Prognostic factors and survival according to tumour subtype in women presenting with breast cancer bone metastases at initial diagnosis: a SEER based study

Xiao Li
China Medical University

Xiaoli Zhang
China Medical University

Jie Liu
China Medical University

Research article

Keywords: Breast cancer, Bone metastases, Tumour subtype, Prognosis factor, Survival

---

Abstract

Background: Tumour subtype have a significant effect on bone metastasis in breast cancer, but population-based estimates of the prognosis of bone metastases at diagnosis of breast cancer are lacking. The aim of this study was to analyse the influence of tumour subtype and other factors in the prognostic and survival of patients with bone metastases of breast cancer. Methods: Using the Surveillance, Epidemiology, and End Results Program (SEER) data of 2012 to 2016 conducted a retrospective cohort study to investigate patients with bone metastases in breast cancer. Patients characteristic according subtypes were compared using chi-square, overall survival (OS), prognostic factor calculated using the Kaplan-Meier method and the Cox proportional hazards model. Results: A total of 3384 patients were included in this study. 63.42% were HR+/HER2-, 19.86% were HR+/HER2+, 9.34% were HR-/HER2-, and 7.39% were HR-/HER2+. Median OS for the whole population was 38 months, and 33.9% of the patients were alive at five-year. The median OS and five-year survival rate among the different molecular subtype of breast cancer patients are significant differences (p<0.05). Multivariate Cox regression analysis showed that age of 55-59 (HR=1.270), black race (HR=1.320), grade in III or IV (HR=1.952), HR-/HER2- (HR=2.727), lung metastases (HR=1.249), live metastases (HR=1.840), brain metastases (HR=1.812) only bone metastases (HR=1.237) are independent risk factors of prognosis; married (HR=0.812), HR+/HER2+ (HR=0.618), HR-/HER2+ (HR=1.237), insurance (HR=0.597) and surgery (HR=0.512) are independent protection factors of prognosis. Conclusions: There were substantial differences in OS according to tumour subtype. In addition to tumour subtype, other independent predictors of OS are age at diagnosis, race, marital status, insurance, grade, surgery and visceral metastases. Tumour subtype, as a significant prognostic factor, warrant further investigation. Keywords: Breast cancer, Bone metastases, Tumour subtype, Prognosis factor, Survival

Background

Breast cancer is the second most common type of cancer in women and the second leading cause of cancer-related death in women, if untreated, the cancer can spread to other areas of the body.In these patients, it is not the primary tumour, but its metastases at distant sites that are the main cause of death [1]. Approximately 5–10% of patients have distant metastases at the time of diagnosis[2, 3], bone is the most common site of metastasis in breast cancer patients, above 55% of breast cancer patients developing bone metastases[4]. Bone metastases are associated with lower survival in patients with advanced breast cancer and the 5-year cause-specific survival for these patients is only 24% to 39%[5]. Data showed that patients with breast cancer survive a median of 24–55 months after detection of bone metastases[6-8]. Breast cancer patients with bone metastases seem to have a longer survival than those with cancer in other metastatic sites[9].

According to the classification by hormone receptor status (HR) and human epidermal growth factor receptor-2 (HER2), breast cancer can be divided into HR+/HER2-, HR+/HER2+, HR-/HER2 and HR-/HER2+ [10]. After the molecular subtype of breast cancer were put forward, they quickly became the focus of

research. The strong association of hormonal receptor status with bone metastasis was proposed early in 1991[11]. With a deeper understanding of the modulated genes and pathways in the various subgroups, it had become more evident that bone metastasis was most abundant among the hormonal receptor-positive subtype[12]. The researchers found that the clinical manifestations, pathological results, gene expression and prognosis of different subtype of breast cancer were very different. The relationship between molecular subtype and the patterns of distant metastases has been documented. Evidence had shown that bone metastases risk depends on breast cancer subtype, HR+ patients were more likely to have bone metastases[13]. The molecular differences in the tumour subtype were often accompanied by differences in clinical features and overall survival[10].

Notably, once tumour metastasizes to bone, it is incurable, bone metastases are associated with lower survival in patients with advanced breast cancer and an increased risk of serious complications during the patients' disease course. The consequences of bone metastases include reduced survival, morbidity, pain and reduced quality of life[14]. Therefore, in order to improve their survival time and outcome, it has great significance to identify the influencing factors of clinical prognosis in patients with bone metastasis of breast cancer. The aim of this study was to analyse the influence of tumour subtype and other factors in the prognostic and survival of patients who present with bone metastases at the time of initial diagnosis of breast cancer.

Methods

Data source and patient selection

We abstracted data from the Surveillance, Epidemiology, and End Results (SEER) 18 registries research database. The SEER of the National Cancer Institute is a coordinated system of population-based cancer registries that collects cancer incidence and survival data from 18 geographic areas throughout the United States that together represent approximately 28% of the U.S. population and includes various diverse ethnic groups. A data use agreement submission was required to access the SEER Research Data File[15]. We submitted the data agreement form to the SEER administration, after acceptance of the agreement, the SEER*Stat Version 8.3.5 software and data files were downloaded directly from the SEER website.

