

Symptomatic Metastases have Poorer Prognosis in Breast Cancer Patients Under Intensive Surveillance

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Abstract

Purpose The purpose of this study was to investigate risk factors for post-metastasis overall survival (PMOS), and to analyze the effect of early detection of distant metastases before symptoms occur on survival in breast cancer patients under intensive surveillance.

Methods A total of 7,840 patients underwent surgery for breast cancer from January 2010 to December 2014 at Samsung Medical Center; of these, we retrospectively studied 316 metastatic breast cancer patients. The patients were divided into two groups based on method of metastases detection, routine surveillance without symptoms (asymptomatic group) or follow-up for new-onset symptoms (symptomatic group).

Results Multivariate analysis of PMOS showed that the patients with multiple metastases had a 1.872 fold risk of PMOS ($p = 0.011$) compared to the patients with bone metastasis only. The hazard ratio for the symptomatic group was higher than that for the asymptomatic group ($p < 0.001$). When patients were stratified by tumor subtype, patients who were HR-positive and asymptomatic on diagnosis of distant metastasis had a better prognosis than those who were HR-positive and symptomatic on diagnosis. However, patients who were HER2-positive showed no significant survival difference between two groups.

Conclusion Breast cancer patients who were diagnosed with distant metastasis after symptoms occurred had a poorer prognosis than patients who were diagnosed before symptoms had developed. It is important to follow up patients regularly for symptoms related to distant metastases. Our findings validate the need for intensive surveillance, suggesting reconsideration of the guidelines for metastases screening in breast cancer patients.

Introduction

The global burden of breast cancer in women is substantial and on the rise in several countries [1, 2]. Although the incidence of breast cancer has steadily increased, the overall survival rate for breast cancer has improved in recent years due to early detection and advances in primary treatment; therefore, the number of breast cancer survivors has been gradually increasing [3]. As the number of breast cancer survivors increases, interest in patient surveillance for distant metastases has increased.

The benefit of intensive surveillance for postoperative metastasis in breast cancer patients before symptoms occur has long been debated because there is no evidence that early detection of distant metastases could improve overall survival of patients. The National Comprehensive Cancer Network (NCCN) guidelines do not recommend routine testing for recurrence or distant metastasis in asymptomatic patients during follow-up for breast cancer and rather recommend that patients should be tested only if they develop symptoms [4]. However, as both diagnostic imaging and treatment of metastatic breast cancer improve, some clinicians have come to believe that intensive surveillance for postoperative metastasis is necessary in breast cancer patients before symptoms occur, and the

prognosis of metastatic breast cancer patients can be better when distant metastasis is detected in an early state as a small tumor.

The purpose of this study was to investigate risk factors for post-metastasis overall survival (PMOS) in breast cancer patients under intensive surveillance, and to ascertain whether early detection of distant metastases before symptom onset confers a prognostic benefit in these patients.

Methods

Patients

A total of 7,840 patients underwent surgery for breast cancer from January 2010 to December 2014 at Samsung Medical Center. Of these, nine patients with stage IV at diagnosis were excluded; The patients had palliative breast surgery because of wound care or progressive/stable disease on breast lesion despite the improvement of metastatic organ. In addition, patients with locoregional recurrence, lack of follow up or electric medical records after metastasis, or without distant metastasis were excluded. Finally, we conducted a retrospective review of 316 breast cancer patients. These patients were divided into two groups based on presence or absence of symptoms at the time of metastasis detection; the asymptomatic group had 204 patients (64.6%) while the symptomatic group had 112 patients (35.4%) (Fig. 1).

Inclusion criteria were periodically monitored for metastases through imaging and laboratory tests. Physical examination, tumor markers, breast ultrasonography, mammography, breast magnetic resonance imaging, chest computerized tomography, abdomino-pelvic computerized tomography and bone scan were conducted at 1-year intervals depending on disease stage. Imaging and laboratory tests were conducted in accordance with South Korean health insurance policies. A total of 316 metastatic breast cancer patients was divided into two groups: the asymptomatic group included patients who were diagnosed with distant metastasis without symptoms during regular follow-up, while the symptomatic group included patients who were diagnosed with distant metastasis with symptoms either during or before the regular follow-up period. Patients diagnosed with distant metastasis received palliative treatment according to our institution's guidelines. Patients were defined as having a family history of breast cancer when a first- or second-degree relative had a history of breast cancer. This study was approved by the Institutional Review Board of Samsung Medical Center (IRB file no. 2020-06-012).

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). Continuous variables were compared with Student's t-test, and categorical variables were compared with Chi-square test and Fisher's exact test. Continuous variables were reported as median and interquartile range (IQR). Categorical variables were reported as the number and percentage. PMOS was analyzed using univariable and multivariable Cox regression analyses, and the Kaplan-Meier method with log-rank

percent (95%) confidence intervals and odds ratios were calculated, and statistical significance was defined as $p < 0.05$ for all tests.

