Clinicopathologic features of single bone metastasis in breast cancer

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Abstract

The most common site for metastasis in patients with breast cancer is the bone. In this case series, we investigated patients whose surgical and medical treatment for primary breast cancer was conducted at our center and first disease recurrence was limited to only 1 bone.

We analyzed 910 breast cancer patients, 863 had no metastasis and 47 cases had a single bone metastasis ≥ 6 months after their first diagnosis. Demographic, epidemiological, histopathological and intrinsic tumor subtype differences between the non-metastatic group and the group with solitary bone metastases and their statistical significance were examined. Among established breast cancer risk factors, we studied twenty-nine variables.

Three variables (Type of tumor surgery, TNM Stage III tumors and mixed type (invasive ductalcarcinoma + invasive lobular carcinoma) histology) were significant in multivariate logistic regression analysis. Accordingly, the risk of developing single bone metastasis was approximately 15 times higher in patients who underwent mastectomy and 4.8 and 2.8 times higher in those with TNM Stage III tumors and with mixed type (invasive ductal carcinoma + invasive lobular carcinoma) histology, respectively.

In conclusion, the risk of developing single bone metastasis is likely in non-metastatic patients with Stage III tumors and possibly in mixed type tumors. Knowing this risk, especially in patients with mixed type tumors, may be instrumental in taking measures with different adjuvant therapies in future studies. Among these, treatment modalities such as prolonged hormone therapy and addition of bisphosphonates to the adjuvant treatments of stage III and mixed breast cancer patients may be considered.

Abbreviations: ILC = invasive lobular carcinoma, SBM = single bone metastasis.

Keywords: Breast cancer, isolated bone metastasis, metastatic disease

1. Introduction

The most common site for metastasis in patients with breast cancer is the bone.[1,2] In addition, it is the first site of distant metastasis in 25% to 40% of patients with advanced breast cancer.[3] Compared to cases with other solid organ metastases, patients with bone metastases have a considerably better outcome, with an average of 2 to 5 years of overall survival after diagnosis.[4,5] Following the destruction of bone tissue via breast cancer cells, growth factors secreted by osteoblasts and osteoclasts in this region result in the proliferation of tumor cells and dissemination to other regions.[6] In some breast cancer cases, bone-only metastasis occurs in a single bone. In these patients, the implementation of appropriate treatment can prevent subsequent development of metastases at skeletal or extraosseous sites and provides an extended survival.[7]

In this case series, we investigated patients whose surgical and medical treatment for primary breast cancer was conducted at our center and whose first disease recurrence was limited to only 1 bone regardless of location. In an autopsy study, the correlation between the extent of disease and the dominant metastatic involvement site in breast cancer cases was investigated and it was found that the prevalence of extensive disease was least common in metastases affecting the bone.[8] Thus, the high frequency of bone only metastasis in breast cancer women and the lack of coexistence with extensive disease, may suggest that transition from non-metastatic phase to bone-only metastasis can be a sequential process. For this reason, we aimed to identify the differences between this group and a group of patients with no metastases, during the same period, with regard to demographics,

family history, tumor histopathology and biology, and intrinsic tumor subtype. Thus, we planned to determine factors effective in predicting isolated and single bone metastases (SBM) along with their predictive strength, before the breast cancer has metastasized to remote solid organs.

2. Materials & methods

Female patients, diagnosed with a first invasive breast cancer, and operated on between July 1982 and September 2018 at the University of Health Sciences, Izmir Bozyaka Education and Research Hospital were considered for the study. There were 1480 cases in our series, of which 932 had no metastasis and formed the comparison group of this study. In total, 94 cases had SBM in our series, of which 24 already had the isolated bone metastasis at the time of diagnosis and 7 were diagnosed with SBM 1–3 months following breast cancer diagnosis. The last 2 groups were excluded and the remaining 63 patients with SBM developed ≥6 months after breast cancer diagnosis were included in our study. Besides, 454 patients with multiple bone or other solid organ metastases with or without bone, or missing regular follow-up data were excluded from the study. In order to create a homogeneous patient pool where more up-to-date approaches are applied in terms of diagnosis and treatment, we also excluded 85 patients from the 1980s and 1990s (Table 1). Thus, statistical data were obtained from a total of 910 patients which comprised those with SBM (Group I) and those without metastasis (Group II). SBM refers to metastasis detected in a single bone limited to only 1 anatomical site. In almost all cases of bone metastasis, diagnosis was made by bone scintigraphy. Any suspected cases were confirmed using magnetic resonance imaging and positron emission tomography-computed tomography.(Bone scintigraphy and radiography were used as diagnostic modalities for bone metastasis in elderly patients.)Bone biopsy was performed only for the purpose of determining the treatment protocol in cases with stable disease or progression after first-line treatment.