We used SEER*Stat version 8.3.5 to generate a case listing. We extracted cases of woman aged 40-60 with brain metastases breast cancer diagnosed from 2012 to 2016.Selected this age group woman because the incidence of breast cancer rises after age 40, and the natural mortality of the elderly is high, age is the most important prognostic factor for bone metastases[16].

Patients diagnosed by either autopsy or death certificate were excluded. Patients must be have complete dates of survival month and the follow-up must be active. The analysis was restricted to a diagnosis confirmed by histopathology, and only duct, lobular and other carcinomas based on the primary site were included (International Classification of Disease for Oncology, Third Edition (ICD-O-3) codes 8500 to

8543). Tumour stage was registered according to the American Joint Committee on Cancer Staging System six edition. We excluded patients whose molecular subtype was unknown.

We generated a case listing with information on the following variables: year of diagnosis, age at diagnosis, race/ethnicity, marital status at diagnosis，grade, laterality, ICD-O-3 Hist/behav, AJCC Stage Group 6th ed, surgery prim site, bone/ lung/ liver \brain metastases, American Joint Committee on Cancer pathological stage, tumour subtype, cause-specific death classification, vital status, and survival (months).

Statistical Analyses

Descriptive statistics were used to examine the following baseline characteristics of the breast cancer with bone metastases patients: year of diagnosis, age, race/ ethnicity, insurance, marital status, grade, surgery, laterality, histology, liver, lung, brain, bone only metastases, BCSS (time from the breast cancer diagnosis to death due to breast cancer) and OS (the time from the breast cancer diagnosis to death due to any cause).

These variables were stratified by molecular subtype. *P*-values for comparing the frequency distributions among the subgroups were calculated using the chi-squared () test. Within each variable, patients with unknown data were excluded from the comparative analysis. OS were used as the primary study outcomes, we used the Kaplan-Meier method to generate survival curves and analyse the differences between the curves using the log-rank test. A Cox proportional hazards regression was used to assess the independent association of several variables with OS. Hazard ratios (HR) and their 95% confidence interval (95%CI) were estimated using the Cox model. P value of 0.05 or less was considered statistically significant. All P values were 2-tailed. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc) and IBM SPSS version 23.0.

Results

Patient characteristics

A total of 3384 patients were diagnosed with bone metastases from breast cancer at initial presentation between 2012 and 2016 and were included in this study. 2146 patients (63.42%) were diagnosed with HR+/HER2- breast cancer, 672 patients (19.86%) were HR+/HER2+ breast cancer, 316 patients (9.34%) were HR-/HER2- breast cancer, and250 patients (7.39%) were HR-/HER2+ breast cancer.

The demographic and clinical characteristics of the study based on breast cancer subtype showed in table1. Patients with bone metastases from HR-/HER2- breast cancer more likely were black race (*P* < 0.05), higher tumour grade (*P* < 0.05) and histology type classification of duct carcinoma (*P* < 0.05). HR-/HER2- breast cancer showed even higher incidence of combine with brain metastasis (P < 0.05), and

more likely to die from breast cancer (*P* < 0.05), patients with bone metastases from HR-/HER2- breast cancer HR-/HER2+ showed even higher incidence of combine with lung metastasis and liver (*P* < 0.05).

Survival analysis

A median follow-up of 17 months (range, 1−60 months), 1315 deaths were reported (796 in the HR+/HER2- group, 198 in the HR+/HER2+ group, 224 in the HR-/HER2- group and 97 in the HR-/HER2+ group).

Median OS for the entire population was 38 months (95%CI: 35.89−40.11 months), and 33.9% of the patients (95% CI, 30.6−37.2%) were alive at 60 months, shown in Fig1. Analysis of OS according to tumour subtype showed significant differences with patients with bone metastases, the five-year survival rate was 32.7% for HR+/HER2-, 48.8% for HR+/HER2+, 8.6% for HR-/HER2- and 36.1% for HR-/HER2+. Patients with bone metastases of HR-/HER2- breast cancer experiencing the shortest survival (median OS: 11 months; 95% CI: 9.9−12.1 months), whereas patients with HR+/HER2+ breast cancer experiencing the longest survival, median OS was 52 months (95% CI was not estimable; *P*<0.001).

The impact of the presence of metastases at each individual visceral site on OS is shown in Fig.3. Patients with lung metastases had significantly shorter survival (median OS: 23 months; 95% CI: 19.98−26.02 months) as compared with patients without liver metastases (median OS: 42 months; 95% CI: 39.77−44.23 months; *P* <0 .05; Fig. 3a). Patients with liver metastases (median OS: 22 months; 95% CI: 19.10−24.86 months) versus no lung metastases (median OS: 44 months; 95% CI: 41.14−46.86 months; P <0 .05; Fig. 3b). Patients with metastases to the brain (median OS: 14 months; 95% CI: 11.08−40.10 months) and those with metastases to the brain and other sites (median OS: 40 months; 95% CI: 37.80−42.20 months; *P* <0 .001; Fig. 3c). A similar finding was seen for with metastases to the bone only (median OS: 46 months; 95% CI: 42.56−49.44 months) and those with metastases to the bone and other sites (median OS: 24 months; 95% CI: 24.61−26.38 months *P* <0 .05; Fig. 3d).

Unadjusted models for the overall patient population were consistent with log-rank analysis (except laterality) and revealed that patients who were older, black race, single, uninsured, duct histology, III or IV Grade,primary bilateral breast cancer, triple-negative subtype, Visceral metastases and those who did not receive surgery to the primary tumour had shorter OS (Table 2).