Results

Patients characteristics

The baseline characteristics of the patients were similar between the two groups with respect to age, surgery type, histopathology, and pathologic stage. There were significantly more patients with hormone receptor (HR)-positive breast cancer in the asymptomatic group than in the symptomatic group (69.7% vs. 53.6%, $p = 0.013$). There was no significant difference in number of patients positive for human epidermal growth factor receptor 2 (HER2) between the two groups. There were significantly more patients who underwent neoadjuvant chemotherapy (42.9% vs. 28.4%, $p = 0.009$) or adjuvant radiotherapy (90.2% vs. 76.0%, $p = 0.002$) in the symptomatic group than in the asymptomatic group; however, there was no significant difference in number of patients who underwent adjuvant chemotherapy between the two groups (Table 1).

Table 1
Clinicopathologic characteristics of the patients

Variable	Total, N (%) Median [IQR]	Asymptomatic group, N (%) Median [IQR]	Symptomatic group, N (%) Median [IQR]	<i>p</i>
Number of patients	316	204 (64.6)	112 (35.4)	
Age (years)	46.00 [39.00–53.00]	47.00 [39.00–53.00]	44.00 [38.00–52.75]	0.072
BMI (kg/ m^2)	23.63 [21.88–25.90]	23.60 [21.91–25.90]	23.71 [21.91–25.89]	0.849
Menopause state				0.624
Pre-menopause	206 (65.2)	131 (64.2)	75 (67.0)	
Menopause	110 (34.8)	73 (35.8)	37 (33.0)	
Family history				0.307
Yes	36 (11.4)	26 (12.7)	10 (8.9)	
No	280 (88.6)	178 (87.3)	102 (91.1)	
Location				0.360
Right	144 (45.6)	98 (48.0)	46 (41.1)	
Left	162 (51.3)	101 (49.5)	61 (54.5)	
Bilateral	10 (3.2)	5 (2.5)	5 (4.5)	
Breast surgery				0.499
BCS	164 (51.9)	103 (50.5)	61 (54.5)	
Mastectomy	152 (48.1)	101 (49.5)	51 (45.5)	
Axillary surgery				0.446
SLNB	85 (26.9)	52 (25.5)	33 (29.5)	
ALND	231 (73.1)	152 (74.5)	79 (70.5)	

BMI body mass index, *BCS* breast conserving surgery, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection, *IDC* invasive ductal carcinoma, *HR* hormone receptor, *NAC* neoadjuvant chemotherapy

* Pathologic T and N stage were compared in patients without neoadjuvant chemotherapy

** Clinical T, clinical N, ypT, and ypN stages were assessed only in patients who underwent

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Variable	Total, N (%) Median [IQR]	Asymptomatic group, N (%) Median [IQR]	Symptomatic group, N (%) Median [IQR]	<i>p</i>
Histopathology				0.406
IDC	294 (93.0)	188 (92.2)	106 (94.6)	
Others	22 (7.0)	16 (7.8)	6 (5.4)	
Pathologic T*	210	146 (69.5)	64 (30.5)	0.353
T1	71 (33.8)	50 (34.2)	21 (32.8)	
T2	111 (52.9)	79 (54.1)	32 (50.0)	
T3	25 (11.9)	14 (9.6)	11 (17.2)	
T4	3 (1.4)	3 (2.1)	0 (0.0)	
Pathologic N*	210	146 (69.5)	64 (30.5)	0.359
N0	68 (32.4)	47 (32.2)	21 (32.8)	
N1	84 (40.0)	63 (43.2)	21 (32.8)	
N2	27 (12.9)	18 (12.3)	9 (14.1)	
N3	31 (14.8)	18 (12.3)	13 (20.3)	
Pathologic prognostic stage*	210	146 (69.5)	64 (30.5)	0.359
1	43 (20.5)	30 (20.5)	13 (20.3)	
2	102 (48.6)	75 (51.4)	27 (42.2)	
3	65 (31.0)	41 (28.1)	24 (37.5)	
HR				0.013
Positive	198 (62.7)	138 (69.7)	60 (53.6)	
Negative	118 (37.3)	66 (32.4)	52 (46.4)	
C-erbB-2				0.498

