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ORIGINAL ARTICLE

Survival outcome of adjuvant endocrine therapy alone for patients with lymph node-positive, hormone-responsive, HER2-negative breast cancer

Sung Ui Jung [a], Guiyun Sohn [b], Jisun Kim [b], Il Yong Chung [b], Jong Won Lee [b], Hee Jeong Kim [b], Beom Seok Ko [b], Byung Ho Son [b], Sei-Hyun Ahn [b], Seung Wook Yang [b], Sae Byul Lee [b,*]

[a] *Division of Breast, Department of Surgery, University of Kosin College of Medicine, Kosin University Gospel Hospital, Busan, South Korea*
[b] *Division of Breast, Department of Surgery, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea*

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Adjuvant endocrine therapy;
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Summary *Background/Objective:* The prognosis of hormone receptor-positive and HER2-negative breast cancer is better than that of other subtypes. Current guidelines recommend chemotherapy for N1 breast cancer patients. However, this has the possibility to be over-treatment.
Methods: This was a retrospective study of 18,549 patients who were surgically treated for invasive breast cancer, at a single center in South Korea, between January 1993 and December 2012. N1 stage breast cancer patients who were hormone receptor-positive and HER2-negative were enrolled, and propensity score matching was performed to compare patients treated with anti-hormonal therapy alone (N = 83) and those treated with chemotherapy followed by anti-hormonal therapy (N = 85).
Results: In survival analysis, the survival parameters of the endocrine therapy-only group and the chemotherapy with endocrine therapy group were respectively 96.1% and 94.0% for 5-year recurrence free survival (RFS), 89.6% and 94.0% for 10-year RFS, 97.4% and 94.0% for 5-year distant metastasis-free survival (DMFS), 93.2% and 94.0% for 10-year DMFS, 98.7% and 98.8% for 10-year breast cancer-specific survival (BCSS), and 98.7% and 98.8% for 10-year overall survival (OS). There were no significant differences in RFS ($p = 0.871$), DMFS ($p = 0.491$), BCSS ($p = 0.569$) and OS ($p = 0.731$) between the two groups.

* Corresponding author. Division of Breast and Endocrine Surgery, Department of Surgery, University of Ulsan College of Medicine, Asan Medical Center, 88, Olympic-ro 43-gil, Songpa-Gu, Seoul, 05505, South Korea. Fax: +82 2 3010 6710.
E-mail address: newstar153@hanmail.net (S.B. Lee).

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Conclusion: Several patients with clinicopathologic features like hormone receptor positivity and HER2 negativity can avoid chemotherapy even with lymph node metastasis. Future studies with a long-term follow-up and a larger number of patients are required for validating our results.

1. Introduction

Breast cancer is one of the most common malignant tumors that affect women worldwide. The prognosis of breast cancer varies greatly depending on whether the expressions of the hormone receptor and HER2 are positive or negative.[1] Five molecular subtypes of breast cancer have been identified through gene expression studies, each of which has a different prognosis.[2–4] These subtypes include luminal A, luminal B, HER2-overexpressing and basal-like, and unclassified breast cancer. HER2-overexpressing and basal-like subtypes are hormone receptor-negative and have poor prognoses.[1,5] Among the five breast cancer subtypes classified according to hormone receptor and HER2 status, the luminal A subtype, which is hormone receptor-positive and HER2-negative, accounts for 70% of all breast cancers.[6] In addition, the luminal A subtype is known to have a better prognosis and a low local or regional recurrence risk compared with other breast cancer subtypes. A study has reported that lymph node-negative patients with luminal A subtype breast cancer who received only anti-hormonal therapy had the same prognosis as patients who received both anti-hormonal therapy and chemotherapy.[7]