Multivariate Cox analyses confirmed that age of 55-59 (vs. age of 40-44, HR=1.270, 95%CI: 1.032-1.563), black race (vs. white race, HR=1.320, 95%CI: 1.129-1.543), grade in III or IV (vs. grade in, HR=1.952, 95%CI: 1.485-2.564), HR-/HER2- (vs. HR+/HER2-, HR=2.727, 95%CI: 2.268-3.278), lung metastases (vs. no, HR=1.249 , 95%CI: 1.036-1.506), live metastases (vs. no, HR=1.840, 95%CI: 1.511-2.240), brain metastases (vs. no, HR=1.812, 95%CI: 1.463-2.245), only bone metastases (vs. no, HR=1.237, 95%CI: 1.024-1.465) are independent risk factors of prognosis; married status (vs. single, HR=0.812, 95%CI: 0.701-0.940), insurance (vs. no, HR=0.597, 95%CI: 0.466-0.764) and surgery (vs. no, HR=0.512, 95%CI: 0.438-0.599) are independent protection factors of prognosis. Histology, primary laterality did not reach significance with this test. Multivariate Cox model is shown in Table 3.

Discussion

Bones metastases are the most common distant metastatic site in breast cancer, severe complications, low quality of life and poor prognosis in patients, the rate of survival significantly decreased are often associated with the occurrence of bone metastases[14]. Our study analyzed recently available data on the subtype in bone metastatic breast cancer patients from the SEER registries, in an attempt to analysis differences in the effects of the breast cancer subtype and other factors on the patient prognosis.

Bone metastasis is most abundant among the HR+ subtype, the distribution of our study patient tumour subtype is similar to other studies in the published literature[12,17,18]. Our studies have identified the subgroups of patients with HR+/HER2- breast cancer is the most prone to bone metastasis, secondly is HR+/HER2+ breast cancer. HR-/HER2- has a particular propensity to metastasize to the brain and lung, brain metastasis is more common than for the other subtype, and the bone metastasis is relatively less likely to occur, this is consistent with previous research[19]. This may be due to different molecular subtype of breast cancer lead to different metastasis sites due to their special molecular biological characteristics.

The median OS for the entire cohort was 38 months of the patients,this is similar with Kuchuk 's study that from 294 electronic records of metastatic breast cancer patients were reviewed ,they found the median OS from bone metastasis diagnosis is 40 months in bone metastasis patients[20].The median OS is 46 months for patients with only bone metastases ,those with bone and other sites metastases is 24 months in our study is similar to the survival reported by previous authors in recent years[8]. Study of 815 patients with de novo or recurrent metastatic breast cancer and identified that patients with visceral metastases as well as those with multiple metastatic sites had worse OS, findings consistent with our results[21]. The five year survival rate is 33.9% which is similar with previous studies that shown 24–39% of patients alive in five year after diagnosis of bone metastases[5]. It may be due to the fact that the subjects of this study are menopausal women, the age of the previous subjects is unlimited, the proportion of elderly patients is large and the prognosis is poor, and with the improving of treatment methods in recent years, the prognosis of the patients has been improved.

Our study shown the five-year survival rate of HR+/HER2+ patients is the highest, reached 5.6 times of HR-/HER2- patients. Patients with HR+/HER2+ breast cancer had the longest median survival period. However, our study have shown that the incidence of bone metastasis in HR-/HER2- breast cancer was low, but patients with HR-/HER2- tumour had the worst prognosis. And OS in patients with HR-/HER2- breast cancer were significantly lower than those in patients with other molecular subtype, with the shortest median survival time. The large difference in prognosis observed across all tumour subtype confirms that breast cancer is a heterogeneous disease, even in the specific group of patients with bone metastases. The improvements in OS seen in HER2+ patients could be explained in part by the efficacy of HER2-targeted agents. In Dawood' s large-scale, randomized study , there were 2019 women with metastatic breast cancer that showed HER2+ patients who received trastuzumab had improved prognosis compared with HER2- patients[22]. However, the HR-/HER2- is an invasion subtype, with the

characteristics of rapid progress, strong aggressiveness, high degree of malignancy, easy occurrence of distant metastasis, rapid relapse[23-25]. Therefore,

Our study includes tumour subtype as a prognostic factor and provides evidence of a clear association of age, race, marital status, insurance, tumour grade, histology, subtype, and visceral metastases in bone metastasis patients with OS. This was similar with previous study. The Denmark data were population-based health registries, included all women in diagnosed during 1999−2011 with regional or stage II/III breast cancer, showed predictors of recurrence, metastases, and mortality included age, hormone receptor status, and stage at diagnosis[28]. Ahn ' study showed ER- negative and bone metastasis combined with visceral metastasis is a risk factor for OS [8]. Iqbal J' study showed US women diagnosed with invasive breast cancer, the survival varied by race and ethnicity, black women are more likely to die due to breast cancer within 7 years compared with non-Hispanic white or Asian women[29]. The protective effect of marriage for survival, that can be explained by patients can gained better economic resources and greater social support in marriage[30]. Although some factors have been found in previous studies, no covariates have been adjusted for other factors, or fewer covariates have been adjusted. We used a Cox proportional regression model by adjusting for all the factors and demonstrated the tumour subtype were prognosis factors.

