The Impact of IncRNA Dysregulation on Clinicopathology and Survival of Breast Cancer: A Systematic Review and Meta-analysis

Tian Tian,1,5 Meng Wang,1,2 Shuai Lin,1,5 Yan Guo,2 Zhiming Dai,3 Kang Liu,1 Pengtao Yang,1 Cong Dai,1 Yuyao Zhu,1 Yi Zheng,1 Peng Xu,1 Wenge Zhu,4 and Zhijun Dai1

1Department of Oncology, The Second Affiliated Hospital of Xi’an Jiaotong University, Xi’an 710004, Shaanxi Province, China; 2School of Life Science and Technology, Xi’an Jiaotong University, Xi’an 710049, Shaanxi Province, China; 3Department of Anesthesia, The Second Affiliated Hospital of Xi’an Jiaotong University, Xi’an 710004, Shaanxi Province, China; 4Department of Biochemistry and Molecular Medicine, The George Washington University Medical School, Washington, DC 20052, USA

Dysregulation of multiple long non-coding RNAs (lncRNAs) was reported to play major roles in breast cancer (BC). Here we aimed to collect most of the relevant literature to assess the prognostic value of lncRNAs in BC. To this end, we systematically searched PubMed, Embase, Web of Science, Chinese National Knowledge Infrastructure (CNKI), and Wanfang to identify published articles on the associations of lncRNAs with clinicopathology and/or survival of BC. Via this searching, we identified 70 articles involving 9,307 BC patients and regarding 48 lncRNAs. The expression of 41 lncRNAs was related to one or more clinicopathological parameters of BC, including tumor size; lymph node metastasis; histological grade; TNM stage; and estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) statuses (p < 0.05). Dysregulation of 28 lncRNAs was associated with overall survival, and abnormal expression of 9 lncRNAs was linked to disease-free survival. Furthermore, the expression level of 3 lncRNAs was correlated with metastasis-free survival, 3 lncRNAs with relapse-free survival, and 3 lncRNAs with progression-free survival. Our analysis showed that multiple lncRNAs were significantly associated with BC clinicopathology and survival. A large-scale study is needed to verify the prognostic value of these lncRNAs in BC.

INTRODUCTION

Breast cancer (BC) is the most common type of cancer among women and the main cause of female cancer death in the world.1 Although the survival rates of BC have been improved by early detection and progress in treatment, it remains to be a frequent malignancy with a poor survival.2,3 Many studies on the role of lncRNAs in BC revealed that the expression level of lncRNAs was associated with BC clinical features and possibly making them diagnostic or prognostic biomarkers or potential therapeutic targets for cancer.15–17

In recent years, more and more BC studies have focused on long non-coding RNAs (lncRNAs) because of their key roles in human diseases, including cancer.9 lncRNAs are a class of RNA transcripts, with a length of >200 nt, that do not encode proteins. They were proven to be involved in diverse biological processes, such as chromosome remodeling, epigenetic modulation, and transcriptional and posttranscriptional modifications.10,11 Studies have revealed that lncRNAs play an important role in cancer biology, and the expression of specific lncRNAs is implicated in the development and progression of cancer.12 For example, enforced expression of HOTAIR in epithelial cancer cells can induce genome-wide re-targeting of polycomb repressive complex 2 (PRC2), leading to altered histone H3 lysine 27 methylation and gene expression, and thus it promotes cancer invasiveness and metastasis in a manner dependent on PRC2.13 In BC, BCAR4 can bind to two transcription factors (SNIP1 and PUNTS) with extended regulatory consequences, and it relieves inhibition of RNA polymerase II (Pol II) via activation of the PP1 phosphatase. Thus, it activates a noncanonical Hedgehog/GLI2 pathway that promotes cell migration.14 Moreover, a large number of lncRNAs, such as MALAT1, MEG3, HOTAIR, CCAT2, H19, etc., are dysregulated in multiple tumors, including BC, hepatocellular carcinoma, and kidney cancer, possibly making them diagnostic or prognostic biomarkers or potential therapeutic targets for cancer.15–17

Traditionally, we used clinicopathological features, including tumor size, lymph node status, TNM stage, histological grade, hormone receptor status, and human epidermal growth factor receptor 2 (HER-2) amplification, to predict the patient outcome.4 In addition, several biomarkers, such as tumor-associated macrophages (TAMs), microRNAs, matrix metalloproteinases (MMPs), retinoic acid receptor α (RARA), Ki-67, aromatase, osteopontin, etc., have also been identified.7

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These authors contributed equally to this work.

