Clinicopathologic and outcome characteristics of breast cancer with liver metastases (BCLM): a population study of the SEER database and a registry analysis of 1728 women

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Abstract
Background Breast cancer patients generally have a worse prognosis in presence of liver metastasis. The purpose of this study was to evaluate the risk factors and prognosis of breast cancer patients with liver metastases (BCLM). Methods Data on 311,573 breast cancer patients from the Surveillance, Epidemiology, and End Results (SEER) database diagnosed 2010 to 2016 and 1728 BCLM patients from Fudan University Shanghai Cancer Center (FUSCC) were analyzed for further exploration. We extracted the clinicopathological characteristics for analysis by two independent authors. Logistic regression was used to identify factors associated with the risk of liver metastases. Survival analysis was completed using Cox proportional hazards regression model and Kaplan-Meier analysis. Results Young age, invasive ductal carcinoma, higher pathological grade, and subtype of triple-negative and human epidermal growth factor receptor 2 positive (HER2+), were associated with increased risk of the liver metastases. The median overall survival (OS) after BCLM diagnosis was 20.0 months in the SEER database and 27.3 months in the FUSCC dataset. We observed that hormone receptor-positive (HR+)/HER2+ patients had the longest median OS 38.0 for SEER vs. 34.0 months for FUSCC), whereas triple-negative breast cancer had the poorest OS (9.0 vs. 15.6 months) in both SEER and FUSCC. According to the results from the FUSCC, the subtype of HR+/HER2+ (hazard ratio (HR)=2.62; 95% confidence interval (CI)=1.88-3.66; P<0.001) and HR-/HER2+ (HR=3.43; 95% CI=2.28-5.15; P<0.001) were associated with a significantly increased death risk in comparison with subtype of HR+/HER2-, if the patients did not receive HER2-targeted therapy. For BCLM patients who had received HER2-targeted therapy, however, HR+/HER2+ was an indicator for decreased death risk in comparison of the subtype of HR+/HER2- (HR=0.74; 95% CI=0.58-0.95; P<0.001). Conclusions BCLM is associated with poor survival, depending on HR/HER2-defined subtypes. Patients with HR+/HER2+ subtype displayed the longest median survival than HR+/HER2- and triple-negative BCLM patients. HER2-targeted therapy should be recommended for HER2+ BCLM patients.

Introduction
Breast cancer is the most frequently diagnosed cancer and is the second leading cause of cancer-related death among women in developed countries[1]. More than 5% of cases are metastatic disease
at the time of diagnosis [2], while almost 30% of patients newly diagnosed with localized or regional disease will recur [3]. Notably, the incidence of BCLM is only second to bone and lung metastasis [4], accounting for 71% of all patients in an autopsy study [5]. The 5-year relative survival among breast cancer patients is satisfactory, 91% for all stages combined and 26% for those diagnosed with metastatic breast cancer[2], whereas the presence of liver metastasis(LM) represents a catastrophic event and is an ominous prognostic factor with a median associated survival time that ranges from 3 months to 15 months despite treatment [6]. As a result of the lack of proven benefit, there are no recommendations for routine laboratory or imaging studies for metastasis screening in the absence of clinical signs and symptoms related to relapse according to breast cancer follow-up or surveillance guidelines[7]. Thus, BCLM patients who usually present asymptptomatically or with atypical symptoms tend to be ignored in the beginning stage of LM.

It is universally acknowledged that the risk of LM is largely dependent on breast cancer subtypes, and patients with HER2+ and triple-negative subtypes are more likely to have metastasis to the liver than patients with HR+/HER2- tumors [8]. However, there are still many controversies about the influence of breast cancer subtype on the survival of BCLM patients. Triple-negative breast cancer was independently associated with worse survival after liver metastasis [9, 10]. Positive HR status was significantly associated with improved outcome [11]. Moreover, HR+/HER2+ BCLM patients showed the longest median survival (31 months) [10], suggesting that HER2 positivity was a protective factor. However, data from other retrospective studies showed that HER2 status had no effect on survival [12, 13].

The purpose of this study was to utilize the SEER database to study the epidemiology of BCLM at the time of cancer diagnosis and validate the role of breast cancer subtypes with the help of single institutional experiences in the FUSCC dataset. We also sought to examine the effect of HER2-targeted therapy, hoping to provide optimal therapeutic strategies for specific BCLM patients.

Methods

Study population

Within the SEER Research Data 1975–2016 dataset, the data from 446,792 breast cancer patients 18
years or older who were diagnosed from January 1, 2010 to December 31, 2016 were extracted[14]. After patients whose disease had not been histologically confirmed (n=6,406) or who had multiple primary malignant tumors (n=116,452) were removed, we identified 323,934 patients. Patients with carcinoma in situ (n=405) or unknown LM status (n=5,113) were not included, leaving 318,416 patients in the cohort. Subsequently, patients who were diagnosed via autopsy or with a death certificate (n=22) and those who had an unknown follow-up or whose survival months equaled 0 (n=6,821) were excluded. Finally, there were 311,573 invasive breast cancer patients in the final cohort for further analysis, among whom there were 15,884 patients with de novo MBC at initial diagnosis (Figure S1).

Within FUSCC dataset, which included data collected between January 2007 and December 2018, there were a total of 3,453 female MBC patients. Patients (n=3,048) with detailed medical records and who had been histologically confirmed were enrolled. The diagnosis of LM was based on the radiologic scan, the biopsy of metastatic lesions or the surgical resection specimens. Patients without LM (n=1,252) were not included, leaving 1,796 patients in the cohort. Subsequently, the key exclusion criteria were bilateral breast cancer (n=9) with different subtypes, carcinoma in situ (n=2), unknown age (n=1), and the presence of other invasive neoplasms (n=56). Ultimately, 1,728 BCLM patients were eligible for subsequent analysis (Figure S2). Of these HER2-positive BCLM patients (n=626), 528 patients treated with or without HER2-targeted therapy were utilized to explore the effect of HER2-targeted therapy in this specific population. Patient follow-up was performed on June 15, 2019, and the median follow-up time was 17.4 months (interquartile range [IQR], 8.5 to 31.0 months).

