Int J Clin Exp Med 2019;12(9):11645-11656
www.ijcem.com /ISSN:1940-5901/IJCEM0086301

Original Article

Clinicopathological features and treatment outcomes in patients with initially diagnosed stage IV breast cancer bone metastasis

Jianna Sun[1,2,3,4], Lingjun Kong[4], Chongxi Ren[4], Hong Liu[1,2,3]

[1]Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin 300060, China; [2]Key Laboratory of Cancer Prevention and Therapy, Tianjin 300060, China; [3]Tianjin's Clinical Research Center for Cancer, Tianjin 300060, China; [4]Cangzhou Hospital of Integrated TCM-WM • Hebei, Cangzhou, Hebei 061001, China

Received September 27, 2018; Accepted February 12, 2019; Epub September 15, 2019; Published September 30, 2019

Abstract: Background: Initially diagnosed stage IV breast cancer bone metastasis (IDBCBM) presents as a relatively low incidence proportion, and limited studies have analyzed the disease characteristics of this subset of patients. Method: A total of 74 patients with IDBCBM who were treated at our center between March 2007 and November 2016 were included in the study. Their clinicopathological characteristics and treatment outcomes were retrospectively analyzed. Univariate and multivariate analyses were performed to determine the effects of each variable on overall survival (OS). Results: The median age of the patients was 53.3 years. The median OS was 34.3 months, and the 3-year and 5-year OS rates were 37.8% and 12.2%, respectively. Patients whose initial distant metastasis was only in the bone had a better prognosis, with a median OS of 41.7 months, and their 3-year and 5-year OS rates were 54.5% and 20.4%, respectively. In the univariate analysis, molecular subtypes, hormone receptor status, HER-2 expression, nodal status, Ki-67 index, number of sites of bone metastases, initial mode of metastasis, mode of medication, and loco-regional treatment were correlated with poor prognosis. Multivariate analysis demonstrated that the Ki-67 index, number of sites of bone metastases, mode of medication, and initial metastasis location were independent factors that significantly impacted OS. Conclusions: Ki-67 >20%, >5 metastatic sites, bone plus visceral metastases, and single mode therapy were associated with poor prognosis for OS in IDBCBM. Loco-regional treatment, including surgery and radiotherapy of primary tumor, might confer a survival advantage.

Keywords: Initial diagnosis, stage IV breast cancer bone metastasis, clinicopathological characteristics, treatment, prognosis

Introduction

Breast cancer, a complex and heterogeneous disease, is the most common malignancy among females worldwide. It accounts for approximately 15% of all female primary cancers in China and has a significant upward trend in incidence rates [1]. In America, it is estimated that breast cancer accounted for 30% of all new cancer cases (252,710) among women in 2017, and approximately 5% of breast cancer patients present with stage IV disease at their primary diagnosis [2]. According to the American Joint Committee on Cancer staging system [3], stage IV breast cancer is defined as breast cancer that has metastasized to distant organs at the time of initial diagnosis, and postoperative recurrence and metastasis are common in the progression of the disease. Currently, there is an increasing interest in stage IV breast cancer, as the proportion of this type of cancer seems to have increased in recent years compared with the incidence in the past [4].

Initially diagnosed stage IV breast cancer is different from the recurrence and metastases of breast cancer. Recent studies on advanced breast cancer have mostly been conducted on patients with postoperative progression, and few studies have been conducted on patients with initially diagnosed stage IV breast cancer. Previous studies have shown that stage IV br-

east cancer commonly metastasizes to distant organs, such as the bone, liver, lungs, and brain. Among these organs, the bone is thought to be the most common site for stage IV breast cancer metastasis, and the incident rate is nearly 58% [5]. Furthermore, patients with bone metastases generally survive for longer than patients with metastases at other sites [6]. However, initially diagnosed stage IV breast cancer bone metastasis (IDBCBM) presents a relatively low incidence proportion, and there have been limited studies analyzing the disease characteristics in this subset of patients [7-9].

Although treatment strategies for stage IV breast cancer have significantly improved in the last two decades due to a better understanding of the heterogeneity of the disease, it remains an incurable disease with a median overall survival (OS) of 2-3 years and a 5-year survival rate of only 25% [10]. To date, the standard therapeutic approach is palliative care. Systemic therapy is considered the mainstay of treatment, including chemotherapy, endocrine therapy, radiotherapy, and/or targeted therapy. In addition, some retrospective studies have suggested that achieving a sustained complete remission seems to be associated with a longer survival [11], but the true impact of loco-regional treatment of the primary breast cancer on long-term outcome remains controversial. Additionally, current consensus guidelines do not recommend routine screening for bone metastases in patients with localized breast cancer unless it is directed by signs or symptoms [12]. Among patients with IDBCBM, there is a lack of data regarding patient characteristics, clinical outcomes and risk factors, which need to be furthered studied.

Therefore, in this study, the clinicopathological characteristics and treatment outcomes of IDBCBM patients were retrospectively analyzed. We also attempted to investigate the potential impact of loco-regional treatment of the primary tumor in IDBCBM patients. Moreover, the prognostic factors related to the overall survival of the patients to guide goal-directed therapy for patients were examined.

Materials and methods

Study design and patient data

This is a retrospective study conducted in a cohort of female patients with initially diagnosed stage IV breast cancer bone metastasis at the Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer. The clinical data of 74 patients who were treated at The Second Department of Breast Cancer, Tianjin Medical University Cancer Institute and Hospital were collected from March 2007 to November 2016. Inclusion criteria were as follows: 1) no cancer-related treatment was received before admission, and after admission, biopsies were performed via fine needle aspiration (FNA) at the first diagnosis of breast cancer; 2) during the same period, bone metastasis was confirmed through computerized tomography (CT), magnetic resonance imaging (MRI), radionuclide bone scan (ECT) and/or bone biopsy; 3) the site of distant metastasis was in the bone only or the bone plus concurrent lung, liver, brain and/or other organ metastases; 4) complete clinical pathology and follow-up data were available; and 5) no other malignancies were present. The exclusion criteria for our analysis were as follows: 1) metastatic breast cancer was detected after surgery or adjuvant therapy; 2) lack of pathology or imaging reports in our hospital; and 3) incomplete or refusal to provide follow-up information. Approval for the research protocol was provided by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital (protocol number 2017-AF29-058). A written informed consent form was obtained from each participant prior to participation in the study, and all methods were performed in accordance with the guidelines and regulations.

