 1.407          | 1.421         |
|                   | 1.080-1.835    | 1.084-1.864   |
|                   | 0.012          | 0.011         |
| N stage           | 0.271          |               |
| N0                | Reference      |               |
| N1                | 1.137          | 1.421         |
|                   | 0.944-1.369    | 1.084-1.864   |
|                   | 0.175          | 0.011         |
| N2                | 1.151          |               |
|                   | 0.898-1.475    |               |
|                   | 0.267          |               |
| N3                | 1.241          |               |
|                   | 1.000-1.540    |               |
|                   | 0.050          |               |
| Insurance status  | <0.001         | 0.002         |
| Uninsured         | Reference      | Reference     |
| Insured           | 0.552          | 0.619         |
|                   | 0.412-0.739    | 0.459-0.835   |
|                   | <0.001         | 0.002         |
| Marital status    | <0.001         | 0.047         |
| Never Married     | Reference      | Reference     |
| Married           | 0.761          | 0.814         |
|                   | 0.641-0.904    | 0.682-0.972   |
|                   | 0.002          | 0.023         |
| Previous married  | 1.017          | 0.941         |
|                   | 0.8560-1.218   | 0.772-1.146   |
|                   | 0.850          | 0.544         |
| Median household income<sup>2</sup> | 0.546 |               |
| Low               | Reference      |               |
| High              | 0.958          | 0.546         |
|                   | 0.836-1.100    |               |
| Surgery           | <0.001         | <0.001        |
| No                | Reference      | Reference     |
| Yes               | 0.508          | 0.585         |
|                   | 0.442-0.585    | 0.504-0.680   |
|                   | <0.001         | <0.001        |
| Chemotherapy      | <0.001         | <0.001        |
| No/Unknown        | Reference      | Reference     |
| Yes               | 0.388          | 0.384         |
|                   | 0.331-0.456    | 0.323-0.457   |
|                   | <0.001         | <0.001        |

OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; <sup>1</sup>Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; <sup>2</sup>Median household income: defined by earnings above the median of the median household income in this sample.
| Variable                  | Univariate |          | Multivariate |          |
|--------------------------|------------|----------|--------------|----------|
| Radiotherapy             |            | 0.034    |              | 0.947    |
| No/Unknown               | Reference  |          | Reference    |          |
| Yes                      | 0.855      | 0.740-0.988 | 0.034       | 1.005    |
|                          |            |          |              | 0.862-1.172 | 0.947    |
| Number of metastatic sites | <0.001    |          |              | <0.001    |
| 1 site                   | Reference  |          | Reference    |          |
| 2 sites                  | 1.627      | 1.392-1.900 | <0.001      | 1.479    |
|                          |            |          |              | 1.257-1.740 | <0.001    |
| > 2 sites                | 2.447      | 1.949-3.071 | <0.001      | 2.359    |
|                          |            |          |              | 1.863-2.987 | <0.001    |

OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; 1Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; 2Median household income: defined by earnings above the median of the median household income in this sample.
Table 6
Univariate and Multivariate Cox regression analyses of prognostic factors for OS in patients with DM

| Variable   | Univariate | Multivariate |
|------------|------------|--------------|
|            | HR         | 95% CI       | P value | HR         | 95% CI       | P value |
| Age        |            |              |         |            |              |         |
| < 45       | 1.007      | 0.786-1.289  | 0.959   | 1.022      | 0.791-1.319  | 0.870   |
| 45-69      |            |              |         |            |              |         |
| ≥ 70       | 1.341      | 1.017-1.770  | 0.038   | 1.157      | 0.847-1.581  | 0.358   |
| Race       |            |              |         |            |              |         |
| White      |            |              |         |            |              |         |
| Black      | 0.974      | 0.802-1.183  | 0.788   |            |              |         |
| Other      | 0.987      | 0.680-1.433  | 0.945   |            |              |         |
| Grade¹     |            |              |         |            |              |         |
| Grade I    |            |              |         |            |              |         |
| Grade II   | 1.036      | 0.453-2.371  | 0.933   |            |              |         |
| Grade III  | 0.983      | 0.439-2.201  | 0.967   |            |              |         |
| Grade IV   | 0.795      | 0.283-2.234  | 0.663   |            |              |         |
| Laterality |            |              |         |            |              |         |
| Left       |            |              |         |            |              |         |
| Right      | 0.942      | 0.794-1.117  | 0.491   |            |              |         |
| T stage    |            |              |         |            |              |         |
| T1         |            |              |         |            |              |         |
| T2         | 1.069      | 0.768-1.486  | 0.694   | 1.290      | 0.919-1.812  | 0.141   |
| T3         | 1.061      | 0.750-1.500  | 0.738   | 1.246      | 0.873-1.778  | 0.226   |
| T4         | 1.406      | 1.017-1.943  | 0.039   | 1.630      | 1.166-2.281  | 0.004   |
| N stage    |            |              |         |            |              |         |
| N0         |            |              |         |            |              | 0.540   |

OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval;¹ Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated;² Median household income: defined by earnings above the median of the median household income in this sample.
| Variable                      | Univariate |          |          | Multivariate |          |
|-------------------------------|------------|----------|----------|--------------|----------|
| N1                            | 1.131      | 0.901-1.420 | 0.287    |              |          |
| N2                            | 1.228      | 0.909-1.658 | 0.180    |              |          |
| N3                            | 1.165      | 0.890-1.525 | 0.266    |              |          |
| Insurance status              |            |          |          | **0.003**    | 0.004    |
| Uninsured                     |            |          |          |              |          |
| Insured                       | 0.539      | 0.360-0.806 | 0.003    | 1.630        | 1.166-2.281 | 0.004    |
| Marital status                |            |          |          | **0.015**    |          | **0.146** | |
| Never Married                 |            |          |          |              |          |
| Married                       | 0.833      | 0.670-1.036 | 0.100    | 0.815        | 0.651-1.021 | 0.076    |
| Previous married              | 1.109      | 0.882-1.394 | 0.378    | 0.946        | 0.732-1.224 | 0.674    |
| Median household income\(^2\) |            |          |          | 0.740        |          |
| Low                           |            |          |          |              |          |
| High                          | 1.030      | 0.867-1.223 | 0.740    |              |          |
| Surgery                       |            |          |          | <**0.001**   |          | <**0.001** | |
| No                            |            |          |          |              |          |
| Yes                           | 0.527      | 0.444-0.626 | <**0.001** | 0.545        | 0.454-0.654 | <**0.001** | |
| Chemotherapy                  |            |          |          | <**0.001**   |          | <**0.001** | |
| No/Unknown                    |            |          |          |              |          |
| Yes                           | 0.386      | 0.317-0.470 | <**0.001** | 0.411        | 0.331-0.511 | <**0.001** | |
| Radiotherapy                  |            |          |          | **0.004**    |          | 0.437     |
| No/Unknown                    |            |          |          |              |          |
| Yes                           | 0.758      | 0.628-0.914 | 0.004    | 0.921        | 0.748-1.133 | 0.437    |
| Metastatic sites              |            |          |          | **0.013**    |          | <**0.001** | |
| Bone                          |            |          |          |              |          |
| Brain                         | 1.687      | 1.166-2.441 | 0.006    | 1.676        | 1.145-2.453 | 0.008    |

OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; \(^1\)Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; \(^2\)Median household income: defined by earnings above the median of the median household income in this sample.
| Variable | Univariate  | Multivariate |
|----------|------------|--------------|
| Liver    | 1.276      | 1.003-1.624  | 0.047 | 1.334 | 1.043-1.707 | 0.022 |
| Lung     | 1.034      | 0.849-1.260  | 0.740 | 0.861 | 0.700-1.058 | 0.155 |

OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; ¹Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ²Median household income: defined by earnings above the median of the median household income in this sample.
Table 7
Univariate and Multivariate Cox regression analyses of prognostic factors for CSS in patients with DM