**Study variables**

The studied variables are shown in detail in Tables 3-5, including age at diagnosis, sex, race, marital status, insurance status, histology, pathological grade, number of extrahepatic metastatic sites in lung, brain and bone, and subtype. Because of different study objectives and data accessibility, some adjustments were made in the Tables. Incidence was defined as the number of BCLM patients divided by the total number of breast cancer patients or metastatic breast cancer (MBC) patients at initial
diagnosis in the first cohort, and patients were stratified by breast cancer subtypes. In the second cohort, the proportion of patients that had recurrent LM was also computed among the entire cohort and the two subgroups. First LM refers to de novo LM or LM as the initial site of relapse after early breast cancer, whereas subsequent LM suggests that patients develop LM during their disease course. Breast cancer subtypes were categorized as follows: HR-positive (estrogen receptor(ER)-positive and/or progesterone receptor(PR)-positive)/HER2-negative(HR+/HER2-); HR-positive HER2-positive(HR+/HER2+); HR-negative/HER2-positive(HR-/HER2+); triple-negative (HR-/HER2-) and unknown. Survival was calculated from the date of diagnosis of LM to the date of death from any cause, and surviving patients were censored at the date of last follow-up. Of these 626 HER2+ BCLM patients, 528 patients who were known to have undergone HER2-targeted therapy were divided into two groups, among which one group (435) received HER2-targeted therapy after LM and the other group (93) did not. To assess the strength of the association between HER2-targeted therapy and survival, two groups that were treated with or without HER2-targeted therapy were used for further analysis.

**Statistical analysis**

Univariate and multivariate logistic regression analyses were performed to determine the relationship between study variables and the presence of de novo LM. Odds ratios (ORs) with 95% CIs were also calculated. Univariate and multivariate Cox regression analyses were adopted to identify the prognostic factors associated with increased all-cause mortality. We also calculated HRs and 95% CIs in the Cox regression model. For further validation of these prognostic factors, the second cohort from the FUSCC database was used. The Kaplan-Meier method and a log-rank test were used to estimate survival and evaluate differences between survival curves. Statistical analyses were performed using R (version 3.5.1; R Foundation, Vienna, Austria), and a two-sided P-value less than 0.05 was considered statistically significant.

**Results**

**Incidence**

A total of 311,573 patients from SEER database diagnosed between 2010 and 2016 were included in
the present study. Of these patients, there were 15,884 MBC patients and 4,067 BCLM patients at initial diagnosis. As presented in Table 1, the 4,067 BCLM patients accounted for 1.31% of the entire cohort and 25.6% of the MBC patients, including 1612 patients with HR+/HER2- subtype tumors (39.64%), 884 with HR+/HER2+ tumors (21.74%), 601 with HR-/HER2+ tumors (14.78%), 544 with triple-negative tumors (13.38%), and 426 with unknown tumors (10.47%). The proportion of patients with HR-/HER2+ tumors ranked highest (4.27% of the entire cohort and 44.13% of the metastatic subclass), while those with HR+/HER2- tumors ranked lowest proportion in both entire and metastatic patients (0.76% of the entire cohort and 19.34% of the metastatic subclass, Table 1). For patients from FUSCC, liver metastasis as the first distant metastasis, attributed to 35.59% proportion of all MBC patients (Table 2).

Using breast cancer patients aged between 18-40 as reference, the increase of age was associated with significant trend towards decreased risk of liver metastasis, with OR of 0.59, 0.46, and 0.46 for those aged between 41-60, 61-80 and those older than 80-years age, respectively (P<0.001 for all, Table 3). The risk of liver metastasis was decreased in Hispanic (OR=0.82, 95% CI=0.74-0.91; P<0.001) and Asian or Pacific Islander patients (OR=0.81; 95% CI=0.72-0.92; P=0.001), but was increased for black patients (OR=1.54; 95% CI=1.41-1.67; P<0.001) in comparison with white patients. Married (OR=0.64; 95% CI=0.60-0.68; P<0.001) and insured status (OR=0.53; 95% CI=0.45-0.63; P<0.001) was associated with significantly decreased risk of liver metastasis when compared with the status of unmarried and uninsured, respectively. Compared with infiltrating duct carcinoma, lobular carcinoma (OR=0.68; 95% CI=0.59-0.77; P<0.001) and the mix of infiltrating duct and lobular carcinoma (OR=0.66; 95% CI=0.55-0.79; P<0.001) were both associated with decreased risk of liver metastasis. Tumors with higher pathological grade more inclined to metastatic to liver, with increased risk in the comparison of grade II versus I (OR= 3.89; 95% CI=3.28-4.65; P<0.001) and grade III/IV versus I (OR=8.59; 95% CI=7.26-10.23; P<0.001). The analysis on molecular subtype indicated that HR+/HER2+ (OR=3.13; 95% CI=2.87-3.41; P<0.001), HR-/HER2+ (OR=4.75; 95% CI= 4.30-5.25; P<0.001), and triple-negative subtypes (OR=1.92; 95% CI=1.73-2.12; P<0.001) were all predictors for increased risk of liver metastasis in comparison with HR+/HER2- subtype, indicating the important
role in disease progression played by HER2 status.