Demographic and clinicopathological features

Demographic information and tumor characteristics that were collected and analyzed included age at diagnosis, medical history, pathological type, tumor stage, tumor grade, nodal status, molecular subtype, hormone receptor (HR) status, human epidermal growth factor receptor-2 (HER-2) expression, classification, and number of metastatic sites. The use of therapy, including mode of medication (mainly systemic chemotherapy), endocrine therapy, radiation therapy and targeted therapy, was also recorded. Patients who underwent surgery of the primary tumor were included in the surgery group, and loco-regional treatment included both surgery and radiotherapy of the primary tumor. All surgeries were palliative. The most common imaging modality for diagnosing bone metastasis

was bone scintigraphy, followed by direct radiography. Bone biopsy and fine-needle aspiration biopsy were used as the diagnostic methods in only three patients.

Immunohistochemistry and molecular subtype

Immunohistochemistry was used to detect the expression of the estrogen receptor (ER) and progesterone receptor (PR). Positive expression was defined as a percentage of ER- or PR-positive cells ≥1%. Immunohistochemistry was used to detect the expression of HER-2 and Ki-67, and the results were assessed according to the scoring system recommended by the American Society of Clinical Oncology (ASCO) and the American College of Pathologists guidelines (CAP). HER-2-negative status was determined by staining results of (-) or (+); HER-2-positive status was determined by staining results of (+++). Once HER-2 staining (++) was verified by fluorescence *in situ* hybridization (FISH), a sample was assigned as HER-2 positive. Otherwise, the sample was categorized into the unknown expression group in this study. According to the recommendations of the St. Gallen consensus meeting in 2013, breast cancer was categorized into one of four subtypes, namely, luminal A, luminal B (HER-2 negative, positive), HER-2 positive, and basal-like (triple negative), based on the expression status of ER, PR, HER-2 and Ki-67 [13, 14]. In particular, the Ki-67 index was categorized as high when 20% or more of the tumor cells were immune-stained according to the criteria mentioned above, and this index was used throughout the course of this study within the breast cancer spectrum. Furthermore, the approach to and outcome of treatment in breast cancer is determined by the molecular subtype. Scilicet, these subtypes are associated with distinct pathological features, treatment responses and clinical outcomes [15].

Follow-up

Most of the patients in the group were followed up by phone, outpatient review, and inpatient examination. Very few patients were followed up on site. The follow-up time began at the time of diagnosis of breast cancer bone metastasis and continued until the follow-up deadline of Dec. 31, 2017 or until the patient died. OS was calculated from the time of diagnosis until the last follow-up or until death due to any cause.

Statistical analysis

Descriptive statistics were used to examine the following baseline characteristics of the breast cancer patients: year of diagnosis, age, tumor size, regional node status, tumor grade, molecular subtype, surgery, and radiation. Continuous variables were assessed using the independent *t*-test. Associations between categorical variables were assessed using the Chi-square test when appropriate. OS was used as the primary study outcome. We used the Kaplan-Meier method to generate survival curves and analyzed the differences between the curves using the log-rank test. Univariate and multivariate Cox proportional hazard models were applied to assess the independent association of several variables with OS, which were reported as hazard ratios and their 95% confidence intervals (95% CIs). All statistical analyses were performed using GraphPad Prism 5 software and SPSS statistical software, version 22.0 (SPSS Inc., Chicago, IL, United States). A two-sided *P*-value less than 0.05 was considered statistically significant.

Results

Patient characteristics

The median age of the 74 patients with IDBCBM was 53.3 years (26-82 years). The histopathology types were mainly invasive ductal carcinomas and invasive carcinomas. Among them, one case was an invasive papillary carcinoma, and the other two cases were invasive lobular carcinomas. The clinical and pathological features of the study population are presented in **Table 1**. The size of the primary tumor was mostly T2 (32 cases, 43.2%). Immunohistochemical results showed that HR (ER and/or PR)-positive cases accounted for 68.9% (51 cases), with 35.1% (26 cases) HER-2 expression positive and 50% (37 cases) negative, and the remaining 11 cases were unknown. The Ki-67 index of ≤20% and >20% accounted for 24.3% (18 cases) and 68.9% (51 cases), respectively. The remaining 5 cases are unknown. The molecular subtypes were as follows: 13 cases of luminal A, 38 cases of luminal B, 18 cases of HER-2 positive and 5 cases of triple negative. Among the 74 patients, the treatments used were as follows: 69 (93.2%) cases of chemotherapy, 21 (28.3%) cases of radiotherapy, 30 (40.5%) cases of endocrine therapy, 8 (10.8%)

Table 1. Clinicopathological features and treatments in 74 patients with bone metastasis only or bone plus accompanying visceral metastasis

Characteristics	BMO (%)	BVM (%)	Total (%)	*P* value
Age (years)				0.257
≤55	22 (50.0)	19 (63.3)	41 (55.4)	
>55	22 (50.0)	11 (36.7)	33 (44.6)	
Primary tumor size				0.045
≤5 cm	28 (63.6)	12 (40.0)	40 (54.1)	
>5 cm	16 (36.4)	18 (60.0)	34 (45.9)	
Nodal status				0.880
N0	7 (15.9)	7 (23.3)	14 (18.9)	
N1	7 (15.9)	4 (13.3)	11 (14.9)	
N2	17 (38.7)	11 (36.7)	28 (37.8)	
N3	13 (29.5)	8 (26.7)	21 (28.4)	
Ki-67 index				0.118
≤20%	13 (33.3)	5 (16.7)	18 (26.1)	
>20%	26 (66.7)	25 (83.3)	51 (72.9)	
Molecular subtypes				0.007
Luminal A	12 (27.3)	1 (3.4)	13 (17.6)	
Luminal B	24 (54.5)	12 (40.0)	36 (48.6)	
HER-2 positive	6 (13.6)	14 (46.6)	20 (27.1)	
Triple negative	2 (4.6)	3 (10.0)	5 (6.7)	
Number of sites of bone metastases				0.029
≤5	26 (59.1)	10 (33.3)	36 (48.6)	
>5	18 (40.9)	20 (66.7)	38 (51.4)	
HR status				0.003
Positive	36 (81.8)	15 (50.0)	51 (68.9)	
Negative	8 (18.2)	15 (50.0)	23 (31.1)	
HER-2 expression				0.010
Positive	11 (25.0)	15 (50.0)	26 (35.1)	
Negative	26 (59.1)	6 (20.0)	32 (43.2)	
Unknown	5 (11.4)	6 (20.0)	11 (14.9)	
Triple negative	2 (4.5)	3 (10.0)	5 (6.8)	
Endocrinotherapy				0.045
Yes	22 (50.0)	8 (26.7)	30 (40.6)	
No	22 (50.0)	22 (73.3)	44 (59.4)	
Targeted therapy				0.004
Yes	1 (2.3)	7 (23.4)	8 (10.8)	
No	43 (97.7)	23 (76.6)	66 (89.2)	
Medication mode				0.989
MMT	25 (56.8)	17 (56.7)	42 (56.8)	
SMT	19 (43.2)	13 (43.3)	32 (43.2)	
Radiotherapy				0.426
Yes	14 (31.8)	7 (23.3)	21 (28.4)	
No	30 (68.2)	23 (76.7)	53 (71.6)	
Surgery of primary tumor				<0.001
Yes	32 (72.7)	8 (26.7)	40 (54.1)	
No	12 (27.3)	22 (73.3)	34 (45.9)	

