The Difference in Prognostic Outcomes Between *De Novo* Stage IV and Recurrent Metastatic Patients with Hormone Receptor-positive, HER2-negative Breast Cancer

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Abstract. *Background/Aim: Patients with de novo stage IV and recurrent metastatic breast cancer are often treated with the same strategies, although the difference in prognostic outcomes remains unclear. The objective of this retrospective chart review study was to compare the prognostic outcomes between two types of patients with hormone receptor-positive (HR+), HER2-negative (HER2−) breast cancer. Patients and Methods: We estimated overall survival of the two groups and evaluated the progressive course of the disease using disease-free interval (DFI) and interval from the end of adjuvant treatment to the first recurrence (AFI). Results: We studied 172 patients with HR+/HER2− breast cancer, of which 65 were de novo and 107 were recurrent. Median OS between de novo and recurrent BC was 4.85 and 3.45 years, respectively (p=0.046). Recurrent patients with a DFI<2 years were found to have a significantly poorer prognosis than recurrent patients with a DFI≥2 years (p=0.016) and de novo patients (p=0.002). Similarly, recurrent patients with an AFI<1 year had a significantly poorer prognosis compared to de novo patients (p=0.026). Conclusion: De novo patients had better prognoses than recurrent patients with DFI<2 years or AFI<1 year, likely due to their therapy-naïve status or lower resistance to systemic treatment.*

Breast cancer (BC) is the most common malignancy diagnosed in women, and leads to cancer mortality worldwide (1, 2). The

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majority of BC patients are diagnosed at an early disease stage, receive surgery and adjuvant treatment, and become long-term survivors who can be classified as disease-free (3-5). However, patients that develop metastatic disease during or after standard of care are generally incurable. In these cases a primary treatment goal is symptom palliation (6, 7). Patients with distant metastasis at initial diagnosis are classified as *de novo* stage IV metastatic patients and can be viewed as a distinct subgroup (8, 9), and these patients could be considered a poor prognostic group with incurable disease. However, a previous report suggested that *de novo* BC patients tend to have a better prognosis relative to recurrent BC patients (10). *De novo* BC patients may have a better response to systemic therapy due to their treatment-naïve status, while recurrent BC patients are more likely to show therapeutic resistance to systemic therapy after undergoing adjuvant treatment. There could also be biological differences other than the therapeutic factors between *de novo* and recurrent BC patients (11-13). Metastatic BC patients could form heterogeneous groups and present with varying metastatic patterns and prognostic outcomes, therefore requiring distinct treatment approaches based on BC subtype (14, 15). Treatment strategies have continuously advanced thanks to improved understanding of the heterogeneity of metastatic disease, which can have distant patterns of recurrence and varying prognostic impacts (15, 16). These approaches, which include endocrine therapies, targeted therapies, and various types of chemotherapies, are selected according to metastatic and prognostic patterns or BC subtypes based on immunohistochemical or molecular classifications (17). Although the difference in metastatic patterns and survival outcomes between *de novo* and recurrent BC patients is still unclear, these patients have often been treated with the same strategies. The objective of this retrospective study is to examine the prognostic outcomes between these groups of patients, both with the hormone receptor positive (HR+), and HER2-negative (HER2−) subtype. A better understanding of the metastatic course and prognostic factors for these patients

Table I. *Baseline characteristics at the initial diagnosis of distant metastasis.*

Characteristics	De novo BC	Recurrent BC	p-Value
Number	65 (38%)	107 (62%)	
Age			0.983
<50 years	12 (18%)	20 (19%)	
50-70 years	16 (25%)	25 (23%)	
≥70 years	37 (57%)	62 (58%)	
Stage (UICC Classification)			
I		20 (19%)	
II		68 (63%)	
III		19 (18%)	
Histological Grade			0.070
Low (1+2)	39 (60%)	74 (69%)	
High (3)	19 (29%)	16 (15%)	
Unknown	7 (11%)	17 (16%)	
First metastatic site			
Multiple	21 (32%)	45 (42%)	0.202
Visceral	35 (54%)	57 (53%)	0.942
Liver	12 (18%)	28 (26%)	0.246
Lung	23 (35%)	26 (24%)	0.163
Bone	33 (51%)	55 (51%)	0.936
Soft tissue	23 (35%)	44 (41%)	0.454
Brain	0	3 (3%)	0.173
Primary treatment			
Chemotherapy	28 (43%)	37 (35%)	0.265
Endocrine therapy	37 (57%)	70 (65%)	
DFI			
<2 years		20 (19%)	
2-5 years		47 (44%)	
≥5 years		40 (37%)	
AFI			
<1 year		70 (68%)	
1-3 years		19 (18%)	
≥3 years		14 (14%)	

