



The Prognostic Impact of Synchronous Ipsilateral Multiple Breast Cancer: Survival Outcomes according to the Eighth American Joint Committee on Cancer Staging and Molecular Subtype

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Background: In the current American Joint Committee on Cancer staging system of breast cancer, only tumor size determines T-category regardless of whether the tumor is single or multiple. This study evaluated if tumor multiplicity has prognostic value and can be used to subclassify breast cancer. **Methods:** We included 5,758 patients with invasive breast cancer who underwent surgery at Samsung Medical Center, Seoul, Korea, from 1995 to 2012. **Results:** Patients were divided into two groups according to multiplicity (single, n=4,744; multiple, n=1,014). Statistically significant differences in lymph node involvement and lymphatic invasion were found between the two groups ($p < .001$). Patients with multiple masses tended to have luminal A molecular subtype ($p < .001$). On Kaplan-Meier survival analysis, patients with multiple masses had significantly poorer disease-free survival (DFS) ($p = .016$). The prognostic significance of multiplicity was seen in patients with anatomic staging group I and prognostic staging group IA ($p = .019$ and $p = .032$, respectively). When targeting patients with T1-2 N0 M0, hormone receptor-positive, and human epidermal growth factor receptor 2 (HER2)-negative cancer, Kaplan-Meier survival analysis also revealed significantly reduced DFS with multiple cancer ($p = .031$). The multivariate analysis indicated that multiplicity was independently correlated with worse DFS (hazard ratio, 1.23; 95% confidence interval, 1.03 to 1.47; $p = .025$). The results of this study indicate that tumor multiplicity is frequently found in luminal A subtype, is associated with frequent lymph node metastasis, and is correlated with worse DFS. **Conclusions:** Tumor multiplicity has prognostic value and could be used to subclassify invasive breast cancer at early stages. Adjuvant chemotherapy would be necessary for multiple masses of T1-2 N0 M0, hormone-receptor-positive, and HER2-negative cancer.

Key Words: Breast neoplasms; Multiplicity; Disease-free survival; Prognosis; Molecular subtype

Several studies have been conducted on the multiplicity of breast cancer over the past decades. Multiplicity in breast cancer is a concept that includes multifocality and multicentricity. The term multifocality is used when there are two or more invasive tumors within the same breast quadrant, while the term multicentricity is used to denote the existence of tumors in different quadrants.¹ The reported incidence of multiple breast cancers ranges from less than 10% to 70%.²⁻⁴ Multiplicity in breast cancer has been reported to correlate with a higher frequency of lymphovascular invasion and lymph node involvement.^{3,5-15} However, the clinical significance of multiplicity and its influence on prognosis are controversial. Therefore, the current edition of the tumor,

node, and metastasis (TNM) classification in breast cancer uses only the dimension of the largest tumor focus when the tumor demonstrates multiplicity. In light of this fact, the present research analyzed, via a large retrospective study of breast cancer patients uniformly treated at a single institution, the impact of multiple breast cancers on disease-specific survival in relation to other clinicopathological factors.

MATERIALS AND METHODS

Study population

We identified 5,758 patients with invasive breast cancer who

underwent conserving breast surgery or total mastectomy at Samsung Medical Center in Seoul, Korea, from 1995 to 2012. For inclusion in the study, patients needed to meet the following criteria: no distant metastasis at the time of diagnosis, no neo-adjuvant therapy prior to surgery, and a follow-up period longer than 36 months. The mean age of the patients was 47 years (age range, 21 to 86 years), and the median follow-up period was 64 months. This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB No. 2018-06-098-001). Formal written informed consent was not required due to a waiver by the appropriate IRB.