**Survival**

Median survival among BCLM patients, as stratified by subtype, is displayed in Table 1 and 2. The median survival among the entire cohort was 20.00 months in the SEER database (vs 27.30 months in the FUSCC database), with patients with the HR+/HER2+ subtype experiencing the longest median survival (38.00 vs 34.00 months) and patients with the triple-negative subtype experiencing the shortest median survival (9.00 vs 15.63 months) in the two cohorts. Additionally, breast cancer patients with first LM showed distinctly longer survival times than those patients with subsequent liver metastases when the time was calculated from the diagnosis of BCLM (33.80 vs 17.47 months, Figure 2A). However, patients with LM at the time of initial diagnosis had a shorter survival time than MBC patients developing liver metastases during the subsequent disease course when the time was calculated from the diagnosis of MBC (42.57 vs 33.80 months, Figure 2B). The overall survival estimate and the overall survival stratified by subtype or extent of extrahepatic metastatic disease are graphically displayed in Figure 1. Multivariate Cox proportional hazards models were used to assess the prognostic factors of patients with BCLM in the SEER database (Table 4). We also used FUSCC dataset for further validation (Table 5). In the SEER database, older patients had worse survival, with a HR of 1.39, 1.84 and 3.62 for patients aged 41-60, 61-80, and >80 years in comparison with those aged 18-40 years ($P<0.001$ for all). Moreover, black and Hispanic race were associated with increased death risk compared with white race, with a HR of 1.35 ($P<0.001$) and 1.16 ($P=0.028$), respectively. SEER database also showed a prolonged survival in presence of the status of married and insurance (HR=0.84 for married vs. unmarred, and 0.71 for insured vs. uninsured, with $P<0.001$ for all). For the survival comparisons among clinical factors, we found that increased pathological grade, treatment without chemotherapy and surgery of primary site, increased number of extrahepatic metastatic sites and triple-negative pathological type were all associated with poor prognosis. Specifically, compared with grade I disease, the HR was 1.35 ($P=0.013$) for grade II and 1.69 for grade III-IV ($P<0.001$), respectively. Treatment without surgery of primary site and chemotherapy generated a HR of 1.52 and 1.63, respectively compared with those received the
treatments (P<0.001 for all). As expected, the HR increased from 1.42 to 3.43 as number of extrahepatic sites increased from 1 to 3, compared with no metastasis (P<0.001 for all). In line of most previous studies, triple-negative subtype remained the deadliest type of cancer, with HR of 2.46 in comparison with HR+/HER2- cancers (P<0.001). Interestingly, compared with HR+/HER2- subtype, we observed that HER2+ might decrease the death risk in the SEER database, with HR of 0.69 for HR+/HER2+ (P<0.001) and 0.85 (P=0.014) for HR-/HER2+ subtype, likely because of the adoption of HER2-targeted therapy. The significant association of age and number of extrahepatic metastasis sites with poor prognosis of the BCLM patients was successfully validated in FUSCC datasets (Table 5). Although the patients with triple negative BCLM had the worst survival, we did not observe significant difference between survival of HER2+ patients with HR+/HER2- patients (P>0.05) in FUSCC dataset.

HER2-targeted therapy

We next explore whether HER2-targeted therapy might modulate survival of patients with different subtype. We found that in presence of treatment without HER-2 targeted therapy, HER2+ patients had a poor survival compared with HR+/HER2- patients, with HR of 2.62 for HR+/HER2+ and 3.43 for HR-/HER2+ patients (P<0.001 for all, Table 6). When HR+/HER2+ BCLM patients received HER2-targeted therapy after liver metastasis, their prognosis was found to be better than HR+/HER2- patients, with HR of 0.74 (P<0.001). However, we only observed an insignificant trend towards decreased death risk induced by HER2-targeted therapy for HR-/HER2+ patients compared with HR+/HER2- patients, with HR of 0.84 (P=0.110). Overall survival among BCLM patients with or without HER2-targeted therapy stratified by subtype were visualized in Figure 2.

Discussion

The incidence of BCLM in patients and the subsequent survival of such patients was described in this study. It was reported that the incidence of liver as the first metastatic site varied from 17.8%-35% [11, 15, 16]. We found that the incidence of first LM was 25.6% in the SEER database and 35.59% in the FUSCC database, similar to a previous study. Purushotham et al suggested that patients with young age and high-grade and invasive ductal carcinoma had an increased risk of visceral metastases [17].Zengel et al compared the clinicopathological features of patients with invasive ductal, invasive
lobular, and invasive ductal and lobular carcinoma (mixed-type) of the breast. They found that the ratio of bone metastases was higher in invasive lobular carcinoma and mixed-type tumors than in invasive ductal carcinoma [18]. In this study, we also found that young age, invasive ductal carcinoma, and high pathological grade were significantly associated with the presence of de novo LM, consistent with the previously published literature. In addition, our current results demonstrated that patients with the HER2-positive and triple-negative subtypes had significantly greater odds of having liver metastases at diagnosis than patients with the HR+/HER2- subtype, and these findings are in accordance with previously published data focused primarily on the metastatic pattern of breast cancer subtypes[8, 15-17]. In one study, no evidence of metastases was detected by liver ultrasonography or chest radiography in patients with stage I or II disease, while the prevalence of a positive liver ultrasound and positive chest X-ray was 6% and 7%, respectively, among patients with stage III breast cancer[19]. Because studies have shown no additional value of routine systemic imaging in patients with early-stage disease, guidelines have reiterated that these studies are not indicated for patients with early breast cancer in the absence of signs or symptoms of metastatic disease[19-21]. When liver metastases are identified early, they are usually amenable to diverse and potentially effective treatments, such as stereotactic body radiation therapy (SBRT), interventional therapy or hepatic resection[13, 22-26], which may eventually lead to long-term survival in selected patients. Our results support the need for further investigation of the high-risk populations of patients with liver metastases.