We acknowledge that the study has some limitations. SEER database could not know the expression status of ki-67, the ki-67 index value is a prognostic factor in primary breast cancer and is a proliferation marker that also distinguishes between luminal A and luminal B breast cancer[26].Breast cancer is generally divided into luminal A and luminal B , according to HR 、HER2 status and ki-67 in the course of clinical diagnosis and treatment[27]. This may contribute to some disparities between our investigation and clinical applications. We do not have information with regards to radiotherapy or systemic treatments of this cohort, which may contribute to some of the differences observed in survival according to prognostic variables. Addition,the pathological data could not be centrally reviewed and were collected from different local pathology laboratories.

Conclusions

In conclusion, our results revealed a relatively good prognosis of bone metastasis, the median OS for patients was 38 months, 33.9% of patients were alive at five years. Subtype is a significant prognostic factor, the prognosis of patients with HR-/HER2- subtype is the worst, median OS only 11 months. Except tumour subtype, race, marital status, insurance, grade, site of metastases, surgery are independent predictors of OS.

Abbreviations

OS: overall survival;

BCSS: time from the breast cancer diagnosis to death due to breast cancer

ER: estrogen receptor

PR: progesterone receptor

HR-: ER- and PR-;

HR+: ER+ or\and PR+

HR: hazard ratio

HER2: human epidermal growth factor receptor-2

CI : confidence interval

ICD-O-3 : International Classification of Diseases for Oncology, 3rd Edition;

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of supporting data

The datasets used and analyzed for the current study will be available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The Natural Science Foundation of LiaoNing Province supported this work (2015020469).

Authors' contributions

LX and LJ conceived the study design and analytical concept. LX conducted the data acquisition, performed statistical analyses and drafted the manuscript. All authors contributed to the interpretation of results and the critical revision of the manuscript. All authors participated in the revision of the manuscript and approved the final manuscript.

Acknowledgements

Not applicable.

Authors' information

Affiliations

Li Xiao. Department of Health Statistics, School of Public Health, China Medical University, Shenyang, China. lixiao@cmu.edu.cn.

Zhang Xiaoli. Department of Health Statistics, School of Public Health, China Medical University, Shenyang, China. xlzhang@cmu.edu.cn.

Liu Jie. Department of Health Statistics, School of Public Health, China Medical University, Shenyang, China. jliu05@cmu.edu.cn.

Corresponding author

Correspondence to Liu Jie , jliu05@cmu.edu.cn.

References

[1] Surveillance Epidemiology, and End Results Program. Introduction to Breast Cancer. https://www.training.seer.cancer.gov/breast/intro/. Accessed 9 July 2019.

[2] Kimbung S, Loman N, Hedenfalk I. Clinical and molecular complexity of breast cancer metastases. Semin Cancer Biol. 2015, 35: 85-95.

[3] Yong M, Jensen AO, Jacobsen JB, Norgaard M, Fryzek JP, Sorensen HT. Survival in breast cancer patients with bone metastases and skeletal-related events: a population-based cohort study in Denmark (1999-2007). Breast Cancer Res Treat. 2011, 129(2): 495-503.

[4] Body JJ, Quinn G, Talbot S, Booth E, Demonty G, Taylor A, Amelio J. Systematic review and meta-analysis on the proportion of patients with breast cancer who develop bone metastases. Crit Rev Oncol Hematol. 2017, 115: 67-80.

[5] Desantis CE, Fedewa SA, Goding SA, Kramer JL, Smith RA, Jemal A. Breast cancer statistics, 2015: Convergence of incidence rates between black and white women. CA Cancer J Clin. 2016, 66(1): 31-42.

[6] Plunkett TA, Smith P, Rubens RD. Risk of complications from bone metastases in breast cancer. implications for management. Eur J Cancer. 2000, 36(4): 476-482.

[7] Yavas O, Hayran M, Ozisik Y. Factors affecting survival in breast cancer patients following bone metastasis. Tumori. 2007, 93(6): 580-586.

[8] Ahn SG, Lee HM, Cho SH, Lee SA, Hwang SH, Jeong J, Lee HD. Prognostic factors for patients with bone-only metastasis in breast cancer. Yonsei Med J. 2013, 54(5): 1168-1177.

[9] Gong Y, Liu YR, Ji P, Hu X, Shao ZM. Impact of molecular subtypes on metastatic breast cancer patients: a SEER population-based study. Sci Rep. 2017, 7: 45411.

[10] Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A. 2001, 98(19): 10869-10874.

[11] Koenders PG, Beex LV, Langens R, Kloppenborg PW, Smals AG, Benraad TJ. Steroid hormone receptor activity of primary human breast cancer and pattern of first metastasis. The Breast Cancer Study Group. Breast Cancer Res Treat. 1991, 18(1): 27-32.

[12] Smid M, Wang Y, Zhang Y, Sieuwerts AM, Yu J, Klijn, JG, Foekens JA, Martens JW. Subtypes of breast cancer show preferential site of relapse. Cancer Res. 2008, 68(9): 3108-3114.