BC: Breast cancer; DFI: disease-free interval; AFI: interval from the end of adjuvant treatment to the first recurrence.

Table II. *Median survival time for de novo and recurrent BC according to function of clinical characteristics.*

Characteristics	*De novo* BC Median (range)	Recurrent BC Median (range)
All	2.91 (0.11-11.76)	2.28 (0.02-10.55)
Age at enrollment		
<50 years	3.71 (0.39-10.57)	2.63 (0.02-5.47)
50-70 years	3.71 (0.35-11.76)	2.41 (0.13-10.55)
≥70 years	0.97 (0.11-5.13)	1.92 (0.10-6.56)
Stage (UICC Classification)		
I		3.13 (0.19-6.63)
II		2.41 (0.02-10.55)
III		1.78 (0.25-6.33)
Histological Grade		
Low (1+2)	3.39 (0.14-11.58)	2.49 (0.02-10.55)
High (3)	1.45 (0.11-5.01)	1.78 (0.36-3.98)
First metastatic site		
Multiple	1.46 (0.26-11.76)	2.28 (0.19-10.55)
Visceral	2.09 (0.14-11.76)	2.39 (0.13-10.55)
Liver	1.77 (0.26-11.58)	2.06 (0.13-6.84)
Lung	1.84 (0.14-11.76)	2.02 (0.19-10.55)
Bone	3.67 (0.11-11.76)	2.28 (0.02-10.55)
Soft tissue	2.03 (0.26-6.25)	2.23 (0.10-10.55)
Primary treatment		
Chemotherapy	2.68 (0.26-11.76)	2.19 (0.02-8.72)
Endocrine therapy	3.00 (0.11-11.58)	2.40 (0.10-10.55)
DFI		
<2 years		2.03 (0.02-6.26)
2-5 years		2.50 (0.10-10.55)
≥5 years		2.15 (0.19-8.72)
AFI		
<1 year		2.11 (0.02-10.55)
1-3 years		3.68 (0.19-8.72)
≥3 years		2.33 (0.48-6.56)

BC: Breast cancer; DFI: disease-free interval; AFI: interval from the end of adjuvant treatment to the first recurrence.

could improve treatment decisions and provide clinical benefit. This analysis may also help in comprehending and interpreting current clinical research and indicate targets for future clinical studies of metastatic HR+/HER2– BC.

Patients and Methods

Patient characteristics. We retrospectively reviewed the clinical records of *de novo* and recurrent metastatic HR+/HER2- BC patients treated between January 2000 and March 2013 in Sakai City Medical Center, Japan. Cases of *de novo* metastatic BC were classified as stage IV by the UICC TNM classification of malignant tumors, seventh edition. Recurrent patients demonstrated a distant metastasis after removal of the primary breast cancer and standard adjuvant treatment, and patients with locoregional recurrence were excluded from this analysis. This study was approved by the institutional review board and all enrolled patients provided informed consent.

Subtype classification. Estrogen receptor (ER) and progesterone receptor (PR) positivity was defined as score >2 by the Allread scoring system, and HR positivity was defined as ER and/or PR positive breast cancer. HER2 negativity was defined as an immunohistochemistry score of 0, 1+, or 2+ with a negative fluorescence *in situ* hybridization result (a ratio <2.0).