The median survival after LM diagnosis was 20.00 months in the SEER database (vs 27.30 months in the FUSCC dataset) and varied significantly by tumor subtype. In both approximately 30% of the population from the SEER dataset (from the United States) and patients treated at the Academic Cancer Center from the FUSCC data, HR+/HER2+ patients had the longest survival (median survival, 38.00 vs 34.00 months), whereas triple-negative breast cancer was associated with the poorest survival (median survival, 9.00 vs 15.63 months). Both HR+/HER2+ and HR-/HER2+BCLM patients had a more favorable outcome than HR+/HER2-BCLM patients in the SEER database, but there was no significant difference in the FUSCC dataset. According to the data from FUSCC, HER2-positive BCLM
patients who did not receive HER2-targeted therapy after liver metastases had worse outcomes, similar to those of the triple-negative subgroup, whereas significantly improved clinical outcomes were observed among the population receiving HER2-targeted therapy after LM, and HR+/HER2+ patients had a 26% reduction in the hazard ratio for overall mortality, findings that were identical to the SEER data. Although the results from HER2-positive BCLM patients receiving HER2-targeted therapy in the FUSCC database were still slightly different from those found with the SEER database, they indicated that HR+/HER2+ or even HR-/HER2+BCLM patients had a better prognosis than HR+/HER2- BCLM patients owing to the introduction of HER2-targeted therapy. The gene that encodes HER2 is amplified and overexpressed in 15-20% of newly diagnosed breast cancers[27], which is associated with a worse survival for women with breast cancer[28]. Nevertheless, diverse HER2-directed drugs have significantly improved survival in patients with HER2-positive metastatic breast cancer, including monoclonal antibodies (trastuzumab and pertuzumab), several HER2 tyrosine kinase inhibitors (lapatinib, neratinib, and pyrotinib), and an antibody−drug conjugate, trastuzumab emtansine[29-34]. Even for the many patients with HER2-positive metastatic breast cancer, which is a virtually incurable disease, antiHER2 therapy results in considerable and long-lasting improvement in quality of life and overall survival[35]. Furthermore, continuous anti-HER2 therapy is of utmost significance for the improvement of survival outcomes in metastatic breast cancer[31, 36, 37]. However, these treatments are expensive and require expertise in delivery, factors that limit their availability in and continuous use for patients without adequate health insurance and those in lower-income countries[35], which may result in differences between the SEER and the FUSCC data. Historically, the HR+/HER2- subtype was associated with the best prognosis in early breast cancer[38], whereas the HR+/HER2+ subtype had the most favorable outcome, and there were no statistical differences in the HR+/HER2- and HR-/HER2+ subgroups among de novo metastatic breast cancer patients in the HER2-targeted therapy era[39]. Among breast cancer patients with de novo brain or bone metastases, results that were consistent with those of de novo metastatic breast cancer patients were seen[40, 41]. Interestingly, the HR-/HER2+ subgroup had a worse prognosis than the HR+/HER2- subgroup among breast cancer patients with de novo lung metastases[42]. In contrast,
we found that even HR-/HER2+ BCLM patients had a better prognosis than the HR+/HER2- subgroup in this study, which was different from the findings in breast cancer with other metastatic sites. There are several potential reasons. HR+/HER2- patients with visceral metastases are often considered less likely to respond to hormonal therapy than those without visceral metastases[43]. In the FALCON study, the median progression-free survival (PFS) in patients receiving fulvestrant 500mg as first-line treatment with and without visceral disease was 13.8 months and 22.3 months, respectively[44]. M. He et al found that heterogeneity existed among different visceral metastatic sites, and the median PFS was longer in patients with lung metastases than in those with liver metastases after fulvestrant therapy (9.6 and 3.7 months, respectively, \( P < 0.001 \))[43]. Kimbung et al also identified a 17-gene liver metastasis-specific signature (including CDH11, COL11A1, FBN1, MFAP5, SFRP4, and SPON1), which was significantly and independently prognostic for poor relapse-free and overall survival in ER-positive tumors[45]. Fortunately, substantial progress has been made after major advances in our understanding of the biology of ER+/HER2- breast cancer in the past 20 years, such as the development of CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib), mTOR inhibitors (everolimus and temsirolimus), PI3K inhibitors (alpelisib and taselisib), histone deacetylase inhibitors (tucidinostat and entinostat)[46]. Subgroup analyses suggested that patients with visceral metastases also benefited from the addition of these targeted therapies to endocrine therapy[47-50]. On the basis of the above findings, endocrine therapy combined with these novel targeted therapies may be a more appropriate choice for HR+/HER2- BCLM patients than endocrine therapy alone, but further research is required.

In addition, we also found that survival was poorer among elderly BCLM patients and patients with more extrahepatic metastatic sites in both cohorts, in agreement with previous studies[10, 11, 17, 45]. Interestingly, unmarried and uninsured status were associated with decreased overall median survival in the first cohort. These results indicated that lower socioeconomic status (SES), whether measured at the individual or area level, is associated with numerous health disadvantages and increased mortality across races and ethnicities[1]. Several retrospective studies showed that locoregional treatment correlated with significantly improved survival in patients with de novo
metastatic breast cancer[51], and a similar result was observed in this study. However, there is no evidence to suggest that locoregional treatment of the primary tumor affects overall survival in patients with metastatic breast cancer at initial presentation according to a randomized controlled trial[51]. Therefore, the survival benefits associated with surgery may be attributed to selection bias.

Limitations

We acknowledge that there are some limitations in our study. First, this retrospective study inevitably resulted in selection biases, and we had a limited ability to control potential confounding factors, thus affect the final result. Second, some detailed information that may have effects on survival was not available in the SEER and FUSCC databases, including other metastatic sites (such as the pleura and contralateral breast), number and maximum diameter of liver metastases and performance status. Third, it was not possible to further evaluate the effect of different HER2-targeted therapies, endocrine therapies and surgery on the prognosis of liver metastases to provide more individualized treatment for these specific populations because there was a lack of more detailed treatment information.

Conclusions

Despite these limitations, our study is the largest to study the epidemiologies, prognostic factors and clinical outcomes among BCLM patients. Breast cancer patients with young age, invasive ductal carcinoma, high pathological grade, and triple-negative and HER2+ subtypes have an increased risk of the presence of de novo liver metastases, and this lends support to screening for liver metastases in patients at high risk of liver metastases to aid in the early diagnosis and treatment of BCLM patients. Furthermore, HR+/HER2+ or even HR-/HER2+ BCLM patients had a better prognosis than HR+/HER2- BCLM patients owing to the introduction of HER2-targeted therapy. HER2-targeted based therapy may be the best therapeutic strategy for HER2+ BCLM patients.

Abbreviations

BCLM: breast cancer with liver metastases;

SEER: Surveillance, Epidemiology, and End Results;

FUSCC, Fudan University Shanghai Cancer Center;
HER2: human epidermal growth factor receptor 2;
HR: hormone receptor;
OS: overall survival;
+: positive;
-, negative;
HR, hazard ratio;
CI: confidence interval;
LM: liver metastasis;
MBC: metastatic breast cancer;
ER: estrogen receptor;
PR: progesterone receptor;
ORs: Odds ratios;
SBRT: stereotactic body radiation therapy;
PFS: progression-free survival;
SES: socioeconomic status

Declarations

Author Contributions:
Lei, Ji and Lei, Cheng contributed equally.

