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Post-relapse survival in patients with early and late distant recurrence in estrogen receptor-positive, HER2-negative breast cancer

Akiko Ogiya[1], Kieko Yamazaki[1], Rie Horii[2], Tadahiko Shien[3], Yoshiya Horimoto[4], Norikazu Masuda[5], Touko Inao[6], Mitsuchika Hosoda[7], Naoko Ishida[7], Tomofumi Osako[8], Masato Takahashi[9], Yumi Endo[10], Yuichiro Miyoshi[3], Hiroyuki Yasojima[5], Nobumoto Tomioka[9], Hiroko Yamashita[7*]; Collaborative Study Group of Scientific Research of the Japanese Breast Cancer Society

[1] Breast Surgical Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

[2] Division of Pathology, Cancer Institute of the Japanese Foundation for Cancer Research, Tokyo, Japan

[3] Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan

[4] Department of Breast Oncology, Juntendo University School of Medicine, Tokyo, Japan

[5] Department of Surgery, Breast oncology, NHO Osaka National Hospital, Osaka, Japan

[6] Department of Breast & Endocrine Surgery, Graduate School of Medical Science Kumamoto University, Kumamoto, Japan

[7] Breast Surgery, Hokkaido University Hospital, Sapporo, Japan

[8] Department of Breast and Endocrine Surgery, Kumamoto City Hospital, Kumamoto, Japan†

†Present address: Kumamoto Shinto General Hospital, Kumamoto, Japan

[9] Department of Breast Surgery, NHO Hokkaido Cancer Center, Sapporo, Japan

[10] Department of Oncology, Immunology and Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

***Corresponding author:** Hiroko Yamashita

Breast Surgery, Hokkaido University Hospital, Kita 14, Nishi 5, Kita-ku,

Sapporo 060-8648, Japan

Tel: +81-11-706-7381, **Fax:** +81-11-706-7384

E-mail: hirokoy@huhp.hokudai.ac.jp

Key words: Breast cancer, Post-relapse survival, Prognosis, Estrogen receptor-positive, Endocrine therapy

Abstract

Background: Few studies have been performed on post-relapse survival in patients with early and late distant recurrence in estrogen receptor (ER)-positive, HER2-negative breast cancer.

Methods: A total of 205 patients with early distant recurrence and 134 patients with late distant recurrence of ER-positive, HER2-negative breast cancer who had undergone breast surgery or neoadjuvant chemotherapy between January 2000 and December 2004 were registered from nine institutions. Prognostic factors for post-relapse survival in patients with early and late recurrence were analyzed.

Results: Post-relapse survival was significantly longer in patients with late recurrence than in patients with early recurrence. Predictive factors for post-relapse survival in patients with early recurrence were lack of adjuvant chemotherapy, a long disease-free interval, and long durations of endocrine therapies and chemotherapies after relapse. In patients with late recurrence, post-relapse survival was significantly improved for those individuals with one metastatic organ at relapse and individuals who were treated with first-line and subsequent endocrine therapies for prolonged periods. Moreover, ER expression in primary breast tumors of late recurrence patients was significantly higher with a duration of first-line endocrine therapy > 6 months than in those with a duration ≤ 6 months.

Conclusion: Predictors for prognosis after relapse differed between patients with early and late distant recurrence. Endocrine responsiveness after relapse is a key factor for improved post-relapse survival, and it is thus important to establish whether metastatic tumors are

endocrine-resistant in ER-positive, HER2-negative recurrent breast cancer.

Abbreviations

ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor type 2; Ki67 LI, Ki67 labeling index; IHC, immunohistochemistry

Introduction

Women with estrogen receptor (ER)-positive breast cancer remain at particular risk for late recurrence, which is defined as relapse more than five years after initial treatment [1, 2]. Encouragingly, extended adjuvant endocrine therapy can reduce the frequency of late recurrence [3-6]. Accurate and reliable estimates of the risk of recurrence after five years of endocrine therapy, which would enable appropriate decisions regarding extended periods of this treatment modality, are therefore required. The risk of long-term relapse is related to the number of positive lymph nodes and the large size of invasive tumors [7-10]. Furthermore, multi-parametric molecular assays, including IHC4, OncotypeDX, EndoPredict, PAM50, and Breast Cancer Index, have been developed for predicting early (relapse less than five years after initial treatment) and/or late distant recurrence [8, 11].

Predictive factors for early and late recurrence, especially in postmenopausal ER-positive breast cancer, have previously been reported. However, there are few studies on predictors of prognosis after relapse. We previously demonstrated that high expression of ER, increased phosphorylation of ERα serine 167, and low expression of Ki67 and p53 in primary breast tumors were associated with response to first-line endocrine therapy and post-relapse survival in ER-positive metastatic breast cancer [12-15]. In these cases, tamoxifen was mainly used as an adjuvant endocrine therapy and/or as first-line endocrine therapy after relapse. However, prognostic factors after relapse might differ between women who receive adjuvant tamoxifen and those who are treated with aromatase inhibitors among postmenopausal women

with ER-positive metastatic breast cancer. Furthermore, post-relapse survival might differ between patients with early or late recurrence. Recently, novel targeting agents such as everolimus, CDK 4/6 inhibitors, and PI3K inhibitors have been used in combination with endocrine therapies in ER-positive metastatic breast cancer [16, 17]. Therefore, understanding the response to endocrine therapy and survival in metastatic ER-positive breast cancer is critical in order to develop appropriate treatment strategies that utilize novel targeted agents [17].