Correspondence: Zhijun Dai, Department of Oncology, The Second Affiliated Hospital of Xi’an Jiaotong University, Xi’an 710004, Shaanxi Province, China
E-mail: dzj0911@xjtu.edu.cn

Correspondence: Wenge Zhu, Department of Biochemistry and Molecular Medicine, The George Washington University Medical School, Washington, DC 20052, USA
E-mail: wz6812@gwu.edu
| IncRNAs | Reference | Country | Race  | Number of Patients | Expression in Tumor | Method       | Sample Type | Cutoff | Survival | Follow-up (Month) | Quality Score |
|---------|-----------|---------|-------|--------------------|---------------------|--------------|-------------|--------|----------|------------------|---------------|
| MALAT1  | 26        | China   | Asian | 43                 | upregulated         | qRT-PCR       | tissue      | median | OS       | 60               | 7             |
|         | 25        | China   | Asian | 118                | upregulated         | qRT-PCR       | tissue      | NR     | OS       | 50               | 7             |
|         | 20        | France  | Caucasian | 446          | upregulated         | qRT-PCR       | tissue      | 3.02-fold | NR      | NR                | 7             |
|         | 24        | China   | Asian | 139                | upregulated         | qRT-PCR       | tissue      | median | OS       | 55               | 7             |
|         | 22        | China   | Asian | 204                | upregulated         | qRT-PCR       | tissue      | 75% expression | RFS     | 65               | 8             |
|         | 21        | China   | Asian | 135                | downregulated       | qRT-PCR       | tissue      | NR     | NR      | NR                | 6             |
|         | 23        | China   | Asian | 78                 | upregulated         | qRT-PCR       | tissue      | median | DFS      | 60               | 8             |
|         | 27        | China   | Asian | 86                 | upregulated         | qRT-PCR       | tissue and serum | median | OS      | NR                | 5             |
|         | 31        | China   | Asian | 120                | upregulated         | qRT-PCR       | tissue      | NR     | OS       | 90               | 6             |
|         | 32        | Iran    | Caucasian | 48           | normal              | qRT-PCR       | tissue      | median | NR      | NR                | 6             |
|         | 61        | Netherlands | Caucasian | 747         | upregulated         | qRT-PCR       | tissue      | quartile | OS, MFS | >120             | 7             |
|         | 60        | China   | Asian | 67                 | upregulated         | qRT-PCR       | tissue      | 8-fold | OS      | 60               | 7             |
|         | 62        | Germany | Caucasian | 129          | NR                  | qRT-PCR       | tissue      | median | MFS      | 120              | 8             |
|         | 15        | America | Caucasian | 132        | upregulated         | qRT-PCR       | tissue      | 125-fold | OS, MFS | 180              | 8             |
|         | 83        | Denmark | Caucasian | 488        | NR                  | microarray    | tissue      | mean   | OS, RFS  | 86               | 8             |
|         | 84        | Italy   | Caucasian | 336        | NR                  | qRT-PCR       | tissue      | median | OS      | 40               | 5             |
|         | 85        | China   | Asian | 30                 | NR                  | qRT-PCR       | tissue      | median | NR      | NR                | 6             |
|         | 44        | America | Caucasian | 94         | NR                  | ISH           | tissue      | median | DFS      | 48               | 7             |
|         | 43        | China   | Asian | 112                | upregulated         | qRT-PCR       | serum       | median | DFS      | 48               | 7             |
| MEG3    | 28        | China   | Asian | 90                 | downregulated       | qRT-PCR       | tissue      | NR     | OS, DFS  | 80               | 6             |
|         | 29        | China   | Asian | 207                | downregulated       | qRT-PCR       | tissue      | median | OS, DFS  | 80               | 6             |
|         | 30        | China   | Asian | 257                | downregulated       | qRT-PCR       | tissue      | ΔCt = 8.065 | OS, RFS | 60               | 8             |
| TUSC7   | 34        | China   | Asian | 42                 | downregulated       | qRT-PCR       | tissue      | median | NR      | NR                | 6             |
|         | 35        | Germany | Caucasian | 96          | NR                  | qRT-PCR       | tissue      | NR     | NR      | NR                | 6             |
| BCAR4   | 36        | Netherlands | Caucasian | 786        | NR                  | qRT-PCR       | tissue      | detection limit | OS, PFS, MFS | 97              | 8             |
| TP73-AS1| 37        | China   | Asian | 86                 | upregulated         | qRT-PCR       | tissue      | median | NR      | NR                | 8             |
|         | 36        | China   | Asian | 36                 | upregulated         | qRT-PCR       | tissue      | median | OS      | 48               | 8             |
| NEAT1   | 40        | China   | Asian | 118                | upregulated         | qRT-PCR       | tissue      | NR     | OS      | 60               | 6             |
|         | 39        | China   | Asian | 70                 | upregulated         | qRT-PCR       | tissue      | NR     | OS      | 60               | 6             |
|         | 40        | China   | Asian | 40                 | upregulated         | qRT-PCR       | tissue      | 2-fold | OS      | 24               | 6             |
| TUG1    | 41        | China   | Asian | 100                | upregulated         | qRT-PCR       | tissue      | mean   | NR      | NR                | 7             |
|         | 42        | China   | Asian | 58                 | downregulated       | qRT-PCR       | tissue      | mean   | NR      | NR                | 6             |
| CRNDE   | 46        | China   | Asian | 103                | upregulated         | qRT-PCR       | tissue & serum | NR      | OS      | NR                | 6             |