The single most reliable prognostic indicator is the involvement of axillary lymph nodes. Moreover, the risk of recurrence in the N1 stage has been reported to be several times higher than in the N0 stage.[8] Chemotherapy is widely used in the treatment of estrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive breast cancer. The NCCN Guidelines also recommend chemotherapy for axillary lymph node metastasis (greater than 2 mm).[9] In a recent study, additional adjuvant chemotherapy with tamoxifen was found to reduce the risk of recurrence and mortality by 3% and 20%, respectively, in hormone receptor-positive breast cancer.[10] However, it is associated with increased toxicity and is of little survival benefit.[11,12] In addition, it is a factor that can contribute to excessive medical costs. The treatment of hormone receptor-positive breast cancer is controversial because of overtreatment.[13] Recently, some studies, such as The Rx for Positive Node, Endocrine Responsive Breast Cancer (RxPONDER) study, and The Microarray In Node-negative and 1−3 positive lymph node Disease may Avoid Chemotherapy trial (MINDACT) study, have reported that patients with lymph node-positive cancer may be excluded from chemotherapy if they are classified as low-risk patients.[14,15] The study was conducted to identify groups that do not benefit from chemotherapy in the N1 stage. A study has reported that clinically low-risk or genomic low-risk groups do not benefit from chemotherapy, even if they are treated for hormone-positive, HER2-negative, and N1 stage cancers.[15] Therefore, we attempted to determine whether luminal A breast cancer patients with the best prognosis could be excluded from adjuvant chemotherapy. The purpose of this study was to evaluate whether adjuvant hormonal therapy is possible without systemic chemotherapy.

2. Methods

2.1. Study design

From January 1993 to December 2012, we retrospectively studied 18,549 patients who underwent surgical treatment for breast cancer at Asan Medical Center. The patients met the following criteria: (1) ER-positive and/or PR-positive breast cancer, (2) HER-2-negative breast cancer, (3) positive axillary lymph node status, (4) radical excision of the primary tumor, and (5) sentinel node biopsy or axillary lymph node dissection. Hormone receptor status was based on data in medical records, which was determined by enzyme immunoassay. HER2 status was confirmed by immunohistochemical staining. A negative HER2 receptor status was defined as 1 + or 2 + with negative fluorescence *in situ* hybridization. Patients with male breast cancer, bilateral breast cancer, distant metastasis, neo-adjuvant chemotherapy, or previous or simultaneous malignant tumors were excluded. The diagram of inclusion-exclusion criteria is shown in Fig. 1.

A total of 119 patients did not receive chemotherapy and were administered tamoxifen or an aromatase inhibitor (anti-hormonal therapy group), whereas the chemotherapy group received anti-hormonal therapy with chemotherapy. In some patients, a gonadotropin-releasing hormone (GnRH) agonist was administered (3.6 mg) every 28 days for 2 years for ovarian function suppression.

Recurrence-free survival (RFS) and overall survival (OS) were the primary endpoints. In addition, we evaluated the interval without systemic metastasis. Patients with local recurrence, regional recurrence, and systemic recurrence were included in the RFS analysis. However, contralateral breast cancer patients were not included.

2.2. Statistical analysis

The RFS period was defined as the time from operation to disease recurrence or death. The breast cancer-specific survival (BCSS) period was defined as the time from operation to cancer-caused death, based on the Korean registry cause-of-death code. The distant metastasis-free survival (DMFS) period was defined as the time from operation to distant metastasis or death. In addition, the OS period was defined as the time from operation to death from any cause.

Pearson's chi-square test was used to compare patient characteristics between treatment groups. The