Clinicopathological evaluation

Clinicopathological information, including multiplicity, age, tumor size, axillary nodal status, and histological grade, was obtained from electronic medical records or surgical pathology reports. According to the eighth edition of the American Joint Committee on Cancer (AJCC) staging, a patient with multiple breast cancer was defined if two or more separate masses were grossly or microscopically identified in a resection specimen no matter whether they were present in the same or different quadrants. In some cases, through assistance of careful gross examination and correlation with imaging findings, we can determine multiple breast cancer. Pathological tumor stage was assessed according to the eighth AJCC TNM classification.¹⁶ If an invasive carcinoma has been transected by vacuum-assisted biopsy or excisional biopsy, then the sizes in each fragment were not added together, and correlation with the size on breast imaging was helpful to determine the best size for classification. If there had been a prior core needle biopsy or incisional biopsy showing a larger area of invasion than in the excisional specimen, the largest dimension of the invasive carcinoma in the prior specimen should be used for T classification. Histological grade was evaluated according to the Scarff-Bloom-Richardson classification modified by Elston and Ellis.¹⁶ The expression status of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) were evaluated by immunohistochemistry based on the surgical specimen. For ER and PR, only nuclear (not cytoplasmic) staining was scored. A positive test was defined as positive staining greater than or equal to 1% of tumor cells. A negative test was defined as staining of less than 1% of tumor cells. HER2 was scored as 0, 1+, 2+, or 3+. Only membrane staining intensity and pattern were evaluated using the recommendations of the American Society of Clinical Oncology/College of American Pathologists.^{17,18} A positive test was defined as a staining score of 3+. Tumors with a 2+ score were submitted

for silver *in situ* hybridization. The tumor was considered positive for *HER2* amplification if the *HER2*/chromosome 17 probe signal ratio was greater than 2.0 and/or the average *HER2* copy number was greater than 6.0 signals per cell. Molecular subtypes of breast cancer were classified into luminal A, luminal B1, luminal B2, HER2, and triple-negative subtypes based on histological grade and the results of ER, PR, and HER2 immunohistochemistry as follows: luminal A (ER-positive and/or PR-positive, HER2-negative, and low histological grade [grade 1 or 2]); luminal B1 (ER-positive and/or PR-positive, and HER2-positive); luminal B2 (ER-positive and/or PR-positive, HER2-negative, and high histological grade [grade 3]), HER2-positive (ER-negative, PR-negative, and HER2-positive); and triple-negative (ER-negative, PR-negative, and HER2-negative).¹⁹

Statistical analysis

The primary outcome was disease-free survival (DFS), defined as the time interval from the date of surgery to the date of first recurrence, including local or distant. Survival curves were estimated using the Kaplan-Meier method, and survival differences were analyzed by log-rank test. The clinicopathological variables were analyzed in univariate and multivariate analyses of DFS with Cox proportional hazards model. Statistical analysis was performed using the R v3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

Patients were divided into two groups according to multiplicity. We found breast cancers involving a single mass in 4,744 cases (82.4%) and breast cancers involving multiple masses in 1,014 cases (17.6%). Table 1 shows the results of the comparison between patients with a single mass and patients with multifocal or multicentric masses.

Patients with multiple cancers were more likely to be young and have undergone total mastectomy. Statistically significant differences in lymph node positivity (single 38.0% vs multiple 47.3%, $p < .001$) and lymphatic invasion (single 24.7% vs multiple 32.6%, $p < .001$) were found between the two groups. In addition, multiplicity was associated with non-high histological grade ($p < .001$), ER positivity ($p < .001$), PR positivity ($p < .001$), and HER2 negativity ($p = .003$) of tumor. Therefore, breast cancers with multiple masses were more likely to have luminal A molecular subtype and less likely to be triple-negative subtype compared to those with a single mass ($p < .001$).