Abbreviations: BMO, bone metastasis only; BVM, bone plus accompanying visceral metastasis; HR, hormone receptor; HER-2, human epidermal growth factor receptor-2; MMT, multimodal therapy; SMT, single mode therapy.

cases of targeted therapy, and 40 (54%) cases of primary tumor surgery. Five patients (6.7 %) underwent surgery for metastases, including two cases of posterior lumbar decompression and internal fixation, one case of percutaneous lumbar vertebroplasty and two cases of liver metastases.

Distant metastases at initial diagnosis

There were 44 cases of bone metastasis only (BMO) and 30 cases of bone metastasis acco mpanied by visceral metastasis (BVM) in the study. The number of cases of metastasis to the liver, lung, liver, and lung, and brain were 14 (18.9%), 11 (14.9%), 3 (4.1%), and 2 (2.7%), respectively. The number of sites of bone metastases (NBM) was ≤5 in 36 cases and >5 in 38 cases. According to the initial mode of metastasis (IMM), the 74 patients were divided into two groups: the BMO group and the BVM group. The results showed that tumor size, molecular subtype, NBM, HR status, HER-2 expression, endocrine therapy, targeted therapy, and surgery of the primary tumor were significantly different between the two groups (**Table 1**). According to the NBM in the BMO group, the patients were divided into two groups: metastatic sites (MS) ≤5 and MS >5. The results showed that tumor size,

Table 2. Clinicopathological features and treatments in 44 patients with bone metastasis only according to the number of sites of bone metastases

Characteristics	Cases (%)		Total (%)	*P* value
	NBM ≤5	NBM >5		
Tumor size				0.728
≤5 cm	16 (61.5)	12 (66.7)	28 (63.6)	
>5 cm	10 (38.5)	6 (33.3)	16 (36.4)	
Molecular subtypes				0.395
Luminal A	9 (34.6)	3 (16.6)	12 (27.3)	
Luminal B	14 (53.8)	10 (55.6)	24 (54.5)	
HER-2 positive	2 (7.7)	4 (22.2)	6 (13.6)	
Triple negative	1 (3.9)	1 (5.6)	2 (4.6)	
HR status				0.169
Positive	23 (88.5)	13 (72.2)	36 (88.8)	
Negative	3 (11.5)	5 (27.8)	8 (18.2)	
HER-2 expression				0.780
Positive	6 (23.1)	5 (27.8)	11 (25.0)	
Negative	15 (57.6)	11 (61.0)	26 (59.1)	
Unknown	4 (15.4)	1 (5.6)	5 (11.4)	
Triple negative	1 (3.9)	1 (5.6)	2 (4.5)	
Endocrinotherapy				1.000
Yes	13 (50.0)	9 (50.0)	22 (50.0)	
No	13 (50.0)	9 (50.0)	22 (50.0)	
Surgery of primary tumor				0.950
Yes	19 (73.1)	13 (72.2)	32 (72.7)	
No	7 (26.9)	5 (27.8)	12 (27.3)	

Abbreviations: NBM, number of sites of bone metastases; HR, hormone receptor; HER-2, human epidermal growth factor receptor-2.

molecular subtype, HR status, HER-2 expression, endocrine therapy, and surgery of primary tumor were not significantly different between the two groups (**Table 2**).

Survival

The median OS of the 74 patients was 34.3 months, and the 3-year and 5-year survival rates were 37.8% and 12.2%, respectively. The median OS in the BMO group was 41.7 months, and the 3-year and 5-year survival rates were 54.5% and 20.4%, respectively. The median OS in the BVM group was 23.4 months, and the 3-year and 5-year survival rates were 13.3% and 0%, respectively.

Prognostic analysis

The results of the univariate analysis indicated that nodal status, molecular subtype, HR status, HER-2 expression status, Ki-67 index, IMM, NBM, mode of medication (MM) and loco-regional treatment were significantly associated with OS in the study (**Table 3**). Multivariate analysis showed that the IMM, NBM, MM, and Ki-67 index were independent prognostic factors for OS in patients with IDBCBM (**Table 4**). The patients with BMO, MS ≤5, Ki-67 ≤20% or multimodal therapy (MMT) had a better prognosis than those with BVM, MS >5, Ki-67 >20% or single mode therapy (SMT) (**Table 5**; **Figure 1A-D**). According to MS, the OS was not different in patients with different IMMs, and according to IMM, the OS was significant different in patients with different NBM (**Table 5**; **Figure 1E-H**). The comparative analysis of loco-regional treatment and surgical treatment indicated that loco-regional treatment improved survival. There was no significant difference between the surgery group and the non-surgery group (P= 0.0622) (**Table 6**; **Figure 2A**). Loco-regional treatment was a favorable prognostic factor for OS (hazard ratio, 1.935; 95% CI, 1.092-3.427; P=0.0237) in the study (**Table 6**; **Figure 2B**).

Discussion

This study investigated and analyzed the clinicopathological characteristics and treatment outcomes among patients with IDBCBM using medical record data from oncological practices within our medical institutions. To the best of our knowledge, this is the first single-center cohort study that focused on exploring the association between survival and clinicopathological factors in female patients with IDBCBM. The results indicate that high Ki-67 index, SMT, M-BM, and BVM are associated with poor prognosis for OS in patients with IDBCBM, and loco-regional treatment including surgery and radiotherapy of primary tumor might have a positive impact on survival rates.