Demographic, epidemiological, histopathological and intrinsic tumor subtype differences between the non-metastatic group and the group with solitary bone metastases and their statistical significance were examined.

Among established breast cancer risk factors, we studied twenty-nine variables. These variables were examined in 3 groups and shown in 3 separate tables.

'History of hormone use' denotes administration of oral contraceptive drugs in premenopausal patients and estrogen or estrogen-progesterone combinations in pre- and postmenopausal cases. 'Hormone replacement therapy' refers to the regular hormone treatment taken at postmenopausal period.

'Co-morbidity' in patients consisted of hypertensive atherosclerotic heart disease, chronic obstructive pulmonary disease, congestive heart failure, cerebrovascular disease and autoimmune diseases.

The intrinsic (molecular) subtypes of breast cancer are defined as follows:

Luminal A: Hormone-receptor positive (HR+ / estrogen-receptor and/or progesterone-receptor positive), HER2 negative, has low levels of Ki-67 (<15%) and nuclear grade is low (Grade I).

Luminal B: HR+ and either HER2 positive or HER2 negative with high levels of Ki-67 (>14%). Nuclear grade is moderate or high (Grade II-III).

Triple-negative/basal-like: HR negative and HER2 negative. Nuclear grade is moderate or high (Grade II-III).

HER2-enriched: HR negative and HER2 positive. Nuclear grade is high (Grade-III).

The primary endpoint of this study was to determine different variables and their effectiveness on the development of SBM. Our secondary endpoint is to suggest whether or not any modification of treatment-related variables can be made, and to suggest new treatment regimen hypotheses that may interfere with the transition from non-metastatic phase to SBM.

3. Statistical analysis

In univariate analyses, Group I (n=47) and Group II (n=863) were compared using chi-square test for categorical variables and student t-test for continuous variables. Multivariate analyses were conducted with logistic regression using the outcome variables to explore possible predictors of isolated bone metastasis. The variables that were found significant in univariate analyses were added to initial multivariate models. The variables that lost their significance in the multivariate model were then removed from the model to form a final multivariate model covering only the variables that were found significant in multivariate analysis. Odds ratios (OR) and 95% confidence intervals were calculated for each possible predictor and adjusted for the other variables in the model. Survival over time was estimated and survival curves were drawn according to Kaplan-Meier analysis.

4. Results

The distribution of patients according to different decades is shown in Table 1. The mean and median times to onset of SBM after surgery were 44.5 and 23 months, respectively. Among the demographic variables, there were no statistically significant differences between Group I and Group II (Table 2). On the other hand, analysis of factors related to treatment shows the incidence of single bone metastasis to be significantly higher in patients who underwent mastectomy because of high cancer stage at admission and who did not receive hormone therapy and radiotherapy during the treatment period (Table 3).

SBM developed in 8.1% (45/555) of patients who underwent mastectomy compared to only 0.6% (2/343) of those who received breast conserving surgery. Surgery was not performed in 4 patients in Group II. Of these; 2 patients refused surgical intervention. The 79-year-old patient with Alzheimer disease and congestive cardiomyopathy was not operated and she died of cardiac reason after 2 years of follow-up. The last patient had a biopsy diagnosis of lymphoepithelioma-like carcinoma of the breast. Unexpectedly, she had a rapidly progressive course and deceased during neoadjuvant chemotherapy sessions.

Table 1

Distribution of patients according to different decades.

Diagnosis Date	Without metastasis No (%)	Single Bone Metastasis No (%)	Total No (%)
1980s	7 (0,8)	1 (1,6)	8 (0,8)
1990s	62 (6,7)	15 (23,8)	77 (7,7)
2000s	863 (92,6)	47 (74,6)	910 (91,4)
Total	932 (100)	63 (100)	995 (100)

Table 2

Correlation between demography and single bone metastasis.