Survival outcomes and progressive courses. The primary aim of this study was to assess differences in the survival outcomes and progressive courses of recurrent BC patients compared to *de novo* BC patients. Overall survival (OS) was defined as the time from the date of initial diagnosis to the time of death or last follow-up for *de novo* patients. For recurrent BC patients, OS was defined as the time from the date of the first distant metastasis to the time of death or last follow-up, and disease-free interval (DFI) was defined as the time from the diagnosis of primary nonmetastatic breast cancer to the date of the first distant metastasis. In this study, we also calculated the interval from the end of adjuvant treatment to the first distant metastasis (AFI).
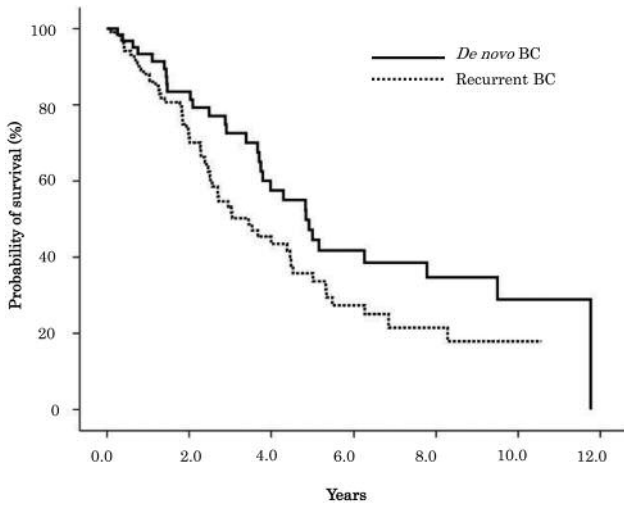
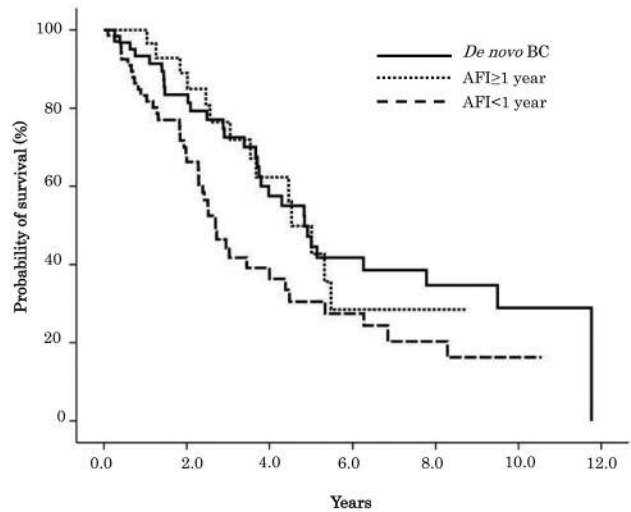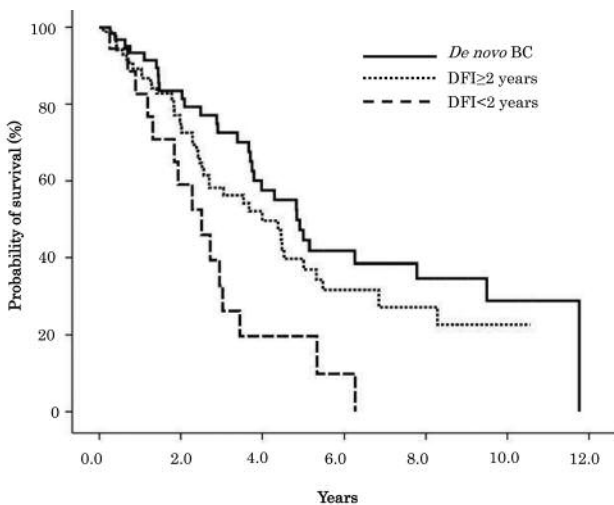Figure 1. *Overall survival for de novo and recurrent BC patients*.

Figure 2. *Overall survival for de novo and recurrent BC patients with DFI≥2 years and DFI<2 years*.

