Response to First-line Recurrence Treatment Influences Survival in Hormone Receptor-positive, HER2-negative Breast Cancer: A Multicenter Study

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Abstract. Background/Aim: Little evidence is currently available on significant determinants of post-recurrence survival for patients with hormone receptor-positive (HR+), HER2-negative (HER2–) breast cancer. The objective of this study was to evaluate factors influencing post-recurrence survival in HR+/HER2– breast cancer. Patients and Methods: A cohort of 236 patients with recurrent HR+/HER2– breast cancer was retrospectively analyzed to identify significant factors correlating with prognosis after recurrence. Results: Multivariate analysis revealed independent prognostic factors of poor survival as follows: short intervals between recurrence and the end of adjuvant endocrine therapy (ET; p=0.046); short disease-free intervals (p=0.019); liver metastasis (p=0.007) or multiple metastases (p<0.001) at recurrence; and a poor response to first-line treatment (p<0.001). A poor first-line treatment response was significantly associated with a shorter response to a subsequent treatment line (p=0.007). Logistic regression analysis indicated that liver metastasis significantly increased the risk of a poor first-line-ET response (p=0.009). Conclusion: The first-line treatment response was the key to post-recurrence survival in patients with HR+/HER2– breast cancer. Particularly poor responses led to subsequent unfavorable prognostic outcomes.

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Key Words: Breast cancer, recurrence, survival, hormone receptor-positive, HER2-negative.
Patients and Methods

Patient characteristics. The clinical records of 236 patients with recurrent metastatic HR+/HER2− breast cancer treated between January 2000 and December 2013 at Sakai City Medical Center and Kindai University Hospital, in Japan, were retrospectively reviewed. Recurrence was defined as a distant metastasis that occurred after the primary breast cancer was removed and standard adjuvant treatment was performed. Patients with locoregional recurrence were excluded from this analysis. This study was approved by the institutional review board of our hospitals and all enrolled patients provided informed consent.

Subtype classification. Positivity for the estrogen receptor (ER+) or progesterone receptor (PR+) was defined as a score ≥3 using the Allread scoring system; hormone receptor-positivity (HR+) was defined as ER+ and/or PR+. HER2− negativity was defined as an immunohistochemistry score of 0, 1+, or 2+ and as a negative fluorescence in situ hybridization result (ratio <2.0).

Survival outcomes. For patients diagnosed with a first distant recurrence, we assessed the clinicopathological features, treatment regimen, metastatic sites, progression time, and survival outcomes. Overall survival (OS) was defined as the time from the date of the first distant recurrence to the time of death or last follow-up. The treatment-free interval (TFI) was defined as the time between the end of adjuvant treatment and the first distant recurrence. The disease-free interval (DFI) was defined as the interval between the diagnosis of the primary non-metastatic breast cancer and the date of the first distant recurrence. A good response to first-line treatment was defined as a first-line treatment with duration ≥6 months; a poor response was defined when duration was less than 6 months. Progression-free survival (PFS) during a second-line treatment was analyzed in groups with either a good or a poor response to first-line treatment.

Statistical analysis. OS and PFS plots were calculated with the Kaplan-Meier method. Survival curve distributions were compared with the log-rank test. A Cox proportional hazard regression was used to examine associations between different prognostic indicators (i.e., patient- and disease-related clinicopathological factors) and survival outcomes. Regressions were analyzed with hazards ratios (HRs) and 95% confidence intervals (CIs). HRs >1.0 indicated an increased risk of death. Logistic regression was performed to identify risk factors for a poor response to first-line-chemotherapy (CT) and first-line-ET treatments, and those results were analyzed with odds ratios (OR) and 95% CIs. All tests were two-tailed; p-values <0.05 were considered significant. Statistical analyses were performed with the Statistical Software package, SPSS (v.17.0; Chicago, IL, USA).

Results

Characteristics of patients and survival outcomes. Our analyses included 236 patients with recurrent metastatic HR+/HER2− breast cancer (Table I). A poor prognosis was significantly correlated to older age (≥70 years at diagnosis), low ER expression, anthracycline or taxane alone as adjuvant CT, a short DFI (<2 years) or TFI (<1 year), liver metastasis or multiple metastases at first recurrence, and a poor response to first-line treatment. In contrast, a good prognosis was significantly correlated with a longer duration (≥5 years) of adjuvant ET and bone-only metastasis at first recurrence. Survival plots showed that patients with a good response to first-line-CT or first-line-ET treatments had significantly better survival rates after recurrence, compared to those with poor responses to first-line-CT (p=0.028; Figure 1A) or first-line-ET treatments (p<0.001; Figure 1B).