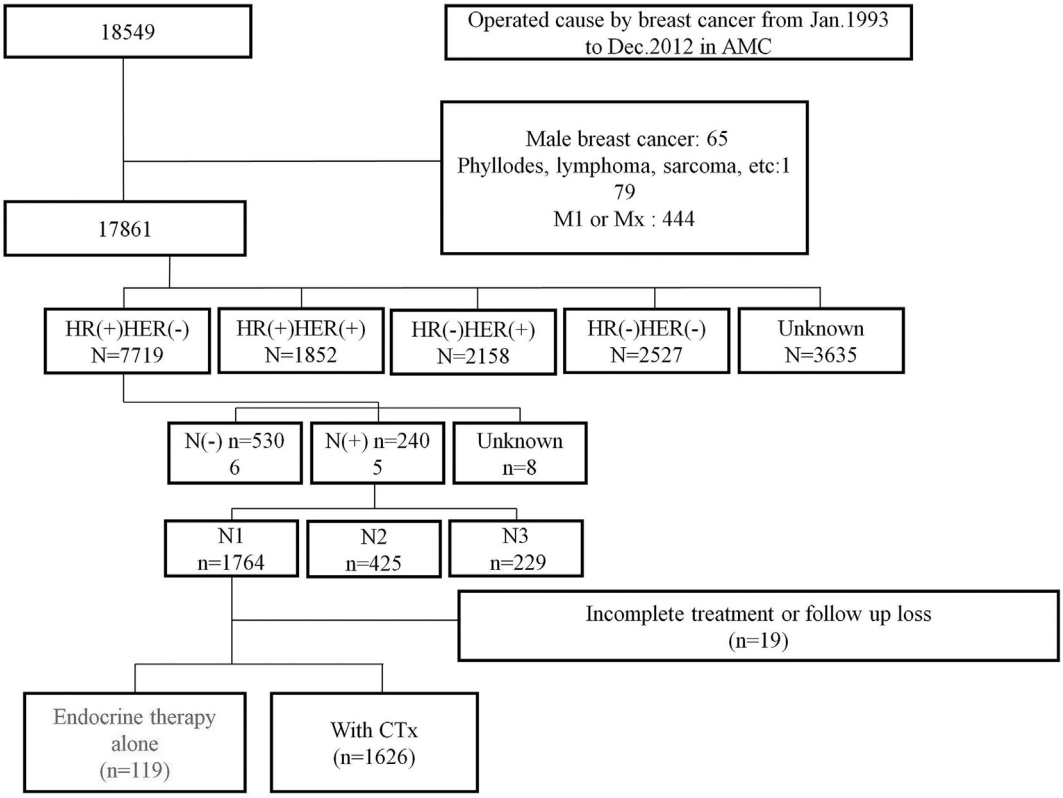

Figure 1 Diagram of inclusion and exclusion criteria. HR, hormone receptor; N, lymph node; ETx, endocrine therapy; CTx, chemotherapy.

Kaplan—Meier curve was used to evaluate RFS, BCSS, DMFS, and OS. The log-rank test was used for comparisons. The Cox proportional hazards (PH) model was used to calculate the adjusted hazard ratio of patient characteristics and other significant prognostic factors and therapeutic effects.

In order to reduce selection bias and clarify the therapeutic effects of other therapies, we performed propensity score matching between the anti-hormonal therapy group and the chemotherapy with anti-hormonal therapy group. To make the two groups as similar as possible in propensity score matching, we considered the age, operation timing, surgical method, histological type, tumor grade, lymphovascular invasion, tumor size, nodal number, nodal size, and hormone receptor status. The two groups were matched 1:1, and survival rates were compared.

All reported p values are two-sided, and a p value of <0.05 was considered statistically significant. Results were analyzed using SPSS ver. 21 for Windows (IBM Co., Armonk, NY).

3. Result

3.1. Patient and tumor characteristics

There were 1764 patients with ER-positive, HER2-negative, and node-positive breast cancer among 18,549 patients treated for breast cancer. Of the 1764 patients, 119 patients (6.8%) received anti-hormonal therapy only, and 1626 patients (93.2%) received chemotherapy with anti-hormonal therapy.

The characteristics of the 119 patients who received anti-hormonal therapy only were recorded. The mean age was 55.5 years, and the median follow-up time was 80 months, ranging from 2 months to 221 months. There were 79 patients (66.4%) with T1, 39 patients (32.8%) with T2, and 1 patient (0.8%) with T3 breast cancer. In addition, there were 73 patients (61.3%) with N1 micro-metastasis and 46 patients (38.7%) with N1 macro-metastasis. There were 97 patients (81.5%) with tumor grade 1, 12 patients (10.1%) with tumor grade 2, and 4 patients (11.8%) with tumor grade 3 tumors. All patients were ER-positive, and 95 patients (79.8%) were PR-positive. Furthermore, 28 patients (23.5%) were positive for lymphovascular invasion, and 46 patients (38.7%) were positive for Ki-67 (Table 1).