We recently reported a multi-institutional joint retrospective study, carried out as Scientific Research of the Japanese Breast Cancer Society, using data from ER-positive, HER2-negative breast cancer patients with early and late distant recurrence [9]. Because all patients in the study were given their initial treatment between 2000 and 2004, almost 80% of postmenopausal women received aromatase inhibitors as adjuvant endocrine therapy, and anthracyclins and/or taxanes were used as adjuvant or neoadjuvant chemotherapy. In the present study, which is a follow-up of the initial multi-institutional joint project, we analyzed factors that were prognostic for post-relapse survival in patients with early and late recurrence.

Patients and methods

Patients and breast cancer samples

Patients with early and late distant recurrence of ER-positive, HER2-negative breast cancer who had undergone breast surgery or neoadjuvant chemotherapy between January 2000 and December 2004 were registered from nine institutions. They were incorporated into a multi-institutional joint study titled ‘Analysis on biological characteristics and factors predicting late recurrence in breast cancer’, and the project was carried out under the auspices of Scientific Research of the Japanese Breast Cancer Society [9]. Early recurrence was defined as relapse within 5 years, and late recurrence was defined as relapse more than 5 years after initial treatment. A total of 205 patients with early recurrence and 134 patients with late recurrence were analyzed in this study; 18 patients with early recurrence and 14 patients with late recurrence in the original cohort were excluded because information regarding first-line treatments after relapse was lacking. Treatment regimens and periods after the recurrence and post-relapse survival were retrospectively compared between the early and late recurrence groups. The study protocol was approved by the institutional review board in all nine institutions and conformed to the guidelines of the 1996 Declaration of Helsinki.

Expression of ER, progesterone receptor (PgR) and Ki67 in primary breast tumors was centrally assessed by immunohistochemistry (IHC). HER2-positive tumors were excluded from this study [9].

Statistical analysis

The chi-squared test, Student's *t*-test and the Mann-Whitney *U*-test were used to compare clinicopathological characteristics and treatments among patients with early and late recurrence. Estimation of post-relapse survival was performed using the Kaplan-Meier methods, and differences between survival curves were assessed with the log-rank test. Univariate and multivariate analyses with Cox proportional hazards regression models were used to identify independent prognostic factors in all patients. p values < 0.05 were considered significant.

Results

Comparison of clinicopathological characteristics and treatments between patients with early and late recurrence

We collected data from a total of 205 women with early distant recurrence and 134 women with late distant recurrence in ER-positive, HER2-negative breast cancer (Table 1). The median disease-free intervals were 33 months (range 1–58 months) in the early recurrence cohort and 91 months (range 60–162 months) in the late recurrence cohort. Of the 43 (21%) patients with early recurrence who did not receive adjuvant endocrine therapy, 12 individuals received adjuvant endocrine therapy for less than 6 months, and 4 patients relapsed before adjuvant endocrine therapy. Fifty-four women (26%) with early relapse and 54 women (40%) with late relapse had multiple metastatic organs at relapse (p = 0.009). In terms of metastatic sites at relapse, the proportion of lung metastases was significantly higher in patients with late relapse than in those with early relapse (35% and 22%, respectively, p = 0.01). The fraction of patients who received endocrine therapy for the first-line treatment after relapse was 65% in the early recurrence cohort and 79% in the late recurrence cohort (p = 0.03). There were no differences between the two cohorts with regard to time-to-progression with respect to first-line endocrine therapy (median 11 months, range 1-120 months versus median 12.5 months, range 0.6-77 months, early versus late relapse). On the other hand, total duration of endocrine therapies after relapse was significantly shorter in patients with early recurrence compared with those with late recurrence (median 14 months, range 0-120 months

versus median 23 months, range 0-78 months, early versus late relapse, $p = 0.001$). The number of chemotherapy regimens was significantly higher in patients with early recurrence compared to those with late recurrence (median 3, range 1-8 versus median 2, range 1-6, early versus late relapse, $p = 0.01$). The median follow-up periods after relapse were 76 months (range 14–177 months) in the early recurrence cohort and 133 months (range 66–175 months) in the late recurrence cohort. Post-relapse survival was significantly longer in patients with late recurrence than in patients with early recurrence ($p = 0.0074$, Fig. 1). The 5-year post-relapse survivals were 35% in patients with early recurrence and 57% in patients with late recurrence.

Factors predicting post-relapse survival in patients with early recurrence

We then analyzed factors predicting post-relapse survival in patients with early recurrence. When analyzing post-relapse survival, setting the cutoff point at 3 years yielded the most significant difference between patient groups. Kaplan-Meier analysis showed that patients whose disease-free interval was more than 3 years displayed longer post-relapse survival compared with patients with shorter disease-free intervals ($p = 0.007$, Fig. 2). The 5-year post-relapse survivals were 29% in patients with a disease-free interval ≤ 3 years and 49% in patients with a disease-free interval > 3 years. Univariate analysis (Table 2) identified that significant correlations between long post-relapse survival and low tumor grade ($p = 0.0001$), high PgR expression ($p = 0.04$), low Ki67 LI ($p = 0.001$), lack of adjuvant

chemotherapy and radiation therapy ($p = 0.02$ and $p = 0.02$, respectively), a long disease-free interval ($p = 0.001$), normal levels of tumor markers (CEA and/or CA15-3) at relapse ($p = 0.04$), a long duration of first-line endocrine therapy after relapse ($p = 0.01$), and long durations of endocrine therapies and chemotherapies after relapse ($p < 0.0001$ and $p < 0.0001$, respectively). Receiving adjuvant endocrine therapy did not affect post-relapse survival. Multivariate analysis revealed significantly improved post-relapse survival in early recurrence patients with lack of adjuvant chemotherapy ($p = 0.001$), a long disease-free interval ($p = 0.002$), and long durations of endocrine therapies and chemotherapies after relapse ($p < 0.0001$ and $p < 0.0001$, respectively) (Table 2).