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Variable	Total, N (%) Median [IQR]	Asymptomatic group, N (%) Median [IQR]	Symptomatic group, N (%) Median [IQR]	<i>p</i>
Positive	64 (20.3)	39 (19.1)	25 (22.3)	
Negative	252 (79.7)	165 (80.9)	87 (77.7)	
Clinical T**	106	58 (54.7)	48 (45.3)	0.459
T1	4 (3.8)	1 (1.7)	3 (6.3)	
T2	35 (33.0)	17 (29.3)	18 (37.5)	
T3	43 (40.6)	25 (43.1)	18 (37.5)	
T4	24 (22.6)	15 (25.9)	9 (18.8)	
Clinical N**	106	58 (54.7)	48 (45.3)	0.763
N0	1 (0.9)	1 (1.7)	0 (0.0)	
N1	17 (16.0)	8 (13.8)	9 (18.8)	
N2	46 (43.4)	27 (46.6)	19 (39.6)	
N3	42 (39.6)	22 (37.9)	20 (41.7)	
yp T**	106	58 (54.7)	48 (45.3)	0.656
yp T0	10 (9.4)	4 (6.9)	6 (12.5)	
yp T1	28 (26.4)	15 (25.9)	13 (27.1)	
yp T2	34 (32.1)	18 (31.0)	16 (33.3)	
yp T3	34 (32.1)	21 (36.2)	13 (27.1)	
yp N**	106	58 (54.7)	48 (45.3)	0.443
yp N0	33 (31.1)	15 (25.9)	18 (37.5)	
yp N1	30 (28.3)	18 (31.0)	12 (25.0)	
yp N2	23 (21.7)	15 (25.9)	8 (16.7)	

BMI body mass index, *BCS* breast conserving surgery, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection, *IDC* invasive ductal carcinoma, *HR* hormone receptor, *NAC* neoadjuvant chemotherapy

* Pathologic T and N stage were compared in patients without neoadjuvant chemotherapy

** Clinical T, clinical N, ypT, and ypN stages were assessed only in patients who underwent

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Variable	Total, N (%) Median [IQR]	Asymptomatic group, N (%) Median [IQR]	Symptomatic group, N (%) Median [IQR]	<i>p</i>
yp N3	20 (18.9)	10 (17.2)	10 (20.8)	
NAC				0.009
NAC (+)	106 (33.5)	58 (28.4)	48 (42.9)	
NAC (-)	210 (66.5)	146 (71.6)	64 (57.1)	
Adjuvant radiotherapy				0.002
(+)	256 (81.0)	155 (76.0)	101 (90.2)	
(-)	60 (19.0)	49 (24.0)	11 (9.8)	
Adjuvant chemotherapy				0.185
(+)	196 (62.0)	132 (64.7)	64 (57.1)	
(-)	120 (38.0)	72 (35.3)	48 (42.9)	
Hormone therapy				0.005
(+)	189 (59.8)	133 (65.2)	56 (50.0)	
(-)	127 (40.2)	71 (34.8)	56 (50.0)	
Target therapy				0.788
(+)	54 (17.1)	34 (16.7)	20 (17.9)	
(-)	262 (82.9)	170 (83.3)	92 (82.1)	
<i>BMI</i> body mass index, <i>BCS</i> breast conserving surgery, <i>SLNB</i> sentinel lymph node biopsy, <i>ALND</i> axillary lymph node dissection, <i>IDC</i> invasive ductal carcinoma, <i>HR</i> hormone receptor, <i>NAC</i> neoadjuvant chemotherapy				
* Pathologic T and N stage were compared in patients without neoadjuvant chemotherapy				
** Clinical T, clinical N, ypT, and ypN stages were assessed only in patients who underwent neoadjuvant chemotherapy				

Eighty-four of the 316 patients (26.6%) had two or more metastatic organs, while 78 patients (24.7%) had bone metastasis only. One hundred fifty four of 316 (48.7%) patients had a single metastatic organ other than bone. There was no significant difference in pattern of metastatic organs between asymptomatic and symptomatic groups ($p = 0.287$) (Table 2).

Table 2
Metastatic pattern of patients diagnosed with distant metastasis

Variable	Total, N (%)	Asymptomatic group, N (%)	Symptomatic group, N (%)	<i>p</i>
Number of patients	316	204 (64.6)	112 (35.4)	
Metastasis				0.287
Single (bone)	78 (24.7)	56 (71.8)	22 (28.2)	
Single (other site)	154 (48.7)	97 (63.0)	57 (37.0)	
Multiple	84 (26.6)	51 (60.7)	33 (39.3)	

Post-metastasis overall survival

At a median follow-up of 33 months after diagnosis of distant metastasis, 160 patients had died (87 in the asymptomatic group and 73 in the symptomatic group). Univariate analysis showed there were no significant differences in clinical or pathologic stage. The patients with multiple metastatic organs had a 2.326-fold (95% CI: 1.457 to 3.714, $p < 0.001$) higher risk of PMOS than the patients with bone metastasis only, and those with one metastatic site other than bone had a 1.783-fold higher risk of PMOS (95% CI: 1.154 to 2.755, $p = 0.009$). On multivariate analysis, the patients with multiple metastatic organs had 1.872-fold (95% CI: 1.152 to 3.040, $p = 0.011$) higher risk of PMOS than the patients with bone metastasis only, however, there was no significant PMOS difference between patients with metastasis to the bone only and those with metastasis to an organ other than bone. On multivariate analysis, the hazard ratio of the symptomatic group was higher than that of the asymptomatic group (HR: 2.402, 95% CI: 1.748 to 3.301, $p < 0.001$) (Table 3). When stratified by subtype, the HR-positive breast cancer subtype showed a significantly better prognosis in the asymptomatic group than in the symptomatic group, whereas there was no difference in PMOS between the two groups for the HER2-positive subtype (Figs. 2,3).