Stage IV breast cancer is a heterogeneous disease whose prognosis may depend on the sites of metastasis or the number of metastatic sites. Previous studies have found that brain and

Table 3. Univariate analysis of related factors of prognosis among 74 patients with initially diagnosed stage IV breast cancer bone metastasis

Variable	Cases (%)	OS (mo)	*P* value
Age (years)			0.274
≤55	41 (55.4)	32.0	
>55	33 (44.6)	37.1	
Family history			0.558
Yes	20 (27.1)	36.3	
No	54 (72.9)	33.5	
Tumor stage			0.246
T0, 1	8 (10.8)	37.9	
T2	32 (43.2)	37.6	
T3	15 (20.3)	32.0	
T4	19 (25.7)	28.9	
Nodal status			0.049
N0	14 (18.9)	42.3	
N1	11 (14.9)	34.3	
N2	28 (37.8)	25.9	
N3	21 (28.4)	38.5	
Ki-67 index			<0.001
≤20%	18 (24.3)	55.9	
>20%	51 (68.9)	26.8	
Unknown	5 (6.8)	32.6	
Number of sites of bone metastases			0.021
≤5	36 (48.6)	41.6	
>5	38 (51.4)	27.3	
Initial metastasis mode			<0.001
BMO	44 (59.5)	41.7	
BVM	30 (40.5)	23.4	
Molecular subtypes			<0.001
Luminal A	13 (17.5)	60.5	
Luminal B	38 (51.4)	31.8	
HER-2 positive	18 (24.3)	23.4	
Triple negative	5 (6.8)	23.6	
HR status			0.001
Positive	51 (68.9)	39.1	
Negative	23 (31.1)	23.4	
HER-2 expression			0.003
Positive	26 (35.1)	24.7	
Negative	32 (43.2)	45.3	
Unknown	11 (14.9)	29.6	
Triple negative	5 (6.8)	23.6	
Medication mode			0.001
MMT	32 (43.3)	44.4	
SMT	42 (56.7)	26.5	
Radiotherapy			0.172
Yes	21 (28.4)	41.2	
No	53 (71.6)	31.5	
Surgery of primary tumor			0.063
Yes	40 (54.1)	39.6	
No	34 (45.9)	28.0	
Loco-regional treatment			0.028
Yes	46 (62.2)	39.4	
No	28 (37.8)	25.8	

Abbreviations: OS, overall survival; MO, month; BMO, bone metastasis only; BVM, bone plus accompanying visceral metastasis; HR, hormone receptor; HER-2, human epidermal growth factor receptor-2; MMT, multimodal therapy; SMT, single mode therapy.

liver metastasis are independent and unfavorable prognostic factors for OS in patients with metastatic breast cancer [16]. In the study by Orging et al. [17], IDBCBM patients with brain and liver metastases had an increased risk of death compared with those with BMO, and patients with lung metastasis had a similar mortality rate compared to those with bone metastasis. These findings are in accordance with reports that analyzed the impact of the number of metastatic sites on survival. The multivariate analysis in this study showed that IMM in patients with IDBCBM was an independent prognostic factor for OS (P=0.007). However, the prognostic value of the sites of metastasis remains controversial in patients with stage IV breast cancer. A study by Gerratana et al. [18] showed that liver metastasis was an independent prognostic factor for OS in patients with stage IV breast cancer, while bone, lung and brain metastases had no effect on survival.

In the present study, NBM was an independent prognostic factor for OS in patients with IDBCBM. The patients with a number of sites of bone metastases ≤5 had a better prognosis than those with a number of sites of bone metastases >5. There was no statistically significant difference in OS in patients with different IMMs according to the number of metastatic lesions. OS was significantly different in patients with different NBM according to IMM. In terms of the survival impact, IMM was primary and NBM was secondary. The metastatic lesions in stage IV breast cancer were mostly asymptomatic, and only a few were found to be related to metastatic sites. Bone radionuclide scanning (ECT) is the most commonly used primary screening method for bone metastases. In this study, only two cases with bone pain as the initial symptom were recorded. The other cases were initially diagnosed with breast lumps, and the primary tumor stage was mainly T2. The results show that the differences in tumor size between the BMO group and the BVM group were statistically significant (P= 0.045) (**Table 1**).

Ki-67, as a tumor cell proliferation index, was also found to be an independent unfavorable prognostic factor for OS in the univariate and multivariate analyses. Ki-67 is a positive marker of nuclear proliferation. Studies have shown that Ki-67 expression can reliably and rapidly reflect the proliferation rate of malignant tu-

Table 4. Multivariate analysis of prognostic factors for overall survival among 74 patients with initially diagnosed stage IV breast cancer bone metastasis

Variable	*B*	*SE*	*P* value	*Exp (B)*	*95% CI for Exp (B)*
HR status	-0.570	0.652	0.381	0.565	0.158-2.208
HER-2 expression	0.160	0.250	0.522	1.173	0.719-1.916
Loco-regional treatment	-0.802	0.564	0.155	0.448	0.148-1.354
Nodal status	0.025	0.136	0.857	1.025	0.785-1.339
Molecular subtypes	-0.235	0.518	0.650	0.790	0.287-2.181
Ki-67 index	1.217	0.340	<0.001	3.378	1.733-6.584
Medication mode	-1.360	0.332	<0.001	0.257	0.134-0.493
Initial metastasis mode	1.068	0.396	0.007	2.910	1.338-6.328
Surgery of primary tumor	0.840	0.599	0.161	2.316	0.716-7.492
Number of sites of bone metastases	0.696	0.332	0.036	2.005	1.046-3.842

Abbreviations: HR, hormone receptor; HER-2, human epidermal growth factor receptor-2.