Factors predicting post-relapse survival in patients with late recurrence

We next analyzed factors predicting post-relapse survival in patients with late recurrence. Kaplan-Meier analysis showed that patients who responded to first-line endocrine therapy (duration > 6 months) had longer post-relapse survival compared with those on first-line endocrine therapy for ≤ 6 months ($p < 0.0001$, Fig. 3). Five-year post-relapse survival was 41% in patients with a duration of first-line endocrine therapy ≤ 6 months and 70% in patients with a duration of first-line endocrine therapy > 6 months. Univariate analysis (Table 3) identified significant correlations between long post-relapse survival and small number of positive lymph nodes ($p = 0.049$), use of radiation therapy, a single metastatic organ at relapse ($p = 0.002$), a long duration of first-line endocrine therapy ($p < 0.0001$), and a

long total duration of endocrine therapies (p= 0.04) after relapse. Multivariate analysis revealed significantly improved post-relapse survival in late recurrence patients with a single metastatic organ at relapse (p = 0.03), a long duration of first-line endocrine therapy (p < 0.0001) and a long total duration of endocrine therapies (p= 0.01) after relapse (Table 3).

Comparison of clinicopathological characteristics and treatments according to response to first-line endocrine therapy after relapse in patients with late recurrence

The above results indicate that duration of first-line endocrine therapy was the most significant prognostic factor for post-relapse survival in patients with late recurrence. Therefore, we compared the clinicopathological characteristics and treatments between a duration of first-line endocrine therapy ≤ 6 months and > 6 months in patients who were treated endocrine therapy as the initial treatment at relapse (Table 4). ER expression in primary breast tumors was significantly higher in patients with a duration of first-line endocrine therapy > 6 months than in those with a duration ≤ 6 months (p = 0.03). The mean percentage of ER positive cells was 66.0% in patients with a duration of first-line endocrine therapy > 6 months, and 51.6% in those with a duration ≤ 6 months (Table 4). Moreover, the total duration of endocrine therapies after relapse was significantly longer in patients with a duration of first-line endocrine therapy > 6 months (p < 0.0001). Mean total duration of endocrine therapies after relapse was 32.7 months in patients that were treated with first-line endocrine therapy for > 6 months, while it was 12.0 months in those with a duration of ≤ 6

months (Table 4). Other clinicopathological factors and treatments were similar, –in patients with late recurrence independently of the duration of first-line endocrine therapy.

Discussion

We investigated the clinicopathological factors and treatments predicting post-relapse survival in ER-positive, HER2-negative breast cancer patients with early and late recurrence. Our results demonstrated that post-relapse survival was significantly longer in patients with late recurrence than in those with early recurrence, and that predictors for prognosis after relapse were different between the two cohorts. Predictive factors for post-relapse survival in patients with early recurrence were lack of adjuvant chemotherapy, a long disease-free interval, and long durations of endocrine and chemotherapies after relapse. In patients with late recurrence, the involvement of metastasis in only one organ at relapse, a long duration of first-line endocrine therapy, and a long total duration of endocrine therapies after relapse significantly improved post-relapse survival. Moreover, ER expression in primary breast tumors of late recurrence patients was significantly higher in patients with a duration of first-line endocrine therapy > 6 months than in those with a duration ≤ 6 months.

Our previous study demonstrated that predictive factors for early and late recurrence were mainly a large tumor size and a large number of positive lymph nodes [9]. However, as expected, tumor size and lymph node status at the initial treatments were not associated with post-relapse survival in patients with both early and late recurrence. Approximately two-thirds of women who relapsed within 5 years had received anthracyclines and/or taxanes as adjuvant or neoadjuvant chemotherapy. Moreover, approximately 90% of patients with early recurrence developed distant metastasis during adjuvant endocrine therapy. Therefore, we infer that most

patients with early recurrence in our study were resistant to standard endocrine therapies and chemotherapies. On the other hand, our present study shows that lack of adjuvant chemotherapy, a long disease-free interval, and long durations of endocrine and chemotherapies after relapse were independent prognostic factors for patients with early relapse; furthermore, low tumor grade and low Ki67 LI were associated with longer post-relapse survival in univariate analysis. The 5-year post-relapse survival was significantly longer in patients with a disease-free interval > 3 years than in patients with a disease-free interval ≤ 3 years. Despite the occurrence of relapse within 5 years of the initial treatments, we suggest that patients with a disease-free interval > 3 years have relatively low-grade tumors that essentially remain responsive to other endocrine or chemotherapeutic agents.