Propensity score matching was performed; 83 patients were assigned to the anti-hormonal therapy group, and 85 patients were assigned to the chemotherapy with anti-hormonal therapy group (Table 2). There was no significant difference between the two groups in age, tumor stage, nodal stage, nodal number, tumor grade, lymphovascular invasion, Ki67 status, ER positivity, PR positivity, operation method, or radiation therapy.

3.2. Survival analysis

The 119 patients who were received anti-hormonal therapy only were followed up for a median of 80 months (range: 2—221 months). A total of 4 recurrences occurred in 5 years: 1 case with local recurrence, 1 case with regional recurrence, and 2 cases with distant metastases. A total of 7

Table 1 The patients characteristics for the anti-hormonal therapy alone before matching (n = 119).

Characteristic	Status	N (%)
Age	Mean (SD)	55.5 (13.1)
Median f/u time	Month (range)	80 (2–221)
T stage	T1	79 (66.4%)
	T2	39 (62.8%)
	T3	1 (0.8%)
N stage	N1mi	73 (61.3%)
	N1	46 (38.7%)
Node number	1	97 (81.5%)
	2	12 (10.1%)
	3	10 (8.4%)
Tumor grade	G1	7 (5.9%)
	G2	91 (67.5%)
	G3	14 (11.8%)
	Unknown	7 (5.9%)
Lymphovascular invasion	Yes	28 (23.5%)
	No	74 (62.2%)
	Unknown	17 (14.3%)
Progesterone receptor	Positive	95 (79.8%)
	Negative	54 (20.2%)
p53	Negative	94 (81.0%)
	1+	11 (9.2%)
	2+	4 (3.4%)
	3+	6 (5.0%)
	Unknown	1 (0.8%)
Ki-67	<20	46 (38.7%)
	≥20	27 (22.7%)
	Unknown	46 (38.7%)
Operation method	Mastectomy	58 (48.7%)
	Breast conserving surgery	61 (51.3%)
Anti-hormonal therapy method	Tamoxifen only	45 (37.8%)
	Tamoxifen + GnRH	44 (37.0%)
	AI	30 (25.2%)

f/u, follow up; GnRH, gonadotrophin releasing hormone; AI, aromatase inhibitor.

recurrences occurred in 10 years: 1 case with local recurrence, 3 cases with regional recurrences, and 3 cases with distant metastases. The 5-year RFS was 96.3%, and the 10-year RFS was 88.9%. Among the 119 patients, there were 2 cases of death events in 5 years and 5 cases of death events in 10 years. In the 5 years, 1 case was associated with death from breast cancer, and 1 case was associated with death from other causes. In the 10 years, 1 case was associated with death caused by breast cancer, and 2 cases were associated with death caused by other factors. The cause of death was unknown in three cases. The Kaplan–Meier survival curve in Fig. 2 shows the RFS and OS of 119 patients who received anti-hormonal therapy only. The 5-year OS was 98.2%, and the 10-year OS was 89.0% (Fig. 2).

After propensity score matching, 83 patients belonged to the anti-hormonal therapy group, and 85 patients belonged to the chemotherapy with anti-hormonal therapy group (Table 2); the median follow-up time of the two groups was 80.5 months and 80.0 months, respectively. The Kaplan–Meier survival curves in Fig. 3 show two groups of RFS, DMFS, BCSS, and OS after propensity score matching. The 5-year RFS of the anti-hormonal therapy group and the chemotherapy with anti-hormonal therapy group was 96.1% and 94.0%, respectively, and the 10-year RFS of the two groups was 89.6% and 94.0%, respectively. On the other hand, the 5-year DMFS of the anti-hormonal therapy group and the chemotherapy with anti-hormonal therapy group was 97.4% and 94.0%, respectively, and the 10-year DMFS of the two groups was 93.2% and 94.0%, respectively. The 10-year BCSS of the anti-hormonal therapy group and the chemotherapy with anti-hormonal therapy group was 98.7% and 98.8%, respectively, and the 10-year OS of the two groups was 98.7% and 98.8%, respectively. There were no significant differences in RFS ($p = 0.871$), DMFS ($p = 0.491$), BCSS ($p = 0.569$), and OS ($p = 0.731$) between the two groups (Fig. 3).