Demographics and History	Group I (mean ± SD) N (%)	Group II (mean ± SD) N (%)	P
Age	53.5 ± 12.3	55.1 ± 13.4	.64
	47	862	
BMI	29.2 ± 5.8	28.5 ± 5.2	
<25	5 (17.2)	142 (26.6)	.36
5–29.9	15 (51.7)	210 (39.3)	
≥30	9 (31.0)	182 (34.1)	
Smoker	8 (23.5)	210 (32.8)	
Non-Smoker	26 (76.5)	431 (67.2)	.26
Pre-Menopause	18 (42.9)	306 (38.3)	
Post-menopause	24 (57.1)	492 (61.7)	.56
Hormone use			
Never use	20 (76.9)	364 (61.3)	.21
OCC	6 (23.1)	200 (33.7)	
HRT	0 (0.0)	30 (5.0)	
HRT			
Yes	14 (41.2)	314 (46.2)	.55
No	20 (58.8)	366 (53.8)	
Diabetics	2 (5.4)	105 (14.5)	.12
Non-Diabetics	35 (94.6)	621 (85.5)	
CO-Morbidities	4 (44.4)	203 (53.7)	.81
Without Co-Morbidities	5 (55.6)	175 (46.3)	
Family History			
(+)	7 (20.0)	163 (23.2)	.66
(−)	28 (80.0)	541 (76.8)	

BMI = body mass index, HRT = hormone replacement therapy.

Table 3

Treatment associated factors and development of single bone metastasis.

Treatment-Associated Factors	Group I N (%)	Group II N (%)	P
Neoadjuvant Treatment			
Yes	5 (10.9)	81 (9.5)	0.46
No	41 (89.1)	769 (90.5)	
Adjuvant Chemotherapy			
No	3 (7.0)	171 (25.2)	
With Anthracyclines	31 (72.1)	395 (58.2)	0.058
With Taxanes	2 (4.7)	20 (2.9)	
With Taxane + Anthracyclines	7 (16.3)	93 (13.7)	
Type Of Surgery			
No Surgery	0 (0.0)	4 (0.5)	
Mastectomy	45 (95.7)	510 (59.6)	<0.0001
Breast Conserving Surgery	2 (4.3)	341 (39.9)	
Axillary Treatment:			
No Surgery	1 (2.1)	12 (1.4)	
Axillary Dissection	40 (85.1)	444 (52.0)	<0.0001
SLNB	2 (4.3)	265 (31.0)	
SLNB+ AD	4 (8.5)	133 (15.6)	
Radiotherapy:			
No	10 (22.7)	200 (25.6)	0.41
Yes	34 (77.3)	581 (74.4)	
Adjuvant Hormonotherapy:			
No	11 (27.5)	152 (22.2)	0.21
Tamoxifen	15 (37.5)	195 (28.5)	
Aromatase inhibitors	14 (35.0)	338 (49.3)	
Tumor Location			
Right	25 (53.2)	414 (48.1)	0.71
Left	19 (40.4)	401 (46.6)	
Bilateral	3 (6.4)	46 (5.3)	

AD = Axillary Dissection, SLNB = Sentinel Lymph Node Biopsy.

Table 4

Tumor histopathology and biology associated factors and development of single bone metastasis.