Our results further show that single metastatic organ at relapse, a long duration of first-line endocrine therapy and a long total duration of endocrine therapies after relapse are independent prognostic factors for post-relapse survival in patients with late recurrence. Breast cancer patients with bone-only metastases had excellent clinical outcomes, especially in hormone receptor-positive breast cancer, and the median post-relapse survival was 79.4 months [18]. Endocrine therapy is usually recommended as first-line treatment for patients with bone-only metastases in ER-positive breast cancer. Here, we demonstrated that 79% of patients with late relapse received endocrine therapy as first-line treatment after relapse. Moreover, 76% of patients who received endocrine therapy as first-line treatment responded to the treatment, such as a duration of first-line endocrine therapy > 6 months. In contrast,

24% of patients who did not respond to first-line endocrine therapy had a worse prognosis, as the 5-year post-relapse survival was 41%; this is similar to the 5-year post-relapse survival in patients with early recurrence (35%). Most patients who do not respond to the first-line endocrine therapy after relapse are likely to be endocrine-resistant, and chemotherapies are usually selected as the second-line treatment [19].

Our results show that in patients with late recurrence, ER expression in primary breast tumors was significantly higher in patients with a duration of first-line endocrine therapy > 6 months than in those treated for shorter periods, whereas other clinicopathological factors were not correlated with response to first-line endocrine therapy. Although ER expression and endocrine responsiveness in metastatic sites are reduced as the disease progresses [20], malignancies at the initial metastatic sites may retain the biology of primary breast tumors, despite the lapse of time since the initial treatments [21]. Furthermore, a recent study showed that an epithelial to mesenchymal transition-related gene signature in the primary breast tumors is related stromal activation and escape from disease dormancy [22].

Recently, inhibitors of mTOR, CDK 4/6, and PI3K have been developed and used in combination with endocrine therapies in ER-positive metastatic breast cancer [16]. Understanding predictors for the response to endocrine therapy and overall survival in metastatic ER-positive breast cancer will facilitate the stratification of patients to be treated with specific targeted molecular therapies.

In conclusion, our study demonstrates that the predictors of prognosis after relapse

are different between patients with early and late distant recurrence. Endocrine responsiveness after relapse is a key factor for improved post-relapse survival, and it is thus important to establish whether metastatic tumors are endocrine-resistant in ER-positive, HER2-negative recurrent breast cancer.

Acknowledgments

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Conflict of interest statement

The authors have no conflict of interest.

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Figure legends

Fig. 1: Post-relapse survival of patients with early and late distant recurrence. The 5-year post-relapse survivals were 35% in patients with early recurrence and 57% in those with late recurrence ($p = 0.0074$).

Fig. 2: Post-relapse survival according to disease-free interval in patients with early recurrence. The 5-year post-relapse survivals were 29% in patients with a disease-free interval ≤ 3 years and 49% in patients with a disease-free interval > 3 years ($p = 0.007$).

Fig. 3: Post-relapse survival according to the duration of first-line endocrine therapy in patients with late recurrence. The 5-year post-relapse survivals were 41% in patients with a duration of first-line endocrine therapy ≤ 6 months and 70% in patients with a duration of first-line endocrine therapy > 6 months ($p < 0.0001$).