We performed Cox proportional hazards regression analysis to identify factors that could influence RFS in the two groups following propensity score matching. In univariate analysis, pathologic tumor size and pathologic nodule size (continuous variables) were significantly associated with RFS. Both variables were also significant in multivariate analysis. The use of chemotherapy was not significant in univariate ($p = 0.871$) and multivariate ($p = 0.561$) analyses. The age at diagnosis was significantly correlated with RFS only in multivariate analysis (Table 3).

4. Discussion

In this study, survival analysis revealed that there was no significant difference in RFS, DMFS, BCSS, and OS between the anti-hormonal therapy group and the chemotherapy with anti-hormonal therapy group. In multivariate analysis, age, pathologic lymph node size, and T stage were independent factors that affected RFS. Our study was a retrospective study specifically demonstrating that clinically low-risk patients would not benefit from chemotherapy. The study was not a randomized controlled trial to identify low-risk patients; it was a study showing that chemotherapy was not required for clinically low-risk patients without genetic testing.

An overview of the results and analyses of individual trials have demonstrated the significant benefit of chemotherapy compared with treatment without chemotherapy.[16] Peto et al. divided patients with ER-positive breast cancer into two groups: an anthracycline-based chemotherapy group and a group without chemotherapy. In comparison between the two groups, the mortality rate from breast cancer in the chemotherapy group was reduced for both elderly women aged 55–69 years and women under 55 years of age.[10] In another study, the treatment of ER-positive breast cancer patients with tamoxifen for 5 years after surgery could reduce the recurrence rate by half and reduce breast cancer mortality by a third. In addition, for this group of patients, a combination of anthracycline-based chemotherapy and tamoxifen administration has been shown to reduce overall mortality by nearly 50%.[16,17]

However, several retrospective studies have indicated that patients with ER-positive breast cancer do not benefit from chemotherapy. Some studies used the Oncotype Dx 21-gene recurrence score (RS) to determine whether chemotherapy should be administered. In the NSABP B20

Table 2 The patient characteristics after matching.

Characteristic	status	Endocrine therapy alone group	Chemotherapy group	*p*-value
Median f/u time	Month (range)	80.5 (49.3)	80.0 (∓35.8)	
Age	Mean (SD)	53.0 (11.6)	52.2 (∓8.4)	
	<50y	37 (44.6%)	33 (38.8%)	0.53
	≥50y	46 (55.4%)	52 (61.2%)	
T stage	T1	56 (67.5%)	54 (63.5%)	0.63
	T2	46 (55.4%)	31 (36.5%)	
N stage	N1mi	52 (62.7%)	54 (63.5%)	1.00
	N1	31 (37.3%)	31 (36.5%)	
Node number	1	69 (83.1%)	67 (78.8%)	0.77
	2	9 (10.8%)	12 (14.1%)	
	3	5 (6.0%)	6 (7.1%)	
Tumor grade	G1	6 (7.2%)	6 (7.1%)	0.60
	G2	61 (73.5%)	69 (81.2%)	
	G3	11 (11.1%)	7 (8.2%)	
	Unknown	5 (6.0%)	3 (3.5%)	
Lymphovascular invasion	YES	20 (24.1%)	20 (23.5%)	0.25
	No	52 (62.7%)	60 (70.6%	
	Unknown	11 (13.3%)	5 (5.9%)	
Ki67	<20	26 (31.8%)	27 (31.8%)	0.99
	≥20	19 (22.9%)	20 (23.5%)	
	Unknown	38 (45.8%)	38 (44.7%)	
Progesterone receptor	Positive	72 (86.7%)	73 (85.9%)	1.00
	Negative	11 (13.3%)	12 (14.1%)	
Surgical method	BCS	54 (65.1%)	54 (63.5%)	0.87
	Mastectomy	29 (34.9%)	31 (36.5%)	
Radiation therapy	Yes	54 (65.1%)	54 (63.5%)	0.87
	No	29 (34.9%)	31 (36.5%)	