Multivariate analysis of factors related to survival after recurrence. The multivariate analysis included all prognostic factors that achieved significance in the univariate analysis (Table II). The multivariate analysis revealed four significantly independent prognostic factors related to an unfavorable survival rate after recurrence: i) a short TFI (<1 year; p=0.046), ii) a liver metastasis (p=0.007) or iii) multiple metastases at first recurrence (p<0.001), and iv) a poor response to first-line treatment (p<0.001).

PFS on second-line treatment for recurrence. Survival plots showed that the PFS was significantly shorter for patients with a poor response to first-line treatment, compared to those with a good response (median PFS: 4.63 months vs. 8.60 months, p=0.001; Figure 2).

Risk factors for a poor response to first-line treatment. A logistic regression analysis showed that a metastasis to bone only significantly increased the risk of a poor response to first-line-CT (p=0.014; Table III). Moreover, liver metastasis was a significant risk factor for a poor response to first-line-ET (p=0.009; Table IV).

Discussion

Several concepts regarding prognosis in HR+/HER2− breast cancer patients were considered important in evaluating their survival after recurrence. First, we considered the primary biological parameters, including nodal status, histological grade, progression degree, and HR or HER2 status. Second, time-based variables that described the time before recurrence were considered, such as duration of adjuvant treatment, TFI, and DFI. Third, we considered post-recurrence characteristics; i.e., metastatic sites and the response or resistance to treatment.