Disease-free survival

DFS was evaluated in patients with single breast mass and multiple masses. Kaplan-Meier survival analysis indicated that

Table 1. Distribution of clinicopathological factors in single and multiple breast cancers (n=5,758)

Characteristic	Single (n=4,744)	Multiple (n=1,014)	p-value
Age (yr)			.001
<47	2,459 (51.8)	591 (58.3)	
≥47	2,285 (48.2)	423 (41.7)	
Operation			<.001
Partial	3,089 (65.1)	470 (46.4)	
Total	1,655 (34.9)	544 (53.6)	
Chemotherapy			.115
Not done	1,113 (23.5)	214 (21.1)	
Done	3,631 (76.5)	800 (78.9)	
Hormonal therapy			<.001
Not done	1,412 (29.8)	214 (21.1)	
Done	3,332 (70.2)	800 (78.9)	
Radiotherapy			<.001
Not done	1,241 (26.2)	426 (42.0)	
Done	3,503 (73.8)	588 (58.0)	
pT			.016
T1	2,720 (57.3)	618 (60.9)	
T2	1,827 (38.5)	370 (36.5)	
T3	197 (4.2)	26 (2.6)	
Lymph node			<.001
Negative	2,941 (62.0)	534 (52.7)	
Positive	1,803 (38.0)	480 (47.3)	
Anatomic stage group			.064
Stage I	2,014 (42.5)	390 (38.5)	
Stage II	2,089 (44.0)	479 (47.2)	
Stage III	641 (13.5)	145 (14.3)	
Lymphatic invasion			<.001
Negative	3,572 (75.3)	683 (67.4)	
Positive	1,172 (24.7)	331 (32.6)	
Histology grade			<.001
Grade 1, 2	3,089 (65.1)	737 (72.7)	
Grade 3	1,655 (34.9)	277 (27.3)	
ER status			<.001
Negative	1,430 (30.1)	232 (22.9)	
Positive	3,314 (69.9)	782 (77.1)	
PR status			<.001
Negative	1,789 (37.7)	278 (27.4)	
Positive	2,955 (62.3)	736 (72.6)	
HER2 status			.003
Negative	3,448 (72.7)	783 (77.2)	
Positive	1,296 (27.3)	231 (22.8)	
Molecular subtype			<.001
Luminal A	2,228 (47.0)	580 (57.2)	
Luminal B1	753 (15.9)	125 (12.3)	
Luminal B2	410 (8.6)	94 (9.3)	
HER2 positive	543 (11.4)	106 (10.5)	
Triple negative	810 (17.1)	109 (10.7)	

Values are presented as number (%).

patients with multiple masses had significantly poorer DFS than did those with a single mass (5-year rate, 88.2% vs 85.2%; $p = .016$) (Fig. 1A). When patients were subclassified according to T-category, Kaplan-Meier survival analysis in the T1 category group revealed significantly worse DFS for multiple breast cancer (5-year rate, 91.3% vs 87.4%; $p = .033$) (Fig. 1B). There was no significant prognostic difference in T2 and T3 category groups ($p = .093$ and $p = .619$, respectively) (Fig. 1C, D). Using the anatomic stage group table in the AJCC eighth edition for tumor staging, breast cancer with multiplicity had poor prognosis in stage I (5-year rate, 92.7% vs 90.3%; $p = .019$) (Fig. 2A). When using the prognostic stage group table in the AJCC eighth edition, multiple breast masses were found to have significantly shorter DFS than single breast masses in stage group IA (5-year rate, 94.9% vs 88.7%; $p = .032$) (Fig. 2B). However, no significant difference was found between single and multiple tumors in the other stage groups (i.e., anatomic staging group II or III and prognostic staging group IB, II, or III) (Fig. 2C).

Patients were divided into five molecular subtypes (i.e., luminal A, B1, and B2; HER2-positive; and triple-negative). The prognostic significance of multiplicity was only seen in patients with luminal A and HER2-positive groups in terms of DFS (5-year rate, 92.8% vs. 88.6%; $p = .013$ and 5-year rate, 86.9% vs 77.8%; $p = .003$, respectively) (Fig. 3A, B). There was no significant difference among the luminal B1 and B2 and triple-negative subtypes ($p = .937$, $p = .453$, and $p = .411$, respectively) (Fig. 3C–E). In addition, when targeting patients with T1–2 N0 M0, hormone-receptor-positive, and HER2-negative cancer, Kaplan-Meier survival analysis revealed a significantly reduced DFS of multiple breast cancer (5-year rate, 95.2% vs 88.6%; $p = .031$) (Fig. 4).