Fig. 1

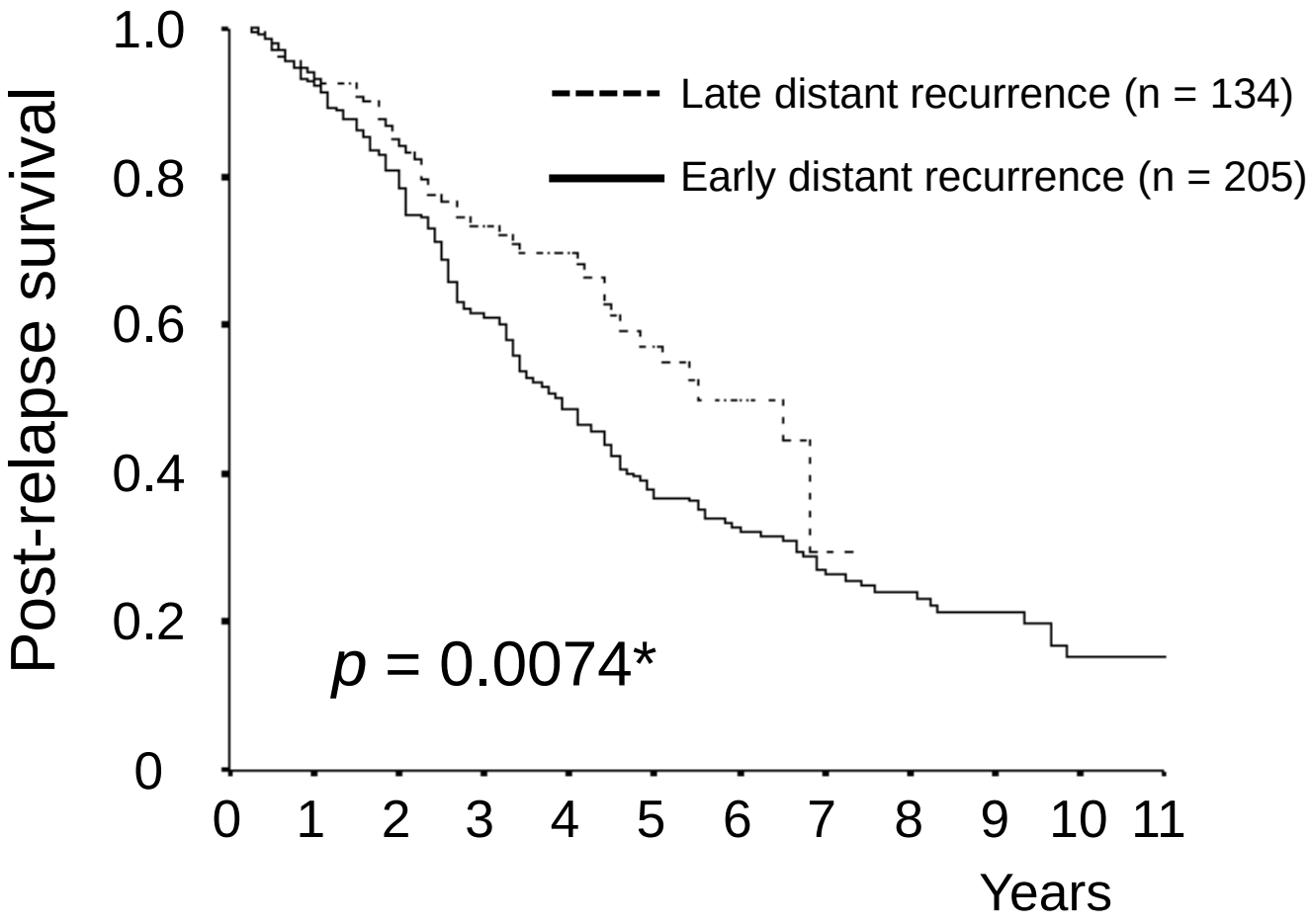

Post-relapse survival
1.0
0.8
0.6
0.4
0.2
0
0 1 2 3 4 5 6 7 8 9 10 11
Years
Late distant recurrence (n = 134)
Early distant recurrence (n = 205)
p = 0.0074*