Study concept and design: Lei, Fan and Zhonghua, wang

Data collection, statistical analysis, or interpretation of data: All authors

Drafting of the manuscript: Lei, Ji, Lei, Cheng, Lei, Fan and Zhonghua, wang

Critical revision of the manuscript: Lei, Fan and Zhonghua, wang

Supervision: Lei, Fan and Zhonghua, wang

Ethics approval and consent to participate

This study was approved by the Institutional Ethics Review Board of FUSCC. All patients signed written informed consent before this study. The data released by the SEER database are available to the public and do not include patient identifiers. Therefore, it was unnecessary to require written consent.
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Competing Interests

The authors have declared that no competing interests exist.

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Tables

Table 1. Incidence Proportion and Median Survival of Patients With Breast Cancer With Identified Liver Metastases at Diagnosis

| Subtype       | With Breast Cancer | With Metastatic Disease | With Liver Metastases | Amo |
|---------------|--------------------|-------------------------|-----------------------|-----|
| HR+/HER2-     | 21112(67.76)       | 8337(52.49)             | 1612(39.64)           | 0.76|
| HR+/HER2+     | 32962(10.58)       | 2511(15.81)             | 884(21.74)            | 2.68|
| HR-/HER2+     | 14089(4.52)        | 1362(8.57)              | 601(14.78)            | 4.27|
| Triple-negative | 33352(10.70)     | 1988(12.52)             | 544(13.38)            | 1.63|
| Unknown       | 20043(6.43)        | 1686(10.61)             | 426(10.47)            | 2.13|
| All subtypes  | 311573(100)        | 15884(100)              | 4067(100)             | 1.31|

NOTE. HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NA, Not Available. + Denotes positive; - denotes negative; CI, confidence interval
Table 2. Proportion and Median Survival among Patients of Breast Cancer With Identified Liver Metastases by Subtype (FUSCC)

| Subtype     | Patients of Liver Metastases, No. (%) | Survival \(^a\) Among Patients With Liver Metastases, Median (95% CI), months | Among Patients With Liver Metastases, Median (95% CI), months |
|-------------|--------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------|
|             | With Breast Cancer Liver Metastases | With Liver Metastases \(^b\) | With First Subsequent Liver Metastases \(^c\) | Among Entire population | With Liver Metastases | With First Liver Metastases | With Subsequent Liver Metastases |
| HR+/HER2-   | 767(44.39)                           | 414(38.09) | 353(55.07) | 28.53(26.10-31.80)   | 38.30(32.30-44.17)   | 18.47(16.93-23.27) |
| HR+/HER2+   | 305(17.65)                           | 215(19.78) | 90(14.04)  | 34.00(29.40-40.30)   | 42.43(38.17-58.50)   | 20.87(16.30-29.30) |
| HR-/HER2+   | 321(18.58)                           | 249(22.91) | 72(11.23)  | 33.60(27.33-38.03)   | 35.47(29.93-42.37)   | 18.77(13.77-45.40) |
| Triple-negative | 270(15.63)                          | 170(15.63) | 100(15.60) | 15.63(12.50-19.47)   | 20.20(16.60-23.37)   | 9.10(8.20-13.50)  |
| Unknown     | 65(3.76)                             | 39(3.59)   | 26(4.06)   | 18.90(14.87-34.87)   | 23.30(14.17-NA)       | 15.67(13.30-NA)   |
| All subtypes | 1728(100)                            | 1087(100)  | 641(100)   | 27.30(25.57-29.40)   | 33.80(31.20-37.73)   | 17.47(16.30-19.77) |

NOTE. HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NA, Not Available; + Denotes positive; – denotes negative; \(^a\), Time from diagnosis of liver metastases; \(^b\), including the presence of liver metastases at initial diagnosis or liver metastases as the first metastatic site; \(^c\), including the presence of liver metastases during the subsequent clinical course; CI, confidence interval

Table 3. Univariable and Multivariable Logistic Regression for the Presence of Liver Metastases at Diagnosis of Breast Cancer(SEER)

| Variable                          | Patients, No. Among Entire Cohort | Among Subset With Metastatic Disease |
|-----------------------------------|-----------------------------------|--------------------------------------|
|                                   | Patients (n=311573) | With Liver Metastases (n = 4067) | Univariable | Multivariable | Univariable | Multivariable |
| Age at diagnosis, y               | 18-40    | 21313 | 494 | 1[Reference] | 1[Reference] | 1[Reference] | 1[Reference] |
|                                   | 41-60    | 13729 | 1882 | 0.59(0.53- <0.00 1* | 0.59(0.54- <0.00 1* | 0.72(0.63- <0.00 1* | 0.71(0.63- <0.00 1* |

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| Sex      | Male  | 2267 | 26 | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
|----------|-------|------|----|---------------|---------------|---------------|---------------|---------------|---------------|
| Female   | 30930 | 4041 | 6  | 0.505         | 1.38(0.93-2.14) | 0.127         | 2.26(1.52-3.50) | <0.00         | 1             |

| Race     | White | 20740 | 2565 | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
|----------|-------|-------|------|---------------|---------------|---------------|---------------|---------------|---------------|
| Black    | 35062 | 737   | <0.00 | 1.54(1.67) | <0.00 | 1.14(1.26) | 0.007         | 1.03(0.93-1.14) | <0.00 | 1             |
| Hispanic | 37499 | 427   | 0.112 | 0.82(0.74-0.91) | <0.00 | 0.91(0.81-1.02) | 0.112         | 0.78(0.69-0.88) | <0.00 | 1             |
| Asian or Pacific Islander | 27997 | 305   | 0.035 | 0.81(0.72-0.92) | <0.00 | 1.05(0.91-1.21) | 0.484         | 0.94(0.81-1.08) | 0.387         |

| Ethnicity | Unknown | 1858 | 10 | 0.43(0.22-0.76) | 0.38(0.19-0.68) | <0.00 | 0.67(0.32-1.28) | 0.258         | 0.68(0.32-1.30) | 0.272         |

| Marital status | Unmarried | 12334 | 2011 | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
|----------------|-----------|-------|------|---------------|---------------|---------------|---------------|---------------|
| Married        | 17172     | 1827  | 0.65(0.61-0.69) | <0.00 | 0.64(0.60-0.68) | <0.00 | 1.07(0.99-1.15) | 0.086         | 1.01(0.94-1.09) | 0.804         |