Table 3

Univariate and multivariate analyses of prognostic variables for post-metastasis overall survival

Variables		N (%)	Univariate		Multivariate	
			HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Symptom	no	204 (64.6)	Ref.		Ref.	
	Yes	112 (35.4)	2.445 (1.785– 3.348)	< 0.001	2.402 (1.748– 3.301)	< 0.001
HR	no	118 (37.3)	Ref.		Ref.	
	Yes	198 (62.7)	0.406 (0.297– 0.555)	< 0.001	0.443 (0.318– 0.618)	< 0.001
C-erbB-2	no	252 (79.7)	Ref.		Ref.	
	Yes	64 (20.3)	1.479 (0.977– 2.237)	0.062	2.098 (1.371– 3.209)	0.001
Metastasis	Single (bone)	78 (24.7)	Ref.	0.001	Ref.	0.035
	Single (other site)	154 (48.7)	1.783 (1.154– 2.755)	0.009	1.432 (0.905– 2.268)	0.125
	Multiple	84 (26.6)	2.326 (1.457– 3.714)	< 0.001	1.872 (1.152– 3.040)	0.011
Pathologic T*		210				
	T1	71 (33.8)	Ref.	0.526		
	T2	111 (52.9)	1.374 (0.854– 2.211)	0.191		
	T3	25 (11.9)	1.113 (0.547– 2.262)	0.768		
	T4	3 (1.4)	0.643 (0.087– 4.754)	0.665		
Pathologic N*		210				

HR hormone receptor

* Pathologic T and N stage were compared in patients without neoadjuvant chemotherapy

** Clinical T, clinical N, vpT, and vpN stages were assessed only in patients who underwent

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Variables	N (%)	Univariate		Multivariate	
		HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
N0	68 (32.4)	Ref.	0.811		
N1	84 (40.0)	0.981 (0.593– 1.621)	0.940		
N2	27 (12.9)	1.059 (0.536– 2.093)	0.869		
N3	31 (14.8)	1.301 (0.701– 2.416)	0.405		
Clinical T**	106				
T1	4 (3.8)	Ref.	0.256		
T2	35 (33.0)	0.400 (0.135– 1.183)	0.098		
T3	43 (40.6)	0.369 (0.127– 1.069)	0.066		
T4	24 (22.6)	0.321 (0.104– 0.989)	0.048		
Clinical N**	106				
N0	1 (0.9)	Ref.	0.645		
N1	17 (16.0)	1.510 (0.197– 11.595)	0.692		
N2	46 (43.4)	0.985 (0.134– 7.255)	0.988		
N3	42 (39.6)	1.161 (0.157– 8.575)	0.884		
yp T**	106				
yp T0	10 (9.4)	Ref.	0.601		
yp T1	28 (26.4)	1.608 (0.649– 3.984)	0.305		

HR hormone receptor

* Pathologic T and N stage were compared in patients without neoadjuvant chemotherapy

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Variables	N (%)	Univariate		Multivariate	
		HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
yp T2	34 (32.1)	1.114 (0.444– 2.796)	0.818		
yp T3	34 (32.1)	1.259 (0.512– 3.096)	0.616		
yp N**	106				
yp N0	33 (31.1)	Ref.	0.372		
yp N1	30 (28.3)	1.373 (0.741– 2.546)	0.313		
yp N2	23 (21.7)	0.881 (0.438– 1.773)	0.723		
yp N3	20 (18.9)	1.519 (0.785– 2.938)	0.214		
<i>HR</i> hormone receptor					
* Pathologic T and N stage were compared in patients without neoadjuvant chemotherapy					
** Clinical T, clinical N, ypT, and ypN stages were assessed only in patients who underwent neoadjuvant chemotherapy					

Discussion

In our study, breast cancer patients diagnosed with distant metastasis after symptom onset had a poorer prognosis than patients without symptom at diagnosis. When stratified by tumor subtype, asymptomatic patients with HR-positive breast cancer had a better prognosis than symptomatic patients; however, there was no significant survival difference between symptomatic and asymptomatic patients with HER2-positive breast cancer. Our data demonstrate that it is important to follow up patients regularly for symptoms related to distant metastases before symptom onset in breast cancer patients, and this can be beneficial for prognosis.