| Variable | Univariate | Multivariate |
|----------|------------|--------------|
|          | HR         | 95% CI       | P value | HR         | 95% CI       | P value |
| Age      |            |              |         |            |              |         |
| < 45     | Reference  |              |         | Reference  |              |         |
| 45-69    | 0.970      | 0.754-1.247  | 0.811   | 0.980      | 0.755-1.271  | 0.877   |
| ≥ 70     | 1.289      | 0.971-1.710  | 0.079   | 1.126      | 0.819-1.550  | 0.464   |
| Race     |            |              |         |            |              |         |
| White    | Reference  |              |         | Reference  |              |         |
| Black    | 0.964      | 0.789-1.179  | 0.722   |            |              |         |
| Other    | 1.010      | 0.691-1.477  | 0.957   |            |              |         |
| Grade¹   |            |              |         |            |              |         |
| Grade I  | Reference  |              |         | Reference  |              |         |
| Grade II | 0.955      | 0.416-2.190  | 0.913   |            |              |         |
| Grade III| 0.932      | 0.416-2.088  | 0.864   |            |              |         |
| Grade IV | 0.792      | 0.282-2.228  | 0.659   |            |              |         |
| Laterality|            |              |         |            |              |         |
| Left     | Reference  |              |         | Reference  |              |         |
| Right    | 0.953      | 0.799-1.136  | 0.590   |            |              |         |
| T stage  |            |              |         |            |              |         |
| T1       | Reference  |              |         | Reference  |              |         |

OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; ¹Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ²Median household income: defined by earnings above the median of the median household income in this sample.
| Variable         | Univariate |          |          |          |          |          |          |
|------------------|------------|----------|----------|----------|----------|----------|----------|
|                  |            |          | Multivariate |          |          |          |          |
|                  |            |          |            |          |          |          |          |
| T2               | 1.085      | 0.768-1.532 | 0.644     | 1.280    | 0.898-1.825 | 0.172    |
| T3               | 1.144      | 0.799-1.638 | 0.463     | 1.314    | 0.910-1.900 | 0.146    |
| T4               | 1.471      | 1.048-2.062 | 0.025     | 1.657    | 1.168-2.351 | 0.005    |
| N stage          |            |          | 0.272     |          |          |          |          |
| N0               | Reference  |          |          |          |          |          |          |
| N1               | 1.211      | 0.954-1.537 | 0.116     |          |          |          |          |
| N2               | 1.259      | 0.918-1.727 | 0.153     |          |          |          |          |
| N3               | 1.297      | 0.981-1.715 | 0.068     |          |          |          |          |
| Insurance status | <0.001     |          | 0.001     |          |          |          |          |
| Uninsured        | Reference  |          | Reference |          |          |          |          |
| Insured          | 0.442      | 0.293-0.668 | <0.001   | 0.471    | 0.307-0.724 | 0.001    |
| Marital status   | 0.026      |          | 0.256     |          |          |          |          |
| Never Married    | Reference  |          | Reference |          |          |          |          |
| Married          | 0.839      | 0.670-1.050 | 0.125     | 0.846    | 0.669-1.069 | 0.160    |
| Previous married | 1.103      | 0.871-1.398 | 0.416     | 0.976    | 0.748-1.275 | 0.861    |
| Median household income<sup>3</sup> |          |          | 0.784     |          |          |          |          |
| Low              | Reference  |          |          |          |          |          |          |
| High             | 1.025      | 0.858-1.224 | 0.784     |          |          |          |          |
| Surgery          | <0.001     |          | <0.001    |          |          |          |          |
| No               | Reference  |          | Reference |          |          |          |          |

OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; <sup>1</sup>Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; <sup>2</sup>Median household income: defined by earnings above the median of the median household income in this sample.
| Variable            | Univariate               | Multivariate        |
|---------------------|--------------------------|---------------------|
| Yes                 | 0.540 0.452-0.645 <0.001 | 0.558 0.462-0.673 <0.001 |
| Chemotherapy        | <0.001                   | <0.001              |
| No/Unknown          | Reference                 | Reference           |
| Yes                 | 0.403 0.328-0.494 <0.001 | 0.435 0.347-0.545 <0.001 |
| Radiotherapy        | 0.009 0.496              |
| No/Unknown          | Reference                 | Reference           |
| Yes                 | 0.773 0.637-0.937 0.009 0.929 0.750-1.149 0.496 |
| Metastatic sites    | 0.011 0.001              |
| Bone                | Reference                 | Reference           |
| Brain               | 1.819 1.255-2.637 0.002 1.809 1.233-2.656 0.002 |
| Liver               | 1.237 0.960-1.593 0.100 1.281 0.989-1.660 0.061 |
| Lung                | 1.084 0.885-1.329 0.435 0.899 0.728-1.111 0.325 |

OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; 
Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; 
Median household income: defined by earnings above the median of the median household income in this sample.