| Unknown       | 16496 | 229 | 0.85(0.74-0.97) | 0.83(0.72-0.96) | 0.013         | 0.111(0.94-1.30) | 0.206         | 0.95(0.95-1.32) | 0.179         |

| Insurance status | Uninsured | 5417 | 163 | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
|------------------|-----------|-------|------|---------------|---------------|---------------|---------------|---------------|
| Insured          | 30040     | 3821  | 0.42(0.36-0.49) | <0.00 | 0.53(0.45-0.63) | <0.00 | 1.07(0.99-1.15) | 0.875         | 1.01(0.94-1.09) | 0.804         |

| Unknown           | 5756 | 83 | 0.47(0.36-0.61) | <0.00 | 0.48(0.35-0.67) | <0.00 | 1.11(0.94-1.30) | 0.206         | 1.12(0.95-1.32) | 0.179         |

| Histology        | Infiltrating duct carcinoma | 23495 | 2971 | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
|------------------|-----------------------------|-------|------|---------------|---------------|---------------|---------------|---------------|
| Lobular carcinoma | 27050 | 246 | 0.72(0.63-0.81) | <0.00 | 0.68(0.59-0.77) | <0.00 | 0.50(0.43-0.57) | <0.00 | 0.53(0.46-0.62) | <0.00 | 1             |
| Subtype                  | Pathological Grade | Infiltrating duct and lobular carcinoma | Other | Pathological Grade | Infiltrating duct and lobular carcinoma | Other |
|-------------------------|-------------------|----------------------------------------|-------|-------------------|----------------------------------------|-------|
|                         | I                 | 66365 144                               | 1[Reference] | 1[Reference] | 1[Reference] | 1[Reference] |
|                         | II                | 12978 1147                              | 4.10(3.46-4.90) | 3.89(3.28-4.65) | 1.60(1.33-1.94) | 1.51(1.25-1.83) |
|                         | III/IV            | 98850 1939                              | 9.20(7.80-10.95) | 8.59(7.26-10.23) | 2.41(2.01-2.91) | 2.35(1.94-2.83) |
|                         | Unknown           | 16572 837                               | 9.20(7.80-10.95) | 20.75(17.32-25.02) | 2.41(2.01-2.91) | 1.58(1.29-1.95) |
| Extrahepatic metastatic to lung, brain and bone, No | | | | | | |
| 0                       | 29840 1060        | 1[Reference] | 1[Reference] | 1[Reference] | 1[Reference] |
| 1                       | 9408 1696         | <0.00(1* 61.69(56.9-66.84) | <0.00(1* 58.49(53.84-63.57) | <0.00(1* 0.38(0.35-0.42) | <0.00(1* 0.39(0.35-0.43) |
| 2                       | 2747 891          | <0.00(1* 134.6(7121-148.8) | <0.00(1* 123.1(5110-136.7) | <0.00(1* 0.83(0.74-0.92) | <0.00(1* 0.86(0.77-0.96) |
| All                     | 343 177           | <0.00(1* 299.1(0240-372.9) | <0.00(1* 246.1(7195-310.3) | <0.00(1* 1.82(1.46-2.87) | <0.00(1* 1.88(1.50-2.37) |
| Unknown                 | 668 243           | <0.00(1* 160.3(9135-189.7) | <0.00(1* 299.1(0240-372.9) | <0.00(1* 1.42(1.18-1.71) | <0.00(1* 1.55(1.28-1.87) |
| Subtype                 | HR+/HER2          | 21112 1612                               | 1[Reference] | 1[Reference] | 1[Reference] | 1[Reference] |
|                         | -HR+/HER2         | 32962 884                               | 3.58(3.30-3.89) | 3.13(2.87-3.41) | 2.27(2.05-2.50) | 2.11(1.90-2.33) |
|                         | +HR               | 14089 601                               | 5.79(5.26-6.37) | 4.75(4.30-5.25) | 3.30(2.93-3.72) | 3.01(2.67-3.41) |
|                         | -HR/-HE/R2+       | 33352 544                               | 2.16(1.95-2.37) | 1.92(1.73-2.12) | 1.57(1.40-1.76) | 1.50(1.34-1.69) |
|                         | Unknown           | 20043 426                               | 2.82(2.53-3.14) | 1.48(1.31-1.68) | 1.39(1.22-1.57) | 1.34(1.17-1.53) |

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Notes: a including divorced, separated, single (never married), and widowed; b including insured/No specifics Any Medicaid; c including other histology of invasive breast cancer except Infiltrating duct carcinoma, Lobular carcinoma and Infiltrating duct and lobular carcinoma;
+ denotes positive; - denotes negative; * denotes a statistically significant P-value; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OR, odds ratio; CI confidence interval

Table 4. Univariable and Multivariable Cox Regression for OS of Liver Metastases at Diagnosis of Breast Cancer (SEER)

| Variable          | Patients, No. | Overall Survival |            |            |
|-------------------|---------------|------------------|------------|------------|
|                   | (n=31157)     | Overall Survival | Univariable| Multivariable|
|                   | With Liver Metastases (n = 4067) | Hazard Ratio (95% CI) | P Value | Hazard Ratio (95% CI) | P Value |
| Age, y            |               |                  |            |            |
| 18-40             | 21313         | 494              | 1[Referenc e] | 1[Referenc e] |
| 41-60             | 137299        | 1882             | 1.52(1.32-1.76) | <0.001* | 1.39(1.20-1.61) | <0.001* |
| 61-80             | 129497        | 1414             | 2.17(1.88-2.51) | <0.001* | 1.84(1.58-2.15) | <0.001* |
| >80               | 23464         | 277              | 4.44(3.65-5.39) | <0.001* | 3.62(2.76-4.74) | <0.001* |
| Sex               |               |                  |            |            |
| Male              | 2267          | 26               | 1[Referenc e] | 1[Referenc e] |
| Female            | 309306        | 4041             | 2.01(0.28-14.31) | 0.485 | 1.58(0.22-11.36) | 0.649 |
| Race a            |               |                  |            |            |
| White             | 207400        | 2565             | 1[Referenc e] | 1[Referenc e] |
| Black             | 35062         | 737              | 1.21(1.09-1.33) | <0.001* | 1.35(1.22-1.50) | <0.001* |
| Hispanic          | 37499         | 427              | 0.99(0.87-1.13) | 0.895 | 1.16(1.02-1.32) | 0.028* |
| Asian or Pacific  | 27997         | 305              | 0.86(0.74-1.02) | 0.078 | 0.90(0.76-1.05) | 0.182 |
|                  |                |                |              |              |
|------------------|----------------|----------------|--------------|--------------|
| Islander         |                |                |              |              |
| American Indian/Alaska Native | 1757 23 | 0.96(0.58-1.59) | 0.869 | 1.01(0.60-1.68) | 0.984 |
| Unknown          | 1858 10       | 0.34(0.09-1.37) | 0.129 | 0.28(0.07-1.15) | 0.078 |