According to the NCCN guidelines, it is recommended to perform annual mammography and a full history and physical examination one to four times per year for 5 years as routine follow-up for breast cancer patients who underwent primary treatment. Unless there are clinical signs and symptoms suggestive of recurrent disease, laboratory and imaging studies are not recommended for routine screening for distant metastasis [4]. Although the incidence of breast cancer has been steadily increasing in recent years, the overall survival rate of breast cancer patients has improved due to early diagnosis and advancements in treatment. As such, the number of breast cancer survivors has been increasing [5]. With advancements in diagnosis and treatment of breast cancer, it has become more important to detect recurrence or distant

metastasis early through appropriate follow-up in breast cancer patients who received initial treatment, as well as breast cancer survivors in remission, to improve overall survival and quality of life. Several previous studies have reported that detection of ipsilateral breast recurrence or contralateral breast cancer in the asymptomatic phase leads to improved survival relative to that associated with detection in the symptomatic phase [5, 6]. However, other studies have shown that survival is not improved by intensive surveillance programs in asymptomatic breast cancer patients [7–10]. Previous studies regarding follow-up for distant metastases in asymptomatic breast cancer patients are insufficient, and there is no evidence for the necessity of a follow-up program for breast cancer survivors.

Several prognostic factors, such as biological breast cancer subtypes, tumor size, nodal involvement, and histologic grade, have been linked to an elevated risk of distant metastasis in breast cancer after primary treatment [11, 12]. In this study, there was no difference in PMOS according to cancer stage. However, in HR-positive patients, the asymptomatic subgroup had a significantly longer PMOS. According to a study analyzing data from the Surveillance, Epidemiology, and End Results (SEER) population-based database [12], patients with HR-positive and HER2-negative cancer were most likely to develop metastasis, while patients with HR-negative and HER2-positive cancer were less likely to develop metastasis regardless of metastatic pattern. In addition, the sites of distant metastasis differed by breast cancer subtype. Other studies reported differences in time to metastatic disease and overall survival after diagnosis of metastasis according to tumor subtype [13, 14]. In our study, we compared the PMOS of asymptomatic patients to that of symptomatic patients; however, further study is needed on the method for optimal post-op surveillance by breast cancer subtype by analyzing metastatic patterns, including metastatic frequency, site, and time to metastasis, of each breast cancer subtype.

Our study showed that PMOS was significantly shorter in breast cancer patients with multiorgan metastases or non-bone-specific metastasis at time of diagnosis of distant metastasis. Bone is the most common site of metastasis in breast cancer patients [12]. Several studies have reported that patients with bone metastasis have a better prognosis than patients with other single- or multi-organ metastases, and a significant survival benefit can be achieved in select patients [13, 15–20]. In breast cancer patients who have either bone metastasis only or one metastatic organ, early detection before metastatic progression can confer a survival benefit; therefore, routine follow-up in asymptomatic breast cancer patients who underwent primary treatment is reasonable. Treatment for metastasis should be conducted in the early phase when the tumor burden is small, and it is necessary to follow up more actively in patients with high risk of metastasis.

As above, it can be seen that not only the breast cancer stage, but also subtype and sites of metastasis affect prognosis of metastatic breast cancer patients [13, 21, 22]. As treatment of metastatic breast cancer has improved depending on the tumor subtypes, early detection and treatment may be important when the tumor burden is small without symptoms. With respect to the HER2-positive subtype, availability of new target therapies and other treatment options for HER2-positive patients with distant metastasis result in good prognosis, and screening for distant metastases might be reasonable after

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that detect recurrences or distant metastases, the imaging modalities, such as US, MRI, and PET-CT, as post-treatment surveillance are potentially useful and show high sensitivity and accuracy for detecting recurrences or distant metastases [24]. With advanced diagnostic imaging and treatments, early diagnosis and treatment can improve prognosis when the tumor burden is small in breast cancer patients with distant metastasis.

This study had a few limitations. This study was a retrospective review performed at a single institution; therefore, there is a possibility of selection bias. In addition, patients in the asymptomatic group might have caused lead time bias due to early detection of distant metastases. Finally, all breast cancer patients are given equal healthcare in accordance with the national insurance policies in Korea, resulting in regular annual surveillance, and in this study, symptomatic metastases had poorer prognosis than asymptomatic metastases during intensive surveillance. The ideal study design would be to divide patients without regular surveillance according to presence of symptoms to discover if the prognosis of asymptomatic metastases is good. However, since all patients were routinely monitored in this study, the inclusion criteria were divided and analyzed according to presence of symptoms during the regular surveillance period. Research related to surveillance for distant metastasis in breast cancer patients is progressing [25], however, further studies will be necessary to evaluate whether asymptomatic metastasis is a good prognostic factor, and to investigate the term or modality of intensive surveillance. Despite these limitations, this study is meaningful because our results demonstrate poor prognosis of distant metastasis after symptoms occur in breast cancer patients under intensive surveillance.