OS, overall survival; DFS, disease-free survival; MFS, metastasis-free survival; RFS, relapse-free survival; PFS, progression-free survival; NR, not report; ISH, in situ hybridization.
outcome.\textsuperscript{17–19} By far, however, no study has evaluated these associations systematically. Therefore, we conducted this systematic review to clarify the present state of knowledge about the correlations between lncRNAs and BC clinicopathology and survival.

RESULTS

Characteristics of Included Studies

A total of 991 articles was identified by mining databases and manual searching, and 732 articles were left after removing duplication. After screening titles and abstracts, 111 full-text articles remained for further assessment, and 41 articles were excluded according to the selection criteria. Finally, 70 articles involving 9,307 patients were included in the review. The main characteristics and quality score of studies included in the meta-analysis are presented in Table 1, and the information on the rest of the studies is shown in Table S1. Most of these articles were published within the last 3 years. Among all these articles, 63 articles involving 48 lncRNAs described the clinicopathological features of BC, and 48 articles involving 32 lncRNAs investigated the survival of BC.

Association of lncRNA Expression with Clinicopathological Features of BC

Ten lncRNAs, MALAT1, MEG3, CCAT2, BCAR, TUSC7, TP73-AS1, NEAT1, TUG1, HOTAIR, and CRNDE, were included in meta-analyses for clinicopathological features of BC, and 48 articles involving 32 lncRNAs investigated the survival of BC.

Figure 1. Forest Plots of the Significant Associations between the Expression of Five lncRNAs and Clinical Features of Breast Cancer

Each square indicates a study, and the area of squares is proportional to the weight of the study. The diamond represents the pooled OR and 95% CI.
Another 24 lncRNAs were also correlated with OS of BC. Among them, the elevated expression of 7 lncRNAs (FGF14-AS2, AFAP1-AS1, EPB41L4A-AS2, BC040587, EGOT, GAS6-AS1, and FENDRR) related to a better survival, while increased expression of the other 17 lncRNAs (BCAR4, HOTTIP, CCAT1, Z38, TUNAR, CRNDE, HULC, MVII, TP73-AS1, linc-ITGB1, PVT1, UCA1, OR3A4, DANC, LINP1, SNHG15, and SUMO1P3) related to a worse survival (Figure 4). The expression of 9 lncRNAs (MALAT1, HOTTIP, MVII, LINC00978, linc-ITGB1, MEG3, GAS6-AS1, HOTAIR, and LINP1) had an impact on disease-free survival (DFS) of BC. Furthermore, MALAT1, MEG3, and HOTAIR levels had a relationship with relapse-free survival (RFS); CCAT1, MEG3, and FENDRR levels were associated with progression-free survival (PFS); and the expression of BCAR4 was related to MFS. The detailed information is provided in Table 3.

**DISCUSSION**

Increasing evidence has demonstrated that lncRNAs are involved in the initiation and progression of cancer and participate in multiple biological behaviors of cancer, including cell proliferation, apoptosis, migration, and metastasis. Aberrant expression of lncRNAs has been observed in various types of cancer, including BC. Previous reviews and meta-analyses have reported the prognostic values of lncRNAs in multiple cancers, such as colorectal cancer, ovarian cancer, prostate cancer, lung cancer, etc. However, no one investigated BC specifically. Since many studies found that dysregulation of multiple lncRNAs may have an impact on the prognosis of BC, we conducted this systematic review to highlight the prognostic values of lncRNAs in BC. To our knowledge, this review is a thorough work that comprehensively clarifies the association of lncRNA expression with clinicopathological features and survival of BC.