| Marital status  |                |                |              |              |
| Unmarried       | 123349 2011   | 1\[Reference\] | 1\[Reference\]|              |
| Married         | 171728 1827   | 0.75(0.70-0.82) | <0.001* | 0.84(0.77-0.91) | <0.001* |
| Unknown         | 16496 229     | 0.96(0.81-1.14) | 0.664 | 0.89(0.75-1.06) | 0.2 |

| Insurance status|                |                |              |              |
| Uninsured       | 5417 163      | 1\[Reference\] | 1\[Reference\]|              |
| Insured         | 300400 3821   | 0.75(0.62-0.91) | 0.003* | 0.71(0.59-0.86) | <0.001* |
| Unknown         | 5756 83       | 0.94(0.68-1.30) | 0.717 | 0.83(0.57-1.22) | 0.348 |

| Histology       |                |                |              |              |
| Infiltrating duct carcinoma | 234958 2971 | 1\[Reference\] | 1\[Reference\]|              |
| Lobular carcinoma | 27050 246 | 1.14(0.97-1.34) | 0.112 | 0.87(0.74-1.03) | 0.101 |
| Infiltrating duct and lobular carcinoma | 16392 133 | 0.94(0.68-1.30) | 0.717 | 0.89(0.70-1.13) | 0.323 |
| Other           | 33173 717     | 1.43(1.30-1.58) | <0.001* | 1.18(1.05-1.33) | 0.005* |

| Pathologic al Grade |                |                |              |              |
| I                 | 66365 144     | 1\[Reference\] | 1\[Reference\]|              |

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| II       | 129786 | 1147 | 1.08(0.86-1.37) | 0.515   | 1.35(1.07-1.72) | 0.013* |
|---------|--------|------|-----------------|---------|-----------------|-------|
| III/IV  | 98850  | 1939 | 1.30(1.04-1.64) | 0.022*  | 1.69(1.34-2.14) | <0.001* |
| Unknown | 16572  | 837  | 1.59(1.26-1.01) | <0.001* | 1.59(1.23-2.05) | <0.001* |

**Surgery of primary site**

| Yes     | 285989 | 952  | 1.72(1.56-1.89) | <0.001* | 1.52(1.38-1.68) | <0.001* |
|---------|--------|------|-----------------|---------|-----------------|-------|
| No      | 22831  | 3052 | 0.93(0.62-1.38) | <0.001* | 0.96(0.64-1.43) | <0.001* |
| Unknown | 2753   | 63   |                 |         |                 |       |

**Radiotherapy**

| Yes     | 162703 | 1082 | 1.03(0.94-1.12) | 0.528   | 0.95(0.87-1.04) | 0.27  |
|---------|--------|------|-----------------|---------|-----------------|-------|
| No/Unknown | 148870 | 2985 |                 |         |                 |       |
| Chemotherapy**

| Yes     | 130572 | 2802 |                 |         |                 |       |
|---------|--------|------|-----------------|---------|-----------------|-------|
| No/Unknown | 181001 | 1265 | 2.03(1.87-2.20) | <0.001* | 1.63(1.50-1.78) | <0.001* |

**Extrahepatic metastatic sites to lung, brain and bone, No**

| 0     | 298407 | 1060 |                 |         |                 |       |
|-------|--------|------|-----------------|---------|-----------------|-------|
| 1     | 9408   | 1696 | 1.49(1.34-1.65) | <0.001* | 1.42(1.28-1.58) | <0.001* |
| 2     | 2747   | 891  | 1.94(1.73-2.18) | <0.001* | 1.85(1.65-2.09) | <0.001* |
| All 3 | 343    | 177  | 2.94(2.44-3.56) | <0.001* | 3.43(2.77-4.26) | <0.001* |
| Unknown | 668    | 243  | 1.92(1.62-2.28) | <0.001* | 1.62(1.36-1.93) | <0.001* |

**Subtype**

| 27 |
| Variable                     | Patients, No. | Overall Survival | Univariable | Multivariable |
|------------------------------|---------------|------------------|-------------|--------------|
|                              | Patients (n=1728) | Hazard Ratio (95% CI) | P Value | Hazard Ratio (95% CI) | P Value |
| Age at diagnosis, y          |               |                  |            |              |
| 21-40                        | 288           | 1[Reference]     |            | 1[Reference] |
| 41-60                        | 1143          | 1.34(1.11-1.62)  | 0.003*     | 1.38(1.09-1.74) | 0.006* |
| >60                          | 297           | 1.39(1.10-1.75)  | 0.005*     | 1.55(0.86-2.80) | 0.145  |

Notes: a including divorced, separated, single (never married), and widowed; b including insured/No specifics Any Medicaid; c including other histology of invasive breast cancer except Infiltrating duct carcinoma, Lobular carcinoma and Infiltrating duct and lobular carcinoma; + denotes positive; - denotes negative; * denotes a statistically significant P-value; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OR, odds ratio; CI confidence interval.