Table 5. Comparative analysis of overall survival related factors in 74 patients with initially diagnosed stage IV breast cancer bone metastasis

Characteristics	Hazard Ratio	95% CI	*P*-value
IMM (BMO vs. BVM)	0.3274	0.1807-0.5934	<0.0012
NBM (≤5 vs. >5)	0.5458	0.3263-0.9128	0.0210
MM (MMT vs. SMT)	0.4346	0.2605-0.7252	0.0014
Ki-67 (≤20% vs. >20%)	0.2803	0.1623-0.4841	<0.001
MS in BMO (≤5 vs. >5)	0.5185	0.2512-1.070	0.0757
MS in BVM (≤5 vs. >5)	0.9913	0.4369-2.249	0.9834
MS ≤5 (BMO vs. BVM)	0.1856	0.0635-0.5425	0.0021
MS >5 (BMO vs. BVM)	0.5912	0.2860-1.222	0.1561

Abbreviations: CI, confidence interval; IMM , initial metastasis mode; BMO, bone metastasis only; BVM, bone plus accompanying visceral metastasis; NBM, number of sites of bone metastases; MM, medication mode; MMT, multimodal therapy; SMT, single mode therapy; MS, metastatic sites.

mors, and it has the ability to promote lymph node metastasis. The Ki-67 proliferation index level is closely related to tumor differentiation, invasion, metastasis and prognosis [19, 20]. These findings are in accordance with the reports analyzing the impact of the Ki-67 index on OS in patients with IDBCBM.

Related studies have shown that HR-positive patients were more likely to have bone metastasis [21, 22]. In patients with HR (-)/HER-2 (+) and HR (-)/HER-2 (-), visceral metastasis, including liver and lung metastasis, was more common [23-25]. Many researchers have been using the Surveillance, Epidemiology, and End Results (SEER) database to identify and analyze first-stage patients with stage IV breast cancer. Leone BA et al. [26] considered that the different initial sites of metastasis had a significant effect on the subtypes of breast cancer. Yue Gong et al. [27] found that the HER-2 (-)/HR (+) status was associated with more bone metastases, and the HER-2 (+)/HR (-) status was associated with a higher incidence of liver metastasis. Women with HER-2 (-)/HR (-) status were more likely to have brain and lung metastases. Multivariate analysis showed that there was a significant interaction between single metastasis and molecular subtype. San-Gang Wu et al. [28] reached the same conclusion. This study demonstrates that there were differences in molecular subtypes between the patients with BMO and BVM. The proportion of luminal B type was similar between the two groups. There was a significant difference in luminal A type between HER-2 overexpressing and triple negative cases. The statistical results showed that there was a significant difference between the two groups in regard to molecular subtype, HR status and HER-2 expression (all P<0.05, **Table 1**). The BMO group was more likely to be HR positive and HER-2 negative. The molecular subtype is one of the important prognostic factors among many factors affecting the clinical outcomes of metastatic breast cancer [29]. This study found that patients with BMO had a better prognosis than those with BVM, and BMO was associated with different breast cancer molecular subtypes.

Although bone metastases generally do not directly threaten a patient's life, bone metasta-

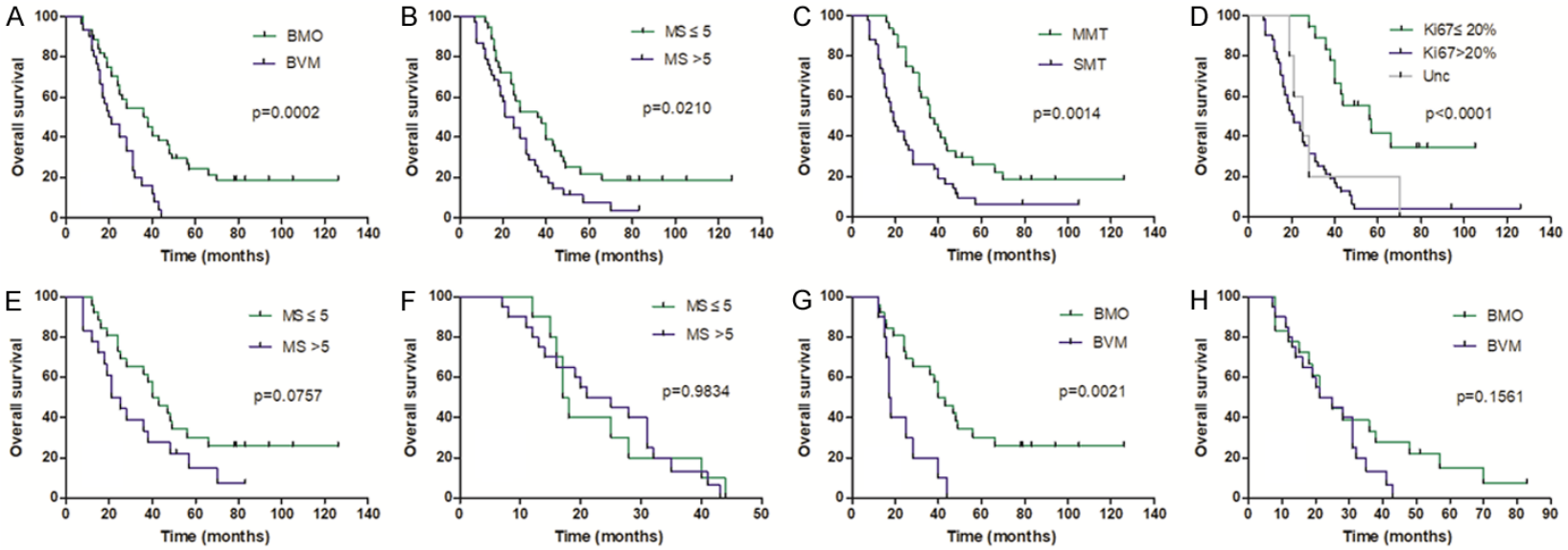

Figure 1. Survival curves of 74 patients with initially diagnosed stage IV breast cancer bone metastasis according to different related factors. A. BMO vs. BVM; B. NBM ≤5 vs. >5; C. MMT vs. SMT; D. Ki-67 index ≤20% vs. >20%; E. MS ≤5 vs. >5 in patients with BMO; F. MS ≤5 vs. >5 in patients with BVM; G. BMO vs. BVM in patients with MS ≤5; H. BMO vs. BVM in patients with MS >5.