[13] Tobin NP, Harrell JC, Lovrot J, Egyhazi BrageS, Frostvik StoltM, Carlsson L, Einbeigi Z, Linderholm B, Loman N, et al. Molecular subtype and tumor characteristics of breast cancer metastases as assessed by gene expression significantly influence patient post-relapse survival. Ann Oncol. 2015, 26(1): 81-88.

[14] Li BT, Wong MH, Pavlakis N. Treatment and Prevention of Bone Metastases from Breast Cancer: A Comprehensive Review of Evidence for Clinical Practice. J Clin Med. 2014, 3(1): 1-24.

[15] Surveillance, Epidemiology, and End Results Program. Data use agreement for the 1975-2016 SEER Research Data File. https://seer.cancer.gov/data/sample-dua.html .Accessed 12 July 2019.

[16] Diessner J, Wischnewsky M, Stuber T, Stein R, Krockenberger M, Hausler S, Janni W, Kreienberg R, Blettner M,Schwentner L. Evaluation of clinical parameters influencing the development of bone metastasis in breast cancer. BMC Cancer. 2016, 16: 307.

[17] Leone BA, Vallejo CT, Romero AO, Machiavelli MR, Perez JE, Leone J, Leone, J P. Prognostic impact of metastatic pattern in stage IV breast cancer at initial diagnosis. Breast Cancer Res Treat. 2017, 161(3): 537-548.

[18] Parkes A, Clifton K, Al-Awadhi A, Oke O, Warneke CL, Litton JK, Hortobagyi GN. Characterization of bone only metastasis patients with respect to tumor subtypes. NPJ Breast Cancer. 2018, 4: 2.

[19] Press DJ, Miller ME, Liederbach E, Yao K, Huo D. De novo metastasis in breast cancer: occurrence and overall survival stratified by molecular subtype. Clin Exp Metastasis. 2017, 34(8): 457-465.

[20] Kuchuk I, Hutton B, Moretto P, Ng T, Addison CL, Clemons M. Incidence, consequences and treatment of bone metastases in breast cancer patients-Experience from a single cancer centre. J Bone Oncol. 2013, 2(4): 137-144.

[21] Lobbezoo DJ, van Kampen RJ, Voogd AC, Dercksen MW, van den Berkmortel F, Smilde TJ, van de Wouw A J, Peters FP, van Riel JM, Peters NA,et al. Prognosis of metastatic breast cancer: are there differences between patients with de novo and recurrent metastatic breast cancer?. Br J Cancer. 2015, 112(9): 1445-1451.

[22] Dawood S, Broglio K, Buzdar AU, Hortobagyi GN, Giordano SH. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. J Clin Oncol. 2010, 28(1): 92-98.

[23] Staaf J, Ringner M, Vallon-Christersson J, Jonsson G, Bendahl PO, Holm K, Arason A, Gunnarsson H, Hegardt C, Agnarsson BA, et al. Identification of subtypes in human epidermal growth factor receptor 2–positive breast cancer reveals a gene signature prognostic of outcome. J Clin Oncol. 2010, 28(11): 1813-1820.

[24] Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA. 2006, 295(21): 2492-2502.

[25] Nguyen PL, Taghian AG, Katz MS, Niemierko A, Abi-Raad RF, Boon WL, Bellon JR, Wong JS, Smith BL, Harris J R. Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. J Clin Oncol. 2008, 26(14): 2373-2378.

[26] Nishimura R, Osako T, Nishiyama Y, Tashima R, Nakano M, Toyozumi Y, Arima N. Prognostic significance of Ki-67 index value at the primary breast tumor in recurrent breast cancer. Mol Clin Oncol. 2014, 2(6): 1062-1068.

[27] Gnant M, Harbeck N, Thomssen C. St. Gallen/Vienna 2017: A Brief Summary of the Consensus Discussion about Escalation and De-Escalation of Primary Breast Cancer Treatment. Breast Care (Basel). 2017, 12(2): 102-107.

[28] Cronin-Fenton D, Kjærsgaard A, Nørgaard M, Amelio J, Liede, A, Hernandez RK, Sorensen HT. Breast cancer recurrence, bone metastases, and visceral metastases in women with stage II and III breast cancer in Denmark. Breast Cancer Res Treat, 167(2): 517-528.

[29] Iqbal J, Ginsburg O, Rochon PA, Sun P, Narod SA. Differences in Breast Cancer Stage at Diagnosis and Cancer-Specific Survival by Race and Ethnicity in the United States. JAMA. 2015;313(2):165–173. doi:10.1001/jama.2014.17322.

[30] Rendall MS, Weden MM, Favreault MM, Waldron H. The protective effect of marriage for survival: a review and update. Demography, 2011. 48(2): p. 481-506.