Tumor histopathology and biology associated factors	Group I N (%)	Group II N (%)	P
Estrogen Receptor	25	498	
	56.6 ± 27.7	62.5 ± 29.6	.58
Progesteron Receptor	25 56.2 ± 28.7	487 55.2 ± 30.0	.57
p53	10	372	
	54.0 ± 21.8	32.8 ± 28.9	.15
Ki67			
<%14	12 (41.4)	407 (61.2)	
>%14	17 (58.6)	258 (38.8)	.027
HISTOLOGY			
Invasive carcinoma (NOS)	30 (63.8)	631 (75.5)	
Invasive lobular carcinoma	5 (10.6)	67 (8.0)	<.0001
Mixed type (ILC+IDC)	11 (23.4)	48 (5.7)	
Inflammatory&Metaplasic&Inv. Micropapillary	0 (0.0)	21 (2.5)	
Others	1 (2.1)	69 (8.3)	
Nuclear Grade			
1	1 (4.8)	34 (6.6)	
2	13 (61.9)	357 (69.3)	.61
3	7 (33.3)	124 (24.1)	
Mitotic Index			
1	7 (35.0)	133 (26.8)	
2	11 (55.0)	307 (61.9)	.72
3	2 (10.0)	56 (11.3)	
TNM Stage			
1	4 (10.0)	204 (26.8)	
2	9 (22.5)	374 (49.2)	<.0001
3	26 (65.0)	181 (23.8)	
4	1 (2.5)	1 (0.1)	
T			
T1	8 (20.0)	314 (40.6)	
T2	18 (45.0)	398 (51.5)	<.0001
T3	6 (15.0)	35 (4.5)	
T4	8 (20.0)	26 (3.4)	
N			
N0	6 (13.6)	392 (48.5)	
N1	11 (25.0)	252 (31.1)	<.0001
N2	9 (20.5)	105 (13.0)	
N3	18 (40.9)	60 (7.4)	
Molecular Subtype			
Luminal A	14 (31.1)	289 (37.0)	
Luminal B	20 (44.4)	325 (41.6)	.88
HER 2 enriched	4 (8.9)	58 (7.4)	
Basal Like	7 (15.6)	110 (14.1)	
Lymphoid vessel invasion			
YES	14 (48.3)	145 (25.0)	.007
N0	15 (52.7)	436 (75.0)	
Blood vessel invasion			
YES	6 (20.7)	101 (17.4)	.40
N0	23 (79.3)	480 (82.6)	

Group I: Solitary bone metastasis after 6 months.
Group II: Breast Cancer patients who did not develop bone metastasis.
IDC = Invasive ductal carcinoma, ILC = Invasive lobular carcinoma, Inv = Invasive, NOS = Not otherwise specified, Pts = Patients.

SBM was observed in 5,2% vs 7,7%of cases with and without surgical intervention in the axilla, respectively. In addition, the frequency of single bone metastases was 5,5% in patients who received radiotherapy and hormone therapy during the treatment and 13,1% in those who did not.

Among the tumor related factors, a significant relationship was found between Group I and the histological group, percentage of

Table 5

Multivariate analysis of predictors of isolated bone metastasis (n=861, Nagelkerke R^2=0.351).

Variable	Categories	β	OR [Exp(B)] (95% CI)	P
Breast surgery	Breast conserving surgery		1 (ref.)	
	Mastectomy	2.70	14.88 (2.97–74.5)	.001
TNM	1		1 (ref.)	
	2	−0.02	0.97 (0.30–3.17)	.969
	3	1.56	4.77 (1.62–14.09)	.005
	4	6.21	496.95 (35.05–7046.02)	<.001
Histologic type	Invasive breast carcinoma, NOS		1 (ref.)	
	Invasive lobular carcinoma	0.28	1.32 (0.48–3.65)	.592
	Mixed type	1.02	2.76 (1.27–6.01)	.01
	Inflammatory/ metaplastic/ invasive micropapillary	−2.06	0.13 (0.006–2.76)	.189
	Other	−1.17	0.31 (0.04–2.37)	.259

NOS=not otherwise specified.

p53, tumor, lymph node and TNM stage and lymph and blood vessel invasion. In conclusion, we found a significant relationship between the treatment modalities, T-N & TNM stage and histology of the primary tumor and the development of SBM. There was a direct correlation between high T-N-TNM stage, presence of lymphoid and vascular invasion and SBM. The frequency of SBM was similar in early stage (Stage I & II) breast cancer patients but significantly higher in patients with Stage III tumors. Surprisingly, SBM developed more frequently in patients with invasive ductal, invasive lobular or mixed type tumors and was uncommon in histological groups with poor molecular subtypes (Table 4).

Of the patients with isolated bone metastasis, the anatomical sites were as follows: Vertebra=28 (lumbar vertebra: 10, Thoracic vertebra: 15, Cervical vertebra: 1, Sacrum: 2), rib=11, humerus= 3, femur=1, Sternum=2, Scapula=1, Clavicle=1.