Univariate analysis using Cox proportional hazard model indicated that high tumor stage (T3) (hazard ratio [HR], 2.44; 95% confidence interval [CI], 1.84 to 3.23; $p < .001$), positive lymph node metastasis (HR, 2.06; 95% CI, 1.8 to 2.36; $p < .001$), high anatomic staging group (i.e., stage III) (HR, 3.47; 95% CI, 2.89 to 4.18; $p < .001$), positive lymphatic emboli (HR, 2.16; 95% CI, 1.88 to 2.49; $p < .001$), high histological grade (i.e., grade 3) (HR, 1.52; 95% CI, 1.33 to 1.74; $p < .001$), negative ER status (HR, 1.23; 95% CI, 1.07 to 1.42; $p < .001$), positive HER2 status (HR, 1.21; 95% CI, 1.05 to 1.40; $p = .004$), and the presence of multiplicity (HR, 1.24; 95% CI, 1.04 to 1.48; $p = .016$) are significant variables associated with lower DFS (Table 2).

These significant factors in the univariate model were included in multivariate analysis, which demonstrated that tumor multiplicity correlated independently with worse DFS (adjusted HR,

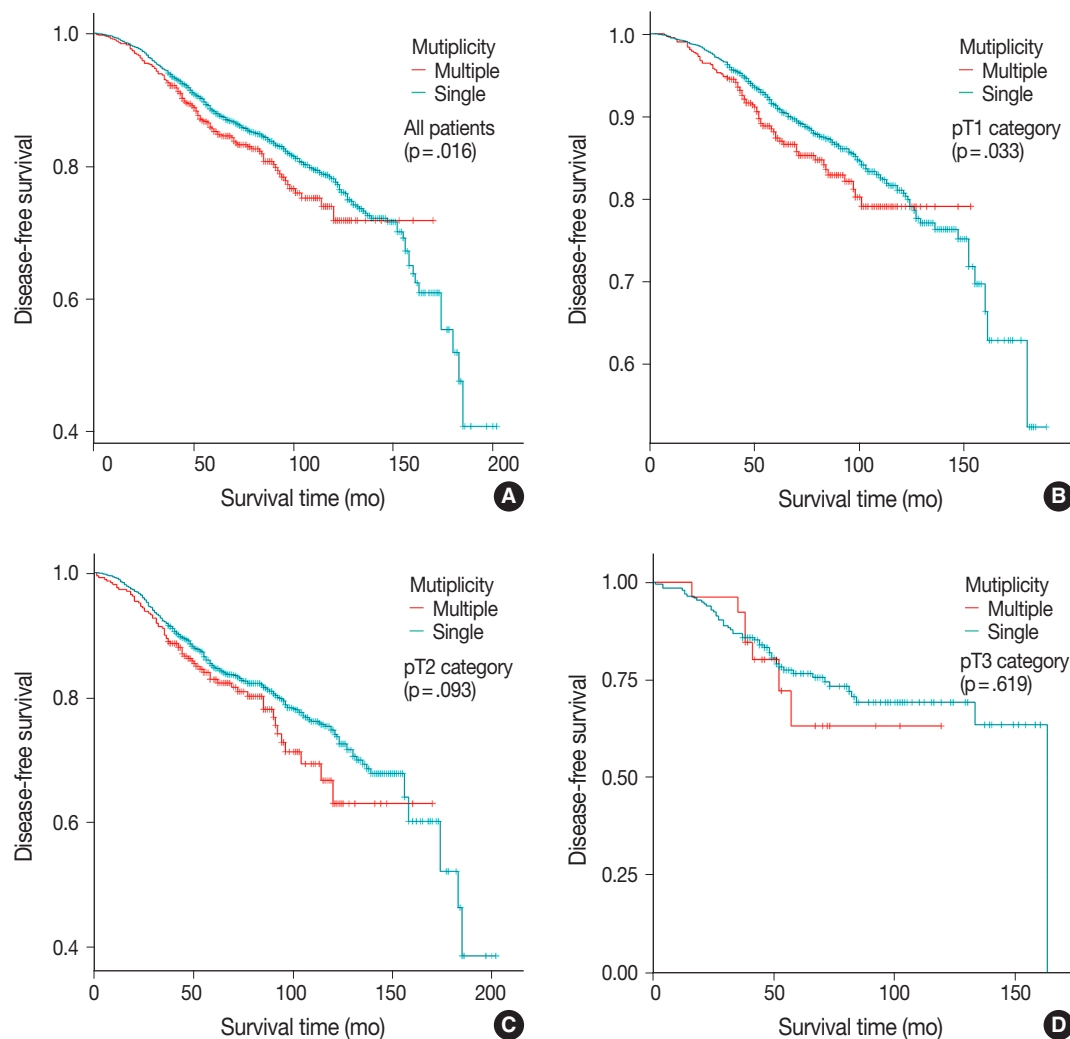


Fig. 1. The Kaplan-Meier curves for disease-free survival in patients with single and multiple masses according to T category. (A) Survival curve of all patients. (B) Survival curve of the T1 category. (C) Survival curve of the T2 category. (D) Survival curve of the T3 category. A significant difference is observed in the T1 category.

1.23; 95% CI, 1.05 to 1.47; $p = .021$). Other independent factors were high tumor stage (T3) (adjusted HR, 1.81; 95% CI, 1.35 to 2.41; $p < .001$), positive lymph node metastasis (adjusted HR, 1.84; 95% CI, 1.60 to 2.13; $p < .001$), and high histological grade (i.e., grade 3) (adjusted HR, 1.33; 95% CI, 1.14 to 1.55; $p < .001$) (Table 3).

DISCUSSION

In the present study, the 17.6% incidence of surgically removed breast cancer with multiplicity is in line with prior data series.^{9,11,20-23} In previous studies, the incidence of multiple breast cancer had a wide range due to different definitions and inclusion criteria for multiple masses. Here, we used the term multiplicity if the cancer showed either multicentricity or multi-

focality. Many researchers have studied the characteristics of multicentric or multifocal breast cancer. In the literature, lymphovascular invasion and axillary nodal involvement were more frequent in multicentric or multifocal breast cancers.^{3,5-15} The higher frequency of lymph node metastases could be due to the greater volume and surface area of multiple breast cancer or different biological behavior.⁸ In agreement with reported series, patients in this study with multiple masses had a higher incidence of lymph node involvement than patients with single mass. In addition, multiplicity was associated with frequent lymphovascular invasion.

Theoretically, as breast cancers with multiplicity are more likely to have lymph node involvement and lymphovascular invasion, it could be inferred that prognosis would be worse than that of single mass breast cancers. Of course, many researchers have studied multiplicity as a prognostic factor in breast cancer. However,