Table 6. Loco-regional treatment of primary tumor for overall survival in 74 patients with initially diagnosed stage IV breast cancer bone metastasis

Characteristics	Hazard Ratio	95% CI	*P*-value
Surgery of primary tumor (yes vs. no)	1.639	0.975-2.755	0.0622
Loco-regional treatment (ST+RT vs. no)	1.935	1.092-3.427	0.0237

Abbreviations: CI, confidence interval; ST, surgical treatment; RT, radiotherapy.

sis of breast cancer is a systemic and incurable disease, and its treatment should aim to improve the quality of life and prolong the survival of patients. Chemotherapy, endocrine and anti-HER-2-targeted therapies are the basic treatments for metastatic breast cancer, and bisphosphonates and denosumab can reduce the risk of skeletal-related events (SRE) after bone metastases. SRE are generally defined as pathological fractures, spinal cord compression, radiotherapy or surgery due to bone metastases, and hypercalcemia [30]. In particular, bisphosphonate drugs have been widely used to treat bone metastases of malignant tumors and reduce the occurrence of SRE. On this basis, combined with pain medications and local radiotherapy, bisphosphonates can significantly improve the quality of life of patients. The survival rate of patients with stage IV breast cancer at initial diagnosis has been improved with new therapies, such as endocrine therapy and the widespread use of monoclonal antibodies [31, 32]. The vast majority of patients in our study received both chemotherapy and bisphosphonate treatment. The differences in endocrine therapy and targeted therapy between patients with BMO and those with BVM group were statistically significant (all P<0.05, **Table 1**), suggesting that endocrine therapy was suitable for the BMO group and that targeted therapy was more utilized in the BVM group. There was no significant difference in MM between the two groups. However, MM was an independent prognostic factor that affected the patient's OS (P=0.001). Patients with MMT had a better prognosis than those with SMT.

Traditionally, systemic treatment, including endocrine therapy, chemotherapy, radiotherapy, targeted therapy, and bisphosphonate treatment, is the primary treatment for patients with IDBCBM. Local treatments, such as surgical removal of primary tumors, are only used to control pain or bleeding. For patients with metastatic breast cancer requiring symptomatic relief or with impending complications, primary tumor surgery should be performed. In addition, this procedure should be performed only if the tumor can be completely removed and there are no life-threatening conditions at other disease sites. However, there is still controversy over the surgical treatment of primary tumors in patients with stage IV breast cancer. Two recent studies have shown that resection of primary tumors results in a survival benefit with a total mortality of 0.65 [33, 34]. Several retrospective studies have also shown that local treatment, including surgery and/or radiation therapy, can improve the survival rate of patients with stage IV breast cancer [35-37]. The findings reported here are in accordance with these reports that analyzed the impact of loco-regional treatment on survival.

In the univariate analysis, patients with IDBCBM who had the primary tumor surgically removed showed significantly improved OS, which is consistent with the results of other studies [34, 38-40]. However, in our multivariate model, no effect of local surgery was observed. Furthermore, some studies did not produce results demonstrating the beneficial effects of surgery, suggesting that the proposed benefits of surgery might be associated with a patient selection bias [41, 42]. In addition, the benefit of local surgery in patients with stage IV breast cancer was not supported by results of a prospective randomized controlled trial conducted in India with 350 patients [43]. The study indicated that there was no evidence that local treatment of primary tumors (including surgery and postoperative adjuvant radiotherapy) affected OS [43]. Nevertheless, in the present study, 62.2% of patients with IDBCBM underwent loco-regional treatment, including surgery and radiotherapy of the primary tumor. Patients with loco-regional treatment were found to have experienced longer OS than those without loco-regional treatment. No differences were found in the patient characteristics between the loco-regional treatment and non-loco-regional treatment groups. The survival benefits in our study might be associated with surgery combined with radiotherapy of the primary tumor.

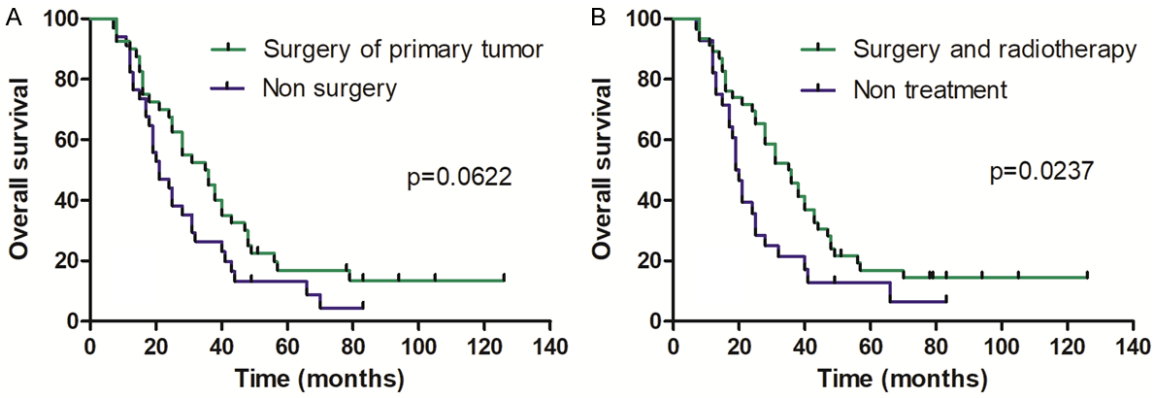

Figure 2. Comparison of survival curves for patients with vs. without surgery of primary tumor (A) and loco-regional treatment vs. non treatment (B). loco-regional treatment includes surgery and radiotherapy of primary tumor. Abbreviations: BMO, bone metastasis only; BVM, bone plus accompanying visceral metastasis; NBM, number of sites of bone metastases; MMT, multimodal therapy; SMT, single mode therapy; MS, metastatic sites; Unc, unknown.

There are a few limitations of our present study. First, the present study is a retrospective analysis and lacks systematic prospective data acquisition; therefore, in part, the completeness of data is limited. This may affect the analysis of clinicopathological features and clinical outcomes. Second, the heterogeneity of data selection based on a single center, especially considering the small sample size, does not exclude a selection bias. This may cause deviations in the analysis. Nevertheless, the work provides important information pertaining to IDBCBM. Although the clinicopathological parameters, risk factors, clinical outcomes, and prognoses of IDBCBM may differ in large sample prospective or retrospective studies in the future, these results provide useful insights into the disease and trends in the current treatment landscape.