In the present study, we systematically reviewed all the published literature regarding the clinical and prognostic values of lncRNAs in BC. We identified a number of relevant lncRNAs, most of which have been studied only once. We found that the expression levels of these lncRNAs were most often linked to tumor size (n = 15), lymph node metastasis (n = 24), and TNM stage (n = 21), while fewer of them associated with histological grade (n = 9), hormone receptor status (n = 9), and HER-2 status (n = 6). Moreover, several lncRNAs were related to more than two clinical features of BC. However, all the lncRNA expression had no relationship with patient age. These results indicated the intrinsic role of lncRNAs in the pathogenesis and progression of BC, which suggested lncRNAs may be important biomarkers for BC. As for survival, most of the studies investigated the relationship between lncRNA expression and OS, and a majority of them (n = 28) had a statistically significant correlation with the OS of BC. Only a few studies evaluated the associations of lncRNA expression with other types of survival, including DFS, MFS, PFS, and RFS, and there was also a strong connection between them. The detailed information is provided in Table 3.

**Table 2. Summary of IncRNAs Related to Clinicopathological Features of Breast Cancer**

| Clinicopathological Feature | IncRNA |
|-----------------------------|--------|
| Tumor size                  | SNHG12, HOTTIP, H19, CRNDE, SPRY4-IT1, FGF14-AS2, AP001P1-3, EGOT, 91H, HOXA-A52, PT11, CRALA, SNHG15, SUMO1P3, ARA |
| LN metastasis               | NEAT1, SNHG12, HOTTIP, CCAT1, AFAP1-AS1, Z38, TUNAR, FGF14-AS2, HULC, EGOT, 91H, HIFI-A52, UCA1, lnc-ROR, HOXA-A52, GAS6-AS1, linc-ITGB1, DANC, PVT1, OR3A4, CRALA, FENDRR, SNHG15, SUMO1P3 |
| Histological grade          | MEG3, CCAT1, TUNAR, EPB41L4A-AS2, HULC, BC040587, GAS6-AS1, DANC, OR3A4 |
| TNM stage                   | TP73-AS1, NEAT1, HOTTIP, CCAT1, AFAP1-AS1, ACT2-AS1, Z38, SPRY4-IT1, FGF14-AS2, EPB41L4A-AS2, HULC, HOXA-A52, linc-ITGB1, DANC, PVT1, OR3A4, CRALA, HOXB-A55, LINP1, SNHG15, SUMO1P3 |
| ER status                   | BCAR4, H19, LINC00978, EPB41L4A-AS2, CRALA |
| PR status                   | MALAT1, H19, EPB41L4A-AS2, CRALA, FENDRR |
| HER-2 status                | TUSC7, 91H, ANRASSF1, OR3A4, FENDRR |

**Prognostic Value of IncRNA Expression for BC Survival**

Five lncRNAs, including MALAT1, MEG3, CCAT2, HOTAIR, and NEAT1, were included in meta-analyses for survival. As shown in Figure 2, patients with high expression of CCAT2, MALAT1, or NEAT1 had shorter overall survival (OS) (hazard ratio [HR] = 1.29, 95% CI: 1.03–1.63, p = 0.03; HR = 2.78, 95% CI: 1.95–3.97, p < 0.01; HR = 1.65, 95% CI: 1.08–2.54, p = 0.02, respectively), while an increased level of MEG3 was associated with better OS (HR = 0.47, 95% CI: 0.37–0.71, p < 0.01). In addition, elevated expression of CCAT2 or HOTAIR was related to poor metastasis-free survival (MFS) (HR = 1.18, 95% CI: 1.02–1.36, p = 0.03; HR = 1.90, 95% CI: 1.41–2.55, p < 0.01, respectively) (Figure 3).
in BC. Hence, these lncRNAs may be independent predictors of prognosis in BC.