Our cohort included about 70% patients with TFI<1 year, which indicated that most registered patients experienced recurrences during or soon after adjuvant ET. These patients should be considered resistant to ET; therefore, they need a more aggressive treatment. Our multivariate analysis showed that TFI<1 year was an independent prognostic factor for post-recurrence survival. Consistent with previous studies, we also found that DFI was a strong significant prognostic factor (17-19). It is reasonable to assume that, due to advances in
| Characteristics                          | N (%)  | Median OS from recurrence (years) | Univariate analysis |
|-----------------------------------------|--------|----------------------------------|---------------------|
|                                         |        |                                  | HR (95% CI)         | p-Value |
| All                                     | 236 (100%) | 4.54                            |                     |         |
| Age at diagnosis                        |        |                                  |                     |         |
| <50 years                               | 80 (34%) | 4.51                            | 0.432 (0.235-0.795) | 0.007   |
| 50-70 years                             | 124 (52%) | 5.05                            | 0.428 (0.241-0.760) | 0.004   |
| ≥70 years                               | 32 (14%) | 1.64                            | 1.00                |         |
| Stage                                   |        |                                  |                     |         |
| I                                       | 36 (15%) | 6.30                            | 1.00                |         |
| IIA+IIB                                 | 74+68 (60%) | 4.44                            | 1.012 (0.758-1.351) | 0.937   |
| IIIA+IIB+IIC                            | 30+21+7 (25%) | 4.73                            | 1.099 (0.780-1.546) | 0.590   |
| Number of positive nodes                |        |                                  |                     |         |
| 0                                       | 75 (32%) | 5.72                            | 0.798 (0.601-1.061) | 0.121   |
| 1-3                                     | 78 (33%) | 4.42                            | 0.837 (0.634-1.106) | 0.211   |
| 4-10                                    | 51 (22%) | 4.58                            | 0.804 (0.590-1.094) | 0.165   |
| 1-3                                     | 32 (14%) | 2.60                            | 1.00                |         |
| ER expression                           |        |                                  |                     |         |
| Visceral metastasis                     | 115 (49%) | 3.66                            | 1.353 (0.919-1.996) | 0.125   |
| No lung metastasis                      | 173 (73%) | 5.05                            | 1.00                |         |
| Multiple metastases                     | 87 (37%) | 2.44                            | 2.375 (1.610-3.509) | <0.001  |
| 0-10                                     | 78 (33%) | 4.42                            | 0.837 (0.634-1.106) | 0.211   |
| 11-20                                   | 51 (22%) | 4.58                            | 0.804 (0.590-1.094) | 0.165   |
| TFI                                      |        |                                  |                     |         |
| ER                                       |        |                                  |                     |         |
| High (≥50%)                              | 125 (53%) | 5.30                            | 0.325 (0.189-0.559) | <0.001  |
| Low (<10%)                              | 28 (12%) | 1.95                            | 1.00                |         |
| Adjuvant CT                             |        |                                  |                     |         |
| Anthracycline                           | 33 (14%) | 2.81                            | 1.00                |         |
| Taxane                                   | 17 (7%) | 2.53                            | 1.016 (0.491-2.101) | 0.965   |
| Anthracycline+Taxane                    | 73 (31%) | 4.51                            | 0.563 (0.321-0.987) | 0.045   |
| CMF                                      | 20 (8%) | 8.20                            | 0.355 (0.151-0.836) | 0.018   |
| None                                     | 76 (32%) | 7.52                            | 0.510 (0.292-0.894) | 0.019   |
| Adjuvant ET                             |        |                                  |                     |         |
| AI                                       | 109 (46%) | 5.72                            | 1.00                |         |
| TAM                                      | 91 (39%) | 4.44                            | 1.133 (0.745-1.721) | 0.561   |
| AI/TAM                                   | 16 (7%) | 5.05                            | 0.981 (0.440-2.188) | 0.964   |
| Unknown                                  | 14 (6%) | -                               | -                   |         |
| Adjuvant ET duration                    |        |                                  |                     |         |
| <1 year                                  | 44(19%) | 1.86                            | 1.00                |         |
| 1-3 years                                | 90 (38%) | 4.44                            | 0.414 (0.256-0.669) | <0.001  |
| 3-5 years                                | 61 (26%) | 6.96                            | 0.315 (0.174-0.572) | <0.001  |
| ≥5 years                                 | 36 (15%) | 7.80                            | 0.248 (0.116-0.532) | <0.001  |
| TFI                                      |        |                                  |                     |         |
| <1 year                                  | 162 (69%) | 3.66                            | 1.00                |         |
| ≥1 year                                  | 55 (23%) | 5.55?                           | 0.467 (0.264-0.824) | 0.009   |
| DFI                                      |        |                                  |                     |         |
| <2 years                                 | 53 (22%) | 2.31                            | 1.00                |         |
| 2-5 years                                | 94 (40%) | 4.73                            | 0.472 (0.297-0.748) | 0.001   |
| ≥5 years                                 | 89 (38%) | 5.33                            | 0.367 (0.221-0.609) | <0.001  |
| Age at recurrence                        |        |                                  |                     |         |
| <50 years                                | 47 (20%) | 4.51                            | 0.794 (0.444-1.422) | 0.438   |
| 50-70 years                              | 132 (56%) | 4.73                            | 0.738 (0.461-1.181) | 0.205   |
| ≥70 years                                | 57 (24%) | 4.83                            | 1.00                |         |
| Response to 1L treatment                 |        |                                  |                     |         |
| Good (CT+ET)                             | 29+76 (45%) | 7.56                            | 1.00                |         |
| Poor (CT+ET)                             | 42+66 (46%) | 2.44                            | 3.511 (2.307-5.343) | <0.001  |
| Metastatic site at recurrence            |        |                                  |                     |         |
| Bone only                                | 79 (34%) | 7.68                            | 0.583 (0.377-0.905) | 0.016   |
| No bone only                             | 157 (66%) | 3.66                            | 1.00                |         |
| Lung metastasis                          | 63 (27%) | 5.72                            | 0.900 (0.580-1.397) | 0.638   |
| No lung metastasis                       | 173 (73%) | 4.51                            | 1.00                |         |
| Liver metastasis                         | 49 (21%) | 1.95                            | 2.681 (1.776-4.049) | <0.001  |
| No liver metastasis                      | 187 (79%) | 5.46                            | 1.00                |         |
| Visceral metastasis                      | 115 (49%) | 3.66                            | 1.353 (0.919-1.996) | 0.125   |
| No visceral metastasis                   | 121 (51%) | 4.73                            | 1.00                |         |
| Single metastasis                        | 149 (63%) | 5.55                            | 1.00                |         |
| Multiple metastases                      | 87 (37%) | 2.44                            | 2.375 (1.610-3.509) | <0.001  |

ER, Estrogen receptor; CT, chemotherapy; CMF, cyclophosphamide methotrexate fluorouracil; ET, endocrine therapy; AI, aromatase inhibitor; TAM, tamoxifen; TFI, treatment-free interval; DFI, disease-free interval; 1L, first-line.
adjuvant treatments, a prolonged DFI implies clinical improvement concerning survival outcomes. Our multivariate analysis indicated that both TFI and DFI should be regarded as important time parameters related to post-recurrence survival. Understanding these time-based variables before recurrence could largely contribute to decisions regarding optimal therapeutic strategies after recurrence.