BCS, breast conserving surgery.

study, a low RS of 18 points and negative axillary lymph node status were reported for the low-risk group, who did not benefit from chemotherapy.[18] The SWOG 8814 study suggests that patients with involved axillary lymph nodes but with a low RS do not benefit from anthracycline-based chemotherapy, whereas those with a higher RS would benefit from chemotherapy independent of the number of positive nodes.[19] As a prospective study, the Trial Assigning Individualized Options for Treatment (TAILORx) trial did not benefit from the administration of chemotherapy to ER-positive, HER2-negative, and node-negative breast cancer patients with an Oncotype Dx RS of below 11 points.[7]

Axillary lymph node metastasis is known as the most accurate indicator of breast cancer prognosis. Stemmer

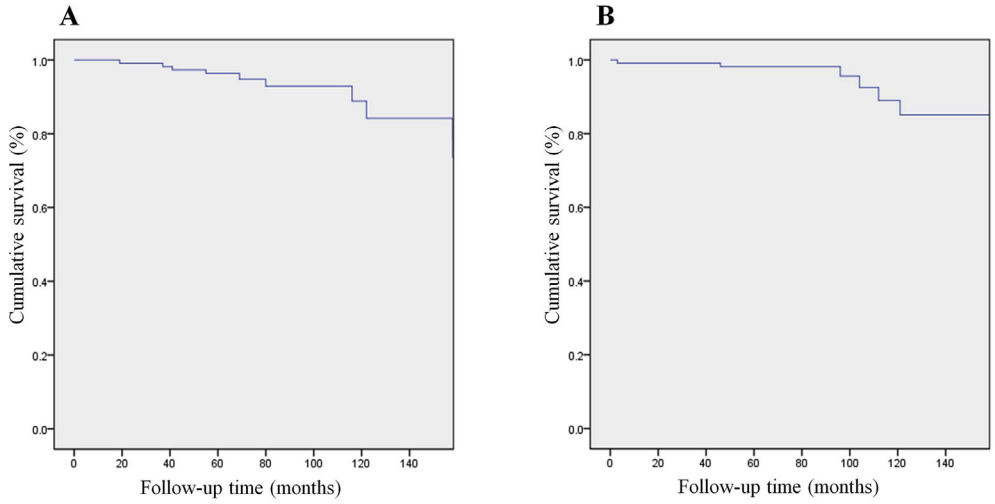

Figure 2 Kaplan—Meier survival curves for the (A) recurrence-free survival and (B) overall survival of the endocrine therapy (ETx) group before matching. 5-year recurrence-free survival: 96.3%, 10-year recurrence-free survival: 88.9%, 5-year overall survival: 98.2%, and 10-year overall survival: 89.0%.