**Discussion**

In the manuscript, we discovered that 4.13% of TNBC patients had DM at the time of diagnosis. Among DM patients, 3.07% had multiple metastases. The most metastatic sites were bone (24.46%, 251/1026) followed by lung (23.78%, 244/1026). Multivariate cox analysis indicated that age, high tumor grade, T, N and marital status were significant risk elements for DM. It is consistent with previous studies of other tumors [18–20]. In addition, T stage, insurance status, marital status, surgery treatment, chemotherapy, location and number of metastases were confirmed to be associated with the diagnosis of DM patients. Moreover, only TNBC was included in this study, which is more convincing to think that this data is the only representative of TNBC. Last but not least, with the rapid improvement in the understanding and diagnosis of the disease, earlier TNBC or smaller breast lumps will be detected in clinical practice.

There have also been previous studies on distant metastasis in BC patients. A retrospective study collected and analyzed information from 2033 BC patients from 2012 to 2014 and showed that high
tumor grade, T, and N were significant risk factors for DM [21]. Another study identified 1173 BC liver metastases from the SEER database. Classification, marital status, surgery, radiotherapy, chemotherapy, tumor size and tumor subtypes were identified as risk factors for liver metastases from BC [22]. These conclusions are similar to our results. But only a few studies have focused on the triple negative subtype and combined metastatic pattern based on a larger sample size. In our study, 36.94% (379/1,026) of metastatic patients had multiple metastases. In addition, compared with patients with a single metastasis, patients with multiple metastases had a poorer survival advantage, and the more metastases there were, the worse the prognosis was (Table 4, 5). Furthermore, diverse combination of metastatic sites represented different prognosis.

Our results indicated that patients with DM have a significantly poor prognosis. Besides, the greater the number of metastases, the worse the prognosis. Hence, we further to identify the risk factors of DM and metastasis in patients with prognostic factors is very essential. In primary bladder cancer, high pathological grade, N and T were positively correlated with bone metastasis [20]. Another meta-analysis showed that poor tumor differentiation was related to the risk of metastasis in cutaneous squamous cell carcinoma [23]. In DM patients, the results of multi-COX analysis indicated that tumor grade, age at first diagnosis, T, N, marital status and surgical treatment were the significant influence affecting the OS. This is in line with what many previous studies have confirmed. In a BC study based on Asian female patients, age, grade, TNM stage, and chemotherapy have been shown to be associated with BC long-term survival [24]. Another SEER database study found that race, age, grade, molecular subtype, surgery, brain and liver metastases were independently associated with BC specific survival [25].

However, there remain several limitations in our study that should not be ignored. First, we failed to get more information from SEER database, including lymphatic or vascular invasion, multifocality, the sequence and specific arrangement of multiple metastases and even molecular biomarkers. Secondly, the database lacked several important clinical information, including LDH, hemoglobin, neutrophil count, platelet count, etc. If we include these, we can improve the comprehensiveness of analysis and conclusion. Furthermore, limitations include a lack of information on rare subtypes of TNBC that may alter treatment, such as metaplasia, adenoid cystic, and acrosine subtypes. Last but not least, the main population for this study is Americans, and whether the results applied to other populations was questionable.

**Conclusion**

About 4.13% of TNBC patients had DM at the time of initial diagnosis, and 36.94% of them had multiple metastases. Compared with non-DM patients, DM patients represented worse prognosis. Meanwhile, the survival was significantly reduced while the number of metastases increasing. In addition, the predictors and prognostic factors of DM were also studied with the expectation of providing potential value for clinical guidance.

**Declarations**
Acknowledgements

We confirmed that all methods were carried out in accordance with relevant guidelines and regulations.

Author Contributions

Zhao Yunian designed the study. Gao Yang wrote the manuscript. Gu Kang, Bian Chuanzhen and Yan Ping analyzed the data. All authors read and approved the final manuscript.

Competing Interests

The authors declare no conflict of interests.

References

1. Beyer K, Zhou Y, Laud P, McGinley E, Yen T, Jankowski C, Rademacher N, Namin S, Kwarteng J, Beltrán Ponce S, Nattinger A. Mortgage Lending Bias and Breast Cancer Survival Among Older Women in the United States. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2021:JCO2100112.