Statistical analysis. OS plots were calculated using the Kaplan-Meier method, and the distributions of the survival curves were compared using log-rank tests. The Cox proportional hazard regression model was used to examine the prognostic evaluation between the groups using several prognostic indicators, such as patient and disease related clinicopathological factors, DFI, and AFI. A 95% confidence interval (CI) was calculated for all hazard ratios (HR) in the Cox regression analysis. We evaluated the results of the univariate and multivariate Cox proportional hazards model with hazards ratios (HR) >1.0 indicating an increased risk of death. Statistical analyses was performed using the Statistical Software package SPSS (v.17.0; Chicago, IL, USA).

Figure 3. *Overall survival for de novo and recurrent BC patients with AFI≥1 year and AFI<1 year.*

Results

A total of 172 patients with HR+ and HER2– breast cancer were included in the analysis. Of these, 65 (38%) were *de novo* and 107 (62%) were recurrent metastatic patients. The characteristics of the patients and tumors at the initial disgnosis of distant metastasis were compared between the groups with a chi-square test and are summarized in Table I. In general, characteristics were well balanced between the groups. A majority of recurrent BC patients (68%) developed initial distant metastases during or within one year after adjuvant treatment.

OS estimates according to clinical characteristics are summarized in Table II. Median OS between *de novo* and recurrent BC was 4.85 and 3.45 years, respectively, and the difference was statistically significant (*p*=0.046) (Figure 1). Kaplan-Meyer survival curves show OS of *de novo* patients, recurrent BC patients with a DFI<2 years, and reccurent BC patients with a DFI≥2 years (Figure 2), as well as among *de novo*, recurrent BC patients with an AFI<1 year, and recuurent patients with an AFI≥1 year (Figure 3).

Tables III and IV respectively show the results of the univariate and multivariate analyses, performed to identify factors that affect the prognosis of *de novo* and recurrent BC patients. Univariate analysis showed that *de novo* BC patients had significantly better OS compared to recurrent BC patients (HR=0.634, 95%CI=0.404-0.995, *p*=0.047). Recurrent BC patients with a DFI<2 years were associated with a statistically significant increased risk of death compared to recurrent BC patients with a DFI≥2 years (HR=2.046, 95%CI=1.130-3.706,

Table III. *Univariate Cox regression analyses for overall survival.*

Variable	HR	95%CI	*p*-Value
Age (≥50 years *vs*. <50 years)	1.411	0.861-2.311	0.172
Histological grade (High (3) *vs*. Low (1+2))	1.806	0.997-3.269	0.051
Multiple metastasis as initial metastatic site	1.560	1.015-2.398	0.043
Visceral metastasis as initial metastatic site	1.151	0.754-1.757	0.514
Lung metastasis as initial metastatic site	1.422	0.846-2.390	0.184
Liver metastasis as initial metastatic site	2.725	1.751-4.255	<0.001
Bone metastasis as initial metastatic site	0.855	0.560-1.304	0.466
Soft tissue metastasis as initial metastatic site	0.625	0.403-0.970	0.036
De novo vs. Recurrent BC	0.634	0.404-0.995	0.047
DFI<2 years *vs*. DFI≥2 years	2.046	1.130-3.706	0.018
DFI<2 years *vs. de novo* BC	2.929	1.539-5.574	0.001
DFI≥2 years *vs. de novo* BC	1.373	0.854-2.207	0.191
AFI<1 year *vs*. AFI≥1 year	1.783	0.968-3.287	0.064
AFI<1 year *vs. de novo* BC	1.792	1.108-2.898	0.017
AFI≥1 year *vs. de novo* BC	1.070	0.561-2.042	0.837

HR: Hazard ratio; CI: confidence interval; BC: breast cancer; DFI: disease-free interval; AFI: interval from the end of adjuvant treatment to the first recurrence.