In conclusion, the median age of the patients with IDBCBM was 53.3 years, and the median OS was 34.3 months in this study. Shorter survival was observed in patients with Ki-67 >20%, MS >5, SMT, or BVM, and the aforementioned four factors, including Ki-67 index, NBM, IMM and MM, were independent prognostic factors for OS in patients with IDBCBM. Although both loco-regional treatment and primary surgery were not independent prognostic factors in the multivariate analysis, loco-regional treatment appeared to result in a survival benefit in patients with IDBCBM. Further randomized clinical trials are necessary to confirm the clinicopathological factors that are associated with IDBCBM, and new therapies could be investigated to improve the clinical outcomes of this disease.

Acknowledgements

We would like to acknowledge the Department of Surgical Oncology at Cangzhou Clinical College of Integrated Traditional Chinese and Western Medicine of Hebei Medical University. Informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Disclosure of conflict of interest

None.

Abbreviations

IDBCBM, initially diagnosed with stage IV breast cancer bone metastasis; OS, overall survival; HR, hormone receptor; HER-2, human epidermal growth factor receptor-2; ER, estrogen Receptor; PR, progesterone Receptor; ST, surgical treatment; RT, radiotherapy; Unc, unknown; VS., versus; MS, metastatic sites (including extraosseous metastatic sites); BMO, bone metastasis only; BVM, bone plus accompanying visceral metastasis; NBM, number of sites of bone metastases; IMM, initial metastasis mode; MM, medication mode; SMT, single mode therapy; MMT, multimodal therapy; CI, confidence interval.

Address correspondence to: Hong Liu, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin 300060, China. E-mail: lh713@163.com

References

[1] Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ and He J. Cancer statistics in China, 2015. CA Cancer J Clin 2016; 66: 115-132.

[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017; 67: 7-30.

[3] National comprehensive cancer network (NCCN): clinical practice guidelines in oncology. Breast Cancer. 2016; version 1. 2016. J Natl Compr Canc Netw 2015; 13: 1475-1485.

[4] Li S, Zhao J, Zhu L, Su F and Chen K. Development and validation of a nomogram predicting the overall survival of stage IV breast cancer patients. Cancer Med 2017; 6: 2586-2594.

[5] Body JJ, Quinn G, Talbot S, Booth E, Demonty G, Taylor A and 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.

[6] von Moos R, Body JJ, Rider A, de Courcy J, Bhowmik D, Gatta F, Hechmati G and Qian Y. Bone-targeted agent treatment patterns and the impact of bone metastases on patients with advanced breast cancer in real-world practice in six European countries. J Bone Oncol 2017; 11: 1-9.

[7] Shen T, Siegal GP and Wei S. Clinicopathologic factors associated with de novo metastatic breast cancer. Pathol Res Pract 2016; 212: 1167-1173.

[8] Hernandez RK, Wade SW, Reich A, Pirolli M, Liede A and Lyman GH. Incidence of bone metastases in patients with solid tumors: analysis of oncology electronic medical records in the United States. BMC Cancer 2018; 18: 44.

[9] Cetin K, Christiansen CF, Sværke C, Jacobsen JB and Sørensen HT. Survival in patients with breast cancer with bone metastasis: a Danish population-based cohort study on the prognostic impact of initial stage of disease at breast cancer diagnosis and length of the bone metastasis-free interval. BMJ Open 2015; 5: e007702.

[10] Cardoso F, Spence D, Mertz S, Corneliussen-James D, Sabelko K, Gralow J, Cardoso MJ, Peccatori F, Paonessa D, Benares A, Sakurai N, Beishon M, Barker SJ and Mayer M. Global analysis of advanced/metastatic breast cancer: decade report (2005-2015). Breast 2018; 39: 131-138.

[11] Cardoso F, Costa A, Senkus E, Aapro M, André F, Barrios CH, Bergh J, Bhattacharyya G, Biganzoli L, Cardoso MJ, Carey L, Corneliussen-James D, Curigliano G, Dieras V, El Saghir N, Eniu A, Fallowfield L, Fenech D, Francis P, Gelmon K, Gennari A, Harbeck N, Hudis C, Kaufman B, Krop I, Mayer M, Meijer H, Mertz S, Ohno S, Pagani O, Papadopoulos E, Peccatori F, Penault-Llorca F, Piccart MJ, Pierga JY, Rugo H, Shockney L, Sledge G, Swain S, Thomssen C, Tutt A, Vorobiof D, Xu B, Norton L and Winer E 3rd. ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 3). Ann Oncol 2017; 28: 3111.

[12] Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, Elias AD, Farrar WB, Forero A, Giordano SH, Goetz MP, Goldstein LJ, Isakoff SJ, Lyons J, Marcom PK, Mayer IA, McCormick B, Moran MS, O'Regan RM, Patel SA, Pierce LJ, Reed EC, Salerno KE, Schwartzberg LS, Sitapati A, Smith KL, Smith ML, Soliman H, Somlo G, Telli ML, Ward JH, Kumar R and Shead DA. Breast cancer, version 4. 2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2018; 16: 310-320.

[13] Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, Senn HJ; Panel members. Personalizing the treatment of women with early breast cancer: highlights of the St gallen international expert consensus on the primary therapy of early breast cancer 2013. Ann Oncol 2013; 24: 2206-2223.

[14] Kondov B, Milenkovikj Z, Kondov G, Petrushevska G, Basheska N, Bogdanovska-Todorovska M, Tolevska N and Ivkovski L. Presentation of the molecular subtypes of breast cancer detected by immunohistochemistry in surgically treated patients. Open Access Maced J Med Sci 2018; 6: 961-967.

[15] Dai X, Li T, Bai Z, Yang Y, Liu X, Zhan J and Shi B. Breast cancer intrinsic subtype classification, clinical use and future trends. Am J Cancer Res 2015; 5: 292929-43.

[16] Bonotto M, Gerratana L, Poletto E, Driol P, Giangreco M, Russo S, Minisini AM, Andreetta C, Mansutti M, Pisa FE, Fasola G and Puglisi F. Measures of outcome in metastatic breast cancer: insights from a real-world scenario. Oncologist 2014; 19: 608-615.

[17] Ording AG, Heide-Jørgensen U, Christiansen CF, Nørgaard M, Acquavella J and Sørensen HT. Site of metastasis and breast cancer mortality: a Danish nationwide registry-based cohort study. Clin Exp Metastasis 2017; 34: 93-101.

[18] Gerratana L, Fanotto V, Bonotto M, Bolzonello S, Minisini AM, Fasola G and Puglisi F. Pattern of metastasis and outcome in patients with breast cancer. Clin Exp Metastasis 2015; 32: 125-133.