2. Mayer I, Zhao F, Arteaga C, Symmans W, Park B, Burnette B, Tevaarwerk A, Garcia S, Smith K, Makower D, Block M, Morley K, Jani C, Mescher C, Dewani S, Tawfik B, Flaum L, Mayer E, Sikov W, Rodler E, Wagner L, DeMichele A, Sparano J, Wolff A, Miller K. Randomized Phase III Postoperative Trial of Platinum-Based Chemotherapy Versus Capecitabine in Patients With Residual Triple-Negative Breast Cancer Following Neoadjuvant Chemotherapy: ECOG-ACRIN EA1131. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2021:JCO2100976.

3. Gao C, Polley E, Hart S, Huang H, Hu C, Gnanaolivu R, Lilyquist J, Boddicker N, Na J, Ambrosone C, Auer P, Bernstein L, Burnside E, Eliassen A, Gaudet M, Haiman C, Hunter D, Jacobs E, John E, Lindström S, Ma H, Neuhausen S, Newcomb P, O'Brien K, Olson J, Ong I, Patel A, Palmer J, Sandler D, Tamimi R, Taylor J, Teras L, Trentham-Dietz A, Vachon C, Weinberg C, Yao S, Weitzel J, Goldgar D, Domchek S, Nathanson K, Couch F, Kraft P. Risk of Breast Cancer Among Carriers of Pathogenic Variants in Breast Cancer Predisposition Genes Varies by Polygenic Risk Score. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2021:JCO2001992.

4. Bandera E, Qin B, Lin Y, Zeinomar N, Xu B, Chanumolu D, Llanos A, Omene C, Pawlish K, Ambrosone C, Demissie K, Hong C. Association of Body Mass Index, Central Obesity, and Body Composition With Mortality Among Black Breast Cancer Survivors. JAMA oncology. 2021.

5. Weigelt B, Reis-Filho J. Histological and molecular types of breast cancer: is there a unifying taxonomy? Nature reviews Clinical oncology. 2009;6(12):718-730.

6. Siegel R, Miller K, Jemal A. Cancer statistics, 2019. CA: a cancer journal for clinicians. 2019;69(1):7-34.

7. DeSantis C, Ma J, Gaudet M, Newman L, Miller K, Goding Sauer A, Jemal A, Siegel R. Breast cancer statistics, 2019. CA: a cancer journal for clinicians. 2019;69(6):438-451.
8. DeSantis C, Miller K, Goding Sauer A, Jemal A, Siegel R. Cancer statistics for African Americans, 2019. CA: a cancer journal for clinicians. 2019;69(3):211-233.

9. Liedtke C, Mazouni C, Hess K, André F, Tordai A, Mejia J, Symmans W, Gonzalez-Angulo A, Hennessy B, Green M, Cristofanilli M, Hortobagyi G, Pusztai L. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2008;26(8):1275-1281.

10. Lehmann B, Bauer J, Chen X, Sanders M, Chakravarth A, Shyr Y, Pietenpol J. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. The Journal of clinical investigation. 2011;121(7):2750-2767.

11. Pérez-García J, Soberino J, Racca F, Gion M, Stradella A, Cortés J. Atezolizumab in the treatment of metastatic triple-negative breast cancer. Expert opinion on biological therapy. 2020;20(9):981-989.

12. Anwar M, Chen Q, Ouyang D, Wang S, Xie N, Ouyang Q, Fan P, Qian L, Chen G, Zhou E, Guo L, Gu X, Ding B, Yang X, Liu L, Deng C, Xiao Z, Li J, Wang Y, Zeng S, Hu J, Zhou W, Qiu B, Wang Z, Weng J, Liu M, Li Y, Tang T, Wang J, Zhang H, Dai B, Tang W, Wu T, Xiao M, Li X, Liu H, Li L, Yi W. Pyrotinib treatment in patients with HER2-positive metastatic breast cancer and brain metastasis: exploratory final analysis of real-world, multicenter data. Clinical cancer research: an official journal of the American Association for Cancer Research. 2021.

13. Chiou A, Liu C, Moreno-Jiménez I, Tang T, Wagermaier W, Dean M, Fischbach C, Fratzl P. Breast cancer-secreted factors perturb murine bone growth in regions prone to metastasis. Science advances. 2021;7(12).

14. Weigelt B, Peterse J, van ’t Veer L. Breast cancer metastasis: markers and models. Nature reviews Cancer. 2005;5(8):591-602.