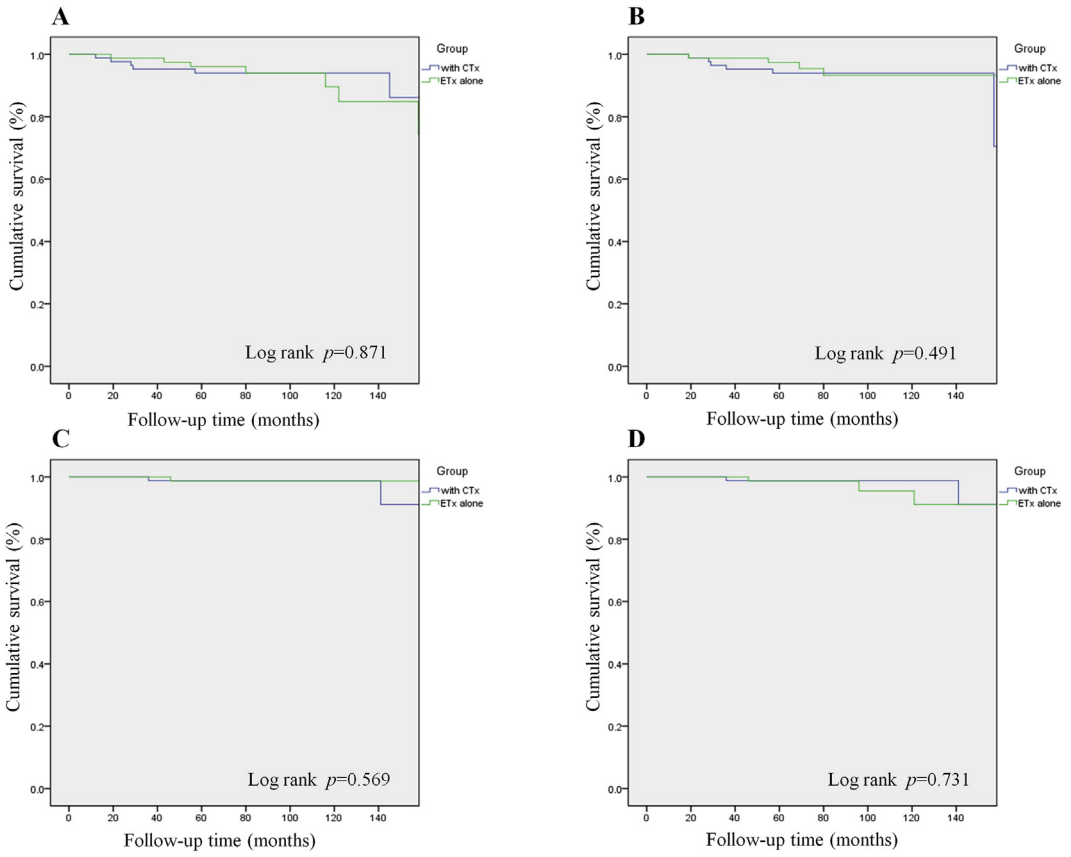

Figure 3 Kaplan—Meier survival curves for the (A) recurrence-free survival, (B) distant metastasis-free survival, (C) breast cancer-specific survival, and (D) overall survival of the endocrine therapy (ETx) group and the chemotherapy with endocrine therapy (CTx with ETx) group.

Table 3 Univariate and multivariate Cox regression analysis for disease-free survival.

Characteristics	Univariate		Multivariate	
	HR (CI 95%)	*p*-value	HR (CR 95%)	*p*-value
Type of breast surgery				
Mastectomy/BCS	1.96 (0.62—6.23)	0.256		
LVI				
Yes/No	2.29 (0.61—8.54)	0.219		
Pathologic tumor stage				
T1/T2	0.16 (0.43—0.57)	0.005	0.12 (0.31—0.49)	0.003
Pathologic nodal stage				
N1/N1mi	1.93 (0.64—5.78)	0.240		
Pathologic nodal size	1.09 (1.03—1.15)	0.001	1.11 (1.04—1.18)	0.001
Pathologic nodal number	1.06 (0.44—2.69)	0.849	0.90 (0.36—2.26)	0.817
Tumor grade				
G3/G1,2	0.89 (0.11—7.06)	0.915		
PR status				
Yes/No	2.34 (0.71—7.67)	0.161		
Chemotherapy				
Yes/No	0.91 (0.30—2.74)	0.871	0.69 (0.20—2.41)	0.561
Ki67				
<20%/≥20%	0.24 (0.25—2.32)	0.219		
Age				
<50/≥50	2.50 (0.80—7.81)	0.116	5.02 (1.26—20.07)	0.023

HR, hazard ratio; BCS, breast conserving surgery; LVI, lymphovascular invasion; PR, progesterone receptor.

et al. conducted a study on N1 micrometastasis and 1—3 positive nodes and found that the percentage of N1 micrometastasis was 42% and that of 1—3 positive nodes was 58%. They performed validation using the RS of Oncotype Dx, and a RS of <18 demonstrated very good clinical results.[20] The ongoing RxPONDER trial was designed as a multicenter phase III randomized trial for hormone receptor-positive and HER2-negative breast cancer patients with N1 stage and a 21-gene assay RS of 25 or less. The trial compared the outcomes of anti-hormonal therapy alone with chemotherapy followed by anti-hormonal therapy.[21] Although the results are not yet conclusive, a RS of 25, as suggested in the RxPONDER trial, has been used by many clinicians as a standard value.[14]