[19] Liu M, Lawson G, Delos M, Jamart J, Ide C, Coche E, Weynand B, Desuter G, Hamoir M, Remacle M and Marbaix E. Predictive value of the fraction of cancer cells immunolabeled for proliferating cell nuclear antigen or Ki67 in biopsies of head and neck carcinomas to identify lymph node metastasis: comparison with clinical and radiologic examinations. Head Neck 2003; 25: 280-288.

[20] Tut VM, Braithwaite KL, Angus B, Neal DE, Lunec J and Mellon JK. Cyclin D1 expression in transitional cell carcinoma of the bladder: correlation with p53, waf1, pRb and Ki67. Br J Cancer 2001; 84: 270-275.
[21] Soni A, Ren Z, Hameed O, Chanda D, Morgan CJ, Siegal GP and Wei S. Breast cancer subtypes predispose the site of distant metastases. Am J Clin Pathol 2015; 143: 471-478.
[22] Smid M, Wang Y, Zhang Y, Sieuwerts AM, Yu J, Klijn JG, Foekens JA and Martens JW. Subtypes of breast cancer show preferential site of relapse. Cancer Res 2008; 68: 3108-3114.
[23] Kennecke H, Yerushalmi R, Woods R, Cheang MC, Voduc D, Speers CH, Nielsen TO and Gelmon K. Metastatic behavior of breast cancer subtypes. J Clin Oncol 2010; 28: 3271-3277.
[24] Kast K, Link T, Friedrich K, Petzold A, Niedostatek A, Schoffer O, Werner C, Klug SJ, Werner A, Gatzweiler A, Richter B, Baretton G and Wimberger P. Impact of breast cancer subtypes and patterns of metastasis on outcome. Breast Cancer Res Treat 2015; 150: 621-629.
[25] Vona-Davis L, Rose DP, Gadiyaram V, Ducatman B, Hobbs G, Hazard H, Kurian S and Abraham J. Breast cancer pathology, receptor status, and patterns of metastasis in a rural appalachian population. J Cancer Epidemiol 2014; 2014: 170634.
[26] Leone BA, Vallejo CT, Romero AO, Machiavelli MR, Pérez JE, Leone J and Leone JP. Prognostic impact of metastatic pattern in stage IV breast cancer at initial diagnosis. Breast Cancer Res Treat 2017; 161: 537-548.
[27] Gong Y, Liu YR, Ji P, Hu X and Shao ZM. Impact of molecular subtypes on metastatic breast cancer patients: a SEER population-based study. Sci Rep 2017; 7: 45411.
[28] Wu SG, Li H, Tang LY, Sun JY, Zhang WW, Li FY, Chen YX and He ZY. The effect of distant metastases sites on survival in de novo stage-IV breast cancer: a SEER database analysis. Tumour Biol 2017; 39: 1010428317705082.
[29] Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, Deming SL, Geradts J, Cheang MC, Nielsen TO, Moorman PG, Earp HS and Millikan RC. Race, breast cancer subtypes, and survival in the carolina breast cancer study. JAMA 2006; 295: 2492-2502.
[30] Ibrahim T, Mercatali L and Amadori D. A new emergency in oncology: bone metastases in breast cancer patients (review). Oncol Lett 2013; 6: 306-310.
[31] Dawood S, Broglio K, Ensor J, Hortobagyi GN and Giordano SH. Survival differences among women with de novo stage IV and relapsed breast cancer. Ann Oncol 2010; 21: 2169-2174.
[32] de Glas NA, Bastiaannet E, de Craen AJ, van de Velde CJ, Siesling S, Liefers GJ and Portielje JE. Survival of older patients with metastasised breast cancer lags behind despite evolving treatment strategies-a population-based study. Eur J Cancer 2015; 51: 310-316.
[33] Ruiterkamp J and Ernst MF. The role of surgery in metastatic breast cancer. Eur J Cancer 2011; 47 Suppl 3: S6-22.
[34] Petrelli F and Barni S. Surgery of primary tumors in stage IV breast cancer: an updated meta-analysis of published studies with meta-regression. Med Oncol 2012; 29: 3282-3290.
[35] Mauro GP, de Andrade Carvalho H, Stuart SR, Mano MS and Marta GN. Effects of loco-regional radiotherapy in patients with metastatic breast cancer. Breast 2016; 28: 73-78.
[36] Warschkow R, Güller U, Tarantino I, Cerny T, Schmied BM, Thuerlimann B and Joerger M. Improved survival after primary tumor surgery in metastatic breast cancer: a propensity-adjusted, population-based SEER trend analysis. Ann Surg 2016; 263: 1188-1198.
[37] Thomas A, Khan SA, Chrischilles EA and Schroeder MC. Initial surgery and survival in stage IV breast cancer in the United States, 1988-2011. JAMA Surg 2016; 151: 424-431.
[38] Wu SG, Li FY, Chen Y, Sun JY, Lin HX, Lin Q and He ZY. Therapeutic role of axillary lymph node dissection in patients with stage IV breast cancer: a population-based analysis. J Cancer Res Clin Oncol 2017; 143: 467-474.
[39] Kolben T, Kolben TM, Himsl I, Degenhardt T, Engel J, Wuerstlein R, Mahner S, Harbeck N and Kahlert S. Local resection of primary tumor in upfront stage IV breast cancer. Breast Care (Basel) 2016; 11: 411-417.
[40] Ruiterkamp J, Voogd AC, Bosscha K, Tjan-Heijnen VC and Ernst MF. Impact of breast surgery on survival in patients with distant metastases at initial presentation: a systematic review of the literature. Breast Cancer Res Treat 2010; 120: 9-16.
[41] Cady B, Nathan NR, Michaelson JS, Golshan M and Smith BL. Matched pair analyses of stage IV breast cancer with or without resection of primary breast site. Ann Surg Oncol 2008; 15: 3384-3395.
[42] Leung AM, Vu HN, Nguyen KA, Thacker LR and Bear HD. Effects of surgical excision on survival of patients with stage IV breast cancer. J Surg Res 2010; 161: 83-88.
[43] Badwe R, Hawaldar R, Nair N, Kaushik R, Parmar V, Siddique S, Budrukkar A, Mittra I and Gupta S. Loco-regional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. Lancet Oncol 2015; 16: 1380-1388.