In conclusion, breast cancer patients diagnosed with distant metastasis after symptoms occurred had a poorer prognosis than patients without symptoms at diagnosis. Detection of symptomatic distant metastases was associated with aggravated PMOS in breast cancer patients. Therefore, it is important to follow up patients regularly for symptoms related to distant metastases. Our findings validate the need for intensive surveillance in this patient population, suggesting reconsideration of the guidelines for metastases screening in breast cancer patients.

Abbreviations

PMOS Post-metastasis overall survival

NCCN National Comprehensive Cancer Network

HR Hormone receptor

HER2 Human epidermal growth factor receptor 2

Declarations

Funding

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No funding was obtained for this study.

Conflicts of interest

The authors declare that they have no competing interests.

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Code availability

Not applicable.

Authors' contributions

SMJ, and SKL contributed to the conception and design of the study. SMJ, JMR, BJC, JHY, JEL, SWK, and SJN collected and analyzed the data. SMJ, SKL wrote and reviewed the manuscript. All authors reviewed and approved the final version of the manuscript.

Ethics approval

The data, including demographic factors, pathologic findings, and perioperative treatment were collected from the electronic medical records after Institutional Review Board Approval in Samsung Medical Center (IRB file no. 2020-06-012).

Consent to participate

Signed informed consent from the patients was not required.

Consent for publication

Not applicable.