Fig. 2

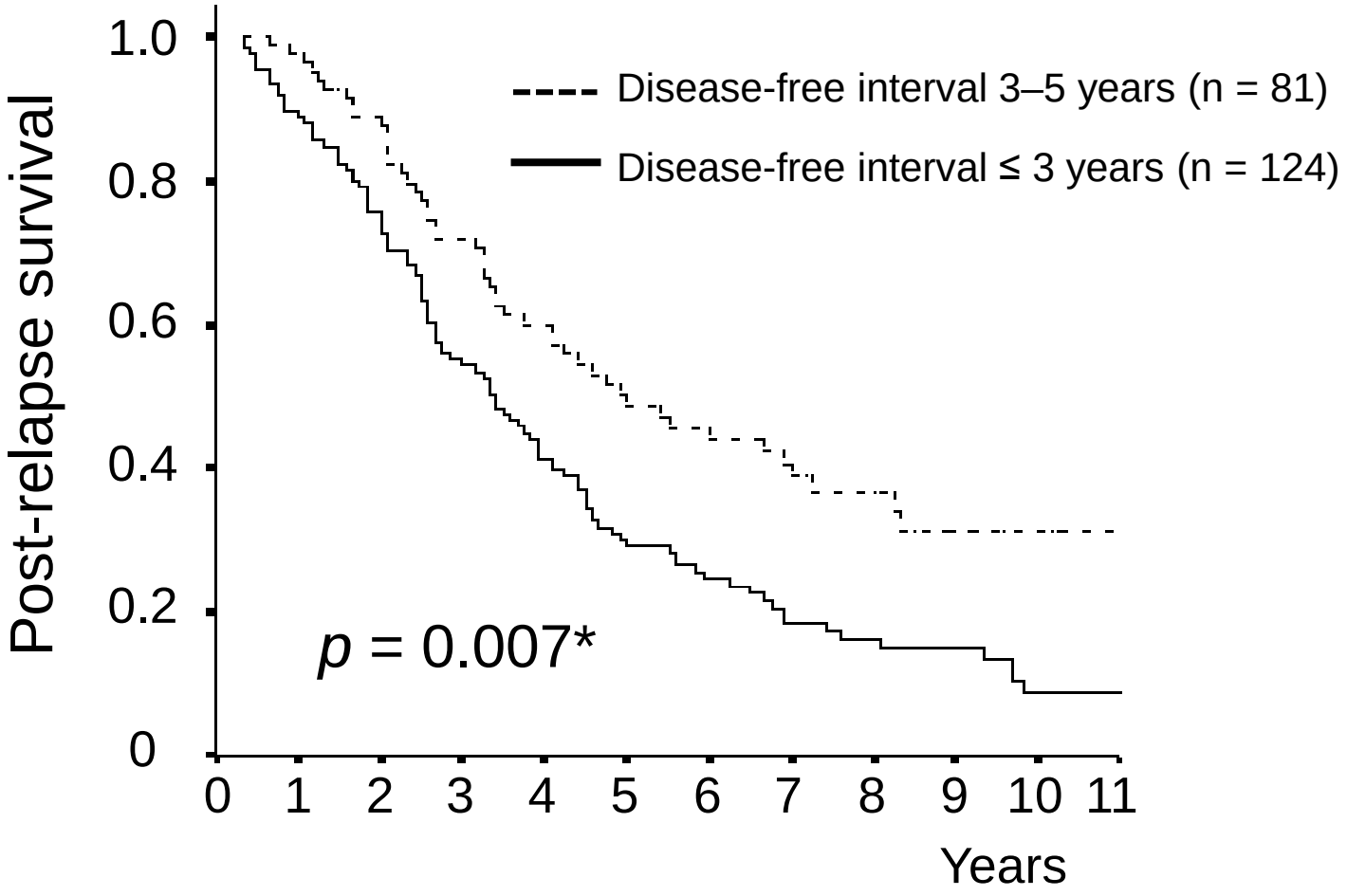

Post-relapse survival
1.0
0.8
0.6
0.4
0.2
0
0 1 2 3 4 5 6 7 8 9 10 11
Years
Disease-free interval 3–5 years (n = 81)
Disease-free interval ≤ 3 years (n = 124)
p = 0.007*

Fig. 3

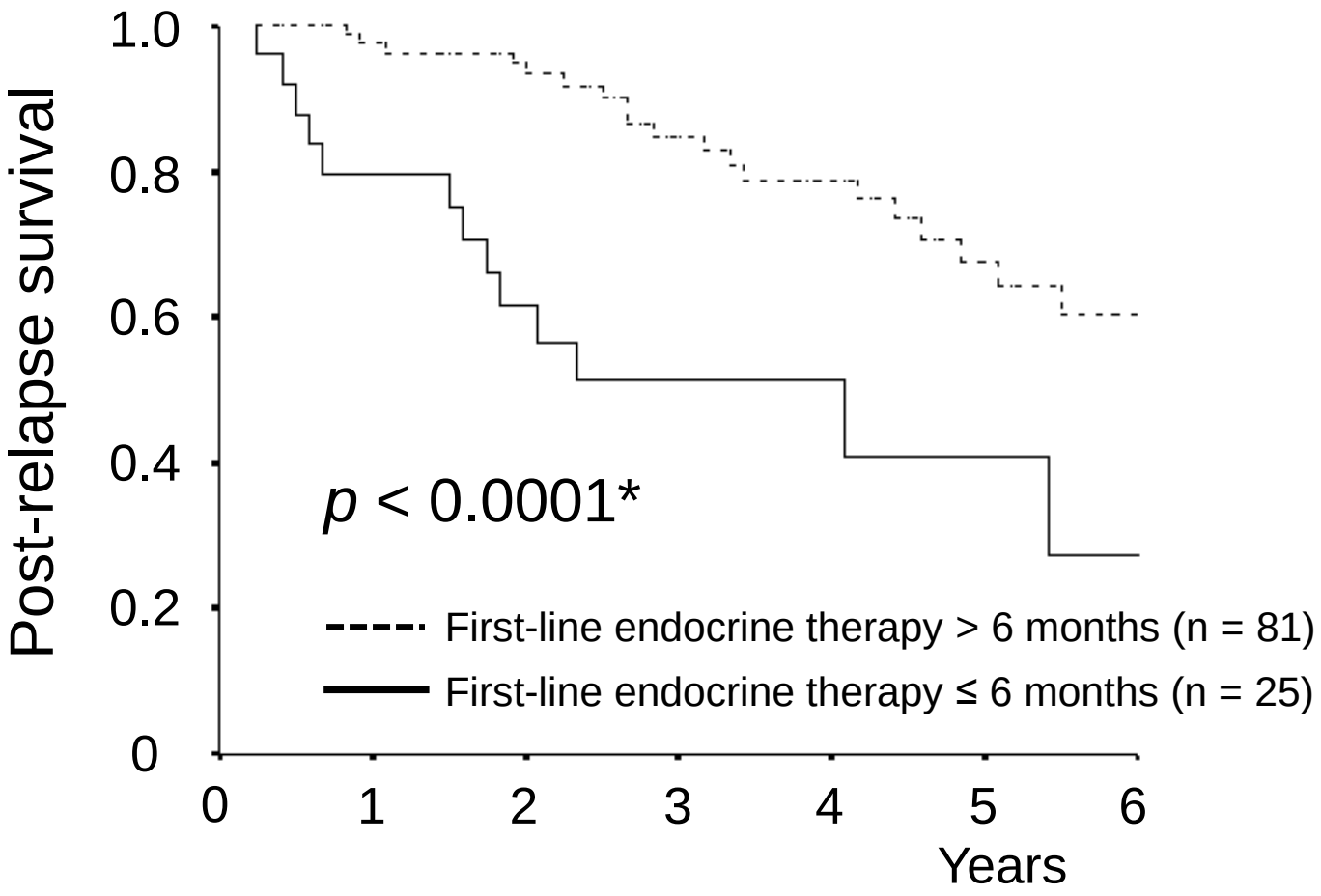

Post-relapse survival
1.0
0.8
0.6
0.4
0.2
0
0
1
2
3
4
5
6
Years
p < 0.0001*
First-line endocrine therapy > 6 months (n = 81)
First-line endocrine therapy ≤ 6 months (n = 25)

Table 1. Comparison of clinicopathological characteristics and treatments between patients with early and late recurrence