The most frequently evaluated lncRNAs in BC included MALAT1, MEG3, CCAT2, and HOTAIR. All of them are statistically significant predictors of BC prognosis. The expression of MALAT1, CCAT2, and HOTAIR was increased in BC, and the upregulation was associated with shorter survival. The expression of HOTAIR was downregulated in BC. Tumor with a lower MEG3 expression tended to be poorly differentiated, and the survival of patients was worse. This indicated the oncogenic role of MALAT1, CCAT2, and HOTAIR in BC, whereas MEG3 may be a tumor suppressor of BC. In terms of mechanism, MALAT1 was reported to mainly act as a competing endogenous RNA (ceRNA) to sponge microRNAs, thus regulating cell progression, invasion, and metastasis in BC through their targets.24–26 CCAT2 can promote BC tumor growth and metastasis by regulating Wnt- and transforming growth factor β (TGF-β)-signaling pathways.80,94 HOTAIR was proven to promote BC metastasis through inducing or repressing critical genes in cell proliferation and migration as well as modulating the cancer epigenome.13,95 As for MEG3, it can inhibit cell proliferation, invasion, and angiogenesis both by sponging microRNAs and through regulating signaling transduction, such as the AKT and TGF-β pathways.28,96,97

![Figure 2. Forest Plots of the Associations between the Expression of Five IncRNAs and Breast Cancer Overall Survival](https://www.moleculartherapy.org)
Overall, the results are comprehensive and credible because the quality of included articles is relatively high. However, there are still limitations in our analysis. First, heterogeneity exists between studies regarding the same lncRNA, and the heterogeneity is stubborn owing to the differences in methodology, such as sample selection, tissue preservation, determination of cutoff value, and statistical analysis. Second, almost all the studies in our review reported a statistically significant result. Although the Begg’s funnel plot suggested there is no publication bias on OS (Figure S1), we still suspect that selective reporting bias is prominent in the literature regarding lncRNA and BC prognosis. Third, about half of the included studies had a small sample size (<100), and small studies are considered associating with inflated estimates of effect size and higher heterogeneity. Lastly, language bias may exist since only two languages were used in the literature review.
Our analysis demonstrated the prognostic value of lncRNAs in BC, and it highlighted the important biological function of lncRNAs in BC progression. These lncRNAs may exert their effects by directly binding to functional protein, modulation of DNA methylation, or post-transcriptional regulation of target genes. These genes and proteins include those that are involved in tumorigenesis and metastasis, such as Wnt, P53, PI3K, MYC, etc. Therefore, dysregulation of certain lncRNAs may have an effect on the development of BC, thus influencing the outcome of BC. Though the exact mechanisms are not yet fully clarified, we believe they will be better understood in the future with more studies in this field.

In conclusion, this systematic review identified a number of lncRNAs that were correlated with BC clinicopathological features and survival, and almost all the lncRNAs are statistically significant predictors of BC prognosis. The weightiness of these correlations is difficult to ascertain due to a lot of uncontrollable factors. Hence, a large-scale study with a standardized process of detection, analysis, and report is needed to further verify the prognostic value of these lncRNAs in BC.

### MATERIALS AND METHODS

This review has been performed based on preferred reporting items for systematic reviews and meta-analyses (PRISMA). Two authors (T.T. and M.W.) reviewed potentially eligible articles independently. The Newcastle-Ottawa Scale was used to assess the quality of each study. The following information was extracted from each included study: (1) original study focus on human beings; (2) investigated the relationship between lncRNA expression and clinicopathological features or survival of BC; (3) reported an OR or HR with 95% CI or there were sufficient data to calculate them; (4) full text was available. Exclusion criteria were as follows: (1) lacked key information, such as clinical parameters and survival curves, or lacked usable data; (2) reprocessed data from public databases; (3) HRs were for a combination of multiple lncRNAs; and (4) reviews, letters, single case reports, and conference abstracts. If multiple articles published by the same author reporting overlapping data, only the most complete one was included. The details about the selection process are shown in Figure 5.

### Quality Assessment and Data Extraction

Two authors (T.T. and M.W.) reviewed potentially eligible articles independently. The Newcastle-Ottawa Scale was used to assess the quality of each study. The following information was extracted from each included study: (1) original study focus on human beings; (2) investigated the relationship between lncRNA expression and clinicopathological features or survival of BC; (3) reported an OR or HR with 95% CI or there were sufficient data to calculate them; (4) full text was available. Exclusion criteria were as follows: (1) lacked key information, such as clinical parameters and survival curves, or lacked usable data; (2) reprocessed data from public databases; (3) HRs were for a combination of multiple lncRNAs; and (4) reviews, letters, single case reports, and conference abstracts. If multiple articles published by the same author reporting overlapping data, only the most complete one was included. The details about the selection process are shown in Figure 5.