Tables

Table1 Patient characteristics according to tumour subtype

Characteristics	HR+/HER2-	HR+/HER2+	HR-/HER2-	HR-/HER2+	Total	P value
	2146(63.42)	672(19.86)	316(9.34)	250(7.39)	3384(100)	
Year of diagnosis						0.981
2012	422(19.66)	133(19.79)	55(17.41)	51(20.40)	661(19.53)	
2013	441(20.55)	138(20.54)	68(21.52)	52(20.80)	699(20.66)	
2014	425(19.80)	125(18.60)	65(20.57)	46(18.40)	661(19.53)	
2015	428(19.94)	143(21.28)	59(18.67)	45(18.00)	675(19.95)	
2016	430(20.04)	133(19.79)	69(21.84)	56(22.40)	688(20.33)	
Age at diagnosis						0.221
40-44 years	283(13.19)	107(15.92)	31(9.81)	28(11.20)	449(13.27)	
45-49 years	465(21.67)	128(19.05)	65(20.57)	50(20.00)	708(20.92)	
50-54 years	638(29.73)	202(30.06)	110(34.81)	81(32.40)	1031(30.47)	
55-59 years	760(35.41)	235(34.97)	110(34.81)	91(36.40)	1196(35.34)	
Race						<0.001
White	1574(73.35)	481(71.58)	218(68.99)	170(68.00)	2443(72.19)	
Black	353(16.45)	127(18.90)	81(25.63)	43(17.20)	604(17.85)	
Other [a]	211(9.83)	64(9.52)	16(5.06)	33(13.20)	324(9.57)	
Unknown	8(0.37)	0(0.00)	1(0.32)	4(1.60)	13(0.38)	
Marital status						0.771
Single	620(28.89)	189(28.13)	89(28.16)	73(29.20)	971(28.69)	
Married	1049(48.88)	342(50.89)	150(47.47)	113(45.20)	1654(48.88)	
Other [b]	377(17.57)	111(16.52)	64(20.25)	47(18.80)	599(17.70)	
Unknown	100(4.66)	30(4.46)	13(4.11)	17(6.80)	160(4.73)	
Insurance						0.49
Insured	104(4.85)	42(6.25)	17(5.38)	11(4.40)	174(5.14)	
Uninsured	2027(94.45)	623(92.71)	297(93.99)	235(94.00)	3182(94.03)	
Unknown	15(0.70)	7(1.04)	2(0.63)	4(1.60)	28(0.83)	

Grade						<0.001
I	247(11.51)	21(3.13)	4(1.27)	2(0.80)	274(8.10)	
II	1017(47.39)	244(36.31)	64(20.25)	67(26.80)	1392(41.13)	
III or IV	619(28.84)	334(49.70)	230(72.78)	149(59.60)	1332(39.36)	
Unknown	263(12.26)	73(10.86)	18(5.70)	32(12.80)	32(12.80)	
Histology						<0.001
Ductal	1571(73.21)	559(83.18)	277(87.66)	216(86.40)	2623(77.51)	
Lobular	353(16.45)	28(4.17)	13(4.11)	6(2.40)	400(11.82)	
Others	222(10.34)	85(12.65)	26(8.23)	28(11.20)	361(10.67)	
Laterality						0.153
Right	1054(49.11)	330(49.11)	156(49.37)	102(40.80)	1642(48.52)	
Left	1070(49.86)	337(50.15)	155(49.05)	146(58.40)	1708(50.47)	
Bilateral, single primary	5(0.23)	4(0.60)	2(0.63)	1(0.40)	12(0.35)	
Unknown	17(0.79)	1(0.15)	3(0.95)	1(0.40)	22(0.65)	
Lung metastases						<0.001
No	1643(76.56)	452(67.26)	216(68.35)	158(63.20)	2469(72.96)	
Yes	449(20.92)	205(30.51)	96(30.38)	89(35.60)	839(24.79)	
Unknown	54(2.52)	15(2.23)	4(1.27)	3(1.20)	76(2.25)	
Liver metastases						<0.001
No	1691(78.80)	418(62.20)	208(65.82)	132(52.80)	2449(72.37)	
Yes	423(19.71)	244(36.31)	101(31.96)	155(46.00)	883(26.09)	
Unknown	32(1.49)	10(1.49)	7(2.22)	3(1.20)	52(1.54)	
Brain metastases						<0.001
No	1992(92.82)	595(88.54)	263(83.23)	214(85.60)	3064(90.54)	
Yes	107(4.99)	62(9.23)	44(13.92)	31(12.40)	244(7.21)	
Unknown	47(2.19)	15(2.23)	9(2.85)	5(2.00)	76(2.25)	
Only bone metastases						<0.001
No	748(34.86)	360(53.57)	170(53.80)	168(67.20)	1446(42.73)	

Yes	1326(61.79)	300(44.64)	140(44.30)	80(32.00)	1846(54.55)
Unknown	72(3.36)	12(1.79)	6(1.90)	2(0.80)	21(2.72)
Surgery					0.971
No	1541(71.81)	489(72.77)	225(71.20)	180(72.00)	2435(71.96)
Yes	588(27.40)	179(26.64)	88(27.85)	68(27.20)	923(27.28)
Unknown	17(0.79)	4(0.60)	3(0.95)	2(0.80)	26(0.77)
Breast cancer -specific death					<0.001
No	1502(69.99)	504(75.00)	140(44.30)	165(66.00)	2311(68.29)
Yes	644(30.01)	168(25.00)	176(55.70)	85(34.00)	1073(31.71)
Status					<0.001
Alive	1350(62.91)	474(70.54)	92(29.11)	153(61.20)	2069(61.14)
Dead	796(37.09)	198(29.46)	224(70.89)	97(38.80)	1315(38.86)

Other [a] (American Indian/AK Native, Asian/Pacific Islander)

Other [b] (Divorced/Widowed/Separated)

Unknown patients are excluded from the comparative analysis.