A retrospective study of node-positive and luminal type A breast cancer has been performed in South Korea. The study analyzed the OS and disease-free survival (DFS) of patients with node-positive, luminal A type breast cancer who received endocrine therapy alone or chemotherapy with endocrine therapy and found no difference between the two groups. In multivariate analysis, axillary lymph node metastasis and PR status were independent factors affecting OS and DFS. Overall, the results indicated that some patients with luminal A breast cancer may not benefit from systemic chemotherapy.[22]

The MINDACT study differentiated patients in high-risk and low-risk groups by genetic and clinical factors. In the high-clinical risk and low-genomic risk group, the rate of survival without distant metastasis was 94.7%. They achieved a goal of more than 92% in the 95% confidence interval. Survival analysis revealed that the use of adjuvant chemotherapy for patients with low clinical risk and high genomic risk was not superior to chemotherapy. For patients with high clinical risk and low genomic risk, the use of adjuvant chemotherapy resulted in a higher 5-year survival rate compared with treatment without chemotherapy. The survival rate without distant metastasis was 1.5% higher, the DFS rate was 2.8% higher, and the OS rate was 1.4% higher in the chemotherapy group compared with the group without chemotherapy; however, these results were not statistically significant.[15]

Adjuvant! Online is a web-based computer program that can predict the prognosis of breast cancer patients for 10 years.[23] In 2001, when Adjunct online began, there was not enough data on the effectiveness of chemotherapy. There is study that combining IBCSG data underestimate the effects of endocrine therapy alone and overestimate extra benefits.[24] However, in the MINDACT trial, low-clinical risk patients have been identified using this tool. According to their modified Adjuvant! Online clinical assessment the criteria for low-risk classification was only tumor grade 1 in the N1 stage patients with hormone receptor positive and HER-2 negative.[15] In our study, tumor grade 2 was 91 patients (65.7%) and tumor grade3 was 14 patients (11.1%) in N1 stage. According to Adjuvant online! tool, they were high risk group. In this study, 76.8% of high-risk patients were included, but 5-year RFS and 10-year RFS showed good prognosis of 96.3% and 88.9%, respectively. And that was showed good prognosis even after matching. We think that these results will include a significant number of patients with a low risk of actual recurrence within the clinical high-risk group. We believe that some validation tools, such as gene assay, are additionally needed in patients at high clinical risk, and this data may be the basis for that.

There are some limitations in our study. First, there is a limit to the interpretation of retrospective studies. Second, relatively few patients were enrolled in the endocrine treatment group, and a large number of patients in the chemotherapy group were eliminated during the propensity score matching process. Third, there was only a single node in most patients; thus, it may be challenging to reflect the entire N1 class. Fourth, in our study, we tried to eliminate significant differences between the two groups through propensity score matching, but there is still some difference between the two groups. Finally, there was something unknown in the data, especially ki67 that is important for risk assessment could affect the outcome.

Nevertheless, an advantage of our study is that we could match the node size and number, unlike previous studies. In both groups, the number of N1 micrometastasis and N1 macroscopic metastasis was also matched, and there was no difference in RFS and OS between the two groups. Previously, N1 macrometastasis was highly recommended as a criterion for chemotherapy; however, this study demonstrated that chemotherapy may be avoided even with N1 macrometastasis.

According to the Adjuvant! Online, the low-risk group of N1 stage cancers is only nuclear grade 1 tumors. However, the patient population included patients with nuclear grade 2 and 3 tumors. We recommend the use of new low-risk criteria that may include nuclear grade 2 tumors.

5. Conclusions

Low-risk patients include patients with hormone receptor-positive, HER2-negative, and N1 stage breast cancer. Even if chemotherapy is omitted, the survival rate of some patients may not be affected. Clinical factors alone may be sufficient to distinguish low-risk patients. We could use these clinical factors in combination with genetic assays to identify low-risk patients and prevent these patients from experiencing the side effects of chemotherapy. Nevertheless, further studies using a large number of patients with a long-term follow-up period will be necessary for verification.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflicts of interest

The authors declare that they have no conflict of interest.

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