Table IV. *Multivariate Cox regression analyses for overall survival.*

Variable	HR	95%CI	*p*-Value
De novo *vs*. Recurrent BC	0.679	0.429-1.075	0.099
Multiple metastasis as initial metastatic site	1.190	0.685-2.066	0.538
Liver metastasis as initial metastatic site	2.849	1.745-4.651	<0.001
Soft tissue metastasis as initial metastatic site	0.604	0.359-1.015	0.057

HR: Hazard ratio; CI: confidence interval; BC: breast cancer.

p=0.018), and *de novo* BC patients (HR=2.929, 95%CI=1.539-5.574, *p*=0.001). Recurrent BC patients with an AFI<1 year were associated with a statistically significant increased risk of death compared to *de novo* BC patients (HR=1.792, 95%CI=1.108-2.898, *p*=0.017). There was no significant difference in risk of death among *de novo* BC, recurrent BC with a DFI≥2 years, and AFI≥1 year patients. Multiple metastasis and liver metastasis as the first metastatic site both had an increased risk of death that was statistically significant. Liver metastasis as the first metastatic site was also associated with statistically significant increased risk of death in multivariate analysis.

Discussion

The increasing application of novel cancer treatments including chemotherapy, endocrine therapy, and molecular-targeted therapy has improved the survival of metastatic BC patients (18-20). These treament advances have resulted in decreasing recurrence rates for early-stage breast cancer (3-5). However, although the difference in the prognostic outcomes of metastatic diseases between *de novo* and recurrent BC patients is still unclear, these patients have often been treated using the same strategy. Previous reports have indicated that *de novo* BC patients have better survival than recurrent BC patients (10-12), and our study also confirms these results. Metastatic BC forms heterogeneous groups with varying prognostic outcomes, requiring the development of a distinct treatment approach for each BC subtype (14-16). Most previous studies have reported survival outcomes of metastatic disease regardless of BC subtype in a large patient cohort and have not examined survival as a function of HR/HER2 status (10-12). Yardley *et al*. studied the survival outcomes of *de novo* and recurrent metastatic patients with HER2+ BC. The HER2+ BC subtype is distinct from other subtypes, and requires a specific treatment strategy, such as anti-HER2 targeted therapy (13). Our study is the first report of a survival analysis between *de novo* and recurrent BC patients with HR+/HER2– BC. This is the most common BC subtype, and has a specific course of progression (21, 22). This subtype requires endocrine therapy but in some cases not chemotherapy in an adjuvant setting, and

requires various treatment strategies in a metastatic setting (23, 24). A survival analysis of metastatic disease according to BC subtype could help in choosing an optimal treatment strategy in the patient population (25).

A majority of the recurrent BC patients in this study (68%) developed metastatic disease during or within a year after adjuvant endocrine treatment, and may be likely to develop a resistance to systemic therapy. Therefore, recurrent BC patients with an AFI<1 year had a poorer prognosis than patients with an AFI≥1 year or *de novo* BC patients. Recurrent BC patients with a longer DFI or an AFI≥1 year were also found to have a better prognosis, equivalent to *de novo* BC patients. There could be multiple reasons why recurrent BC patients with an AFI<1 year or a shorter DFI have a poorer prognosis. One reason may be due to ineffective adjuvant treatment or poor carry-over effect of adjuvant treatment. BC patients who experienced a distant recurrence within or soon after adjuvant treatment may present with therapeutic resistance, also leading to poorer prognostic outcomes. In contrast, *de novo* disease is therapy-naive, and therefore likely to show less resistance to systemic therapy (10-12). BC patients with longer DFI or patients who developed a distant recurrence some years after adjuvant treatment may have a better response to systemic therapy. This study could contribute to a better understanding of differences in survival outcomes between *de novo* and recurrent HR+/HER2– BC, and even more conclusice results could be obtained with a larger spectrum of metastatic patients and treatment analysis.

In conclusion, we studied differences in survival outcomes between *de novo* and recurrent HR+/HER2– BC patients. *De novo* BC led to a better prognosis than recurrent BC with a DFI<2 years or an AFI<1 year. This may be because of resistance to systemic therapy due to ineffective adjuvant treatment or poor carry-over effect. This study could aid in understanding valuable clinical relationships between these patients, leading to effective treatment strategies for HR+/HER2– metastatic disease, as well as improved interpretation of results from clinical trials.

Conflicts of Interest

The Authors declare no conflicts of interest.

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