	Early recurrence (n = 205)	Late recurrence (n = 134)	*P*-value
Menopausal status (at the time of the initial therapy)			
Premenopausal	104 (51%)	55 (41%)	0.08
Postmenopausal	101 (49%)	79 (59%)	
Tumor category (pathological)			
pT1	60 (29%)	58 (43%)	
pT2	100 (49%)	61 (46%)	
pT3	34 (17%)	9 (7%)	0.03*
pT4	8 (4%)	4 (3%)	
Unknown	3 (2%)	2 (2%)	
No. of positive lymph nodes			
0	46 (22%)	50 (37%)	
1-3	64 (31%)	54 (40%)	
4-9	38 (19%)	13 (10%)	<0.0001*
≥ 10	55 (27%)	17 (13%)	
Unknown	2 (1%)	0	
Histological type			
Invasive ductal carcinoma	192 (94%)	126 (93%)	
Invasive lobular carcinoma	12 (6%)	3 (2%)	0.03*
Other	1 (0.5%)	5 (6%)	
Tumor grade			
1	60 (29%)	54 (40%)	
2	90 (44%)	53 (40%)	0.09
3	55 (27%)	27 (20%)	
ER (%), median (range)	70.0 (1-100)	70.0 (1-100)	0.71
PgR (%), median (range)	30.0 (0-100)	30.0 (1-100)	0.45
Ki67 LI (%), median (range)	14.0 (0-53.0)	9.2 (0-70.0)	0.01*
Neoadjuvant chemotherapy			
Yes	48 (23%)	14 (10%)	0.002*
No	157 (77%)	120 (90%)	
Adjuvant therapy			
Endocrine therapy			
Yes	162 (79%)	122 (91%)	
No	43 (21%)	10 (8%)	0.001*
Unknown	0	2 (2%)	
Chemotherapy			
Yes	126 (62%)	76 (57%)	
No	78 (38%)	58 (43%)	0.47
Unknown	1 (0.5%)	0	
Radiotherapy			
Yes	98 (48%)	45 (34%)	
No	105 (51%)	88 (66%)	0.03*
Unknown	2 (1%)	1 (1%)	

Elevation of serum levels of tumor markers at relapse			
No elevation	88 (43%)	59 (44%)	
CEA only	24 (12%)	27 (20%)	
CA15-3 only	41 (20%)	20 (15%)	0.17
Both CEA and CA15-3	45 (22%)	26 (20%)	
Unknown	7 (3%)	2 (2%)	
No. of metastatic organs at relapse			
Single	151 (74%)	80 (60%)	0.009*
Multiple	54 (26%)	54 (40%)	
Metastatic site at relapse			
Bone	101 (49%)	63 (47%)	0.69
Liver	42 (20%)	20 (15%)	0.20
Lung	46 (22%)	47 (35%)	0.01*
Brain	3 (1%)	2 (1%)	0.98
Other	46 (22%)	29 (22%)	0.86
First-line treatment after relapse			
Endocrine therapy	134 (65%)	106 (79%)	
Chemotherapy	63 (31%)	26 (19%)	0.03*
Other	5 (2%)	0	
None	3 (2%)	2 (2%)	
Time-to-progression of first-line endocrine therapy (months)			
median (range)	11 (1-120)	12.5 (0.6-77)	0.41
Total duration of endocrine therapies after relapse (months)			
median (range)	14 (0-120)	23 (0-78)	0.001*
No. of chemotherapy regimens after relapse			
median (range)	3 (1-8)	2 (1-6)	0.01*
Total duration of chemotherapies after relapse (months)			
median (range)	19 (2-126)	18.5 (2-59)	0.12

*$p < 0.05$ is considered significant.

Table 2. Univariate and multivariate analyses of factors predicting post-relapse survival in patients with early recurrence

	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Menopausal status	1.278	0.928-1.761	0.13			
Tumor category (pathological)	0.999	0.998-1.001	0.43			
No. of positive lymph nodes	1.109	0.997-1.001	0.47			
Histological type	1.806	0.915-3.565	0.09			
Tumor grade	1.463	1.173-1.824	0.001*	1.293	0.940-1.780	0.11
ER status (%)	1.000	0.995-1.005	0.99			
PgR status (%)	0.995	0.990-1.000	0.04*	1.002	0.995-1.009	0.56
Ki67 LI (%)	1.024	1.010-1.038	0.001*	1.001	0.980-1.022	0.94
Neoadjuvant chemotherapy	1.011	0.695-1.470	0.96			
Adjuvant therapy						
Endocrine therapy	0.873	0.595-1.279	0.49			
Chemotherapy	1.002	1.000-1.004	0.02*	2.508	1.455-4.325	0.001*
Radiotherapy	1.002	1.000-1.003	0.02*	1.000	0.997-1.002	0.77
Disease-free interval	0.982	0.972-0.993	0.001*	0.975	0.959-0.991	0.002*
No. of metastatic organs at relapse	1.246	0.867-1.790	0.23			
Elevation of CEA and/or CA15-3 at relapse	1.001	1.000-1.002	0.04*	1.000	1.000-1.003	0.10
First-line treatment after relapse	1.451	1.079-1.951	0.01*			
Duration of first-line endocrine therapy ($\leq$ 6 months vs. > 6 months)	0.588	0.384-0.900	0.01*	0.816	0.462-1.441	0.48
Total duration of endocrine therapies after relapse (months)	0.967	0.957-0.976	<0.0001*	0.933	0.917-0.950	<0.0001*
No. of chemotherapy regimens after relapse	1.003	0.931-1.080	0.93			
Total duration of chemotherapies after relapse (months)	0.982	0.974-0.989	<0.0001*	0.944	0.929-0.959	<0.0001*

*$p < 0.05$ is considered significant.