In our study, eleven variables were directly related to the development of SBM in univariate analysis. Those found significant were entered into multivariate analyses with logistic regression to explore possible predictors of isolated bone metastasis (Table 5). Three variables (Type of tumor surgery,

TNM Stage III tumors and mixed type (invasive ductal carsinoma + invasive lobular carcinoma [ILC]) histology) were found to be significant in multivariate logistic regression analysis. Accordingly, the risk of developing single bone metastasis was approximately 15 times higher in patients who received mastectomy compared to those with breast conserving surgery and 4.8 and 2.8 times higher in those with TNM Stage III tumors and with mixed type (invasive ductal carsinoma + ILC) histology, respectively.

The mean and median overall survival values for Group II were 29.0±1.3 and 32.0±7.8 years and for Group I, 9.9±1.1 and 7.0±0.7 years, respectively (P<.001) (Fig. 1).

5. Discussion

In our large series of 910 patients, breast cancer patients who developed SBM after treatment were compared to patients with no metastasis. In the multivariate logistic regression analysis, the risk of developing SBM was considerably higher in patients who received mastectomy, had Stage III and mixed type tumors. Unfortunately, this means that factors with the greatest predictive value in the transition from a non-metastatic phase to single bone metastasis are not modifiable. However, the most important message that can be derived from our data is that the tumor stage is an independent higher risk factor for developing bone metastases in patients with ILC and especially those with mixed type tumors. In our study, single bone metastasis was 2.8 times more frequently observed in patients with mixed type tumors compared to those with Ductal not otherwise specified or Invasive Lobular Carcinoma. The incidence of SBM development in invasive ductal, lobular, and mixed type cases were 4.5%, 6.9%, and 18,6% respectively.

Bone-only metastasis has a fairly good prognosis when compared to other visceral metastasis.[2,9] In a cohort of women treated for early-stage (stage I, II, or III) breast cancer in Canada; 10 years probability of bone metastasis was 10.3% for the first recurrence and 12.5% for any bone recurrence.[10] The median survival of breast cancer patients after detection of bone metastases is 24 to 65 months.[2,4,11] However, in our study, the median survival of patients in Group I is 7 years. This can be attributed to the fact that all cases have single bone metastasis and that almost all of them were treated with current and effective methods. In addition, this result is consistent with 7.5 years of median overall survival from the largest published patient group with bone only metastasis.[12]
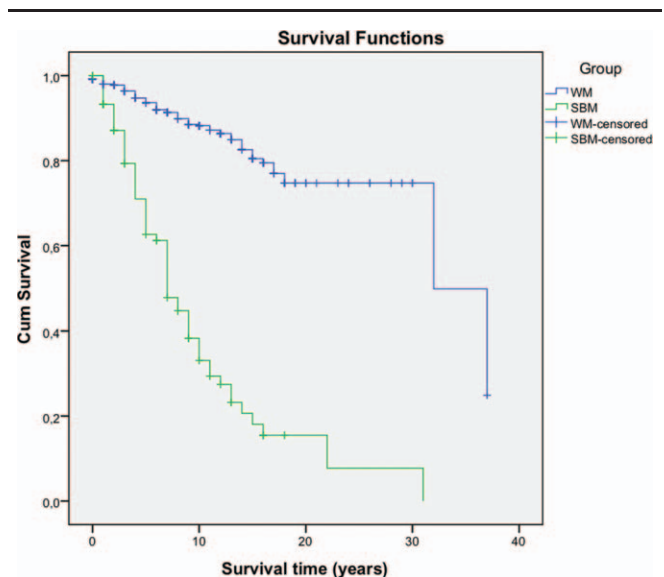

Figure 1. Survival analysis of study groups.

In many studies, the relationship between demographic and clinical parameters and bone metastasis has been investigated. However, the results were either irrelevant or conflicting between factors such as age, menopausal status, body mass index and metastasis.[3,10,13] In our previous study, bone metastasis was observed as the most frequent remote organ spread for the 3 histologic subtypes, with a frequency of 14.3% for invasive ductal, 17.9% for invasive lobular, and 25.5% for mixed-typecarcinomas ($P=.107$). With respect to other remote organ metastasis and new onset of different malignancies, we found no difference between these groups.[14] On the other hand, in our current study, the relationship between histological type and SBM was significant, demonstrating patients with ILC and especially mixed-typetumors having a 1.3 and 2.8 times higher risk of developing bone metastases. Although there are many studies in the literature suggesting that ILC causes bone metastasis, the generally accepted opinion is that such a relationship occurs because ILCs are mostly in the Luminal A and B subtypes.[3,14,15]