Table 2 Univariate Analysis of Prognostic Factors

Characteristics	Median OS	P value	HR	95%CI for HR
Age at diagnosis		<0.001		
40-44 years	42		Reference	
45-49 years	41		1.013	0.829-1.237
50-54 years	39		1.103	0.915-1.329
55-59 years	32		1.364	1.139-1.634
Race		<0.001		
White	41		Reference	
Black	28		1.498	1.315-1.707
Other a	38		1.003	0.824-1.220
Marital status		<0.001		
Single	32		Reference	
Married	42		0.723	0.638-0.819
Other b	35		0.903	0.772-1.057
Insurance		<0.001		
Uninsured	26		Reference	
Insured	38		0.633	0.513-0.781
Grade		<0.001		
I	48		Reference	
II	44		1.214	0.953-1.547
III or IV	28		2.071	1.634-2.625
Histology		0.003		
Ductal	36		Reference	
Lobular	44		0.748	0.624-0.897
Others	40		0.856	0.713-1.028
Laterality		0.084		
Right	38		Reference	

Left	38	1.058	0.949-1.179
Bilateral, single primary	13	2.254	1.008-5.039
Tumour subtype		<0.001	
HR+/HER2-	39	Reference	
HR+/HER2+	52	0.747	0.640-0.873
HR-/HER2-	11	3.571	3.071-4.152
HR-/HER2+	35	1.132	0.917-1.397
Bone+Lung metastases		<0.001	
No	42	Reference	
Yes	23	1.888	1.679-2.123
Bone+Liver metastases		<0.001	
No	44	Reference	
Yes	22	2.182	1.950-2.443
Bone+Brain metastases		<0.001	
No	40	Reference	
Yes	14	2.674	2.245-3.184
Only bone metastases		<0.001	
No	46	Reference	
Yes	24	2.29	2.04-2.559
Surgery		<0.001	
No	32	Reference	
Yes	52	0.496	0.433-0.568

Table 3 Multivariate Analysis of Prognostic Factors

Characteristics	P value	HR	95%CI for HR
Age at diagnosis			
40-44 years		Reference	
45-49 years	0.546	0.932	0.742-1.171
50-54 years	0.923	1.011	0.816-1.252
55-59 years	0.024	1.27	1.032-1.563
Race			
White		Reference	
Black	0.001	1.32	1.129-1.543
Other a	0.114	1.2	0.957-1.505
Marital status			
Single		Reference	
Married	0.005	0.812	0.701-0.940
Other b	0.087	0.855	0.715-1.023
Insurance(yes vs no)	<0.001	0.597	0.466-0.764
Histology			
Ductal		Reference	
Lobular	0.743	1.041	0.820-1.322
Others	0.348	1.107	0.896-1.367
Laterality			
Right		Reference	
Left	0.534	1.04	0.918-1.179
Bilateral, single primary	0.18	2.198	0.695-06.956
Grade			
I		Reference	
II	0.322	1.142	0.878-1.486
III or IV	<0.001	1.952	1.485-2.564

Tumour subtype			
HR+/HER2-		Reference	
HR+/HER2+	<0.001	0.500	0.414-0.603
HR-/HER2-	<0.001	2.727	2.268-3.278
HR-/HER2+	<0.001	0.618	0.475-0.805
Site of metastases			
Lung(yes vs no)	0.02	1.249	1.036-1.506
Live(yes vs no)	<0.001	1.84	1.511-2.240
Brain(yes vs no)	<0.001	1.812	1.463-2.245
Only bone(yes vs no)	0.0285	1.237	1.024-1.465
Surgery(yes vs no)	<0.001	0.512	0.438-0.599