### Statistical Analysis

ORs and their 95% CIs were used to estimate the association of lncRNAs with clinical features of BC. Patients were divided into two groups for comparison (for instance, histological grade III versus I and II, TNM stages III and IV versus I and II, and ER/PR status positive versus negative). As for survival rates, HRs with corresponding 95% CIs were used. All the ORs and HRs were calculated for high expression of lncRNAs. When two or more different studies investigated the same lncRNA, a meta-analysis was carried out to combine the effect size. The Z test was used to determine the significance of ORs or HRs. Heterogeneity between studies was tested using the following keywords and search terms were used: long noncoding RNA or long ncRNA or IncRNA or lincRNA or long intergenic non-coding RNA or long untranslated RNA, BC or breast carcinoma or breast tumor or breast neoplasm, and clinical or clinicopathological or clinicopathology or survival or odds ratio or OR or hazard ratio or HR. Additionally, references in relevant articles were also screened manually. The languages of the retrieved literature were confined to English and Chinese.

### Inclusion and Exclusion Criteria

Studies were included if they fulfilled the following criteria: (1) original study focus on human beings; (2) investigated the relationship between lncRNA expression and clinicopathological features or survival of BC; (3) reported an OR or HR with 95% CI or there were sufficient data to calculate them; (4) full text was available. Exclusion criteria were as follows: (1) lacked key information, such as clinical parameters and survival curves, or lacked usable data; (2) reprocessed data from public databases; (3) HRs were for a combination of multiple lncRNAs; and (4) reviews, letters, single case reports, and conference abstracts. If multiple articles published by the same author reporting overlapping data, only the most complete one was included. The details about the selection process are shown in Figure 5.

### Table 3. Summary of Other Significant Associations of lncRNAs with Breast Cancer Survival

| Survival | lncRNA   | HR and 95% CI | Analysis | Reference |
|----------|----------|---------------|----------|-----------|
| DFS      | MALAT1   | 2.36 (1.04–5.38) | univariate | 22       |
| DFS      | HOTTIP   | 4.08 (1.13–14.71) | multivariate | 53       |
| DFS      | MVIH     | 2.55 (1.06–6.12) | multivariate | 47       |
| DFS      | LINC00978| 2.27 (1.24–4.16) | multivariate | 65       |
| DFS      | lin-ITGB1| 3.13 (1.89–6.14) | multivariate | 97       |
| DFS      | MEG3     | 0.59 (0.36–0.96) | univariate | 28       |
| DFS      | GAS56-AS1| 0.28 (0.13–0.60) | multivariate | 60       |
| DFS      | HOTAIR   | 1.89 (1.15–3.11) | univariate | 43       |
| DFS      | LINP1    | 8.40 (1.72–41.06) | univariate | 76       |
| RFS      | MALAT1   | 2.02 (1.02–3.98) | multivariate | 72       |
| RFS      | MEG3     | 0.37 (0.15–0.87) | multivariate | 91       |
| RFS      | HOTAIR   | 0.47 (0.26–0.87) | multivariate | 88       |
| PFS      | CCAT1    | 3.59 (2.00–7.84) | multivariate | 52       |
| PFS      | MEG3     | 0.37 (0.13–0.88) | multivariate | 22       |
| PFS      | FENDRR   | 0.578 (0.454–0.735) | multivariate | 57       |
| MFS      | BCAR4    | 4.11 (1.03–1.94) | univariate | 70       |

DFS, disease-free survival; MFS, metastasis-free survival; RFS, relapse-free survival; PFS, progression-free survival.
Q statistic and I^2 test. When I^2 value was more than 50%, which indicated a significant heterogeneity, the random-effects model was utilized. Otherwise, the fixed-effects model was used. All statistical analyses were done with the software Review Manager 5.3 (Cochrane Collaboration, London, UK). A p value less than 0.05 was considered statistically significant.

SUPPLEMENTAL INFORMATION
Supplemental Information includes one figure and three tables and can be found with this article online at https://doi.org/10.1016/j.omtn.2018.05.018.

AUTHOR CONTRIBUTIONS
T.T. and Zhijun Dai conceived and designed the study. T.T. and M.W. searched and reviewed literature. S.L., Y.G., Zhiming Dai, K.L., and C.D. contributed to data collection, analysis, and interpretation. P.Y., Y. Zhu, Y. Zheng, and P.X. prepared tables and figures. T.T. drafted the manuscript. Zhijun Dai and W.Z. revised the manuscript. All authors approved the final manuscript.

CONFLICTS OF INTEREST
The authors declare that they have no competing interest.

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