Table 5. Univariable and Multivariable Cox Regression for OS among patients of Breast Cancer with Liver Metastases (FUSCC)
|                          | Count | Hazard Ratio | p-value         | Lower CI       | Upper CI       |
|--------------------------|-------|--------------|-----------------|----------------|----------------|
| **Pre- or perimenopause**|       |              |                 |                |                |
| Postmenopause            | 1104  |              |                 |                |                |
| BMI                      |       |              |                 |                |                |
| <18.5                    | 95    |              |                 |                |                |
| 18.5-24.9                | 955   |              |                 |                |                |
| >=25                     | 393   |              |                 |                |                |
| Unknown                  | 285   |              |                 |                |                |
| **Histology**            |       |              |                 |                |                |
| Infiltrating duct carcinoma | 1396 |              |                 |                |                |
| Lobular carcinoma        | 31    |              |                 |                |                |
| Other                    | 301   |              |                 |                |                |
| **De novo metastatic diseases** | | | | | |
| No                       | 1526  |              |                 |                |                |
| Yes                      | 202   |              |                 |                |                |
| **Surgery of primary site** | | | | | |
| No surgery               | 1509  |              |                 |                |                |
| Yes                      | 219   |              |                 |                |                |
| **Prior Chemotherapy**   |       |              |                 |                |                |
| No                       | 226   |              |                 |                |                |
| Yes                      | 1502  |              |                 |                |                |
| **Prior Radiotherapy**   |       |              |                 |                |                |
| No                       | 848   |              |                 |                |                |
| Yes                      |       |              |                 |                |                |
| Initial Local recurrence |  |  |  |  |  |
|-------------------------|---|---|---|---|---|
| No                      | Yes | 1.33(1.17-1.51) | <0.001* | 1.20(1.04-1.39) | 0.014* |
|                         | Unknown | 0.77(0.54-1.08) | 0.122 | 0.67(0.45-0.99) | 0.046* |

| Recurrent sequence |  |  |  |  |  |
|-------------------|---|---|---|---|---|
| First LM<sup>a</sup> | Yes | 1.56(1.25-1.95) | <0.001* | 1.00(0.77-1.29) | 0.974 |
| Subsequent LM<sup>b</sup> | 2.16(1.90-2.46) | <0.001* | 1.58(1.33-1.87) | <0.001* |

| Extrahepatic metastatic sites to lung, brain, bone and lymph nodes, No |  |  |  |  |  |
|---------------------------------------------------------------|---|---|---|---|---|
| 0                              | Yes | 1.54(1.30-1.83) | <0.001* | 1.16(0.95-1.41) | 0.15 |
| 1                              | Yes | 2.16(1.80-2.59) | <0.001* | 1.56(1.23-1.97) | <0.001* |
| 2                              | Yes | 2.57(2.08-3.18) | <0.001* | 2.05(1.51-2.79) | <0.001* |
| 3                              | Yes | 5.49(3.56-8.47) | <0.001* | 4.59(2.42-8.69) | <0.001* |
| All 4                          | Yes | | | | |

| Subtype |  |  |  |  |  |
|---------|---|---|---|---|---|
| HR+/HER2− | 767 | 1[Reference] | 1[Reference] | 1[Reference] | 1[Reference] |
| HR+/HER2+ | 305 | 0.82(0.68-0.98) | 0.033* | 1.02(0.83-1.25) | 0.851 |
| HR-/HER2+ | 321 | 0.84(0.70-1.01) | 0.067 | 1.13(0.92-1.40) | 0.242 |
| Triple-negative | 270 | 1.83(1.53-2.20) | <0.001* | 2.17(1.78-2.63) | <0.001* |
| Unknown | 65 | 1.11(0.79-1.57) | 0.544 | 1.63(1.10-2.43) | 0.015* |
Notes:  a, including the presence of liver metastases at initial diagnosis or liver metastases as the first metastatic site; b, including the presence of liver metastases during the subsequent clinical course; + denotes positive; – denotes negative; *denotes a statistically significant P-value; BMI, body mass index; LM, liver metastases; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; CI confidence interval

Table 6. Univariable and Multivariable Cox Regression for OS among patients of Breast Cancer Liver Metastases with or without HER2-target therapy (FUSCC)

| Variable | Patient s, No. | Overall Survival (With Target Therapy) | Patient s, No. | Overall Survival (Without Target Therapy) |
|----------|----------------|----------------------------------------|----------------|------------------------------------------|
|          |                | Univariable | Multivariable | Univariable | Multivariable | Univariable | Multivariable |
|          |                | Patients (n=1472) | Hazard Ratio (95% CI) | P Value | Patients (n=1130) | Hazard Ratio (95% CI) | P Value |
| Subtype  |                |             |                  |             |               |             |                  |
| HR+/HER2− | 767            | 1[Reference] | 1[Reference]    | 767        | 1[Reference] | 1[Reference] |
| HR+/HER2+ | 206            | 0.56(0.45-0.70) | <0.00 | 0.74(0.58-0.95) | 0.017* | 55 | 2.41(1.78-3.55) | <0.001 |
| HR−/HER2+ | 229            | 0.60(0.48-0.75) | <0.00 | 0.81(0.63-1.05) | 0.110 | 38 | 3.29(2.31-4.70) | <0.001 |
| Triple-negative | 270 | 1.83(1.53-2.20) | <0.00 | 2.17(1.78-2.63) | <0.001 | 270 | 1.83(1.53-2.20) | <0.001 |

Adjust for Age at diagnosis, years; Menopause status; BMI, body mass index; Histology; Stage at diagnosis; Surgery of primary site; Prior Chemotherapy; Prior Radiotherapy; Initial Local recurrence; Recurrent sequence; Extrahepatic metastatic sites to lung, brain, bone and lymph nodes, No + denotes positive; – denotes negative; *denotes a statistically significant P-value; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; CI confidence interval

Supplemental Figure Legends
S1 Selection of patients (SEER)
S2 Selection of patients (FUSCC)
Figures
Overall Survival Among Patients of Breast Cancer with Liver Metastases

A. Overall survival (SEER)
B. Survival stratified by the extent of extrahepatic metastatic disease (SEER)
C. Survival stratified by subtype (SEER)
D. Overall survival (FUSCC)
E. Survival stratified by the extent of extrahepatic metastatic disease (FUSCC)
F. Survival stratified by subtype (FUSCC)

Figure 1
A. Survival stratified by Recurrent sequence (Time from diagnosis of liver metastases) B. Survival stratified by Recurrent sequence (Time from metastasis) C. Overall Survival Among Patients of Breast Cancer Liver Metastases with targeted therapy stratified by subtype (FUSCC) D. Overall Survival Among Patients of Breast Cancer Liver Metastases without targeted therapy stratified by subtype (FUSCC)

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.
Figure S1.pdf
Figure S2.pdf