Figures
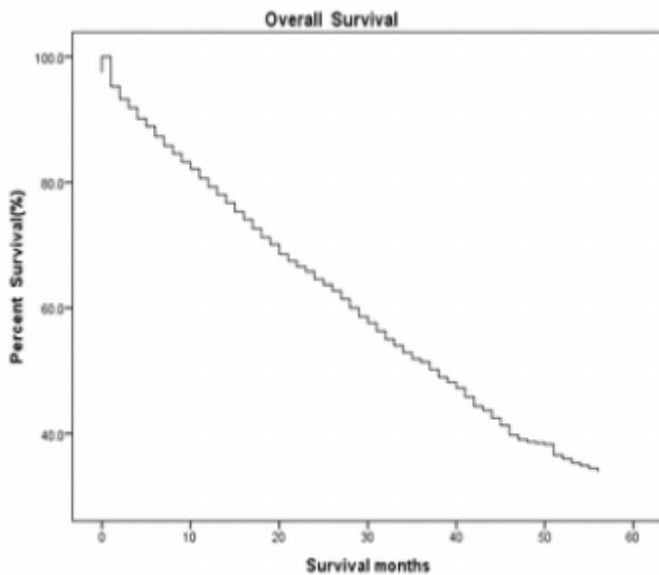
Figure 1

Kaplan–Meier curve for overall survival for the entire population
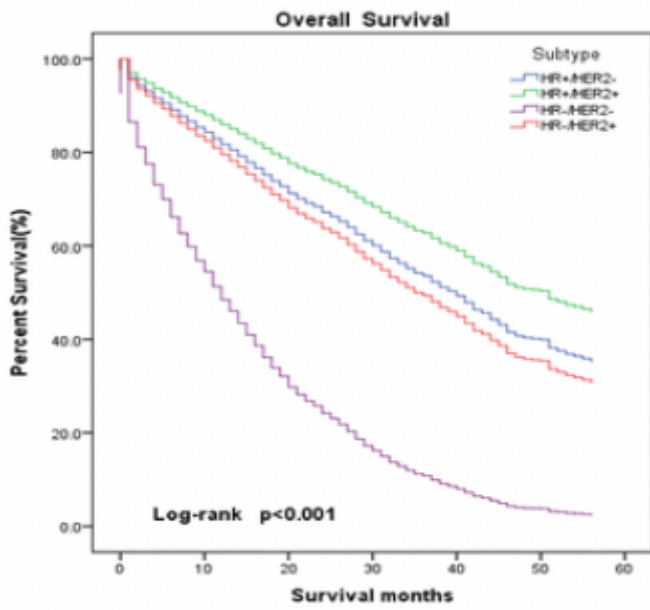
Figure 2

Kaplan−Meier curve for overall survival for the entire population
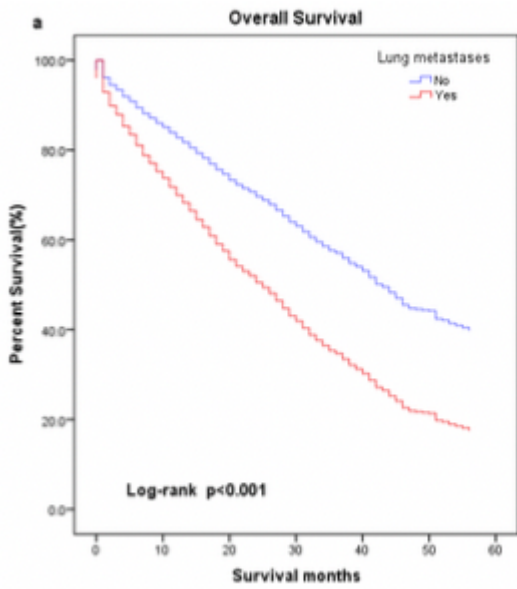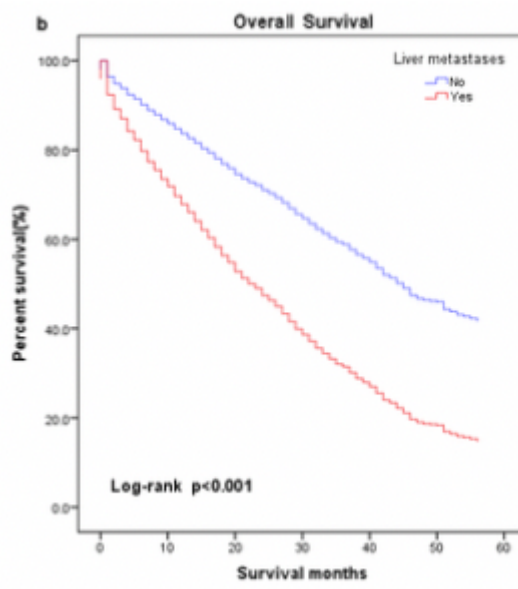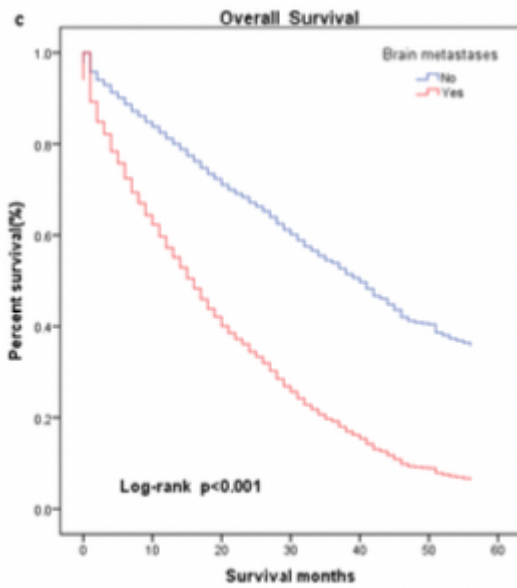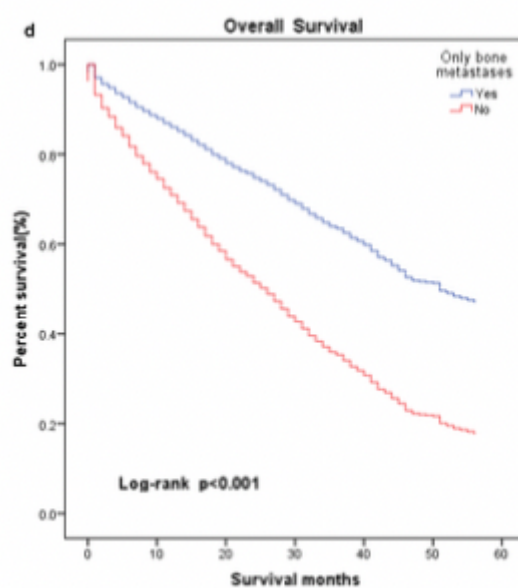
Figure 3

Kaplan–Meier curves for overall survival according to metastases site.