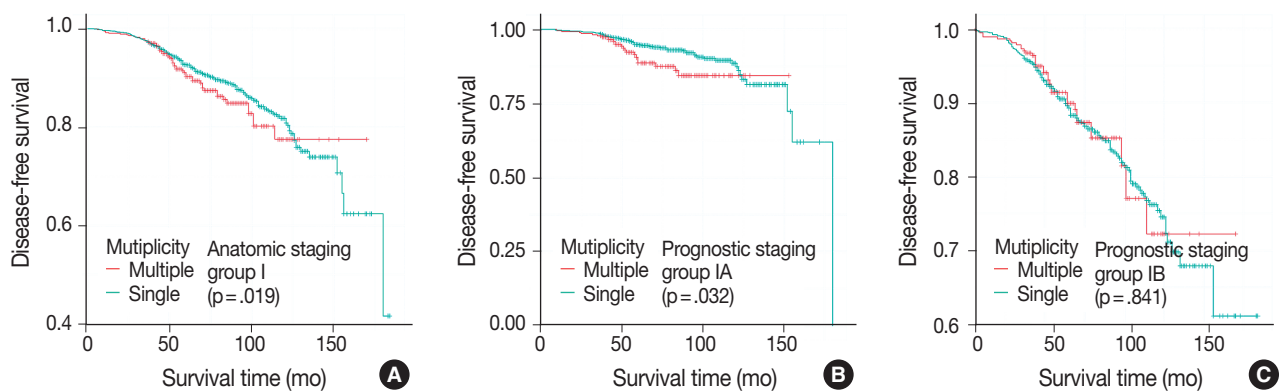


Fig. 2. The Kaplan-Meier survival curves for disease-free survival of patients with single and multiple masses in different Anatomic and prognostic staging groups. (A) Survival curve of the anatomic staging group I. (B) Survival curve of the prognostic staging group IA. (C) Survival curve of the prognostic staging group IB. The anatomic staging group I and prognostic staging group IA show a significant difference.