Table 3. Univariate and multivariate analyses of factors predicting post-relapse survival in patients with late recurrence

	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Menopausal status	1.622	0.873-3.016	0.13			
Tumor category (pathological)	0.777	0.494-1.222	0.27			
No. of positive lymph nodes	1.333	1.002-1.774	0.049*	1.212	0.849-1.730	0.29
Histological type	0.864	0.410-1.824	0.70			
Tumor grade	1.167	0.787-1.729	0.44			
ER status (%)	1.003	0.994-1.013	0.45			
PgR status (%)	1.000	0.991-1.008	0.95			
Ki67 LI (%)	1.012	0.992-1.033	0.24			
Neoadjuvant chemotherapy	0.712	0.220-2.300	0.57			
Adjuvant therapy						
Endocrine therapy	0.863	0.339-2.196	0.76			
Chemotherapy	1.014	0.559-1.839	0.96			
Radiotherapy	1.002	1.000-1.004	0.04*	1.025	0.487-2.153	0.95
Disease-free interval	0.991	0.944-1.006	0.23			
No. of metastatic organs at relapse (Single vs. multiple)	2.570	1.413-4.676	0.002*	2.185	1.076-4.438	0.03*
Elevation of CEA and/or CA15-3 at relapse	0.997	0.985-1.010	0.68			
First-line treatment after relapse	1.580	0.815-3.064	0.18			
Duration of first-line endocrine therapy ($\leq$ 6 months vs. > 6 months)	0.858	0.800-0.921	<0.0001*	0.252	0.119-0.534	<0.0001*
Total duration of endocrine therapies after relapse (months)	1.014	1.000-1.028	0.04*	1.021	1.004-1.038	0.01*
No. of chemotherapy regimens after relapse	1.077	0.925-1.254	0.34			
Total duration of chemotherapies after relapse (months)	0.986		0.19			

*$p < 0.05$ is considered significant.

Table 4. Comparison of clinicopathological characteristics and treatments according to response to first-line endocrine therapy after relapse in patients with late recurrence

	Duration of first-line endocrine therapy		*P*-value
	≤ 6 months (n = 25)	> 6 months (n = 81)	
Menopausal status (at the time of the initial therapy)			
Premenopausal	11 (44%)	31 (38%)	0.65
Postmenopausal	14 (56%)	50 (62%)	
Tumor category (pathological)			
pT1	8 (32%)	36 (44%)	
pT2	14 (56%)	36 (44%)	
pT3	1 (4%)	5 (6%)	0.7
pT4	1 (4%)	3 (4%)	
Unknown	1 (4%)	1 (1%)	
No. of positive lymph nodes			
0	11 (44%)	32 (40%)	
1-3	11 (44%)	33 (41%)	
4-9	0	9 (11%)	0.37
≥ 10	3 (12%)	7 (9%)	
Unknown			
Histological type			
Invasive ductal carcinoma	22 (88%)	76 (94%)	
Invasive lobular carcinoma	2 (8%)	1 (1%)	0.2
Other	1 (4%)	4 (5%)	
Tumor grade			
1	11 (44%)	34 (42%)	
2	8 (32%)	34 (42%)	0.56
3	6 (24%)	13 (16%)	
ER (%), median (range)	60 (1-100)	80 (1-100)	0.03*
PgR (%), median (range)	50 (0-100)	30 (0-100)	0.59
Ki67 LI (%), median (range)	7.7 (0-50)	9.3 (0-50)	0.83
Neoadjuvant chemotherapy			
Yes	24 (96%)	72 (89%)	0.45
No	1 (4%)	9 (11%)	
Adjuvant therapy			
Endocrine therapy			
Yes	24 (96%)	74 (91%)	
No	1 (4%)	6 (7%)	0.71
Unknown	0	1 (1%)	
Chemotherapy			
Yes	12 (48%)	34 (42%)	0.65
No	13 (52%)	47 (58%)	
Radiotherapy			
Yes	19 (76%)	50 (62%)	0.24
No	6 (24%)	31 (38%)	
Disease-free interval (months)			
mean ± SD	92.8 ± 24.9	94.0 ± 25.1	0.84

Elevation of CEA and/or CA15-3 at relapse			
No elevation	7 (28%)	42 (52%)	
CEA only	5 (20%)	15 (19%)	
CA15-3 only	5 (20%)	9 (11%)	0.16
Both CEA and CA15-3	8 (32%)	13 (16%)	
Unknown	0	2 (3%)	
No. of metastatic organs at relapse			
Single	15 (60%)	54 (67%)	0.68
Multiple	10 (40%)	27 (33%)	
First-line endocrine therapy			
Aromatase inhibitors	18 (72%)	61 (75%)	
SERM	6 (24%)	17 (21%)	0.9
Fulvestrant	1 (4%)	2 (3%)	
LHRH agonist	0	1 (1%)	
Total duration of endocrine therapies after relapse (months)			
median (range)	6 (1-63)	29.5 (7-78)	<0.0001*
No. of chemotherapy regimens after relapse			
median (range)	1 (0-5)	0 (0-6)	0.06
Total duration of chemotherapies after relapse (months)			
median (range)	4 (0-39)	0 (0-49)	0.16

*$p < 0.05$ is considered significant.