The metastatic site at first recurrence has been regarded as an important predictive factor for survival after recurrence (11, 18, 20, 21). Our multivariate analysis showed that the first metastatic site was independently associated with post-recurrence survival; in particular, both liver and multiple metastases strongly predicted a poor outcome after recurrence. This finding supported the assumption that liver and multiple metastases are indicative of extensive spreading or disseminated cancer cells, which leads to poor survival outcomes (19, 22).

Table II. Multivariate analysis of survival after recurrence.

| Characteristics                  | Multivariate analysis  |
|----------------------------------|------------------------|
|                                 | HR (95% CI)            | p-Value |
| Age at diagnosis ≥70 years       | 1.406 (0.955-2.070)    | 0.084   |
| Low ER expression                | 1.397 (0.996-1.957)    | 0.053   |
| Adjuvant A/T                     | 0.908 (0.681-1.211)    | 0.512   |
| Adjuvant ET≥5 years              | 0.916 (0.554-1.516)    | 0.733   |
| TFI<1 year                       | 1.576 (1.008-2.465)    | 0.046   |
| DFI<2 years                      | 1.411 (1.057-1.883)    | 0.019   |
| Response to 1L treatment         | 0.586 (0.457-0.752)    | <0.001  |
| Bone-only metastasis             | 0.743 (0.531-1.041)    | 0.084   |
| Liver metastasis                 | 1.456 (1.110-1.912)    | 0.007   |
| Multiple metastases              | 1.727 (1.271-2.347)    | <0.001  |

ER, Estrogen receptor; A/T, anthracycline or taxane chemotherapy; ET, endocrine therapy; TFI, treatment-free interval; DFI, disease-free interval; 1L, first-line.
Here, it was found that the response to the first-line recurrence treatment, regardless of whether it was based on CT or on ET, was an independent prognostic factor for post-recurrence survival in HR+/HER2– patients. Furthermore, the PFS response to second-line treatments depended on how good the response to the first-line treatment was, as this correlated with prolonged survival outcomes in general. This finding suggested that the first-line treatment response might be the most important factor in post-recurrence survival for patients with metastatic HR+/HER2– breast cancer. In agreement with this, our study revealed that a poor response to the first-line treatment was significantly related to unfavorable survival after recurrence. Previous studies have also reported several predictors of the response to second-line therapy or specifically to ET for treating recurrence (11, 17, 19, 21). Most patients with a poor response to first-line ET are resistant to it (15, 16); therefore, CT should be selected as the second-line treatment. However, little is known about the risk factors associated with the first-line treatment response. Our logistic regression analysis showed that liver metastasis at recurrence was a significant risk factor for a poor response to first-line-ET, regardless of whether patients were resistant to this type of therapy. This finding suggested that patients with liver metastasis should be treated with first-line CT to improve the subsequent prognosis. Recently, new molecular targeted drugs, such as inhibitors of mTOR, CDK4/6, and PIK3CA, have become clinically available for treatments in combination with ET for HR+/HER2– metastatic cancer patients (12, 23). The continuous development of novel cancer treatments and molecular targeted therapies may improve the survival of these patients (24-28). In particular, for those at high risk, optimal treatments for recurrence, in addition to novel targeted agents, could reduce the cancer’s resistance to the subsequent treatments and lead to a better prognosis.

The present study had certain limitations. First, as a retrospective chart review without validation, it was not possible to avoid a selection bias. However, the selection of patients with HR+/HER2– recurrent breast cancer, and the exclusion of HER2+, triple negative, or de novo breast...
cancer patients, allowed the study of post-recurrence survival in HR+/HER2− metastatic breast cancer patients despite the small sample size. Moreover, here we presented realistic data, based on actual clinical practice. Future studies with a larger cohort of patients might provide more conclusive evidence of prognostic value for the factors we identified.

In conclusion, this retrospective study using real-world medical records identified clinical prognostic factors that predicted the post-recurrence survival in HR+/HER2+ metastatic breast cancer. We found that the response to a first-line treatment for recurrence could be the most important factor for post-recurrence survival. Moreover, liver metastasis at recurrence was identified as both a strong risk factor for a poor response to first-line treatment for recurrence as well as a significant prognostic factor for unfavorable survival after recurrence. Our study provided frontline physicians with important clinical clues to achieving optimal treatment strategies and for accurately assessing patients with HR+/HER2− metastases.

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