Some limitations exist in the present study. Most importantly, it is a case series analysis with few exclusions, although the data used were collected very regularly and the percentage of cases followed up was high. Also, no case with missing data was included in the statistical analysis. Current treatments have undoubtedly affected overall survival and disease-free survival outcomes. In our study, patients who belong to 1980 and 1990 era were exposed to the diagnostic and treatment modalities specific to that period. The fact that 85 patients belonging to this period were excluded from the study in order to avoid any errors in the statistics may have weakened the power of our study. Also, in multivariate logistic regression analysis, the inclusion of only 861 patients with complete parameters may have affected the results.

6. Conclusion

In conclusion, the risk of developing isolated bone metastases is likely in non-metastatic patients with Stage III tumors and possibly in mixed-type tumors. Knowing this risk, especially in patients with mixed type tumors, may be instrumental in taking measures with different adjuvant therapies in future studies. Among these, treatment modalities such as prolonged hormone therapy and addition of bisphosphonates to the adjuvant treatments of stage III and mixed breast cancer patients may be considered.

Acknowledgments

Author contributions

B.Z., A.U. and M.K. contributed to the conception of the study. B.Z., M.K., A.U. and C. S. performed the operations, B.Z., M.K. contributed to the recruitment of the patients., F.T. evaluated the pathological specimens. Z.A. evaluated the radiological images. B.Z collected the data. A.U., B.Z. and R.D. analysed and interpreted the data. A.U., B.Z., M.K. and R.D. made a major contribution to the writing and reviewing of the manuscript. B.Z., R.D. reviewed the manuscript. All authors read and approved the final manuscript.

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References

[1] James JJ, Evans AJ, Pinder SE, et al. Bone metastases from breast carcinoma: histopathological - radiological correlations and prognostic features. Br J Cancer 2003;89:660–5.
[2] Pulido C, Vendrell I, Ferreira AR, et al. Bone metastasis risk factors in breast cancer. Ecancermedicalscience 2017;11:715.
[3] Diessner J, Wischnewsky M, Stüber T, et al. Evaluation of clinical parameters influencing the development of bone metastasis in breast cancer. BMC Cancer 2016;16:307.
[4] Ahn SG, Lee HM, Cho SH, et al. Prognostic factors for patients with bone-only metastasis in breast cancer. Yonsei Med J 2013;54:1168–77.
[5] Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer. Br J Cancer 1987;55:61–6.
[6] Pluijm G, Lowik C, Papapoulos S. Tumour progression and angiogenesis in bone metastasis from breast cancer: new approaches to an old problem. Cancer Treat Rev 2000;26:11–27.
[7] Plunkett T, Smith P, Rubens R. Risk of complications from bone metastases in breast cancer: implications for management. Eur J Cancer 2000;36:476–82.
[8] Cummings MC, Simpson PT, Reid LE, et al. Metastaticprogression of breastcancer: insightsfrom 50 years of autopsies. J Pathol 2014;232:23–31.
[9] Parkes A, Clifton K, Al-Awadhi A, et al. Characterization of bone only metastasis patients with respect to tumor subtypes. NPJ Breast Cancer 2018;4:2.
[10] Liede A, Jerzak KJ, Hernandez RK, et al. The incidence of bone metastasis after early-stage breast cancer in Canada. Breast Cancer Res Treat 2016;156:587–95.
[11] Body JJ, Quinn G, Talbot S, et al. 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.
[12] Parkes A, Warneke CL, Clifton K, et al. Prognostic factors in patients with metastatic breast cancer with bone-only metastases. Oncologist 2018;23:1282–8.
[13] Inkampe AK, Bates T. Impact of a raised body mass index on breast cancer survival in relation to age and disease extent in diagnosis. Breast J 2010;16:156–61.
[14] Zengel B, Yararbas U, Duran A, et al. Comparison of the clinicopathological features of invasive ductal, invasive lobular,and mixed(invasive ductal + invasive lobular) carcinoma of the breast. Breast Cancer 2015;22:374–81.
[15] Sastre-Garau X, Jouve M, Asselain B, et al. Infiltrating lobular carcinoma of the breast. Clinicopathologic analysis of 975 cases with reference to data on conservative therapy and metastatic patterns. Cancer 1996;77:113–20.