15. Correia A, Guimaraes J, Auf der Maur P, De Silva D, Trefny M, Okamoto R, Bruno S, Schmidt A, Mertz K, Volkman K, Terracciano L, Zippelius A, Vetter M, Kurzedecer, Weber W, Bentires-Alj M. Hepatic stellate cells suppress NK cell-sustained breast cancer dormancy. Nature. 2021.

16. Tsilimigras D, Brodt P, Clavien P, Muschel R, D’Angelica M, Endo I, Parks R, Doyle M, de Santibañes E, Pawlik T. Liver metastases. Nature reviews Disease primers. 2021;7(1):27.

17. Chen Y, Jiang T, Zhang H, Gou X, Han C, Wang J, Chen A, Ma J, Liu J, Chen Z, Jing X, Lei H, Wang Z, Bao Y, Baqri M, Zhu Y, Bindra R, Hansen J, Dou J, Huang C, Zhou J. LRRC31 inhibits DNA repair and sensitizes breast cancer brain metastasis to radiation therapy. Nature cell biology. 2020;22(10):1276-1285.

18. Zhang Y, Guo Y, Zhou X, Wang X, Wang X. Prognosis for different patterns of distant metastases in patients with uterine cervical cancer: a population-based analysis. Journal of Cancer. 2020;11(6):1532-1541.

19. Wang Z, Chen M, Pan J, Wang X, Chen X, Shen K. Pattern of distant metastases in inflammatory breast cancer - A large-cohort retrospective study. Journal of Cancer. 2020;11(2):292-300.

20. Zhang C, Liu L, Tao F, Guo X, Feng G, Chen F, Xu Y, Li L, Han X, Baklaushev V, Bryukhovetskiy A, Wang X, Wang G. Bone Metastases Pattern in Newly Diagnosed Metastatic Bladder Cancer: A Population-
Based Study. Journal of Cancer. 2018;9(24):4706-4711.

21. Pan H, Wang H, Qian M, Mao X, Shi G, Ma G, Yu M, Xie H, Ling L, Ding Q, Zhang K, Wang S, Zhou W. Comparison of Survival Outcomes Among Patients With Breast Cancer With Distant vs Ipsilateral Supraclavicular Lymph Node Metastases. JAMA network open. 2021;4(3):e211809.

22. Xiong Y, Shi X, Hu Q, Wu X, Long E, Bian Y. A Nomogram for Predicting Survival in Patients With Breast Cancer Liver Metastasis: A Population-Based Study. Frontiers in oncology. 2021;11:600768.

23. Thompson A, Kelley B, Prokop L, Murad M, Baum C. Risk Factors for Cutaneous Squamous Cell Carcinoma Recurrence, Metastasis, and Disease-Specific Death: A Systematic Review and Meta-analysis. JAMA dermatology. 2016;152(4):419-428.

24. Fan R, Chen Y, Nechuta S, Cai H, Gu K, Shi L, Bao P, Shyr Y, Shu X, Ye F. Prediction models for breast cancer prognosis among Asian women. Cancer. 2021;127(11):1758-1769.

25. Zheng Y, Wang X, Fan L, Shao Z. Breast Cancer-Specific Mortality in Small-Sized Tumor with Stage IV Breast Cancer: A Population-Based Study. The oncologist. 2021;26(2):e241-e250.

Figures

Figure 1
Flowchart of patient selection.

A

B

C

Figure 2
PMRs of TNBC patients. (A) PMRs of TNBC patients with DM and without DM; (B) PMRs of TNBC patients with different numbers of metastatic sites; (C) PMRs of TNBC patients with different metastatic organ.

Figure 3
Kaplan–Meier curves of OS in TNBC patients according to metastatic status: with or without DM (A), 1 site versus >1 sites (C), 2 sites versus >2 sites (E), the number of metastatic sites (G), Kaplan–Meier curves of CSS in TNBC patients according to metastatic status: with or without DM (B), 1 site versus >1 sites (D), 2 sites versus >2 sites (F), the number of metastatic sites (H).

Figure 4

Kaplan–Meier curves of OS in TNBC patients according to metastatic status: with single site (A), with two sites (C), with three sites (E). Kaplan–Meier curves of CSS in TNBC patients according to metastatic status: with single site (B), with two sites (D), with three sites (F).

Supplementary Files

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- TableS1.doc