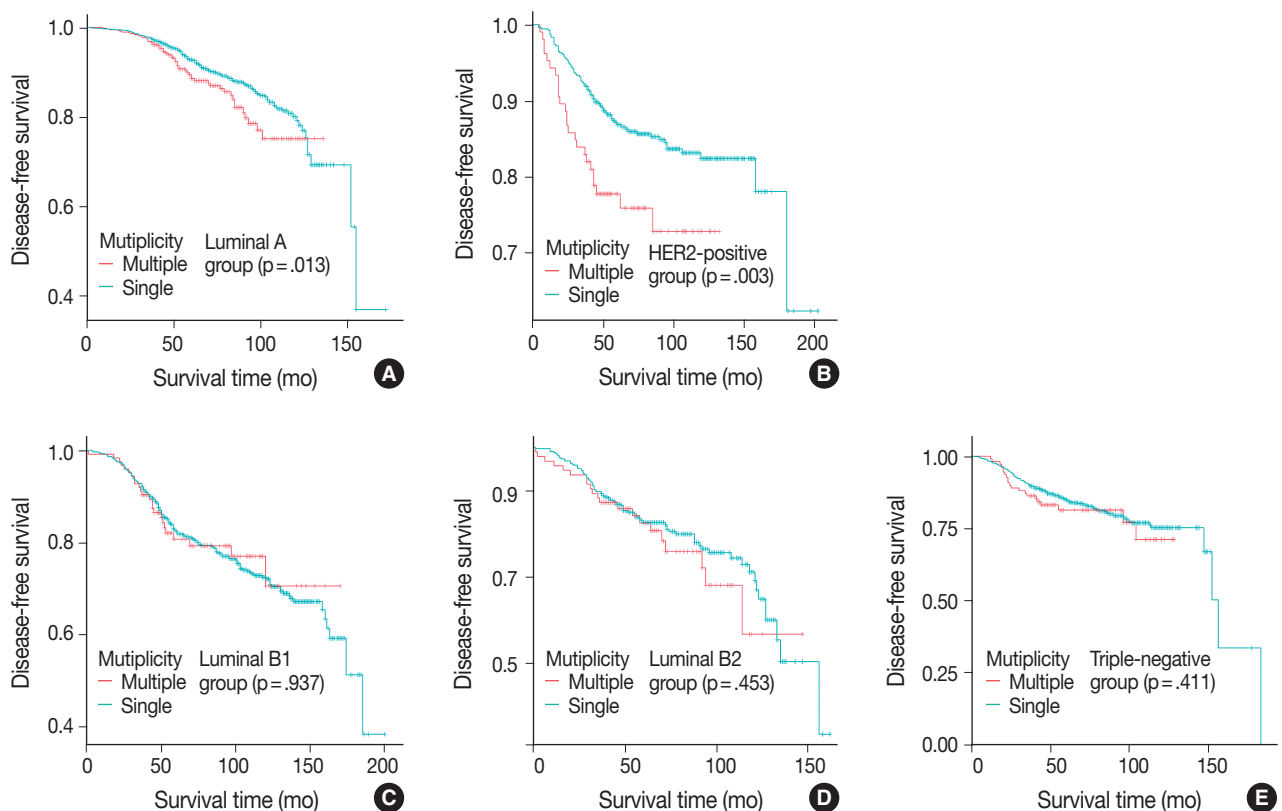


Fig. 3. Molecular subgroup analysis of the association between multiplicity and disease-free survival. The Kaplan-Meier survival curve of luminal A (A), human epidermal growth factor receptor 2 (HER2)-positive (B), luminal B1 (C), luminal B2 (D), and triple-negative groups (E). The difference is significant in patients of the luminal A and HER2-positive groups.

the biological and clinical significances of multiplicity are still debated.^{3,7,9,11,12,14,20,21,24-26} Vlastos *et al.*¹¹ studied 284 patients with early-stage breast cancer and found that locoregional recurrence, distant metastasis, and disease-specific survival and DFS were not different between multicentric versus unicentric tumors. On the other hand, Yerushalmi *et al.*³ analyzed 1,554 patients

and found multicentric/multifocal tumors to be associated with worse breast cancer-specific survival. Additionally, Neri *et al.*²² reported on 191 cases of breast cancer and found multifocal/multicentric breast cancer to be related to significantly worse prognosis with breast cancer-specific survival.

The results of our study suggest that multicentric and multi-

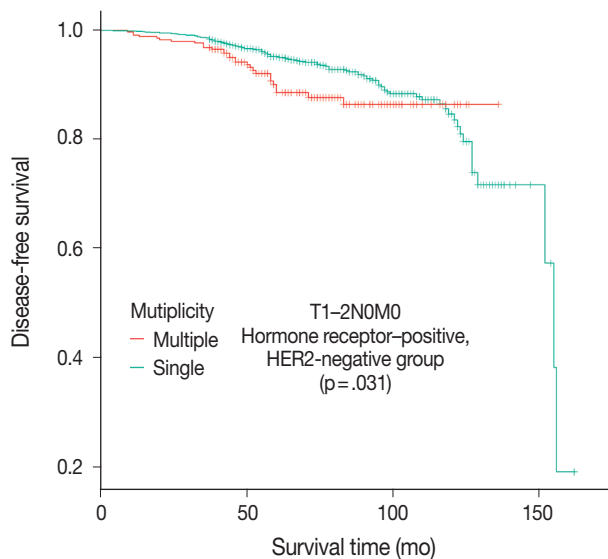


Fig. 4. The Kaplan-Meier survival curves for disease-free survival in patients with T1–2 N0 M0, hormone receptor–positive, and human epidermal growth factor receptor 2 (HER2)–negative cancer. Comparison between patients with single mass and multiple masses.

focal breast cancers may have different biological behaviors. Multiple masses were more likely to have non-high histology grade, ER positivity, PR positivity, and HER2 negativity compared with single mass cases. Interestingly, we found that breast cancers with multiplicity were associated with luminal A molecular subtype and non-high histology grade, which are known to have good prognosis. Additionally, multiple breast masses of the luminal A group were found to have a significantly shorter DFS than single breast masses in Kaplan-Meier survival analysis ($p = .013$). As with luminal A, multiplicity had prognostic significance in the HER2-positive group. According to our results, close observation during follow-up is needed, especially in patients of the luminal A and HER2-positive groups with multiple breast cancer. There have been conflicting reports about hormonal receptor status.^{22,27}

As in our study, Moon *et al.*²⁷ identified frequent ER positivity and HER2 negativity of multiple breast cancers in a series of 2,882 patients. Conversely, however, Neri *et al.*²² reviewed 1,158 patients and found an association between multiplicity and ER-negative and HER2-positive status. On the other hand, Moon *et al.*²⁷ reported that the difference in overall survival was significant only in patients with the triple-negative subtype.