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Figures

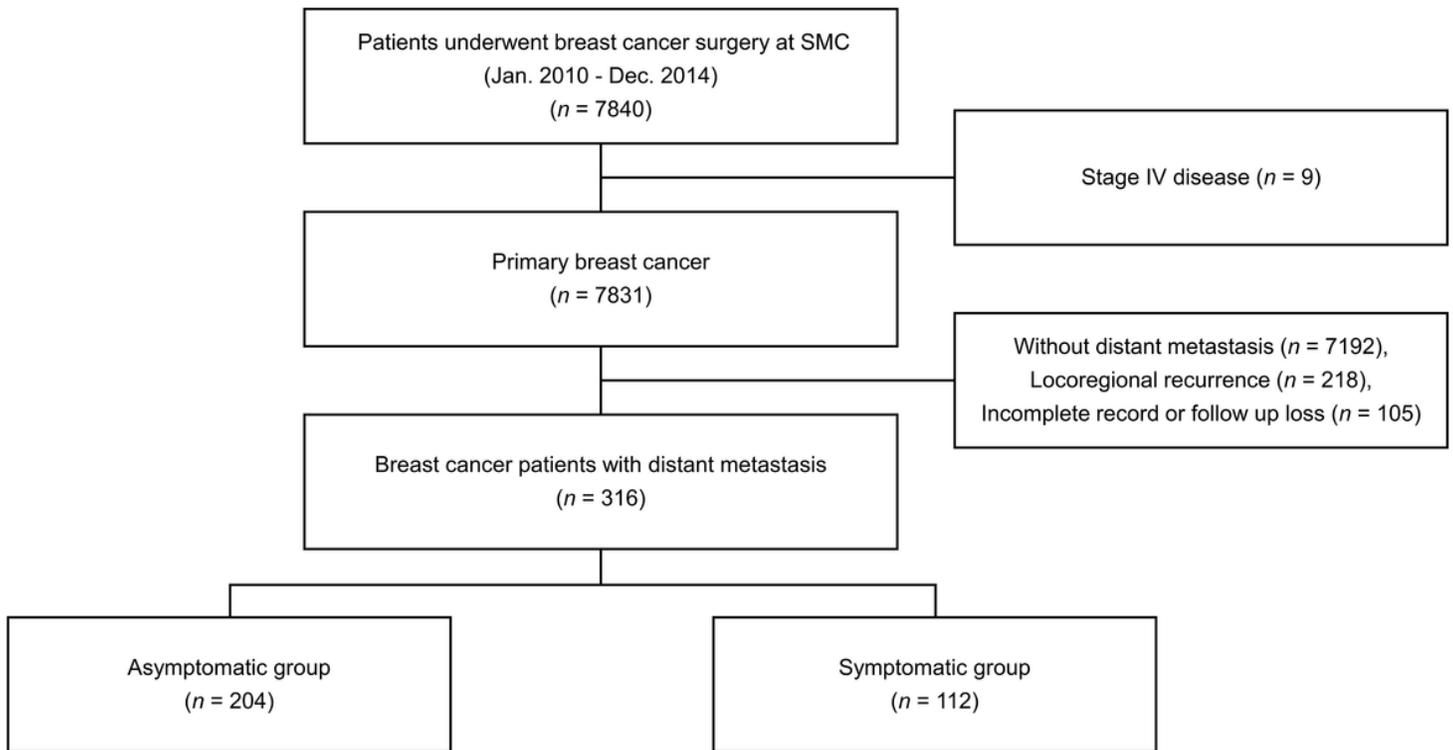


Figure 1

Schematic flow of patients

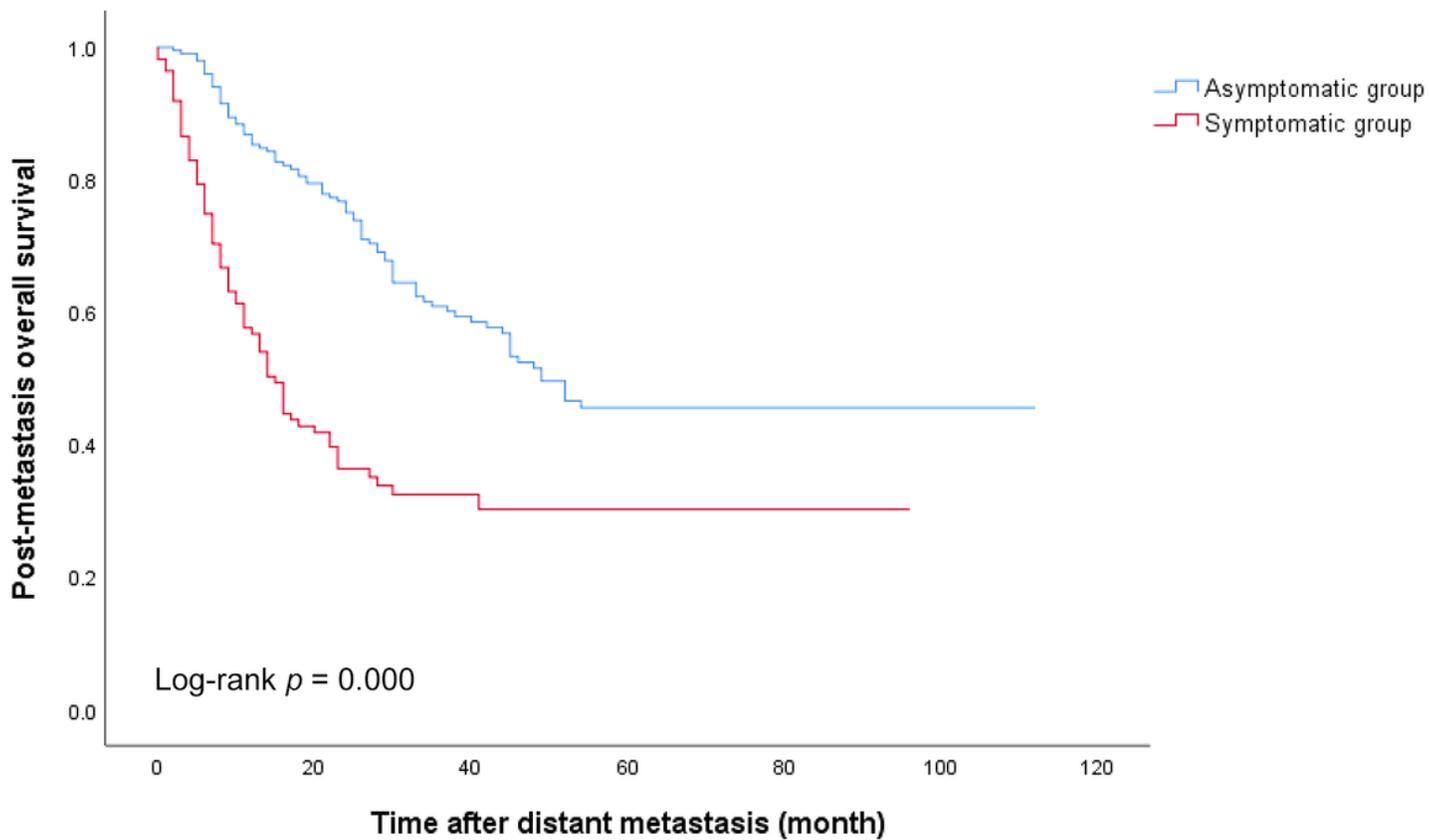


Figure 2

Kaplan-Meier curve of post-metastasis overall survival according to presence of symptoms