Our results show that breast cancer with multiplicity has a negative effect on DFS, especially in early-stage cancer. The results of multivariate analysis confirmed the independent prognostic value of multiplicity, and Kaplan-Meier survival curve showed significantly reduced DFS for patients with multiple masses in the T1 stage group ($p = .033$). The AJCC eighth edition

Table 2. Univariate Cox proportional hazards ratio analysis

	Hazard ratio	95% CI	p-value
Multiplicity			
Single	1		
Multiple	1.24	1.04–1.48	.016
Age (yr)			
≥ 47	1		
< 47	1.08	0.94–1.24	.258
pT			
T1	1		
T2	1.57	1.37–1.81	< .001
T3	2.44	1.84–3.23	< .001
Lymph node			
Negative	1		
Positive	2.06	1.80–2.36	< .001
Anatomic stage			
Stage I	1		
Stage II	1.65	1.40–1.95	< .001
Stage III	3.47	2.89–4.18	< .001
Lymphatic invasion			
Negative	1		
Positive	2.16	1.88–2.49	< .001
Histology grade			
Grade 1, 2	1		
Grade 3	1.52	1.33–1.74	< .001
ER status			
Positive	1		
Negative	1.23	1.07–1.42	.004
HER2 status			
Negative	1		
Positive	1.21	1.05–1.40	.009
Molecular Subtype			
Luminal A	1		
Luminal B1	1.8	1.49–2.18	< .001
Luminal B2	2.17	1.73–2.71	< .001
HER2 positive	1.37	1.09–1.73	.007
Triple negative	1.83	1.51–2.23	< .001

CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

presents the Prognostic Stage Group table in addition to the anatomic stage group table using the T, N, and M categories. The Prognostic Stage Group table includes the anatomical T, N, and M categories; tumor grade; and the status of ER, PR, and HER2 biomarkers. The prognostic significance of multiplicity in terms of DFS was only seen in patients with anatomic staging group I and prognostic staging group IA by Kaplan-Meier survival analysis ($p = .019$ and $p = .032$, respectively). Therefore, the negative prognostic impact of multiplicity could be considered for subclassification in at least early breast cancer patients.

The Oncotype Dx genomic test is now performed for consideration of adjuvant chemotherapy in patients with T1–2 N0 M0, hormone receptor–positive, and HER2-negative cancer.²⁸

Table 3. Multivariate Cox proportional hazards ratio analysis

	Hazard ratio	95% CI	p-value
Multiplicity			
Single	1		
Multiple	1.23	1.05–1.47	.021
pT			
T1	1		
T2	1.27	1.09–1.47	.002
T3	1.81	1.35–2.41	<.001
Lymph node			
Negative	1		
Positive	1.84	1.60–2.13	<.001
Histology grade			
Grade 1, 2	1		
Grade 3	1.33	1.14–1.55	<.001
ER status			
Positive	1		
Negative	1.09	0.93–1.28	.255
HER2 status			
Negative	1		
Positive	1.1	0.95–1.28	.206

CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

In this patient population in our study, multiple breast masses were found to have a significantly shorter DFS than single breast mass ($p = .031$). Based on the difference of prognosis, adjuvant chemotherapy would be necessary for multiple breast masses even without the Oncotype Dx test.

Our study has several limitations. First, this retrospective study had a relatively short-term follow-up period (median duration, 64 months). Second, molecular subtype was evaluated only using the largest among multiple masses. Because intertumoral heterogeneity could be a factor affecting survival, a further study should be conducted to investigate the relationship between intertumoral heterogeneity and survival in multiple breast cancer. Finally, patients with neoadjuvant therapy were not included. Therefore, the evaluation of advanced stage breast cancer was relatively limited.

In conclusion, the results of this study indicate that tumor multiplicity is frequently found in luminal A breast cancer, is associated with frequent lymph node metastasis, and is correlated with worse DFS. Tumor multiplicity has prognostic value and could be used to subclassify invasive breast cancer in the early stage. Adjuvant chemotherapy would be necessary for multiple breast masses of the T1–2 N0 M0, hormone-receptor-positive, and HER2-negative cancer groups.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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