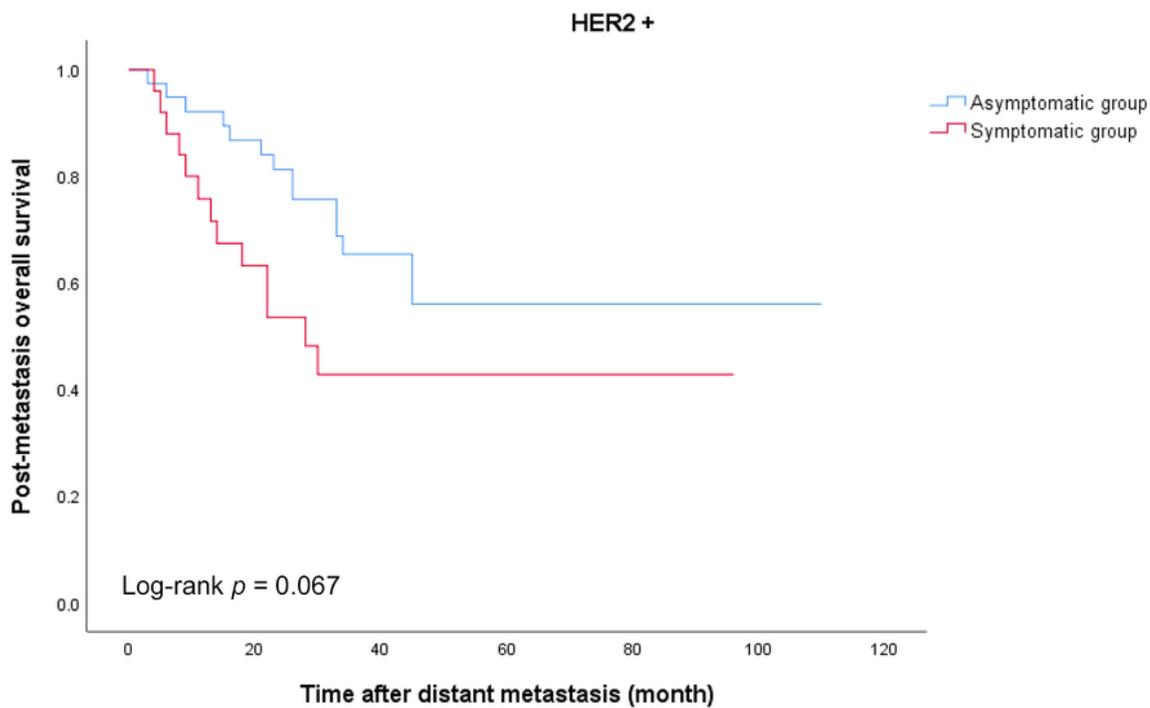
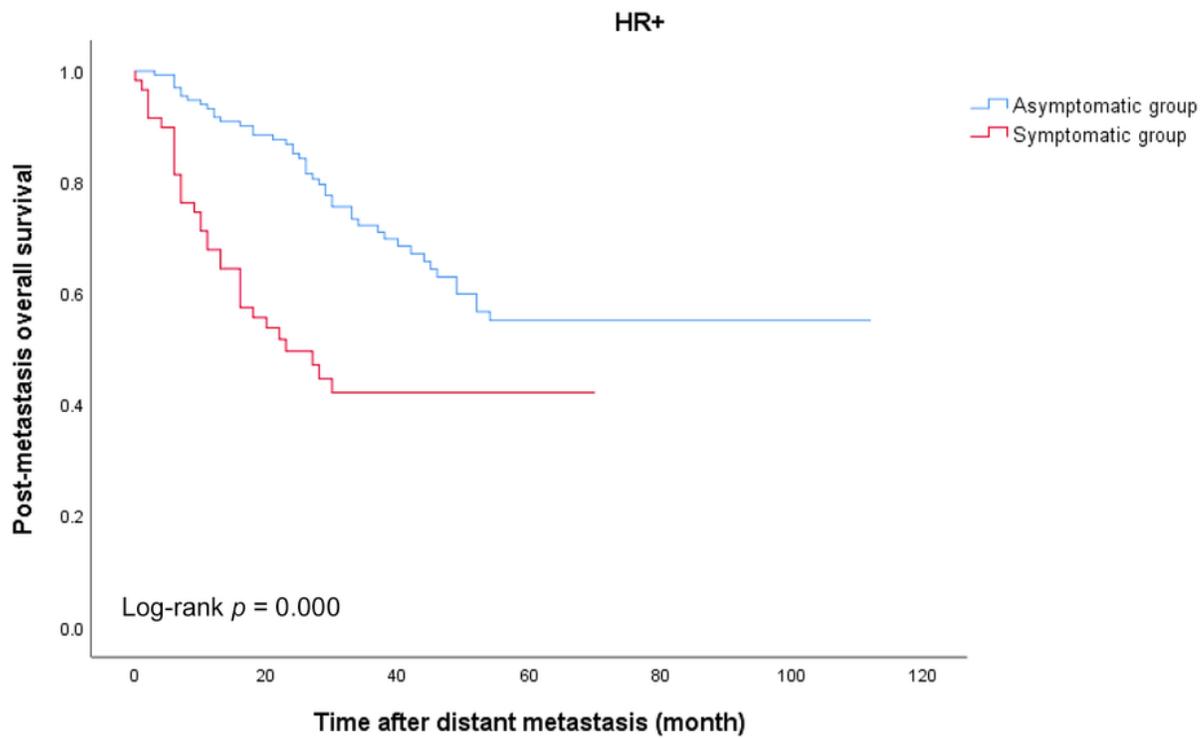


Figure 3

Kaplan-Meier curve of post-metastasis overall survival according to presence of symptoms and stratified by tumor subtype